รายงานวิจัยฉบับสมบูรณ์

โครงการ "การวิจัยเวชพันธุศาสตร์ทางคลินิกและอณูพันธุศาสตร์"

Clinical Genetics and Molecular Genetics Research

โดย นายพีรนิธ กันตะบุตร และคณะ

สิงหาคม 2544

สัญญาเลขที่ BRG/18/2544

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มหาวิทยาลัยเชียงใหม่

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

(ความเห็นในรายงานนี้เป็นของผู้วิจัย สกว.ไม่จำเป็นต้องเห็นด้วยเสมอไป)

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I would like to thank The Thailand Research Fund (TRF) for supporting our research projects. Without their support these projects would not have been possible. Even though the knowledge obtaining from these research projects would not go directly to them, we are grateful to the patients and their parents for their kind cooperation in letting us use their medical and dental information for research and publications. I am glad some of them became friends of myself. Hope someday soon, the knowledge gained from these projects will benefit their children or grandchildren or other people who they don't know but are affected with the same conditions.

Besides co-authors who are listed in the papers, there were a lot of people who helped to make these projects happened. We are thankful to them for their help and friendship.

Once again, I really appreciate the help from TRF especially Prof. Vichai Boonsaeng for seeing the good in me and granting me the mental and financial supports. The most effective coordination of this project is truly credited to Ms. Sujaree Son-ngay.

Abstract

Project code: BRG44-8-0018

Project Title: Clinical and Molecular Genetics Research

Investigators: Dr. Piranit Kantaputra

Department of Pediatric Dentistry, Faculty of Dentistry, Chiang Mai University

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Project Period: May 15, 2001-August 31, 2005

This research project supported by TRF has produced 18 publications in the international journals. The reprints of the articles are enclosed in this final report.

Paper 1: Laurin-Sandrow syndrome with additional associated manifestations. Am J Med Genet 2001;98:210-215.
Kantaputra PN.

A Thai man with Laurin-Sandrow syndrome (LSS, MIM 135750), the ninth reported case, is described. He had an underdeveloped nasal bone, scar-like seams under the nose, large heads of mandibular condyles, and brachymesophalangy of toes as newly observed findings of the syndrome. He also had mental retardation. The patient had duplication of ulna, with triphalangeal thumbs, and polydactyly of one finger. The triphalangeal thumbs were non-opposable. Carpal bones were malformed. Mirror image polydactyly of the toes was present. There were nine toes on the right and eight on the left. Joint abnormalities were observed at his elbows, wrists, knees, ankles, fingers, and toes. Synostosis of severely malformed tarsal bones was noted. This appears to be the first case of LSS with anomalies not limited to the nose and limbs. The relationship between LSS, tibial hemimelia-polysyndactyly-triphalangeal thumbs syndrome, triphalangeal thumb-polysyndactyly syndrome, preaxial polydactyly types 2 and 3, and Haas-type syndactyly is discussed.

Paper 2: "Mental retardation, obesity, mandibular prognathism with eye and skin anomalies (MOMES syndrome): A Newly recognized autosomal recessive syndrome.

Am J Med Genet 103:283-288, 2001.

We report two daughters of a Thai family affected with mental retardation, delayed speech, obesity, craniofacial manifestations, and ocular anomalies. Craniofacial manifestations included macrocephaly, maxillary hypoplasia, mandibular prognathism, and crowding of teeth. Ocular anomalies consisted of blepharophimosis, blepharoptosis, decreased visual acuity, abducens palsy, hyperopic astigmatism, and accommodative esotropia. Chronic atopic dermatitis, lateral deviation of the great toes, and cone-shaped epiphyses of the toes were observed. The disorder is suggested to be autosomal recessive. The combination of findings found in our patients has not hitherto been described.

It has been recognized as a "NEW" syndrome in Online Mendelian Inheritance in Man (OMIM).

Paper 3: Cryptophthalmos, dental and oral abnormalities, and brachymesophalangy of second toes: New syndrome or Fraser syndrome?

Am J Med Genet 2001;98:263-268.

Kantaputra P, Eiumtrakul P, Matin T, Opastirakul S, Visrutaratna P, Mevate U.

We report on an 8-year-old Thai girl with bilateral complete cryptophthalmos, facial asymmetry, delayed bone age, brachymesophalangy and medial deviation of the second toes, and dental anomalies. The dental anomalies consist of delayed dental development, congenital absence of the second premolars, microdontia of the deciduous molars. A fibrous band of the buccal mucosa was found. Dental anomalies are rare among patients with Fraser syndrome. They have not been reported in either isolated or other syndromic cryptophthalmos. The oral manifestations and brachymesophalangy of the second toes found in our patient may represent newly recognized findings associated with cryptophthalmos or they may represent a newly recognized syndrome.

Paper 4: Digital dysmorphism with craniofacial and other new associated abnormalitites"

Clinical Dysmorphology 2001;10:171-175.

Kantaputra PN, Chalidapong P, Visrutaratna P.

We report digitotalar dysmorphism in a grandfather, father, and a daughter. All the affected members had clasped thumbs. The father had a short stature, large zygomatic arch and a flat mandibular condyle. The newly recognized findings found in the affected girl were large maxillary deciduous central incisors, a short proximal phalanx of the second finger, and a large subcutaneous hemangioma of the back. Her paternal grandfather had only congenital clasped thumbs. Congenital clasped thumb is a very heterogeneous anomaly and related to many syndromes. The findings in the reported family which are consistent with digitotalar dysmorphism, include congenital clasped thumbs, ulnar deviation of fingers, and a congenital vertical tali.

Paper 5: Dentinogenesis imperfecta-associated syndromes.

Am J Med Genet 2001:104:75-78.

Kantaputra PN

This paper reviews the conditions that are related to dentinogenesis imperfecta.

Paper 6: A newly recognized syndrome of skeletal dysplasia with opalescent and rootless teeth.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001 Sep;92(3):303-7.

Kantaputra PN.

A Thai girl with skeletal dysplasia and dental anomalies was seen. Her anomalies consisted of disproportionately short stature, short neck, broad and depressed nasal bridge, broad chest in the anteroposterior dimension, kyphosis, widely spaced nipples, and protruded abdomen. Radiographic testing indicated that she had a large sella turcica, platyspondyly, hypoplastic acetabulum, and a small body of mandible. Both her deciduous and

permanent teeth were equally opalescent, and most were rootless, with root development of the mandibular teeth more severely affected. Some maxillary roots were extremely short and tapered. Hypodontia was also observed. These findings represent a unique and hitherto undescribed syndrome of skeletal dysplasia with concomitant dental anomalies.

Paper 7: **Van der Woude syndrome with sensorineural hearing loss, large craniofacial sinuses, dental pulp stones, and minor limb anomalies: Report of a four-generation Thai family**

Am J Med Genet 108:275-280, 2002

Kantaputra PN, Sumitsawan Y, Schutte BC, Tochareontanaphol C.

A four-generation Thai family affected with Van der Woude syndrome is reported. The disorder appeared to be originally inherited from a person who was half Thai and half Pakistani. The lip lesions found in this family were varied and did not appear to be related to other phenotypes. There were some clinical manifestations possibly specific for the condition in this family. They included sensorineural hearing loss, prominent frontal bone, large frontal/sphenoidal/maxillary sinuses with increased mastoid air cells, long tooth roots, dental pulp stones, ankyloglossia, brachydactyly of hands, brachyphalangy, and hyperphalangy of toes, and single flexion crease of the fifth fingers. Fluorescence in situ hybridization analysis revealed no visible deletion at a 1q32-41 region.

Paper 8: **A Thai mother and son with distal symphalangism, hypoplastic carpal bones, microdontia, dental pulp stones, and narrowing of zygomatic arch: A new distal symphalangism syndrome?**

Am J Med Genet 109:56-60, 2002

Kantaputra PN, Kinoshita A, Limwonges C, Praditsup O, Niikawa N.

A Thai mother and son with distal symphalangism and other associated abnormalities are reported. Distal and middle phalanges of fingers and toes 2-5 were either aplastic/hypoplastic or fused between the corresponding digits. The second fingers and fourth fingernails were most severely affected in both patients. The mother's hands were less severely affected; the middle and

distal phalanges of her hands were malformed and fused. Besides the absence of fusion lines, the shape of the fused middle and distal phalanges was quite different from that of other types of fusion, i.e., fused bones in both patients did not maintain the normal configuration of bone, referring to as "middle-distal phalangeal complex". Distal symphalangism was observed in toes 2-5 of the mother and in toe 3 of the son. Both patients had additional clinical manifestations such as narrowing of the zygomatic arch, dental pulp stone, microdontia of a mandibular permanent central incisor, cone-shaped epiphyses of middle phalanges of fingers, and absence of scaphoid, trapezium, trapezoid, and pisiform bones. Mutation analysis of *NOG* and *ROR2*, the genes responsible for proximal symphalangism and brachydactyly type B, respectively, was negative.

It has been recognized as a "NEW" syndrome in Online Medelian Inheritance in Man (OMIM).

Paper 9: A dominantly inherited malformation syndrome with short stature, upper limb anomaly, minor craniofacial anomalies, and absence of TBX5 mutations: Report of a Thai family

Am J Med Genet 2002;111:301-306.

Kantaputra PN, Yamasaki K, Ishida T, Kishino T, Niikawa N.

We report on a Thai family with dominantly inherited malformation syndrome with upper limb anomalies, short stature, quadricuspid aortic valve, and minor craniofacial anomalies. The affected individuals comprised a mildly affected mother, a moderately affected daughter, and a most severely affected son. The daughter and son had short stature. The craniofacial abnormalities comprised frontal bossing, hypoplastic nasal bones, depressed nasal bridge, and broad nasal alae. The upper limb defects varies among the patients, ranging from radial ray defects in the mother through radial and ulnar ray defects with unilateral humeral hypoplasia in the daughter to radial ray defects with severe oligodactyly and bilateral humeral hypoplasia in the son. All patients in this family had hypoplasia of the shoulder girdle and resembled what is observed in many families with Holt-Oram syndrome. Moreover, the son showed quadricuspid aortic valve with mild aortic regurgitation. However,

the present family did not show any mutation of the *TBX5* gene, a disease-causing gene of Holt-Oram syndrome. The present family deserves further investigation on other genes that play a role in the development of the upper limbs, particularly of radial rays.

Paper 10: Apparently new osteodysplastic and primordial short stature with microdontia, opalescent teeth, and rootless molars in two siblings.
Am J Med Genet 2002;111:420-428.
Kantaputra PN

A Thai man and his sister affected with a newly recognized syndrome of proportionate primordial short stature are reported. The patients had severe intrauterine and postnatal growth retardation, prominent nose and nasal bridge, small pinnae, large sella turcica, areas of hypo- and hyperpigmentation of skin, dry and thin scalp hair, and long and straight clavicles. Ivory epiphyses and cone-shaped epiphyses of the hands were found when they were young, but most of them disappeared as they grew up. Scaphoid and trapezium had angular appearance. The second toes were unusually long. Distal symphalangism of toes and barchymesophalangy of fingers were noted. The findings that appear to distinguish this syndrome from the previously reported syndromes are long second toes, opalescent and rootless teeth, severe microdontia, severely hypoplastic alveolar process, and unerupted tooth. The mode of inheritance is suspected to be autosomal recessive.

Paper 11: A New Syndrome of Symphalangism, Multiple Frenula, Postaxial Polydactyly, Dysplastic Ears, Dental Anomalies, and Exclusion of NOG and GDF5 genes.
Am J Med Genet 120A:381-385, 2003
Kantaputra PN, Pongprot Y, Praditsap O, Pho-iam T, Limwongse C.

A Thai girl with a unique combination of limb and craniofacial anomalies is reported. Manifestations include blepharoptosis; prominent nose; hypodontia;

multiple, hyperplastic frenula; and dysplastic ears. Limb anomalies include short stature, postaxial polydactyly of both hands and the left foot, proximal and distal symphalangism of fingers, and congenital absence of the distal phalanges of toes 2-5. Mutation analyses of *NOG* and *GDF5*, the genes responsible for symphalangism-related syndromes, were negative.

Collaborated with Molecular Genetic Unit, Siriraj Hospital Medical School.

This has been considered a new syndrome by OMIM. It has been recognized as "Thai Symphalangism Syndrome"

Paper 12: Thyroid Dysfunction in a Patient with Aglossia.

Am J Med Genet 122A:274-277, 2003.

Kantaputra P, Tanpaiboon P.

We report a Thai girl who had aglossia, micrognathia, microsomia, collapse of mandibular arch, persistence of buccopharyngeal membrane, microcephaly, and mild developmental delay. Thyroid function tests indicated that she had subclinical hypothyroidism. Thyroid scan revealed normal uptake of the whole thyroid gland. Tongue morphogenesis is integrally linked to the normal development of thyroid gland, and abnormal tongue morphogenesis could potentially result in a functional thyroid disorder. We propose that micrognathia, microsomia, congenital absence of mandibular incisors, and collapse of the mandibular arch are the result of abnormal tongue development.

Paper 13: Heterozygous mutation in the SAM domain of p63 underlies Rapp-Hodgkin ectodermal dysplasia.

J Dent Res. 2003 Jun;82(6):433-7.

Kantaputra PN, Hamada T, Kumchai T, McGrath JA.

Several ectodermal dysplasia syndromes, including Ectrodactyly-Ectodermal dysplasia-Clefting (EEC) and Ankyloblepharon-Ectodermal Dysplasia-Clefting (AEC) syndromes, are known to result from mutations in the *p63* gene. We investigated whether Rapp-Hodgkin syndrome (RHS) is also caused by mutations in the p63 gene. We identified a heterozygous de novo germline missense mutation, S545P, in the sterile-alpha-motif (SAM) domain of p63, in

a Thai patient affected with RHS. This is the first genetic abnormality to be described in RHS. The amino acid substitution is the most downstream missense mutation in *p63* reported thus far. Histological assessment of a skin biopsy from the patient's palm showed hyperkeratosis and keratinocyte cell-cell detachment in the upper layers of the epidermis, along with numerous apoptotic keratinocytes. Collectively, these investigations demonstrate that RHS is also caused by mutations in *p63* and that the clinical similarities to AEC syndrome are paralleled by the nature of the inherent mutation.

We were the first group who found the gene responsible for Rapp-Hodgkin Ectodermal Dysplasia.

Paper 14: Thirteen-Year-Follow up report on Mesomelic Dysplasia, Kantaputra Type (MDK), and comments on the paper of the second reported family of MDK by Shears et al. (Invited Comments)

Am J Med Genet 2004;128A:1-5.

Kantaputra PN.

This is the 13-year-follow up report on Mesomelic dysplasia, Kantaputra type. It was the genetic bone disorder I discovered 13 years ago in Chiang Mai. Recently there have been reports of this syndrome in The Holland and England.

Paper 15: Microcephalic Osteodysplastic Primordial Dwarfism with severe microdontia and skin anomalies: Confirmation of a New Syndrome.

Am J Med Genet 2004;130A:181-190.

Kantaputra PN, Tanpaiboon P, Unachak K, Praphanphoj V.

We report two related Thai children having a new syndrome of microcephalic osteodysplastic primordial dwarfism (MOPD). The findings which classify them as having MOPD include IUGR, microcephaly, prominent nose and nasal bridge, small pinnae, short stature, cone-shaped and ivory-epiphyses, delayed bone age, slender long bones, and abnormal pelvis. The findings that distinguish them as having newly recognized syndrome consist of severe

microdontia, malformed teeth, single-rooted or rootless teeth, severely hypoplastic alveolar bone, cafe au lait spots, acanthosis nigricans, and areas of hypo- and hyperpigmented skin. The reported patients appear to have the same condition as the family reported by Kantaputra [2002: Am J Med Genet 111:420-428].

Paper 16: A Novel mutation in IRF6 underlies hearing loss, pulp stones, large craniofacial sinuses, and limb anomalies in Vna der Woude syndrome patients.
Oral Biosci Med 2004;1:277-282.
Kantaputra PN, Limwongse C, Assawamakin A, Praditsap O, Kemaleelakul U, Miedzybrodzka ZH, Kondo S, Schutte B.

Van der Woude (VWS) and popliteal pterygium syndromes are caused by mutations in the interferon regulatory factor (*IRF6*) gene. Two Thai VWS families demonstrating newly recognized findings of VWS are reported. The phenotype in the first family includes sensorineural hearing loss, cleft lip and palate, lower lip anomalies, ankyloglossia, hypodontia, dental pulp stones, large craniofacial sinuses, and limb anomalies. Molecular analysis of *IRF6* revealed an 11 bp deletion in exon 4. This frameshift mutation truncates IRF6 just after the DNA binding domain. The mutation implies that IRF6 can affect dental pulp calcification, pneumatization of craniofacial sinuses, and ear and limb development. The second family consists of an affected brother and sister. Both have lower lip anomalies and the sister has cleft lip and palate. Interstingly, both have abnormal shape of the mandibular deciduous and permanent molars. Mutation analysis of *IRF6* was negative, suggesting that the mutations may be located outside of the coding exons or in other loci.

Paper 17: A newly recognized syndrome involving limbs, pelvis, and genital organs or a variant of Al-Awadi/Raas-Rothschild syndrome?
Am J Med Genet 2005;132:63-67.
Kantaputra PN, Tanpaiboon P.

We report on a 3-year-old Thai boy with limb, pelvic, and genital malformations. The combination of findings found in this patient is similar to that of Al-Awadi/Raas-Rothchild syndrome (AARRS) or limb/pelvis hypoplasia/aplasia syndrome. The upper limbs are more severely affected than the lower ones. Unlike that of AARRS, the radial ray is more severely affected than the ulnar ray. The presence of humeroulnar synostosis and humero-ulnar-radial synostosis and the absence of a radius distinguishes it from AARRS. The similarities and dissimilarities between the features in the present patient and other limb-pelvic hypoplasia/aplasia syndromes are discussed. The findings in this group of patients appear to demonstrate limb-pelvis-genital organ developmental field defects.

Paper 18: Response to: Microcephalic osteodysplastic primordial dwarfism with severe microdontia and skin anomalies by Dr. Judith Hall. Am J Med Genet 130:181-190.

Kantaputra PN. and Tanpaiboon P.

Introduction & Summary

With the kind support from The Thailand Research Fund (TRF), we have discovered **8 new genetic syndromes.** We were the first in the world who found that *p63* gene is responsible for causing Rapp-Hodgkin Ectodermal Dysplasia. We have produced total of **18 international publications**.

Output from these Research Projects

1. I have presented the result of the project 5 at The Eleventh Robert J. Gorlin Conference on Dysmorphology" on the 10th of October, 2001 at University of Minnesota.
2. "Apparently new Microcephalic osteodysplastic and primordial short stature with microdontia, opalescent teeth, and rootless molars in two sibs." It was presented at the meeting of International Association of Oral pathology (IAOP) in Singapore. August 5-8, 2002.
3. The New syndromes of symphalangism were presented at The Twelfth Robert J. Gorlin Conference on Dysmorphology" on the 13th of October, 2002 at University of Minnesota.
4. Van der Woude Syndrome project was present at the IADR Southeast Asian Meeting in Ho Chin Minh, Vietnam, September 2003.
5. New syndrome of Microcephalic Osteodysplastic Primordial Dwarfism was presented at The Thailand Dental Faculty Research Meeting in Chiang Mai October, 2003.
6. The findings from these projects have been presented several times in teaching lectures at meetings and seminars in Thailand, China, and The United States of America.
7. The results of these projects have been broadcasted as interviews in radio programs in Thailand and in the newspaper (ไทยรัฐ).

Collaborations

We collaborated with The Molecular Genetics Unit of Siriraj Hospital Medical School (Dr. Chanin Limwongse) and Craniofacial Genetic Laboratory, School of Medicine, University of Iowa (Prof. Jeff C. Murray and Dr. Brian Schutte). Collaborating with a Genetic Skin Group at St. John Dermatology Institute, London (Prof. John A. McGrath), we found the gene and mutation responsible

for Rapp-Hodgkin Ectodermal Dysplasia. We still have worked with these great scientists in a few ongoing projects.

ไทยรัฐ ๑.

มช.วิจัยพบ 7 โรคพันธุกรรมใหม่คนไทย

● พบครั้งแรกของโลก "ยีน P63" ● ลุยวิจัยเชิงลึกหาต้นตอหวังเฝ้าระวัง

ทันตแพทย์พีรนิจ กันตะบุตร ภาควิชาทันตกรรมสำหรับเด็ก คณะทันตแพทยศาสตร์ ม.เชียงใหม่ กล่าวถึงโครงการศึกษาด้านเวชพันธุศาสตร์ทางคลินิกและอณูชีวพันธุศาสตร์ ซึ่งได้ทุนจากสำนักงานกองทุนสนับสนุนการวิจัย (สกว.) ว่า การศึกษาพบโรคทางกรรมพันธุ์ชนิดใหม่ถึง 7 โรค เช่น พบว่ายีนชนิดหนึ่งชื่อยีน P63 เป็นยีนที่ทำให้เกิดโรค Rapp-Hodgkin Syndrome โดยผู้ป่วยโรคนี้จะมีความผิดปกติของร่างกายคล้ายโรคสังข์ทอง เช่น ผิวหนังแห้ง ผมและฟันไม่ค่อยมี แต่มีลักษณะของปากแหว่งเพดานโหว่ร่วมด้วย ทำให้รับประทานอาหารได้ลำบากและมีคุณภาพชีวิตที่ต่ำลง ซึ่งเป็นการค้นพบสาเหตุของโรคนี้เป็นครั้งแรกในโลก โดยโรคนี้ถ่ายทอดทางกรรมพันธุ์ ซึ่งถ้าหากผู้ป่วยมีบุตร บุตรที่คลอดมาก็จะมีโอกาสเป็นโรคนี้ได้ถึง 50% การค้นพบนี้ทำให้สามารถวินิจฉัยก่อนคลอดได้ว่าลูกคนต่อไปมีโอกาสเป็นโรคหรือไม่ นอกจากนี้ เมื่อ 13 ปีที่แล้ว ยังพบโรคกันตะบุตร ซินโดรมใน จ.เชียงใหม่ ซึ่งผู้ป่วยมีแขนและขาสั้นและไม่มีส้นเท้ามาแต่กำเนิด ทั้งตระกูลมาถึง 4 ชั่วอายุคน ถึง 16 คน โดยอยู่ในขั้นศึกษาหายีนที่ทำให้เกิดโรคนี้

ทันตแพทย์พีรนิจกล่าวด้วยว่า นอกจากนี้ กำลังศึกษายีนที่เป็นสาเหตุของโรคการเกิดมาตัวเล็กของมนุษย์ ซึ่งบางรายเกิดมามีน้ำหนักแรกเกิดเพียง 900 ... โรคที่ทำให้ผู้ป่วยมีนิ้วมือข้างละ 2-3 นิ้วเท่านั้น และมีความผิดปกติของแขนขา มีลักษณะมือที่งอกมาจากไหล่ หรือกรณีผู้ป่วยที่เกิดมาไม่มีฟัน ซึ่งสัมพันธ์กับฮอร์โมนไทรอยด์ผิดปกติ ศึกษายีนที่ทำให้เกิดผมร่วง ซึ่งทำให้รู้ว่ายีนที่ควบคุมการเจริญเติบโตของผมขณะเป็นผู้ใหญ่ ต่างจากตอนเป็นเด็ก ศึกษากรณีโรคอ้วนในเด็กที่มีปัญญาอ่อนร่วมด้วย หรือกรณีของโรคเท้าแสนปม ที่ผู้ป่วยไม่มีขาเลย โดยมีลักษณะของเนื้อเยื่อเต็มใบหน้า ตลอดจนโรคเพดานโหว่ที่เกิดขึ้นเฉพาะ

ทันตแพทย์พีรนิจกล่าวอีกว่า การศึกษายีนค้นพบโรคทางกรรมพันธุ์ที่เกิดขึ้นใหม่ในประเทศไทยหลายโรค ไม่ว่าจะเป็นโรคที่เกิดจากความผิดปกติของยีนเหล่านี้ ไม่ได้เกิดจากการกินยาหรือจากสารเคมีที่มีพิษ แต่เป็นความบังเอิญที่เกิดขึ้น เหมือนกับบางคนที่เกิดมามีไฝ ซึ่งอธิบายไม่ได้ว่าทำไมถึงมีไฝเกิดขึ้นตรงนั้น และอาการที่มีโรคปากแหว่งเพดานโหว่ อะไรเป็นสาเหตุทำให้เกิดภาวะความผิดปกติ หรือกลายพันธุ์ ซึ่งยังไม่สามารถตอบคำถามได้ชัดเจน ซึ่งลักษณะผิดปกติเหล่านี้ ยังพบผู้ป่วยจำนวนน้อยรายในประเทศไทย แต่การหาสาเหตุที่แท้จริงได้จากความผิดปกติของยีนเหล่านี้ จะเป็นการเฝ้าระวังโรค และช่วยให้สามารถวินิจฉัยลักษณะการทำงานของยีน ซึ่งจะนำไปสู่การรักษาโรคและเพิ่มคุณภาพชีวิตของ

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Laurin-Sandrow Syndrome With Additional Associated Manifestations

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A Thai man with Laurin-Sandrow syndrome (LSS, MIM 135750), the ninth reported case, is described. He had an underdeveloped nasal bone, scar-like seams under the nose, large heads of mandibular condyles, and brachymesophalangy of toes as newly observed findings of the syndrome. He also had mental retardation. The patient had duplication of ulna, with triphalangeal thumbs, and polydactyly of one finger. The triphalangeal thumbs were non-opposable. Carpal bones were malformed. Mirror image polydactyly of the toes was present. There were nine toes on the right and eight on the left. Joint abnormalities were observed at his elbows, wrists, knees, ankles, fingers, and toes. Synostosis of severely malformed tarsal bones was noted. This appears to be the first case of LSS with anomalies not limited to the nose and limbs. The relationship between LSS, tibial hemimelia-polysyndactyly-triphalangeal thumbs syndrome, triphalangeal thumb-polysyndactyly syndrome, preaxial polydactyly types 2 and 3, and Haas-type syndactyly is discussed.

KEY WORDS: **Laurin-Sandrow syndrome; additional manifestations; mirror image polydactyly; tibial hemimelia-polysyndactyly-triphalangeal thumbs syndrome**

INTRODUCTION

Laurin-Sandrow syndrome (LSS, MIM 135750) is a rare autosomal-dominant disorder characterized by preaxial polysyndactyly of hands and feet in mirror-image fashion, congenital absence of the radius and tibia with duplication of the ulna and fibula (dimelia), and nasal defects. The nasal defects consist of hypoplasia of the nasal alae, columella groove, and incomplete external nares along the inferior margin [Laurin et al., 1964; Sandrow et al., 1970; Kogekar et al., 1993; Martin et al., 1993; Martinez-Frias et al., 1994; Hatchwell and Dennis, 1996]. Eight cases have been reported [Martinez-Frias et al., 1994; OMIM]. The gene responsible for LSS remains unknown.

Here I report a new case of LSS, with previously unreported findings including mild mental retardation, an underdeveloped nasal bone, scar-like seams under the nose, large heads of mandibular condyles, and brachymesophalangy of the toes.

CLINICAL REPORT

General Findings

The patient, a cheerful 54-year-old Thai man (Fig. 1a), was the only child in a non-consanguineous marriage. His family history was unremarkable. He was mildly mentally retarded. He appeared older than his age, and had not been married. The result of chromosome analysis on the patient was 46,XY. His eyebrows were arched. His alar nasi and nasal bridge were broad. There were two scar-like seams under his nose, running from the inferior margin of each nostril to the upper lip. His mustache hair was found over the seams of his fibrous tissue. His philtrum was void of mustache hair (Fig. 1a). A lateral cephalogram revealed an underdeveloped nasal bone and a large head of the mandibular condyle (Fig. 1b).

Upper Limbs

The patient's right hand was in a flexed position, and its movement was markedly restricted. The movement of his elbows and the supination and pronation of his hands were very limited. His thumbs were triphalan-

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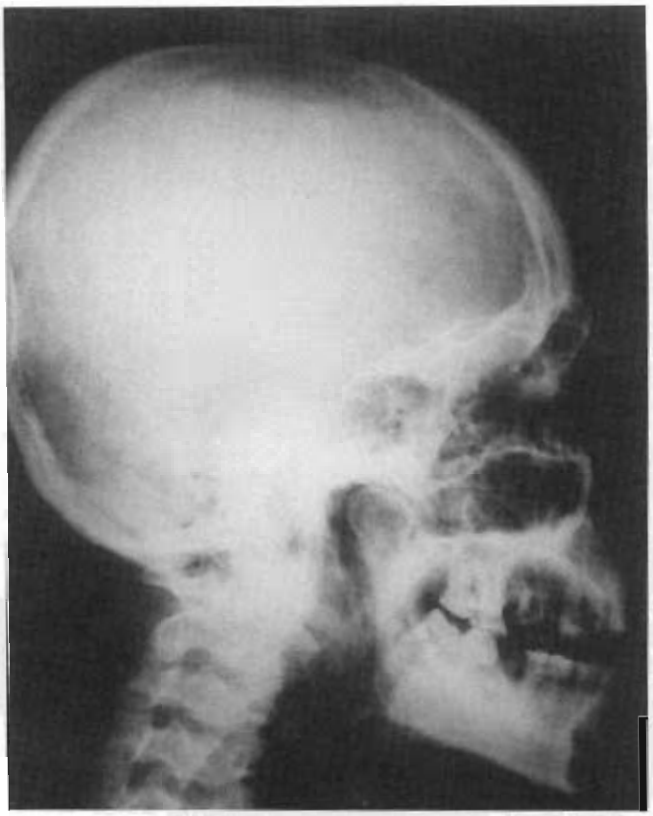

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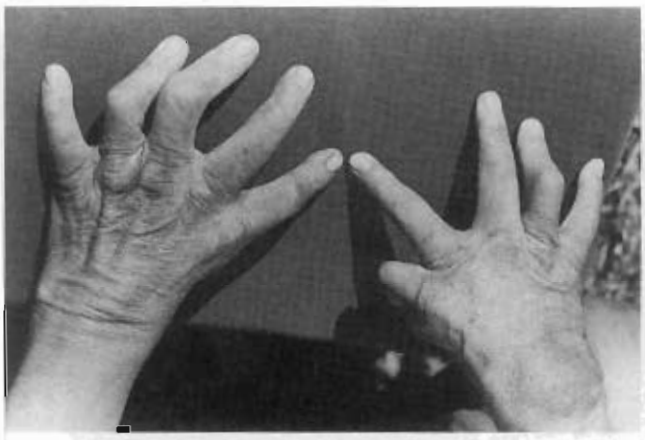

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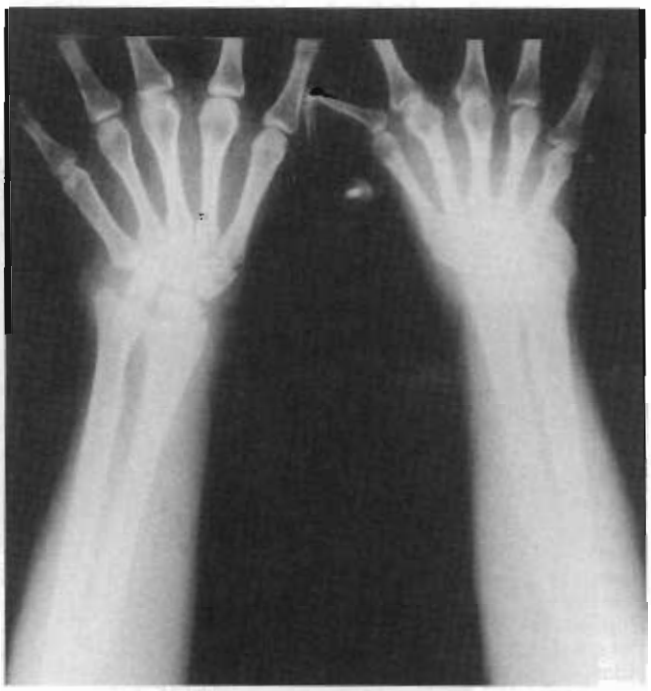

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Fig. 1. a) The patient with scar-like seams under his nose. Hair on the seams of fibrous tissue. b) Lateral cephalogram shows underdeveloped nasal bone and large head mandibular condyle. c) Triphalangeal thumbs. Interphalangeal joint abnormality. d) Triphalangeal thumbs, flexion contracture of fingers and preaxial polydactyly of a poorly developed finger medial to the right triphalangeal thumb. Note malformation and missing carpal bones. e) Duplication of ulna and malformed carpal bones.

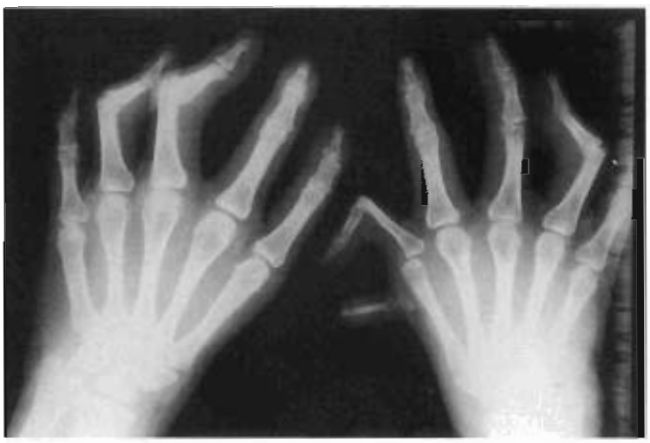

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Fig. 1. *(Continued).*

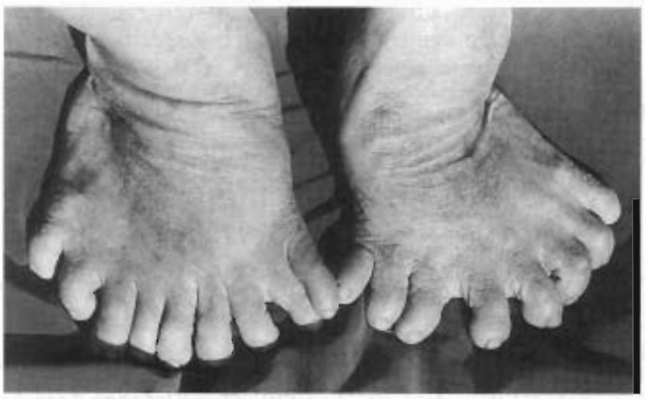
geal and opposable. On his right hand he had an additional poorly developed finger, located radial to the triphalangeal thumb. All proximal interphalangeal joints and distal interphalangeal joints of his right fingers 2 and 3 were flexed (Fig. 1c). A radiograph revealed the absence of his radii. His ulna was duplicated. The ulnae, however, did not appear identical. The scaphoids and lunates were malformed. The trapezia, triquetrums, and pisiforms were all missing (Fig. 1d and Fig. 1e). His extra finger contained only a small and slender proximal phalanx, with a small round bone proximal to it. The finger's metacarpal bone was not evident. Also, there was a dislocation at the right first metacarpophalangeal joint. The middle phalanges of the left first and fifth fingers were short. And all distal and middle phalanges of the fourth fingers were tapered distally (Fig. 1e).

Lower Limbs

His left leg was shorter than his right. His right leg was slightly bowed. His right knee was dislocated, causing difficulty in walking. Both of his knees, especially the right one, had limited extension. His feet were extremely widened, with evident polydacytyly. There were nine toes on his right foot and eight toes on his left foot. Both of his great toes were absent. The toes in the place of his great toes were triphalangeal, and similar in morphology to his second toes. His extra toes were somewhat similar in pairs, according to their

TABLE I. Manifestations of Reported and Present Cases of Laurin-Sandrow Syndrome

Manifestations	Laurin et al. [1964]	Sandrow et al. [1970] Father	Sandrow et al. [1970] Daughter	Kogekar et al. [1993]	Martin et al. [1993] Father	Martin et al. [1993] Daughter	Martinez-Frias et al. [1994]	Hatchwell and Dennis [1996]	Present case	Frequency (M/F)
Gender	M	M	F	M	M	F	F	F	M	5/4
Underdeveloped nasal bone	N	N	N	N	Y	N	N	N	Y	2/9
Groove collumella	N	N	Y	Y	Y	Y	N	Y	N	5/9
Unfused/groove nares	N	Y	Y	Y	N	N	Y	Y	N	5/9
Redundant nasal tissue	N	N	Y	Y	N	N	N	N	N	2/9
Scar-like tissue under the nose	N	N	N	N	N	N	N	N	Y	1/9
Large head of condyle	N	N	N	N	N	N	N	N	Y	1/9
Restricted elbow	Y	N	Y	Y	N	N	N	N	Y	4/9
Duplication of ulna	Y	N	Y	N	N	N	N	N	Y	3/9
Wrist deformity	Y	N	Y	N	N	Y	N	N	Y	4/9
Number of fingers (R/L)	6/6	6/6	10/10	6/5	6/6	9/10	5/5	5/5	6/5	
Absence of thumb	Y	Y	Y	N	N	Y	Y	Y	Y	7/9
Mirror hand	Y	Y	Y	N	N	Y	N	N	N	4/9
Complete syndactyly	Y	Y	Y	Y	Y	Y	Y	Y	N	8/9
Knee abnormality	Y	Y	Y	Y	N	Y	N	N	Y	6/9
Short tibia	Y	N	N	Y	N	Y	N	N	Y	4/9
Short fibula	N	N	N	Y	N	N	N	N	Y	2/9
Duplication of fibula	Y	N	Y	N	N	N	N	N	N	2/9
Pes equinovarus	Y	Y	Y	Y	N	Y	N	Y	N	6/9
Number of toes (R/L)	10/10	NA	10/10	8/9	8/8	10/10	5/5	8/7	9/8	
Mirror foot	Y	Y	Y	Y	N	Y	Y	Y	Y	8/9
Interphalangeal joint deformity	Y	Y	Y	Y	N	Y	Y	Y	Y	7/9
Brachymesophalangy of toes	N	N	N	N	N	N	N	N	Y	1/9
Cryptorchidism	N	Y	N	Y	N	N	N	N	N	2/9



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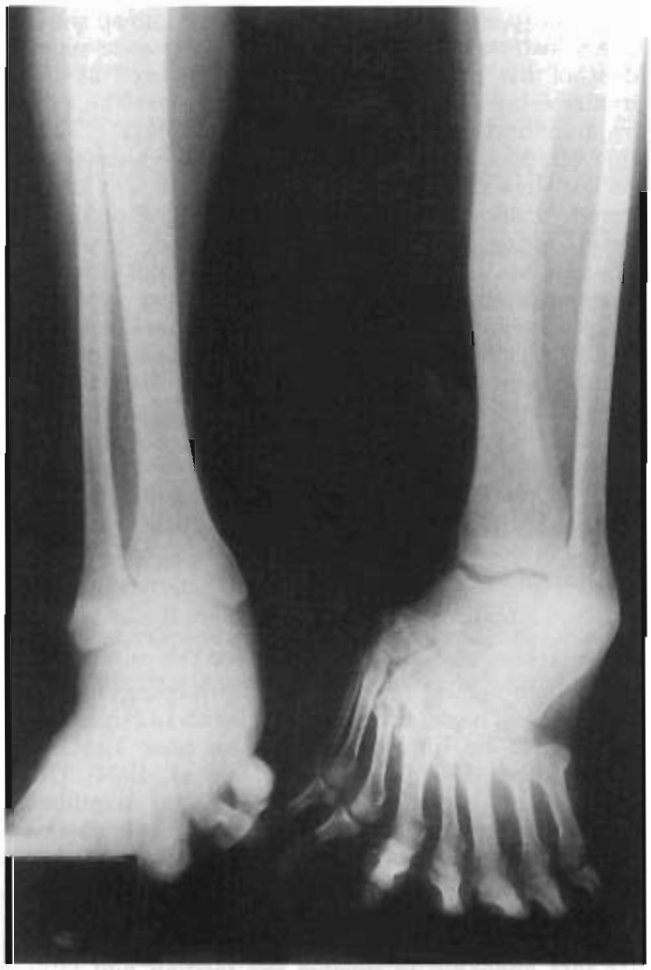

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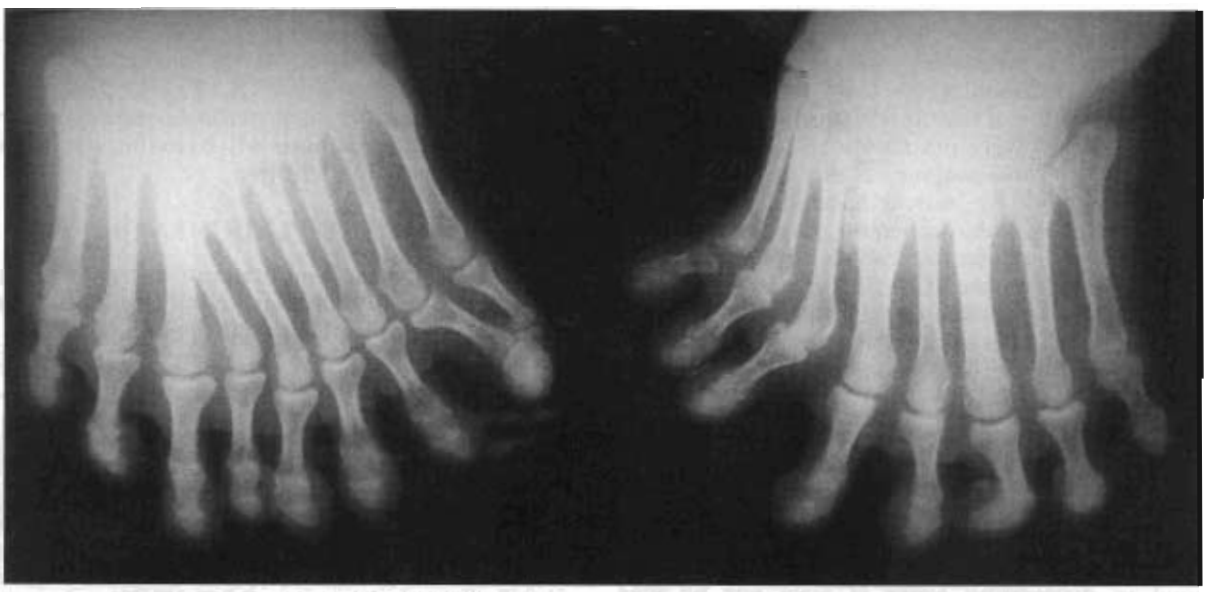

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Fig. 2. a) Very large feet with 9 toes on the right and 8 toes on the left. Morphology of the extra toes is similar in pairs. b) Left tibia and fibula are thick and short. Slightly bowed left tibia. Synostoses of malformed tarsal bones. c) Large left metatarsals 1 and 3. The most medial left toe is biphalangeal. Large right metatarsal 3 and brachymesophalangy of all toes.

morphology, except for the most medial one on the left side, which was small, unpaired, and poorly-developed. Most of his toes had flexion contractures at their proximal interphalangeal joints (Fig. 2a). The radiographs of his legs and feet were remarkable (Fig. 2b and Fig. 2c). His left tibia and fibula were shorter and thicker than his right ones. His left tibia was slightly bowed. Dislocation was observed at his left ankle. His tarsal bones were severely malformed. Synostosis between his talus, calcaneus, cuboid, and navicular bones was observed. Two supernumerary cuneiform bones were found medial to his medial cuneiform bones (Fig. 2b). There were eight and nine metatarsals of his left and right feet, respectively. His right metatarsal 3, and left metatarsals 1 and 3, were larger than others were. All of his toes were triphalangeal, except for the most medial one on his left foot, which was biphalangeal. This biphalangeal toe did not articulate properly with its metatarsal. Brachymesophalangy of all of his toes was noted. The proximal ends of his left fifth metatarsals were broad (Fig. 2c).

DISCUSSION

The limb defects of this patient are consistent with those of LSS. Anomalies associated with LLS have been reported to be limited to only the nose and limbs [Martin et al., 1993; Martinez-Frias et al., 1994]. These anomalies included a large head of the mandibular condyle, and mental retardation. Other newly observed craniofacial manifestations are summarized in Table I. Brachymesophalangy of toes is a common developmental variation; but involvement of all toes is a new finding. All nasal defects in previously reported LSS patients appeared to involve the median and lateral nasal process. The present patient did not have the columella groove, which is a characteristic feature for LSS. Instead, he had an underdeveloped nasal bone and scar-like seams under his nose, which may have developed from the processes.

The patient described is the third reported case of LSS with duplication of the ulna [Sandrow et al., 1970], although the ulnae were not identical. Unlike what is found in the present patient, a duplicated ulna is usually accompanied by "mirror hand" [Pintilie et al., 1964; Gropper, 1983]. A duplicated ulna with mirror-image polydactyly can be induced experimentally in a *Hoxb8* transgenic mouse [Charite et al., 1994]. All radial-ray carpal bones are usually absent in cases of radial aplasia, but this is not the case in the present patient nor in the *Hoxb8* transgenic mouse [Charite et al., 1994].

Mirror-image polydactyly is generally described *where preaxial supernumerary digits are arranged in descending order of size from a single central digit* with the absence of a thumb or a great toe [Temtamy and McKusick, 1978; Viljeon and Kidson, 1990]. The supernumerary toes in the present patient were not arranged in descending order of size; but he was considered to have mirror-image polydactyly of the foot, since he had duplicated postaxial digits in the preaxial side.

It is likely that LSS is related causally to tibial hemimelia-polysyndactyly-triphalangeal thumb syndrome (THPTTS), since a girl with LSS had a father with characteristic features of THPTTS, although he was diagnosed as having LSS. The father had postaxial polydactyly of his hands and preaxial and postaxial polysyndactyly of his feet that did not fit the diagnosis of LSS. Without deep columella grooves at their noses, this family might have been diagnosed as THPTTS [Martin et al., 1993]. Balci et al. [1999] reported a large Turkish family affected with triphalangeal thumb-polysyndactyly syndrome (TTPS). Interestingly, many members of this family had short columellae and depressions of the nose tips [Balci et al., 1999]. In addition, a boy diagnosed as THPTTS with fibular dimelia, mirror feet, and hands with five digits had a father with preaxial polydactyly types 2 and 3 (PPD-2/3), in a large family affected with THPTTS [Vargas et al., 1995]. A phenotype similar to this boy was described in a mother and her son [Pfeiffer and Roeskau, 1971]. Complete syndactyly of fingers, with absent thumb or Haas-type syndactyly, is the most consistent manifestation of LSS (Table I). This manifestation has been described in all reported cases, except for the father of one patient [Sandrow et al., 1970]. Complete syndactyly of fingers is associated with THPTTS and TTPS [Ofodile, 1982; Balci et al., 1999; Kantaputra and Chalidapong, 2000]. Haas-type syndactyly has been reported either alone or as a part of other syndromes. It is probable that Haas-type syndactyly is related causally to LSS.

The gene for tetramelic mirror-image polydactyly that is not related to LSS has been mapped to chromosome 14q13 [Kim et al., 1997; Matsumoto et al., 1997]. This may imply that mirror polydactyly is etiologically heterogeneous. The gene responsible for TTPS, THPTTS, and mirror polydactyly with tibial hemimelia have been mapped to chromosome 7q36 [Vargas et al., 1998; Balci et al., 1999; Heus et al., 1999; Zguricas et al., 1999]. All these lines of evidence may indicate that LSS, THPTTS, TTPS, PPD-2/3, and Haas-type syndactyly are pathogenetically-related to each other. This hypothesis will be maintained until the putative gene(s) are identified.

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REFERENCES

Balci S, Demirtas M, Civelek B, Piskin M, Sensoz O, Akarsu AN. 1999. Phenotypic variability of triphalangeal thumb-polysyndactyly syndrome linked to chromosome 7q36. Am J Med Genet 87: 399–406.

Charite J, De Graff, W S, Shen J, Deschamps J 1994. Ectopic expression of Hoxb-8 causes duplication of the ZPA in the forelimb and homeotic transformation of axial structure. Cell 78: 589–601.

Gropper PT. 1983. Ulnar dimelia. J Hand Surg 8: 487–491.

Haas SL. 1940. Bilateral complete syndactylism of all fingers. Am J Surg 50: 365–366.

Hatchwell E, Dennis N. 1996. Mirror hands and feet: a further case of Laurin-Sandrow syndrome. J Med Genet 33: 426–428.

Heus HC, Hing A, Baren MJV, Joose M, Breedveld GJ, Wang JC, Burgess A, Donnis-Keller H, Berglund C, Zguricas J, Scherer SW, Rommens JM, Oostra BA, Heutink P. 1999. A physical map and transcriptional map of the preaxial polydactyly locus on chromosome 7q36. Genomics 57: 342–351.

Kantaputra PN, Chalidapong P. 2000. Are triphalangeal thumb-polysyndactyly syndrome (TPTPS) and tibial hemimelia-polysyndactyly-triphalangeal thumbs syndrome (THPTTS) identical? A father with TPTPS and his daughter with THPTTS in a Thai family. Am J Med Genet 93: 126–131.

Kim KC, Wakui K, Yamagishi A, Ohno T, Sato M, Imaizumi S, Aihara T, , Fukushima Y, , Ohashi H. 1997. Tetramelic mirror-image polydactyly and a de novo balanced translocation between 2p23.3 and 14q13. Am J Med Genet 68: 70–73.

Kogekar N, Teebi AS, Vockley J. 1993. Sandrow syndrome of mirror hands and feet and facial abnormalities. Am J Med Genet 46: 126–128.

Laurin CA, Favreau JC, Labelle P. 1964. Bilateral absence of the radius and tibia with bilateral reduplication of the ulna and fibula. A case report. J Bone Joint Surg 46: 137–142.

Martin RA, Jones MC, Jones KL. 1993. Mirror hands and feet with a distinct nasal defect, an autosomal dominant condition. Am J Med Genet 46: 129–131.

Martinez-Frias ML, Espejo P, Gomez MA, de Leon RG, Moro LG. 1994. Laurin-Sandrow syndrome (mirror hands and feet and nasal defects): Description of a new case. J Med Genet 31: 410–412.

Matsumoto N, Ohashi H, Kato R, Fujimoto M, Tsujita T, Sasaki T, Nakano M, Miyoshi O, Fukushima Y, Niikawa N. 1997. Molecular mapping of a translocation breakpoint at 14q13 in a patient with mirror-image polydactyly of hands and feet. Hum Genet 99: 450–453.

Ofodile FA. 1982. Synpolydactyly in three generations of a Nigerian family. East African Med J 59: 835–839.

OMIM.http://www.ncbi.nlm.nih.gov/omim

Pfeiffer RA, Roeskau M. 1971. Agenesis der Tibia, fibulaverdoppelung und spiegelbildliche Polydaktylie (diplopodie) bei Mutter und Kind. Z Kinderheilk 111: 38–50.

Pintilie D, Hatmanu D, Olaru I, Panoza GH. 1964. Double ulna with symmetrical polydactyly. A case report. J Bone Joint Surg 46: 89–93.

Sandrow RE, Sullivan PD, Steel H. 1970. Hereditary ulnar and fibular dimelia with peculiar facies. A case report. J Bone Joint Surg 52: 367–370.

Temtamy SA, McKusick VA. 1978. The Genetics of Hand Malformations. New York: Alan R. Liss, Inc., for the National Foundation March of Dimes. BD:OAS XIV(3): p. 364–392.

Vargas FR, Pontes RL, Llerena JC, Jr, de Almeida JCC. 1995. Absent tibiae-polydactyly-triphalangeal thumbs with fibular dimelia: Variable expression of the Werner (McKusick 188770) syndrome? Am J Med Genet 55: 261–264.

Vargas FR, Roessler E, Gaudenz K, Belloni E, Whitehead AS, Kirke PN, Mills JL, Hoper G, Stevenson RE, Cordeiro I, Correia P, Felix T, Gereige R, Cunningham ML, Canum S, Antonarakis SE, Strachan T, Tsui LC, Scherer SW, Muenke M. 1998. Analysis of the human Sonic Hedgehog coding and promoter regions in sacral agenesis, triphalangeal thumb, and mirror polydactyly. Hum Genet 102: 387–392.

Viljeon DL, Kidson SH. 1990. Mirror polydactyly: pathogenesis based on a morphogen gradient theory. Am J Med Genet 35: 229–235.

Zguricas J, Heus H, Morales-Peralta E, Breedveld G, Kuyt B, Mumcu EF, Bakker W, Akarsu N, Kay SPJ, Hovius SER, Heredero-Baute L, Oostra BA, Heutink P. 1999. Clinical and genetic studies on 12 preaxial polydactyly families and refinement of the localization of the gene responsible to a 1.9 cM region on chromosome 7q36. J Med Genet 36: 32–40.

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Mental Retardation, Obesity, Mandibular Prognathism With Eye and Skin Anomalies (MOMES Syndrome): A Newly Recognized Autosomal Recessive Syndrome

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We report two daughters of a Thai family affected with mental retardation, delayed speech, obesity, craniofacial manifestations, and ocular anomalies. Craniofacial manifestations included macrocephaly, maxillary hypoplasia, mandibular prognathism, and crowding of teeth. Ocular anomalies consisted of blepharophimosis, blepharoptosis, decreased visual acuity, abducens palsy, hyperopic astigmatism, and accommodative esotropia. Chronic atopic dermatitis, lateral deviation of the great toes, and cone-shaped epiphyses of the toes were observed. The disorder is suggested to be autosomal recessive. The combination of findings found in our patients has not hitherto been described.

KEY WORDS: atopic dermatitis blepharophimosis blepharoptosis cone-shaped epiphysis hyperopic astigmatism; mandibular prognathism; mental retardation; obesity

INTRODUCTION

The presence of mental retardation, obesity, and eye abnormalities have been previously described in a number of syndromes including Bardet-Beidel syndromes (BBS) [Beales et al., 1997], Laurence-Moon syndrome [Farag and Teebi, 1988], Cohen syndrome [Horn et al., 2000; Kivitie-Kallio et al., 2000], Prader-Willi syndrome [Olander et al., 2000], macrosomia, obesity, macrocephaly, and ocular abnormalities (MOMO) syndrome [Moretti-Ferreira et al., 1993; Zannolli et al., 2000], and Camera-Marugo-Cohen syndrome [Lambert et al., 1999]. We would like to report two daughters of a Thai family with similar clinical manifestations consisting of mental retardation, obesity, blepharophimosis, blepharoptosis, hyperopic astigmatism, abducens palsy, cone-shaped epiphyses of toes, maxillary hypoplasia, and mandibular prognathism. To the best of our knowledge, the combination of these abnormalities has never been reported before.

CLINICAL REPORT

Patient 1

A 12-year-old Thai girl and her affected younger sister (patient 2) came to the Department of Pediatric Dentistry, Faculty of Dentistry, Chiang Mai University for the treatment of dental caries (Fig. 1a,b). She was the first child in a nonconsanguineous marriage. Her younger sister was also affected. Their mother had a spontaneous abortion of the third pregnancy. Her birth weight was 3,500 g (> 90th centile). At age 12 years, her height, weight, and occipitofrontal circumference (OFC) were 148 cm (10–25th centile), 67 kg (> 97th centile), and 56 cm (> 98th centile), respectively. Body mass index (BMI) was 30.6 kg/m^2 (> 95th centile). She was considered obese. Her voice was hoarse with hyponasal speech.

She was reported to have congenital strabismus with refractive error. Ophthalmologic examination at age 14 revealed bilateral blepharophimosis and blepharoptosis. Her vertical palpebral fissures were 2.5 mm and 3.0 mm of the right and left eyes, respectively. Bilateral severe blepharophimosis and blepharoptosis were observed. Right face turning of 30 degrees was secondary to esotropia of the right eye in primary position. The angle of esotropia increased in right gaze. Ocular rotation test revealed marked limitation of

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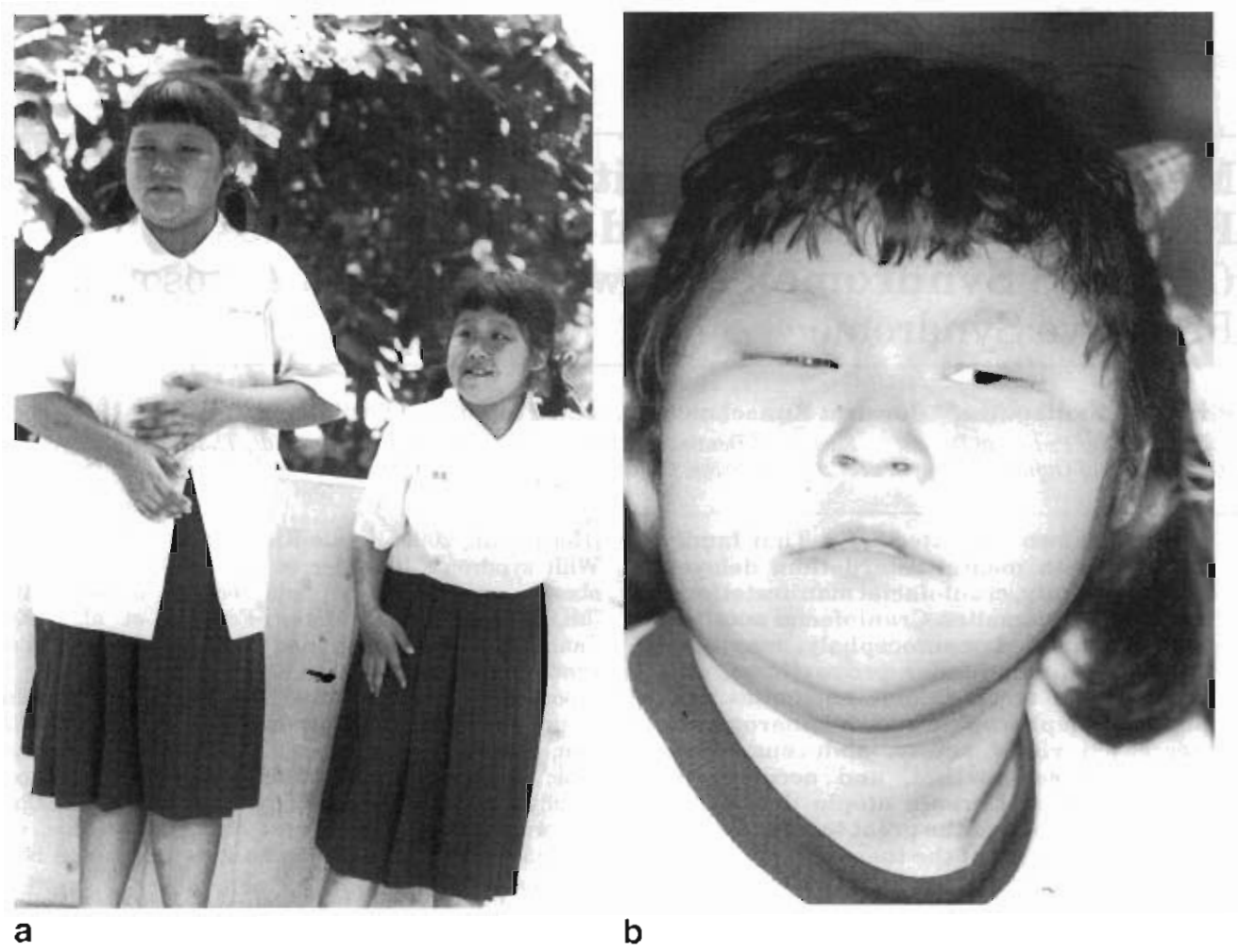

Fig. 1. **a:** Patient 1 at age 13 and patient 2 at age 12. Both are obese and have chubby faces. **b:** Patient 1 showing blepharophimosis, blepharoptosis, and strabismus.

abduction of the right eye (0% RE abduction), being consistent with the finding of right abducens palsy. The eye movement in other directions was unremarkable. The anterior and posterior segment of the eyes were unremarkable. Cycloplegic refraction indicated hyperopic astigmatism. Her best-corrected visual acuities were 6/12 and 6/18 in the right eye and left eyes, respectively. Interpupillary distance was 47 mm.

Oral examination revealed mandibular prognathism, notched maxillary permanent central incisors and crowding of maxillary and mandibular incisors. Lingual or palatal eruption of all permanent lateral incisors due to space deficiency was noted (Fig. 2a). Lateral cephalograph demonstrated maxillary hypoplasia, mandibular prognathism, and large sella turcica (Fig. 2c). Anterior crossbite, a result of maxillary hypoplasia with mandibular prognathism, was observed (Fig. 2a).

Mental retardation was mild. Her IQ was estimated at 45 by WIPPSI (Modified Wesckler Preschool and Primary Scale of Intelligence). Her psychomotor retardation was apparent at age one year. Walking commenced at age 18 months. She spoke single words at age nine months. Since age two years, she was almost always rubbing her hands while talking. Menstruation started at age 12. Her skin was unremarkable. She went to a school for persons with mental retardation. Karyotype analysis showed 46,XX, at the 550 band level.

Patient 2

An 11-year-old Thai girl, the sister of patient 1, was seen by us because of having many cavities and congenital anomalies (Fig. 1a). Her birth weight was 3,450 g (> 90th centile). Severe global development delay with mild autistic and hyperactive behavior was noted. She did not crawl or walk until age three and a half years. At age six years, her IQ was estimated at 15 by WIPPSI, indicating profound mental retardation. BMI was 22.2 kg/m^2 (90th centile) and she was considered at risk of obesity. Delayed speech was noted. She could communicate intelligibly at age eight. Her height was 129 cm (75th centile), weight 37 kg (> 97th centile), and OFC was 53.5 cm (98th centile). Since age five

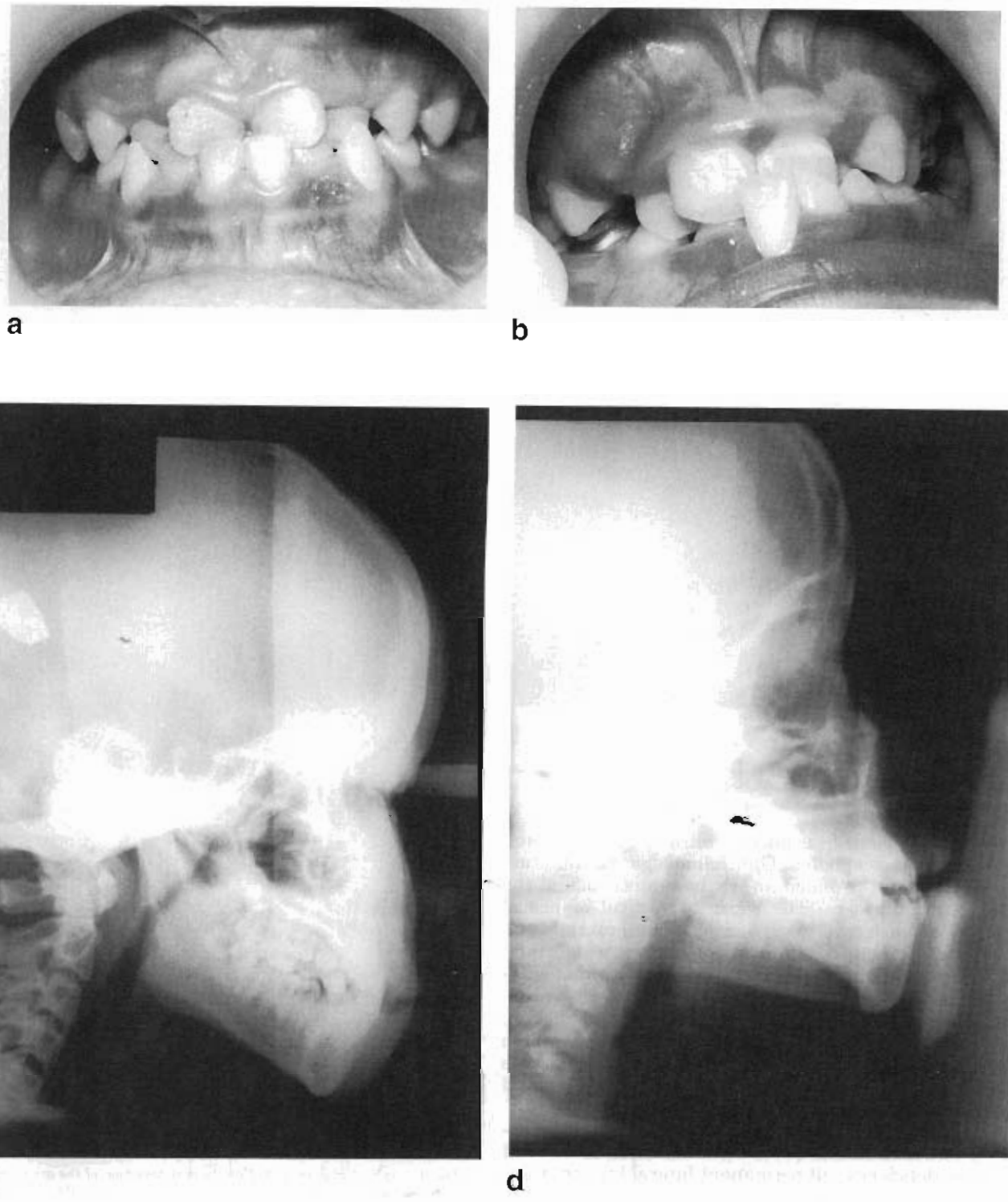

Fig. 2. Crowding of teeth, lingual eruption of the lateral incisors, and anterior crossbite of patient 1 (**a**) and patient 2 (**b**). **c** and **d**: Lateral cephalographs of patient 1 and patient 2, respectively. Both have maxillary hypoplasia and mandibular prognathism. Note large sella turcica in patient 1.

years, she frequently had chronic atopic dermatitis, with signs of erythema, excoriation, lichenification, nodular prurigo lesions, and post-inflammatory hypo- and hyperpigmentations around the eyes and flexural areas of arms and legs (Fig. 3a). The problems became worse in the summer. Chronic insect bite reactions and nodular prurigo-like lesions were observed at the skin of her arms and legs (Fig. 3b).

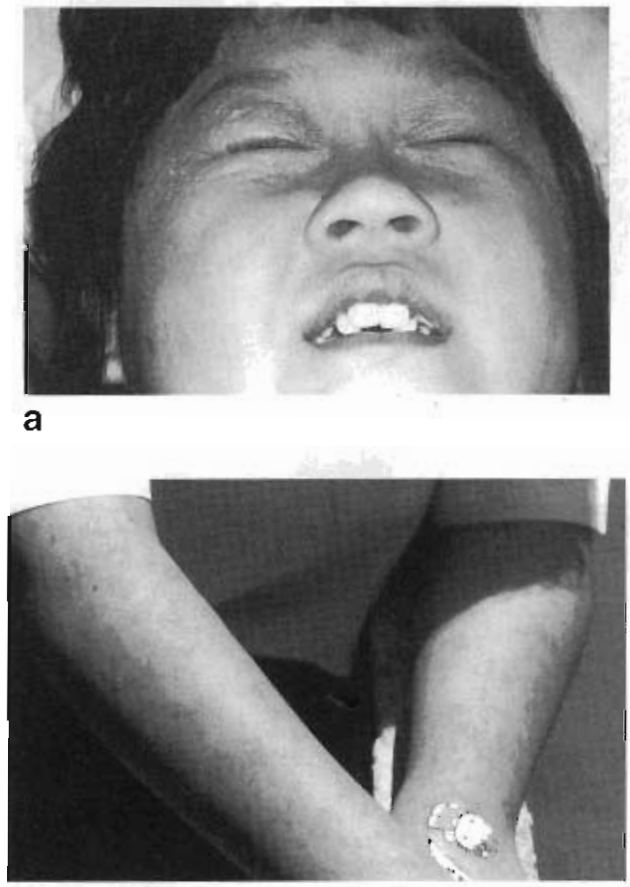

Fig. 3. a: Chronic atopic dermatitis around the eyes. b: Chronic insect bite reactions with nodular prurigo-like lesions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

At age one year, intermittent refractive accommodative esotropia was noted. Ophthalmologic examination at age 13 years revealed an erythematous rash of the eyelids in both eyes. The width of vertical palpebral fissure of each eye was 8 mm. The anterior and posterior segment of the eyes, including retinal findings, were unremarkable. Intermittent esotropia without amblyopia was found. Eye movement was unremarkable except for having 95% left eye abduction. Cycloplegic refraction of both eyes demonstrated high hyperopic astigmatism in both eyes. Telecanthus was noted with intercanthal distance being 28 mm and interpupillary distance of 49 mm.

Oral examination revealed severe crowding of maxillary and mandibular permanent incisors. As a result of space deficiency, all permanent lateral incisors were lingually erupted. Severe maxillary and mandibular anterior crowding was observed. The mandibular permanent lateral incisors were extracted to relieve severe crowding and improve oral hygiene. There were spaces between premolars. Anterior crossbite, a result of maxillary hypoplasia and mandibular prognathism, was observed (Fig. 2b,d). Fillings, pit and fissure sealants, and extraction of teeth were performed under general anesthesia at age seven. She went to a school

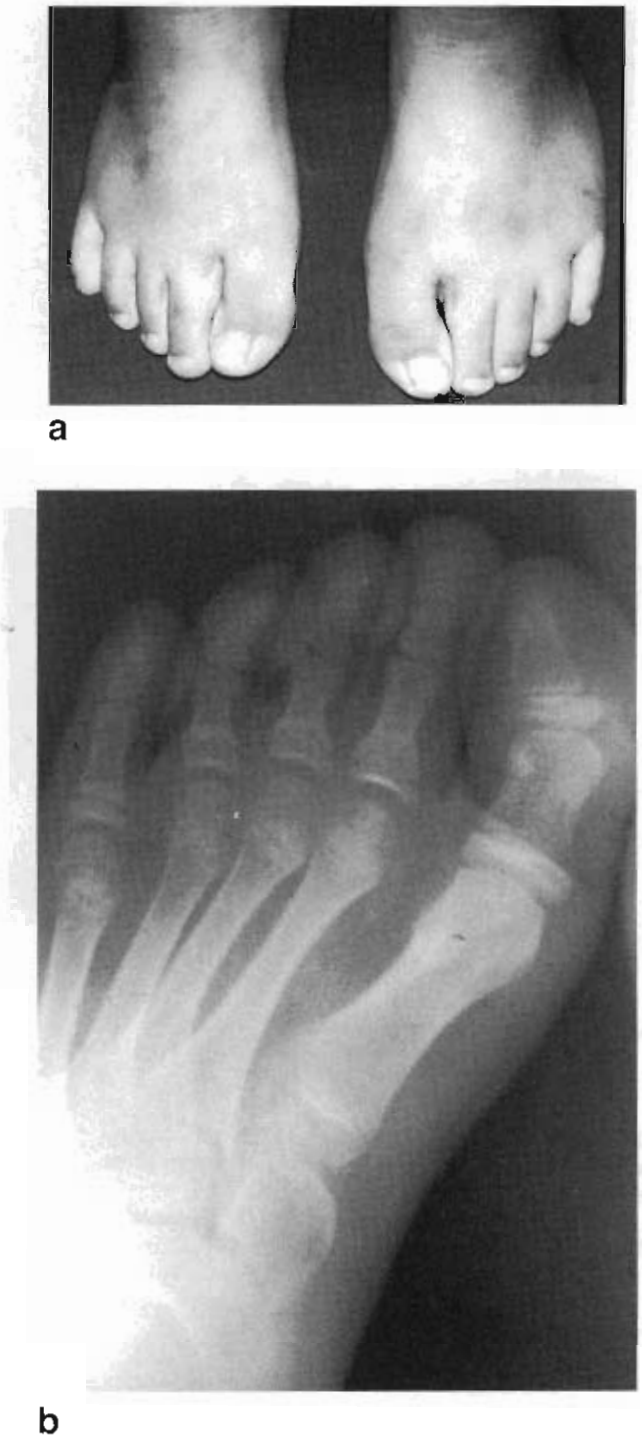

Fig. 4. a: Feet of patient 2. Note lateral deviation of the great toes. b: Foot radiograph of patient 2. Note cone-shaped epiphyses of toes 2, 3, and 4 and lateral deviation of great toe.

for children with mental retardation. Karyotype analysis showed 46,XX at the 550 band level. Clinically and radiographically, lateral deviation of the great toes of both patients was observed. Cone-shaped epiphyses of toes 2, 3, and 4 bilaterally were found in patient 2 (Fig. 4a,b).

TABLE I. Major Features of Mental Retardation-Obesity-Eye Anomaly Syndromes*

Syndromes	Head	Neuro.	Max/mand	Teeth	Eye	Limbs	Other	Genetics
Cohen syndrome (MIM #216550)		M.R./hypotonia	Small max/ mand	Prominent incisors	Retinal degenration myopia/downslanting palpebral fissures	Tapering fingers	Granulocytopenia	AR
Prader-Willi syndrome (MIM #176270)	Narrow bitemporal	M.R./hypotonia			Almond-shaped eyes strabismus, myopia	Small hands, small feet	Hypopigmentation, hypogonadism	Imprinting
MOMO syndrome (MIM #157980)	Macrocephaly	M.R.		Malocclusion taurodontism	Retinal coloboma, downstanding palpebral fissures, nystagmus		Delayed bone age	AD
Bardet-Beidel syndrome (MIM #209900;BBS2)		M.R. delayed speech	Micrognathia high-arch palate	Crowding	Retinal degeneration	Polydactyly	Renal anomalies, hypogonadism	AR
Laurence-Moon syndrome (MIM #245800)		M.R.			Pigmentary retinopathy		Hypogenitalism, hypogonadism	AR
Camera-Marugo-Cohen syndrome (MIM #604257)		Muscle weakness	Retrognathia		Blepharoptosis	Toe syndactyly, deviated toes 1		Sporadic
Present cases	Macrocephaly	M.R., autistic, hyperactive, delayed speech	Small max/ man mand, prognathism	Anterior crossbite, crowding	Esotropia, hyperopic astigmatism, abducens palsy, blepharophimosis, blepharoptosis	Deviated toes, cone-shaped epiphyses of toes	Chronic atopic dermatitis	AR

*AR, autosomal recessive; AD, autosomal dominant; MR, mental retardation.

DISCUSSION

Two daughters of a Thai family are reported. The findings in these patients include mental retardation, obesity, telecanthus, blepharophimosis, blepharoptosis, hyperopic astigmatism, abducens palsy, strabismus, macrocephaly, maxillary hypoplasia, mandibular prognathism, crowding of teeth, lateral deviation of the great toes, and cone-shaped epiphyses of toes. Palatal and lingual eruption of incisors were the result of maxillary hypoplasia. However, the mandible was large relative to the size of maxilla, resulting in mandibular prognathism.

Blepharophimosis, a reduction in the horizontal and vertical dimensions of the palpebral fissure, is a heterogeneous anomaly. It is most often a result of lateral displacement of the inner canthi and abnormalities of the eyelid. Periocular abnormalities, including epicanthal folds and ptosis, are frequent associated anomalies. Blepharophimosis is associated with many syndromes and it has been stated that all individuals with belpharophimosis appear to be at risk for developmental disabilities [Cunniff et al., 1998]. In the present family, blepharophimosis and blepharoptosis were present in patient 1, while patient 2 had telecanthus.

The overlapping phenotypes of the present patients with BBS and Cohen syndrome included mental retardation, retinal degeneration, and obesity. We are aware that some patients (31%) with BBS do not have polydactyly. However, the absence of polydactyly, retinal degeneration and hypogonadism, and the presence of mandibular prognathism, have ruled out the diagnosis BBS [Beales et al., 1997]. Having macrocephaly, blepharophimosis, and mandibular prognathism differentiate them from Cohen syndrome [Horn et al., 2000; Kivitie-Kallio et al., 2000]. The presence of obesity and its autosomal recessive inheritance and the absence of congenital heart diseases, deafness, and microdontia distinguish them from Ohdo blepharophimosis syndrome [Mhanni et al., 1998]. The patient shared telecanthus, blepharophimosis and blepharoptosis with blepharophimosis-ptosis-epicanthus inversus syndrome (BPES). However, the absence of epicanthus inversus and the presence of obesity and mental retardation and its autosomal recessive inheritance do not support the diagnosis BPES [Cunniff et al., 1998; De Baere et al., 2000].

It is noteworthy that the major pathology of the eyes in mental retardation-obesity-eye anomalies syndromes, except that of our patients, is almost always of the retina (Table I). Chronic atopic dermatitis and toe anomalies found in patient 2 have never been described in any of the mental retardation-obesity-eye anomaly syndromes. The combination of findings of *M*ental retardation, *O*besity, *M*andibular prognathism, *E*ye and *S*kin abnormalities found in our patients appears to be a newly recognized syndrome. The presence of the disorder in two daughters of normal parents suggests that the disorder is inherited as autosomal recessive. We would like to propose the acronym "MOMES" for this syndrome.

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REFERENCES

Beales PL, Warner AM, Hitman GA, Thankker R, Flinter FA. 1997. Bardet-Biedl syndrome: a molecular and phenotypic study of 18 families. J Med Genet 34:92–98.

Cunniff C, Curtis M, Hassed SJ, Hoyme HE. 1998. Blepharophimosis: a causally heterogeneous malformation frequently associated with developmental disabilities. Am J Med Genet 75:52–54.

De Baere E, Fukushima Y, Small K, Udar N, Camp GV, Verhoeven K, Pajotie A, De Paepe A, Messiaen L. 2000. Identification of *BPESC1*, a novel gene disrupted by a balanced chromosomal translocation, t(3;4)(q23;p15.2), in a patient with BPES. Genomic 68:296–304.

Farag TI, Teebi AS. 1988. Bardet-Biedl and Laurence-Moon syndromes in a mixed Arab population. Clin Genet 33:78–82.

Horn D, Krebsova A, Kunze J, Reis A. 2000. Homozygosity mapping in a family with microcephaly, mental retardation, and short stature to a Cohen syndrome region on 8q21.3–8q22.1: redefining a clinical entity. Am J Med Genet 92:285–292.

Kivitie-Kallio S, Summanen P, Raitta C, Norio R. 2000. Ophthalmologic findings in Cohen syndrome. A long-term follow-up. Ophthalmology 107:1737–1745.

Lambert DM, Watters G, Andermann F, Der Kaloustian VM. 1999. The Camera-Marugo-Cohen syndrome: report of two new patients. Am J Med Genet 86:208–214.

Mhanni AA, Dawson AJ, Chudley AE. 1998. Vertical transmission of the Ohdo blepharophimosis syndrome. Am J Med Genet 77:144–148.

Moretti-Ferreira D, Koiffmann CP, Listik M, Setian N, Wajntal A. 1993. Macrosomia, obesity, macrocephaly and ocular abnormalities (MOMO syndrome) in two unrelated patients: delineation of newly recognized overgrowth syndrome. Am J Med Genet 46:555–558.

Olander E, Stamberg J, Steinberg L, Wulfsberg EA. 2000. Third Prader-Willi syndrome phenotype due to maternal uniparental disomy 15 with mosaic trisomy 15. Am J Med Genet 93:215–218.

Zannolli R, Mostardini R, Hadjistilianou T, Rosi A, Berardi R, Morgese G. 2000. MOMO syndrome: a possible third case. Clin Dysmorphol 9:281–284.

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Brief Clinical Report

Cryptophthalmos, Dental and Oral Abnormalities, and Brachymesophalangy of Second Toes: New Syndrome or Fraser Syndrome?

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We report on an 8-year-old Thai girl with bilateral complete cryptophthalmos, facial asymmetry, delayed bone age, brachymesophalangy and medial deviation of the second toes, and dental anomalies. The dental anomalies consist of delayed dental development, congenital absence of the second premolars, microdontia of the deciduous molars. A fibrous band of the buccal mucosa was found. Dental anomalies are rare among patients with Fraser syndrome. They have not been reported in either isolated or other syndromic cryptophthalmos. The oral manifestations and brachymesophalangy of the second toes found in our patient may represent newly recognized findings associated with cryptophthalmos or they may represent a newly recognized syndrome.

KEY WORDS: brachymesophalangy; cryptophthalmos; delayed dental development; dental abnormality; Fraser syndrome; hypodontia; microdontia

INTRODUCTION

Cryptophthalmos is a condition of congenital absence of eyelids and palpebral fissure with skin passing continuously from the forehead onto the cheek over the malformed eye [François, 1969; Saal et al., 1992]. The term cryptophthalmos which means "hidden eyes" was coined by Zehender [1872]. Cryptophthalmos is a major component of Fraser (cryptophthalmos–syndactyly) syndrome which is a rare autosomal recessive disorder characterized by cryptophthalmos, syndactyly of fingers and toes, abnormal genitalia, renal agenesis, and malformation of nose, ears, and larynx [Thomas et al., 1986; Guttuso et al., 1987]. However, having cryptophthalmos does not mean the patients have Fraser syndrome since sporadic and nonsyndromic cryptophthalmos have been reported. Autosomal dominant cryptophthalmos has also been described [Coover, 1910; 1915; Goldberg, 1912; Magruder, 1921]. Oral manifestations associated with Fraser syndrome are rare. They consist of ankyloglossia [Gupta and Saxena, 1962; Ide and Wollschlaeger, 1969; Guttuso et al., 1987; Boyd et al., 1988], crowding of teeth [Ide and Wollschlaeger, 1969], and fusion of deciduous teeth [Bialer and Wilson, 1988; Bierich et al., 1991]. Oral manifestations in isolated or syndromic cryptophthalmos not related to Fraser syndrome have not been reported.

We here report on a girl having asymmetric face and nose, delayed bone age, delayed dental development, congenital absence of the second premolars, microdontia of deciduous molars, fibrous band of buccal mucosa, brachymesophalangy and medial deviation of the second toes, and bilateral complete cryptophthalmos not related to Fraser syndrome.

CLINICAL REPORT

An 8-year-old Thai girl was seen by us for dental cavities. Her height, weight, and OFC were 21 kg (25th

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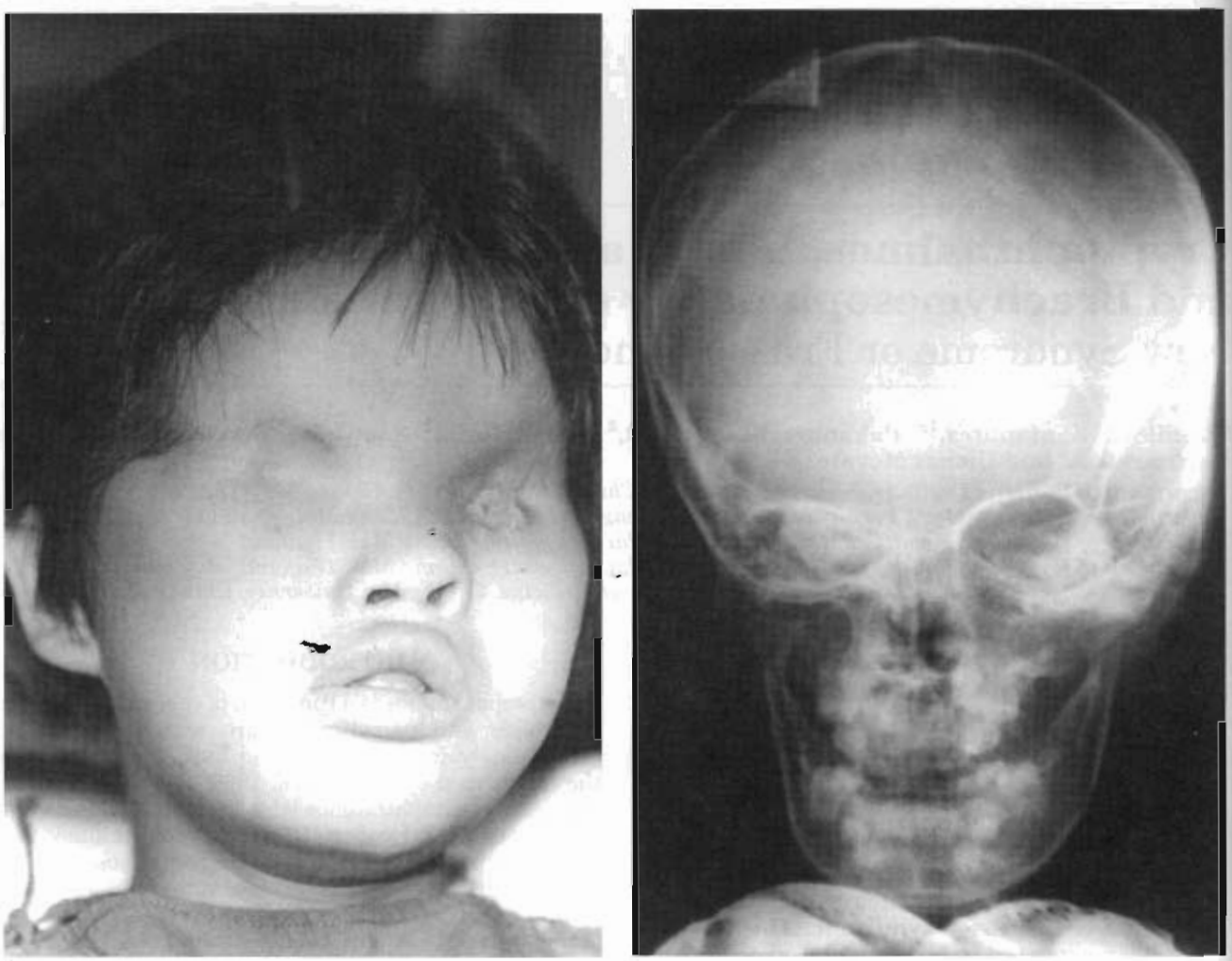
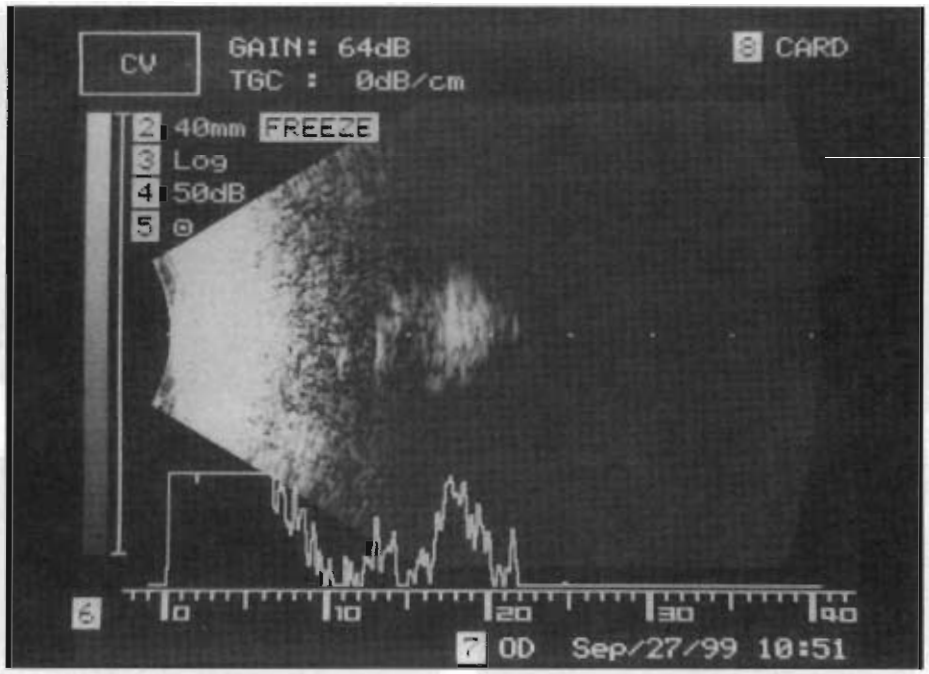


Fig. 1. **a:** A Thai girl with bilateral complete cryptophthalmos. Surgical scar on the left side, broad and depressed nasal bridge, and asymmetric nose. **b:** Asymmetric cranium.

centile), 119 cm (50th centile), and 49 cm, respectively. She was an intelligent young girl with normal physical and mental development. Parents were non-consanguineous. Her family history was unremarkable. She was born with bilateral complete cryptophthalmos. A surgical attempt to expose the left eyeball failed, leaving a scar (Fig. 1a). G-banded chromosomes were normal (46,XX). Physical examination showed right complete cryptophthalmos, a surgical scar at the place of her left palpebral fissure, broad and depressed nasal bridge, and broad and asymmetric alae nasi. Low anterior hairline was observed. The eyebrows were absent but replaced by the extension of hair from the temporal areas. The palpebral fissures and eyelashes were absent. Ultrasonography of the right eyes showed a rudimentary globe without functional structures. The anterior chamber and vitreous space silent acoustic signals were not demonstrated (Fig. 2a). The left eye was microphthalmic and more developed than the right one. The overall axial length was 14 mm (normal, 22 mm). No details of the anterior segment compartments were observed suggesting the fusion of eyelids with the anterior segment structures. Retinal curvature and partially developed vitreous space were verified by silent acoustic signal (Fig. 2b).

She had thick upper and lower lips (Fig. 1a), multiple caries, and small deciduous molars. Cavities were restored by a family dentist. The permanent teeth had not erupted (Fig. 3a–c). The maxillary arch form was asymmetric. Anterior deepbite and posterior crossbite were noted (Fig. 3a). A thick fibrous band of the size 1×3 cm was found at the left buccal mucosa near the corner of the mouth (Fig. 3d).

Radiography showed facial asymmetry. The left temporal and zygomatic areas were smaller than those of the right (Fig. 1b). Bone age was five years. Panoramic radiography demonstrated delayed dental development. The roots of the mandibular second deciduous molars were short. All second premolars were absent. Coronoid processes were small. The mandibular first



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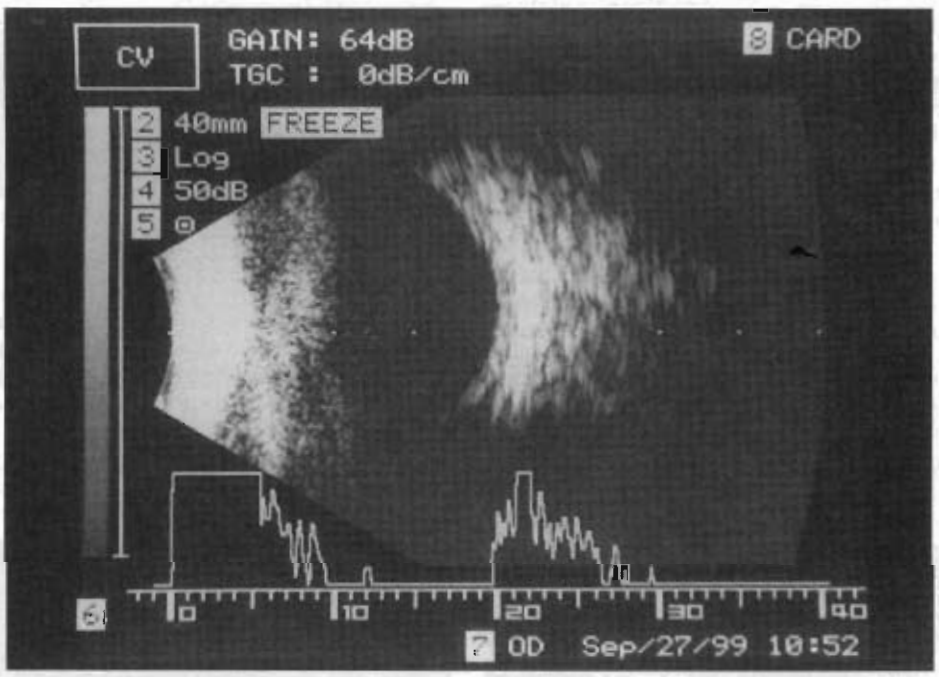

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Fig. 2. Ultrasonograms. **a:** A rudimentary globe of the right eye. No compartments or acoustic signal of the anterior segments. Vitreous space is obliterated. **b:** Microphthalmic globe of the left eye. No details of anterior segment compartments suggestive of fusion of the eyelids with the anterior structures. Note retinal curvature and partially developed vitreous space.

permanent molars had normal root development but had not erupted yet (Fig. 4a,b).

The left great toe was shorter than the right one. Medial deviation of the second toes was observed. Their toe nails were medially displaced. Radiographically, the middle phalanges of the second toes were small and medially deviated (Fig. 5a,b). Ultrasonograms of kidneys and urinary bladders were unremarkable.

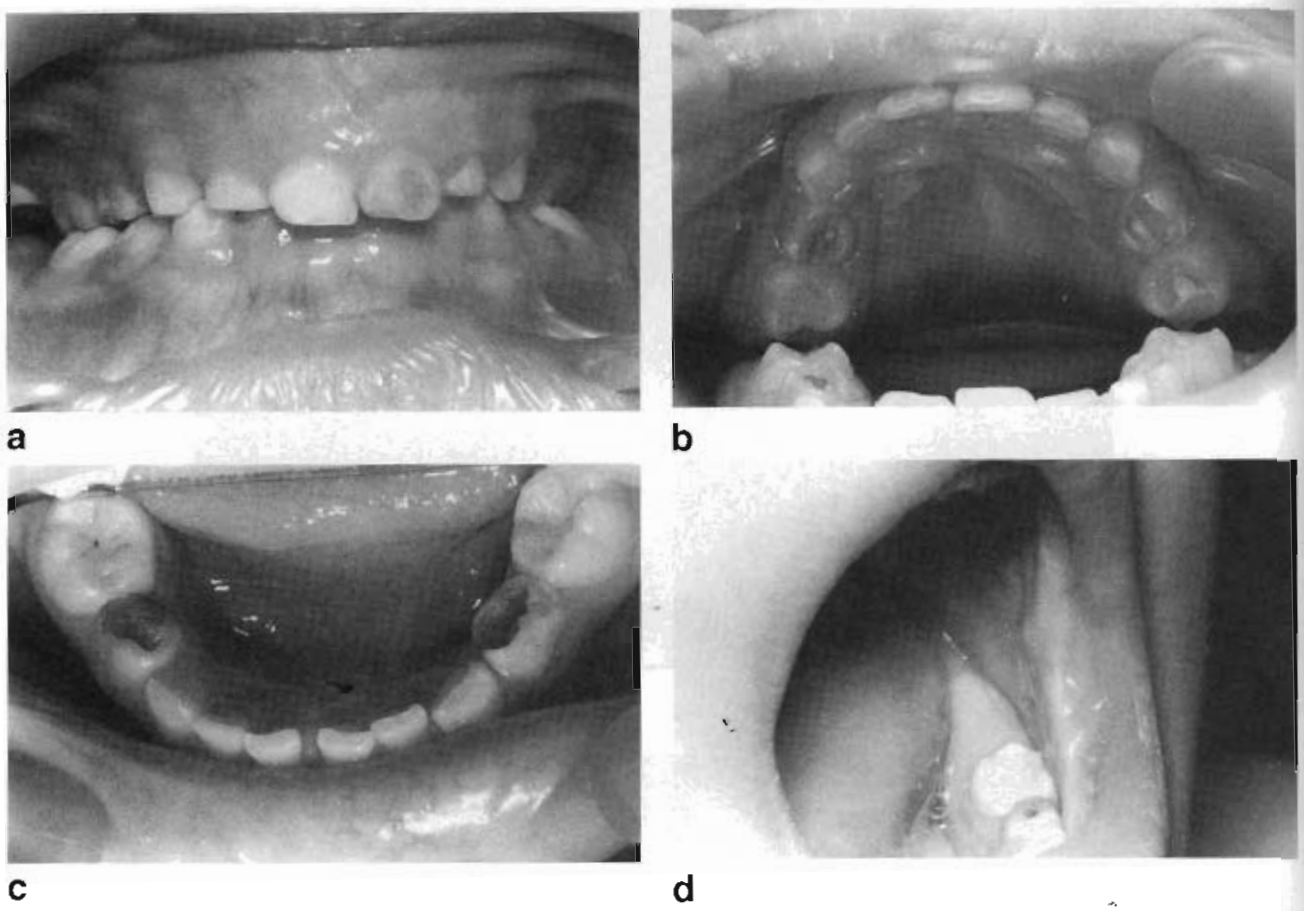


Fig. 3. **a:** Anterior deepbite and posterior crossbite. **b:** Small maxillary deciduous molars. **c:** Small mandibular deciduous molars. **d:** Thick fibrous band of buccal mucosa.

DISCUSSION

We reported on an 8-year-old Thai girl with bilateral cryptophthalmos, asymmetric head and nose, delayed bone age, delayed dental development, prolonged retention of the deciduous teeth, congenital absence of the second premolars, small deciduous molars, fibrous band of the buccal mucosa, brachymesophalangy and medial deviation of the second toes. Her clinical manifestations did not appear to be Fraser syndrome in view of the absence of the important diagnostic features of the syndrome including syndactyly and urogenital anoma-

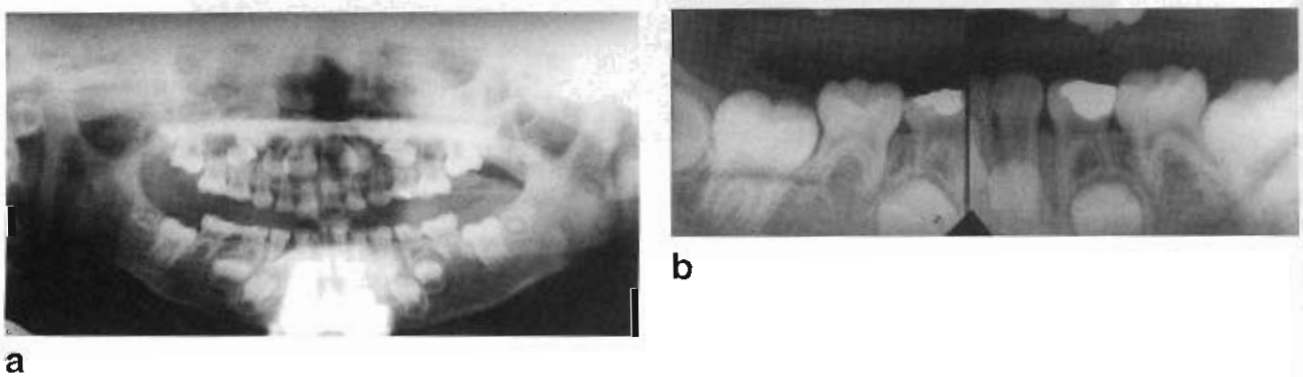
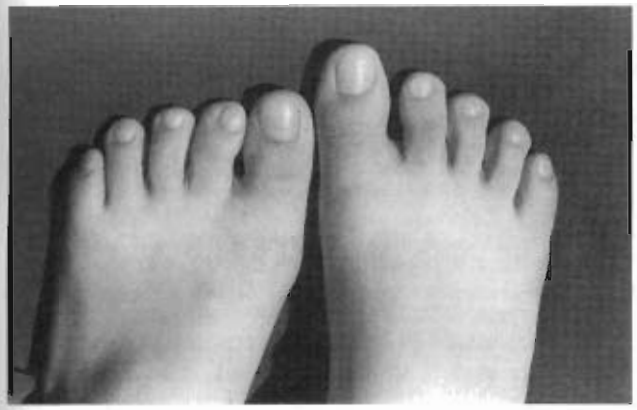


Fig. 4. **a:** Panoramic radiograph at age 7 6/12 years shows delayed dental development, congenital absence of second premolars, small deciduous molars, small coronoid processes. **b:** Periapical radiographs at age 8 6/12 years shows small deciduous molars. Roots of the second deciduous molars are short.



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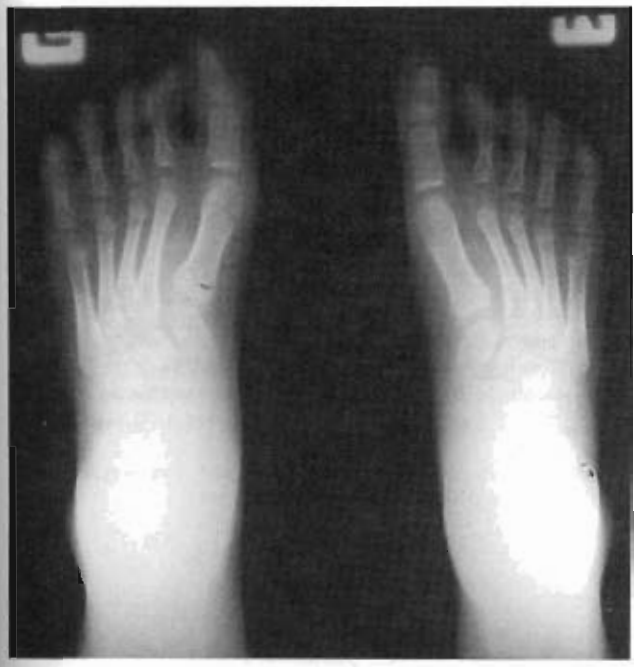

b

Fig. 5. **a:** Right great toe is longer than the left one. Medially deviated second toes. Medially displaced second toenails. **b:** Small middle phalanges and medial deviation of the second toes.

lies. It has been reported that cryptophthalmos may be isolated or syndromic but not obligatory to Fraser syndrome [Koenig and Spranger, 1986; Thomas et al., 1986; Pankau et al., 1994]. Some patients with the syndrome did not have cryptophthalmos and some patients with cryptophthalmos did not have Fraser syndrome. Among the patients with cryptophthalmos, the incidence of isolated cryptophthalmos is 22% [Thomas et al., 1986]. Autosomal dominant isolated cryptophthalmos has been described [Coover, 1910; Magruder, 1920; Saal et al., 1992].

Three types of cryptophthalmos exist. First, complete cryptophthalmos like that found in the patient we described is characterized by congenital absence of the eyelids with the skin extending continuously from the forehead to the cheeks passing the orbit. The eyebrow is usually absent or poorly developed. The globe is absent or microphthalmic with anterior and posterior dysgenesis. The second type is incomplete cryptophthalmos which consists of rudimentary lid structures and conjunctival sac formation. The globe may be microphthalmic and covered with skin. The third type is abortive cryptophthalmos or congenital symblepharon. The upper eyelid is adherent to the superior aspect of the globe and fuses with the upper cornea as an epidermal membrane. The lower eyelid is normal. The size of the globe is normal [François, 1969; Saal et al., 1992]. Saal et al. [1992] described what they claimed to be the fourth type of cryptophthalmos. It is characterized by fused well-formed eyelids. The eyebrows and eyelashes are normal. The conjunctival sac is absent leading to the adherence of cornea to the overlying fat, muscle, and connective tissue. The globe is microphthalmic. The same type has been described previously [Coover, 1910]. Cryptophthalmos can be classified according to the presence of eyelids into two types; that with fused eyelids [Coover, 1910; Saal et al., 1992] and that without eyelids. Cryptophthalmos without eyelids, like our patient, has skin unbroken from the forehead to the cheeks. It appears from the literature that the presence of eyebrow is related to the presence of eyelid. When the eyelid is present, eyebrow is normal [Koenig and Spranger, 1986; Mina et al., 1988; Pankau et al., 1994]. But when the eyelid is absent, the eyebrow is usually absent or poorly developed [Boyd et al., 1988; Bierich et al., 1991].

Brachyphalangy of the middle and distal phalanges of fingers and toes has been reported to be associated with Fraser syndrome [Ramsing et al., 1990]. Brachymesophalangy of the second fingers and toes has been reported in a family affected with fused eyelids, airway anomalies, and ovarian cysts [Mena et al., 1991]. Brachymesophalangy of the second toes in the patient we described may be coincidental or it may be dysmorphogenetically related to cryptophthalmos and other anomalies.

Dental anomalies reported with Fraser syndrome were not specific. They have been reported as malformed teeth [Ide and Wollschlaeger, 1969], deformed teeth [Steidl, 1962], and crowding of teeth [François, 1969]. Fusion of the mandibular deciduous lateral incisor and bicuspid has been reported twice [Bialer and Wilson, 1988; Bierich et al., 1991]. They must have been mistakenly reported. The fusion must have been between the mandibular deciduous lateral incisor and canine. Fusion of teeth may result from a failure of programmed cell death of the tissue between two tooth germs. It is of interest to note that in both of these instances fusion of teeth took place on the same side of incomplete cryptophthalmos. Both patients had mental retardation, hypotonia, and delayed development. Dental anomalies have not been reported in isolated or other syndromic cryptophthalmos not related to Fraser syndrome. It is possible that they have been overlooked.

Delayed bone age, delayed dental development, congenital absence of the second premolars, microdontia of deciduous molars, fibrous band of the buccal mucosa, and brachymesophalangy of the second toes appear to be newly recognized findings associated with cryptophthalmos. Dental anomalies have not been reported to be associated with isolated cryptophthalmos or other syndromic cryptophthalmos not related to Fraser syndrome. These features may be coincidental or they may represent a newly recognized syndrome.

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REFERENCES

Bialer MG, Wilson WG. 1988. Syndromic cryptophthalmos. Am J Med Genet 30:835–837.

Bierich JR, Christie M, Heinrich JJ, Martinez AS. 1991. New observations on midline defects: coincidence of anophthalmos, microphthalmos and cryptophthalmos with hypothalamic disorders. Eur J Pediatr 150:246–249.

Boyd PA, Keeling JW, Lindenbaum RH. 1988. Fraser syndrome (cryptophthalmos-syndactyly syndrome: a review of eleven cases with postmortem findings. Am J Med Genet 31:159–168.

Coover DH. 1910. Cryptophthalmia. J Am Med Assoc 55:370–371.

Coover DH. 1915. Cryptophthalmia. Opthalmoscope 13:586.

François J. 1969. Syndrome malformatif avec cryptophthalmie. Acta Genet Gemellol (Roma) 18:18–50.

Goldberg HG. 1912. Cryptophthalmos: congenital ankyloblephalon. Ophthal Res 21:200.

Gupta SP, Saxena RC. 1962. Cryptophthalmos. Brit J Ophthalmol 46:629–632.

Guttuso J, Patton MA, Baraitser M. 1987. The clinical spectrum of the Fraser syndrome: report of three new cases and review. J Med Genet 24:549–555.

Ide CH, Wollschlaeger PG. 1969. Multiple congenital abnormalities associated with cryptophthalmia. Arch Ophthalmol 81:638–644.

Koenig R, Spranger J. 1986. Cryptophthalmos-syndactyly syndrome without cryptophthalmos. Clin Genet 29:413–416.

Magruder AC. 1921. Cryptophthalmos. Am J Ophthalmol 4:48–51.

Mena W, Krassikoff N, Philips JB, III. 1991. Fused eyelids, airway anomalies, ovarian cysts, and digital abnormalities in siblings: a new autosomal recessive syndrome or a variant of Fraser syndrome? Am J Med Genet 40:377–382.

Mina MMF, Greenberg C, Levin B. 1988. ENT abnormalities associated with Fraser syndrome: case report and literature review. J Otolaryngol 17:233–236.

Pankau R, Partsch CJ, Janig U, Meinecke R. 1994. Fraser (cryptophthalmos-syndactyly) syndrome: a case with bilateral anophthalmia but presence of normal eyelids. Genet Counsel 5:191–194.

Ramsing M, Rehder H, Holzgreve W, Meinecke P, Lenz W. 1990. Fraser syndrome (cryptophthalmos with syndactyly) in the fetus and newborn. Clin Genet 37:84–96.

Saal HM, Traboulsi EII, Gavaris P, Samanngo-Sprouse CA, Parks M. 1992. Dominant syndrome with isolated cryptophthalmos and ocular anomalies. Am J Med Genet 43:785–788.

Steidl P. 1962. Un cas de cryptophtalmie. Un Med Canada 91:159–161.

Thomas IT, Frias JL, Felix V, Sanchez de Leon J, Hernandez RA, Jones MC. 1986. Isolated and syndromic cryptophthalmos. Am J Med Genet 25:85–96.

Zehender W. 1872. Ein Missgeburt mit Hautuberwachsenen Augen oder Kryptophthalmus. Klin Monatsbl Augenheilkd 10:225–249.

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Digitotalar dysmorphism with craniofacial and other new associated abnormalities

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We report digitotalar dysmorphism in a grandfather, father, and a daughter. All the affected members had clasped thumbs. The father had a short stature, large zygomatic arch and a flat mandibular condyle. The newly recognized findings found in the affected girl were large maxillary deciduous central incisors, a short proximal phalanx of the second finger, and a large subcutaneous hemangioma of the back. Her paternal grandfather had only congenital clasped thumbs. Congenital clasped thumb is a very heterogeneous anomaly and related to many syndromes. The findings in the reported family which are consistent with digitotalar dysmorphism, include congenital clasped thumbs, ulnar deviation of fingers, and a congenital vertical tali.
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Keywords: congenital clasped thumb, digitotalar dysmorphism, distal arthrogryposis, flexed fingers, large deciduous central incisor, rocker bottom foot

INTRODUCTION

Digitotalar dysmorphism (DTD; MIM *126050) or hereditary ulnar drift (HUD) is a very rare autosomal dominant disorder characterized by congenital clasped thumbs (CCT), flexion deformity and ulnar deviation of the fingers, narrowing of the middle phalanges, single palmar crease, moderate proportionate short stature, flexion deformity of toes, and rocker bottom feet due to vertical tali. Approximately 24 cases have been reported (Sallis and Beighton, 1972; Stevenson *et al.*, 1975; Dhaliwal and Myers, 1985).

We report a Thai girl, her father, and paternal grandfather affected with DTD. Newly recognized findings found in this family include a short proximal phalanx of the second finger, a large subcutaneous hemangioma of the back, a large zygomatic arch, a flat mandibular condyle, and large maxillary deciduous central incisors. Autosomal dominant inheritance is confirmed by male-to-male transmission and both sexes were affected.

CLINICAL REPORT

Patient 1

A 1-year-old Thai girl was seen at the Department of Orthopaedic Surgery, Chiang Mai University Hospital regarding her rocker bottom feet and CCT. Her weight and OFC were 6.1 kg (<3 centile) and 43 cm (−2SD) respectively. She appeared to have normal facial features and height. Her karyotype was normal female (46,XX). Her developmental milestones were normal. Large deciduous central incisors were observed (Figure 1A). Physical examination revealed bilateral CCT, hypoplastic thenar eminences, and flexion contracture of the left third and fourth fingers at the proximal

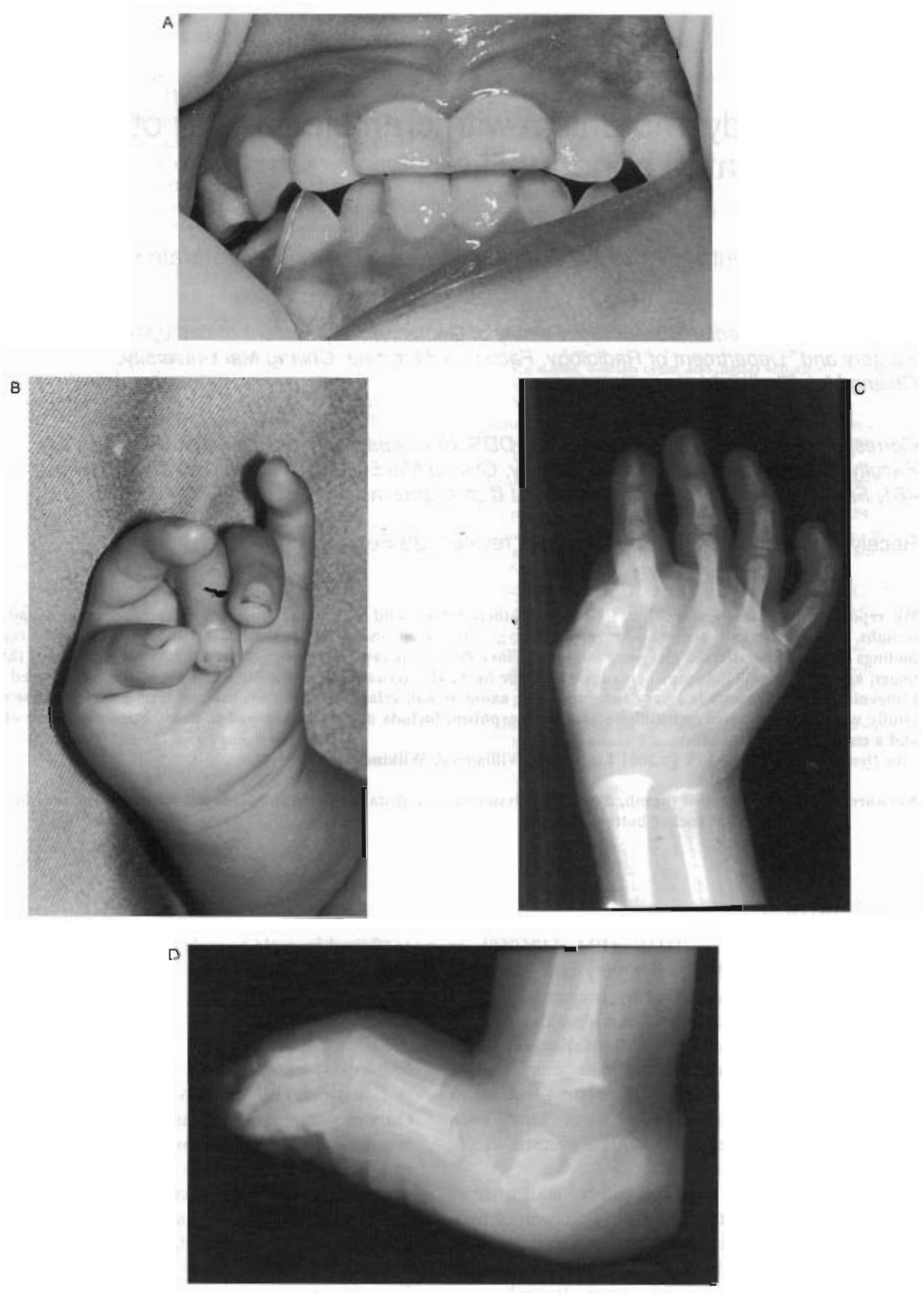

FIGURE 1. Patient 1 A) Large maxillary deciduous central incisors. B) Left clasped thumb with flexed third and fourth fingers. C) Medial dislocation of left cuboid bone. D) Vertical talius. The calcaneus is in equinus position.

interphalangeal (IP) joints. The thumbs were clasped at the MCP joints and the distal phalanges could be extended (Figure 1B).

Radiologically a short left second proximal phalange was observed. Narrowing of the middle phalanx of the fingers was not observed. Rocker bottom feet were noted. Radiographs showed vertical tali and medially dislocated cuboid bones. Calcanei were in equinus position (Figure 1C and D).

There was a soft tissue lump with the diameter of 4.5 cm at the middle of her back. The size of the lump increased with age, but it has never been painful. Magnetic resonance imaging (MRI) demonstrated a hemangioma of the size $5.2 \times 0.9 \times 4.1$ cm in the subcutaneous tissue of the back at T10-L2 without spinal canal involvement.

Patient 2

Patient 2, the father of patient 1, was a 37-year old Thai man. His intelligence and facial features were normal. He was proportionately short with height of 147 cm (<3 centile). Like his daugther, he also had CCT with hypoplastic thenar muscles, and bilateral single palmar creases. All fingers were flexed and had ulnar deviation. Narrowing of the middle phalanges of fingers was not observed (Figure 2B). Hand radiographs demonstrated CCT at the MCP joints. A panoramic radiograph showed normal dental development. The left zygomatic arch was larger than the right one. The head of the left mandibular condyle was flat and the styloid processes were long (Figure 2C). Lateral skull X-ray demonstrated a large posterior clinoid process and a large opening of sella turcica and flat cerebral surface

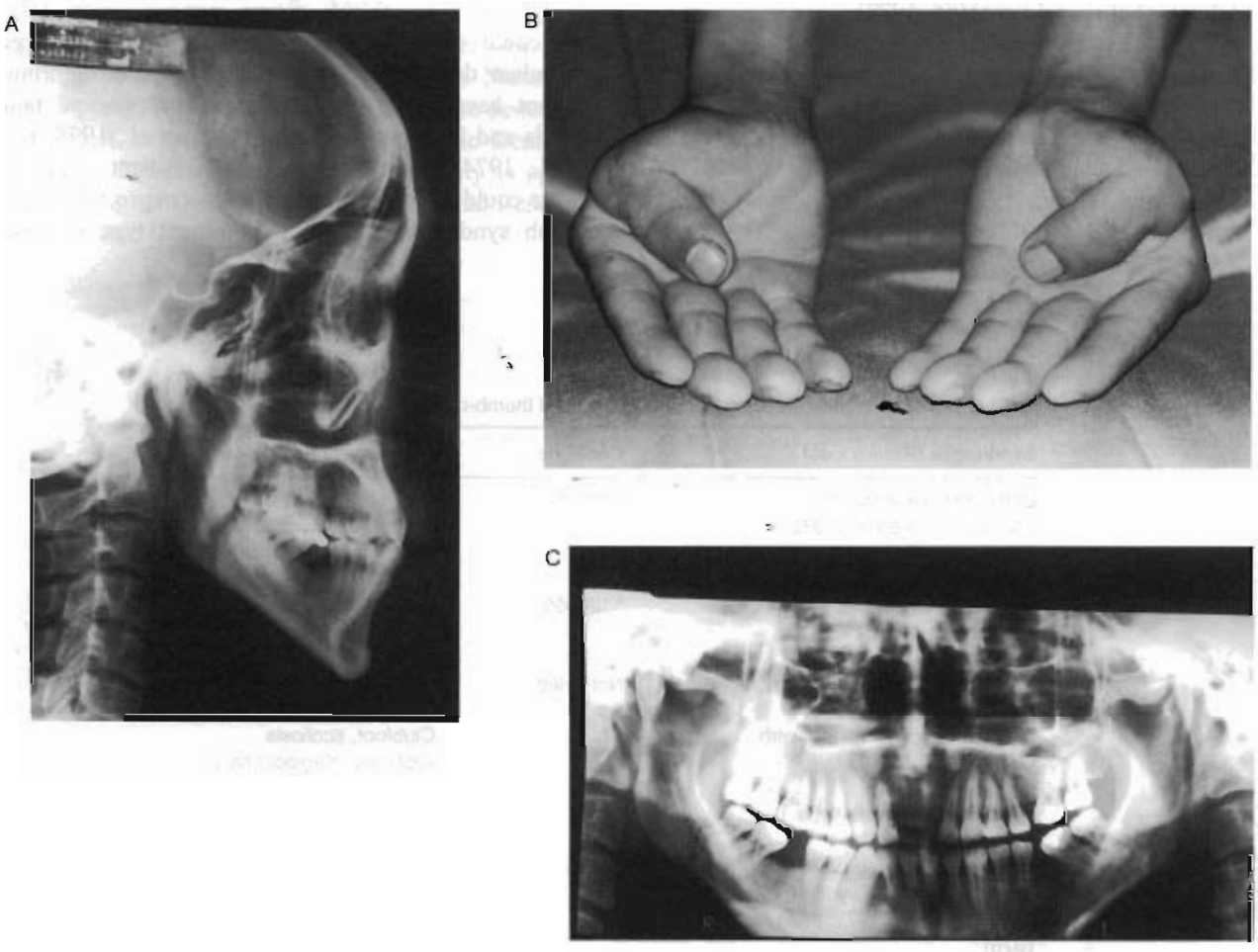

FIGURE 2. Patient 2. A) Lateral skull X-ray shows large posterior clinoid process and large opening of the sella turcica. B) Patient 2's hands. Thumbs are clasped at MCP joints with ulnar deviation of fingers. C) Panoramic radiograph reveals large left zygomatic arch and flat left condylar head.

of the greater wing of the sphenoid bone (Figure 2A). No other anomalies were observed. His father also had CCT without other anomalies and died of an unknown cause at age 30.

DISCUSSION

We report a grandfather, father, and daughter with DTD. The diagnosis was based on characteristic findings including CCT, flexed and ulnar deviated fingers, rocker bottom feet, and autosomal dominant inheritance. Newly recognized findings found in this family include, a short proximal phalanx of the second finger, a large subcutaneous hemangioma of the back, a large zygomatic arch, a flat mandibular condyle, and large maxillary deciduous central incisors. The male-to-male transmission confirms the autosomal dominant mode of inheritance of the condition. The narrowing of the middle phalanges of the fingers which appeared to be a important feature of the syndrome was not found in our patients (Sallis and Beighton, 1972).

CCT, a highly heterogeneous anomaly, is a consistent feature. It has been reported to be associated with DTD (Sallis and Beighton, 1972), whistling face-windmill vane hand syndrome (MIM *193700) (Hall *et al.*, 1982), adducted thumb syndrome (MIM *201550) (Fitch and Levy, 1975), adducted thumb-clubfoot syndrome (MIM 601776) (Dundar *et al.*, 1997), congenital clasped thumbs (MIM 314100), MASA syndrome (MIM 303350) (Gareis and Mason, 1984), hydrocephalus due to congenital stenosis of the aqueduct of Sylvius (HSAS; MIM 307000) (Edwards, 1961) and distal arthrogryposis multiplex congenita, distal, types 1 (AMCD1; MIM *108120), 2 (AMCD2; MIM 108130), and 2B (AMCD2B; MIM. *601680) (Hall *et al.*, 1982).

DTD and HUD (dominantly inherited ulnar drift) are considered the same entity (MIM *126050). Interestingly, patients with HUD do not have congenital vertical talus which is a characteristic feature of DTD (Stevenson *et al.*, 1975). Both DTD and HUD share similar hand anomalies with congenital clasped thumb syndrome, autosomal dominant type (Miranda *et al.*, 1998) and ulnar deviation of the fingers with clubfoot deformity (Fisk *et al.*, 1974). Congenital clasped thumb syndrome, autosomal dominant type (Miranda *et al.*, 1998) and ulnar deviation of the fingers with clubfoot deformity (Fisk *et al.*, 1974) are very rare and have not been listed in OMIM. Some patients with DTD, congenital clasped thumb, autosomal dominant type, and ulnar deviation of fingers with clubfoot deformity do not have either CCT or congenital vertical talus (Sallis and Beighton, 1972; Miranda *et al.*, 1998; Fisk *et al.*, 1974). As having only CCT, Patient 2 and his father could have been diagnosed as congenital clasped thumb syndrome, autosomal dominant type or ulnar

TABLE 1. Possible differentiating features of clasped thumb-related syndromes

Syndromes (References)	OMIM no.	Differentiating features
Digitotalar dysmorphism (Sallis and Beighton, 1972) (Dhaliwal and Meyers, 1985)	*126050	CVT short stature scoliosis, kyphoscoliosis single palmar crease scoliosis
Hereditary ulnar drift (Stevenson *et al.*, 1975)	*126050	No CVT single palmar crease, plagiocephaly
Congenital clasped thumb, AD (Miranda *et al.*, 1998)	Not listed	Hypoplastic MPS No foot anomalies
Ulnar deviation of fingers with Clubfoot deformity (Fisk *et al.*, 1974)	Not listed	Clubfoot, scoliosis kyphosis, plagiocephaly
Distal Arthrogryposis type 1 (Hall *et al.*, 1982)	*108120	Several major joint contractures
Christian syndrome (Adducted thumbs syndrome) (Christian *et al.*, 1971; Fitch and Levy, 1975)	*201550	Cleft palate, craniostenosis, swallowing difficulties microcephaly, autosomal recessive inheritance

CVT, congenital vertical talus; MP, middle phalanges of fingers; AD, autosomal dominant type.

deviation of fingers with clubfoot deformity. This may suggest that DTD, congenital clasped thumb syndrome, autosomal dominant type, and ulnar deviation of fingers with clubfoot deformity may be the same condition with inter and intrafamilial variability We are not convinced that our patients had distal arthrogryposis type 1 because the phenotype in this family was much milder and contracture of distal joints was limited only at MCP joints of thumbs and IP joints of fingers (Hall *et al.*, 1982). However, they may be allelic. Table 1 shows possible differentiating features among clasped thumb-related syndromes. Even though the newly recognized findings in our patients were minor, they may be useful in differentiating this syndrome from other clasped thumb-related syndromes.

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REFERENCES

Christian JC, Andrews PA, Conneally PM, Muller J (1971). The adducted thumbs syndrome. An autosomal recessive disease with arthrogryposis dysmyelination, craniostenosis and cleft palate. *Clin Genet* **2**:95–103.

Dhaliwal AS, Myers TL (1985). Digitotalar dysmorphism. *Orthop Rev* **14**:90–94.

Dundar M, Demiryilmaz F, Demiryilmaz I, Kumandas S, Erkilic K, Kendirci M, Tuncekl M, Ozyazgan I, Tolmie JL (1997). An autosomal recessive adducted thumb-club foot syndrome observed in Turkish cousins. *Clin Genet* **51**: 61–64.

Edwards JH (1961). The syndrome of hydrocephalus. *Arch Dis Child* **36**:486–493.

Fitch M, Levy EP (1975). Adducted thumb syndromes. *Clin Genet* **8**:190–198.

Fisk J, House J, Bradford D (1974). Congenital ulnar deviation of fingers with club foot deformities. *Clin Orthop Rel Res* **104**:200–205.

Gareis FJ, Mason JD (1984). X-linked mental retardation associated with bilateral clasp thumb anomaly. *Am J Med Genet* **17**:333–338.

Hall JG, Reed SD, Greene G (1982). The distal arthrogryposis; delineation of new entities-review and nosologic discussion. *Am J Med Genet* **11**:185–239.

Miranda A. Zenteno JC, Santiago E, Kofman-Alfaro S (1998). Autosomal dominant inheritance of adducted thumbs and other digital anomalies. *Clin Genet* **54**:83–85.

Sallis JG, Beighton P (1972). Dominantly inherited digitotalar dysmorphism. *J Bone Joint Surg* **54B**:509–515.

Stevenson RE, Scott CI Jr, Epstein M (1975). Dominantly inherited ulnar drift. Birth *Defects, Original Articles Series* **XI(5)**:75–77.

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Letter to the Editor

Dentinogenesis Imperfecta-Associated Syndromes

To the Editor:

I read the very interesting article by Fonseca in the Journal [2000] regarding dentinogenesis imperfecta (DI)-associated Schimke immuno-osseous dysplasia (SIOD). It appeared to be the first report of SIOD associated with DI. However, further confirmation is needed. In fact, this study has raised an interesting notion of other DI-associated syndromes. It is well known that DI type I (DI-I) is associated with some of the osteogenesis imperfectas (OI), especially types IB, IIIB, and IVB [Lund et al., 1998; O'Connell and Marini, 1999]. DI-I is more likely to occur with short stature and long bone deformity. This is why it is usually associated with OI type III and IV, not type I [Wenstrup, 1997]. The incidence of DI-I in OI type I is rare [Luder and Steinmann, 1997]. The accuracy of making diagnosis of OI might have played an important role. Association of DI with OI type II is poorly documented.

A search of the literature came up with a few other DI-associated syndromes and their modes of inheritance (Table I). DI is the most common genetic disease of dentition. Actually it is the most common autosomal dominant disorder affecting humankind [Aplin et al., 1999; Witkop, 1957], DI is not inherited as autosomal recessive as stated by Fonseca [2000]. Association with autosomal recessive disorders is extremely rare [Komorowska et al., 1989; Moog et al., 1999; Fonseca, 2000]. Several syndromes are associated with dental findings which are clinically and radiographically similar to those observed in DI-II (Table I). When conditions are found to be associated with DI, it is crucial to question if it is really DI or some phenocopy.

Making the diagnosis of DI is also worth discussing. Dentin dysplasia type II looks similar or, sometimes, identical to DI in the primary dentition and may mislead some clinicians [Witkop, 1988]. Discoloration of teeth appears to be the minimum criteria for clinicians in making diagnosis. Having denticles, pulpal obliteration, and bulbous-shaped molars, but absence of tooth discoloration, does not fulfill the diagnostic criteria. It appears that the radiographic features are overruled by the clinical ones. Clinically normal teeth from patients with OI have also been reported to have dentin aberrations [Lygidakis et al., 1996]. The absence of discoloration or opalescence of teeth does not mean dentin is unaffected. From the molecular genetics and biochemical points of view, discoloration of teeth should not be the minimal criteria for making diagnosis of DI.

DI was not believed to be associated with any particular molecular aberration in any OI type [Lund et al., 1998]. Until recently, mutation-specific DI has been associated with OI type IV [Pallos et al., 2001]. DI-I and II have different genetic defects that have a similar phenotype. DI-I phenotype is more varied [Levin, 1981] and its presence is related only to the severity of OI-I but not OI-II or OI-III. Bone deformity of OI-I is more severe when it is associated with DI [Paterson et al., 1983; Lund et al., 1998; Lindau et al., 1999] To the contrary, some studies have shown that the clinical and microscopic findings of DI-I are not related to the severity of the bone disorders [Lukinmaa et al., 1987; Luder and Steinmann, 1997].

The discoloration of teeth affected with DI is thought to be independent of type I collagen defects. The discoloration in the primary dentition is classified as yellow/brown or opalescent gray. The yellow/brown DI is more prevalent and more prone to attrition than the opalescent gray [Lund et al., 1998; O'Connell and Marini, 1999]. In a Thai boy and his family members affected with DI-II, the crown was unusually translucent. Its enamel could practically be seen through, and wore off easily as he aged (Fig. 1a and b). Enamel of teeth with DI has been described as normal, and the severe attrition is the result of weakening of dentin. However, irregular with lower degree of mineralization of enamel from patients with OI with or without DI has recently been reported [Lygidakis et al., 1996; Lindau et al., 1999]. This might be a reason why the enamel of teeth with DI is very translucent and wears very quickly (Fig. 1b and c). The enamel of teeth with DI can also be affected with fluorosis (Fig. 1c and d).

Those with DI in primary dentition may be absent of DI in the permanent dentition. Interestingly, those with DI in the permanent dentition always had DI in the primary dentition [Luder and Steinmann, 1997; Lund et al., 1998; O'Connell and Marini, 1999]. DI-I and DI-II have a very similar phenotype. Type III collagen is more prevalent in DI-I than DI-II [Sauk et al., 1980; Gage et al., 1986; O'Connell and Marini,

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TABLE I. Dentinogenesis Imperfecta-Associated Syndromes

Syndromes	MIM No.	Modes	Genes	References
OI type IB	166240	AD	*COL1A1* and *COL1A2*	Levin et al. [1980]; Byers [1993]
OI type IVB	166220	AD	*COL1A1* and *COL1A2*	Falk et al. [1986]
OI type IIIB	259420	AD	*COL1A1* and *COL1A2*	Lund et al. [1998]; O'Connell and Marini [1999]
OI type II/III without abnormal type I collagen	259440	AR	Unknown	Williams et al. [1989]
OI with opalescent teeth, blue sclerae and wormian bones, but without fractures	166230	AD	Unknown	Beighton [1981]
Cortical defects, wormian bones, and DI	604922	AR	Unknown	Moog et al. [1999]
Ehlers-Danlos syndrome type II	130010	AD	*COL5A1*[a]	Komorowska et al. [1989]; De Paepe et al. [1997]; Bouma et al. [2001]
Goldblatt syndrome	184260	AD	*COL2A1*	Goldblatt et al. [1991]; Bonaventure et al. [1992]
Schimke immuno-osseous dysplasia	242900	AR	Unknown	Fonseca [2000]
Skeletal dysplasia with opalescent and rootless teeth	NA	NA	Unknown	Kantaputra [2001, in press]

[a]Ehlers-Danlos syndrome type II has been reported to be caused by mutations in *COL5A1*. However, none of the studied patients was reported to have DI.

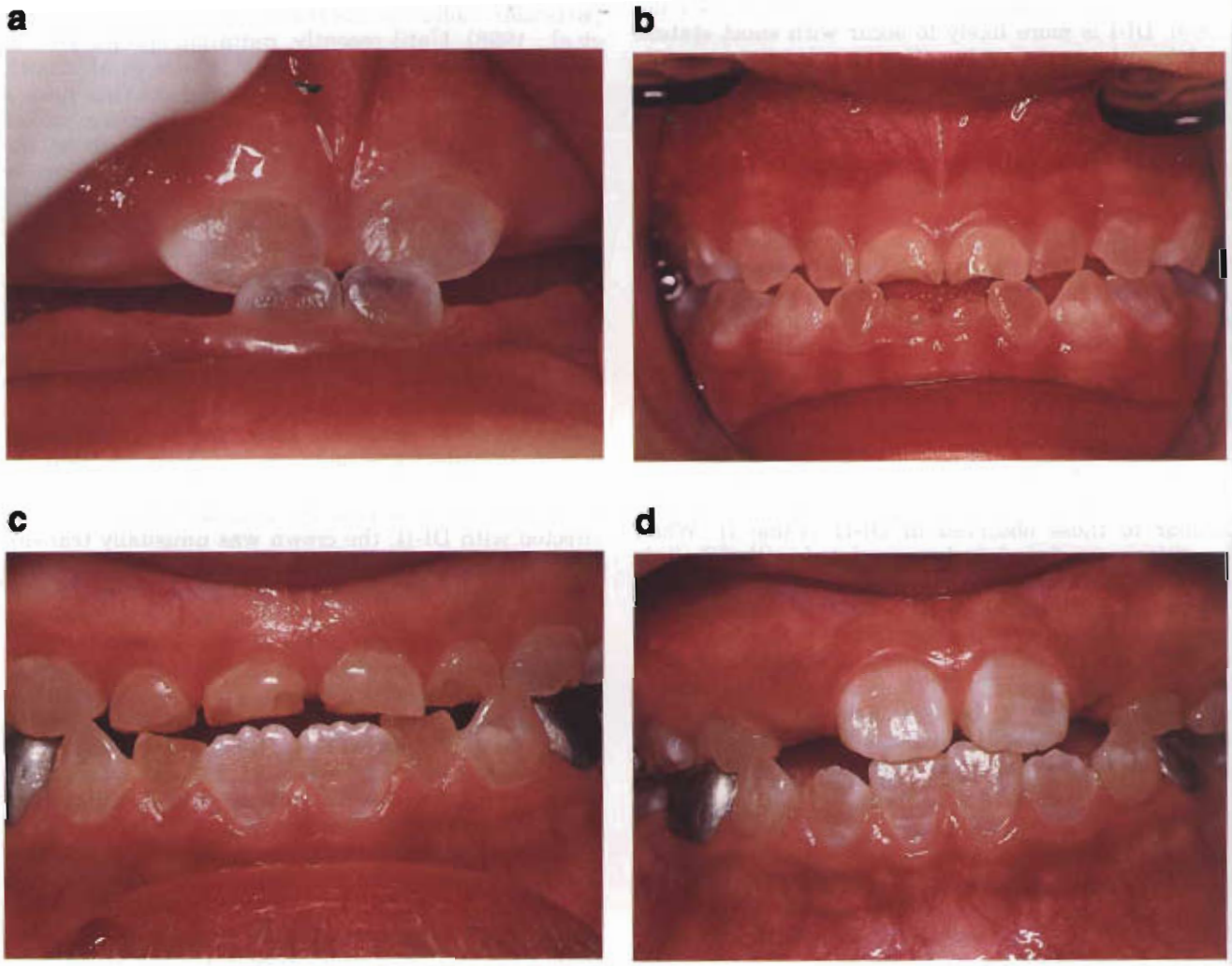

Fig. 1. **a:** At age nine months. Unusually translucent DI type II. **b:** Age four years. Note enamel wear and primary teeth became more opaque. **c:** Age six. Enamel wear and enamel fluorosis of the permanent incisor. **d:** Age eight. Permanent teeth are less translucent. Enamel fluorosis of all permanent incisors.

1999]. The same is true for hyperfibers and dentin matrix vesicles [Waltimo, 1994]. However, there have been no definite differentiating criteria between DI-I and DI-II. The primary defects in OI are mutations in type I collagen gene (*COL1A1* and *COL1A2*) [Byers, 1993; Wenstrup, 1997]. DI-II is not a collagen defect but a disorder of dentin mineralization. The basic defects appear to be in the non-collagenous dentin matrix proteins, especially dentin phosphoryn (DMP2) [Thotakura et al., 2000] and dentin sialophosphoprotein (DSPP) [MacDougall, 1998]. It has been reported that reduced expression of DSPP is associated with DI-II in mice overexpressing TGF-1 [Thyagarajan et al., 2001].

Recently, mutations in *DSPP* gene have been shown to cause DI-II [Xiao et al., 2001; Zhang et al., 2001]. Two families reported by Xiao et al. [2001] had DI-I with progressive sensorineural hearing loss with the absence of OI [Xiao et al., 2001]. Actually, it should not have been reported as DI-I, since DI-I is used to describe DI in those with OI. The expression of *DSPP* gene was detected in the inner ear of mice. This might have been related to the hearing loss in these particular families [Xiao et al., 2001]. However, it is interesting to note that so many other families with DI without OI have not been reported to have sensorineural hearing loss.

Primary teeth are more severely affected than the permanent ones in DI-I and DI-II, and this may imply that the gene expression is more marked in the primary teeth than in the permanent ones. This might have been related to the timing of gene expression and the period of dental development [Luder and Steinmann, 1997]. Biochemical and ultrastructural studies of dentin of teeth affected with various types of DI may lead us to a better understanding of the basic defects of these conditions. This might provide the differentiating features of DI-I and DI-II in order to substantiate the notion that "All DIs are not created equal". Hopefully, in the future we will be able to understand more and differentiate each particular DI among various types of DI-associated syndromes.

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REFERENCES

Aplin HM, Hirst KL, Dixon MJ. 1999. Refinement of the dentinogenesis imperfecta type II locus to an interval of less than 2 centimorgans at chromosome 4q21 and the creation of a yeast artificial chromosome contig of the critical region. J Dent Res 78:1270–1276.

Beighton P. 1981. Familial dentinogenesis imperfecta, blue sclerae, and wormian bones without fractures: another type of osteogenesis imperfecta? J Med Genet 18:124–128.

Bonaventure J, Stanescu R, Stanescu V, Allain JC, Muriel MP, Ginisty D, Maroteaux P. 1992. Type II collagen defect in two sibs with Goldblatt syndrome, a chondrodysplasia with dentinogenesis imperfecta, and joint laxity. Am J Med Genet 44:738–753.

Bouma P, Cabral WA, Cole WG, Marini JC. 2001. *COL5A1* exon 14 splice acceptor mutation causes a functional null allele, haploinsufficiency of alpha 1(V) and abnormal heterotypic interstitial fibrils in Ehlers-Danlos syndrome II. J Biol Chem 276:13356–13364.

Byers PH. 1993. Osteogenesis imperfecta. In: Royce PM, Steinmann B, editors. Connective tissue and its heritable disorders. New York: Wiley-Liss. p 317–350.

De Paepe A, Nuytinck L, Hausser I, Anton-Lamprecht I, Naeyaert JM. 1997. Mutations in the *COL5A1* gene are causal in the Ehlers-Danlos syndromes I and II. Am J Hum Genet 60:547–554.

Falk CT, Schwartz RC, Ramirez F, Tsipouras P. 1986. Use of molecular haplotypes specific for the human pro-alpha-2(I) collagen gene in linkage analysis of the mild autosomal dominant forms of osteogenesis imperfecta. Am J Hum Genet 38:269–279.

Fonseca MA. 2000. Dental findings in the Schimke Immuno-osseous dysplasia. Am J Med Genet 93:158–160.

Gage JP, Francis MJO, Whitaker GE, Smith R. 1986. Dentine is biochemically abnormal in osteogenesis imperfecta. Clin Sci 70:339–346.

Goldblatt J, Carman P, Sprague P. 1991. Unique dwarfing, spondylometaphyseal skeletal dysplasia, with joint laxity, and dentinogenesis imperfecta. Am J Med Genet 39:170–172.

Kantaputra PN. 2001. A newly recognized skeletal dysplasia with opalescent and rootless teeth. Oral Surg Oral Med Oral Pathol Oral Radiol Endod (in press).

Komorowska A, Rozynkowa D, Lee KW, Renouf DV, Nicholls AC, Mac Kenzie J, Pope FM. 1989. A Polish variant of isolated dentinogenesis imperfecta with generalized connective tissue defect. Br Dent J 167:239–243.

Levin LS. 1981. The dentition in osteogenesis imperfecta syndromes. Clin Orthop 159:64–74.

Levin LS, Brady JM, Melnick M. 1980. Scanning electron microscopy of teeth in dominant osteogenesis imperfecta. Am J Med Genet 5:189–199.

Lindau B, Dietz W, Lundgren T, Storhaug K, Noren JG. 1999. Discrimination of morphological findings in dentin from oseogenesis imperfecta patients using combinations of polarized light microscopy, microradiography, and scanning electron microscopy. Int J Paediatr Dent 9:253–261.

Luder HU, Steinmann B. 1997. Teeth in osteogenesis imperfecta. A mirror of genetic collagen defects? In: Cohen MM Jr, Baum BJ, editors. Studies in stomatology and craniofacial biology. Amsterdam: IOS Press. p 209–228.

Lukinmaa PL, Ranta H, Ranta K, Kaitila I. 1987. Dental findings in osteogenesis imperfecta: I. Occurrence and expression of type I dentinogenesis imperfecta. J Craniofac Genet Dev Biol 8:75–82.

Lund AM, Jensen BL, Nielsen LA, Skovby F. 1998. Dental manifestations of osteogenesis imperfecta and abnormalities of collagen I metabolism. J Craniofac Genet Dev Biol 18:30–37.

Lygidakis NA, Smith R, Oulis CJ. 1996. Scanning electronmicroscopy of teeth in osteogenesis imperfecta type I. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81:567–572.

MacDougall M. 1998. Refined mapping of the human dentinsialophosphoprotein (DSPP) gene within the critical dentinogenesis imperfecta type II and dentin dysplasia type II loci. Eur J Oral Sci 106:(Suppl 1). 227–233.

Moog U, Maroteaux P, Schrander-Stumpel CTR, van Ooij A, Schrander JJP, Fryn JP. 1999. Two sibs with an unusual pattern of skeletal malformations resembling osteogenesis imperfecta: a new type of skeletal dysplasia. J Med Genet 36:856–858.

O'Connell AC, Marini JC. 1999. Evaluation of oral problems in an osteogenesis imperfecta population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 87:189–196.

Pallos D, Hart PS, Cortelli JR, Vian S, Wright JT, Korkko J, Brunoni D, Hart TC. 2001. Novel *COL1A1* mutation (G599C) associated with mild ostogenesis imperfecta and dentinogenesis imperfecta. Arch Oral Biol 2001:459–470.

Paterson CR, McAillion S, Miller R. 1983. Heterogeneity of osteogenesis imperfecta type I. J Med Genet 20:203–205.

Sauk JJ, Gay R, Miller EJ, Gay S. 1980. Immunohistochemical localization of type III collagen in the dentin of patients with osteogenesis imperfecta and hereditary opalescent dentin. J Oral Pathol 9:210–220.

Thotakura SR, Mah T, Srinivasan R, Takagi Y, Veis A, George A. 2000. The non-collagenous dentin matrix proteins are involved in dentinogenesis imperfecta type II (DGI-II). J Dent Res 79:835–839.

Thyagarajan T, Sreenath T, Cho A, Wright JT, Kulkarni AB. 2001. Reduced expression of dentin sialophosphoprotein is associated with dysplastic dentin in mice overexpressing transforming growth factor-beta 1 in teeth. J Biol Chem 276:11016–11020.

Waltimo J. 1994. Hyperfibers and vesicles in dentin matrix in dentinogenesis imperfecta (DI) associated with osteogenesis imperfecta (OI). J Oral Pathol Med 23:389–393.

Wenstrup RJ. 1997. From genes to tissue in osteogenesis imperfecta. A long and winding road. In: Cohen MM, , Jr, Baum BJ, editors. Studies in stomatology and craniofacial biology. Amsterdam: IOS Press. p 191–207.

Williams EM, Nicholas AC, Daw SCM, Mitchell N, Levin LS, Green B, MacKenzie J, Evans DR, Chudleigh PA, Pope FM. 1989. Phenotypical features of an unique Irish family with severe autosomal recessive osteogenesis imperfecta. Clin Genet 35:181–190.

Witkop C,, Jr. 1957. Hereditary defects in enamel and dentin. Acta Genet Stat Med 7:236–239.

Witkop C Jr. 1988. Amelogenesis imperfecta, dentinogenesis imperfecta, dentin dysplasia revisited: problems in classification. J Oral Pathol 17:547–553.

Xiao S, Yu C, Chau X, Yuan W, Wang Y, Bu L, Fu G, Qian M, Yang J, Shi Y, Hu L, Han B, Wang Z, Huang W, Liu J, Chen Z, Zhao G, Kong X. 2001. Dentinogenesis imperfecta 1 with or without progressive hearing loss is associated with distinct mutations in DSPP. Nature Genet 27:210–204.

Zhang X, Zhao J, Li C, Gao S, Qiu C, Liu P, Wu G, Qiang B, Lo WH, Shen Y. 2001. DSPP mutation in dentinogenesis imperfecta Shields type II. Nat Genet 27:151–152.

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A newly recognized syndrome of skeletal dysplasia with opalescent and rootless teeth

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A Thai girl with skeletal dysplasia and dental anomalies was seen. Her anomalies consisted of disproportionately short stature, short neck, broad and depressed nasal bridge, broad chest in the anteroposterior dimension, kyphosis, widely spaced nipples, and protruded abdomen. Radiographic testing indicated that she had a large sella turcica, platyspondyly, hypoplastic acetabulum, and a small body of mandible. Both her deciduous and permanent teeth were equally opalescent, and most were rootless, with root development of the mandibular teeth more severely affected. Some maxillary roots were extremely short and tapered. Hypodontia was also observed. These findings represent a unique and hitherto undescribed syndrome of skeletal dysplasia with concomitant dental anomalies. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:303-7)**

Dental anomalies, even when minor, have been reported as significant components of many syndromes. Their presence is a valuable diagnostic clue for identification of specific patterns of developmental malformation. Many common and uncommon malformation syndromes exhibit characteristic dental anomalies. For example, globodontia—with multiple enlarged, bulbous, prominent lobules—is a pathognomonic feature of otodental syndrome.[1] Hypodontia is a consistent feature of Ellis-van Creveld syndrome,[2] Van der Woude's syndrome,[3] and Rieger's syndrome.[4] Cemental aplasia, a major cause of premature loss of teeth, is common in patients with hypophosphatasia.[5] Taurodontism has been found in patients with Klinefelter's syndrome and many types of ectodermal dysplasia.[6] Amelogenesis imperfecta and taurodontism have been reported in tricho-dento-osseous syndrome.[7] Enamel hypoplasia, hypodontia, and taurodontism are described in patients with Rapp-Hodgkin syndrome.[8]

Opalescent teeth is the phrase applied to dentition with a blue-gray to amber brown discoloration; this discoloration is often combined with unusual translucency of the crowns. Such opalescence can be seen as an isolated trait in dentinogenesis imperfecta type 2 (DI2) and type 3 (DI3), in coronal dentin dysplasia (dentin dysplasia [DTDP] type 2 [DTDP2]),[9] and in syndromic contexts including osteogenesis imperfecta (OI),[10] Goldblatt syndrome,[11] Schimke-immuno-osseous dysplasia,[12] and a type of Ehlers-Danlos syndrome.[13]

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DTDP is characterized by teeth with abnormal dental pulps and roots and is classified into radicular dentin dysplasia (dentin dysplasia, type 1 [DTDP1]) and coronal dentin dysplasia. DTDP has been reported as an isolated condition and as a component of syndromes such as Singleton-Merten syndrome (MIM *182250).[14] Its association with skeletal dysplasia and sclerotic bone has been described as an autosomal dominant disorder.[15] DTDP1 and taurodontic molars have been observed in patients with tricho-onycho-dental syndrome.[16] An association between DTDP2 and osteogenesis imperfecta type 1 (OI1) has also been described.[17]

Rootless teeth have been observed in patients with DTDP1, and tooth color in DTDP1 is usually normal.[9] The combination of disproportionately short stature, delayed growth development, short neck, protruded abdomen, kyphosis, platyspondyly, hypoplastic acetabulum, broad nasal bridge, and hypodontia with opalescent and rootless teeth has not been previously reported.

CLINICAL REPORT

An 8-year-old girl was referred from the Pediatric Clinic, Chiang Mai University Hospital, to the Department of Pediatric Dentistry, Chiang Mai University, for physical and dental evaluation. She was the second child of a nonconsanguineous marriage. Four other children in the family were healthy. The family history was unremarkable. Her father and mother were proportionately short, with the height of 150 cm (<3 centile) and 145 cm (<3 centile), respectively. Otherwise, they were normal. They belonged to a hill tribe living in the central part of Thailand. Her parents were from the same village; however, the gene pool in this area was not restricted.

She was delivered at 36 weeks of pregnancy. At birth, intrauterine growth retardation and jaundice were noted. Data about birth weight, birth length, and head

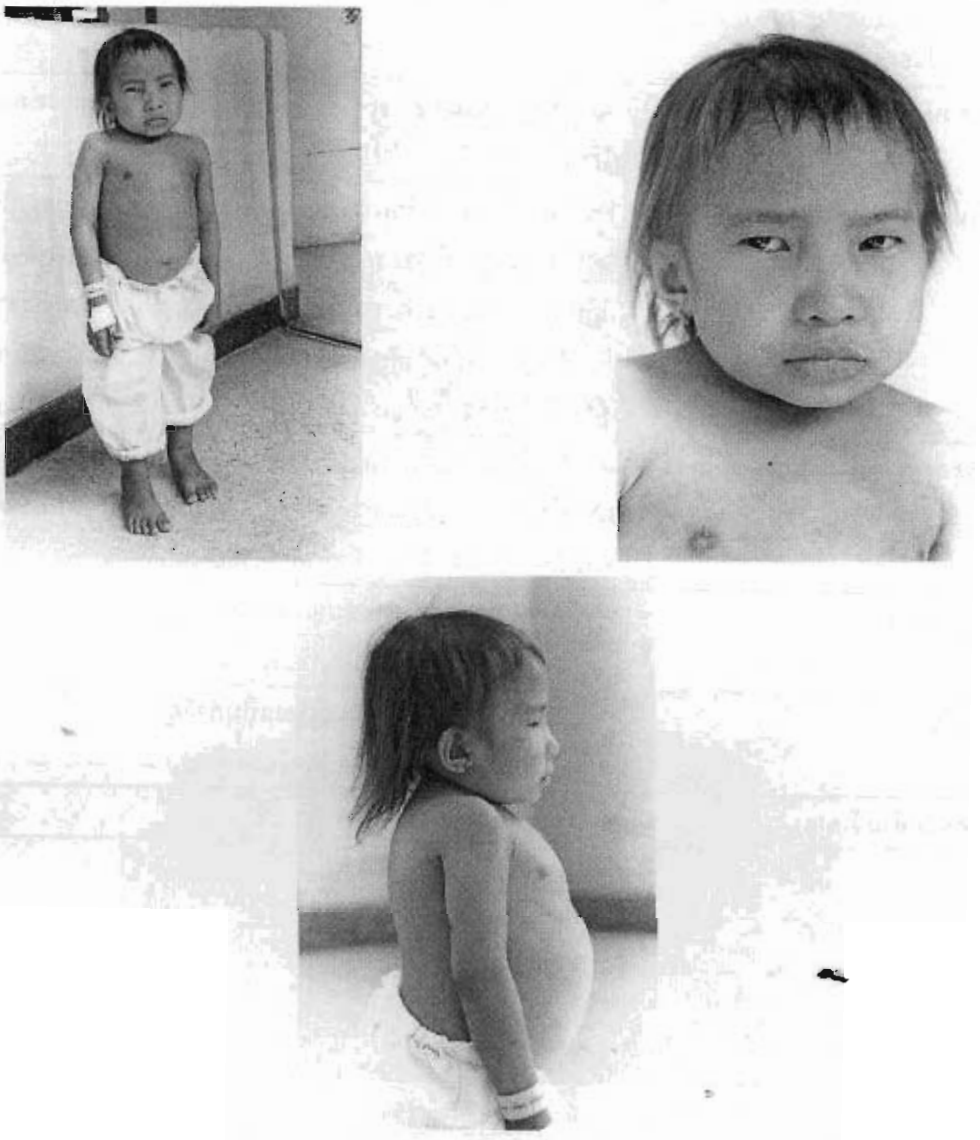

Fig 1. The girl has disproportionately short stature. Her neck is short and her nipples are widely spaced; in addition, she has a broad chest, protruding abdomen, and kyphosis. A broad, depressed nasal bridge also exists.

circumference at birth were not available. After delivery she was hospitalized in the neonatal intensive care unit for 4 weeks. At 8 years, 9 months of age, her height and weight were 78 cm (<3 centile) and 10.5 kg (<3 centile), respectively. She was not short in comparison with the height of her parents. Other than physical growth retardation, her other development was reported as normal.

Physical examination of the patient at 8.5 years old revealed disproportionately short stature, a short neck, light-colored hair, a broad and depressed nasal bridge, a broad chest in the anteroposterior dimension, widely spaced nipples, protruding abdomen, and kyphosis (Fig 1). No hepatosplenomegaly was detected. Crepitation of the lower parts of both lungs was noted. Radiographic examination showed platyspondyly and hypoplasia of acetabulum. Epiphyses and metaphyses were unremarkable. Oral examination revealed opalescent deciduous and permanent teeth (Fig 2). There was no difference between the colors of the deciduous and of the permanent teeth. Tooth size appeared to be normal, and dental age was appropriate to chronological age. Panoramic radiographs demonstrated small body of mandible and congenital absence of the maxillary left first premolar (Fig 3). Crowns of the permanent molars

แบบวัดผล (Measurement Template) ของตัวบ่งชี้ หมายเลข 19

ประเด็นพิจารณา	รายละเอียดของตัวบ่งชี้
ชื่อของตัวบ่งชี้	**มีการปฏิรูปกระบวนการเรียนรู้ที่เน้นผู้เรียนเป็นสำคัญและส่งเสริมการสร้างประสบการณ์จริง**
ความหมายของตัวบ่งชี้	จำนวนกระบวนวิชาที่มีการจัดการเรียนการสอนที่เน้นผู้เรียนเป็นสำคัญ ได้แก่ การค้นคว้าอิสระ การทำโครงการ การศึกษาภาคสนาม การศึกษาภาคปฏิบัติ การสัมมนา การประชุมเชิงปฏิบัติการ และกระบวนวิชาที่มีการสอนโดยเน้นผู้เรียนเป็นสำคัญ (อาจรวมถึงหลักสูตรแบบสหวิทยาการ) เมื่อเปรียบเทียบกับจำนวนกระบวนวิชาทั้งหมดที่ภาควิชารับผิดชอบคำนวณเป็นร้อยละ
วัตถุประสงค์ของตัวบ่งชี้	เพื่อประเมินการตอบสนองของสถาบันการศึกษาต่อการปฏิรูปกระบวนการเรียนรู้ตามเจตนารมณ์และแนวการจัดการศึกษาของพ.ร.บ. การศึกษาแห่งชาติ พ.ศ. 2542 ที่มุ่งให้ผู้เรียนพัฒนาตนเองอย่างเต็มศักยภาพ
สูตรในการคำนวณ	$\frac{\text{จำนวนกระบวนวิชาที่เน้นผู้เรียนเป็นสำคัญ}}{\text{จำนวนกระบวนวิชาที่ภาควิชารับผิดชอบ}} \times 100$
ข้อมูลที่ใช้	1. จำนวนกระบวนวิชาที่เน้นผู้เรียนเป็นสำคัญ 2. จำนวนกระบวนวิชาที่ภาควิชารับผิดชอบ
ผู้รับผิดชอบด้านข้อมูล	ภาควิชา

ข้อมูลพื้นฐาน

รายละเอียด	2543	2544	2545	2546
จำนวนกระบวนวิชาที่เน้นผู้เรียนเป็นสำคัญ	2	2	2	10
จำนวนกระบวนวิชาที่ภาควิชารับผิดชอบ	4	4	4	12
ค่าที่คำนวณได้	50	50	50	83.33

รายละเอียด ปี 2546

รหัสกระบวนวิชา	ชื่อกระบวนวิชา
DPED414591	ปฏิบัติการทันตกรรมสำหรับเด็ก
DPED414601	คลินิกทันตกรรมสำหรับเด็ก
DPED414711	ทันตกรรมสำหรับเด็กขั้นสูง1
DPED414712	ทันตกรรมสำหรับเด็กขั้นสูง2
DPED414751	ทันตกรรมสำหรับเด็กคลินิกขั้นสูง1
DPED414752	ทันตกรรมสำหรับเด็กคลินิกขั้นสูง2
DPED414753	ทันตกรรมสำหรับเด็กพิเศษคลินิก1
DPED414754	ทันตกรรมสำหรับเด็กพิเศษคลินิก2

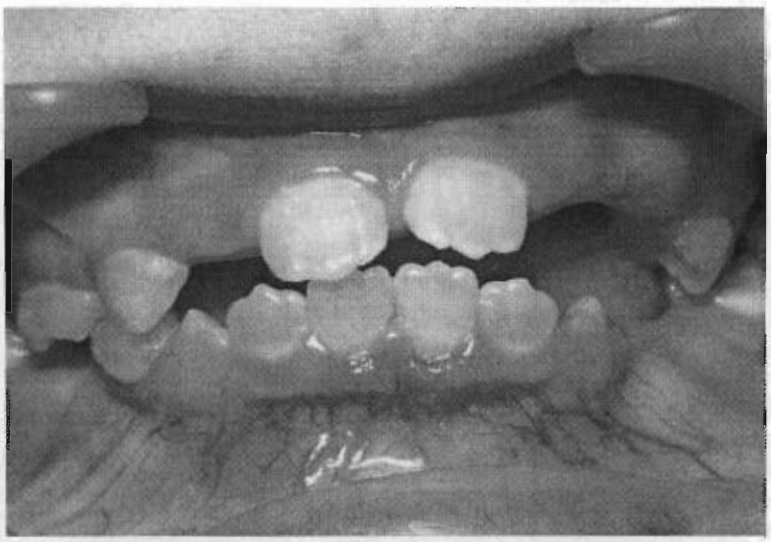

Fig 2. Opalescent teeth.

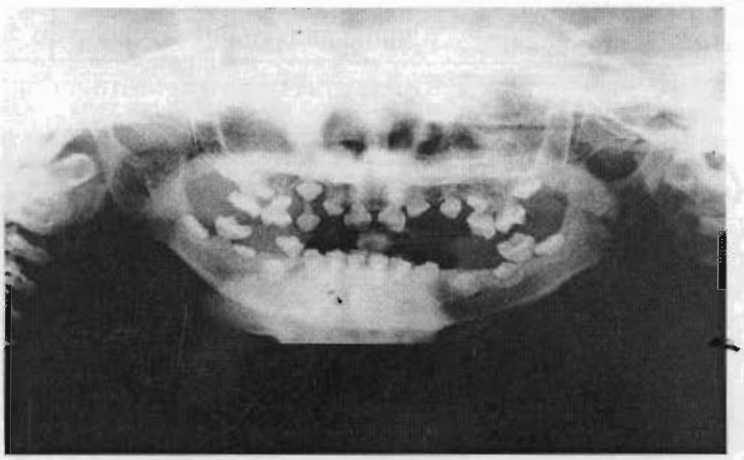

Fig 3. Panoramic radiograph shows small body of mandible, large inferior alveolar canal, and congenital absence of maxillary left first premolar. Some maxillary teeth have short and tapered roots. Most of the mandibular teeth do not have roots. Note obliterated coronal pulp chambers.

and developing premolars were short in occlusocervical direction with pronounced cervical constriction. The roots of most maxillary teeth were extremely short and tapered. The root of the maxillary left permanent lateral incisor was absent. All mandibular permanent teeth lacked roots—except for the second right premolar, which had an extremely short developing root. All erupted teeth had obliterated pulp chambers. The mandibular right first deciduous molar was nearly exfoliated (Fig 3). No teeth were available for histologic examination. A lateral cephalogram revealed underdeveloped nasal bone, cervical platyspondyly, and a very large sella turcica. A narrowing of the interpedunculate distance of the cervical vertebrae was also noted (Fig 4). Glucagon tolerance test results and growth hormone stimulation test results were normal. Urine metabolic screening tests for aminoaciduria and mucopolysaccharidosis had negative results. Immunologic studies were not performed because the patient neither experienced frequent infections nor were there other signs of immunologic defects. She died of respiratory failure at age 11.

DISCUSSION

The patient's short stature might have been a familial trait because both parents were proportionately short

แบบวัดผล (Measurement Template) ของตัวบ่งชี้ หมายเลข 18

ประเด็นพิจารณา	รายละเอียดของตัวบ่งชี้
ชื่อของตัวบ่งชี้	**ร้อยละของกระบวนวิชาที่มีการเรียนการสอนผ่านระบบเครือข่ายคอมพิวเตอร์**
ความหมายของตัวบ่งชี้	สัดส่วนคิดเป็นร้อยละของกระบวนวิชาที่มีการจัดการเรียนการสอนผ่านระบบเครือข่ายคอมพิวเตอร์ของคณะ ในรูปแบบ Online Learning (E-Learning) ทุกระดับ ทั้งนี้จะเป็นการส่งเสริมให้มีการนำเทคโนโลยีการศึกษาที่ทันสมัยมาช่วยในการปรับปรุงคุณภาพการเรียนการสอนของมหาวิทยาลัย และเป็นการส่งเสริมการเรียนรู้ตลอดชีวิต (Life long Learning) ต่อไปในอนาคต ตามแนวทางแห่ง พ.ร.บ. การศึกษาแห่งชาติ พ.ศ. 2542
วัตถุประสงค์ของตัวบ่งชี้	เพื่อประเมินประสิทธิผลการส่งเสริมให้มีการนำเทคโนโลยีการศึกษามาใช้ในการปรับปรุงคุณภาพการเรียนการสอน ตามแนวทางแห่ง พ.ร.บ. การศึกษาแห่งชาติ พ.ศ. 2542 มาตรา 23
สูตรในการคำนวณ	จำนวนกระบวนวิชาที่มีการเรียนการสอนผ่านเครือข่ายคอมพิวเตอร์ x 100 จำนวนกระบวนวิชาที่ภาควิชารับผิดชอบ
ข้อมูลที่ใช้	1. จำนวนกระบวนวิชาที่มีการเรียนการสอนผ่านเครือข่ายคอมพิวเตอร์ 2. จำนวนกระบวนวิชาที่ภาควิชารับผิดชอบ
ผู้รับผิดชอบด้านข้อมูล	ภาควิชา

ข้อมูลพื้นฐาน

รายละเอียด	2543	2544	2545	2546	254
จำนวนกระบวนวิชาที่มีการเรียนการสอนผ่านเครือข่ายคอมพิวเตอร์	0	0	1	0	0
จำนวนกระบวนวิชาที่ภาควิชารับผิดชอบ	4	4	4	12	12
ค่าที่คำนวณได้	0	0	25	0	0

รายละเอียด

รหัสกระบวนวิชา	ชื่อกระบวนวิชา

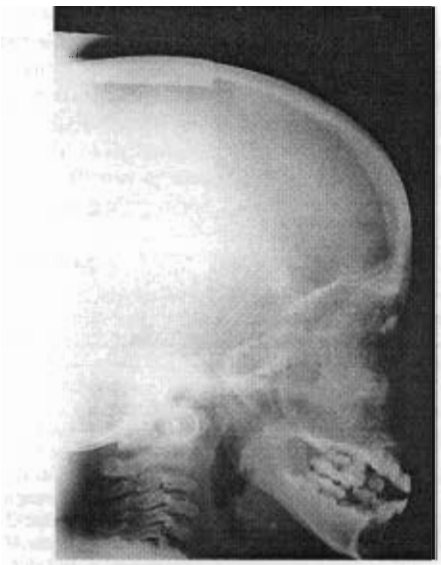

Fig 4. Large sella turcica and cervical platyspondyly.

(<3 centile). However, disproportionately short stature and proportionately short stature are different entities. The disproportionately short stature of the patient must not have been inherited from either of her parents. The disproportionately short stature, short neck, platyspondyly, hypoplastic acetabulum, and kyphosis found in this patient are shared by a number of syndromes; thus, they are not specifically pathognomonic. The conditions sharing these features include Morquio's syndrome, type IVA and type B[18-20] (including the nonkeratosulfate-excreting type[21]), Goldblatt syndrome,[11,22] and Schimke immunoosseous dysplasia.[12] Negative mucopolysaccharide screening tests and lack of both opalescent teeth and corneal opacities rule out all forms of Morquio's syndrome. Short neck, platyspondyly, hypoplastic acetabulum, kyphosis, and opalescent teeth are found in Goldblatt syndrome[11] and Schimke immunoosseous dysplasia.[12] However, lack of spondylometaphyseal dysplasia and generalized joint laxity eliminated Goldblatt syndrome as a diagnostic possibility. The presence of rootless teeth and hypodontia, as well as the absence of evidence of defective cellular immunity and progressive renal disease, distinguished this patient's disorder from previous reports of Schimke immunoosseous dysplasia.[23]

Opalescent teeth are seen in OI. However, the lack of bone fragility, hearing loss, blue sclerae, and hyperflexibility of joints, as well as the presence of rootless teeth in this patient, rule out a diagnosis of OI. The opalescent teeth seen in this patient resembled teeth seen in patients with DTDP2. Lack of progressive calcification of the thoracic aorta, calcific aortic stenosis, osteoporosis, and expansion of the marrow cavities distinguish the current case from Singleton-Merten syndrome.[14] The absence of sclerotic bone has ruled out the syndrome of dentin dysplasia with sclerotic bones and skeletal anomalies.[15]

The craniofacial features of this patient were large sella turcica, small body of mandible, opalescent teeth, obliteration of pulp chambers, rootless teeth, and hypodontia. Opalescent teeth found in this patient were clinically similar to teeth in patients with DI. This may indicate the presence of defective dentin.[24] The deciduous and permanent teeth of this patient shared similar color, which is in contrast with the pattern seen in patients with DI1 and DI2, in which the color of the permanent teeth is less opalescent.[25]

The rootless teeth found in this patient represent a clinically unique feature. Rootlessness has not been reported either as an isolated anomaly or as a syndromic anomaly. This dental malformation is distinct from rootless teeth found in DTDP1, because this patient's teeth did not show development of apical radiolucent areas.[5] Teeth affected with DTDP1 usually demonstrate normal color, yet this patient's teeth were opalescent in both dentitions. This may indicate that the opalescence and rootlessness of her teeth may not fit into any existing classifications of DI or DTDP. The obliteration of pulp chambers in this patient suggests abnormal calcification of dental pulp similar to that seen in patients with DI1, DI2, DTDP1, or DTDP2.[5]

It is of interest to note that contrasting patterns of root development were observed during the comparison of the maxillary and mandibular dentitions. Because the mandibular teeth were more severely affected, the impact on local regulatory mechanisms may have been more pronounced in the mandible. Short-root anomaly has been reported to be associated with a number of short stature–related syndromes.[26-31] However, none are clinically similar to what was observed in this patient.

Disproportionately short stature, platyspondyly, and large or shoe-shaped sella turcica can be seen in patients with Morquio's syndrome, nonkeratosulfate-excreting type (MIM 252300). However, the absence of opalescent and rootless teeth in that syndrome makes this diagnosis unlikely in this patient.[21-32]

In conclusion, it is believed that the combination of opalescent and rootless teeth, hypodontia, large sella turcica, depressed and broad nasal bridge, disproportionately short stature, short neck, widely spaced nipples, broad chest, protruded abdomen, platyspondyly, and hypoplastic acetabulum represent a unique and hitherto undescribed skeletal dysplasia and dental anomaly syndrome.

ชื่อหัวข้อที่สอน **โรคเลือดและมะเร็งในเด็ก**

ศ.เกียรติคุณ นพ. ปัญจะ กุลพงษ์

กระบวนวิชาที่สอน.....DPED582..... **ชั้นปีที่**...5..... **ภาคการศึกษา**...2.....

หน่วยกิตของวิชา.....2.....**หน่วยกิต** **จำนวนชั่วโมงสำหรับหัวข้อนี้**.....1.....**ชั่วโมง**

ภาควิชา(หน่วยวิชา) ทันตกรรมสำหรับเด็ก

รายละเอียดของหัวข้อ

(ระบุหัวข้อหลักและหัวข้อรอง ระบุมาพอเข้าใจ

โรคเลือดชนิดต่าง ๆ : ลักษณะทางคลินิกและการจัดการ

- Aplastic Anaemia
- Childhood ITP
- Hemophilia
- Thalassemia
- Hydrop fetalis
- Leukemia
- Acute myeloid leukemia
- Malignant lymphoma

- ปัจจัยที่มีอิทธิพลต่อการแสดงออกของเด็กในทางทันตกรรม

จุดเน้นของหัวข้อวิชานี้ในกระบวนวิชาที่ท่านสอน

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REFERENCES

1. Levin LS, Jorgenson RJ, Cook RA. Otodental dysplasia: a "new" ectodermal dysplasia. Clin Genet 1975;8:136-44.
2. da Silva EO, Janovitz D, de Albuquerque SC. Ellis-van Creveld syndrome: report of 15 cases in an inbred kindred. J Med Genet 1980;17:349-56.
3. Burdick AB, Bixler D, Puckett CL. Genetic analysis in families with van der Woude syndrome. J Craniofac Genet Dev Biol 1985;5:181-208.
4. Prabhu NT, John R, Munshi AK. Rieger's syndrome: a case report. Quintessence Int 1997;28:749-52.
5. Olsson A, Matsson L, Blomquist HK, Larsson A, Sjodin B. Hypophosphatasia affecting the permanent dentition. J Oral Pathol Med 1996;25:343-7.
6. Jorgenson RJ. The conditions manifesting taurodontism. Am J Med Genet 1982;11:435-42.
7. Price JA, Wright JT, Walker SJ, Crawford PJ, Aldred MJ, Hart TC. Tricho-dento-osseous syndrome and amelogenesis imperfecta with taurodontism are genetically distinct conditions. Clin Genet 1999;56:35-40.
8. Kantaputra PN, Pruksachatkunakorn C, Vanittanakom P. Rapp-Hodgkin syndrome with palmoplantar keratoderma, glossy tongue, congenital absence of lingual frenum and of sublingual caruncles: newly recognized findings. Am J Med Genet 1998;79:343-6.
9. Ranta H, Lukinmaa PL, Waltimo J. Heritable dentin defects: nosology, pathology, and treatment. Am J Med Genet 1993;45: 193-200.
10. O'Connell AC, Marini JC. Evaluation of oral problems in an osteogenesis imperfecta population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:189-96.
11. Goldblatt J, Carman P, Sprague P. Unique dwarfing, spondylometaphyseal skeletal dysplasia, with joint laxity and dentinogenesis imperfecta. Am J Med Genet 1991;39:170-2.
12. da Fonseca MA. Dental findings in the Schimke immuno-osseous dysplasia. Am J Med Genet 2000;93:158-60.
13. Komorowska A, Rozynkowa D, Lee KW, Renouf DV, Nicholls AC, MacKenzie J, et al. A Polish variant of isolated dentinogenesis imperfecta with a generalised connective tissue defect. Br Dent J 1989;167;239-43.
14. Singleton EB, Merten DF. An unusual syndrome of widened medullary cavities of the metacarpals and phalanges, aortic calcification and abnormal dentition. Pediatr Radiol 1973;1:2-7.
15. Morris ME, Augsburger RH. Dentine dysplasia with sclerotic bone and skeletal anomalies inherited as an autosomal dominant trait. A new syndrome. Oral Surg Oral Med Oral Pathol 1977;43:267-83.
16. Koshiba H, Kimura O, Nakata M, Witkop CJ Jr. Clinical, genetic, and histologic features of the trichoonychodental (TOD) syndrome. Oral Surg Oral Med Oral Pathol 1978;46:376-85.
17. Levin LS, Young RJ, Pyeritz RE. Osteogenesis imperfecta type I with unusual dental abnormalities. Am J Med Genet 1988;31:921-32.
18. Holzgreve W, Grobe H, von Figura K, Kresse H, Beck H, Mattei JF. Morquio syndrome: clinical findings in 11 patients with MPS IVA and 2 patients with MPS IVB. Hum Genet 1981;57:360-5.
19. Nelson J, Broadhead D, Mossman J. Clinical findings in 12 patients with MPS IV A (Morquio's disease). Further evidence for heterogeneity. Part I: Clinical and biochemical findings. Clin Genet 1988;33:111-20.
20. Nelson J, Kinirons M. Clinical findings in 12 patients with MPS IV A (Morquio's disease). Further evidence for heterogeneity. Part II: Dental findings. Clin Genet 1988;33:121-5.
21. Norman ME. Two brothers with nonkeratan-sulfate-excreting Morquio syndrome. Birth Defects Orig Artic Ser 1974; 10(12):466-9.
22. Bonaventure J, Stanescu R, Stanescu V, Allain JC, Muriel MP, Ginisty D, et al. Type II collagen defect in two sibs with the Goldblatt syndrome, a chondrodysplasia with dentinogenesis imperfecta, and joint laxity. Am J Med Genet 1992;44:738-53.
23. Saraiva JM, Dinis A, Resende C, Faria E, Gomes C, Correia AJ, et al. Schimke immuno-osseous dysplasia: case report and review of 25 patients. J Med Genet 1999;36:786-9.
24. Lukinmaa PL. Immunofluorescent localization of type III collagen and the N-terminal propeptide of type III procollagen in dentin matrix in osteogenesis imperfecta. J Craniofac Genet Dev Biol 1988;8:235-43.
25. Witkop CJ Jr. Hereditary defects of dentin. Dent Clin North Am 1975;19:25-45.
26. Sauk JJ Jr, Delaney JR. Taurodontism, diminished root formation, and microcephalic dwarfism. Oral Surg Oral Med Oral Pathol 1973;36:231-5.
27. Bottomley WK, Box JM. Dental anomalies in the Rothmund-Thomson syndrome. Report of a case. Oral Surg Oral Med Oral Pathol 1976;41:321-6.
28. Gardner DG, Girgis SS. Taurodontism, short roots, and external resorption, associated with short stature and a small head. Oral Surg Oral Med Oral Pathol 1977;44:271-3.
29. Witkop CJ Jr, Jaspers MT. Teeth with short, thin, dilacerated roots in patients with short stature: a dominantly inherited trait. Oral Surg Oral Med Oral Pathol 1982;54:553-9.
30. Bazopoulou-Kyrkanidou E, Dacou-Voutetakis C, Nassi H, Tosios K, Kyrkanides S, Damoli M. Microdontia, hypodontia, short bulbous roots and root canals with strabismus, short stature, and borderline mentality. Oral Surg Oral Med Oral Pathol 1992;74:93-5.
31. Shaw L. Short root anomaly in a patient with severe short-limbed dwarfism. Int J Paediatr Dent 1995;5:249-52.
32. Danes BS, Bearn AG. Cellular metachromasia, a genetic marker for studying the mucopolysaccharidoses. Lancet 1967;1:241-3.

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Van der Woude Syndrome With Sensorineural Hearing Loss, Large Craniofacial Sinuses, Dental Pulp Stones, and Minor Limb Anomalies: Report of a Four-Generation Thai Family

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A four-generation Thai family affected with Van der Woude syndrome is reported. The disorder appeared to be originally inherited from a person who was half Thai and half Pakistani. The lip lesions found in this family were varied and did not appear to be related to other phenotypes. There were some clinical manifestations possibly specific for the condition in this family. They included sensorineural hearing loss, prominent frontal bone, large frontal/sphenoidal/maxillary sinuses with increased mastoid air cells, long tooth roots, dental pulp stones, ankyloglossia, brachydactyly of hands, brachyphalangy, and hyperphalangy of toes, and single flexion crease of the fifth fingers. Fluorescence in situ hybridization analysis revealed no visible deletion at a 1q32-41 region. © 2002 Wiley-Liss, Inc.

KEY WORDS: dental anomaly; Van der Woude syndrome; brachymesophalangy; lip pit; pulp stone; large craniofacial sinuses; sensorineural hearing loss

INTRODUCTION

Van der Woude syndrome (VWS; MIM 119300) is a multiple anomalies syndrome characterized by congenital lip pits associated with cleft lip with or without cleft palate, hypodontia, and cutaneous syndactyly of toes. It is an autosomal dominant disorder with variable expressivity and incomplete penetrance, and is the most frequent form of syndromic clefting. The VWS locus has been mapped to 1q32-q41 [Schutte et al., 2000], but the VWS gene has not been isolated. The VWS gene expression is believed to be influenced by modifying genes at other loci [Cervenka et al., 1967; Burdick et al., 1985; Sertié et al., 1999]. VWS and popliteal pterygium syndromes (PPS; MIM 119500) have sometimes been present in the same family, and linkage analysis of the two syndromes strongly suggested that they are allelic [Soekarman et al., 1995; Lee et al., 1999].

Here we report on a Thai family in which seven individuals through four generations were affected with VWS and some new clinical manifestations.

CLINICAL REPORTS

The Family

The Thai family consisted of 23 individuals, of which seven were affected with VWS (Fig. 1, Table I). Patient 1 (Proband, IV-2, Fig. 1), a two-year-old girl, came to the Department of Pediatric Dentistry, Faculty of Dentistry, Chiang Mai University for oral examination. Her parents were non-consanguineous. She was born with bilateral cleft lip and palate, and bilateral symmetrical lip nipples (Fig. 2a). The lip nipples were surgically corrected for cosmetic reasons was performed at age three years. Sensorineural hearing loss was detected at age four years. Hypernasal speech secondary to the short secondary palate was noted. Her limbs appear normal except for hyperphalangy of the fifth toes.

Patient 2 (IV-1), an 11-year-old boy, was the elder brother of patient 1. He was born with bilateral symmetrical transverse lip furrows. Fluid sometimes came out at the furrows (Fig. 2b). Oral examination revealed crowding of the mandibular anterior teeth,

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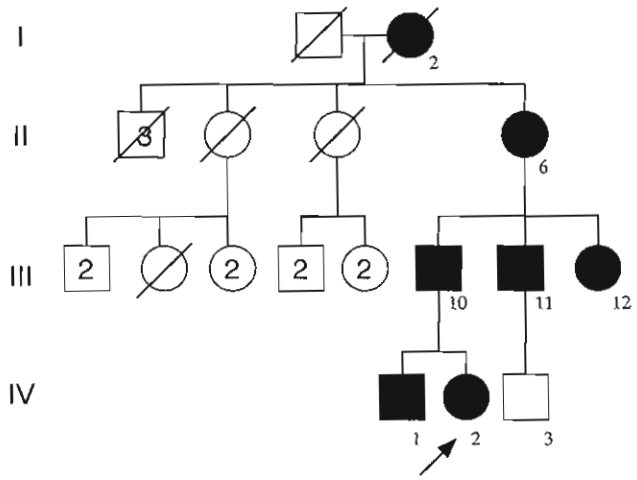

Fig. 1. Pedigree of the family. The closed circle and square depict patients with VWS, and the arrow shows the proband.

anterior crossbite at tooth 22, and ankyloglossia (Fig. 2c). Panoramic radiograph showed long tooth roots, large maxillary sinuses, and normal dental development. Audiometry showed normal hearing of both ears.

Patient 3 (III-10), a 37-year-old man, was the father of patients 1 and 2. He was born with right cleft lip and cleft palate. Sensorineural hearing loss (Fig. 3a) was detected at age nine. Asymmetrical lip nipple and a transverse furrow were observed. He could intentionally move the orbicularis oris muscle at the area of his lip nipples (Fig. 2d). Panoramic radiograph showed normal dental development, large maxillary sinuses, and long tooth roots. The frontal bone over the frontal sinus was very prominent. Lateral cephalograph showed large frontal and sphenoidal sinuses, and mastoid air cells (Fig. 4a). Brachydactyly of fingers, cutaneous syndactyly, and short distal phalanges of toes 2 and 3 were noted (Fig. 4b). Synostosis of the middle and distal phalanges of toes 5 was observed. The middle phalanx of toes 4 and distal phalanges of toes 2 and 3 appeared short.

Patient 4 (III-11) was the younger brother of patient 3. His medical and dental history was unremarkable. Audiometry showed normal hearing bilaterally. Bilateral symmetrical lip pits were observed (Fig. 2e). The pits sometimes were filled with fluid. He also had prominent frontal bone over the frontal sinus, very large frontal and sphenoidal sinuses (Fig. 4c), long mandibular tooth roots with normal dental development, brachydactyly of fingers, and cutaneous syndactyly of toes 2 and 3.

Patient 5 (III-12) was a 21-year-old woman. Her medical and dental history was unremarkable. Her karyotype was 46,XX. Audiometry showed normal hearing bilaterally. Her lip lesions were reported to be similar to those of patient 2. Surgical correction for cosmetic reasons was performed. She had large frontal and maxillary sinuses (Fig. 4d), long tooth roots, and a dental pulp stone in the left maxillary second permanent molar. Limb defects were not observed.

Patient 6 (II-6) was a 57-year-old woman. She had large frontal, sphenoidal, and maxillary sinuses; a small depression near the midline of lower lip (Fig. 2f); congenital absence of the mandibular second premolars; prolonged retention of the right mandibular

TABLE I. Clinical Manifestations in Seven Patients With VWS

	Patients						
Findings	1	2	3	4	5	6	7
Age (years)	5	11	37	34	21	57	Dead
Gender	F	M	M	M	F	F	F
Sensorineural deafness	y	n	y	n	n	y	NA
Craniofacial sinuses							
Large frontal sinus	n	n	y	y	y	y	NA
Large sphenoidal sinus	n	y	y	y	n	y	NA
Large maxillary sinus	n	y	y	y	y	y	NA
Large mastoid air cells	n	y	y	n	n	y	NA
Oral findings							
CL/CP	y	n	y	n	n	n	y
Lip pits	n	n	n	y	n	y	y
Lip nipples (conical elevation)	y	y	y	n	y	n	n
Hypodontia	n	n	n	n	n	y	NA
Long tooth roots	n	n	y	y	y	y	NA
Pulp stones	n	n	n	n	y	y	NA
Ankyloglossia	n	y	n	n	n	n	NA
Limb anomalies							
Brachydactyly of fingers	n	n	y	y	n	n	n
Single crease of the 5th finger	n	n	n	n	n	y	n
Short middle phalanges of the 5th fingers	n	n	n	n	n	y	NA
Toes 2/3 syndactyly	n	n	y	y	n	y	y
Short middle phalanges of toes 4	n	NA	y	NA	n	n	NA
Short distal phalanges of toes 2 and 3	y	y	y	NA	n	n	NA
Hyperphalangy of toes	y	n	n	n	n	n	NA

F, female; M, male; y, yes; n, no; NA, not available.

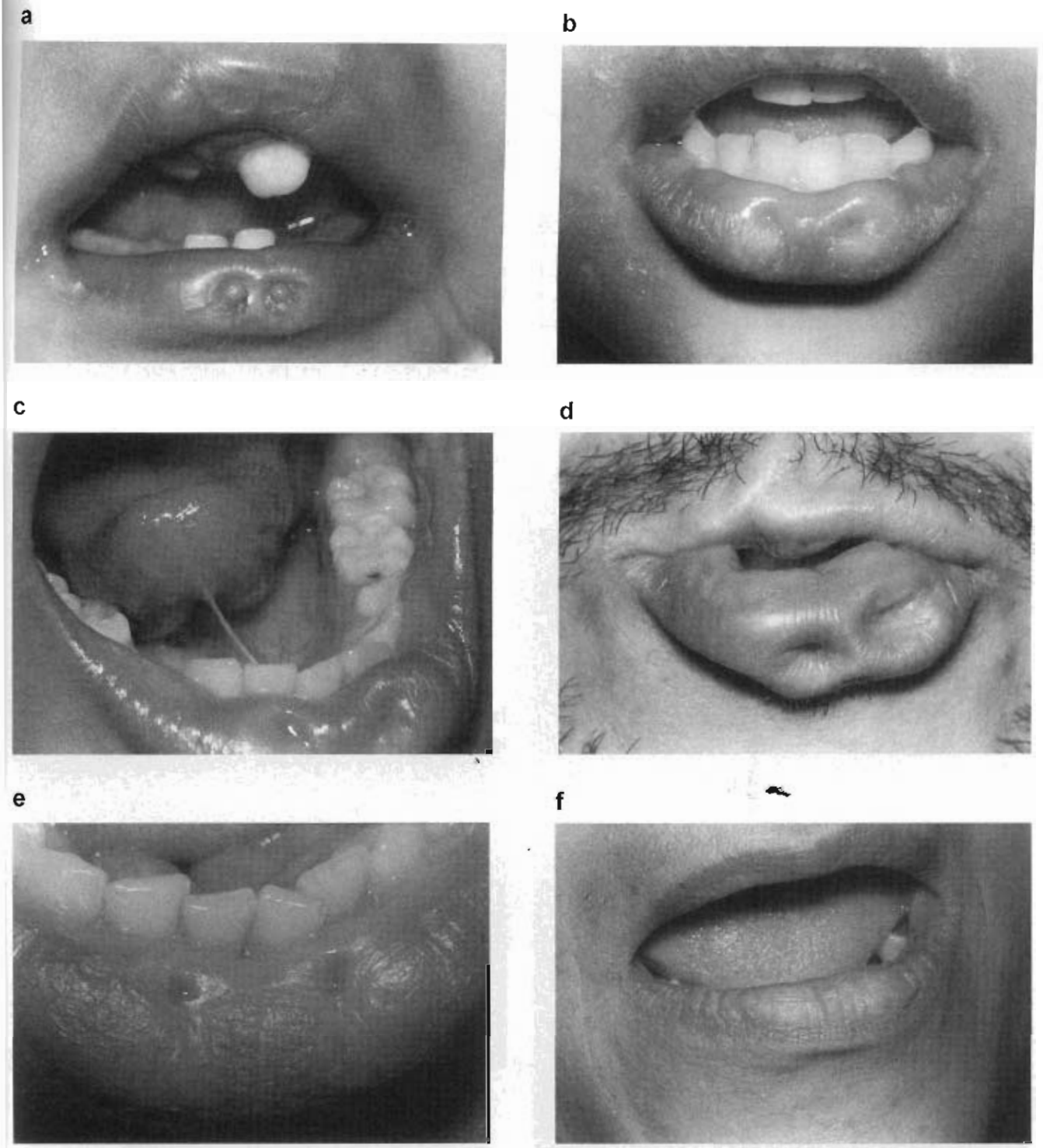

Fig. 2. Lip lesions in the patients. Bilateral lip pits in patient 1 (**a**), patient 2 (**b**), patient 3 (**d**), and patient 4 (**e**); lower lip depression in patient 6 (**f**); and ankyloglossia in patient 2 (**c**).

primary second molar; long tooth roots (Fig. 4e); dental pulp stones in all permanent molars; single flexion crease of the left fifth finger; short middle phalanges of both fifth fingers; and cutaneous syndactyly of toes 2 and 3.

Patient 7 (I-2) was half Thai and half Pakistani, and reported to have single lip pit and unilateral cleft lip and palate and be the first individual with lip pits in the family. Her parents and brother were said to be normal.

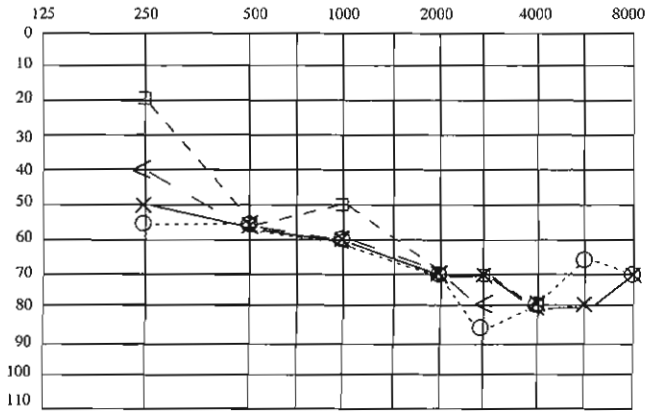

Fig. 3. Audiogram of patient 3, showing sensorineural hearing loss.

Flourescence In Situ Hybridization (FISH)

Two bacterial artificial chromosome (BAC) clones, 501i21 and 564a17, were used in this study. Clone 501i21 was located in the VWS critical region and clone 564a7 was outside the region [Schutte et al., 2000]. Chromosome preparation, probe labeling, and hybridization were done as described previously [Franke, 1972; Tochareontanaphol et al., 1994; Schutte et al., 2000]. Hybridization images were recorded with a Zeiss microscope connected with Metasystem computer software. As a result, both probe signals appeared at 1q32 of chromosomes 1 from patient 5, indicating that there is no visible deletion at 1q32 region in the patient.

DISCUSSION

We reported a large Thai family with VWS. In this family, the lip lesions were varied, ranging from bilateral lip pits to a small depression mark near the midline of lower lip seen in patient 6, as reported previously [Janku et al., 1980; Ranta and Rintala, 1981;

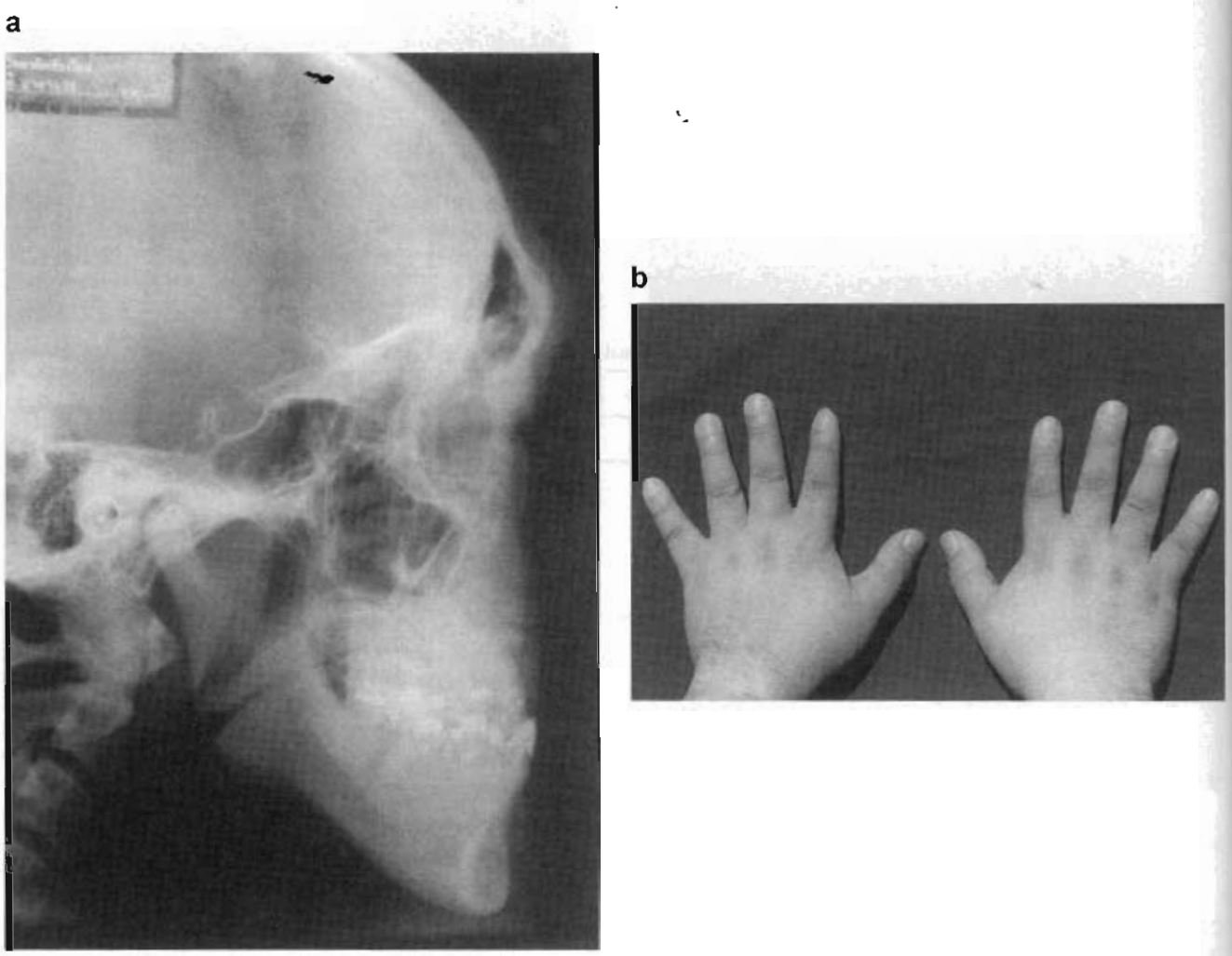

Fig. 4. Large frontal and sphenoidal sinuses and increased mastoid air cells in patient 3 (**a**), brachydactyly of fingers and thumbs in patient 3 (**b**), large frontal sinus in patients 4 (**c**) and 5 (**d**), and hypodontia of the mandibular second premolars in patient 6 (**e**).

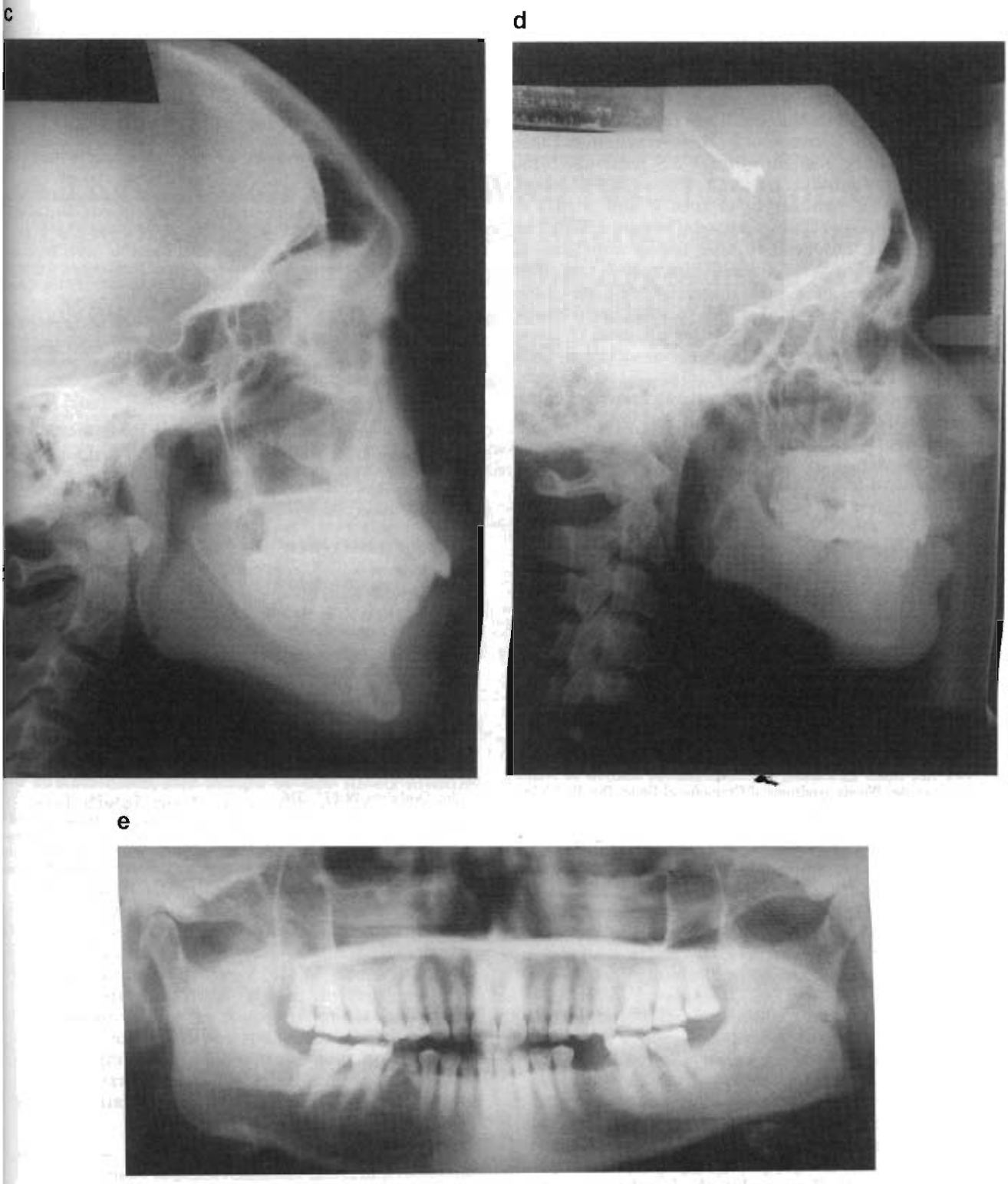

Fig. 4. (*Continued*)

Ranta, 1985]. Ankyloglossia observed in patient 2 has been reported to be a characteristic feature of VWS [Sorricelli et al., 1966; Burdick et al., 1987]. Dental pulp stones found in patients 5 and 6 are very rare in the normal population, and have never been reported in VWS. The presence of pulp stones in VWS patients may imply that there was a defect in dentin mineralization. Long tooth roots seen in patients 3–6 have also never been described, suggesting an effect of the VWS gene on the growth of Hertwig epithelial root sheath.

Sensorineural hearing loss in patients 1 and 3; large craniofacial sinuses, including the frontal, sphenoidal, and maxillary sinuses; and limb anomalies were unique findings in this family. Although conductive hearing loss is often associated with cleft palate, sensorineural hearing loss found in this family is rare in individuals with cleft palate. It remains to be seen whether these abnormalities are seen in other VWS patients. Limb anomalies are rare in patients with VWS [Lipson, 1989]. However, syndactyly of toes 2 and 3 and of fingers 3 and 4 have been reported [Calnan, 1952]. The limb anomalies observed in this family consisted of brachydactyly of fingers, single flexion crease and short middle phalanges of a fifth finger, short distal phalanges of toes 2 and 3, short middle phalanges of toes 4, and hyperphalangy of toes 5. Although most of these features are normal variants, their association with VWS in the family may be significant.

Chromosomal microdeletion has been known to cause VWS in a subset of patients [Bacian and Walker, 1987; Sander et al., 1994; Schutte et al., 1999; Houdayer et al., 2000]. However, FISH analysis did not detect any visible deletion at 1q32 region in our patient.

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REFERENCES

Bacian M, Walker AP. 1987. Lip pits and deletion 1q32-41. Am J Med Genet 26:437–443.

Burdick AB, Bixler D, Puckett CL. 1985. Genetic analysis in families with van der Woude syndrome. J Craniofacial Genet Dev Biol 5:181–208.

Burdick AB, Lian M, Zhuohua D, Ning G. 1987. Van der Woude syndrome in two families in China. J Craniofacial Genet Dev Biol 7:413–418.

Calnan J. 1952. Congenital double lip: record of a case with a note on the embryology. Br J Plast Surg 5:197–202.

Cervenka J, Gorlin RJ, Anderson VE. 1967. The syndrome of pits of the lower lip and cleft lip and/or palate. Genetic considerations. Am J Hum Genet 19:416–432.

Franke U. 1972. Quinacrine mustard fluorescence of human chromosome: characterization of unusual translocation. Am J Hum Genet 24:189–213.

Houdayer C, Soupre V, Kareenty B, Vazquez MP, Odent S, Lacombe D, Le Boue Y, Munnich A, Bahuau M. 2000. 1q32-41 microdeletion with reference to van der Woude syndrome and a clefting entities. Am J Med Genet 91:161–163.

Janku P, Robinow M, Kelly T, Bralley R, Baynes A, Edgerton MT. 1980. The van der Woude syndrome in a large kindred: variability, penetrance, genetic risks. Am J Med Genet 5:117–123.

Lee MM, Winter RM, Malcom S, Saal HM, Chitty L. 1999. Popliteal pterygium syndrome: a clinical study of three families and report of linkage to the Van der Woude syndrome locus on 1q32. J Med Genet 36:888–892.

Lipson A. 1989. Van der Woude syndrome and limb defects: the chance of recurrence. J Med Genet 26:347–348.

Ranta R. 1985. Correlations of sinus, conical elevation, median depression of the lower lip and types of oral clefts. Int J Oral Surg 14: 479–484.

Ranta R, Rintala AE. 1981. Correlations between microforms of the Van der Woude syndrome and cleft palate. Cleft Palate J 20:158–162.

Sander A, Schmeizie R, Murray J. 1994. Evidence for a microdeletion in 1q32-41 involving the gene responsible for the Van der Woude syndrome. Hum Mol Genet 3:575–578.

Schutte BC, Basart AM, Watanabe Y, Laffin JJ, Coppage K, Bjork BC, Daack-Hirsch S, Patil S, Dixon MJ, Murray JC. 1999. Microdeletions at chromosome bands 1q32-q41 as a cause of Van der Woude syndrome. Am J Med Genet 84:145–150.

Schutte BC, Bjork BC, Coppage KB, Malik MI, Gregory SG, Scott DJ, Brentzell LM, Watanabe Y, Dixon MJ, Murray JC. 2000. A primary gene map for the Van der Woude syndrome critical region from 900 kb of genomic sequence at 1q32-q41. Genome Res 10:81–94.

Sertié BC, Sousa AV, Steman S, Pavanello RC, Passos-Bueno MR. 1999. Linkage analysis in a Brazilian family with van der Woude syndrome suggests the existence of a susceptability locus for cleft palate at 17p11.2-11.1. Am J Hum Genet 65:433–440.

Soekarman D, Cobben JM, Vogels A, Spauwen PH, Fryns JP. 1995. Variable expression of the popliteal pterygium syndrome in two 3-generation families. Clin Genet 47:169–174.

Sorricelli DA, Bell L, Alexander WA. 1966. Congenital fistulas of the lower lip. Oral Surg 21:511–516.

Tochareontanaphol C, Cremer M, Schorck E, Bloden L, Cremer T, Reid T. 1994. Multicolor fluorescence in situ hybridization on metaphase chromosomes and interphase halo-preparations using cosmid and YAC clones for the simultaneous high resolution mapping of deletion in dystrophin gene. Hum Genet 93:229–235.

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Clinical Report

A Thai Mother and Son With Distal Symphalangism, Hypoplastic Carpal Bones, Microdontia, Dental Pulp Stones, and Narrowing of the Zygomatic Arch: A New Distal Symphalangism Syndrome?

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A Thai mother and son with distal symphalangism and other associated abnormalities are reported. Distal and middle phalanges of fingers and toes 2–5 were either aplastic/hypoplastic or fused between the corresponding digits. The second fingers and fourth fingernails were most severely affected in both patients. The mother's hands were less severely affected; the middle and distal phalanges of her hands were malformed and fused. Besides the absence of fusion lines, the shape of the fused middle and distal phalanges was quite different from that of other types of fusion, i.e., fused bones in both patients did not maintain the normal configuration of bone, referring to as "middle-distal phalangeal complex". Distal symphalangism was observed in toes 2–5 of the mother and in toe 3 of the son. Both patients had additional clinical manifestations such as narrowing of the zygomatic arch, dental pulp stone, microdontia of a mandibular permanent central incisor, cone-shaped epiphyses of middle phalanges of fingers, and absence of scaphoid, trapezium, trapezoid, and pisiform bones. Mutation analysis of *NOG* and *ROR2*, the genes responsible for proximal symphalangism and brachydactyly type B, respectively, was negative. © 2002 Wiley-Liss, Inc.

KEY WORDS: **absent carpal bone; dental pulp stone; narrow zygomatic arch; fingernail dysplasia; distal symphalangism; proximal symphalangism; brachydactyly type B**

INTRODUCTION

Distal symphalangism (DS, MIM 185700), an autosomal dominant disorder, is characterized by fusion of the distal interphalangeal joints of hands and feet. The index finger is most commonly affected. The skin over affected finger joints lacks interdigital flexion creases. DS is associated with brachydactyly, hypophalangism, absent or rudimentary nails, craniosynostosis [Comings, 1965; Zavala et al., 1975; Poush, 1991], and camptodactyly [Ohdo et al., 1981], but an association with proximal symphalangism is rare [Strasburger et al., 1965]. Proximal symphalangism (MIM 185800) is another entity, characterized by ankylosis of the proximal interphalangeal joints and fusion of carpal and tarsal bones [Strasburger et al., 1965], and caused by mutations in *NOG* that encodes a protein, Noggin [Gong et al., 1999; Dixon et al., 2001]. DS shares many similarities with brachydactyly type B (BDB, MIM 113000), the most severe form of brachydactyly. BDB is an autosomal dominant trait characterized by aplasia/hypoplasia of the middle/distal phalanges of fingers 2–5, fingernail dysplasia, and symphalangism between the middle/distal phalanges. Thumbs are often flattened or bifid, and syndactyly of fingers and toes are

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usually found [Gong et al., 1999; Oldridge et al., 2000]. Although the gene for DS has not been identified, BDB is presumed to be caused by mutations in the tyrosine kinase-like orphan receptor 2 gene (*ROR2*; MIM 602337), which is required for cartilage and growth plate development [Afzal et al., 2000; DeChiara et al., 2000; Oldridge et al., 2000; van Bokhoven et al., 2000].

This report presents a Thai family with clinical diagnosis of DS associated with other manifestations that are hitherto undescribed in this syndrome.

MATERIAL AND METHODS

Clinical Report

Patient 1, a nine-year-old Thai boy came to the Department of Pediatric Dentistry, Faculty of Dentistry, Chiang Mai University for dental care. He was born with a weight of 2,700 g to non-consanguineous parents. His eight-month-old sister was normal. When seen by us at age nine years, his height was 126 cm (< 50 centile) and OFC 50 cm (< 50 centile), and had a prominent nose and small left mandibular permanent central

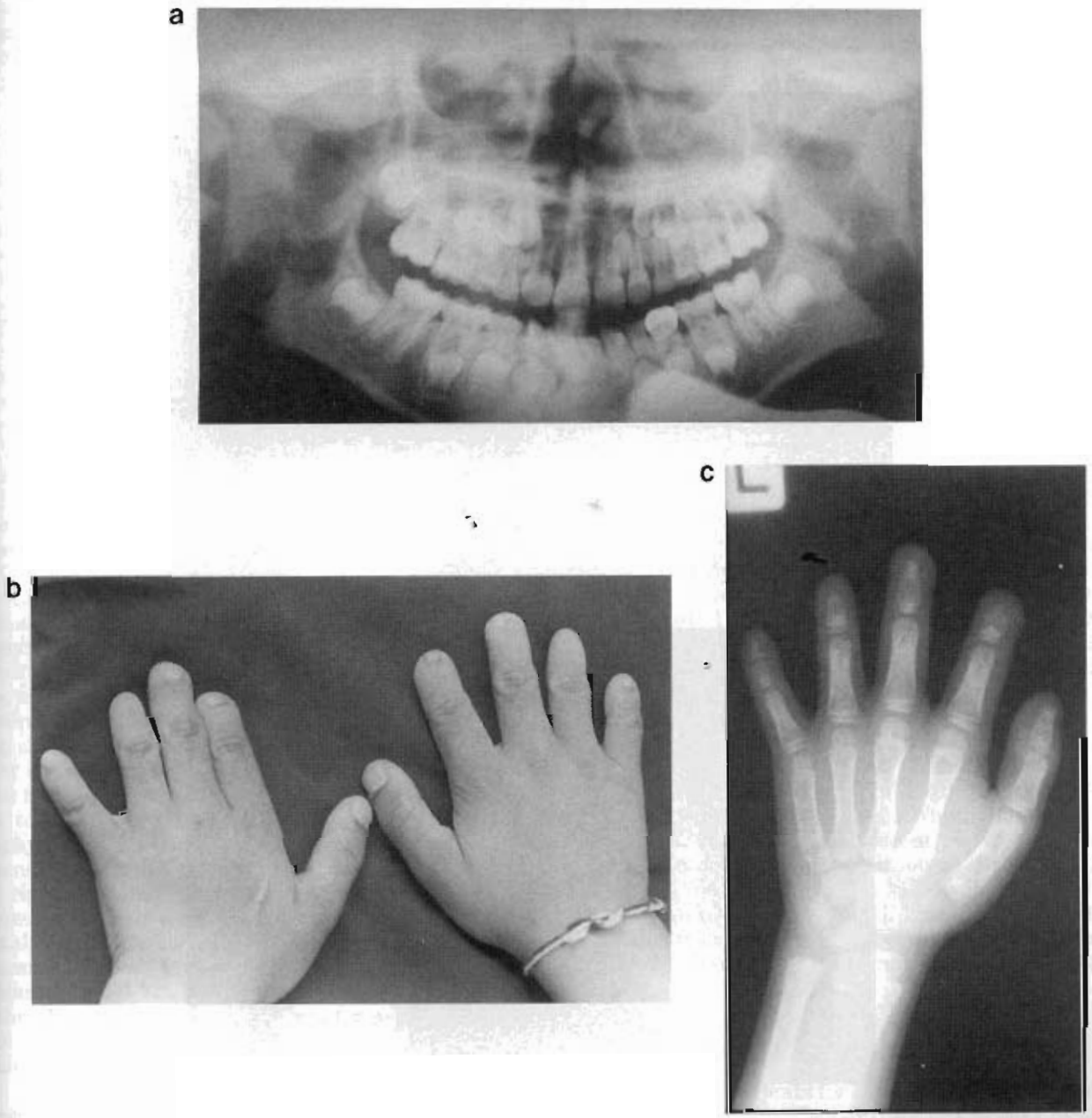

Fig. 1. Patient 1, having a narrowed left zygomatic arch and a dental pulp stone in the left maxillary first permanent molar (a); short fingers with absence of the right third and both fourth fingernails (b); absence of the fourth distal phalanx with fusion of the middle and distal phalanges 2 and 3, cone-shaped epiphyses at the middle phalanges 2 and 4, absence of scaphoid, trapezoid, and pisiform, and a very small ossification center of trapezium (c).

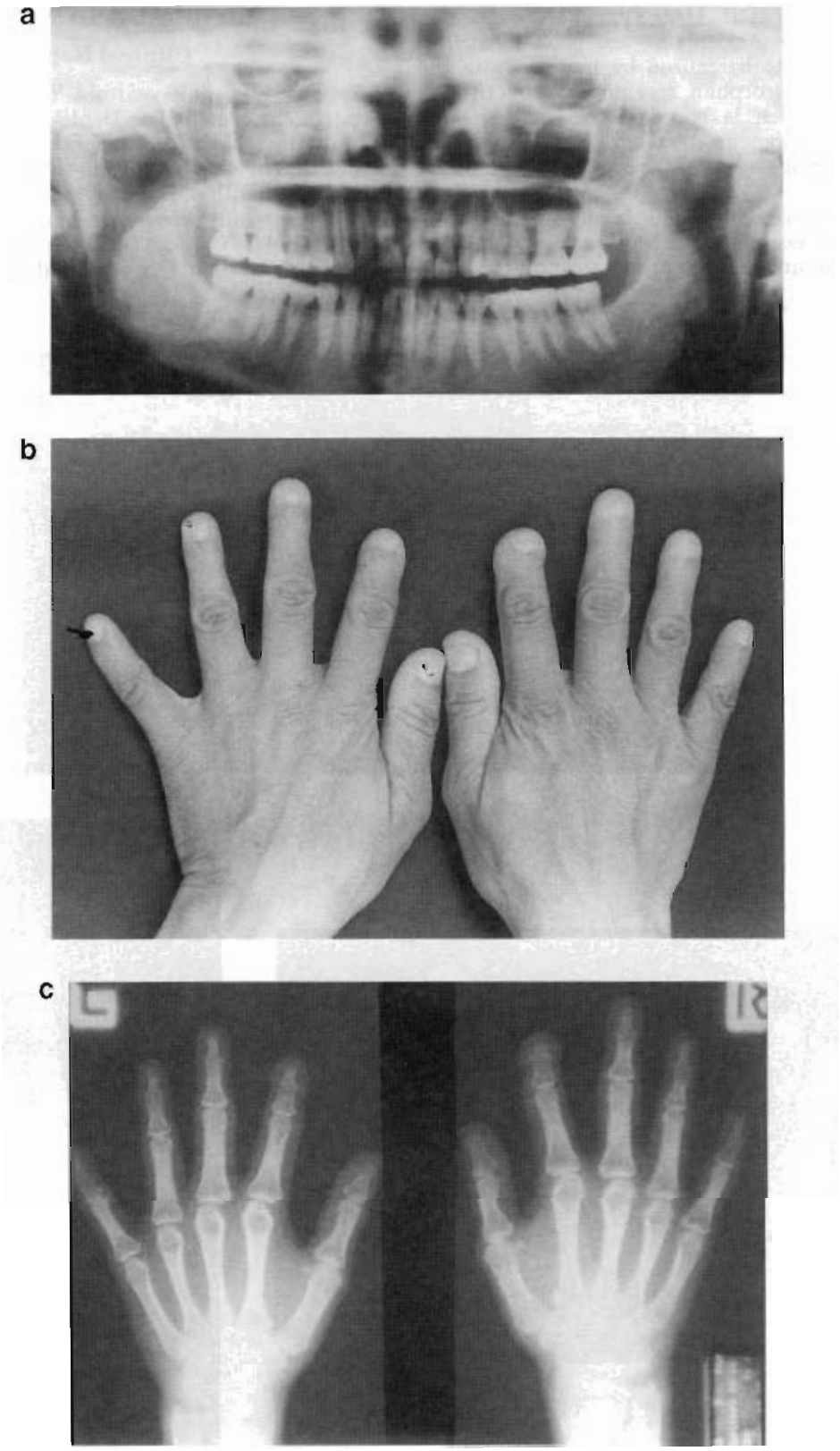

Fig. 2. Patient 2 (the mother), showing narrowing of the right zygomatic arch, and dental pulp stones in the first permanent molars (**a**), short finge with dysplastic fingernails and normal thumbs (**b**), and fusion of the middle and distal phalanges 2–5 (**c**).

incisor. Panoramic radiography showed normal dental development with a pulp stone in the maxillary left first permanent molar. The left zygomatic arch was very narrow (Fig. 1a). Physical examination revealed short fingers with dysplastic fingernails. The right third and both fourth fingernails were absent (Fig. 1b). The dorsal skin covering the distal one-third of these fingers was smooth and shiny. Left fingernails 2, 3, and 5 were hypoplastic. The second fingers were most severely affected. The shortness of fingers did not limit him in doing his regular routine. Each finger had only one flexion crease. Toes 2–5 were also short with normal appearing toenails, and mild cutaneous syndactyly of toes 2 and 3 was observed bilaterally. Hand radiography demonstrated very small ossification centers of the right scaphoid and trapezoid, and the left trapezium, with the absence of the right trapezium, left trapezoid, and both pisiform bones. Both thumbs and their metacarpals were normal. Fusions between middle and distal phalanges of left fingers 2 and 3 and right fingers 2 and 5 were observed, and distal phalanges of right finger 3 and bilateral fingers 4 were absent (Fig. 1c). The right second and the left second and fourth middle phalanges showed cone-shaped epiphyses. Foot radiography showed very short middle and distal phalanges of toes 3–5. The phalanges of the second toes appeared normal. Fusion was observed between middle and distal phalanges of bilateral toes 3 without fusion lines between them. All proximal phalanges and great toes were normal.

Patient 2, a 37-year-old woman, was the mother of patient 1. Her face was asymmetric (left < right) and had a prominent nose with a nasal septum extending below nasal alae and a short philtrum, but was otherwise normal. Her height was 151 cm (50th centile) and OFC 51 cm (3rd centile). She was the second child in a non-consanguineous marriage. Her parents, brother, and sister were all unremarkable. The shortness of fingers was less remarkable than that in patient 1. Like in her son, second fingers were very short with bulbous tips, and most severely affected. Fingernails 3, 2, 4, and 5 were dysplastic in the order of decreasing severity (Fig. 2a). Single flexion crease was observed at the right second and both third fingers. Her thumbs and their nails appeared normal. Toes 2–5 were also short, but toenails were unremarkable. Panoramic radiography showed normal dental development with the absence of all third permanent molars. Narrowing of the right zygomatic arch was evident (Fig. 2b). Pulp stones were observed in all first permanent molars. Distal phalanges of fingers 2–5 were short and appeared fused, with short corresponding middle phalanges (Fig. 2c). Foot radiography showed fusion of the short middle and distal phalanges of toes 2–5 with no fusion lines. A middle part of proximal phalanges 2–4 were narrow.

Mutation Analysis of *NOG* and *ROR2*

Informed consent was obtained from both patients. DNA was extracted from peripheral blood leukocytes by standard procedures. Primer sequences and PCR condition for *NOG* analysis have been described previously [Gong et al., 1999]. Primers were designed in the flanking intron sequences to amplify exons 2–8 of *ROR2*. *ROR2*-exon 9 was amplified in overlapping segments [Schwabe et al., 2000]. PCR was for *ROR2* performed at 94°C for 10 min, followed by 40 cycles at 94°C for 30 sec, 50°C for 30 sec, 72°C for 45 sec, and final extension at 72°C for 10 min. PCR products were purified by QIA quick purification kit (Qiagen, Chataworth, CA), then sequenced with BigDye terminator kit (PE Applied Biosystems, Foster City, CA) and analyzed by an ABI 377 automated sequencer (PE Applied Biosystems). As a result, no mutation in either gene was observed in the two patients.

DISCUSSION

Both patients we have described were clinically diagnosed to have DS because they had brachydactyly, especially at the distal segment of digits, fusion between the distal interphalangeal joints, and the absence of distal phalanges 3 and 4. They also had additional, hitherto undescribed abnormalities, such as cone-shaped epiphyses of middle phalanges 2 and 4, radial-ray carpal-bone anomalies, narrowing of the zygomatic arch, and dental pulp stones. The second fingers were predominantly affected, as reported previously [Inman, 1924; Steinberg and Reynolds, 1948; Poush, 1991], while the thumbs and great toes were intact in both patients, unlike in patients described by Matthews et al. [1987]. Proximal symphalangism (PS) was ruled out, because symphalangism patterns seen in our patients were absolutely different from PS and there was no *NOG* mutation in the patients.

DS shares many manifestations with BDB, including aplasia/hypoplasia of the middle and distal phalanges of fingers 2–5, and fingernail dysplasia [Sillence, 1978; Halpern et al., 1979; Poush, 1991; Oldridge et al., 1999; Oldridge et al., 2000]. As seen in our patient 1, BDB has been reported to have DS and fourth digit hypophalangism [Comings, 1965; Zavala et al., 1975; Temtamy and McKusick, 1978]. In addition to the absence of mutation in *ROR2*, hypoplasia of the distal phalanges confined to the second fingers in patient 2 distinguished the condition in this family from BDB [Inman, 1924; Steinberg and Reynolds, 1948]. When BDB and DS are present together in a patient, it is sometimes confusing to describe the condition as DS with BDB [Comings, 1965] or BDB with DS [Zavala et al., 1975; Temtamy and McKusick, 1978]. Unequivocally differentiating diagnostic features between the two conditions, other than *ROR2* gene analysis, would be worth studying.

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REFERENCES

Afzal AR, Rajab A, Fenske CD, Oldridge M, Elanko N, Ternes-Pereira E, Tuysuz B, Murday VA, Patton MA, Wilkie AM, Jeffery S. 2000. Recessive Robinow syndrome, allelic to dominant brachydactyly type B, is caused by mutation of *ROR2*. Nat Genet 25:419–422.

Comings DE. 1965. Symphalangism and fourth digit hypophalangism. Arch Int Med 115:580–583.

DeChiara TM, Kimble RB, Poueymirou WT, Rojas J, Masiakowski P, Valenzuela DM, Yacopoulos GD. 2000. *Ror2*, encoding a receptor-like tyrosine kinase, is required for cartilage and growth plate development. Nat Genet 24:271–274.

Dixon ME, Armstrong P, Stevens DB, Bamshad M. 2001. Identical mutations in *NOG* can cause either tarsal/carpal coalition syndrome or proximal symphalangism. Genet Med 3:349–353.

Gong Y, Chitayat D, Kerr B, Chen T, Babul-Hirji R, Pal A, Reiss M, Warman ML. 1999. Brachydactyly type B: clinical description, genetic mapping to chromosme 9q, and evidence for a shared ancestral mutation. Am J Hum Genet 64:570–577.

Halpern AA, Wheeler RD, Schurman DJ. 1979. Distal symphalangism: symbrachydactylism arising in a family with distal symphalangism. Clin Orthop 141:251–255.

Inman OL. 1924. Four generations of symphalangism. J Hered 15:329–334.

Matthews S, Farnish S, Young ID. 1987. Distal symphalangism with involvement of the thumbs and great toes. Clin Genet 32:375–378.

Ohdo S, Yamauchi Y, Hayakawa K. 1981. Distal symphalangism associated with camptodactyly. J Med Genet 18:456–458.

Oldridge M, Temple IK, Santos HG, Gibbons RJ, Mustafa Z, Chapman KE, Loughlin J, Wilkie AOM. 1999. Brachydactyly type B: linkage to chromosome 9q22 and evidence of genetic heterogeneity. Am J Hum Genet 64:578–585.

Oldridge M, Fortuna AM, Maringa M, Propping P, Mansour S, Pollitt C, DeChiara TM, Kimble RB, Valenzuela DM, Yancopoulos GD, Wilkie AOM. 2000. Dominant mutations in *ROR2*, encoding an orphan receptor tyrosine kinase, cause brachydactyly type B. Nat Genet 24:375–378.

Poush JR. 1991. Distal symphalangism: a report of two families. J Hered 82:233–238.

Schwabe GC, Tinschert S, Buschow C, Meinecke P, Wolff G, Gillessen-Kaesbach G, Oldridge M, Wilkie AOM, Komec R, Mundlos S. 2000. Distinct mutations in the receptor tyrosine kinase gene ROR2 cause brachydactyly type B. Am J Hum Genet 67:822–831.

Sillence DO. 1978. Brachydactyly, distal symphangism, scoliosis, tall stature, and club feet: a new syndrome. J Med Genet 15:208–211.

Steinberg AG, Reynolds EL. 1948. Further data on symphalangism. J Hered 39:23–37.

Strasburger AK, Hawkins MR, Eldbridge R, Hargrave RL, McKusick VA. 1965. Symphalangism: genetic and clinical aspects. Bull Johns Hopkins Hosp 117:108–127.

Temtamy SA, McKusick VA. 1978. Brachydactyly. In: Bergsman D, Mudge JR, Paul NW, Greene SC, editors. The genetics of hand malformation. New York: Alan R. Liss. p 187–299.

Van Bokhoven H, Celli J, Kayserili H, van Beusekom E, Balci S, Brussel W, Skovby F, Kerr B, Percin EF, Akarsu N, Brunner HG. 2000. Mutation of the gene encoding the *ROR2* tyrosine kinase autosomal recessive Robinow syndrome. Nat Genet 25:423–426.

Zavala C, Hernandez-Ortiz J, Lisker R. 1975. Brachydactyly type B and symphalangism in different members of a Mexican family. Ann Genet 18:131–134.

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Clinical Report

A Dominantly Inherited Malformation Syndrome With Short Stature, Upper Limb Anomaly, Minor Craniofacial Anomalies, and Absence of *TBX5* Mutations: Report of a Thai Family

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We report on a Thai family with dominantly inherited malformation syndrome with upper limb anomalies, short stature, quadricuspid aortic valve, and minor craniofacial anomalies. The affected individuals comprised a mildly affected mother, a moderately affected daughter, and a most severely affected son. The daughter and son had short stature. The craniofacial abnormalities comprised frontal bossing, hypoplastic nasal bones, depressed nasal bridge, and broad nasal alae. The upper limb defects varies among the patients, ranging from radial ray defects in the mother through radial and ulnar ray defects with unilateral humeral hypoplasia in the daughter to radial ray defects with severe oligodactyly and bilateral humeral hypoplasia in the son. All patients in this family had hypoplasia of the shoulder girdle and resembled what is observed in many families with Holt-Oram syndrome. Moreover, the son showed quadricuspid aortic valve with mild aortic regurgitation. However, the present family did not show any mutation of the *TBX5* gene, a disease-causing gene of Holt-Oram syndrome. The present family deserves further investigation on other genes that play a role in the development of the upper limbs, particularly of radial rays. © 2002 Wiley-Liss, Inc.

KEY WORDS: **absent thumb; Holt-Oram syndrome; hypoplastic clavicle; hypoplastic humerus; hypoplastic ulna; oligodactyly; short stature**

INTRODUCTION

The biological role of several genes in limb development has been elucidated, based on recent discoveries of disease-causing genes in several limb malformation syndromes, such as the *TBX5* gene in Holt-Oram syndrome (HOS) [Basson et al., 1997, 1999; Li et al., 1997]. We describe here a Thai family with a dominantly inherited malformation syndrome, characterized by radial and ulnar ray defects, short stature, and minor craniofacial malformations. The upper limb and shoulder girdle defects in the present family are more severe than those of HOS, and the molecular studies did not reveal any mutations in the *TBX5* gene.

CLINICAL REPORT

Patient 1

The proband was a 51-year-old Thai woman born to healthy nonconsanguineous parents (Fig. 1A). She had three affected offspring, a daughter (patient 2; Fig. 2A), a son (patient 3; Fig. 3A), and another son who died a few days after birth and was reported to be absent of thumbs and syndactylous fingers. The proband was healthy with

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normal intelligence. Height and OFC were 153 cm (50th centile) and 53 cm (3rd centile), respectively. She had minor facial dysmorphism, comprising frontal bossing, depressed nasal bridge, and broad nasal alae (Fig. 1A). Medical history and physical examination did not reveal evidence of heart disease. She had slender upper arms, short forearms with clubbed hands, absent thumbs, hypoplasia with flexion contracture of the left second finger, partial cutaneous syndactyly between the left second and third fingers, and camptodactyly of all proximal interphalangeal (PIP) joints predominantly of the right (Fig. 1A). Radiologic examination revealed slenderness of the left clavicle, hypoplastic scapulae with flat glenoid fossae particularly of the left, mild hypoplasia of the left humeral head, bowed ulnae particularly of the left, and radial ray defects, comprising the absence of the radii and thumbs, dysplastic radial carpal bones, brachymesophalongy of fingers 3, 4, and 5, and hypoplasia of the left second metacarpal and phalanges (Fig. 1B). Lateral cephalogram showed underdeveloped nasal bones.

Patient 2

The patient was a 25-year-old woman (Fig. 2A). She was intelligent and healthy. Medical history and physical examination did not show evidence of cardiac problems. The patient refused to have echocardiography performed. She was proportionately short. Height and OFC were 145 cm (5th centile) and 53 cm (3rd centile), respectively. Frontal bossing, depressed nasal bridge, and broad nasal alae were observed. The thorax was narrow with short clavicles (Fig. 2A). The left upper limb was short with dislocation of the left shoulder joint. The right upper limb showed only shortening of the forearm. The right hand was clubbed. Both thumbs were absent. The left second finger was small. The left fourth finger was longer than the third one. Camptodactyly was evident, especially on the right (Fig. 2B). Radiologic examination demonstrated hypoplastic scapulae significantly of the left and severe left humeral hypoplasia with humeroulnar synostosis (Fig. 2C). The radiologic findings of the forearm and hand were similar to those of the proband (Fig. 2D). Lateral cephalogram showed underdeveloped nasal bones.

Patient 3

The patient was a 23-year-old man (Fig. 3A). He was healthy and intelligent. Although clinically asymptomatic, echocardiography showed quadricuspid aortic valve with aortic regurgitation of the mild degree. Height and OFC were 150 cm (<3rd centile) and 53 cm (<3 centile) respectively. Frontal bossing, depressed nasal bridge, and broad nasal alae were evident. The shoulder was narrow and slightly drooped. Dislocation of the shoulder joints with prominent acromial processes was found. The thorax was narrow with short clavicles. The upper limbs were significantly short with clubbed hands (Fig. 3A). Only two fingers with a wide gap between them were present bilaterally. Camptodactyly was seen in the right two fingers and the left ulnar finger

Fig. 1. Patient 1. **A:** Frontal bossing, broad alar nasi, and depressed nasal bridge. Note clubbed hands and flexion contracture of fingers. **B:** Absent radii, hypoplastic and bowed right ulna, and malformed carpal bones. Note brachymesophalangy and interphalangeal joint abnormalities.

(Fig. 3B and D). Radiologic examination showed hypoplasia of the scapulae especially of the left, rudimentary humeri, right humeroulnar synostosis, bowed ulnae, absent radii, and oligodactyly (Fig. 3C and E). Three

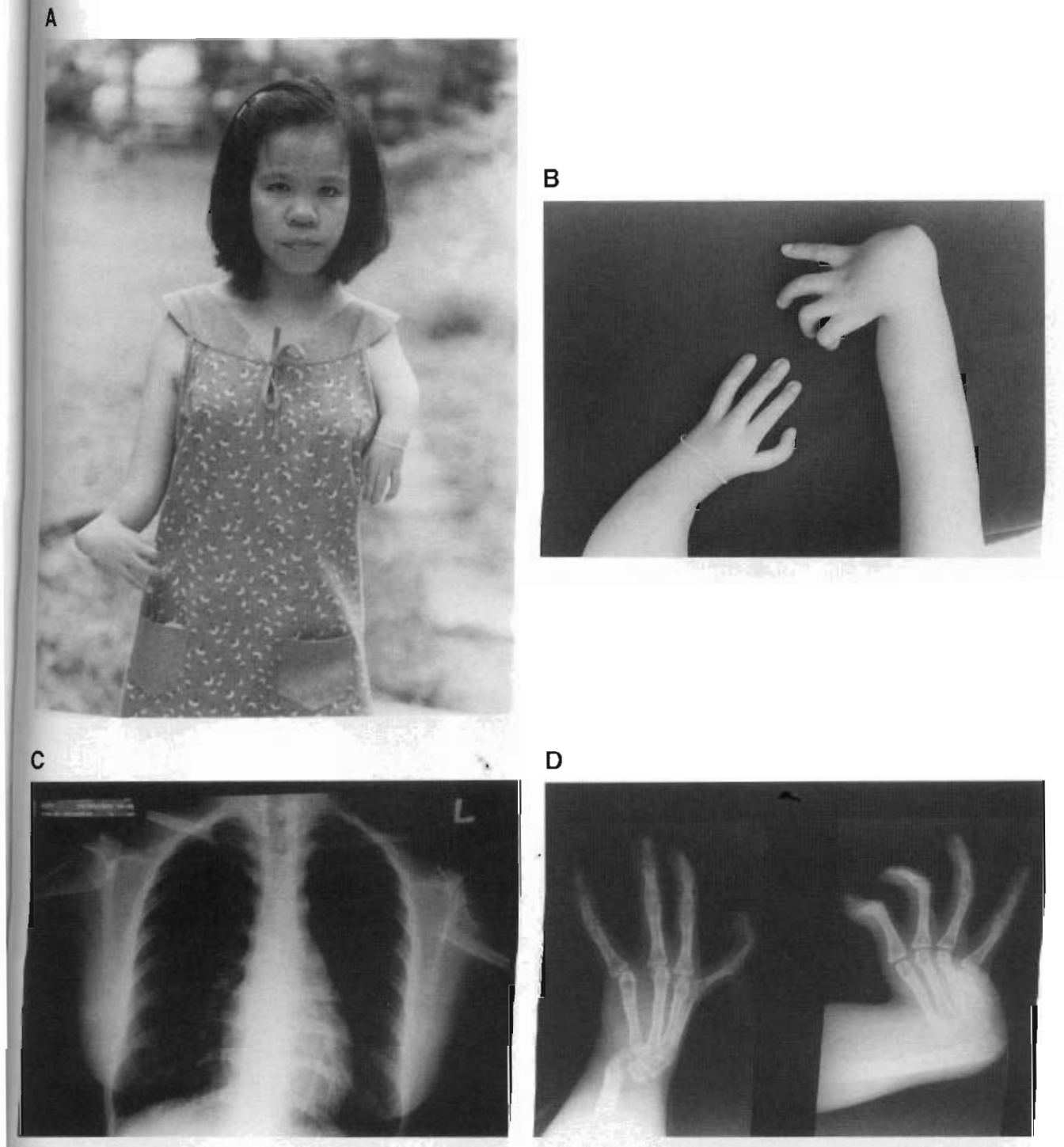

Fig. 2. Patient 2. **A:** Frontal bossing, broad alar nasi, and depressed nasal bridge. Short clavicles. **B:** Very short left arm. Right hand in clubbed position. **C:** Hypoplastic scapulae. Dislocated left shoulder joint. Left humeral hypoplasia with humeroulnar synostosis. **D:** Absence of radii, and thumbs, malformed carpal bones, and hypoplastic ulnae.

metacarpals were present bilaterally, and osseous syndactyly was noted in the proximal ends between the right ulnar metacarpals and distal ends between the left radial metacarpals. The radial fingers consisted of partially duplicated phalanges bilaterally (Fig. 3E). Lateral cephalogram showed underdeveloped nasal bones (Fig. 4).

DNA Isolation

Peripheral blood (10 ml) was obtained from each patient. Epstein-Barr virus–transformed cell lines were established. DNA was isolated from lymphoblastoid cell lines by digestion with proteinase K and phenol-chloroform purification [Sambrook et al., 1989]

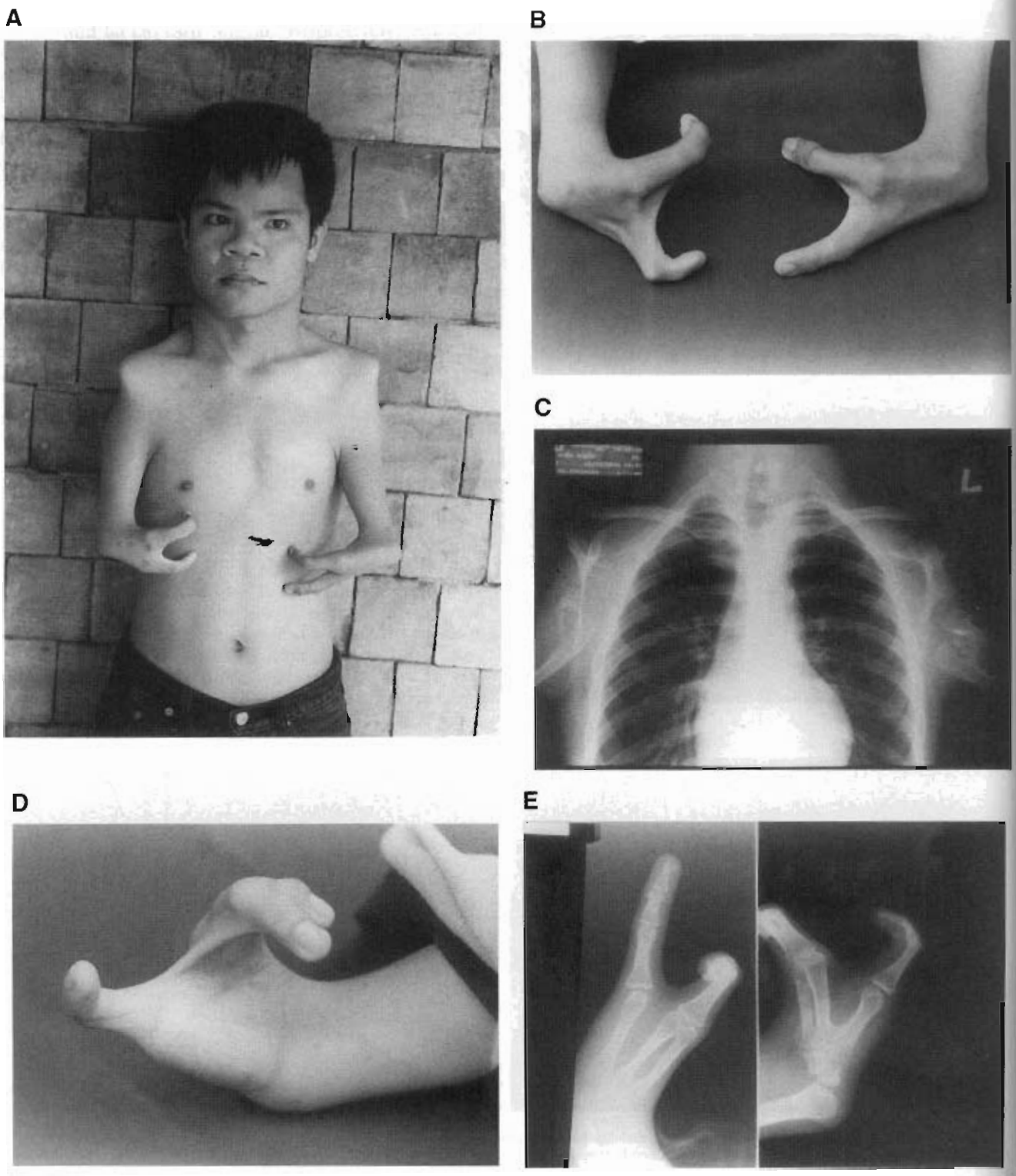

Fig. 3. Patient 3. **A:** Frontal bossing, broad alar nasi, and depressed nasal bridge. Note short clavicles with drooped shoulder, prominent acromions, and very short arms. **B:** Wide gap between syndactylous fingers. Note camptodactyly. **C:** Hypoplastic scapulae. Malformed and dislocated humeri. Right humerus is fused with proximal ulna. **D:** Syndactylous finger. **E:** Two malformed carpal bones. Three metacarpals are present in each hand. Osseous syndactyly of metacarpals. Note partially duplicated phalanges.

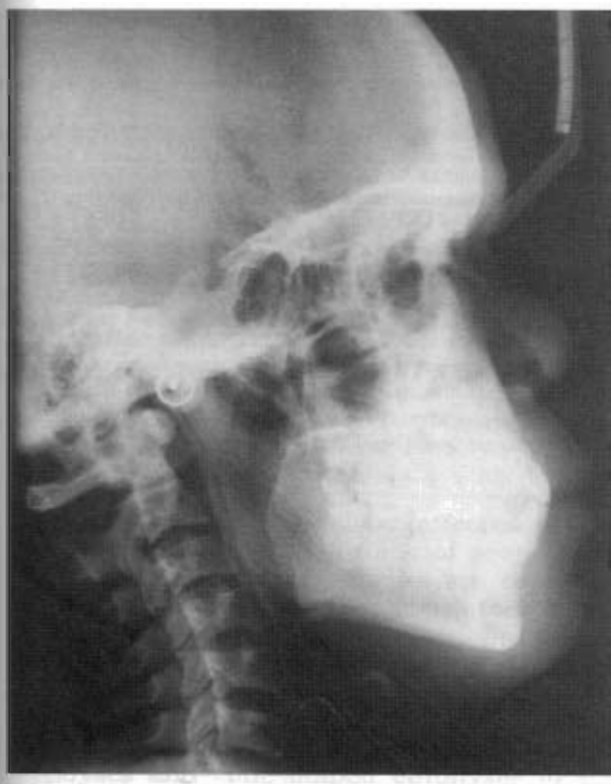

Fig. 4. Lateral cephalogram of Patient 3 shows underdeveloped nasal bones.

TBX5 Gene Mutation Analysis

Exons 2 through 9 of *TBX5* were PCR-amplified from genomic DNA of patient 3 using primers derived from intron sequences flanking each exon (5′ → 3′): exon 2 (bp 1–146)-2GF,R: GCTTCTTGTCCTCAGAGCAGAACCT/CAAGAGAAGCCGAGCAGGAAAGCCA; exon 3 (bp 147–242)-3GF,R: TTCTCCTCGTCCCTCTCTCTACACA/AGTTTGGGGAAGGAATGCCCACTAC; exon 4 (bp 243–361)-4GF,R: AACGGGGCTAGTTTCCGCTTCCACG/CTTTTTGGGAGAAGGTTCCACTTTT; exon 5 (bp 362–509)-5GF,R: CTTGGTGCGTGAACTGAAGCACGC/GAGGGAGACAAGGCTGGGGAATCCAG; exon 6 (bp 510–663)-6GF,R: ACGGCCCAGGCACTGGTTCCTGGG/CAGGGTTTTATCTGGAGACAAAGGG; exon 7 (bp 664–754)-7GF,R: ATTAGCTCATGTCCTGAGGTGGTCT/GTGGGGAGGAGAAAGTTGAGGAATC; exon 8 (bp 755–1098)-8GF,R: CTTTTCTGGTGGATTCTCTCACACC/GGGTAGGAACATGTCAAGGGAACT; exon 9-9GF,R: TACTTTGGACAATATACTGTCTCC/CGACCTTGAGTGCAGAATGTGAAC. PCR conditions used were 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec, for 30 cycles, then kept at 72°C for 10 min. PCR products were then purified by using QIA quick columns per the manufacturer's instructions (Qiagen, Chataworth, CA). Templates were subjected to cycle sequencing by using fluoresceinated dideoxynucleotides and analyzed by Applied Biosystems 377 automated DNA sequencer.

RESULTS

Using the genomic DNA of patient 3, direct sequencing did not show mutations in exons 2–9 of *TBX5*.

DISCUSSION

The pattern of the upper limb defect and its left-sided predominance and possible genetic anticipation in the present family mimicked those reported in some families with HOS [Rybak et al., 1971; Newbury-Ecob et al., 1996; Li et al., 1997]. Short stature found in the present family is seldom found in HOS [Rybak et al., 1971]. Cardiovascular anomalies of HOS are varied. ASD and VSD are common, but, though rare, hypoplastic left heart and hypoplastic peripheral vasculature are described; thus, the quadricuspid aortic valve found in our patient 3 may have been a syndromic constituent, but minor craniofacial changes as in the present family might have been ignored in HOS patients in the context of the presence of other major malformations [Newbury-Ecob et al., 1996; Sletten and Pierpont, 1996]. For these reasons, we were engaged in the work of molecular analysis on the *TBX5* gene in the present family, which ultimately yielded a negative result.

The upper limb anomalies of this family were similar to those reported in a Polish family affected with HOS. Actually, the upper limb anomalies found in that Polish family and in ours were more severe than those usually found in HOS [Rybak et al., 1971; Newbury-Ecob et al., 1996]. Without the presence of short stature and craniofacial features, the diagnosis HOS might have been entertained since HOS may not have congenital heart defects [Rybak et al., 1971; Basson et al., 1999; Cross et al., 2000]. Interestingly, cranial deformity has been mentioned in that Polish family but unfortunately it was not fully described [Rybak et al., 1971]. The short stature and minor craniofacial features reported in the present family were not of their familial traits, since other members of the family did not have them.

As far as the negative molecular findings are concerned, we are aware that approximately two-thirds of HOS patients have negative molecular *TBX5* findings [Cross et al., 2000]. It may not be possible to tell whether the disorder in the present family represents genetic heterogeneity of HOS or a previously undescribed malformation syndrome. There is a possibility that the present family and the one reported by Rybak et al. [1971] had the same disorder, not related to *TBX5* mutations. The presumed gene that causes the present disorder would be expected to be functionally expressed in a multiplicity of tissues, including the upper limbs, heart, and craniofacial regions, as is the *TBX5* gene with expression in the developing heart, forelimbs, trachea, thoracic wall, retina, and telecephalon.

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REFERENCES

Basson CT, Bachinsky DR, Lin RC, Levi T, Elkins JA, Soults J, Grayzel D, Kroumpouzou E, Traill TA, Leblanc-Straceski J, Ranault B, Kucherlapati R, Seidman JG, Seidman CE. 1997. Mutations, in human cause limb and cardiac malformation in Holt-Oram syndrome. Nat Genet 15:30–35.

Basson CT, Huang T, Lin RC, Bachinsky DR, Weremowicz S, Vaglio A, Bruzzone R, Quadrelli R, Lerone M, Romeo G, Silengo M, Pereira A, Krieger J, Mesquita SF, Kamisago M, Morton CC, Pierpont MEM, Muller CW, Seidman JG, Seidman CE. 1999. Different *TBX5* interactions in heart and Limb defined by Holt-Oram syndrome mutations. Proc Natl Acad Sci USA 96:2919–2924.

Cross SJ, Ching YH, Li QY, Armstrong-Buisseret L, Spranger S, Lyonnet S, Bonnet D, Penttinen M, Jonveaux P, Leheup B, Mortier G, Van Ravenswaaij C, Gardiner CA, Brook JD, Newbury-Ecob RA. 2000. The mutation spectrum in Holt-Oram syndrome. J Med Genet 37:785–787.

Li QY, Newbury-Ecob RA, Terrett JA, Wilson DI, Curtis ARJ, Yi CH, Gebuhr T, Bullen PJ, Robson SC, Strachan T, Bonnet D, Lyonnet S, Young ID, Raeburn JA, Buckler AJ, Law DJ, Brook JD. 1997. Holt-Oram syndrome is caused by mutations in *TBX5*, a member of the Brachyury (T) gene family. Nat Genet 15:21–29.

Newbury-Ecob RA, Leanage R, Raeburn JA, Young ID. 1996. Holt-Oram syndrome: a clinical genetic study. J Med Genet 33:300–307.

Rybak M, Kozlowski K, Kleczkowska A, Lewandowska J, Sokolowski J, Soltysik-Wilk E. 1971. Holt-Oram syndrome associated with ectromelia and chromosomal aberrations. Am J Dis Child 121:490–495.

Sambrook J, Fritsch EF, Maniatis T. 1989. Molecular cloning. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press. p 9.14–9.23.

Sletten LJ, Pierpont MEM. 1996. Variation in severity of cardiac disease in Holt-Oram syndrome. Am J Med Genet 65:128–132.

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Clinical Report

Apparently New Osteodysplastic and Primordial Short Stature With Severe Microdontia, Opalescent Teeth, and Rootless Molars in Two Siblings

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A Thai man and his sister affected with a newly recognized syndrome of proportionate primordial short stature are reported. The patients had severe intrauterine and postnatal growth retardation, prominent nose and nasal bridge, small pinnae, large sella turcica, areas of hypo- and hyperpigmentation of skin, dry and thin scalp hair, and long and straight clavicles. Ivory epiphyses and cone-shaped epiphyses of the hands were found when they were young, but most of them disappeared as they grew up. Scaphoid and trapezium had angular appearance. The second toes were unusually long. Distal symphalangism of toes and barchymesophalangy of fingers were noted. The findings that appear to distinguish this syndrome from the previously reported syndromes are long second toes, opalescent and rootless teeth, severe microdontia, severely hypoplastic alveolar process, and unerupted tooth. The mode of inheritance is suspected to be autosomal recessive.

KEY WORDS: **dentinogenesis imperfecta; large nose; microcephaly; microdontia; opalescent teeth; osteodysplasia; primordial dwarfism; rootless teeth; Seckel syndrome**

INTRODUCTION

Primordial "dwarfism" is used to describe patients who have severe intrauterine and postnatal growth retardation. It is a very heterogeneous group of disorder that has been classified into three main types: Seckel syndrome, microcephalic osteodysplastic primordial dwarfism (MOPD) type I/III and type II [Meinecke and Passarge, 1991; Majewski and Goecke, 1998]. Variants of MOPD or Seckel-like syndrome have been described [Shebib et al., 1991; Buebel et al., 1996]. Seckel syndrome, the best known one, is characterized by severe intrauterine and postnatal proportional short stature, severe microcephaly, mild to moderate mental retardation, large and prominent nose, and dislocation of the head of radius [Seckel, 1960]. Patients affected with MOPD can be easily distinguished from those with Seckel syndrome by being disproportionately short and having distinct radiological features [Majewski et al., 1982a, 1982b; Poznanski et al., 1983; Majewski and Goecke, 1998].

Primordial short stature with dental anomalies has been described [Seckel, 1960; Majewski and Goecke, 1982; Shebib et al., 1991; Majewski, 1992; Lin et al., 1995]. However, none, especially anyone with proportionate primordial short stature, has been reported with severe microdontia, opalescent teeth, and rootless molars. A Thai brother and sister affected with a new syndrome of this group of short stature are described. A newly recognized features comprising a newly recognized syndrome include long second toes, long and straight clavicles, distal symphalangism of toes, severe microdontia and malformation of mandibular premolars, severely hypoplastic alveolar processes, opalescent teeth, and rootless molars. The mode of inheritance is suspected to be autosomal recessive.

CLINICAL REPORT

Patient 1

Patient 1 was an 18-year-old man. He and his younger sister (patient 2) were born from healthy and nonconsanguineous parents (Figs. 1A and 2A and B). The older

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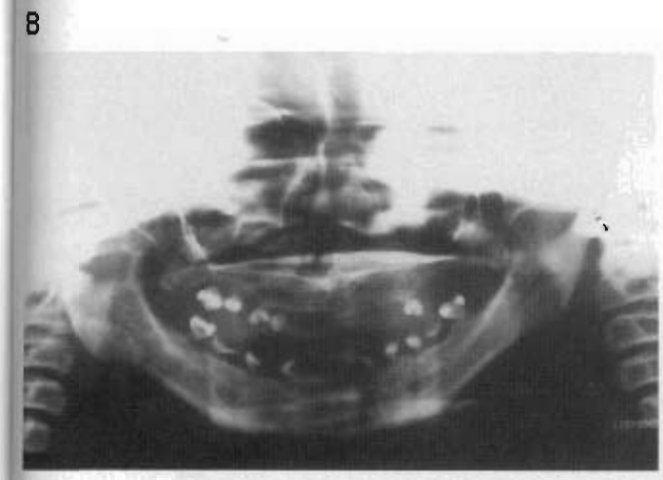


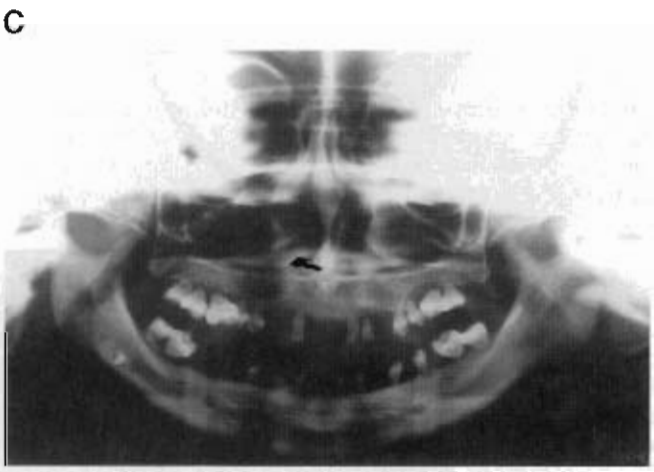


Fig. 1. **A:** Patients 1 and 2 at ages 18 and 16 years old, respectively, and their parents. Proportionate short stature is noted. **B** and **C:** Panoramic radiographs of patients 1 and 2, respectively. Note rootless molars. Dentin of incisors is less radiopaque than that of molars. Lack of cortical bone, and hypoplastic alveolar process. Mandibular premolars are very small.

sister was normal. The patient was born at term. Birth weight was 1,000 g. He started having pubic hair at age 14 years. At age 18 years, axillary hair was not apparent. Intelligence was normal.

On examination, he was proportionately short. Height, weight, and OFC were 102 cm (<3rd centile), 14 k (<3rd centile), and 43 cm (<3rd centile), respectively. Scalp hair was dry and thin. Large nose with prominent nasal bridge was observed. Pinnae were small. Hearing was normal. Like his sister, there were areas of hypo- and hyperpigmentation of the skin that did not follow lines of Blaschko lines. In some areas, the skin appeared poikilodermatous (Fig. 2A and B).

Oral examination revealed generalized microdontia and opalescent teeth. All teeth were small but the mandibular premolars were unusually small and malformed, comprising of many cusps. The mandibular left premolars had the mesio-distal dimension of 4 mm. All teeth were loose and wore off easily. The parents reported that both children had all primary and permanent teeth, but they kept falling out painlessly. The loss of teeth was not a result of dental caries. There was no history of recurrent infections. Chest was narrow. The fingers and thumbs were short, and the elbows bent (Fig. 3C). The second toes were unusually long and both great and second toes were laterally curved. Flexion

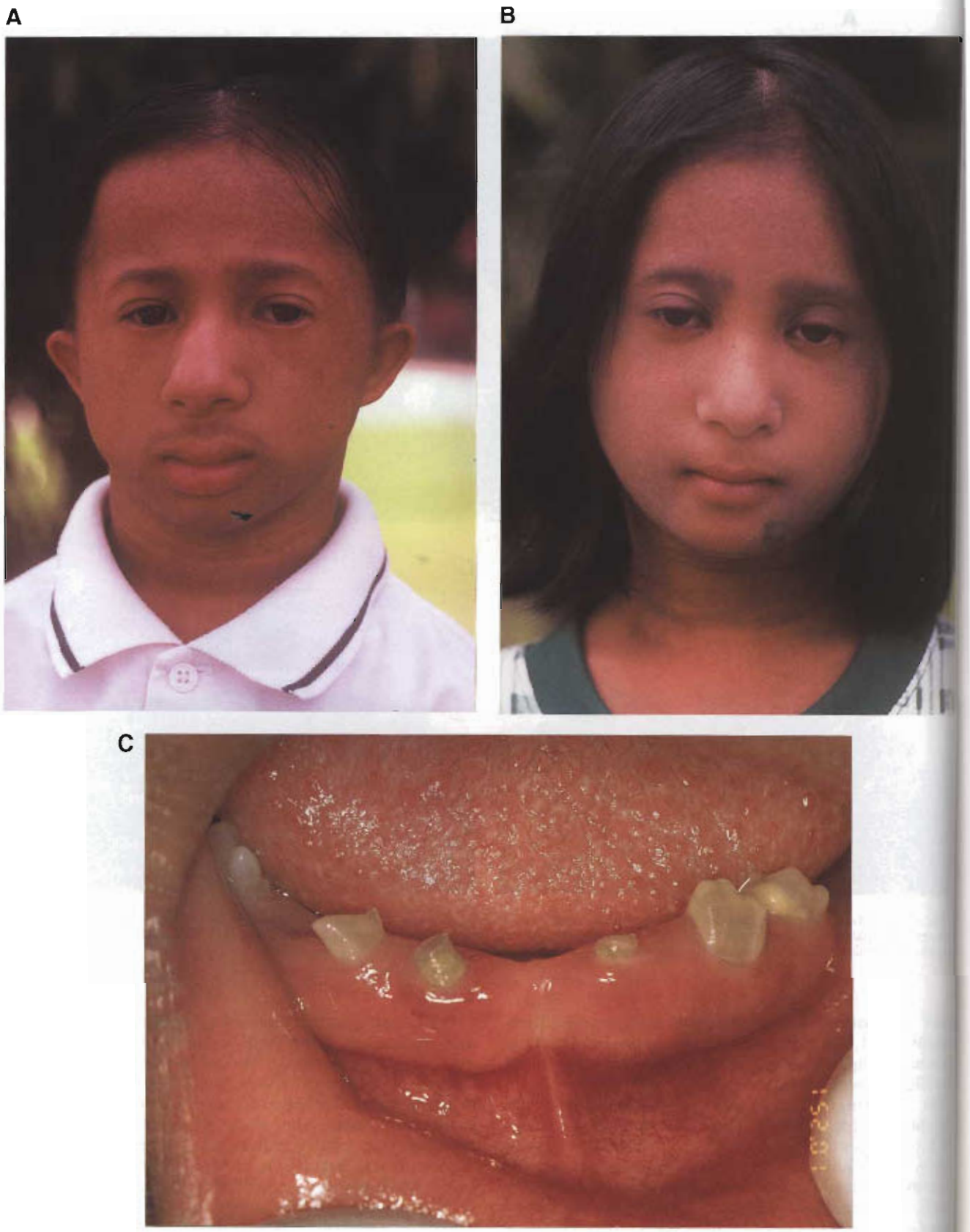


Fig. 2. **A:** Patient 1. **B:** Patient 2. Note large and prominent noses and small pinnae. Scalp hair is thin. **C:** Small and opalescent incisors with severe attrition. **D:** Opalescent teeth. Severe microdontia and malformation of mandibular premolar. Mandibular canine has prominent cingulum.

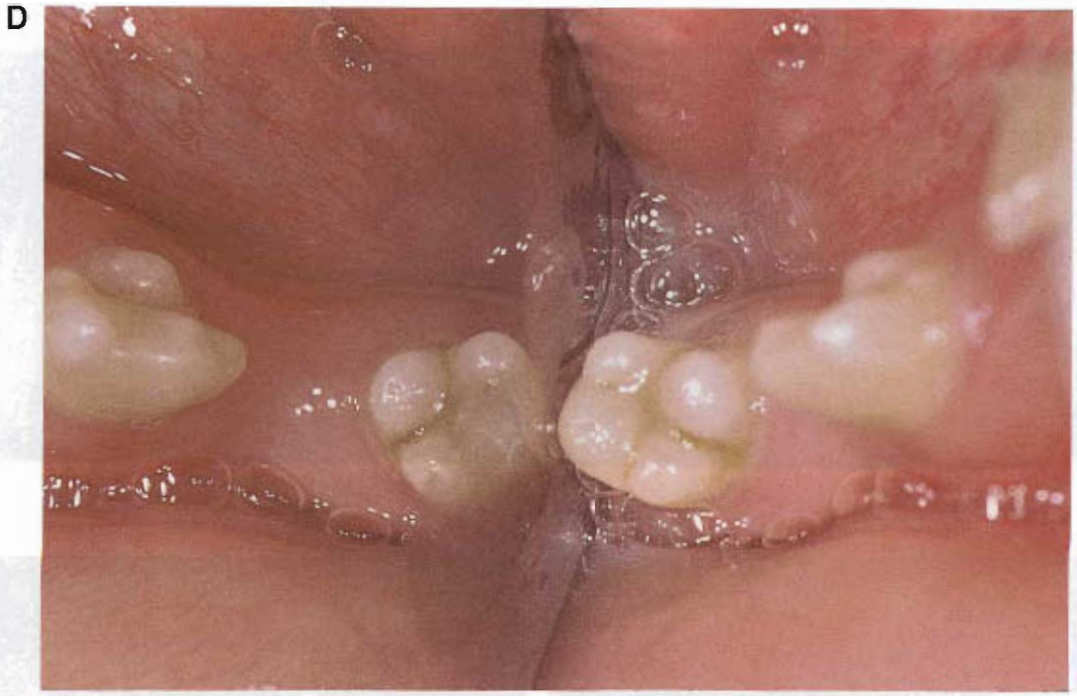


Fig. 2. (*Continued*)

contracture of the distal interphalangeal joints (IPJ) of the toes was observed (Fig. 4A). Flexion contracture of all distal IPJ was observed.

Radiographic examination showed delayed dental development, rootless molars, short-rooted incisors, and narrow root canals of incisors. Like that of his sister, the dentin of the incisors was less radiopaque than those of molars. The crowns of the molars appeared tapered occluso-cervically. Cortical bone of the alveolar process was not evident. Severe hypoplasia of the alveolar process was observed. There was hardly any bone surrounding the roots of the teeth (Fig. 1B and C). Lateral cephalographs at age 14 and 18 years showed digital marking of the skull, progressive alveolar bone loss, progressive loss of teeth, large sella turcica, and long posterior clinoid process (Fig. 5A and B).

Radiographs showed long, straight, and slender clavicles, and hypoplastic scapulae. There were 12 ribs on each side (Fig. 6A). The radius and ulna were slender. The ulna was slightly bowed. Hand radiographs taken at ages 14 and 18 years showed slender fourth and fifth metacarpals (Fig. 3A and B). The trapezium and scaphoid had angular appearance. The radiograph taken at age 14 years showed ivory epiphyses at the middle and distal phalanges of fingers 3 and 4, the distal phalanges of fingers 5, and the proximal phalanx of the right thumb. Cone-shaped epiphyses were observed at the proximal phalanges of fingers 2–5 (Fig. 3A). Ivory epiphyses and cone-shaped epiphyses were not apparent in the radiograph taken at age 18 years (Fig. 3B). Brachymesophalangy was observed. The distal phalanges of the second fingers appeared short (Fig. 3A and B). Foot radiograph showed abnormally long metatarsals and proximal phalanges of toes 2. Distal symphalangism of the fifth toes was noted (Fig. 4B). Pelvic radiograph showed tall and slender pelvic bone with shallow acetabula (Fig. 4D).

Patient 2

Patient 2 was a 16-year-old girl. She was the younger sister of patient 1 (Figs. 1A and 2A and B). Her birth weight was 1,000 g. She started menstruation and pubic hair at ages 13 and 15 years, respectively. Menstruation was reported to be irregular. Like her brother, she had normal intellectual development. On examination, she was proportionately short. Her height, weight, and OFC were 96 cm (<3rd centile), 12 k (<3rd centile), and 41 cm (<3rd centile), respectively. Like that of her brother, the scalp hair, especially at the vertex, was dry and thin. The nose was large with prominent nasal bridge. The pinnae were small. Hearing was normal. One her left thigh and chin there were large areas of café-au-lait spots (Fig. 2B). The chest was narrow and the elbows bent. Fingers were proportionately short. There was limitation of abduction of the left leg. Toes were unremarkable. Like those of her brother, all teeth were small and opalescent. Mandibular premolars were severely small and malformed (Fig. 1B and C).

Radiographs showed narrow root canals of the incisors, short-rooted incisors, rootless molars, and an unerupted right mandibular premolar. The body of mandible was narrow. The crowns of the molars appeared tapered occluso-cervically (Fig. 1C). Lateral cephalograph showed

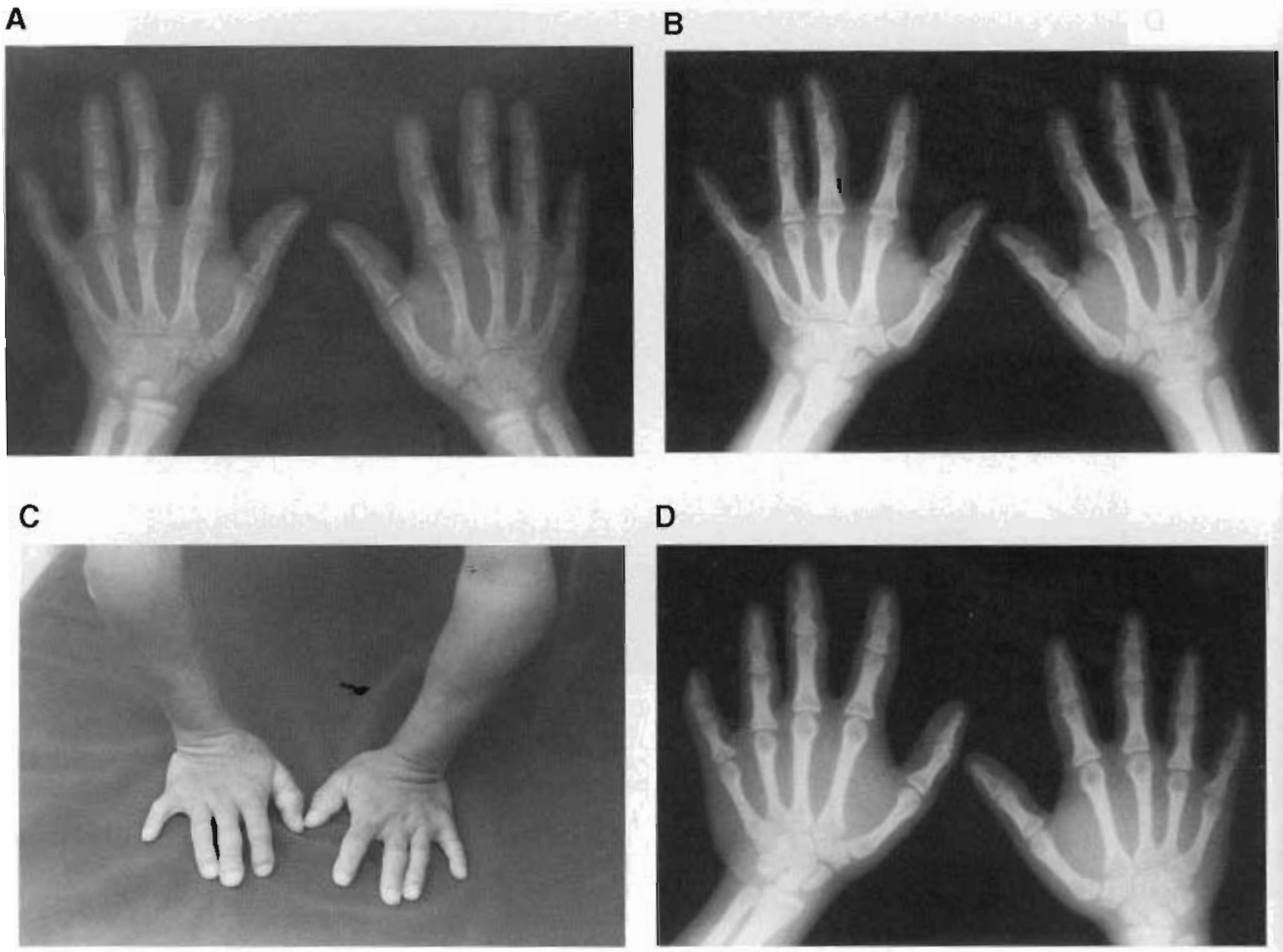


Fig. 3. **A:** Hand radiograph of patient 1 at age 14. Note ivory and cone-shaped epiphyses. Trapezium and scaphoid have angular appearance. **B:** Hand radiograph of patient 1 at age 18. Absence of ivory and cone-shaped epiphyses. Brachymesophalangy and short distal phalanx of the right second finger. Metacarpals 4 and 5 are slender. **C:** Patient 1. Brachydactyly and bent elbows. **D:** Patient 2. Hand radiograph at age 16. Brachymesophalangy is noted. Trapezium and scaphoid have angular appearance. Metacarpals 4 and 5 are slender.

large sella turcica, long posterior clinoid process, and progressive alveolar bone loss. Digital marking of the skull was observed (Fig. 5C and D). Chest radiograph showed long straight and slender clavicles, and hypoplastic scapulae. There were 12 ribs on each side (Fig. 6B). Radiograph of the elbows was unremarkable.

Hand radiographs were taken at ages 12 and 16 years. At age 12, brachymesophalangy of fingers 2–5 and ivory epiphyses at the proximal phalanges of thumbs were observed. Cone-shaped epiphyses were seen at the proximal phalanges of fingers 2 and 3 bilaterally. Like those of her brother, scaphoid and trapezium were angular in shape and metacarpals 4 and 5 appeared slender (Fig. 3D). Pelvic radiograph showed superiorly dislocated left proximal femur and slender femoral shafts (Fig. 4D). Foot radiograph showed short proximal phalanges of the great toes, long metatarsals of the second toes, and flexion contracture of toes 3–5. Brachymesophalangy of toes 2 and 3 was observed. Distal symphalangism of toes 4 and 5 was noted.

DISCUSSION

The major manifestations found in the affected brother and sister were proportionate primordial short stature, microcephaly, severe microdontia, opalescent teeth, rootless molars, severely hypoplastic alveolar bone, distal symphalangism of toes, long second toes, and long, slender, and straight clavicles. Anomaly of tooth size has been described in patients with primordial short stature. Microdontia has been reported in Seckel syndrome [Cervenka et al., 1979] and MOPD [Majewski and Goecke, 1998]. Some patients with those syndromes have been reported to have large teeth [Seckel, 1960; Majewski and Goecke, 1982; Majewski, 1992]. The combination of microdontia, shortness of roots, delayed dental development, and hypoplastic alveolar processes has been described in MOPD [Lin et al., 1995]. The presence of opalescent teeth, severe microdontia, and malformation of mandibular premolars distinguish the current patients from having that particular syndrome.

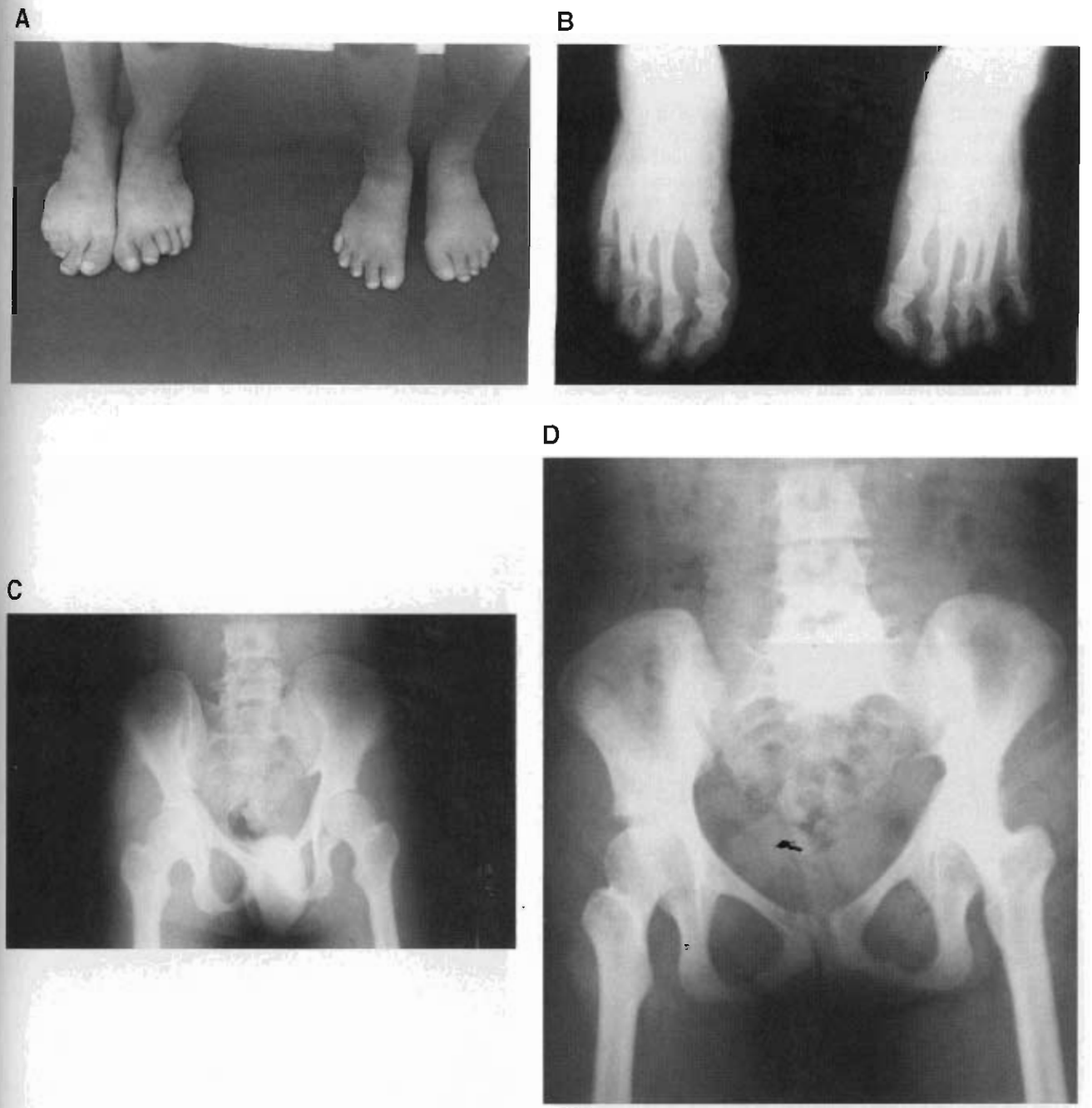


Fig. 4. **A:** From left to right, feet of patients 1 and 2. Feet of patient 1 shows long second toes and lateral deviation of toes 1 and 2. **B:** Patient 1. Very long metatarsals 2 and proximal phalanges 2 of patient 1. **C:** Patient 1. Slender pelvic bone, shallow acetabula, and femoral shafts. **D:** Patient 2. Tall and slender iliac bones and slender ischium and pubic bones, and shallow acetabula. Superiorly dislocated left femoral head.

Opalescent teeth refers to teeth with a blue-gray to amber-brown discoloration. The crowns of the teeth are unusually translucent. It can be seen as an isolated anomaly in hereditary opalescent dentin or dentinogenesis imperfecta type 2 (DI2) and dentin dysplasia type 2 (DTDP2) [Ranta et al., 1993]. Syndromic opalescent teeth have been reported in many syndromes [Kantaputra, 2001a], including osteogenesis imperfectas [O'Connell and Marini, 1999], Goldblatt syndrome [Goldblatt et al., 1991], Schimke-immunoosseous dysplasia [Fonseca, 2000], and a type of Ehlers-Danlos syndrome [Komorowska et al., 1989]. Opalescent and rootless incisors and molars have been described in a girl with disproportionate short stature, delayed growth and development, short neck, protruded abdomen, kyphosis, platyspondyly, hypoplastic acetabulum, broad nasal bridge, and hypodontia [Kantaputra, 2001b]. None of the reported patients either with proportionate or disproportionate primordial short stature had opalescent or rootless teeth. Rootless teeth have been reported

in dentin dysplasia type 1 (DTDP1). Tooth crowns of teeth with DTDP1 are not opalescent [Ranta et al., 1993]. This can distinguish teeth of the reported patient from having DTDP1.

Having ivory epiphyses and cone-shaped epiphyses in both patients was an interesting combination. Hand radiographs taken 4 years apart demonstrated that most of ivory epiphyses disappear as the patients aged. These age-related phenomena are similar to those of Seckel syndrome [Poznanski et al., 1983]. The reported patients share many features with an MOPD patient who was reported to have long and slender clavicles, ivory epiphyses, cone-shaped epiphyses, dislocated hip, with abnormal dental development [Shebib et al., 1991]. The panoramic radiograph of that particular patient and ours showed similar features consisting of microdontia, rootless molars, and severely hypoplastic alveolar process [Shebib et al., 1991]. Disproportionate short stature, synostosis of sagittal suture, short neck, short and bowed forearms, flared distal metaphyses of the femora, hypoplastic pelvis, and delayed intellectual development distinguish that patient from the current patients. Large sella turcica found in the current patients have been seen in MOPD, type Caroline Cachami [Majewski, 1992; Boscherini et al., 1996]. This leaves the question whether the basic defect of this new syndrome involves the pituitary gland. Digital marking of the skulls in both patients is frequently found in patients with craniosynostosis, which they did not appear to have [Howard et al., 1997]. Hypo- and hyperpigmentation of skin found in both patients might reflect mosaic variegated aneuploidy (MVA). However, since they did not follow Blanchko lines and the lack of hypoplasia of brain, Dandy-Walker malformations, seizures, hypotonia, and Wilms tumor in the current patients, the possibility of causing by MVA is not likely [Chitayat et al., 1990; Kajii et al., 1998; Kawame et al., 1999].

The reported patients appear to have a newly recognized syndrome. The features that make this syndrome distinct from the previously described syndromes include hypo- and hyperpigmentation of skin, opalescent teeth, rootless molars, severely hypoplastic alveolar processes, long second toes, and distal symphalangism of toes.

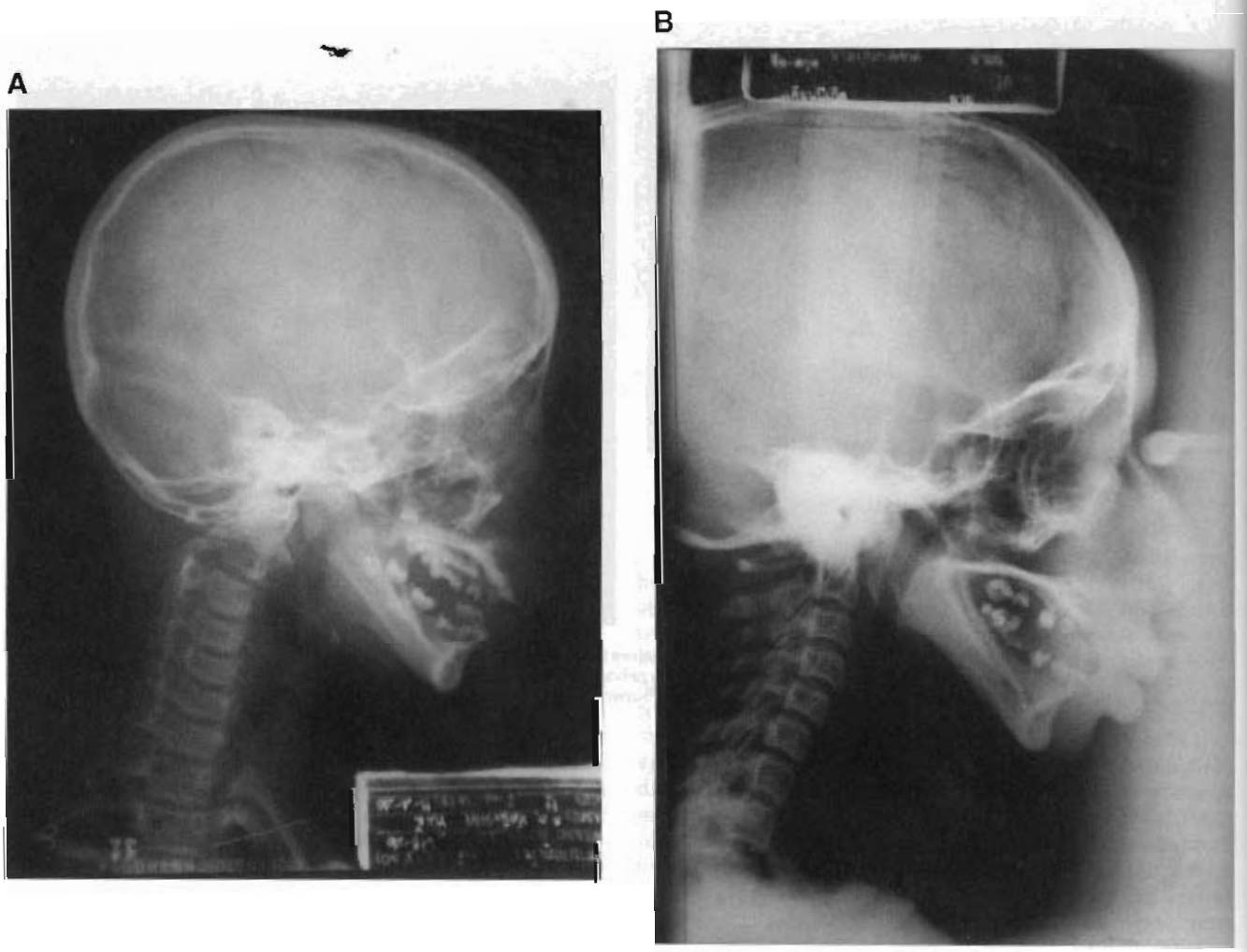
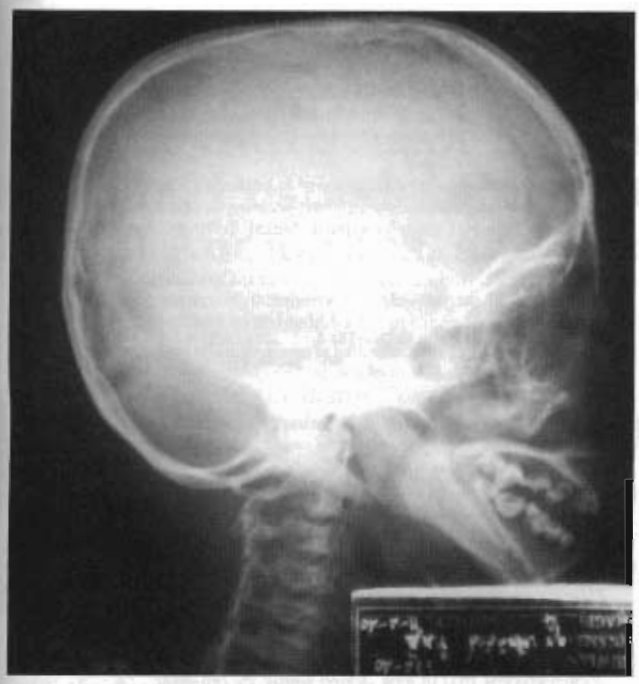
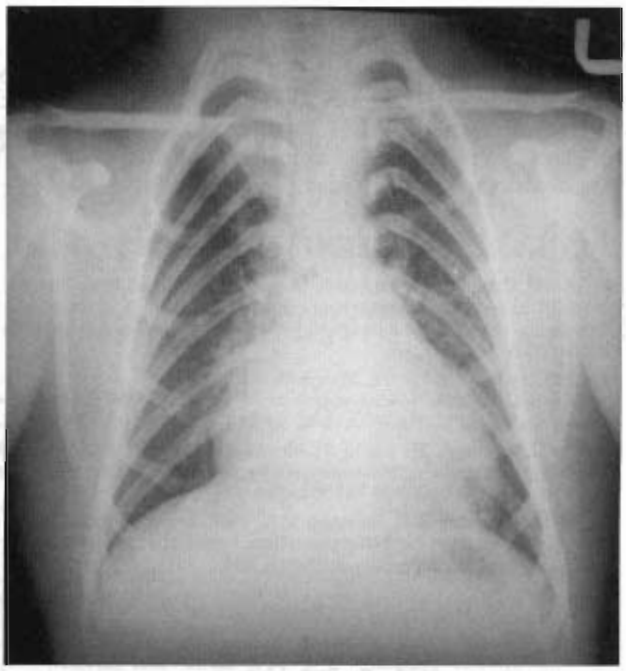
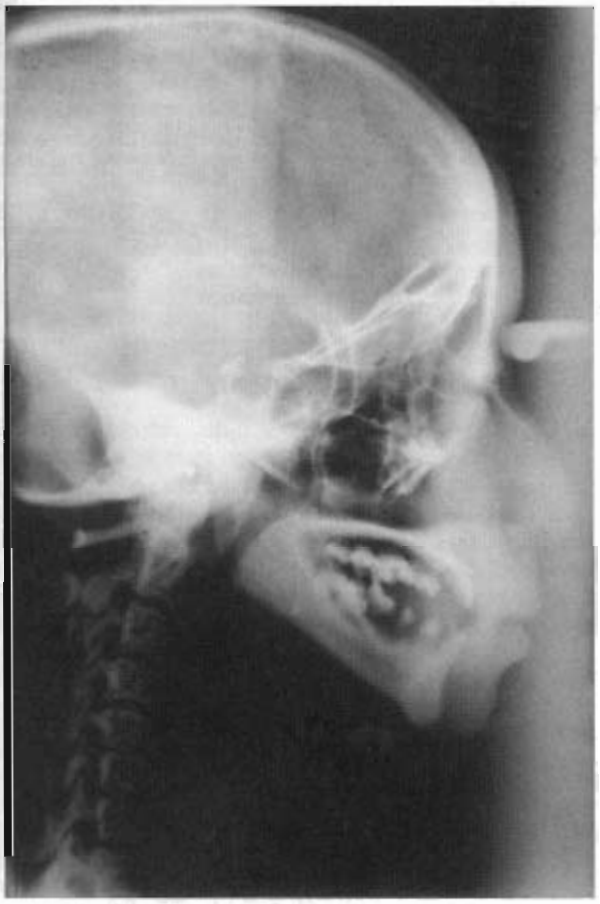


Fig. 5. **A** and **B:** Lateral radiographs of patient 1 at ages 14 and 18, respectively. **C** and **D:** Lateral radiographs of patient 2 at ages 12 and 16, respectively. Note short-rooted incisors, rootless molars, and large sella turcica with long posterior clinoid processes. Progressive alveolar bone loss is seen.







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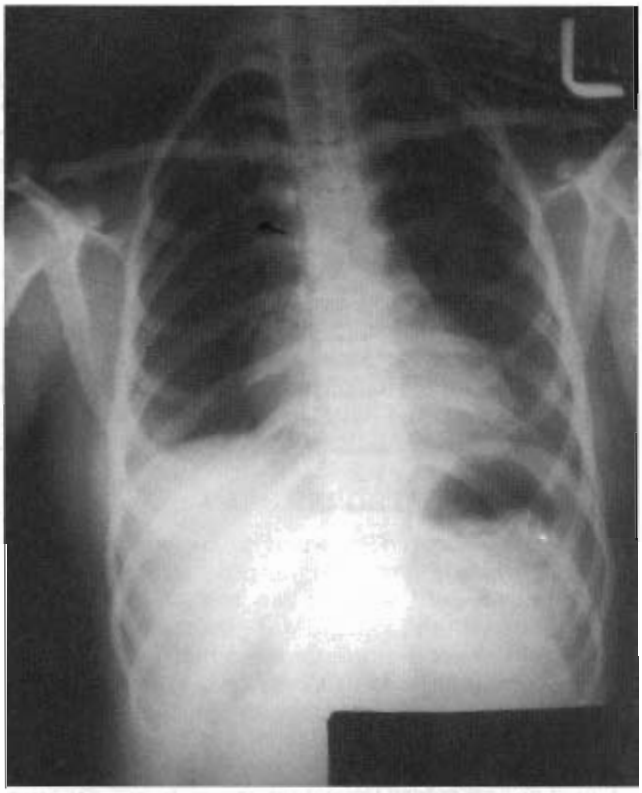

Fig. 6. A and B: Chest radiographs of patients 1 and 2, respectively. Note narrow chests, long, straight and slender clavicles, and hypoplastic scapulae.

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REFERENCES

Boscherini B, Colabucci F, Galasso C, Marietti G, Cappa M, Pasquimo AM. 1996. Clinical and roentgenographic findings in a patient with primordial microcephalic dwarfism type Caroline Crachami. Am J Med Genet 66:269–272.

Buebel MS, Salinas CF, Pai GS, Macpherson RI, Greer MK, Perz-Comas A. A new Seckel-like syndrome of primordial dwarfism. 1996. Am J Med Genet 64:447–452.

Cervenka J, Tsuchiya H, Ishiki T, Suzuki M, Mori H. 1979. Seckel's dwarfism: analysis of chromosome breakage and sister chromatid exchanges. Am J Dis Child 133:555–556.

Chitayat D, Friedman JM, Johnston MM. 1990. Hypomelanosis of Ito-a nonspecific marker of somatic masaicism: report of a case with trisomy 18 mosaicism. Am J Med Genet 35:422–424.

Fonseca MA. 2000. Dental findings in the Schimke immuno-osseous dysplasia. Am J Med Genet 93:158–160.

Goldblatt J, Carman P, Sprague P. 1991. Unique dwarfing, spondylometaphyseal skeletal dysplasia, with joint laxity, and dentinogenesis imperfecta. Am J Med Genet 39:170–172.

Howard T, Paznekas WA, Green ED, Chiang LC, Ma N, De Luna RSO, Delgado CG, Gonzalez-Ramos M, Kline AD, Jabs EW. 1997. Mutations in wwist, a basic helix-loop-helix transcription factor, in Saethre-Chotzen syndrome. Nature Genet 15:36–41.

Kajii T, Kawai T, Takumi T, Misu H, Mabuchi O, Takahashi Y, Tachino M, Nihei F, Ikeuchi T. 1998. Mosaic variegated aneuploidy with multiple congenital abnormalities: homozygosity for total premature chromatid separation trait. Am J Med Genet 78:245–249.

Kantaputra PN. 2001a. Dentinogenesis imperfecta-associated syndromes. Am J Med Genet 104:75–78.

Kantaputra PN. 2001b. A newly recognized skeletal dysplasia with opalescent and rootless teeth. Oral Surg Oral Pathol Oral Med Oral Radiol Endodont 92:303–307.

Kawame H, sugio Y, Fuyama Y, Hayashi Y, Suzuki H, Kyrosawa K, Maekawa K. 1999. Syndrome of microcephaly, Dandy-Walker malformation, and Wilms tumor caused by mosaic variegated aneuploidy with premature centromere division (PCD): report of a new case and review of the literature. J Hum Genet 44:219–224.

Komorowska A, Rozynkova D, Lee KW, Renouf DV, Nicholls AC, Mackenzie J, Pope FM. 1989. A Polish variant of isolated dentinogenesis imperfecta with generalized connective tissue defect. Br Dent J 167: 239–243.

Lin HJ, Sue GY, Berkowitz CD, Brasel JA, Lachman RS. 1995. Microdontia with severe microcephaly and short stature in two brothers: osteodysplastic primordial dwarfism with dental findings. Am J Med Genet 58:136–142.

Majewski F. 1992. Invited editorial comment: Caroline Crachami and the delineation of osteodysplastic primordial dwarfism type III, an autosomal recessive syndrome. Am J Med Genet 44:203–209.

Majewski F, Goecke T. 1982. Studies of microcephalic primordial dwarfism I: approach to a delineation of the Seckel syndrome. Am J Med Genet 12: 7–21.

Majewski F, Goecke TO. 1998. Microcephalic osteodysplastic primordial dwarfism type II: report of three cases and review. Am J Med Genet 80:25–31.

Majewski F, Ranke M, Schinzel A. 1982a. Studies of microcephalic primordial dwarfism II: the osteodysplastic type II of primordial dwarfism. Am J Med Genet 12:23–35.

Majewski F, Stoeckenius M, Kemperdick H. 1982b. Studies of microcephalic primordial dwarfism III: an intrauterne dwarf with platyspondyly and anomalies of pelvis and clavicles-osteodysplastic primordial dwarfism type III. Am J Med Genet 12:37–42.

Meinecke P, Passarge E. 1991. Microcephalic osteodyspalstic primordial dwarfism type I/III in sibs. J Med Genet 28:795–800.

O'Connell AC, Marini JC. 1999. Evaluation of oral problems in an osteogenesis imperfecta population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 87:189–196.

Poznanski AK, Iannaccone G, Pasquino AM, Boscherini B. 1983. Radiologic findings in the hand in Seckel syndrome (bird-headed dwarfism). Pediatr Radiol 13:19–24.

Ranta H, Lukinmaa PL, Waltimo J. 1993. Heritable dentin defects: nosology, pathology, and treatment. Am J Med Genet 45:193–200.

Seckel HPG. 1960. Bird-headed dwarfs: studies in developmental anthropology including human populations. Springfield, IL: Charles C. Thomas.

Shebib S, Hugosson C, Sakati N, Nyhan WL. 1991. Osteodysplastic variant of primordial dwarfism. Am J Med Genet 40:146–150.

American Journal of Medical Genetics 120A:381–385 (2003)

A New Syndrome of Symphalangism, Multiple Frenula, Postaxial Polydactyly, Dysplastic Ears, Dental Anomalies, and Exclusion of *NOG* and *GDF5*

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A Thai girl with a unique combination of limb and craniofacial anomalies is reported. Manifestations include blepharoptosis; prominent nose; hypodontia; multiple, hyperplastic frenula; and dysplastic ears. Limb anomalies include short stature, postaxial polydactyly of both hands and the left foot, proximal and distal symphalangism of fingers, and congenital absence of the distal phalanges of toes 2–5. Mutation analyses of *NOG* and *GDF5*, the genes responsible for symphalangism-related syndromes, were negative. © 2003 Wiley-Liss, Inc.

KEY WORDS: absent distal phalanges; blepharoptosis; hypodontia; microdontia; one-rooted molar; short stature

INTRODUCTION

Symphalangism, characterized by fusion of the phalanges, is a rare anomaly. Proximal and distal symphalangism are defined as fusion between the proximal and middle phalanges and between the middle and distal phalanges, respectively. Proximal symphalangism is more common than distal and both have been reported in association with many syndromes such as proximal symphalangism (SYM1; OMIM 185800), facio-audio-symphalangism syndrome, tarsal-carpal coalition syndrome (TCCS; OMIM 186570), and multiple synostosis syndrome (SYMS1; OMIM 186500). Heterozygous mutations of the *NOG* gene are known to cause these proximal symphalangism-associated syndromes [Gong et al., 1999; Dixon et al., 2001]. Multiple synostosis, type 2, (SYNS2) is caused by a missense mutation in growth/differentiation factor 5 (*GDF5*) or cartilage-derived morphogenetic protein-1 (*CDMP1*) [Akarsu et al., 1999].

Here, we describe a Thai patient with a unique combination of limb and craniofacial anomalies. Manifestations include blepharoptosis; prominent nose; hypodontia; multiple, hyperplastic frenula; and dysplastic ears. Limb anomalies include short stature, postaxial polydactyly of both hands and the left foot, and proximal and distal symphalangism of the fingers. *NOG* and *GDF5* are known to play crucial roles in normal joint development [Akarsu et al., 1999; Gong et al., 1999; Tsumaki et al., 2002]. Because our patient had symphalangism, we thought that the phenotype might be caused by a mutation in *NOG* or *GDF5*. However, molecular studies did not identify any mutations in those genes.

CASE REPORT

The patient was a 12-year-old Thai girl, who was the first child of non-consanguineous, healthy parents (Fig. 1A). The patient was noted to have disproportionately short stature. Intelligence was normal. Her height, weight, and head circumference were 138 cm (3rd–10th centile), 36 kg (50th centile), and 51.5 cm (50th–75th centile), respectively. Hair and skin appeared normal. She had dolichocephaly, bilateral blepharoptosis, highly arched eyebrows, and sloping shoulders. Broad, prominent nasal bridge was observed. The philtrum was broad. The lower part of helices and lobules were hypoplastic (Fig. 1A). Hearing and echocardiography were unremarkable.

Oral examination showed multiple, hyperplastic frenula and highly arched palate (Fig. 1B). The primary

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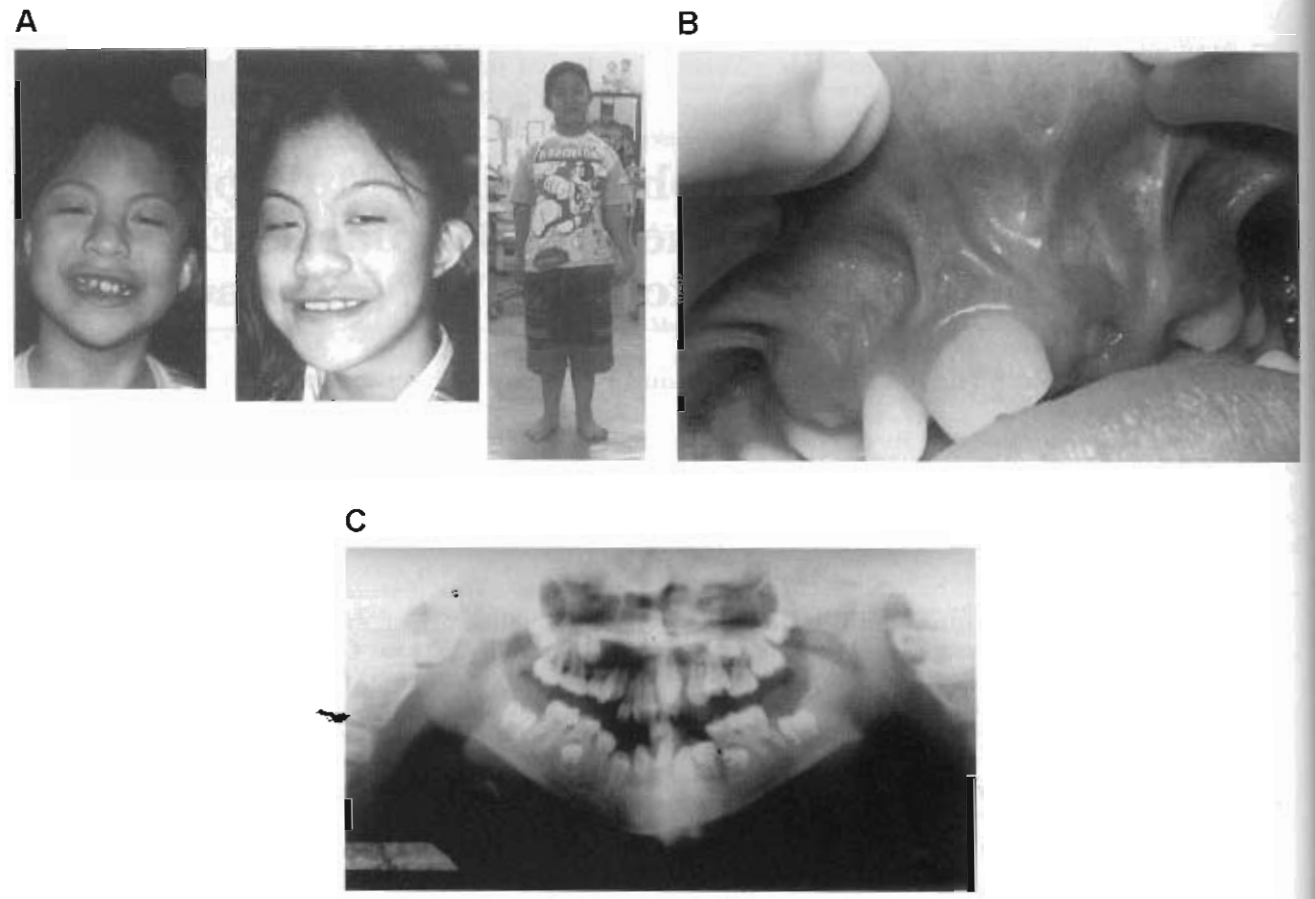

Fig. 1. A: Patient at the ages of 8, 11, and 12 years. B: Large maxillary permanent central incisor. Multiple, hyperplastic frenula. C: Panoramic radiograph at the age of 8 years showed hypodontia, short-rooted incisors, and premolars.

and permanent molars were small. The shape of the mandibular second premolar and first permanent molar resembled that of the mandibular second primary molar and mandibular second permanent molar, respectively. The maxillary first permanent molars and all second permanent molars had one root. Congenital absence of the maxillary permanent lateral incisors, and mandibular permanent central incisors were noted (Fig. 1C).

The hands were small with bilateral postaxial polydactyly. The polydactylous fingers could not be moved voluntarily. Brachydactyly and tapering of all fingers were noted (Fig. 2A). Flexion at the interphalangeal joint (IPJ) was possible only at the distal interphalangeal joint (DIPJ) of the third fingers, making it impossible for her to make a fist. No cutaneous creases were observed over the dorsum of the affected joints. Fingernails were unremarkable (Fig. 2A). Roentgenograms of the hands at the age of 12 years showed normal appearance of the thumbs, short fourth and fifth metacarpals, and fusion of proximal interphalangeal joint (PIPJ) and DIPJ of fingers 2, 4, and 5. The DIPJ of the third fingers appeared normal. All phalanges of the polydactylous fingers were fused with rudimentary metacarpals. Metacarpophalangeal joints (MPJ) of the second and third fingers were narrow bilaterally (Fig. 2B). Hand radiography at the age of 7 years showed brachymesophalangy of fingers 2–5. Cone-shaped epiphyses of the middle phalanges 2–5 were observed. The PIPJ of fingers 2–5 were narrow. The DIPJ of all fingers were wider than the proximal ones and narrower than those seen at the age of 12 years. Symphalangism was seen only at the PIPJ of the polydactylous fingers.

All toes were short. Postaxial polydactyly was found on the left foot; it could not be moved voluntarily. The first toes were broad with slightly dysplastic nails (Fig. 3A). Radiograph of the feet showed congenital absence of the distal phalanges of toes 2–5. The tufts of the distal phalanges of both great toes were not evident. The polydactylous toe appeared to have two phalanges but its metatarsal was absent (Fig. 2B). The metatarsal and tarsal bones appeared normal. A pelvic radiograph was unremarkable.

MUTATIONAL ANALYSIS OF *NOG* AND *GDF5*

Genomic DNA was isolated from peripheral blood samples for mutation analysis of *NOG* and *GDF5*. *NOG* and *GDF5* contain only 1 and 9 coding exons, respectively. Amplification of the entire coding sequence of *NOG* was performed using primers NOG1/NOG5. PCR

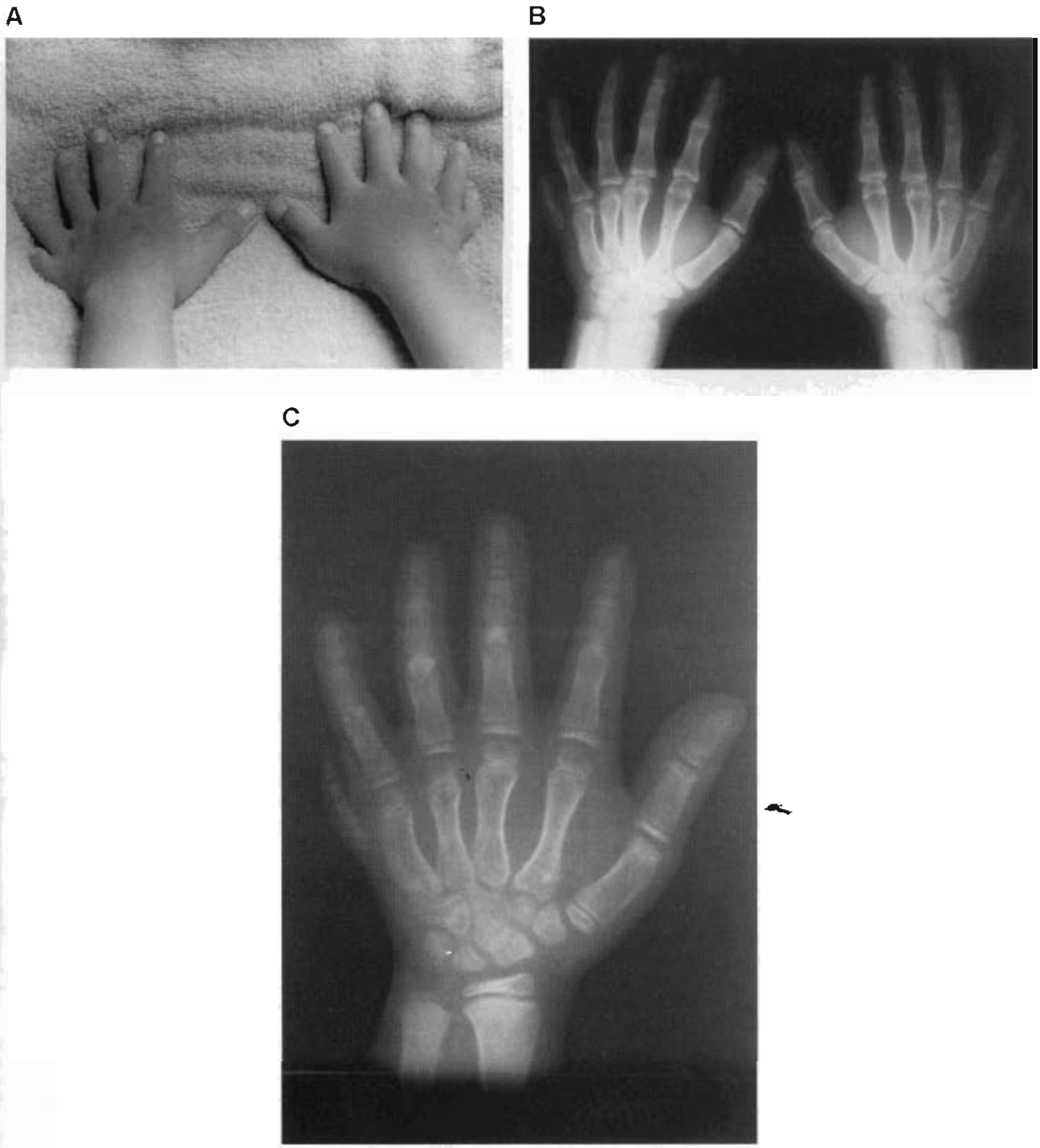

Fig. 2. A: Postaxial polydatyly of hands. B: PA radiograph of hands at the age of 12 years. Note proximal and distal symphalangism. C: PA radiograph at the age of 7 years. Short middle phalanges of all fingers. All IPJ spaces are visible except for that of the proximal IPJ of the polydactylous one.

conditions for NOG have been described elsewhere [Gong et al., 1999]. Direct sequencing did not identify a pathogenic mutation in *NOG* and *GDF5*.

DISCUSSION

Symphalangism, a striking finding in this patient, is rare. Proximal symphalangism-associated syndromes are caused by heterozygous mutations in *NOG* [Gong et al., 1999]. Congenital stapes ankylosis syndrome with no symphalangism has recently been found to be caused by heterozygous nonsense and frameshift mutations in *NOG* [Brown et al., 2002]. Noggin, the protein product of *NOG*, is essential for human joint morphogenesis. It binds and inactivates members of the TGFβ superfamily, such as BMP4 [Brunet et al., 1998; Gong et al.,

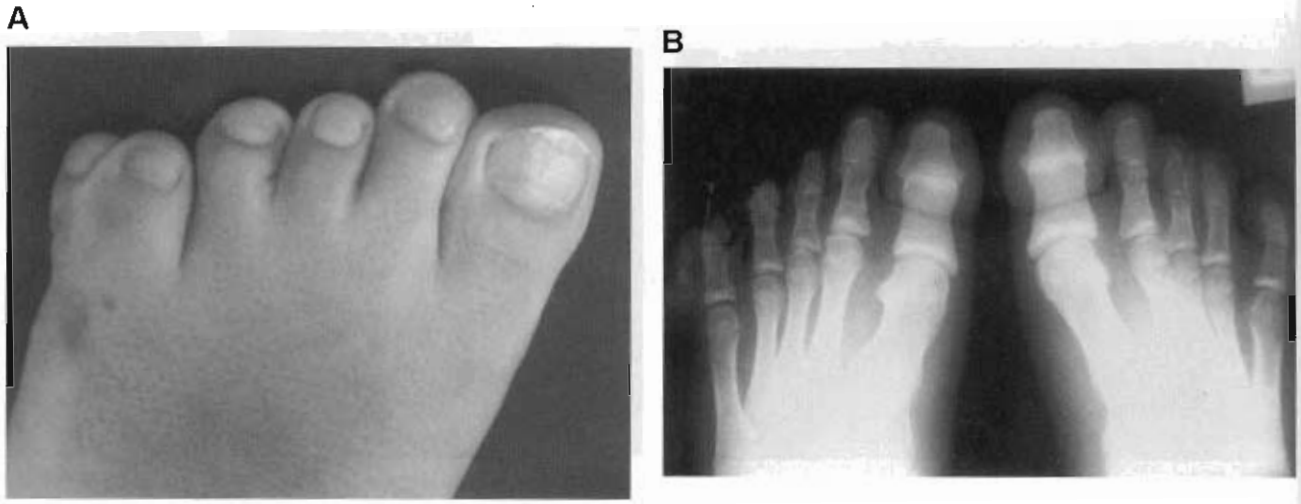

Fig. 3. A: Short toes. Postaxial polydactyly of the left foot. B: Short and broad distal phalanges of the great toes. Proximal IPJ spaces are narrow. Absence of the distal phalanges of toes 2–5. The polydactylous toe lacks metatarsal bone.

1999]. Patients with facio-audio-symphalangism syndrome and multiple synostosis syndrome, unlike those of proximal symphalangism syndrome, have facial manifestations, including a broad hemicylindrical nose, hypoplastic nasal alae, and a short upper lip [da-Silva et al., 1984; Hurvitz et al., 1985].

Symphalangism of both PIPJ and DIPJ in the same patient as reported here is very rare. Comparing the hand radiographs at the age of 7 and 12 years shows that symphalangism proceeds progressively in ulnar-radial [Strasburger et al., 1965; Polymeropoulos et al., 1995; Dixon et al., 2001] and proximo-distal directions [Krakow et al., 1998]. Proximal symphalangism, facio-audio-symphalangism syndrome, symphalangism with tarsal and carpal coalition, and multiple synostosis syndrome may have distal symphalangism as a rarely associated anomaly [Strasburger et al., 1965; Geelhoed et al., 1969; da-Silva et al., 1984; Drawbert et al., 1985; Hurvitz et al., 1985]. Similarly, distal symphalangism, as a distinct autosomal dominant disorder, may rarely have proximal symphalangism as an associated anomaly [Poush, 1991]. Although no mutations were found in *NOG* and *GDF5*, symphalangism in our patient could have resulted from overactivity of BMPs; increased BMP activity results in excess cartilage and failure in joint formation [Dixon et al., 2001; Tsumaki et al., 2002].

Morimoto et al. [2001] reported a patient sharing many similarities with our patient: proximal symphalangism of fingers 2–5, blepharoptosis, malformed ears, short stature, microdontia, high-arched eyebrows, and a prominent nose. However, distal symphalangism; multiple, hyperplastic frenula; hypodontia; malformed molars; polydactyly; absent distal phalanges of toes; absence of mental retardation, chronic renal failure, and hearing loss in our patient distinguish her from having the same syndrome reported by Morimoto et al. [2001]. Finger symphalangism of all IPJ, except for the third DIPJ found in our patient has been described in 9 members of a family [Moumoumi et al., 1991]. Distal symphalangism of the third finger appears to be the rarest form of the symphalangism [Letts et al., 1999]. Thus, we think the pathogenesis in our case may be different from others. Although some of the manifestations in our patient can be found in Ellis–van Creveld syndrome [da-Silva et al., 1980], Pallister–Hall syndrome [Biesecker et al., 1996], or oral-facial-digital syndromes [Toriello, 1993], the pattern of anomalies in our patient is at variance with these conditions.

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REFERENCES

Akarsu N, Haque MF, Ahmad W, et al. 1999. Multiple synostosis type 2 (SYNS2) maps to 20q11.2 and caused by a missense mutation in growth/ differentiation factor 5 (*GDF5*). Am J Hum Genet (Suppl).65:A281.

Biesecker LG, Abbott M, Allen J, Clericuzio C, Feuillan P, Graham JM Jr, Hall J, Kang S, Olney AH, Lefton D, Neri G, Peters K, Verloes A. 1996. Report from the workshop on Pallister–Hall syndrome and related phenotypes. Am J Med Genet 65:76–87.

Brown DJ, Kim TB, Petty EM, Downs CA, Martin DM, Strouse PJ, Moroi SE, Milunsky JM, Lespeerance MM. 2002. Autosomal dominant stapes ankylosis with broad thumbs and toes, hyperopia, and skeletal anomalies is caused by heterozygous nonsense and frameshift mutations in *NOG*, the gene encoding noggin. Am J Hum Genet 71:618–624.

Brunet LJ, McMahon JA, McMahon AP, Harland RM. 1998. Noggin, cartilage morphogenesis, and joint formation in the mammalian skeleton. Science 280:1455–1457.

da-Silva EO, Janovitz D, De Albuquerque SC. 1980. Ellis–van Creveld syndrome: Report of 15 cases in an inbred kindred. J Med Genet 17:349–356.

da-Silva EO, Filho SM, de Albuquerque SC. 1984. Multiple synostosis syndrome: Study of a large Brazilian kindred. Am J Med Genet 18:237–247.

Dixon ME, Armstrong P, Stevens DB, Bamshad M. 2001. Identical mutations in *NOG* can cause either tarsal/carpal coalition syndrome or proximal symphalangism. Genet Med 3:349–353.

Drawbert JP, Stevens DB, Cadle RG, Cadle RG, Hall BD. 1985. Tarsal and carpal coalition and symphalangism of the Furhmann type. J Bone Joint Surg 67A:884–889.

Geelhoed GW, Neel JV, Davidson RT. 1969. Symphalangism and tarsal coalitions: A hereditary syndrome. J Bone Joint Surg 51B:278–289.

Gong Y, Krakow D, Marcelino J, Wilkin D, Chitayat D, Babul-Hirji R, Hudgins L, Cremers CW, Cremers FPM, Brunner HG, Reinker K, Rimoin DL, Cohn DH, Goodman FR, Reardon W, Patton M, Francomano CA, Warman ML. 1999. Heterozygous mutations in the gene encoding noggin affect human joint morphogenesis. Nat Genet 21:302–304.

Hurvitz SA, Goodman RM, Hertz M, Katznelson MBM, Sack Y. 1985. The facio-audio-symphalangism syndrome: Report of a case and review of the literature. Clin Genet 28:61–68.

Krakow D, Reinker K, Powell B, Cantor R, Priore MA, Garber A, Lachman RS, Rimoin D, Cohn DH. 1998. Localization of a multiple synostoses-syndrome disease gene to chromosome 17q21-22. Am J Hum Genet 63:120–124.

Letts M, Davidson D, Beaule P. 1999. Symphalangism in children. Clin Orthop 366:178–185.

Morimoto J, Kaneoka H, Murata T, Sato YN, Ogahara S, Hirose S, Naito S, Naritomi K. 2001. Proximal symphalangism with "coarse" facial appearance, mixed hearing loss, and chronic renal failure: New *malformation syndrome? Am J Med Genet 98:269–272.*

Moumoumi H, Mayelo V, Anthonioz P. 1991. Familial symphalangism syndrome transmitted through five generations. Genet Couns 2:139–146.

Polymeropoulos MH, Poush J, Rubenstein JR, Francomano CA. 1995. Localization of the gene (*SYM1*) for proximal symphalangism to human chromosome 17q21-q22. Genomics 27:225–229.

Poush JR. 1991. Distal symphalangism: A report of two families. J Hered 82:233–238.

Strasburger AK, Hawkins MR, Eldridge R, Hargrave RL, McKusick VA. 1965. Symphalangism: Genetic and clinical aspects. Bull Johns Hopkins Hosp 117:108–127.

Toriello HV. 1993. Oral-facial-digital syndrome, 1992. Clin Dysmorphol 2:95–105.

Tsumaki N, Nakase T, Miyaji T, Kakiuchi M, Kimura T, Ochi T, Yoshikawa H. 2002. Bone morphogenetic protein signals are required for cartilage formation and differently regulate joint developing during skeletogenesis. J Bone Miner Res 17:898–906.

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Heterozygous Mutation in the SAM Domain of p63 Underlies Rapp-Hodgkin Ectodermal Dysplasia

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RESEARCH REPORTS
Clinical

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Heterozygous Mutation in the SAM Domain of p63 Underlies Rapp-Hodgkin Ectodermal Dysplasia

ABSTRACT

Several ectodermal dysplasia syndromes, including Ectrodactyly-Ectodermal dysplasia-Clefting (EEC) and Ankyloblepharon-Ectodermal Dysplasia-Clefting (AEC) syndromes, are known to result from mutations in the *p63* gene. We investigated whether Rapp-Hodgkin syndrome (RHS) is also caused by mutations in the *p63* gene. We identified a heterozygous *de novo* germline missense mutation, S545P, in the sterile-alpha-motif (SAM) domain of p63, in a Thai patient affected with RHS. This is the first genetic abnormality to be described in RHS. The amino acid substitution is the most downstream missense mutation in *p63* reported thus far. Histological assessment of a skin biopsy from the patient's palm showed hyperkeratosis and keratinocyte cell-cell detachment in the upper layers of the epidermis, along with numerous apoptotic keratinocytes. Collectively, these investigations demonstrate that RHS is also caused by mutations in *p63* and that the clinical similarities to AEC syndrome are paralleled by the nature of the inherent mutation.

KEY WORDS: AEC syndrome, dental anomalies, palmoplantar keratoderma, *p63* gene, Rapp-Hodgkin syndrome.

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INTRODUCTION

Rapp-Hodgkin syndrome (RHS), or Rapp-Hodgkin ectodermal dysplasia, was first described over 30 years ago in an affected mother, son, and daughter with a combination of anhidrotic ectodermal dysplasia, cleft lip, and cleft palate (Rapp and Hodgkin, 1968). The clinical syndrome is comprised of a characteristic facies (narrow nose and small mouth), wiry, slow-growing, and uncombable hair, sparse eyelashes and eyebrows, obstructed lacrimal puncta/epiphora, bilateral stenosis of external auditory canals, microsomia, hypodontia, cone-shaped incisors, enamel hypoplasia, dystrophic nails, and cleft lip/cleft palate. Approximately 45 cases of this developmental disorder, usually with autosomal-dominant inheritance, have been reported (Summitt and Hiatt, 1971; Wannarachue *et al.*, 1972; Stasiowska *et al.*, 1981; Silengo *et al.*, 1982; Salinas and Montes, 1988; Rodini *et al.*, 1990; Santos *et al.*, 1990; Breslau-Siderius *et al.*, 1991; Walpole and Goldblatt, 1991; Kantaputra *et al.*, 1998; Neilson *et al.*, 2002), thus defining RHS as a discrete clinical entity (Online Mendelian Inheritance in Man [OMIM] no. 129400).

Nevertheless, RHS does display some clinical overlap with other ectodermal dysplasia syndromes, notably Ectrodactyly-Ectodermal Dysplasia-Clefting (EEC) syndrome (OMIM 129900) and Ankyloblepharon-Ectodermal Dysplasia-Clefting (AEC), also known as Hay-Wells syndrome (Hay-Wells Syndrome, OMIM 106260) (van Bokhoven and McKeon, 2002). Differentiating features of AEC and RHS appear to be the presence of ankyloblepharon in AEC and microsomia in RHS, but making an accurate diagnosis on clinical grounds alone may be difficult. Indeed, this was highlighted in a case of a woman with RHS whose son had features of EEC syndrome (Moerman and Fryns, 1996). The affected child also had ankyloblepharon, a component of AEC syndrome. Other overlap syndromes have also been reported (Cambiaghi *et al.*, 1994; Rowan, 1996), suggesting that perhaps there might be a common genetic pathology to many of these and other related ectodermal dysplasia syndromes. It is noteworthy that some parents with AEC syndrome had affected children without ankyloblepharon. Furthermore, the ankyloblepharon of some affected individuals is so subtle or friable at birth that it often goes unrecognized, and these cases may subsequently be diagnosed as RHS.

The molecular basis of most cases of EEC syndrome has recently been shown to involve mutations in the *p63* gene (Celli *et al.*, 1999). The majority of mutations is comprised of heterozygous missense changes in the DNA-binding domain of p63 (van Bokhoven *et al.*, 2001). Moreover, AEC syndrome has subsequently been reported to result from missense mutations in *p63*, specifically within the sterile alpha motif (SAM) (McGrath *et al.*, 2001). Thus, both these disorders are caused by heterozygous germline mutations in p63, and a genotype-phenotype correlation for the site of the mutation (DNA-binding domain or SAM domain) has been defined. To date, no pathogenetic mutations in *p63* have been reported in patients with RHS. Therefore, in this study we investigated the molecular basis of RHS to further examine the possibility of allelic heterogeneity.

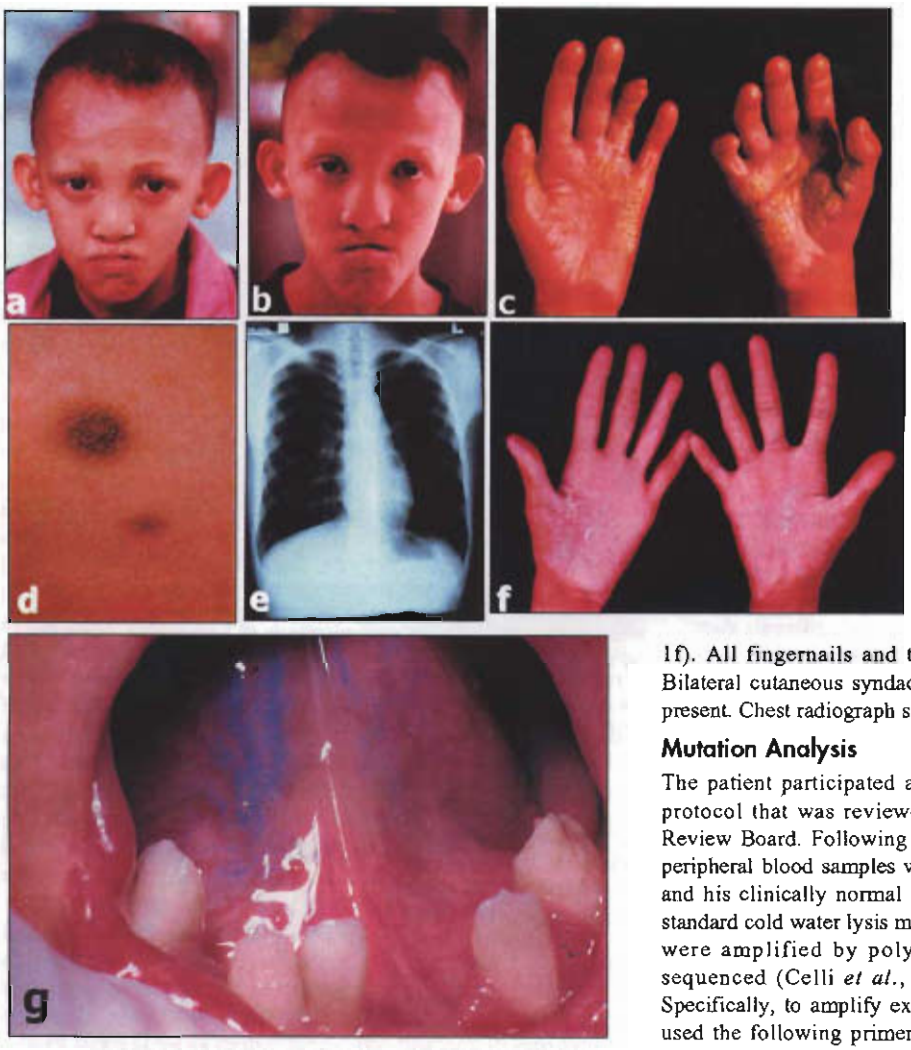

Figure 1. Clinical pictures of the patient. (a) Patient at 8 yrs old. Note repaired cleft lip and palate, microsomia, sparse hair, and diffuse dermatitis of the skin. (b) Patient at 14 yrs old. (c) Keratoderma of palms at 8 yrs. (d) Supernumerary nipple. (e) Hypoplastic scapulae. (f) Keratoderma of palms at 14 yrs. Note improvement of the condition as he aged. (g) Congenitally missing mandibular left central incisor. Enamel hypoplasia of the mandibular right lateral incisor and left canine.

MATERIALS & METHODS

Clinical Details

A 14-year-old Thai boy was seen in The Department of Pediatric Dentistry, Faculty of Dentistry, Chiang Mai University. He had been diagnosed and reported previously as having Rapp-Hodgkin syndrome (Kantaputra *et al.*, 1998) (Figs. 1a, 1b). His clinical findings included characteristic facies, slow-growing and uncombable hair, sparse eyebrows and eyelashes, obstructed lacrimal puncta and epiphora, microsomia, repaired cleft lip and cleft palate (Figs. 1a, 1b), taurodontism, multiple caries, unerupted premolar, glossy tongue, hypodontia, enamel hypoplasia, and congenital absence of the lingual frenum and sublingual caruncles, including submandibular and sublingual salivary gland duct openings (Fig. 1g) (Kantaputra *et al.*, 1998). However, the abnormal scalp hair lacked pili canaliculi, a feature noted in some other cases of RHS (Salinas and Montes, 1988). The ears protruded, with evidence of bilateral bony external auditory canal stenoses, and he had a moderate mixed pattern of hearing loss. Hypoplastic and supernumerary nipples were observed (Fig. 1d). The skin was very dry, with some hypopigmented areas. Diffuse dermatitis of the scalp, face, and forearms was present (Figs. 1a, 1b). Palms and soles demonstrated keratoderma with multiple fissures, although the degree of keratoderma had improved when he became a teenager (Figs. 1c, 1f). All fingernails and toenails were dystrophic and ridged. Bilateral cutaneous syndactyly of the second and third toes was present. Chest radiograph showed hypoplastic scapulae (Fig. 1e).

Mutation Analysis

The patient participated after providing informed consent to a protocol that was reviewed and approved by the Institutional Review Board. Following informed consent given by his father, peripheral blood samples were taken from the affected individual and his clinically normal parents, and DNA was extracted by a standard cold water lysis method. Individual exons of the *p63* gene were amplified by polymerase chain-reaction (PCR) and sequenced (Celli *et al.*, 1999; van Bokhoven *et al.*, 2001). Specifically, to amplify exon 13 and flanking introns of *p63*, we used the following primers: forward primer 5′-CTT ATC TCG CCA ATG CAG TTG G-3′, and reverse primer 5′-AAC TAC AAG GCG GTT GTC ATC AG-3′. The expected PCR product size was 241 base pairs (bp). For PCR amplification, 250 ng of genomic DNA was used as the template in an amplification buffer containing 6.25 pmol of the primers, 37.5 nmol $MgCl_2$, 5 mmol of each nucleotide triphosphate, and 1.25 U *Taq* polymerase (Applied Biosystems, Warrington, UK) in a total volume of 25 μL in an OmniGene thermal cycler (Hybaid, Basingstoke, UK). The amplification conditions were 94°C for 5 min, followed by 38 cycles of 94°C for 45 sec, 53°C for 45 sec, and 72°C for 45 sec. Aliquots (5 μL) of the PCR products were analyzed by 2% agarose gel electrophoresis. PCR products were then sequenced directly with the use of Big Dye labeling in an ABI 310 genetic analyzer (Applied Biosystems). Potential mutation was verified by restriction endonuclease digestion or by direct sequencing (forward and reverse) and assessed in 300 control chromosomes to exclude non-pathogenetic sequence variants.

Skin Biopsy

Following informed consent, a 4-mm punch biopsy was taken from the patient's palm while he was under general anesthetic (given for dental surgery). Skin was fixed in 10% formalin and processed for routine light microscopy with paraffin-embedding. Five-micron sections were stained with hematoxylin and eosin and photographed.

RESULTS

Mutation Analysis

Sequencing of the PCR products spanning exon 13 with the use of DNA from the affected individual revealed a heterozygous T>C point mutation at nucleotide position 1633 within exon 13 (numbering based on the originally published TA-p63α sequence [Yang *et al.*, 1998], GenBank accession no. AF075430). The mutation converted a serine residue (TCC) to proline (CCC) and was designated S545P (Fig. 3). This mutation has not been reported previously in patients with EEC, AEC, or other *p63*-related disorders and was not detected in direct sequencing of DNA from this patient's father or from 150 control subjects. No other heterozygous or homozygous sequence variants for the remainder of the *p63* gene were found in the patient's DNA.

Histological Findings

Light-microscopic examination of palmar skin showed acanthosis and hyperkeratosis with a mild upper dermal interstitial chronic inflammatory cell infiltration and some exocytosis of lymphocytes throughout the upper epidermis. Most notably, in the upper spinous layers of the epidermis there was evidence of abnormal keratinocyte differentiation with numerous apoptotic keratinocytes, acantholysis, and disruption of the granular layer (Fig. 2).

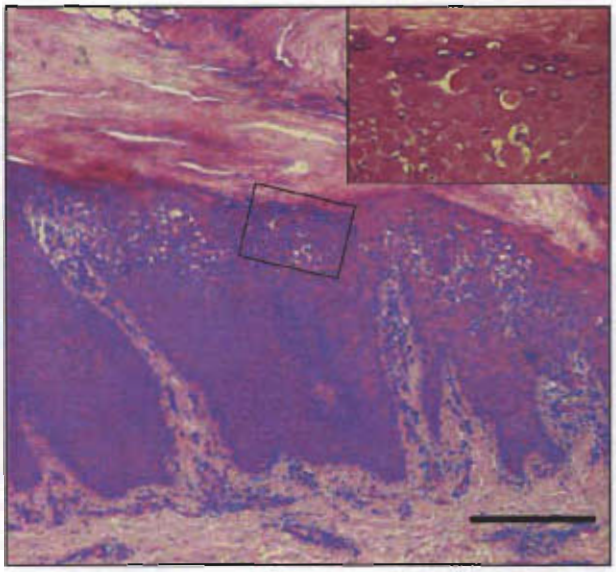

Figure 2. Histology of palmar skin shows acanthosis and hyperkeratosis. There is a mild upper dermal interstitial chronic inflammatory cell infiltrate and exocytosis of lymphocytes within the superficial dermis. Most notably, in the upper spinous cell layers there are numerous apoptotic keratinocytes (seen at higher magnification in the inset) with keratinocyte separation (acantholysis) and disruption of the granular cell layer. Bar = 100 microns.

DISCUSSION

In this study, we have elucidated the molecular basis of RHS in one affected individual. Our findings provide evidence of further allelic heterogeneity for mutations in *p63* and the diverse clinical phenotypes therein. Indeed, we can now provide molecular data to support the earlier reports of clinical overlap between EEC syndrome, AEC syndrome, and RHS (Cambiaghi *et al.*, 1994; Moerman and Fryns, 1996; Rowan, 1996). RHS is clinically most similar to AEC syndrome, and this is borne out at a molecular level. In AEC syndrome, 8 heterozygous germline missense mutations in the SAM domain of p63 have been reported, all of which are clustered within the first 3 of 5 helical domains (McGrath *et al.*, 2001). In contrast, the missense mutation in our case of RHS occurs in the fourth helix of the SAM domain, albeit just 4 amino acids downstream from the most 3′ of the AEC mutations. This raises the fundamental question of whether this subtle difference is sufficient to justify labeling AEC syndrome and RHS as separate entities. To begin to answer this, it is clear that further patients with a clinical diagnosis of RHS will need to be screened for *p63* mutations. Interestingly, recent mutation analysis in one other RHS family (with mixed cleft type) did not reveal any *p63* mutations (Neilson *et al.*, 2002). Locus heterogeneity of RHS therefore cannot be ruled out, further adding to the complexity of attempts to unravel the molecular basis of this ectodermal dysplasia syndrome. From a clinical perspective, we believe that our patient has RHS rather than AEC syndrome because of the presence of the characteristic facies, microsomia, obstructed lacrimal puncta/epiphora, and palmoplantar keratoderma and the absence of ankyloblepharon. At a molecular level, it is necessary to be more circumspect, since little is currently known about the function of the SAM domain other than its potential as a site for protein-protein interactions (Thanos and Bowie, 1999). Characterization of the roles of individual amino acids in these interactions will be necessary to define more specific functions. However, attempts to define genotype-phenotype correlation for *p63*-mutations in ectodermal dysplasia syndromes are further complicated by reported diverse phenotypes arising from identical amino acid substitutions. For example, mutations in arginine 280 may give rise to EEC syndrome, split hand-split foot malformation, or, rarely, no detectable abnormalities (van Bokhoven *et al.*, 2001). Likewise, mutations in arginine 304 have been shown to underlie a spectrum of EEC syndrome phenotypes (Hamada *et al.*, 2002). Clearly, there are other influences on the phenotypic consequences of particular mutations in the TP63 transcription factor, and therefore a simple genotype-phenotype correlation based on a specific amino acid substitution is fundamentally flawed. Until the nature of these additional modifying factors or the full spectrum of inherent gene pathology becomes apparent, we believe that it is still more appropriate to retain the descriptive eponyms such as RHS, which is the most appropriate diagnosis that encompasses the clinical features present in our patient.

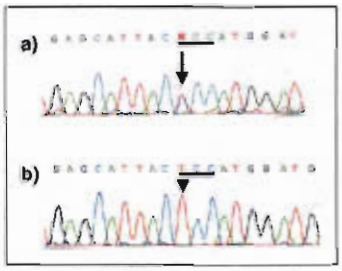

Figure 3. Nucleotide sequencing of *p63* exon 13 from normal (b) and the affected patient (a) shows a heterozygous T>C point mutation that converts a serine residue (TCC) to proline (CCC), designated as S545P.

In addition to disclosing the initial *p63* gene mutation in RHS, our study reports the first histological assessment of the erosive palm- and sole-skin thickening that is a characteristic feature of RHS. TP63 is known to have an important role in the regulation of epidermal stem cell proliferation (Schultz *et al.*, 1997; Mills *et al.*, 1999; Parsa *et al.*, 1999; Yang *et al.*, 1999; de Laurenzi *et al.*, 2000), and its expression in keratinocytes has been used to distinguish stem cells from transit amplifying cells and other keratinocytes (Pellegrini *et al.*, 2001). The missense mutation S545P in the p63 SAM domain clearly perturbs normal epidermal differentiation and maturation, leading to acanthosis (thickening) and hyperkeratosis (increased scale) as well as focal impairment of keratinocyte cell-cell attachment and, most notably, numerous apoptotic keratinocytes (colloid bodies). TP63 is known to influence keratinocyte apoptosis (Yang *et al.*, 1998) in response to certain stimuli such as ultraviolet irradiation (Liefer *et al.*, 2000) and in response to knockout mutations (Flores *et al.*, 2002), but inhibition of apoptosis appears to be abrogated in the presence of the heterozygous missense mutation S545P. Analysis of these clinico-pathological data may therefore provide insight into one of the functions of the p63 SAM domain in normal epithelial physiology. Specifically, our case demonstrates the first example of increased epidermal apoptosis in association with a human germline mutation in *p63*. This is clearly distinct from AEC syndrome, where no increase of apoptosis is observed (McGrath *et al.*, 2001). Palmoplantar keratoderma and mixed hearing loss, found in our patient, have not been reported in other patients affected with RHS (van Bokhoven and Brunner, 2002). The novel finding of hypoplastic scapula might have been related to *p63* mutation, or it might have been a coincidence.

The *p63* mutation detected may also be relevant to our understanding of the dental pathology present in some ectodermal dysplasia syndromes. The present patient has unerupted premolar and taurodontism, *i.e.*, large dental pulp and short roots, and although there are no previous reports of *p63* expression in dental pulps, the findings in our patient give credence to the significance of *p63* expression during dental development, since large pulp chambers are known to occur as a consequence of defective dentin formation in the dental pulp, a key role for normally functioning odontoblasts. This process is evidently disrupted in the RHS patient described here. The SAM domain mutation S545P, and its effects on oral mucosal development, may also be relevant to the pathogenesis of the patient's glossy tongue and absence of lingual frenum and of sublingual caruncles, since these are the rare clinical features in other *p63*-related syndromes.

In summary, this case discloses the molecular basis of RHS and provides new clinico-pathological insight into the consequences of a specific p63 SAM domain mutation on epithelial development.

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REFERENCES

Breslau-Siderius EJ, Lavrijsen AP, Otten FW, van der Schroeff JG, Swart JG (1991). The Rapp-Hodgkin syndrome. *Am J Med Genet* 38:107-110.

Cambiaghi S, Tadini G, Barbareschi M, Menni S, Caputo R (1994). Rapp-Hodgkin syndrome and AEC syndrome: are they the same entity? *Br J Dermatol* 130:97-101.

Celli J, Duijf P, Hamel BC, Bamshad M, Kramer B, Smits AP, *et al.* (1999). Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. *Cell* 99:143-153.

De Laurenzi V, Rossi A, Terrinoni A, Barcaroli D, Levrero M, Costanzo A, *et al.* (2000). p63 and p73 transactivate differentiation gene promoters in human keratinocytes. *Biochem Biophys Res Commun* 273:342-346.

Flores ER, Tsai KY, Crowley D, Sengupta S, Yang A, McKeon F, *et al.* (2002). p63 and p73 are required for p53-dependent apoptosis in response to DNA damage. *Nature* 416:560-564.

Hamada T, Chan I, Willoughby CE, Goudie DR, McGrath JA (2002). Common mutations in Arg304 of the p63 gene in ectrodactyly, ectodermal dysplasia, clefting syndrome: lack of genotype-phenotype correlation and implications for mutation detection strategies. *J Invest Dermatol* 119:1202-1203.

Kantaputra PN, Pruksachatkunakorn C, Vanittanakom P (1998). Rapp-Hodgkin syndrome with palmoplantar keratoderma, glossy tongue, congenital absence of lingual frenum and of sublingual caruncles: newly recognized findings. *Am J Med Genet* 79:343-346.

Liefer KM, Koster MI, Wang XJ, Yang A, Mckeon F, Roop DR (2000). Down-regulation of p63 is required for epidermal UV-B-induced apoptosis. *Cancer Res* 60:4016-4020.

McGrath JA, Duijf PH, Doetsch V, Irvine AD, de Waal R, Vanmolkot KR, *et al.* (2001). Hay-Wells syndrome is caused by heterozygous missense mutations in the SAM domain of p63. *Hum Mol Genet* 10:221-229.

Mills AA, Zheng B, Wang XJ, Vogel H, Roop DR, Bradley A (1999). p63 is a p53 homologue required for limb and epidermal morphogenesis. *Nature* 398:708-713.

Moerman P, Fryns JP (1996). Ectodermal dysplasia, Rapp-Hodgkin type in a mother and severe ectodactyly-ectodermal dysplasia-clefting syndrome (EEC) in her child. *Am J Med Genet* 63:479-481.

Neilson DE, Brunger JW, Heeger S, Bamshad M, Robin NH (2002). Mixed clefting type in Rapp-Hodgkin syndrome. *Am J Med Genet* 108:281-284.

Parsa R, Yang A, McKeon F, Green H (1999). Association of p63 with proliferative potential in normal and neoplastic human keratinocytes. *J Invest Dermatol* 113:1099-1105.

Pellegrini G, Dellambra E, Golisano O, Martinelli E, Fantozzi I, Bondanza S, *et al.* (2001). p63 identifies keratinocyte stem cells. *Proc Natl Acad Sci USA* 98:3156-3161.

Rapp RS, Hodgkin WE (1968). Anhidrotic ectodermal dysplasia: autosomal dominant inheritance with palate and lip anomalies. *J Med Genet* 5:269-272.

Rodini EO, Freitas JA, Richieri-Costa A (1990). Rapp-Hodgkin syndrome: report of a Brazilian family. *Am J Med Genet* 36:463-466.

Rowan DM (1996). Scalp dermatitis, ectodermal dysplasia and cleft lip and palate: Rapp-Hodgkin or AEC syndrome. *Australas J Dermatol* 37:102-103.

Salinas CF, Montes GM (1988). Rapp-Hodgkin syndrome: observations on ten cases and characteristic hair changes (pili canaliculi). *Birth Defects Orig Artic Ser* 24:149-168.

Santos H, Cordeiro MJ, Faro Viana I, Cordeiro I, Colarinha J, Rodrigues ML (1990). Rapp-Hodgkin ectodermal dysplasia. *Acta Paediatr Scand* 79:245-247.

Schultz J, Ponting CP, Hofmann K, Bork P (1997). SAM as a protein interaction domain involved in developmental regulation. *Protein Sci* 6:249-253.

Silengo MC, Davi GF, Bianco R, Costa M, Demarco A, Verona R, *et al.* (1982). Distinctive hair change (pili torti) in Rapp-Hodgkin ectodermal dysplasia syndrome. *Clin Genet* 21:297-300.

Stasiowska B, Sartoris S, Goitre M, Benso L (1981). Rapp-Hodgkin ectodermal dysplasia syndrome. *Arch Dis Child* 56:793-795.

Summitt RL, Hiatt RL (1971). Hypohidrotic ectodermal dysplasia with multiple associated anomalies. *Birth Defects Orig Artic Ser* 7:121-124.

Thanos CD, Bowie JU (1999). p53 family members p63 and p73 are SAM domain-containing proteins. *Protein Sci* 8:1708-1710.

van Bokhoven H, Brunner HG (2002). Splitting p63. *Am J Hum Genet* 71:1-13.

Van Bokhoven H, McKeon F (2002). Mutations in the p53 homolog p63: allele-specific developmental syndromes in humans. *Trends Mol Med* 8:133-139.

van Bokhoven H, Hamel BC, Bamshad M, Sangiorgi E, Gurrieri F, Duijf PH, *et al.* (2001). p63 gene mutations in EEC syndrome, limb-mammary syndrome, and isolated split hand-split foot malformation suggest a genotype-phenotype correlation. *Am J Hum Genet* 69:481-492.

Walpole IR, Goldblatt J (1991). Rapp-Hodgkin hypohidrotic ectodermal dysplasia syndrome. *Clin Genet* 39:114-120.

Wannarachue N, Hall BD, Smith DW (1972). Ectodermal dysplasia and multiple defects (Rapp-Hodgkin type). *J Pediatr* 81:1217-1218.

Yang A, Kaghad M, Wang Y, Gillett E, Fleming MD, Dotsch V, *et al.* (1998). p63, a p53 homolog at 3q27-29, encodes multiple products with transactivating, death-inducing and dominant negative activities. *Mol Cell* 2:305-316.

Yang A, Schweitzer R, Sun D, Kaghad M, Walker N, Bronson RT, *et al.* (1999). p63 is essential for regenerative proliferation in limb, craniofacial and epithelial development. *Nature* 398:714-718.

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Clinical Report

Thyroid Dysfunction in a Patient With Aglossia

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We report a Thai girl who had aglossia, micrognathia, microsomia, collapse of mandibular arch, persistence of buccopharyngeal membrane, microcephaly, and mild developmental delay. Thyroid function tests indicated that she had subclinical hypothyroidism. Thyroid scan revealed normal uptake of the whole thyroid gland. Tongue morphogenesis is integrally linked to the normal development of thyroid gland, and abnormal tongue morphogenesis could potentially result in a functional thyroid disorder. We propose that micrognathia, microsomia, congenital absence of mandibular incisors, and collapse of the mandibular arch are the result of abnormal tongue development.

KEY WORDS: high caries rate; hypodontia; hypothyroidism; micrognathia; persistence of buccopharyngeal membrane

INTRODUCTION

Thyroid gland develops from the foramen cecum on the back of the tongue. A relationship between thyroid dysfunction and abnormal tongue development would be reasonable but has never been reported. We report a Thai girl who had aglossia and subclinical hypothyroidism, which supports our hypothesis. In addition, we also propose that micrognathia, microsomia, congenital absence of mandibular incisors, and collapse of the mandibular arch are the result of abnormal tongue development.

CLINICAL REPORT

A 13-year-old Thai girl came to the Department of Pediatric Dentistry, Faculty of Dentistry, Chiang Mai University for dental care (Fig. 1b). She has had dental care regularly since she was 3 years old (Fig. 1a). Family history was unremarkable and the parents were not consanguineous. Birth weight, birth length, and head circumference (OFC) at birth were 3,430 g (>90th centile), 44 cm (3rd centile), and 37 cm (97th centile), respectively. Karyotype was 46,XX. At age 13 years, her weight, height, and OFC were 29 k. (10th–25th centile), 138 cm (<3rd centile), and 49 cm (<3rd centile), respectively. After birth, tracheostomy was initiated due to respiratory distress as the result of the presence of a buccopharyngeal membrane and oropharyngeal stenosis. At age 10 months, oropharyngeal reconstruction, using a median mandibulotomy approach, was initiated, and an anterior cricoid split with costal graft was performed in order to obtain a patent airway. It is noteworthy that during the surgical procedure, the tongue was not observed.

Oral examination at age 3 years revealed a persistent buccopharyngeal membrane, microsomia, aglossia, congenital absence of mandibular incisors, collapse of the mandibular arch, hypertrophy of the floor of mouth, and multiple carious teeth (Fig. 1c). Between the ages of 3 and 13 years, she kept losing her primary and permanent teeth as a result of rampant dental caries. Pit and fissure sealants were placed on the occlusal surfaces of all premolars and permanent molars in order to prevent occlusal caries. However, the uncontrollable dental caries severely and rapidly invaded all teeth from the mesial, distal, lingual, and buccal surfaces (Fig. 1d).

Her social development appeared delayed, possibly secondary to the physical handicap. She was able to speak, but not very well. She spoke only to her mother and close relatives and was too shy to speak with other people.

Thyroid Function Tests

At age 8 years, thyroid function tests revealed slightly elevated thyrotropin-stimulating hormone (TSH) (6.61 μU/ml) (normal range = 0.5–4.0 μU/ml) and normal Free T4 (FT4) levels (1.06 ng/dl) (normal range = 0.6–1.5 ng/dl) without any clinical symptoms

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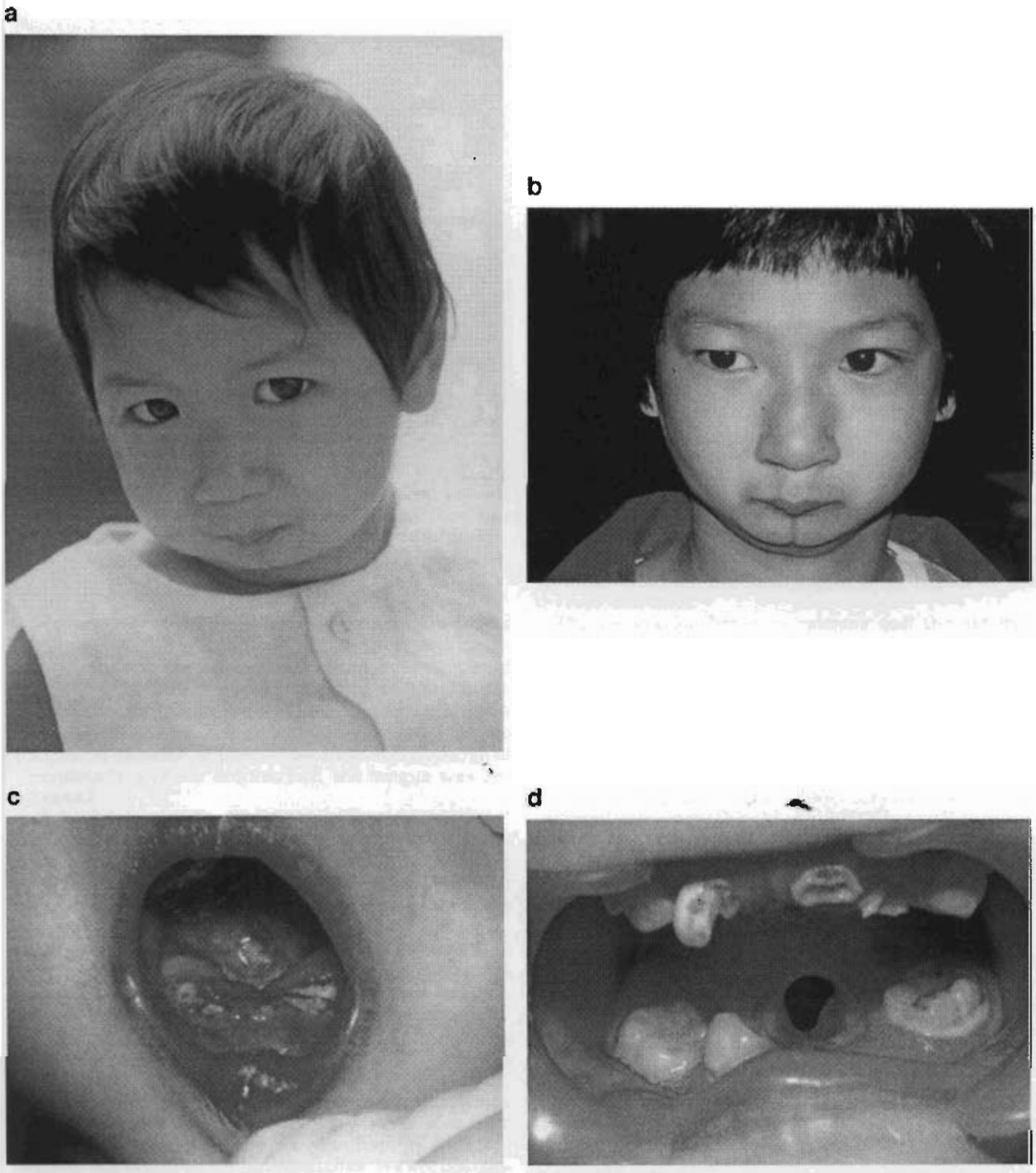

Fig. 1. a: Patient at age 3 years. b: Patient at age 13 years. c: Oral cavity at age 5 years. Note collapsed mandibular arch. Retained roots of primary teeth. d: Oral cavity at age 8 years. Note buccopharyngeal membrane with a very small orifice. Rampant dental caries.

of hypothyroidism. After treatment with levo-thyroxine (thyroid extract), the TSH level decreased to 4.7 μU/ml. Three months after levo-thyroxine was discontinued, TSH level elevated to 5.5 μU/ml. The TSH decreased to normal (3.4 μU/ml) once the thyroid supplement was reinstituted. During the treatment with levo-thyroxine the FT4 level stayed normal (1.5 ng/dl). All these lines of evidence indicated that she had subclinical hypothyroidism, which is characterized by elevated TSH level with normal serum FT4 and T3 [Cooper, 2001]. At age

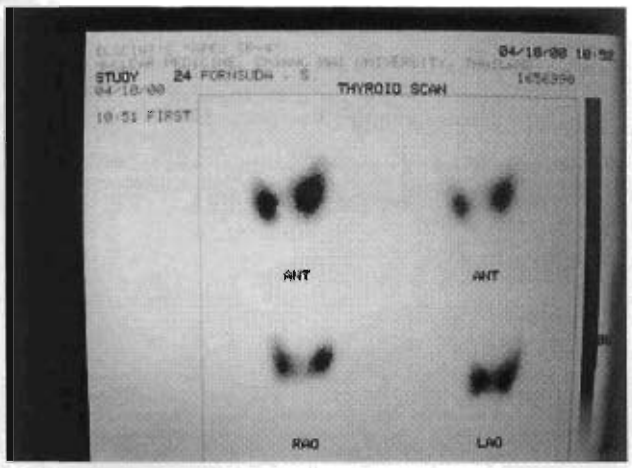

Fig. 2. Thyroid scan at age 10 years showing normal Technetium (Tc) uptake.

10 years, thyroglobulin level was normal (15 ng/ml) and the thyroid Technetium (Tc99) scan revealed normal uptake of the whole thyroid gland. The left lobe was slightly larger than the right (Fig. 2).

DISCUSSION

We have reported a girl who had aglossia, subclinical hypothyroidism, persistence of buccopharyngeal membrane, subglottic stenosis, micrognathia, hypertrophy of the floor of mouth, congenital absence of mandibular permanent incisors, collapse of mandibular arch, and a very high caries rate. The patient was considered to have congenital absence of tongue because during surgical reconstruction of her oropharynx, the tongue was not observed.

Hypoglossia is rare. Most patients with "aglossia" actually have a small nubbin of tongue tissue on close examination [Hall, 1971; Gorlin et al., 2001]. We were not able to confirm the original diagnosis of aglossia because the tiny and opening did not permit the necessary visualization.

Many patients with aglossia or hypoglossia have been reported to have micrognathia, microsomia, congenital absence of mandibular incisors, and collapse of mandibular arch. Most of the patients have normal intelligence [Rosenthal, 1932; Kelln et al., 1968; Hall, 1971; Roth et al., 1972; Johnson and Robinow, 1978; Kuroda and Ohyama, 1981; Weckx, 1990].

The association between hypoglossia and persistent buccopharyngeal membrane is very rare. Flannery [1989] reported such a patient, who had, in addition, costovertebral and auricular anomalies. We are not convinced that a persistent buccopharyngeal membrane, even though found in our patient, is part of the abnormal tongue development since most reported patients with tongue anomalies have not had persistent buccopharyngeal membrane.

The thyroid gland develops from an unpaired primordium, which appears in the ventral midline of the pharynx between the first and second pouches. The thyroid origin later becomes the foramen cecum on the back of the tongue. During the fourth week, proliferation and later an invagination of the endothelium of the foramen cecum develops into the thyroid primordium. It commences at the foramen cecum as a blind-ended sac of thyroglossal duct, which becomes a hollow tube and subsequently enlarges caudally as a bilobed thyroid diverticulum. It then migrates caudally to its final destination by the seventh week at the level between the second and third tracheal cartilages. The thyroglossal duct has been reported to be filled with keratin, debris, and fluid emitted from accessory serous glands adjacent to the tract. The duct later constricts, becomes obliterated [Baughman, 1972], and breaks down by the end of the fifth week [Larsen, 1993], possibly by the programmed cell death. In almost 50% of the population, the distal portion of the thyroglossal duct persists and becomes the pyramidal lobe of the thyroid gland [Carlson, 1999]. Sauk [1971] found that 10% of 200 routine necropsies showed histologic remnants of thyroid tissue within the base of the tongue. In the cervical region, there are many "physiologic" migrations of the thyroid primordium in different directions. The pattern of thyroid migration is somewhat similar to that of the thymus and possibly the parathyroid glands [Carlson, 1999]. On occasion, a thyroid cyst, fistula, adenoma, or adenocarcinoma have been reported in region of the thyroglossal duct.

The association between aglossia and thyroid dysfunction has not been previously reported. Since the thyroid primordium is induced very early during embryonic development before any trace of the tongue appears, the two structures are probably under different modes of control. It is also possible that the tongue forms but disappears for some reason after the thyroid primordium develops.

A high caries rate with a rudimentary tongue has been reported previously [Khalil et al., 1995] as well as in our own patient. Causes of high caries could have been the lack of self-cleansing by the tongue or the composition of the saliva that might predispose to dental caries.

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We thank the patient and her family for allowing us to see her and to use her medical and dental information for publication. Advice from Chanin Limwongse and Bruce M. Carlson is appreciated. This paper is dedicated to Prof. Robert J. Gorlin, my evergreen teacher.

REFERENCES

Baughman RA. 1972. Lingual thyroid and lingual thyroglossal tract remnants. A clinical and histological study with review of the literature. Oral Surg 35:781–799.

Carlson BM. 1999. Human embryology and developmental biology. St. Louis: Mosby. pp 309–316.

Cooper DS. 2001. Subclinical hypothyroidism. N Engl J Med 345:260–265.

Flannery DB. 1989. Syndrome of imperforate oropharynx with costovertebral and auricular anomalies. Am J Med Genet 32:189–191.

Gorlin RJ, Cohen MM Jr, Hennekam RCM. 2001. Syndromes of the head and neck. New York: Oxford University Press. pp 822–829.

Hall BD. 1971. Aglossia-adactylia. BD:OAS VII(7):233–236.

Johnson GF, Robinow M. 1978. Aglossia-adactylia. Radiology 128:127–132.

Kelln EE, Bennett CG, Klingberg WG. 1968. Aglossia-adactylia syndrome. Am J Dis Child 116:549–552.

Khalil KC, Dayal PK, Gopakumar RR, Prashanth S. 1995. Aglossia: A case report. Quintessence Int 26:359–360.

Kuroda T, Ohyama K. 1981. Hypoglossia: Case report and discussion. Am J Orthodont 79:86–94.

Larsen WJ. 1993. Human embryology. Singapore: Churchill Livingstone, Inc. pp 333–337.

Rosenthal R. 1932. Aglossia congenita. Report of a case of the condition combined with other congenital malformations. Am J Dis Child 44:383–389.

Roth JB, Sommer A, Strafford C. 1972. Microglossia-micrognathia. A case report and a survey of 30 others on record. Clin Pediatr 11:357–359.

Sauk JJ. 1971. Ectopic lingual thyroid. J Pathol 102:239–243.

Weckx LLM. 1990. Hypoglossia congenita. Ear Nose Throat J 69:108–113.

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Invited Comment

Thirteen-Year-Follow up Report on Mesomelic Dysplasia, Kantaputra Type (MDK), and Comments on the Paper of the Second Reported Family of MDK by Shears et al.

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INTRODUCTION

In 1992, Professor Robert Gorlin, Professor Leonard Langer, and myself reported a new type of mesomelic dysplasia, which was later named as mesomelic dysplasia, Kantaputra type (MDK; OMIM *156232) [Kantaputra et al., 1992]. The condition was documented in a three-generation Thai family (Fig. 1). MDK is an autosomal dominant disorder, characterized by bilateral severe shortening of the ulnae and shortening and bowing of the radii (Figs. 2 and 3). The fibula is hypoplastic in most patients. Synostosis is observed between tibia and fibula, and the malformed calcaneus and talus. Fibulo–calcaneal complex, the prominent calcaneus fusing with the ventral surface of the distal fibula is a constant feature. It was found in all affected individuals (Figs. 4 and 7). Carpal and tarsal synostoses are present in some affected people, however, the pattern did not appear to be consistent. The affected patients stood on the tip of their toes [Kantaputra et al., 1992]. With great collaboration with Professor Niikawa's group at Nagasaki School of Medicine, the gene of MDK is successfully mapped to chromosome 2q24 and q32 [Fujimoto et al., 1998].

Newly Born Member: What Does she Tell us About the Syndrome?

On examination at age 4 years, the newly born affected member (Patient V1) is an intelligent and cheerful girl. Her upper and lower limb abnormalities are similar to those of her mother and relatives (Figs. 5a–b and 7a–b). Flexion contracture involve more number of interphalangeal joint (IPJ) than that of any members of the family. It is found at the proximal interphalangeal joints (PIPJ) of the left fingers 2, 4, and 5 and the right finger 4. That of the distal interphalangeal joints (DIPJ) is found at the left thumb, left finger 3, and right fingers 2 and 3.

Radiographic findings consist of disproportionate shortening of the radii and ulnae. The ulnae were severely shortened. No distal epiphyses are evident. The distal humeri are large. Trapezium, trapezoid, scaphoid, lunate, and triquetrum are missing. Narrow joint spaces of the PIPJ of the left fingers 4 and 5 and the right finger 4 are observed (Fig. 5a,b).

Lower limb radiographs show shortening of tibiae and fibulae, large distal fibulae, and rectangular fibular prominence on the ventral surface of the left fibula (Fig. 7b). The right fibula does not appear to have fibular prominence (Fig. 7a). The calcaneus is malformed and in upright position, articulating with fibula. No synostosis is observed (Fig. 7a,b).

THIRTEEN YEAR-FOLLOW UP OF PATIENT IV2 AND HIS RELATIVES

Upper Limbs

The previous report was done when he was 8 years old. Thirteen-year-follow up examination of patient IV2 at age 21 years demonstrates progressively bowed radii and narrower spaces between carpal bones leading to their overlapping. Narrow PIPJs of fingers 4 were observed at age 8 years. At 21 years old, flexion contracture of the PIPJ are noted at fingers 4 and 5 bilaterally and narrowness of PIPJs and DIPJs 4 and 5 is observed radiographically on both sides. No symphalangism of fingers and thumbs is observed in him and other affected patients, except for the distal symphalangism of the left finger 5 of patient IV6. Carpal synostosis is not visible.

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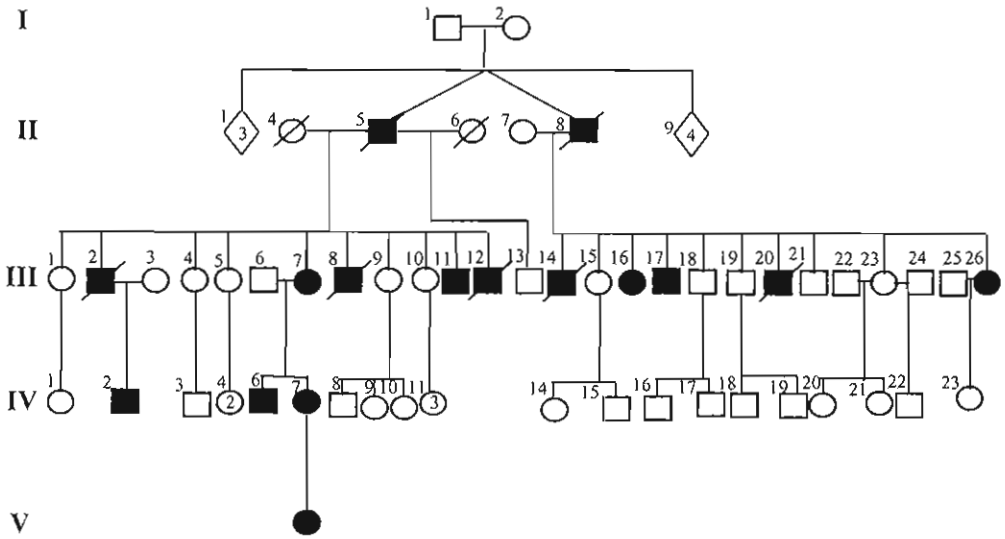


Fig. 1. Pedigree of the Thai family.

Fig. 2. **a**–**c**: Patient IV2 at ages 8, 15, and 21, respectively. **d**: Front row from **left** to **right**. Patients IV7, IV2, V1, III7, and Kantaputra.

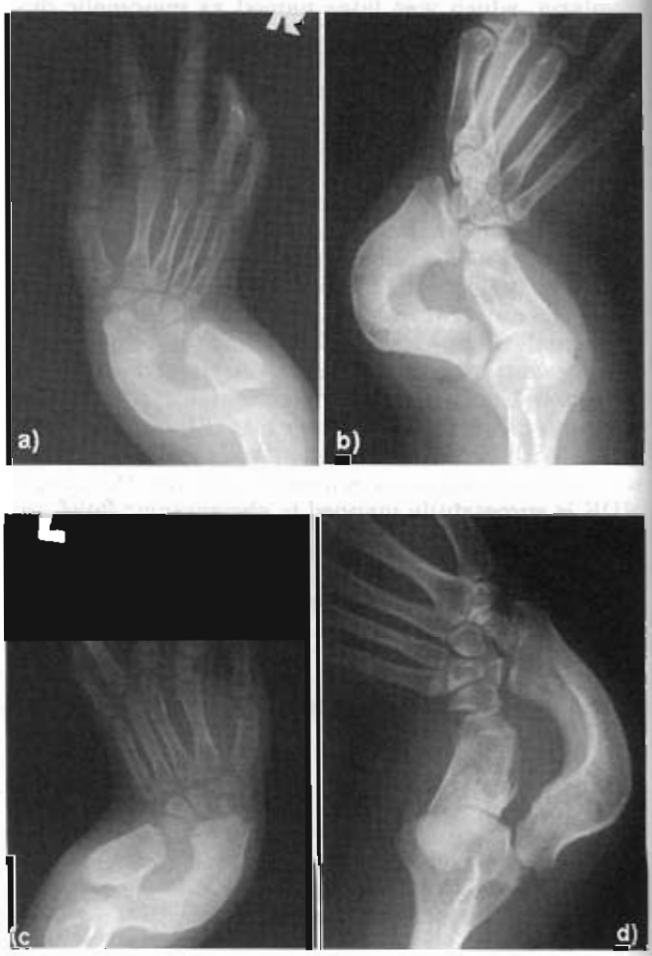
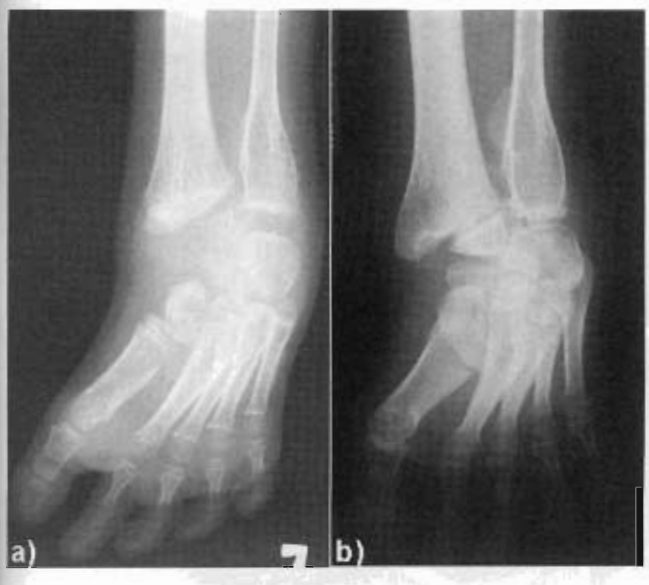


Fig. 3. Arm radiographs of patient IV2. Right arms at (**a**) age 8 and (**b**) 21 years. Left arm at ages (**c**) 8 and (**d**) 21 years. Note progressively bowed radii, large distal humeri, and overlapped carpal bones. Flexion contracture of the distal interphalangeal joints (DIPJ) of fingers 4 and 5 on both sides.



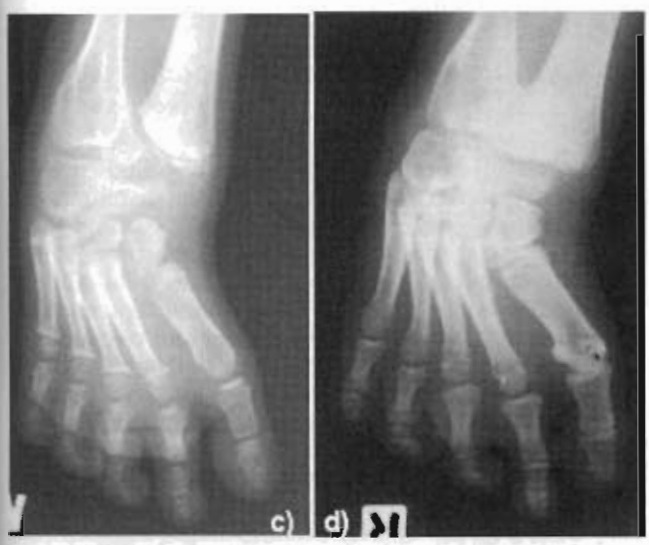


Fig. 4. Foot and ankle radiographs of patient IV2. **a**: Left foot at ages 8 and (**b**) 21 years. Note large distal end of fibula with "fibular prominence," malformed talus, and absence of calcaneus. Right foot at ages (**c**) 8 and (**d**) 21 years. Malformed talus is fused with fibula at age 8 years. Calcaneus is missing. Tibia-talus-fibula synostosis and overlapped tarsal bones with narrow spaces between them at age 21. Note distal symphalangism at toe 5 at age 21.

Distal humeri appear large with dumbbell-shape. This was seen in all affected adults.

Lower Limbs

At age 21 years, right tibia, malformed talus, and distal fibula are fused. The distal ends of the fibulae appeared large especially that of the right one. Spaces between tarsal bones are narrow, resulting in overlapping of tarsal bones. Distal symphalangism of toes 5 is noted in him and patients III17, III26, and IV6. Distal symphalangism of toes 4 is found in Patient III26. In

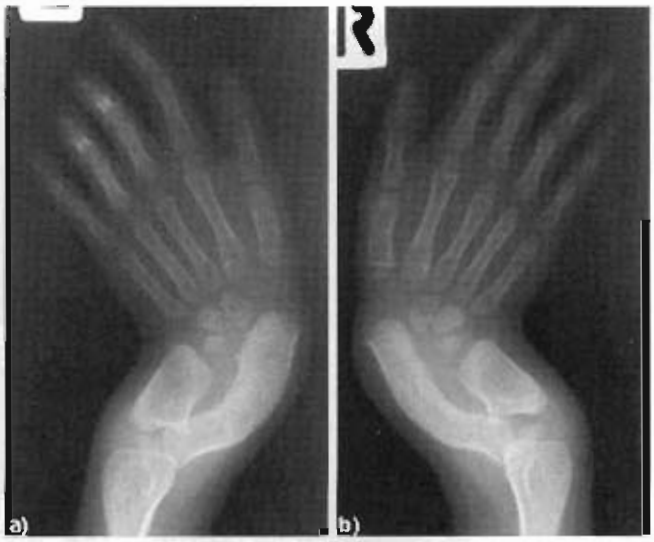


Fig. 5. Arm and hand radiographs of patient V1 at age 4 years. Absence of trapezium, trapezoid, scaphoid, lunate, and triquetrum. Distal humeri were large. No epiphyses of radii and ulnae were evident.

Patient III11, proximal and distal symphalangism are observed at the left toes 2 and 5.

COMMENTS ON THE PAPER OF SHEARS ET AL.

I had the honor to review the very interesting paper of Shears et al. in this issue of *Am J Med Genet*, claiming to report the second reported family of MDK. The upper limb findings are similar to those of the original Thai family. However, the ulnae and radii of the Thai patients are more severely affected, showing more shortening and the radii are more severely bowed (Fig. 3a–d). The arrangement of the carpal bones in all Thai adult patients is more disorganized with narrow spaces among them or some fusion between them. This is not seen in the 4-year-old one. Interestingly as reported in the authors' patients, all Thai patients including the new member of the family have flexion contracture of the PIPJs of the 4th and 5th fingers (Figs. 3 and 5). Flexion contracture of other PIPJ and DIPJ is also observed in other patients. Report of flexion contracture was missed in my original paper.

The similarities between the Thai patients and those of the authors consist of shortening of radii and ulnae, flexion contracture of fingers 4 and 5, tarsal synostosis, talus–calcaneus fusion, and broad distal end of fibula. However, the authors' patients did not look disproportionately short as the Thai patients did. It appears that tibiae of the Thai patients are more severely affected. In addition, they also do not stand like "ballerinas" as the Thai patients do (Fig. 6a–g). I am convinced that "ballerina-like standing" is the result of misarticulation between tibia and talus leading to sharing of the same long axis of the tibia and tarsal bones. Most importantly, the authors' patients do not have fibular prominence,

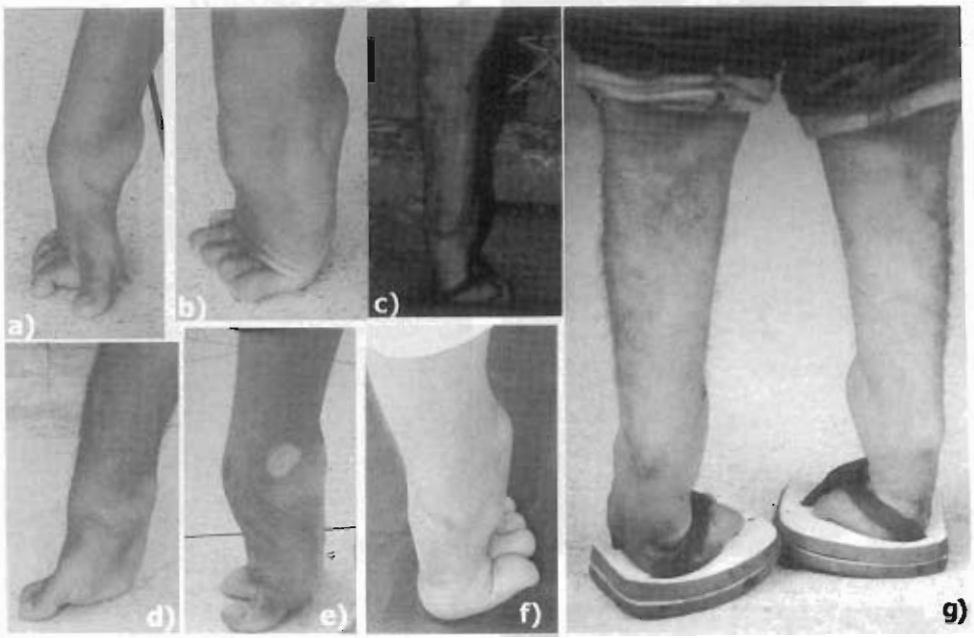


Fig. 6. Tip toe standing on the dorsal of Patients (**a**) and (**b**) V1. **d**: IV2. **e**: III7. Ballerina-like standing of Patients (**c**) III2, (**f**) III17, and (**g**) III11.

which is seen in all affected Thai patients even in the 4-year old one (Fig. 7). This finding appears to be the most consistent or "signature" finding of the syndrome.

The 4-year-old new member of the Thai family has provided us the better understanding of the syndrome. She is the youngest reported patient affected with MDK. Her findings have helped us to understand the development of this rare skeletal dysplasia; especially the prominent bone that we originally called "fibulo-calcaneal complex." The original understanding was based on the absence of a separate calcaneus and there was no fusion line in the large malformed bones. The radiograph of the 4-year-old showed left fibular prominence and a separate calcaneus, indicating that the prominent bone was solely fibula and calcaneus is missing in most Thai patients. Interestingly, the prominent fibula bone is not observed yet on the right fibula. Follow up report is needed in order to understand more on this endochondral bone formation. Regarding the fibula, which was hypoplastic in most Thai patients, in those with normal fibula, it articulated with tibial bony knot (Fig. 8a–d). This is found in four affected ones (II9, II10, III7, and III11). It is noteworthy that both original affected twins died of diabetic mellitus at the ages of 61 and 62.

In conclusion, with less severely affected radii and ulnae, the absence of ballerina-like standing, and the

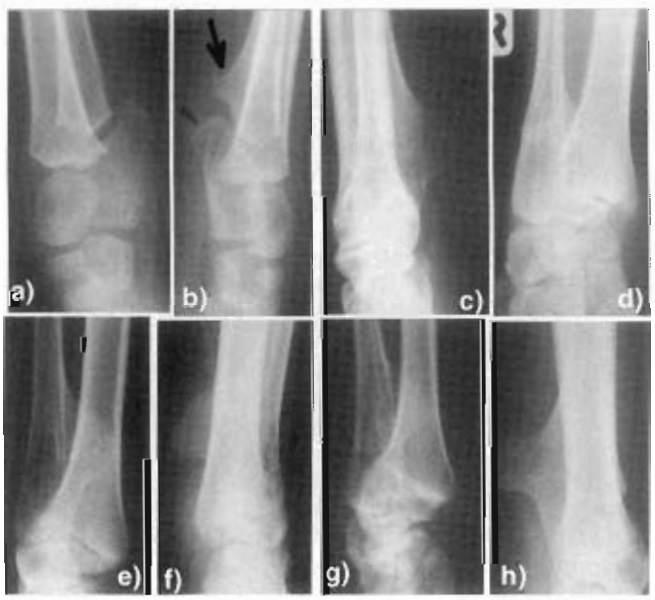


Fig. 7. Ankle radiographs of (**a**) Patient V1. Right ankle. Note vertical-positioned calcaneus. No fibular prominence. **b**: Patient V1. Left ankle. Note fibular prominence (arrow). Malformed and separate calcaneus (arrow head). Fibular prominences in Patients (**c**) IV2, (**d**) IV7, (**e**) IV6, (**f**) III11, (**g**) III7, (**h**) III17.

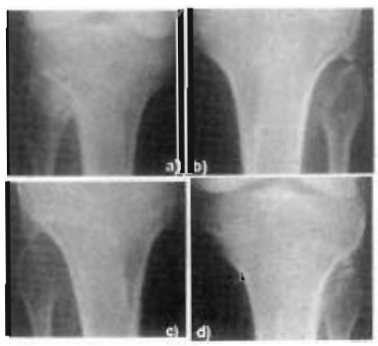


Fig. 8. **a–d**: Tibial bony knot articulates with fibula.

absence of characteristic fibular prominence, I believe the syndrome described by Shears et al. [2003] is unique and deserves its own distinct entity. However, I am convinced that the syndrome is allelic to MDK.

ACKNOWLEDGMENTS

I would like to thank all the patients for their friendship and help in making this project possible. This work is dedicated to Dr. Montri and Mrs. Penprapa Kantaputra, my father and mother.

REFERENCES

Fujimoto M, Kantaputra PN, Ikegawa S, Fukushima Y, Sonta S, Matsuo M, Ishida T, Matsumoto T, Kondo S, Tomita H, Deng HX, D'urso M, Rinaldi MM, Ventruto V, Takagi T, Nakamura Y, Niikawa N. 1998. The gene for mesomelic dysplasia, Kantaputra type is mapped to chromosome 2q24-q32. J Hum Genet 43:32–36.

Kantaputra PN, Gorlin RJ, Langer LO. 1992. Dominant mesomelic dysplasia, ankle, carpal, and tarsal synostosis type: A new type autosomal dominant bone disorder. Am J Med Genet 44:730–737.

Shears DJ, Offiah A, Rutland P, Bither-Glndzing M, Christine H. 2003. Kantaputra mesomelic dysplasia: A second reported family. Am J Med Genet (in press).

American Journal of Medical Genetics 130A:181–190 (2004)

Clinical Report

Microcephalic Osteodysplastic Primordial Dwarfism With Severe Microdontia and Skin Anomalies: Confirmation of a New Syndrome

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We report two related Thai children having a new syndrome of microcephalic osteodysplastic primordial dwarfism (MOPD). The findings which classify them as having MOPD include IUGR, microcephaly, prominent nose and nasal bridge, small pinnae, short stature, cone-shaped and ivory-epiphyses, delayed bone age, slender long bones, and abnormal pelvis. The findings that distinguish them as having newly recognized syndrome consist of severe microdontia, malformed teeth, single-rooted or rootless teeth, severely hypoplastic alveolar bone, café au lait spots, acanthosis nigricans, and areas of hypo- and hyperpigmented skin. The reported patients appear to have the same condition as the family reported by Kantaputra [2002: Am J Med Genet 111:420–428]. This article contains supplementary material, which may be viewed at the American Journal of Medical Genetics website at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html.

KEY WORDS: hyperpigmented skin; hypopigmented skin; hypoplastic alveolar bone; malformed tooth; microdontia; rootless tooth

INTRODUCTION

In 2002, Kantaputra reported a newly recognized autosomal recessive syndrome of microcephalic osteodysplastic primordial dwarfism (MOPD). The uniqueness of that syndrome is the presence of dental, digital, and skin anomalies. The dental anomalies are striking, consisting of severe microdontia, opalescent and rootless molars, and an unerupted tooth. The mandibular premolars are unusually small and malformed, comprising many cusps. In addition, the alveolar process is severely hypoplastic. Digital anomalies include unusually long second toes, distal symphalangism of toes, and brachymesophalangy of fingers. Skin anomalies include café au lait spots, and areas of hypo- and hyperpigmented skin. The hair is dry and sparse [Kantaputra, 2002]. After reviewing all previously reported cases of MOPD, we found that 12 cases of MOPD with microdontia have been reported (Tables I and II). We hypothesize that MOPD with severe microdontia with or without skin anomalies should be classified as a distinct entity.

We report on two related Thai patients with MOPD syndrome, who share many characteristic findings of the novel syndrome reported by Kantaputra [2002].

CLINICAL REPORT

Patient 1

Patient 1 was a 7-year-old boy. He was the only child of healthy, nonconsanguineous parents (Figs. 1 and 2a). He was born at term with weight 1,270 g (<3 centile; <−7.4 SD), length 37 cm (<3 centile; <−8.6 SD), and OFC 28 cm (<3 centile; <−3 SD). At the age of 3, his growth was moderately delayed with a development quotient of 42.

On examination at age 7, he was a cheerful boy with microcephaly, prominent nose and nasal bridge, small pinnae, high-pitched voice, and proportionate short stature (Fig. 2a). His height, weight, and OFC were 83 cm (<3rd centile; <−8.5 SD), 9.5 kg (<3rd centile; <−6 SD), and 41.5 cm (<3rd centile; <−5.5 SD), respectively. His upper and lower ratio was appropriate for age (1.1:1), but his arm span (73 cm) was relatively shorter than his height due to limited elbow extension. Limited abduction of the hips was observed. Clinodactyly of the fifth fingers, deep palmar creases, and medially-deviated toes were noted. Penis and testis were unremarkable. Hearing via auditory brainstem response (ABR) was unremarkable, and development remained globally delayed. Growth hormone secretion following clonidine stimulation at age 3 was normal. Karyotype was 46,XY.

Skin complexion was darker than that of his parents. There were areas of hypo- and hyperpigmentation of the skin which did not follow lines of Blaschko (Fig. 2a,b). The palms appeared hyperpigmented (Fig. 2c). Café-au-lait spots were observed on his body, hands, and thigh (Fig. 2b). Hair was normal.

Oral examination revealed normal shape and color of deciduous crowns. All teeth were mobile. Most deciduous incisors appeared to have premature exfoliation. The remaining deciduous teeth were slightly small. The permanent teeth, especially the maxillary and mandibular permanent incisors were extremely small. The mesiodistal width of a mandibular incisor was 3 mm. The mamelons of all incisors were prominent (Fig. 3a). The carabelli cusp of the maxillary second deciduous molar was large. The mandibular and maxillary right deciduous second molars exfoliated at age 5. The pharynx was very narrow.

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TABLE I. Clinical Manifestations of MOPD Patients With Microdontia With/Without Skin Anomalies

	Cervenka et al. [1979]		Majewski et al. [1982]		Shebib et al. [1991]	Lin et al. [1995]		Majewski and Goecke [1998]		Seymen et al. [2002]	Kantaputra [2002]		Present cases	
	Pt1	Pt2	Pt1	Pt2		Pt1	Pt2	Pt2	Pt3		Pt1	Pt2	Pt1	Pt2
Mode of inheritance	AR	AR	Na	Na	AR	AR	AR	AR	Na	Na	AR	AR	AR	AR
Gender	M	M	M	F	F	M	M	M	M	M	M	F	M	F
Examination														
General														
Age when reported (year)	8	11	2	3	7	10	15	2	2	7	18	16	8	9
Weight (kg)	8	15	6.3	4.2	5.4	18	31	5	6.1	7	14	12	9.5	9.5
Height (cm)	85	104	63.8	61	67	116	125	60.4	65.0	78	102	96	83	83
OFC (cm)	41	44	37	31.5	37.5	47.5	48	40.4	41	40.5	43	41	38.5	38.5
Dis/proportionate short	P	P	P*	P*	D	P	P	D	D	P	P	P	P	P
Postnatal GR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Dev delay/MR	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	Y
Hypertonia	Y	Y	N	N	N	N	N	Y	N	N	N	N	N	N
High-piched voice	Y	Y	Y	Y	Na	Na	Na	Y	Y	N	N	N	Y	Y
Birth history														
Birth weight (g)	1,040	1,500	1,280	1,150	1,250	1,700	1,480	1,320	1,300	800	1,000	1,000	1,270	920
Birth length (cm)	34	Na	38	Na	30	Na	Na	37	39[a]	35	Na	Na	37	31
OFC (cm)	25.5	Na	27.5	Na	Na	Na	Na	28	27.5	25	Na	Na	28	24.5
IUGR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Craniofacial														
Microcephaly	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Craniosynostosis	Na	Na	Y	Y	Y	Na	Na	Na	N	Na	N	N	Y	Y
Strabismus	N	Na	Na	Na	Na	N	Na	Na	N	Na	N	N	N	Y
Small/abnormal pinnae	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Prominent nose	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y
Small maxilla	Na	Na	Na	Na	Na	Na	Na	Na	Na	Y	Y	Y	Y	Y
Micrognathic mandible	Y	Y	Y	Y	Y	Na	Na	Y	Y	Y	Y	Y	Y	Y
Retrognathic mandible	Y	Na	Y	Na	N	Na	Na	Y	Y	Y	N	N	N	N
Teeth														
Microdontia of prim teeth	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Microdontia of perm teeth	Y	Y	Na	Na	Y	Y	Y	Na	Na	Y	Y	Y	Y	Y
Hypodontia	N	Na	Na	Na	Y	N	N	Na	Na	Y	N	N	Y	Y
Taurodontism	N	Na	Na	Na	Na	N	N	Na	Na	Y	N	N	N	N
Malformed teeth	N	Na	N	N	Na	N	N	Na	Na	Y	Y	Y	Y	Y
Opalescent teeth	N	Na	Na	N	Na	N	N	Na	Na	N	Y	Y	N	N
Short root/rootless	Y	Y	Na	Na	Y	Y	Na	Na	Na	Y	Y	Y	Y	Y
Unerupted tooth	N	Na	Na	Na	N	N	N	Na	Na	N	N	Y	N	N
Hair and skin														
Dry/sparse hair	Y	Y	Y	Y	N	Na	Na	Na	Na	Na	Y	Y	N	N
Hyperhirsute	Y	Y	Na	Na	N	Na	Na	Na	Na	Na	N	N	N	N
Skin hyperpigment	N	N	Na	Na	N	Na	Na	Na	Y	Na	Y	Y	Y	Y
Café au lait spots	N	N	Na	Na	Na	Na	Na	Y	Y	Na	Y	Y	Y	Y
Acanthosis nigricans	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	N	N	N	Y
Sclerotic skin	Y	N	Na	Na	Na	Na	Na	Na	Na	Na	N	N	N	N
Arms and hands														
Bowed arms	Na	Na	N	Na	Y	N	N	Na	N	Y	N	N	Y	N
Radial head dislocation	Na	Na	Na	Na	N	N	N	Na	Na	Y	Y	Y	Y	N
Clinodactyly V	Y	Y	Y	Y	Y	Na	Na	Y	Y	Na	N	N	Y	Y
Legs														
Bowed legs	N	N	N	N	N	Na	Na	N	N	Na	N	N	N	N
Coxa valga	Na	Na	N	N	N	Y	Y	N	N	N	Na	Na	N	N
Coxa vara	Na	Na	Y	Y	Y	N	N	Y	Y	Y	Na	Na	N	N
Genitalia (male)														
Cryptorchidism	Y	N	N	—	—	Na	Na	Na	Na	Na	N	—	N	—
Small testis	Na	N	Y	—	—	Na	Na	Na	Na	Na	N	—	N	—
Small penis	N	N	Y	—	—	Na	Na	Na	Na	Na	N	—	N	—

TABLE II. Radiographic Findings of MOPD Patients With Microdontia With/Without Skin Anomalies

	Cervenka et al. [1979]		Majewski et al. [1982]		Shebib et al. [1991]	Lin et al. [1995]		Majewski and Goecke [1998]		Seymen et al. [2002]	Kantaputra [2002]		Present cases	
	Pt1	Pt2	Pt1	Pt2		Pt1	Pt2	Pt2	Pt3		Pt1	Pt2	Pt1	Pt2
Craniofacial														
Increased digital marking	Na	Na	Na	Na	Na	Na	Na	Na	Na	Na	Y	Y	Y	Y
Hypoplastic alv bone	Y	Y	Na	Na	Y	Y	Na	Na	Na	Y	Y	Y	Y	Y
Arms and Hands														
Angular carpal bone	Na	Na	Na?	Na	Y	Na	PIC	Na	PIC	Na	Y	Y	Y	Y
Pseudoepiphysis of MC	Na	Na	Y	Y	Y	Y	Y	Y	Y	Na	N	N	N	Y
Ivory epiphyses	Y	N	N	Na	Y	N	Y	Na	N	Na	Y	Y	Y	Y
Cone-shaped epiphysis	N	N	N	Na	Y	Na	Y	Na	N	Na	Y	Y	Y	Y
Delayed bone age	N	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y
Pelvis and legs														
Hypoplastic/narrow pelvis	Na	Na	Y	Y	Y*	Y	Y	Y	N	Na	Y	Y	Y	Y
Epiphysiolysis of hips	Na	Na	Y	Y	N	N	N	N	Na	Na	N	N	Y	N
Triangular of distal femoral epiphyses	Na	Na	Y	Na	Y	N	N	Y	Y	Na	N	N	N	N
Flaring of distal femeral metaphysis	Na	Na	Y	Y	Y	Y	Y	Y	Y	Na	N	N	Y	Y
Feet														
Ivory epiphysis	Na	Na	Na	Na	Y	Na	Na	Na	Na	Na	N	N	N	Y
Distal symphalangism of toes	Na	Na	Na	Na	Na	N	N	Na	Na	Na	Y	Y	Y	N
Chest														
Long/slender clavicles	Na	Na	Na	Na	Y	Na	Na	Na	N	Na	Y	Y	Y	Y
Hypoplastic scapula	Na	Na	Na	Na	Na	Na	Na	Na	N	Na	Y	Y	Y	Y
11 ribs	Na	Y	Na	Na	Y	Na	Na	Na	N	Na	Y	Y	N	N

Y, present; N, absent; Na, not available.
Patients reported by Cervenka et al. [1979] were reported again in 1981 by Tsuchiya et al. [1981].
*Disproportionately short during the early years of life.

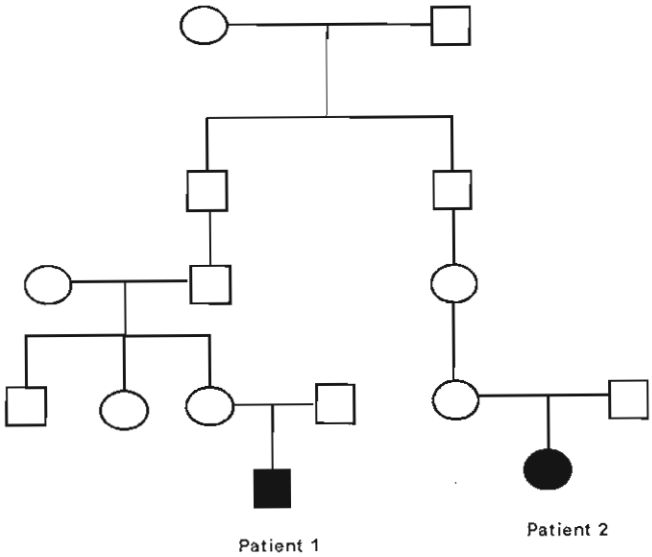
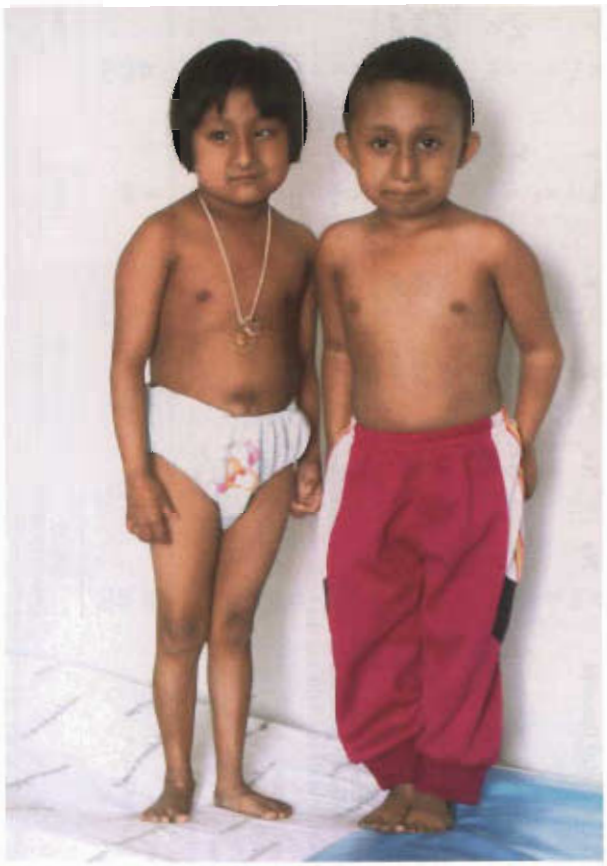


Fig. 1. Pedigree of the families.

Radiographic examination showed thin cranium. Molars were either single- and short-rooted, or rootless (Fig. 4a,b). Obliteration of the root canals was seen in all incisors (Fig. 5a,b). Alveolar process was severely hypoplastic and its cortical bone was not evident. Supernumerary maxillary right permanent molar was noted. All unerupted developing permanent teeth were malformed and very small mesiodistally. Digital marking of the skull was observed (Fig. 4a,b). Clavicles were long, straight, and slender. Scapulae were hypoplastic. There were 11 ribs on each side. The radius and ulna were slender. Radius was slightly bowed and the radial heads were dislocated. There was restricted supination and extension at the elbows.

According to Greulich and Pyle, the bone-age was delayed at age 3 years 3 months and estimated to around age 1 year (SD = 6.6 months). Middle phalanges of finger 5 appeared short and tapered proximo-distally. Epiphyses were observed only at the proximal phalanges of fingers 2–4 (see the online Figure 8a at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). At age 6, bone age was estimated to be of 5 years (SD = 9 months). Distal ulna was slightly short with ulnar deviation of the hand. Ivory epiphyses were observed at proximal phalanges of thumbs, all phalanges of fingers 3 and 4, and the middle and distal phalanges of fingers 2. Cone-shaped epiphyses of the proximal phalanges of fingers

a



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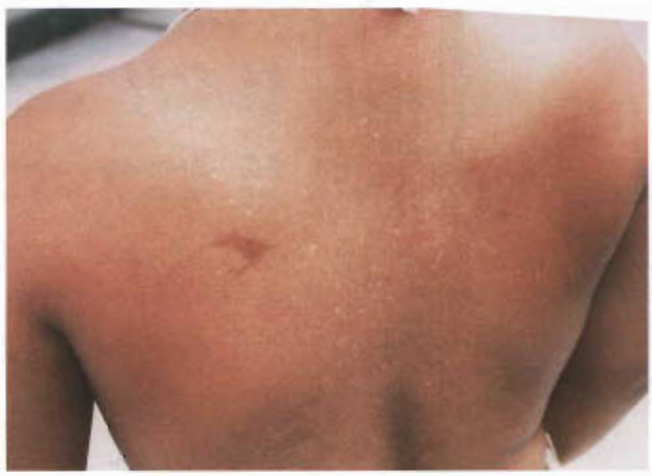

Fig. 2. a: Patient 2 (left) and 1 (right). Note prominent nose and nasal bridge, dark skin, exotropia of Patient 2's eye. b: Dark skin with areas of hypo- and hyperpigmented macules and café au lait spot. c: Hyperpigmented palms.

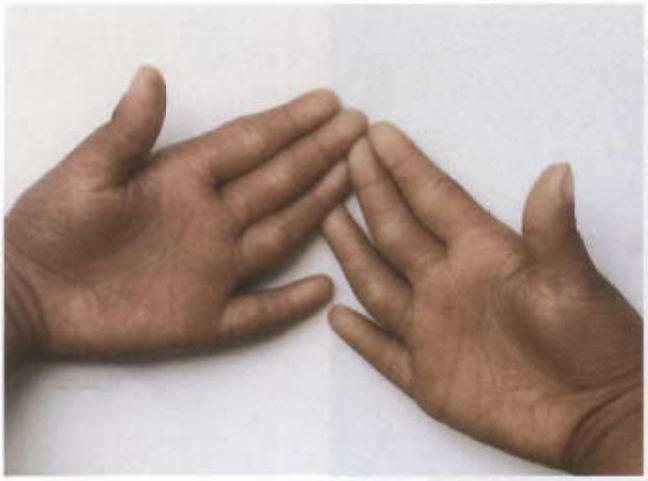

Fig. 2. (*Continued*)

2–4 were observed (see the online Figure 8b at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). Pelvic radiograph demonstrated narrow iliac wings, flat acetabular sockets, thin and elongated pubic and ischial bones, and bilateral epiphysiolysis of the femoral heads (see the online Figure 6b at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). Foot radiograph showed hypoplastic distal phalanges of toes 2–4, ivory epiphyses of proximal phalanges 5, and distal symphalangism of toe 5.

Patient 2

Patient 2 was a 9-year-old girl. She was the only child of healthy and nonconsanguineous parents (Figs. 1 and 2a). Her maternal great grandfather was the younger brother of the great grandfather of Patient 1 (Fig. 1). The patient was born at 32 weeks of pregnancy. Her birth weight, birth length, and OFC were 920 g (<3rd centile; <−1.7 SD), 31 cm (<3 centile; <−2.5 SD), and 24.5 cm (<3rd centile; −1.8 SD), respectively. At birth she suffered from mild respiratory distress syndrome, hyperbilirubinemia, and retinopathy of prematurity, and was in an incubator for 2.5 months. Growth hormone stimulation test with glucagon revealed peak of growth hormone of 2.6 ng/ml (norm >10 ng/ml). IGF1 = 0 ng/ml (norm 7–21 ng/ml). IGBP3 = 2,096 ng/ml. The results indicated primary growth hormone deficiency.

On examination at age 8, her height, weight, and OFC were 83 cm (<3 centile; <−8.9 SD; 50 centile of age 20 months), 8.3 k (<3 centile; <−5.6 SD; 50 centile of age 17 months), and 38.5 cm (<3rd centile; <−8.8 SD; 50 centile of age 2 months), respectively. Physical examination revealed microcephaly, left esotropia, prominent nose and nasal bridge, and small pinnae (Fig. 2a). Proportionate short stature was noted with 1:1 upper and lower segment ratio. Hands, arms, feet, and legs were proportionately short. Arm span was 81.5 cm. Movement of the shoulders, elbows, wrists, hips, knees, and ankles was unremarkable. Palms were dry, and deep palmar and finger flexion creases were noted. Clinodactyly of the fifth fingers was observed. The hair and hearing were normal.

Like that of Patient 1, her skin complexion was darker than that of her parents. Also there were areas of hypo- and hyperpigmented macules in the skin of her chest and back (Fig. 2a). Acanthosis nigricans was observed around her neck and armpits. She sat, stood, walked, and ran at

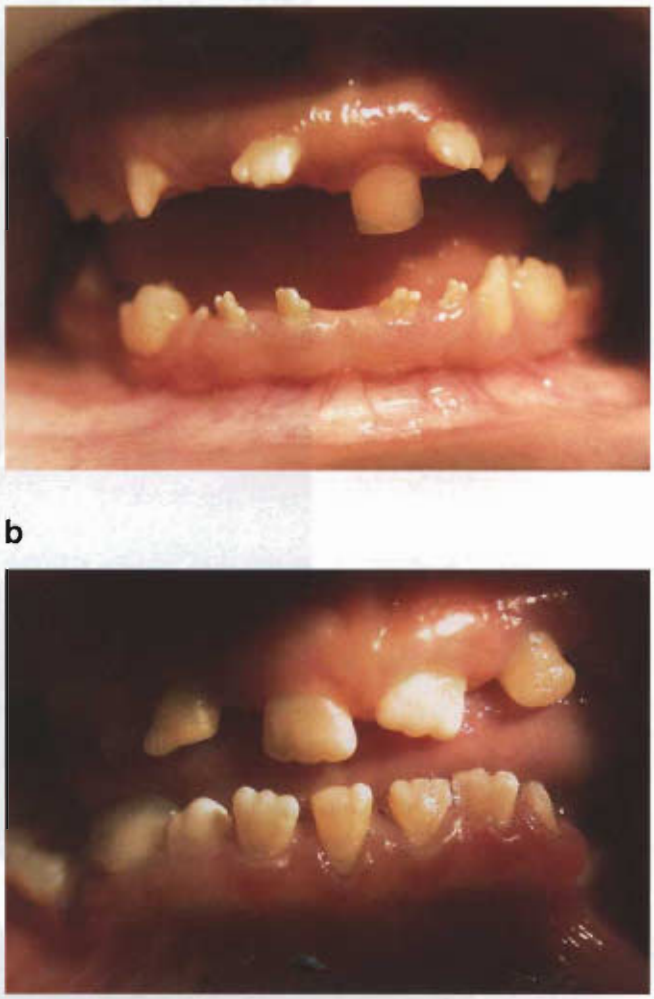

Fig. 3. **a**: Patient 1. Extremely small maxillary and mandibular permanent incisors with prominent mamelons. **b**: Patient 2. Very small and yellowish permenent incisors with prominent mamelons.

ages 9, 18, 22, and 28 months, respectively, and she used single words at 18 months. Her voice was high-pitched, and global developmental delay was observed, with cheerful disposition. Intelligence quotient was 56 according to Stanford Binet form. Karyotype was 46,XX.

Oral examination demonstrated very small and yellowish teeth. Their mamelons were prominent (Fig. 3b). All teeth were mobile. The maxillary right second deciduous molar exfoliated at age 5. The maxillary left first permanent molar had occlusal caries. The maxillary labial frenum was thick. Her gingiva did not appear hyperpigmented like her skin, and was otherwise normal. The pharynx was narrow.

Radiographic examination showed thin cranium, rootless molars, and severely hypoplastic alveolar bone. Cortical bone of the alveolar process was not observed. Rootless molars appeared to float in loose alveolar bone. The crowns of all permanent molars were tapered occluso-cervically. Increased digital marking of the skull was noted (Fig. 4c,d). The dental pulps of all incisors appeared obliterated (Fig. 5c,d). Clavicles were long, straight, and slender. They appeared to be located in horizontal position. Scapulae were hypoplastic. At age 6, hand radiograph showed ivory epiphyses at all

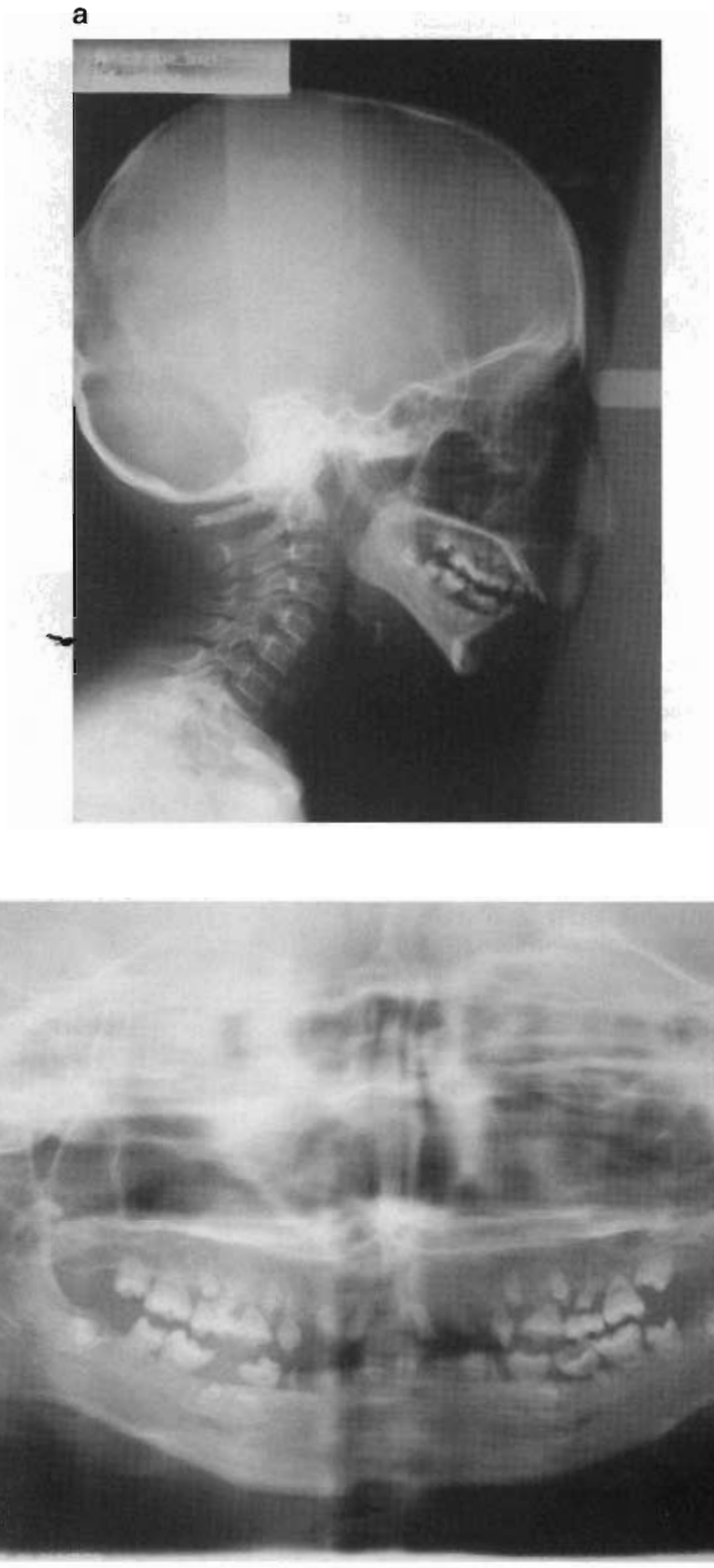

Fig. 4. Patient 1 (**a**) lateral cephalograph. Note increased digital marking of the skull. **b**: Panoramic radiograph. Supernumerary right maxillary permanent molar. Patient 2 (**c**) PA skull radiograph. **d**: Panoramic radiograph. Note single-rooted or rootless molars, severe microdontia of developing permanent premolars and molars, severely hypoplastic alveolar bone, and molar crowns converge occluso-cervically.

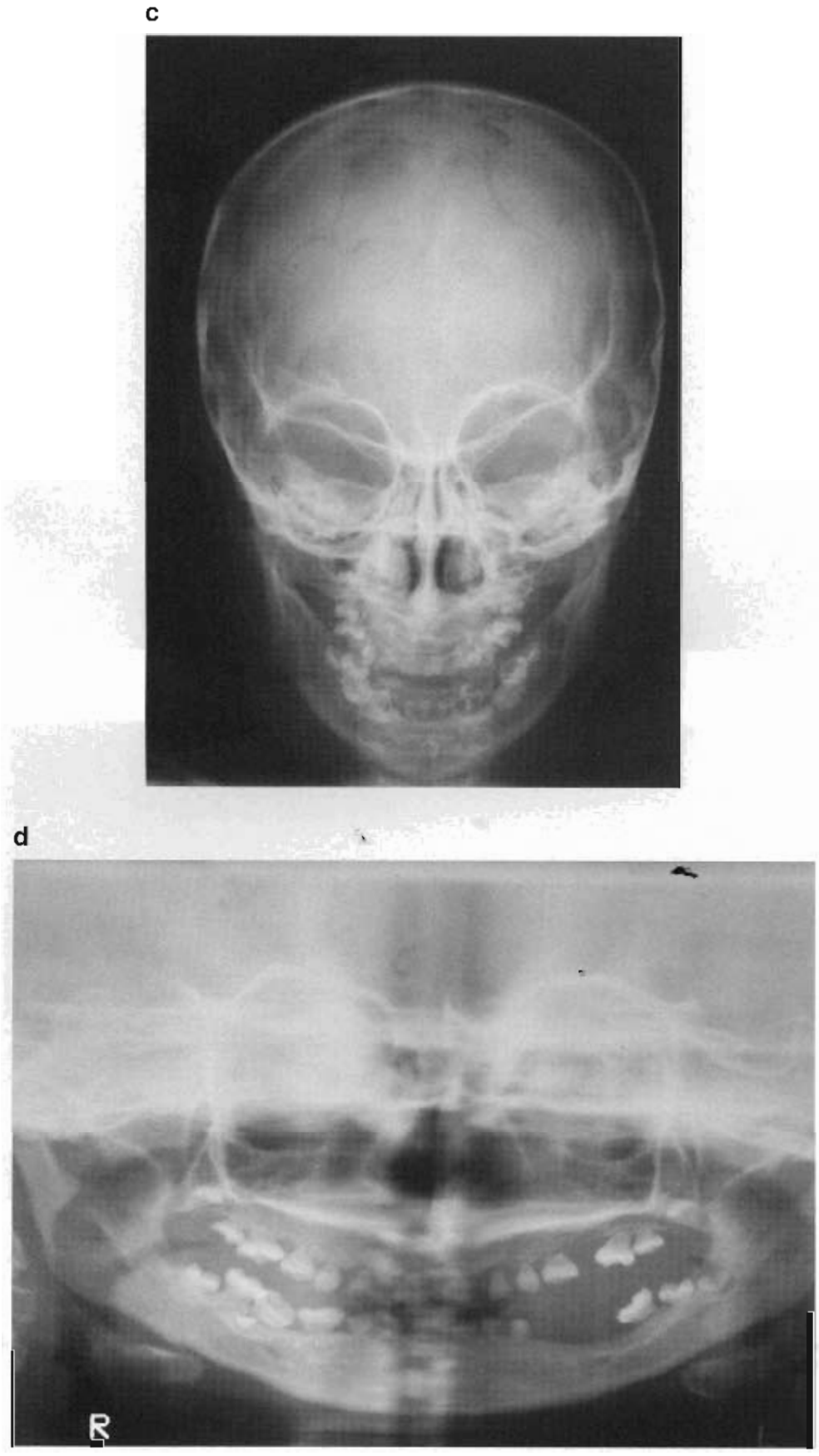

Fig. 4. (*Continued*)

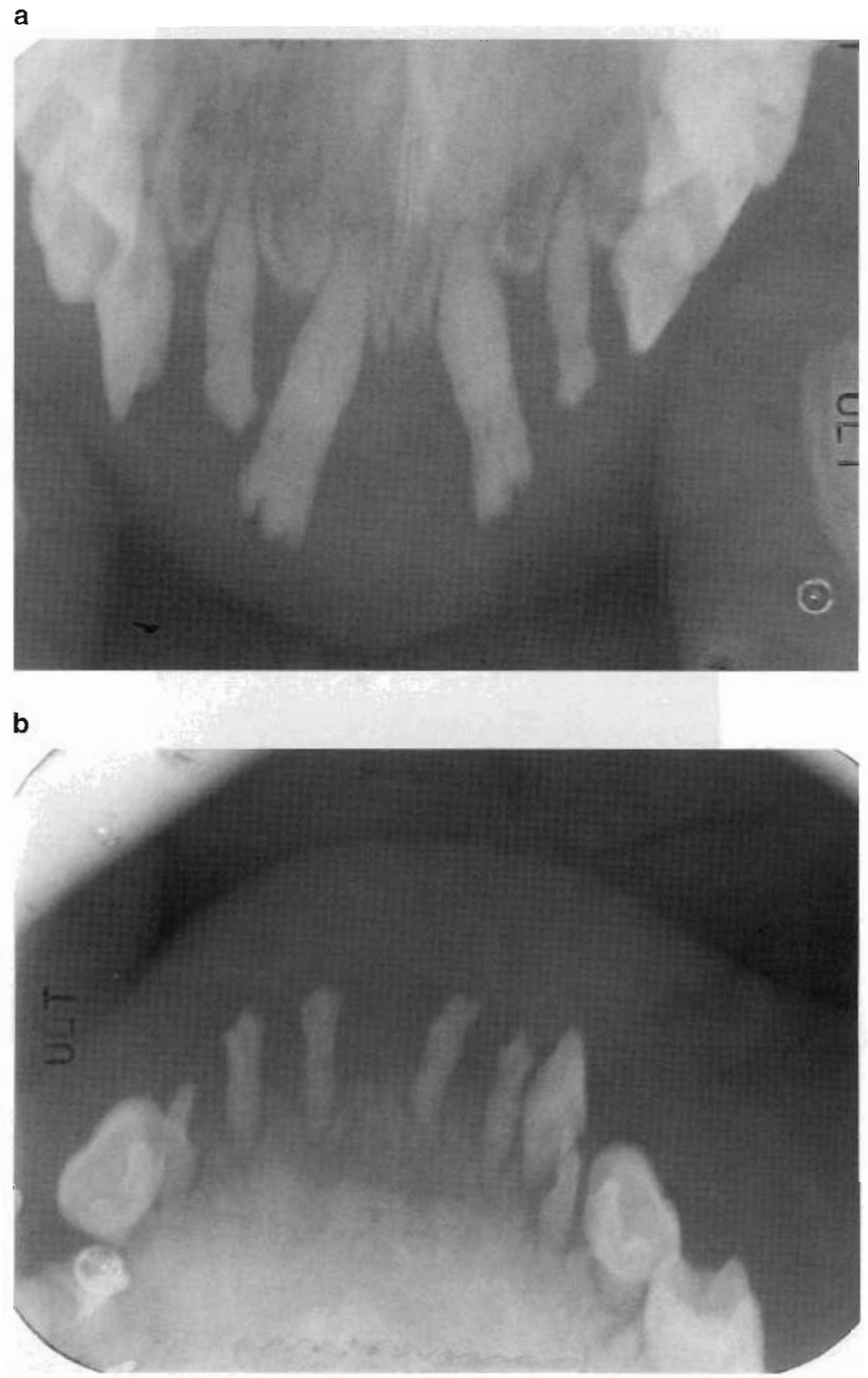

Fig. 5. Periapical radiographs of Maxillary and mandibular incisors of Patient 1 (a) and (b). Patient 2 (c) and (d). Note Severely hypoplastic alveolar bone. Obliteration of dental pulp chambers and root canals.

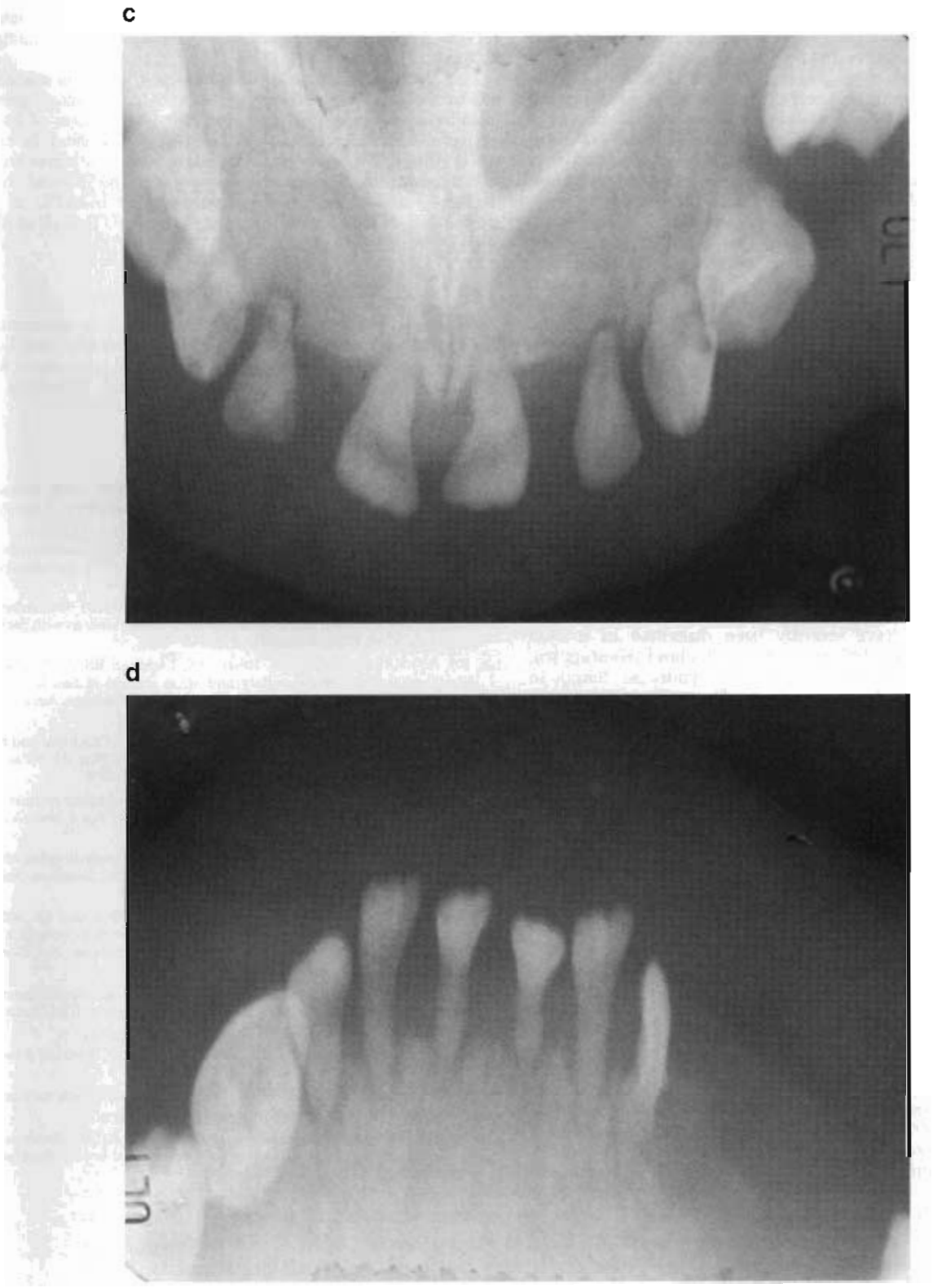

Fig. 5. *(Continued)*

phalanges except at the distal phalanges of her thumbs and the middle and distal phalanges of her 5th fingers, with bone age at 2.6–3 years (see the online Figure 8c at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). At age 8, ivory epiphyses were observed at all phalanges of the hands except for the distal phalanges of thumbs. Large pseudoepiphyses were noted at the proximal ends of metacarpals 2 and 5, and distal radial epiphyses appeared very dense (see the online Figure 8d at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). Eleven ribs were observed on each side. Like those of Patient 1, clavicles were straight and slender (see the online Figure 6a at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). Humerus, radius, ulna, tibia, and fibula were slender (see the online Figure 7b at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). Foot radiograph showed medially deviated toes and ivory epiphyses of all proximal phalanges and distal phalanges 2–5 (see the online Figure 9 at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html).

DISCUSSION

We report on two additional Thai children affected with MOPD and severe microdontia, short and single-rooted molars, rootless molars, and severely hypoplastic alveolar bone, hyperpigmented skin, acanthosis nigricans, café au lait spots, and hypo- and hyperpigmented macules. The combination of dental and dermal features found in these two related children appears unique for MOPD. Interestingly, similar findings have recently been described in a Thai family living in the different part of Thailand [Kantaputra, 2002]. We are convinced that the syndrome found in our patients and that reported by Kantaputra [2002] represents a distinct entity.

Seckel syndrome and MOPD patients usually have normal teeth, and some affected patients even have large teeth [Seckel, 1960; Majewski, 1992; Kjær et al., 2001]. The permanent incisors found in the present patients especially those of Patient 1 were very small. Besides severe microdontia, these patients also had rootless or very short and single-rooted molars, with severely hypoplastic alveolar bone. We have reviewed the previously reported cases of MOPD with microdontia with or without skin anomalies and tabulated them in Tables I and II. Twelve MOPD cases were found to have microdontia. Seven of those had short roots or rootless teeth with severely hypoplastic alveolar processs (Table I). Based on both oral and skin manifestations, we believe the present cases and Thai sibs reported by Kantaputra [2002] have the same disorder.

It appears that the combination of severe microdontia, rootless molars, and severely hypoplastic alveolar bone, café au lait spots, hypo-hyperpigmented macules are the distinguishing features of this "newly" recognized syndrome. Seymen et al., 2002 reported a Turkish boy as having Seckel syndrome. However, with this phenotype and severe microdontia, hypodontia, abnormal molar roots, and hypoplastic alveolar bones, we suspect that he might have the same condition as our patients and those reported by Kantaputra [2002].

The mode of inheritance of this new disorder is suspected to be autosomal-recessive as their maternal great grandfathers were brothers. However, the fathers of both patients denied consanguinity, but they all lived in the same village. While our patients share several features with Seckel syndrome and since it has recently been found that Seckel syndrome is caused by mutations in ATR, it is worthwhile to look for mutation in the gene [O'Driscoll et al., 2003].

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REFERENCES

Cervenka J, Tsuchiya H, Ishiki T, Suzuki M, Mori H. 1979. Seckel's dwarfism: Analysis of chromosome breakage and sister chromatid exchange. Am J Dis Child 133:555–556.

Kantaputra PN. 2002. Apparently new osteodysplastic primordial short stature with severe microdontia, opalescent teeth, rootless molars in two siblings. Am J Med Genet 111:420–428.

Kjær I, Hansen N, Becktor KB, Birkbæk N, Balslev T. 2001. Craniofacial morphology, dentition, and skeletal maturity in four siblings with Seckel syndrome. Cleft Palate Craniofac J 38:645–651.

Lin HJ, Sue GY, Berkowitz CD, Brasel JA, Lachman RS. 1995. Microdontia with severe microcephaly and short stature in two brothers: Osteodysplastic primordial dwarfism with dental findings. Am J Med Genet 58:136–142.

Majewski F. 1992. Invited Editorial Comment: Caroline Crachami and the delineation of osteodysplastic primordial dwarfism type III, an autosomal recessive syndrome. Am J Med Genet 44:203–209.

Majewski F, Goecke TO. 1998. Microcephalic osteodysplastic primordial dwarfism type II: Report of three cases and review. Am J Med Genet 80:25–31.

Majewski F, Ranke M, Schinzel A. 1982. Studies of microcephalic primordial dwarfism II: The osteodysplastic type II of primordial dwarfism. Am J Med Genet 12:23–35.

O'Driscoll M, Ruiz-Perez VL, Woods CG, Jeggo PA, Goodship JA. 2003. A splicing mutation affecting expresion of ataxia-telangiectasia and Rad3-related protein (ATR) results in Seckel syndrome. Nat Genet 33:497–501.

Seckel HPG. 1960. Bird-headed dwarfs: Studies in developmental anthropology including human populations. Springfield, III: Charles C Thomas.

Seymen F, Yuna B, Kayserili H. 2002. Seckel syndrome: Report of a case. J Clin Pediatr Dent 26:305–310.

Shebib S, Hugosson C, Sakati N, Nyhan W. 1991. Osteodysplastic variant of primordial dwarfism. Am J Med Genet 40:146–150.

Tsuchiya H, Kobayashi S, Cervenka J, Mori H, Oguro A. 1981. Analysis of the dentition and orofacial skeleton in Seckel's bird-headed dwarfism. J Maxfac Surg 9:170–175.

A Novel Mutation in *IRF6* Underlies Hearing Loss, Pulp Stones, Large Craniofacial Sinuses, and Limb Anomalies in Van der Woude Syndrome Patients

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Summary: Van der Woude (VWS) and popliteal pterygium syndromes are caused by mutations in the interferon regulatory factor (*IRF6*) gene. Two Thai VWS families demonstrating newly recognized findings of VWS are reported. The phenotype in the first family includes sensorineural hearing loss, cleft lip and palate, lower lip anomalies, ankyloglossia, hypodontia, dental pulp stones, large craniofacial sinuses, and limb anomalies. Molecular analysis of *IRF6* revealed an 11 bp deletion in exon 4. This frameshift mutation truncates IRF6 just after the DNA binding domain. The mutation implies that IRF6 can affect dental pulp calcification, pneumatization of craniofacial sinuses, and ear and limb development. The second family consists of an affected brother and sister. Both have lower lip anomalies and the sister has cleft lip and palate. Interestingly, both have abnormal shape of the mandibular deciduous and permanent molars. Mutation analysis of *IRF6* was negative, suggesting that the mutations may be located outside of the coding exons or in other loci.

Key words: dental pulp stoneIRF6 genelimb anomalyhearing lossVan der Woude syndrome

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INTRODUCTION

Van der Woude syndrome (VWS; OMIM 119300) is characterized by congenital lip pits, cleft lip with or without cleft palate, hypodontia, ankyloglossia, and cutaneous syndactyly of toes. The disorder is caused by mutations in interferon regulatory factor (*IRF6*) and mutations in the same gene also cause popliteal pterygium syndrome (PPS; OMIM 119500) (Kondo et al, 2002). In addition to the VWS phenotype, patients with PPS exhibit webbing of the limbs, toe nail dysplasia, and genital anomalies (Gorlin et al, 2001). From their analysis of 49 VWS mutations and 13 PPS mutations, Kondo et al (2002) suggested that VWS is caused by haploinsufficiency of *IRF6*, whereas PPS is caused by mutations that have a dominant negative effect on IRF6 function.

Recently, we reported a four-generation Thai family with a unique VWS-like phenotype. In addition to lip anomalies, hypodontia, and cleft lip and cleft palate, affected members of this family exhibited sensorineural hearing loss, large craniofacial sinuses, dental pulp stones, and minor limbs anomalies (Kantaputra et al, 2002). Given the VWS-like orofacial features in this

family, we hypothesized that affected members of the family would have a mutation in *IRF6*. With the unique anomalies in this family, we further hypothesized that the mutation would be novel and may provide clues to the structure and function of *IRF6*. Here we report a novel *IRF6* mutation found in this family and suggest that this mutation affects ear and limb development, calcification in the dental pulps, and pneumatization of craniofacial sinuses.

In addition, a new VWS family affected with abnormal shape of mandibular deciduous and permanent molars is reported. Abnormal shape of teeth has never

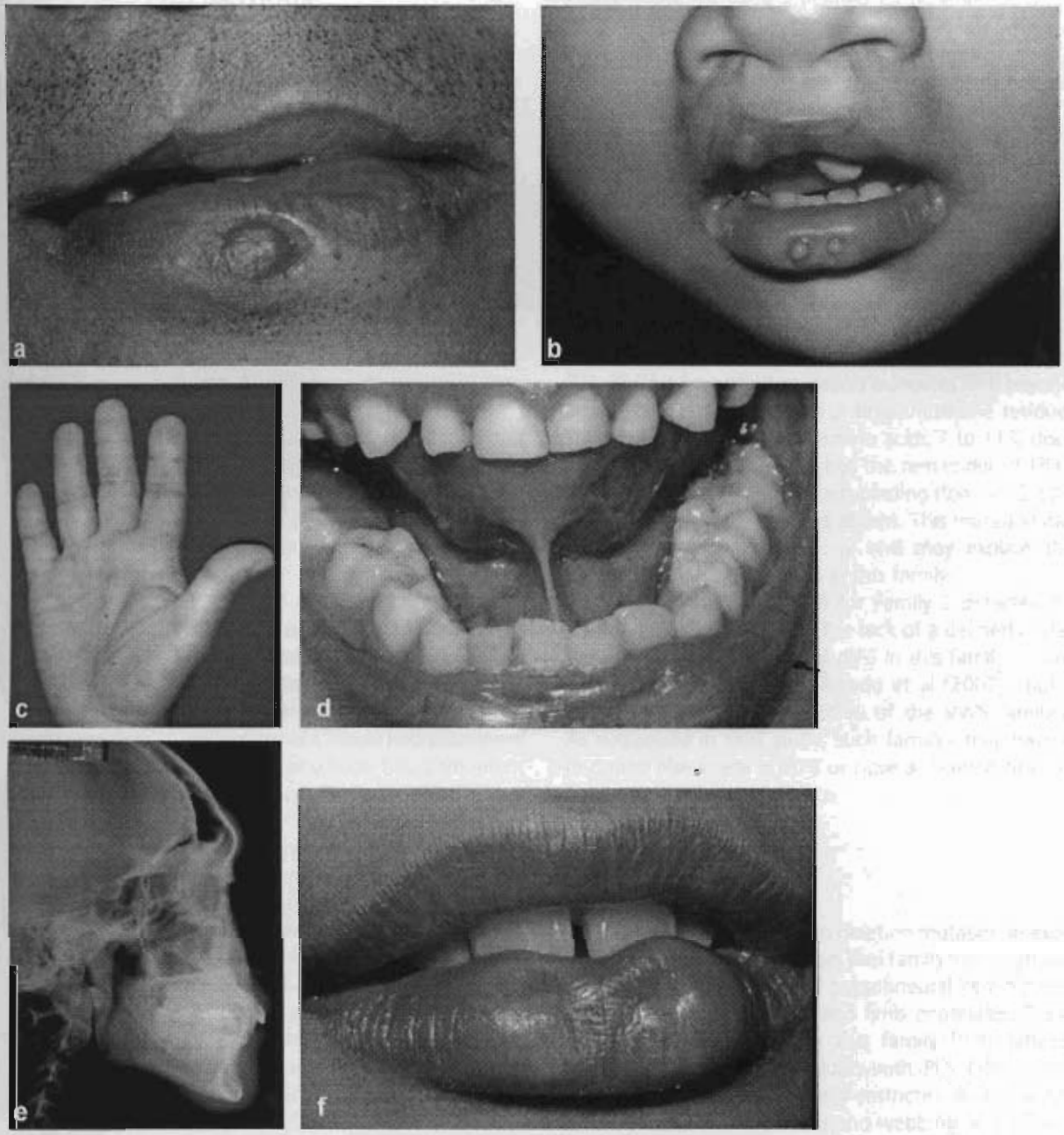

Fig. 1 Family 1: a) Repaired unilateral cleft lip and palate. Lip pit and sulcus; b) Repaired bilateral cleft lip and palate. Lip nipples; c) Single flexion crease of the right fifth finger; d) Ankyloglossia; e) Large frontal sinus; f) Lip sulcuses.

been described to be associated with VWS. The molecular analysis of *IRF6* was negative, supporting the possibilty of VWS-causing mutations outside the coding region, or deletions or mutations in other loci (Kondo et al, 2002).

MATERIALS AND METHODS

Clinical Details

Family 1: This four-generation Thai family consists of 23 individuals, of which seven are affected with VWS. The clinical findings include cleft lip with cleft palate, lower lip anomalies, congenital absence of the mandibular second premolars, ankyloglossia, sensorineural hearing loss, large craniofacial sinuses, long tooth roots, and dental pulp stones. The limb anomalies include a single crease of the fifth finger (Figs. 1a-f), short middle phalanges of the fifth fingers, short middle phalanges of toe 4, short distal phalanges of toes 2 and 3, brachydactyly of fingers, cutaneous syndactyly of toes 2 and 3, and hyperphalangy of toes (Kantaputra et al, 2002).

Family 2: This family consists of an unaffected mother and father, and two affected children (Fig. 1a). The father died of an unrelated disease a few years ago. Clinical manifestations found in the affected daughter (Patient 2.1) were repaired unilateral cleft lip with cleft palate, supernumerary right maxillary lateral incisor, lower lip anomaly, and congenital absence of the mandibular second premolars (Figs. 1a,b). She had cosmetic surgery for her lower lip at age 12 years. The mandibular second deciduous molars had numerous secondary grooves, with prominent lingual cusps. The right mandibular first permanent molar had prominent distolingual cusps. The left mandibular first permanent molar had a very unusual shape. The occlusal table was round, with three prominent lingual cusps and many secondary grooves. The left mandibular second permanent molar was very small with an unusual occlusal configuration (Figs. 2d,e). She had crowding of the maxillary anterior teeth and anterior cross-bite as a result of the hypoplastic maxilla.

The affected son (Patient 2.2) had congenital lip pits and congenital absence of mandibular left second premolar. The shape of his right first permanent molar was unusual. The centrolingual cusp was very prominent, connecting with the mesiobuccal cusp with an oblique ridge (Fig. 2f). The left mandibular second deciduous molar was large mesiodistally, with very a prominent centrolingual cusp (Fig. 2g). The permanent teeth of both patients were affected with dental fluorosis, as a result of high fluoride consumption.

Mutation Analysis

Blood was obtained from all affected individuals and the unaffected mother of Family 2 after the written informed consents were given. DNA was extracted using a conventional technique. Exons 1-8 and part of exons 9 and 10 were amplified by polymerase chain reaction (PCR), using primer sequences as reported elsewhere (Schutte et al, personal communication). The amplified products were purified (Qiagen) and directly sequenced using BigDye labelling in an ABI 377 automated DNA sequencer (Applied Biosystems).

RESULTS

Mutation analysis of all coding exons of *IRF6* for Family 1 revealed an 11 bp deletion within exon 4, 358del(CAG GGC TCG AT), in all affected individuals (Fig. 3). This frameshift mutation truncates IRF6 beyond amino acid P119 and adds a single histidine residue. The DNA binding domain (amino acids 7 to 113) does not appear to be affected, but the remainder of IRF6, including the SMIR/IAD protein binding domain (Eroshkin and Mushegian, 1999) is absent. This mutation has not been reported previously and may explain the unique phenotypic features in this family.

Mutation analysis of *IRF6* for Family 2 detected no disease-causing mutations. The lack of a defined mutation in the coding region of *IRF6* in this family is consistent with the results of Kondo et al (2002); mutations were found in only 50% of the VWS families. As suggested in that study, such families may have a mutation elsewhere in *IRF6* or have a deletion or have a mutation in a second locus.

DISCUSSION

We discovered a novel 11 bp deletion mutation in exon 4 of *IRF6* in a four-generation Thai family with a unique form of VWS that included sensorineural hearing loss, large craniofacial sinuses, and limb anomalies. These anomalies also distinguish this family from families with PPS. Although individuals with PPS exhibit limb anomalies, they are generally restricted to syndactyly of the second and third toes and webbing of the lower limbs which probably reflects a defect in skin development rather than skeletal development. Also, 40% of

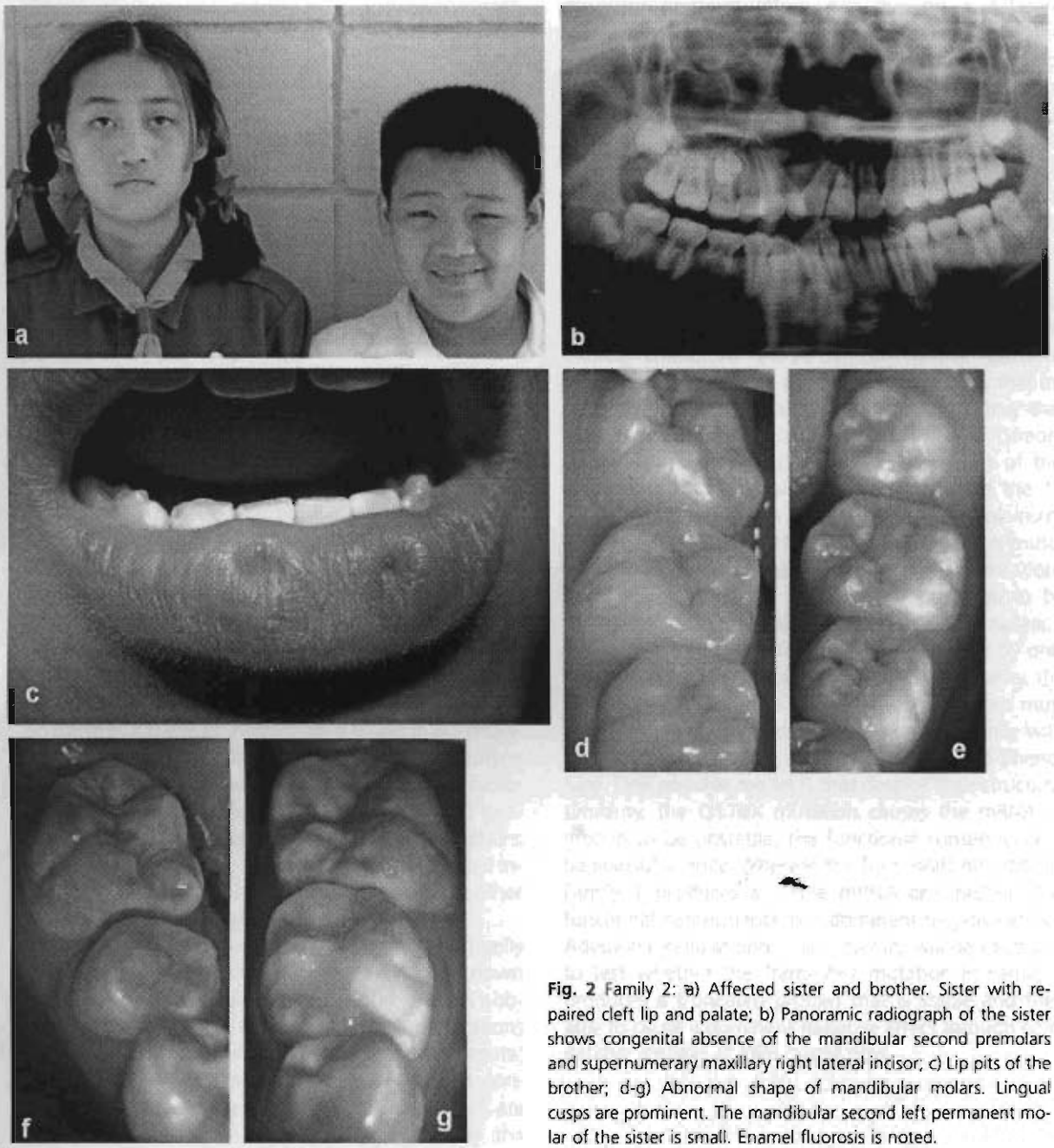

Fig. 2 Family 2: a) Affected sister and brother. Sister with repaired cleft lip and palate; b) Panoramic radiograph of the sister shows congenital absence of the mandibular second premolars and supernumerary maxillary right lateral incisor; c) Lip pits of the brother; d-g) Abnormal shape of mandibular molars. Lingual cusps are prominent. The mandibular second left permanent molar of the sister is small. Enamel fluorosis is noted.

PPS cases exhibit genital anomalies which were not observed in this family. We conclude that this family displays a unique form of VWS. Is the novel mutation found in this family responsible for the unique phenotype?

First, we can try to exclude other genetic and environment factors that might contribute to the novel phenotype. As seen in other VWS families (Burdick et al, 1985), the phenotype in this family is extremely variable and is consistent with the existence of modifying

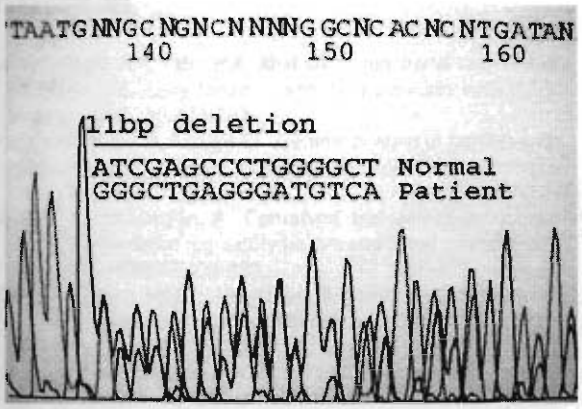

Fig. 3 Sequence from VWS patient with deletion in exon 4 of IRF6. The reverse sequence is shown for the wild type (wt) deleted (del) alleles. The deleted allele is missing 11 nucleotides (lower case) and then picks up the wild type sequence (underlined).

factors. However, six of seven affected individuals in this family had a limb anomaly, four of six had dental anomalies and three of six exhibited deafness. The clustering of these additional anomalies in the affected members of this family suggest a single genetic factor with variable penetrance. The unique phenotype could be due to an intra-genic or linked modifier; however, no other mutations of interest were found in our mutation analysis of *IRF6* in this family. Also, the phenotype is probably not due to a common environment factor since the mothers in this family lived in different geographical regions, different socioeconomic conditions during their pregnancy, and the phenotype of most individuals with VWS in Thailand do not differ from other parts of the world (Shotelersuk et al, 2003).

Second, is this frameshift mutation in this family structurally and functionally distinct from the known PPS-causing mutation in *IRF6*? Kondo et al (2002) observed that nearly all (11/13) PPS-causing-mutations were located in exon 4. However, all of these mutations were missense mutations at residues that contacted the DNA. Consequently, the PPS mutations are predicted to abrogate DNA binding, whereas the frameshift mutation in Family 1 is predicted to leave the DNA-binding domain intact. We conclude that the frameshift mutation in Family 1 is structurally distinct from the known mutations that cause PPS. Functionally, the PPS mutations are predicted to have a dominant negative effect on IRF6 by forming a dimer with the wild type allele, but the dimer is unable to bind to its DNA sites (Kondo et al, 2002). We predict that the frameshift mutation in Family 1 could also cause a dominant negative effect, but through a different mechanism. Since the frameshift mutation is located immediately after the DNA binding domain, the truncated IRF6 could compete for binding of DNA sites, but would not be capable of transactivation. This mode of dominant negative effect was observed previously in cells that express truncated isoforms of IRF7 that only encode the DNA binding domain (Au et al, 2001). Future studies will need to address how dominant negative effects on the same gene can alter the development of distinct sets of tissues.

Third, is the frameshift mutation in this family functionally and structurally distinct from the known VWS-causing mutations in *IRF6*? Functionally, previous studies discovered that distinct microdeletions that include the entire *IRF6* cause VWS, demonstrating that VWS is caused by haploinsufficiency of *IRF6* (Sander et al, 1994; Schutte et al, 1999). In support of this conclusion, Kondo et al (2002) observed that the 49 VWS-causing mutations are consistent with haploinsufficiency, including 22 of 23 protein truncation mutations. In fact, one of the protein truncation mutations from the earlier study, Q118stop, is predicted to be nearly identical structurally to the frameshift mutation in family 1. The Q118stop mutation is shorter by only three amino acids. Despite this structural similarity, the functional consequence of these two mutations must differ, as the 6 affected individuals in the family with the Q118stop mutation exhibit the classic VWS phenotype. One possible model is that despite their structural similarity, the Q118X mutation causes the mRNA or protein to be unstable; the functional consequence is haploinsufficiency. Whereas the frameshift mutation in Family 1 produces a stable mRNA and protein; the functional consequence is a dominant negative effect. Additional cellular and *in vivo* studies will be necessary to test whether the frameshift mutation in Family 1 produces a truncated protein that is stable and then able to cause a dominant negative effect through competitive binding at IRF6 target sites.

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REFERENCES

Au WC, Yeow WS, Pitha PM. Analysis of functional domains of interferon regulatory factor 7 and its association with IRF-3. Virology 2001;280:273-282.

Burdick AB, Bixler D, Puckett CL. Genetic analysis in families with Van der Woude syndrome. J Craniofacial Genet Dev Biol 1985;5: 181-208.

Eroshkin A, Mushegian A. Conserved transactivation domain shared by interferon regulatory factors and Smad morphogens. J Mol Med 1999;77:403-405.

Gorlin RJ, Cohen MM Jr, Hennekam R. Syndromes of the head and neck. New York: Oxford University Press 2001;775:905-907.

Kantaputra PN, Sumitsawan Y, Schutte BC, Tocharoentanaphol C. Van der Woude syndrome with sensorineural hearing loss, large craniofacial sinuses, dental pulp stones, and minor limb anomalies: report of a four-generation Thai family. Am J Med Genet 2002;108:275-280.

Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, et al. Mutations in *IRF6* cause Van der Woude and popliteal pterygium syndromes. Nat Genet 2002;32:285-289.

Sander A, Schmelzle R, Murray J. Evidence for a microdeletion in 1q32-41 involving the gene responsible for Van der Woude syndrome. Hum Mol Genet 1994;3:575-578.

Schutte, BC, Basart AM, Watanabe Y, Laffin JJ, Coppage K, Bjork BC, et al. Microdeletions at chromosome bands 1q32-q41 as a cause of Van der Woude syndrome. Am J Med Genet 1999;84: 145-150.

Shotelersuk V, Srichomthong C, Yoshiura K, Niikawa N. A novel mutation, 1234del(C), of the *IRF6* in a Thai family with Van der Woude syndrome. Int J Mol Med 2003;11:505-507.

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Clinical Report

A Newly Recognized Syndrome Involving Limbs, Pelvis, and Genital Organs or a Variant of Al-Awadi/Raas-Rothschild Syndrome?

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We report on a 3-year-old Thai boy with limb, pelvic, and genital malformations. The combination of findings found in this patient is similar to that of Al-Awadi/Raas-Rothchild syndrome (AARRS) or limb/pelvis hypoplasia/aplasia syndrome. The upper limbs are more severely affected than the lower ones. Unlike that of AARRS, the radial ray is more severely affected than the ulnar ray. The presence of humeroulnar synostosis and humero-ulnar-radial synostosis and the absence of a radius distinguishes it from AARRS. The similarities and dissimilarities between the features in the present patient and other limb-pelvic hypoplasia/aplasia syndromes are discussed. The findings in this group of patients appear to demonstrate limb-pelvis-genital organ developmental field defects. © 2004 Wiley-Liss, Inc.

KEY WORDS: genital anomaly; limb anomaly; pelvic hypoplasia; radius-ulna-humerua synostosis; ulna-humerus synostosis

INTRODUCTION

The syndrome of severe limb, pelvic, and genital malformation has been described in Al-Awadi/Raas-Rothschild syndrome (AARRS) or limb/pelvis-hypoplasia/aplasia syndrome [Al-Awadi et al., 1985; Richieri-Costa, 1987; Raas-Rothschild et al., 1988; Camera et al., 1993; Teebi, 1993], Roberts syndrome (RS) [Van Der Berg and Francke, 1993], Schinzel phocomelia syndrome [Olney et al., 2001], and femur-fibula-ulna (FFU) syndrome [Zlotogora et al., 1983] (Table I). We report on a 3-year-old boy affected with severe malformation of limbs, pelvis, and genital organs. The pattern of malformation appears unique but shares many findings with AARRS.

CLINICAL REPORT

A 3-year-old Thai boy was seen at the Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand for physical evaluation and genetic counseling (Fig. 1a). He had multiple congenital anomalies and his parents were concerned if the inborn child of the pregnant mother would be affected with the same condition. He was the only child of healthy nonconsanguineous parents. Karyotype was 46,XY.

On examination at age 4 years, weight, height, and OFC were 8 kg (<3 centile), 64 cm (<3 centile), and 43.5 cm (<3 centile), respectively. His head and face were unremarkable. Severe malformation of bilateral upper and lower limbs was noted. The arms were severely short, making the hands appear connected with the shoulder (Fig. 1a,b). The left arm was more severely affected than the right one. Its forearm appeared absent. The left thumb was small, short, and free floating. Flexion contracture was observed at the proximal interphalangeal joints (IPJ) of fingers 2–4 (Fig. 1b). The right thumb was small and slender. Flexion contracture of the right fingers was observed at the proximal IPJ 3 and 4. Thenar muscles of both hands were hypoplastic (see the online Fig. 1c at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html).

His penis was unremarkable. There was absence of scrotum and testicles (Fig. 1a,d) (see the online Fig. 1d at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). The testes were neither palpable nor detected by ultrasonography. Rugae was evident. Both kidneys appeared normal. The anus was anteriorly displaced. A sacral dimple was observed. The legs were short. The right and left leg lengths were 24 cm (<3 centile) and 23 cm (<3 centile), respectively. The lower legs appeared connected with the pelvis without the presence of thighs and knees. Feet appeared normal (Fig. 1a).

At age 3 years, he walked independently for 10 steps and sat without support. He could use a spoon and get dressed, but could not undress completely by himself. He sang a song and asked for the meanings of words. He was very friendly and played cooperatively with other children. His gross and fine motor skill appeared delayed as the result of his limb anomalies.

Radiographic examination revealed severely short and malformed left humerus, fusing with the very short ulna (Fig. 2a). There was no evidence of a fusion line. The left radius was completely absent. Capitate-hamate synostosis and pisiform bone were visible. The left first proximal and distal phalanges were very short, and its metacarpal rudimentary (Fig. 2a,b) (see the online Fig. 2b at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). Right humerus was severely short, malformed, and bifurcated. It appeared fused with the severely shortened radius and short ulna with fusion lines. Capitate, hamate, and a very small ossification center were evident. The first metacarpal, proximal, and distal phalanges were short and slender (Fig. 2c,d) (see the online Fig. 2d at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). Eleven ribs were observed on each side. The scapulae appeared hypoplastic. The spine was unremarkable (Fig. 3a).

This article contains supplementary material, which may be viewed at the American Journal of Medical Genetics website at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html.

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TABLE I. Important Features of Limb-Pelvis Hypoplasia/Aplasia Syndromes

Syndromes anomalies	AARRS	Schinzel phocomelia	Roberts syndrome	FFU	Femoral hypoplasia-unusual facies	Present case
Mode of inheritance	AR	AR	AR	Sporadic	Sporadic	Sporadic
Brain malformation	−	−	+	−	−	−
Skull defect	−	++	+	−	−	−
Mental retardation	−	−	++	−	−	−
Face						
Facial involvement	++	++	++	−	++	−
Facial hemangioma	+	−	++	−	−	−
Malformed ears	+	+	++	−	++	−
Abnormal eyes	+	−	++	−	++	−
Cleft lip	−	+	++	−	++	−
Cleft palate	−	+	+	−	+	−
Thorax						
Abnormal clavicles	+	−	−	−	−	−
Abnormal ribs	+	−	+	−	−	−
Thoracic dystrophy	++	−	−	−	−	−
Upper limbs						
Hypoplastic humerus	−	−	++	++	+	−
Bifurcated humerus	−	−	−	++	−	+
Phocomelia	++	++	++	+	−	+
A/hypoplastic thumb	+	−	+	−	−	+
Radial ray predominance	−	−	−	−	−	+
Ulnar ray predominance	++	++	++	+	−	−
Contracture of the elbow	++	−	++	−	++	−
Radius-humerus synostosis	++	−	−	++	+	+
Ulna-humerus synostosis	−	−	−	−	−	+
Radius-ulna-humerus synos	−	−	−	−	−	+
Hands						
Very mobile wrist	+	−	−	−	−	−
Carpal a/hypoplasia	+	−	++	+	−	+
Carpal synostosis	+	−	−	−	−	+
Ectrodactyly	+	+	−	−	−	−
Malformed digits	++	+	−	++	−	+
Contracture of fingers	−	+	−	−	−	+
Oligodactyly	++	++	++	++	−	−
Genital organs						
Cryptorchidism	++	+	+	−	+	+
Micropenis	++	+	−	−	+	−
Enlarged genitalia	−	−	++	−	−	na
A/hypoplastic scrotum	+	++	+	−	+	+
Hypoplastic labia	−	−	−	−	+	na
Upwardly displaced genitalia	+	−	−	−	−	−
Anal anomalies	+	−	−	−	−	+
Pelvis						
Severely malformed pelvis	++	++	++	−	+	+
Lower limbs						
A/hypoplastic femur	++	++	−	++	++	+
A/hypoplastic fibula	++	++	++	++	+	+
Unilateral involvement predominance	−	−	−	++	−	−
A/Hypoplastic tibia	++	++	++	+	−	+
Bifurcated femur	+	−	−	−	−	−
Stick-like appendage	++	++	−	−	−	−
Feet						
Ectrodactyly	−	+	−	−	−	−
Polydactyly	−	+	−	−	+	−
Syndactyly	−	+	−	+	+	−
Oligodactyly	++	−	−	++	−	−
Hypoplastic feet	++	++	++	−	++	−
Miscelleneous						
Hetrochromatin repulsion	−	−	++	−	−	−
Hypoplastic nails	++	++	+	−	−	−
Congenital heart defects	−	−	+	−	+	−
Kidney anomalies	+	+	+	−	+	−
Spine	−	+	−	++	++	

Remarks: Common features, ++; occasional features, +; never been reported, −; not available, na.

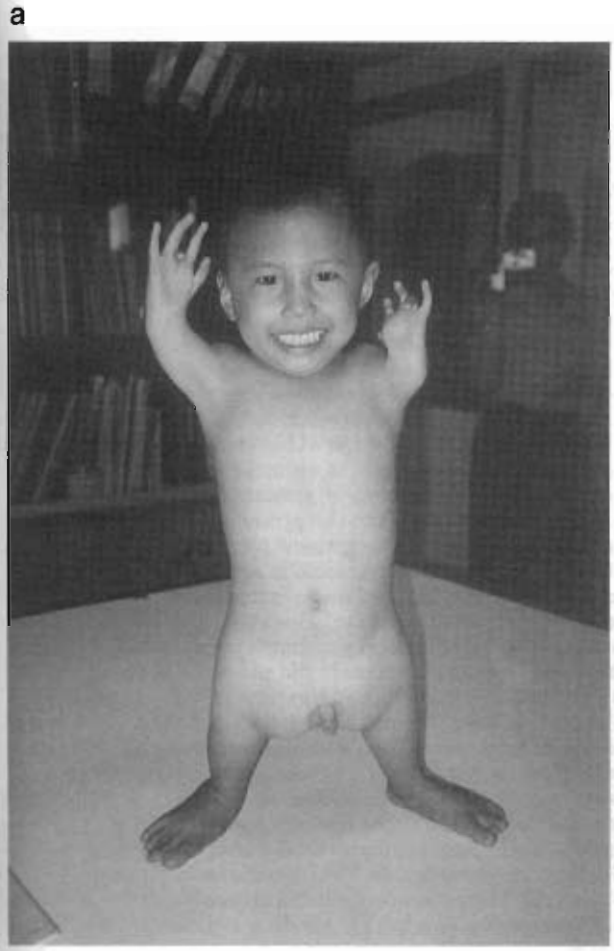

Fig. 1. **a**: Phocomelic appearance of the upper limbs, hypoplastic pelvis, and absent thighs and knees. **b**: Left hand. Hypoplastic thumb, flexion contracture of PIPJ 2–4. **c**: Right hand (see the online Fig. 1c at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). **d**: Cryptorchidism. Hypoplastic scrotum (see the online Fig. 1d at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html).

The pelvis was severely hypoplastic. The pubic bones were completely absent. The iliac bones appeared very small and narrow. The acetabula were triangle-shaped, comprising of iliac bones and ischia. The femora and fibulae were completely

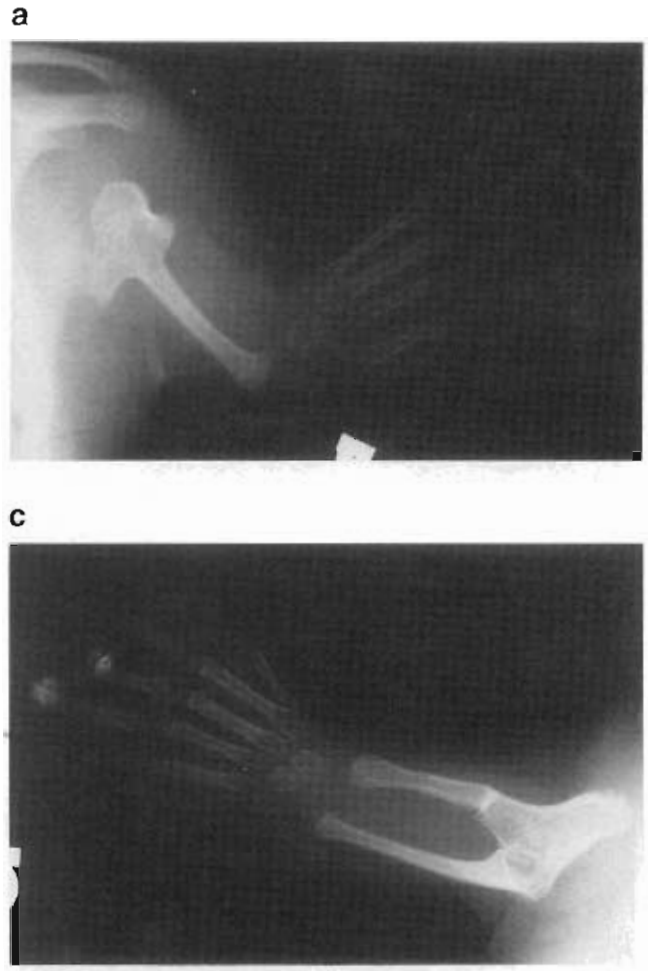

Fig. 2. Radiographs of upper limbs. **a**: Left arm. Malformed humerus fused with hypoplastic ulna. Humerus is dislocated from the shoulder. **b**: Left hand (see the online Fig. 2b at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). Rudimentary first metacarpal. Hypoplastic first proximal phalanx. Capitate-hamate synostosis. Pisiform is observed. **c**: Right arm. Malformed humerus appears bifurcated. Humerus-radius-ulna synostosis. **d**: Right hand (see the online Fig. 2d at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html).

absent. Proximal tibiae were malformed and their shafts slender. They articulated distally with the tali. The proximal tibiae were dislocated from the poorly developed acetabula (Fig. 3b).

DISCUSSION

The combination of findings found in our patient appears unique. However, some of the findings overlap with those of AARRS or limb/pelvis-hypoplasia/aplasia syndrome. AARRS is an autosomal recessive disorder, which is characterized by the presence of profound limb and pelvic deficiency, thoracic dystrophy, and genital anomalies. Limb anomalies consist of short and bowed radii, aplasia of ulna and fibula, hypoplastic or aplastic femur, hypoplasia/aplasia of tarsals, carpals, metatarsals, metacarpals, and phalanges [Al-Awadi et al., 1985; Richieri-Costa, 1987; Raas-Rothschild et al., 1988; Camera et al., 1993; Kumar et al., 1997]. The findings found in our patient appear similar to those of AARRS. However, the presence of humeroulnar synostosis, humero-ulnar-radial synostosis, and absence of radius distinguishes it from having AARRS. In addition, AARRS affects predominantly the ulnar

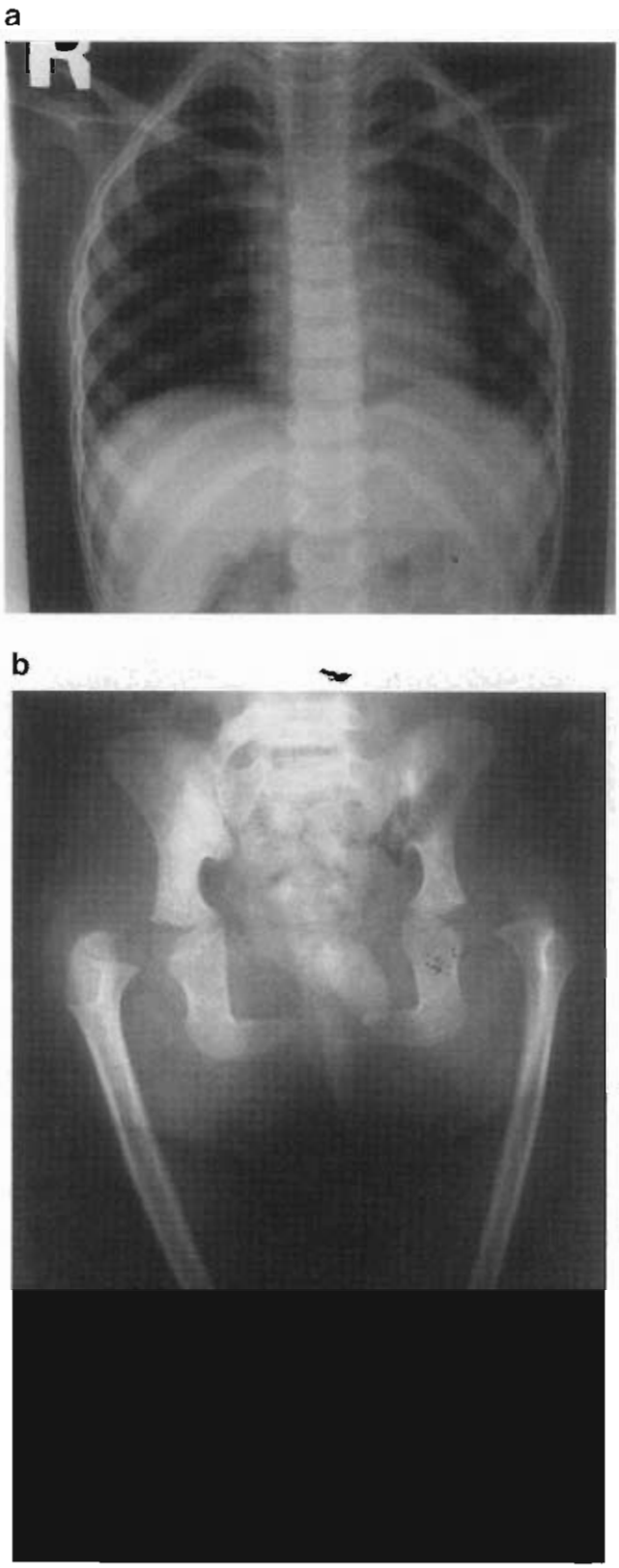

Fig. 3. **a**: Hypoplastic scapulae and dislocated left humerus. Normal spines and thoracic cage. **b**: Very small and narrow iliac bones. Severely hypoplastic pubic bones with absent superior pubic rami. Poorly formed acetabula comprise of iliac and ischium bones. Femora and fibulae are absent. Tibiae are slender with malformed proximal heads.

ray and some toes are almost always missing. In the present patient the radial ray was more severely affected and the feet were normal. Regarding hand anomalies, severity of the hand anomalies in the present patient appears to be very mild compared to those of most cases of AARRS. Hypoplastic nail which is common in AARRS was not present in our patient [Al-Awadi et al., 1985; Camera et al., 1993; Farag et al., 1993]. We are not convinced that unusual facies are component of the AARRS as they were not remarkable in the previously reported cases. We believe that the case reported by Mollica et al. [1995] represented a new autosomal recessive facio-skeleto-genital syndrome, not AARRS, as cleft lip and palate does not seem to be a component of AARRS.

The absence of craniofacial anomalies, especially craniosynostosis and cleft lip and palate, distinguishes it from Roberts syndrome (RS) and femoral hypoplasia-unusual facies syndrome. In addition, the characteristic cytogenetic phenomenon of RS consisting of replusion of heterochromatic regions near centromeres, particularly of chromosomes 1, 9, and 16 and splaying of the short arms of acrocentric chromosomes and of distal Yq was not found in the present patient [Van Der Berg and Francke, 1993]. The present patient resembled patients affected with Schinzel phocomelia syndrome, by virtue of his intercalary limb deficiencies, genitourinary anomalies, and severe pelvic malformation. However, the absence of skull defects rules out Schinzel phocomelia syndrome [Olney et al., 2001]. The pregnancy history did not include the ingestion of thalidomide [Smithhells and Newman, 1992] or the presence of diabetic mellitus [Grix, 1982]. Both conditions could lead to severe limb malformation and approximately 25% of patients with femoral hypoplasia-unusual facies syndrome have diabetic mothers [Grix, 1982; Urban et al., 1997]. The findings of femoral defects and upper limb anomalies found in the present patient can be found in femur-fibula-ulna (FFU) syndrome, but the limb involvement in FFU syndrome is more likely to be unilateral. The presence of genital anomalies and severe radial involvement rules out FFU syndrome [Zlotogora et al., 1983; Sorge et al., 1995].

The constellation of findings found in this patient is unique, even though the majority of them overlap with that of AARRS. However, the possibility of being its variant cannot be excluded. The anomalies found in AARRS, Schinzel phocomelia, Roberts syndrome, and femoral hypoplasia-unusual facies syndrome, and the present case appear to demonstrate limb-pelvis-genital organ developmental field defects.

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REFERENCES

Al-Awadi SA, Teebi A, Farag TI, Naguib KM, El-Khalifa MY. 1985. Profound limb deficiency, thoracic dystrophy, and normal intelligence: A new syndrome. J Med Genet 22:36–38.

Camera G, Ferraiolo G, Leo D, Spaziale A, Pozzola S. 1993. Limb/pelvis-hypoplasia/aplasia syndrome (Al-Awadi/Raas-Rothschild syndrome): Report of two Italian sibs and further confirmation of autosomal recessive inheritance. J Med Genet 30:65–69.

Farag TI, Al-Awadi SA, Marafie MJ, Bastaki L, Al-Othman SA, Mohamed FM, AlSuliman IS, Murthy DSK. 1993. The newly recognised limb/pelvis-hypoplasia/aplasia syndrome: Report of a Bedouin patient and review. J Med Genet 30:62–64.

Grix A Jr. 1982. Malformations in infants of diabetic mothers. Am J Med Genet 13:131–138.

Kumar D, Duggan MB, Mueller RF, Karbani G. 1997. Familial aplasia/hypoplasia of pelvis, femur, fibula, and ulna with abnormal digits in an inbred Pakistani Muslim family: A possible new autosomal recessive disorder with overlapping manifestations of the syndromes of Furmann, Al-Awadi, and Raas-Rothschild. Am J Med Genet 70:107–113.

Mollica F, Mazzone D, Cimino G, Opitz JM. 1995. Severe case of Al-Awadi/Raas-Rothschild syndrome or new, possibly autosomal recessive facio-skeletal-genital syndrome. Am J Med Genet 56:168–172.

Olney RS, Hoyme HE, Roche F, Ferguson K, Hintz S, Madan A. 2001. Limb/pelvis hypoplasia/aplasia with skull defect (Schinzel phocomelia): Distinctive features and prenatal detection. Am J Med Genet 103:295–301.

Raas-Rothschild A, Goodman RM, Meyer S, Katznelson MBM, Winter ST, Gross E, Tamarkin M, Ben-AMI T, Nebel L, Mashisch S. 1988. Pathological features and prenatal diagnosis in the newly recognised limb/pelvis-hypoplasia/aplasia syndrome. J Med Genet 25:687–697.

Richieri-Costa A. 1987. Profound limb deficiency, thoracic anomalies, unusual facies and normal intelligence-the Al-Awadi syndrome-report of a Brazilian patient. Rev Brasil Genet 10:611–616.

Smithhells RW, Newman CGH. 1992. Recognition of thalidomide defects. J Med Genet 29:716–723.

Sorge G, Ardito S, Genuardi M, Pavone V, Rizzo R, Conti G, Neri Katz BE, Opitz JM. 1995. Proximal femoral focal deficiency (PFFD) and fibular a/hypoplasia (FA/H): A model of developmental field defect. Am J Med Genet 55:427–432.

Teebi AS. 1993. Limb/pelvis/uterus-hypoplasia/aplasia syndrome. J Med Genet 30:797.

Urban JE, Ramus RM, Stannard MW, Rogers BB. 1997. Autopsy, radiographic, and prenatal ultrasonographic examination of a stillborn fetus with femoral facial syndrome. Am J Med Genet 71:76–79.

Van Der Berg DJ, Francke U. 1993. Roberts syndrome: A review of 100 casses and a new rating system for severity. Am J Med Genet 47:1104–1123.

Zlotogora J, Rosenmann E, Menashe M, Robin GC, Cohen T. 1983. The femur-fibula-ulna (FFU) complex in siblings. Clin Genet 24:449–452.