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

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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.

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 [illegible] โรคที่ทำให้ผู้ป่วยมีนิ้วมือข้างละ 2-3 นิ้วเท่านั้น และมีความผิดปกติของแขนเด็ก มีลักษณะมือที่นอกจากมาจากไหล่ หรือกรณีผู้ป่วยที่เกิดมาไม่มีนิ้ว ซึ่งสัมพันธ์กับฮอร์โมนไทรอยด์ผิดปกติ ศึกษากรณียีนที่ทำให้เกิดเนื้องอก ซึ่งทำให้รู้ว่ายีนที่ควบคุมการเจริญเติบโตของคนขณะเป็นผู้ใหญ่ ต่างจากตอนเป็นเด็ก ศึกษากรณีโรคอ้วนในเด็กที่มีปัญญาอ่อนร่วมด้วย หรือกรณีของโรคเท้าแสนปม ที่ผู้ป่วยไม่มีขาเลย โดยมีลักษณะของเนื้อเยื่อเต็มใบหน้า ตลอดจนโรคเพดานโหว่ที่เกิดจากยีน

ทันตแพทย์พีรนิจกล่าวอีกว่า การศึกษายังค้นพบโรคทางกรรมพันธุ์ที่เกิดขึ้นใหม่ในประเทศอีกหลายโรค ไม่ว่าจะเป็นโดยโรคที่เกิดจากความผิดปกติของยีนเท่านั้น ไม่ได้เกิดจากการกินยาหรือจากสารเคมีที่มีพิษ แต่เป็นความบังเอิญที่เกิดขึ้น เหมือนกับบางคนที่เกิดมามีไฝ ซึ่งอธิบายไม่ได้ว่าทำไมถึงมีไฝเกิดขึ้นตรงนั้น และอาการที่มีโรคปากแหว่งเพดานโหว่ อะไรเป็นสาเหตุทำให้เกิดการความผิดปกติ หรือกลายพันธุ์ ซึ่งยังไม่สามารถตอบคำถามได้ชัดเจน ซึ่งลักษณะผิดปกติเหล่านี้ ยังพบผู้ป่วยจำนวนน้อยรายในประเทศไทย แต่หากทราบสาเหตุที่แท้จริงได้จากความผิดปกติของยีนเหล่านี้ จะเป็นการเฝ้าระวังโรคและช่วยให้สามารถวินิจฉัยลักษณะการทำงานของยีน ซึ่งจะนำไปสู่การรักษาโรคและเพิ่มคุณภาพชีวิตของ

ไทยรัฐ ๔

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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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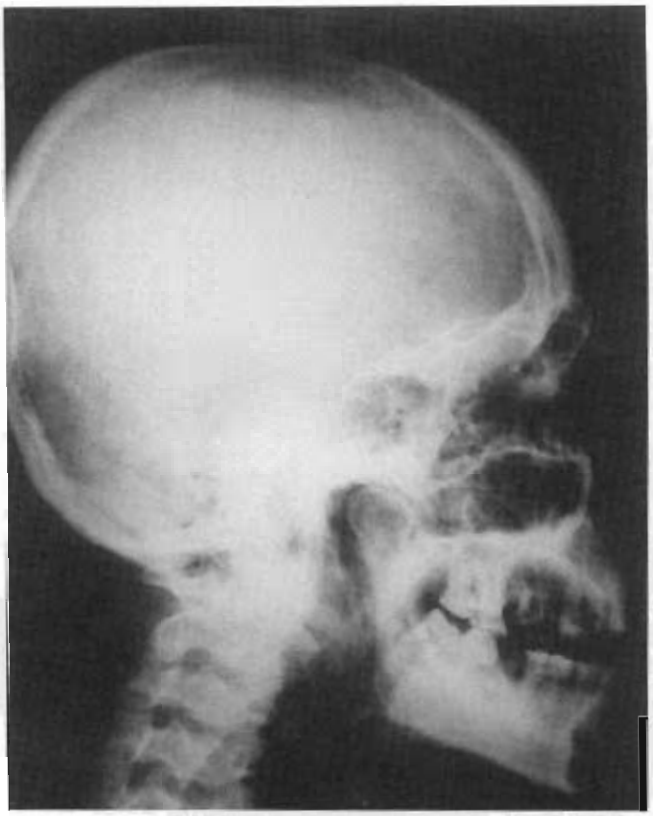

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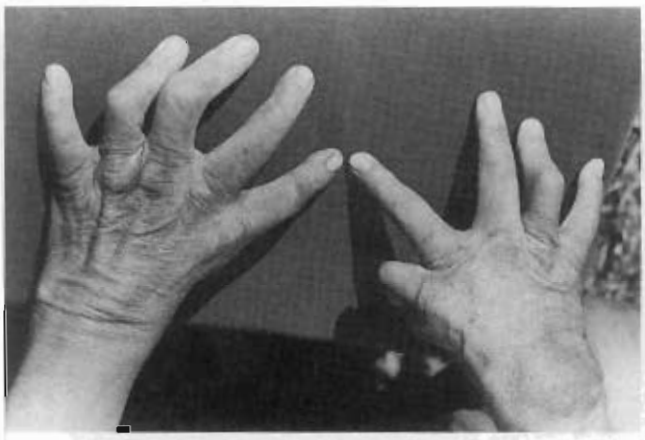

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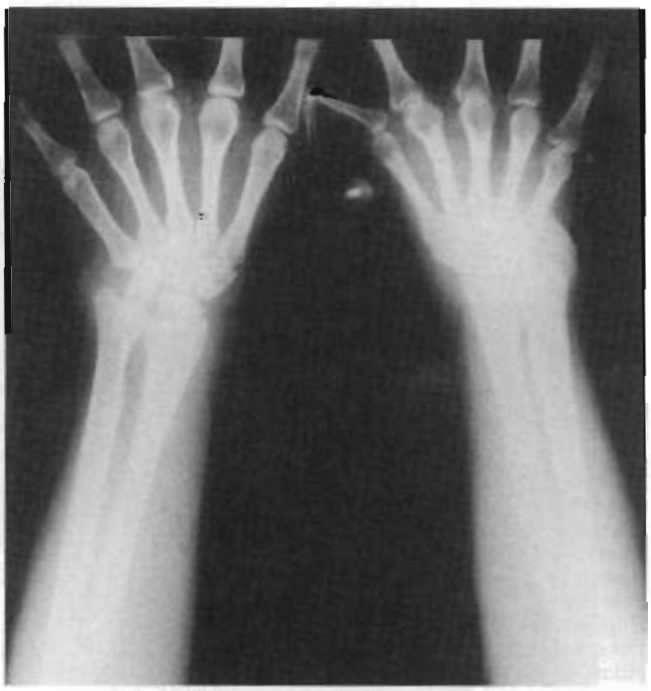

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Fig. 1. a) The patient with scar-like seams under his nose. Hair on the seams of fibrous tissue. b) Lateral cephalogram shows underdeveloped nasal bone and large head mandibular condyle. c) Triphalangeal thumbs. Interphalangeal joint abnormality. d) 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.

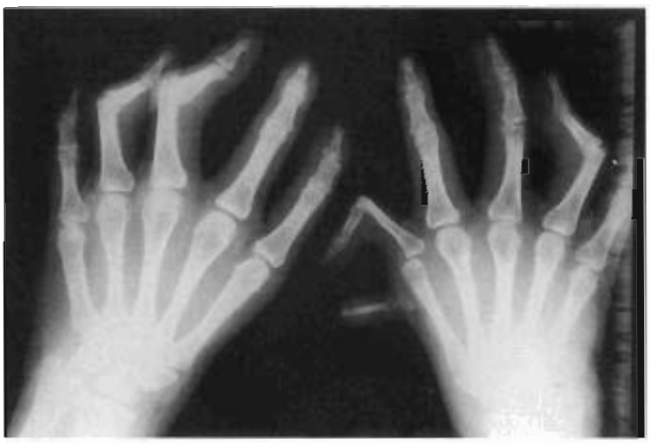

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Fig. 1. *(Continued).*

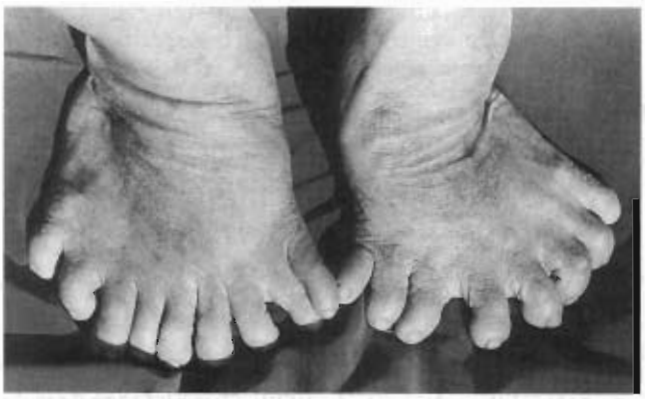
geal and opposable. On his right hand he had an additional poorly developed finger, located radial to the triphalangeal thumb. All proximal interphalangeal joints and distal interphalangeal joints of his right fingers 2 and 3 were flexed (Fig. 1c). A radiograph revealed the absence of his radii. His 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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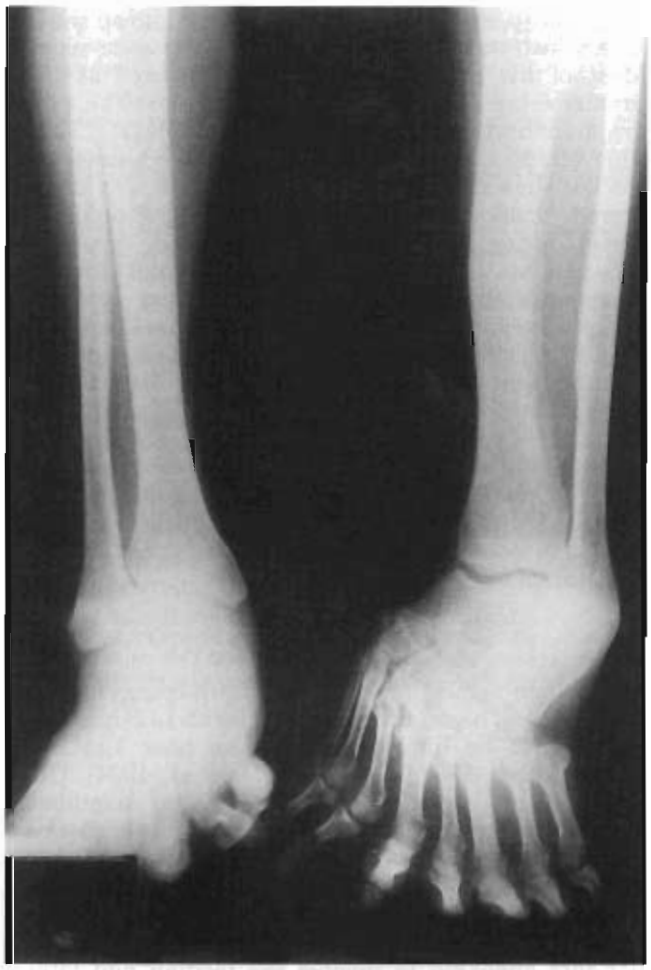

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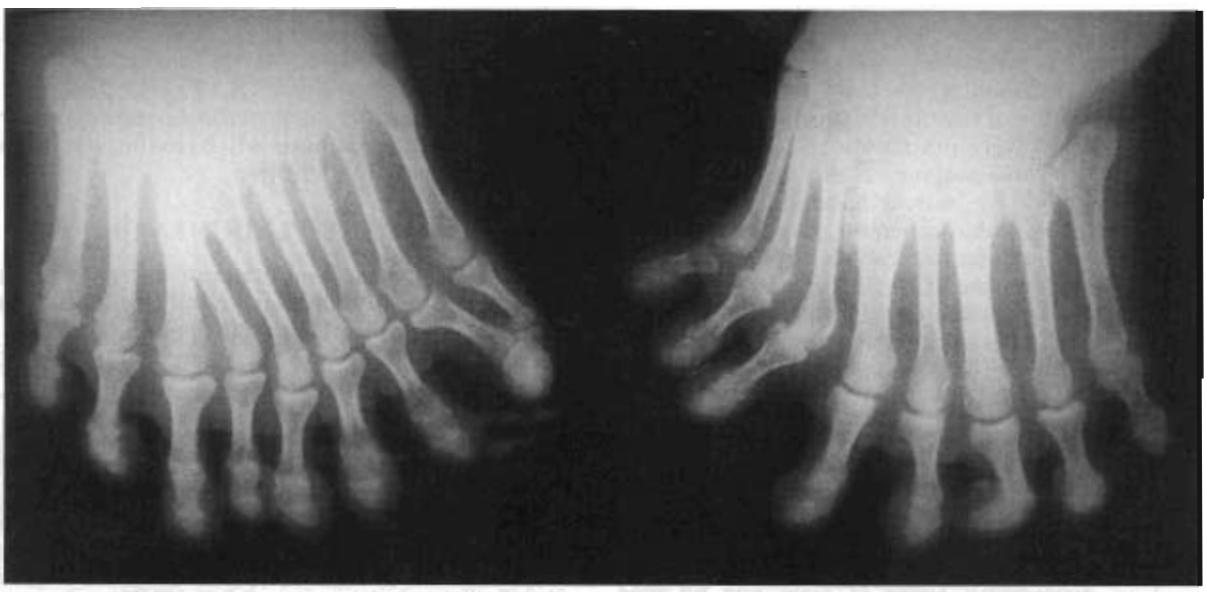

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Fig. 2. a) Very large feet with 9 toes on the right and 8 toes on the left. Morphology of the extra toes is similar in pairs. b) Left tibia and fibula are thick and short. Slightly bowed left tibia. Synostoses of malformed tarsal bones. c) Large left 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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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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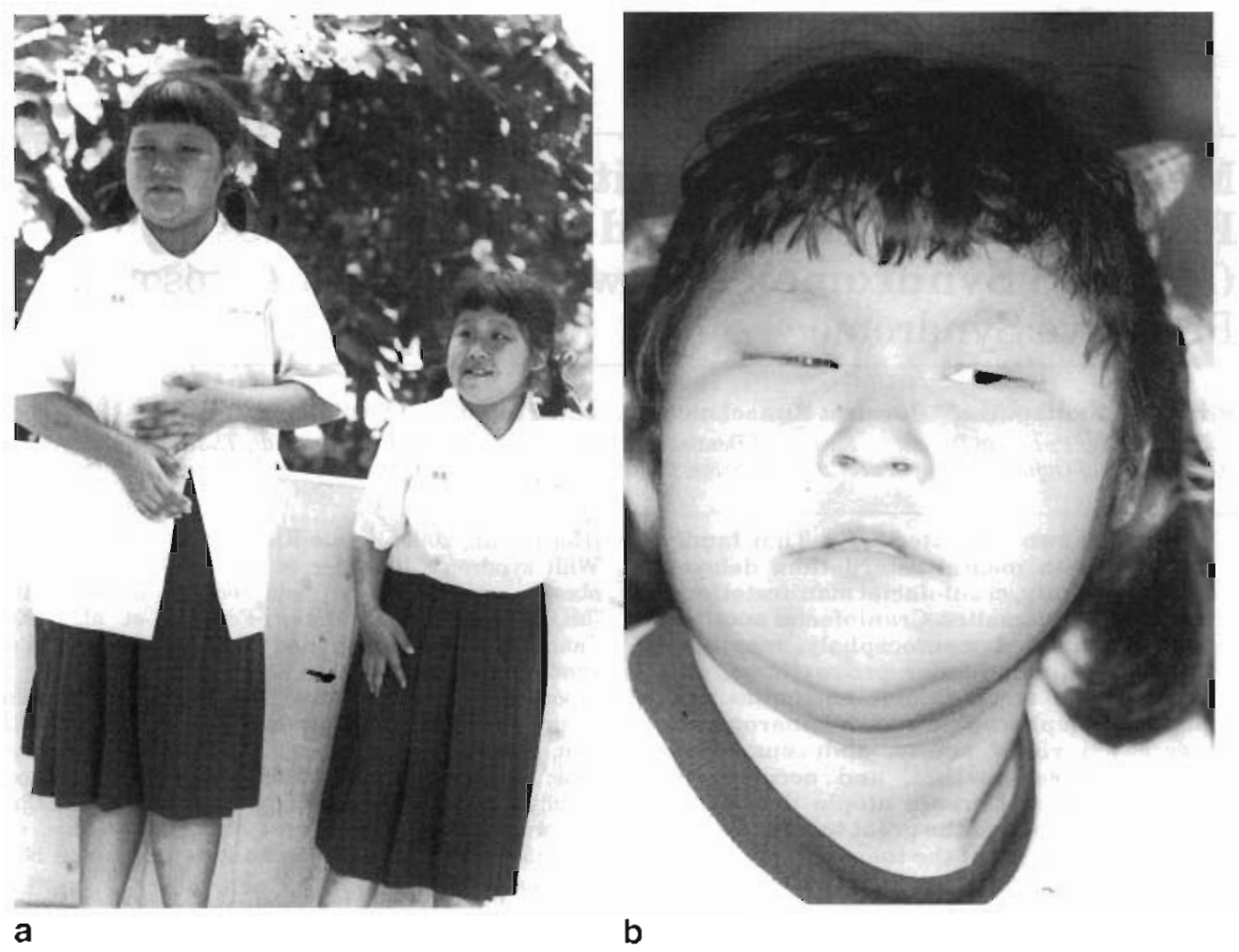

Fig. 1. **a:** Patient 1 at age 13 and patient 2 at age 12. Both are obese and have chubby faces. **b:** Patient 1 showing blepharophimosis, blepharoptosis, and strabismus.

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

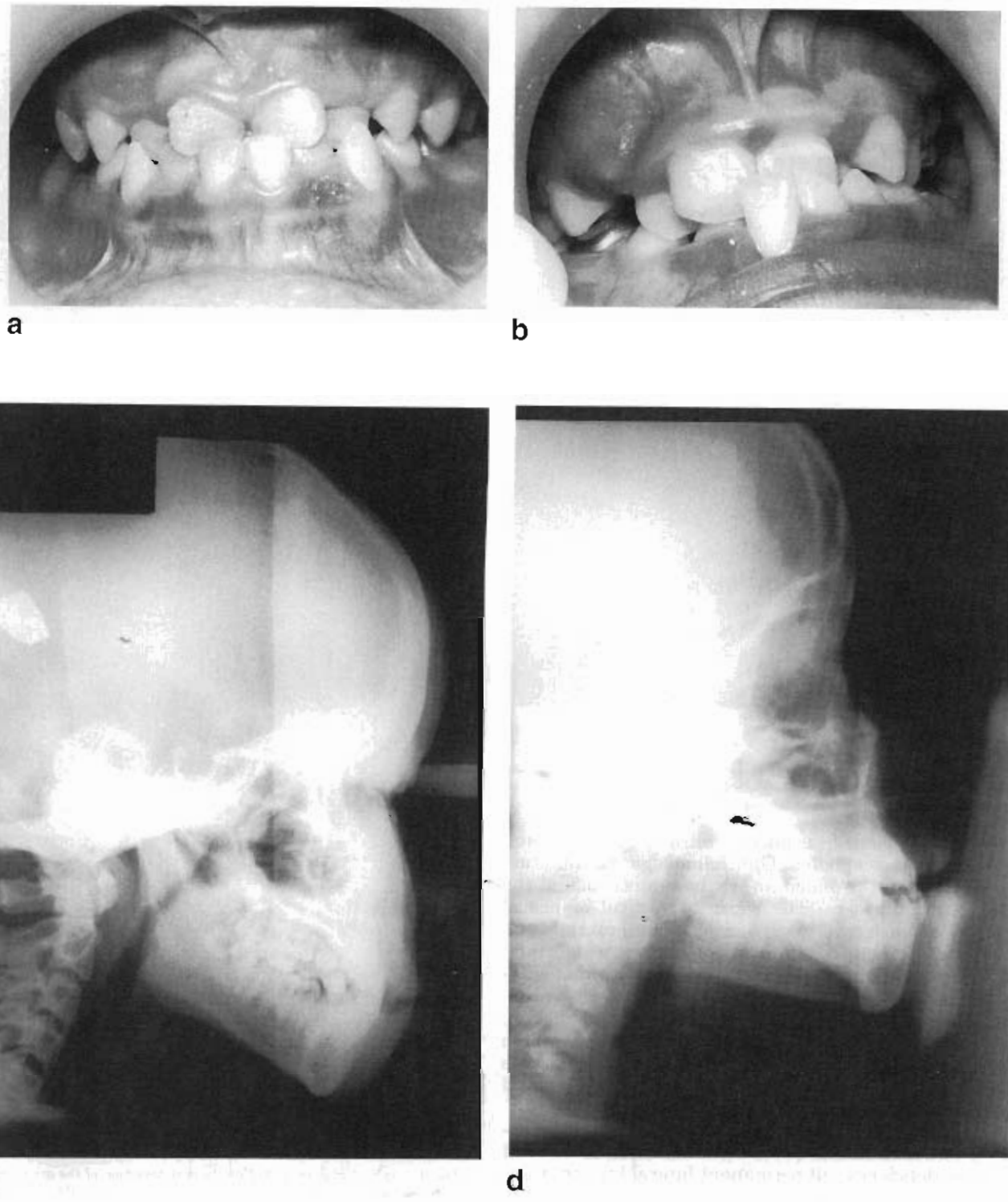

Fig. 2. Crowding of teeth, lingual eruption of the lateral incisors, and anterior crossbite of patient 1 (**a**) and patient 2 (**b**). **c** and **d**: Lateral cephalographs of patient 1 and patient 2, respectively. Both have maxillary hypoplasia and mandibular prognathism. Note large sella turcica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

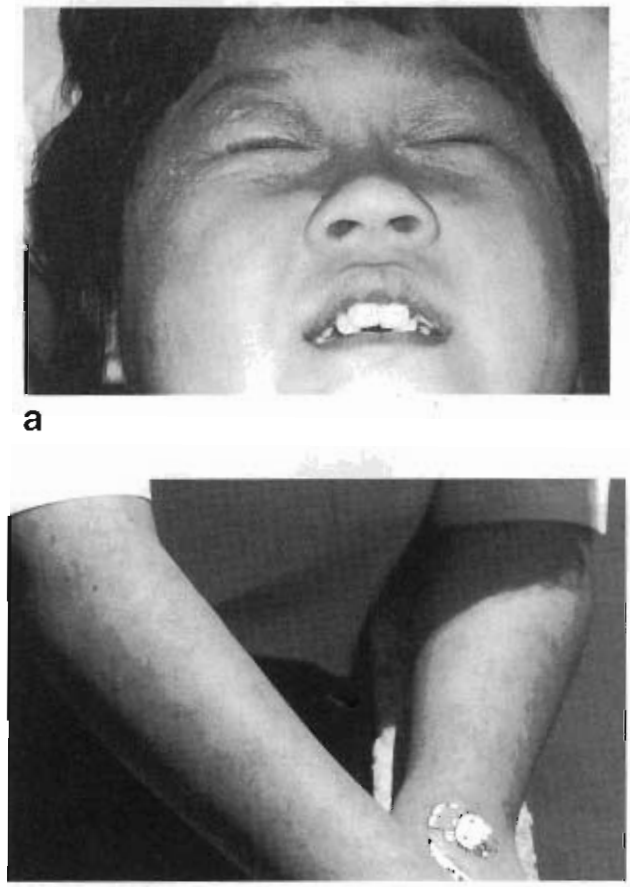

Fig. 3. a: Chronic atopic dermatitis around the eyes. b: Chronic insect bite reactions with nodular prurigo-like lesions. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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

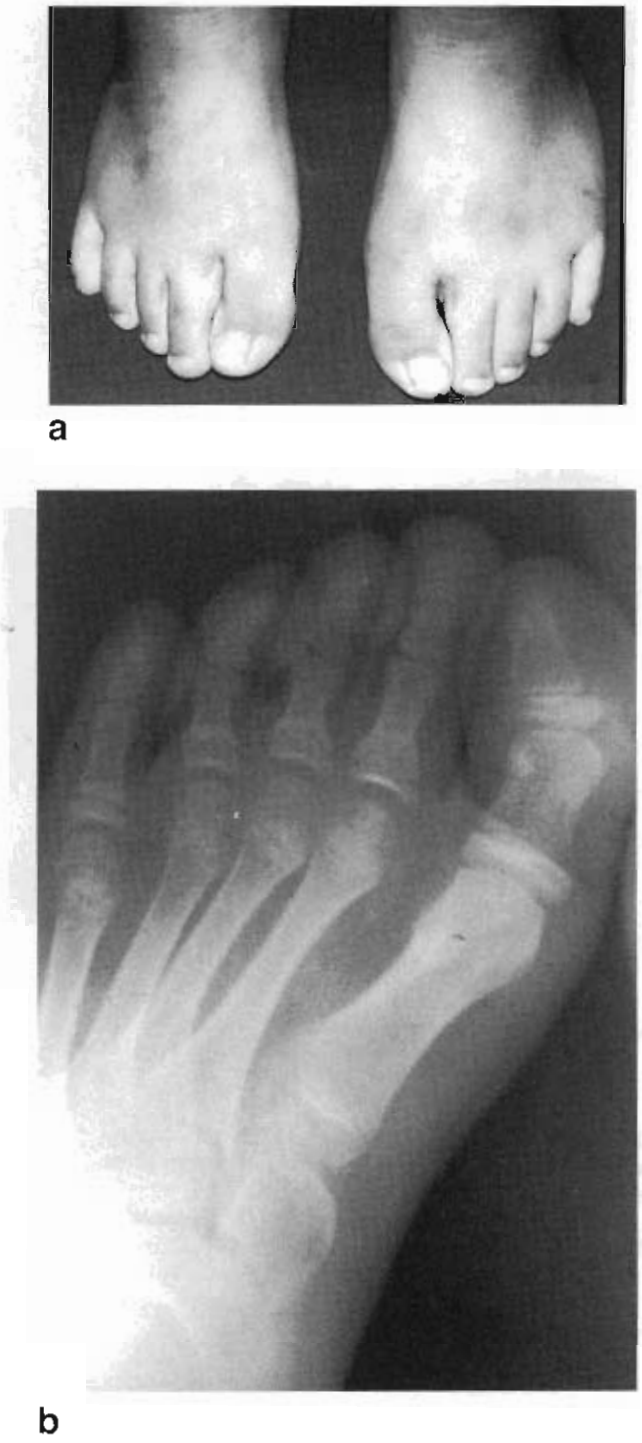

Fig. 4. a: Feet of patient 2. Note lateral deviation of the great toes. b: Foot radiograph of patient 2. Note cone-shaped epiphyses of toes 2, 3, and 4 and lateral deviation of great toe.

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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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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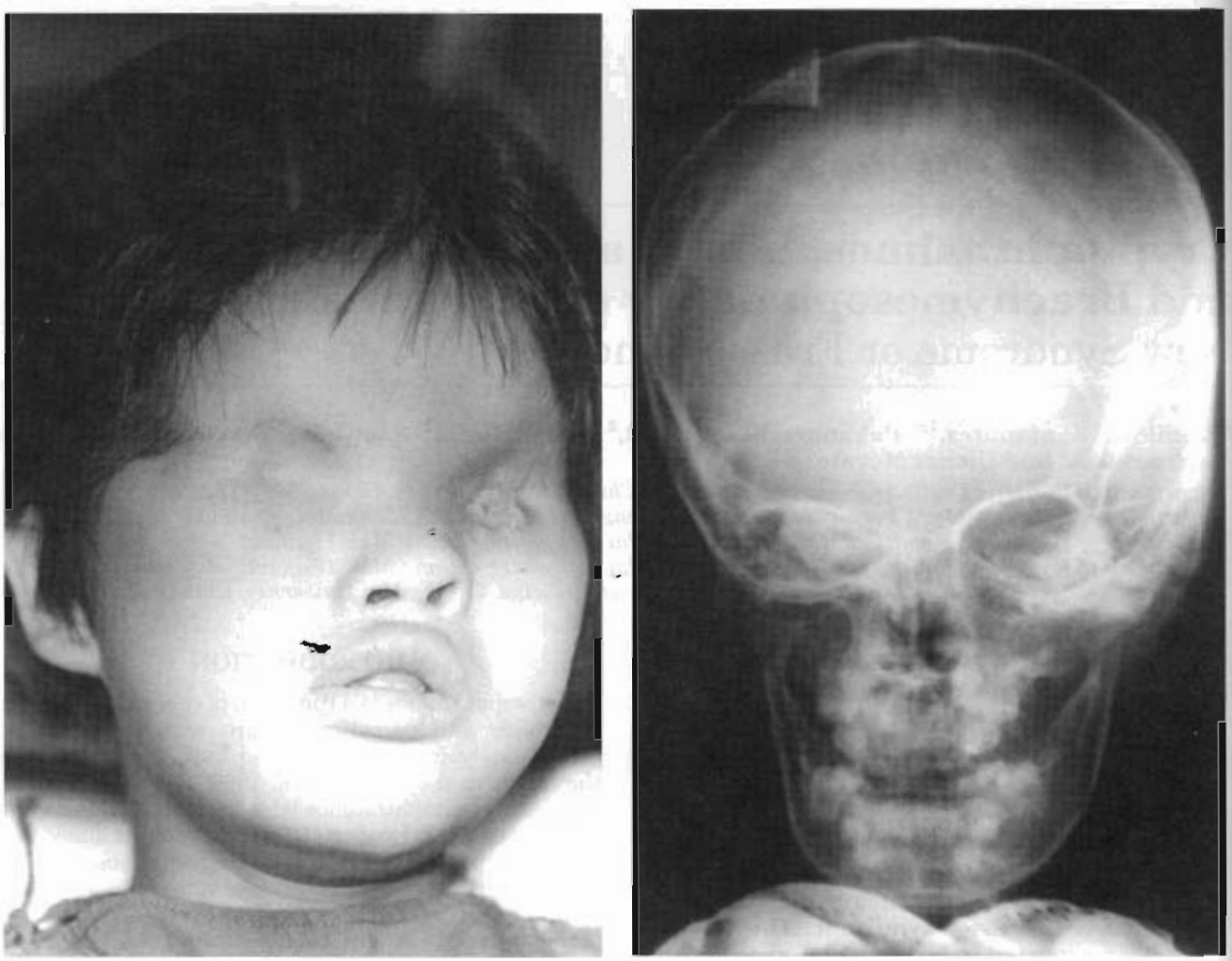
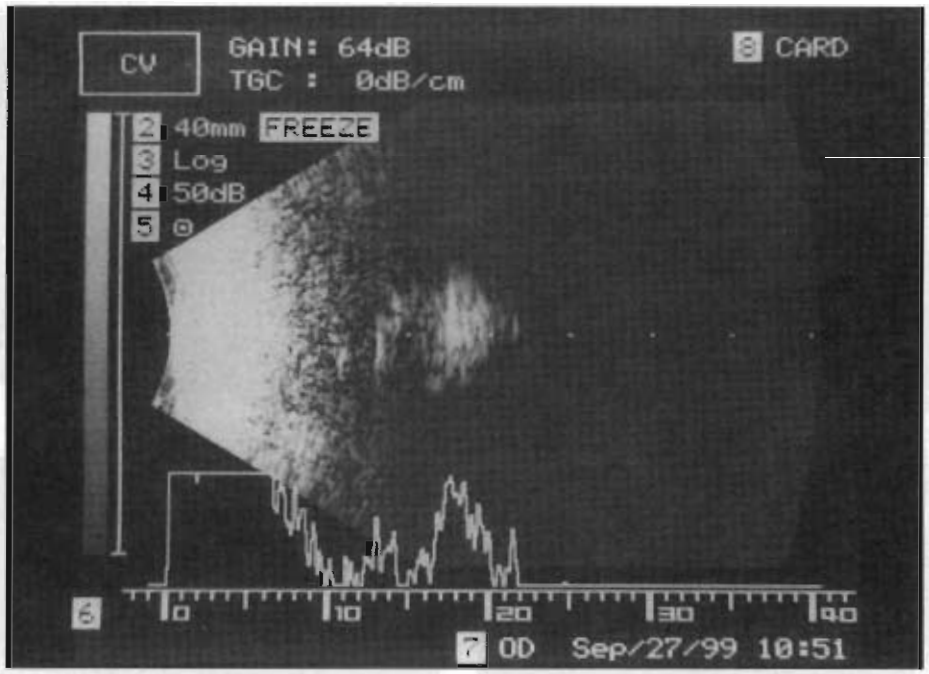


Fig. 1. **a:** A Thai girl with bilateral complete cryptophthalmos. Surgical scar on the left side, broad and depressed nasal bridge, and asymmetric nose. **b:** Asymmetric cranium.

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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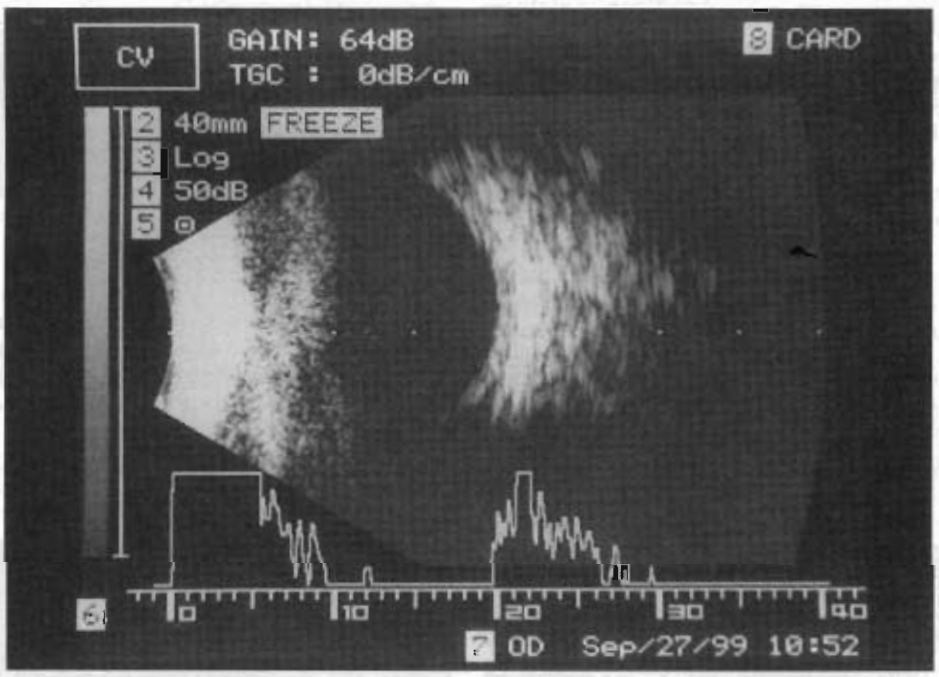

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Fig. 2. Ultrasonograms. **a:** A rudimentary globe of the right eye. No compartments or acoustic signal of the anterior segments. Vitreous space is obliterated. **b:** Microphthalmic globe of the left eye. No details of anterior segment compartments 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.

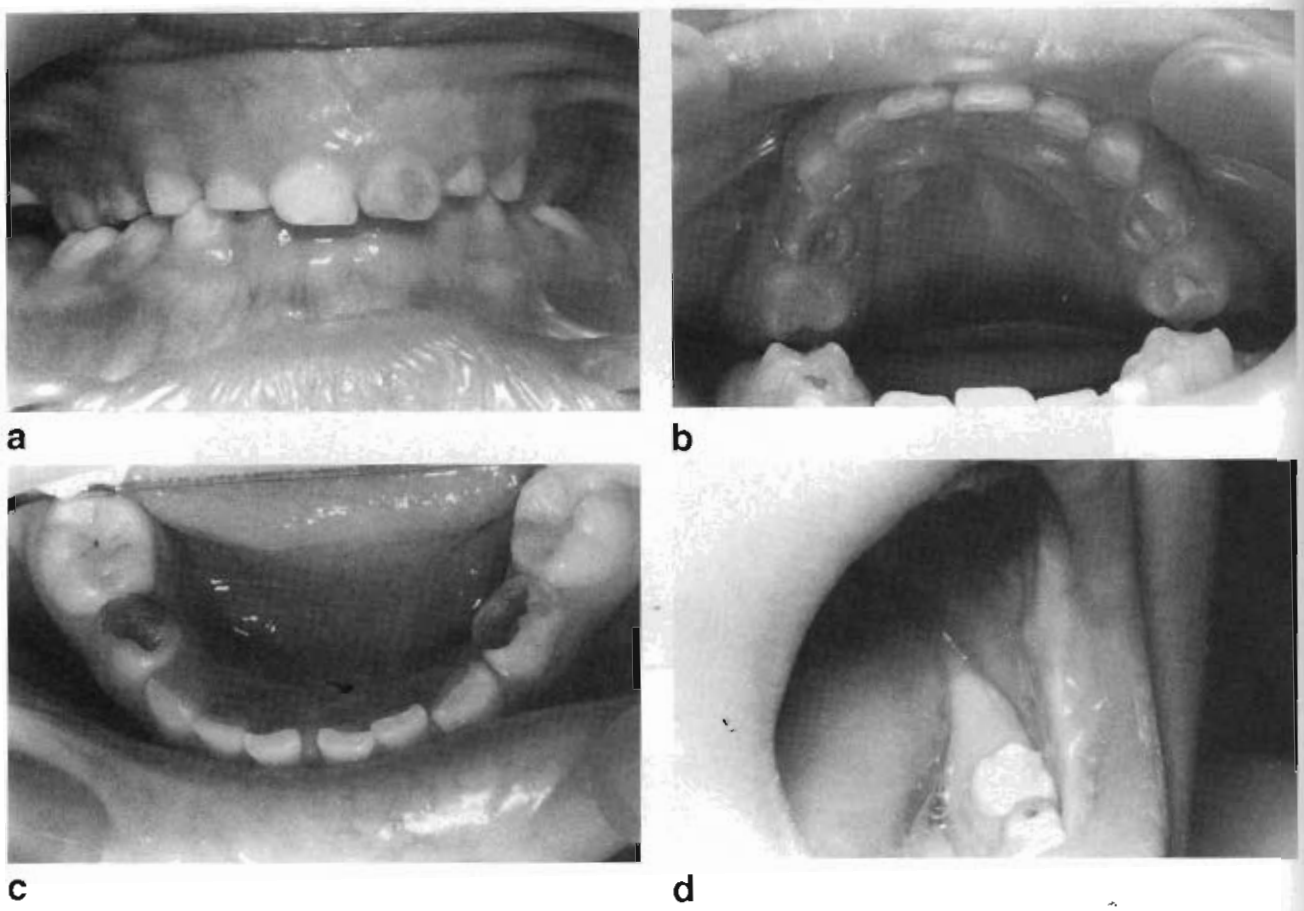


Fig. 3. **a:** Anterior deepbite and posterior crossbite. **b:** Small maxillary deciduous molars. **c:** Small mandibular deciduous molars. **d:** Thick fibrous band of buccal mucosa.

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-

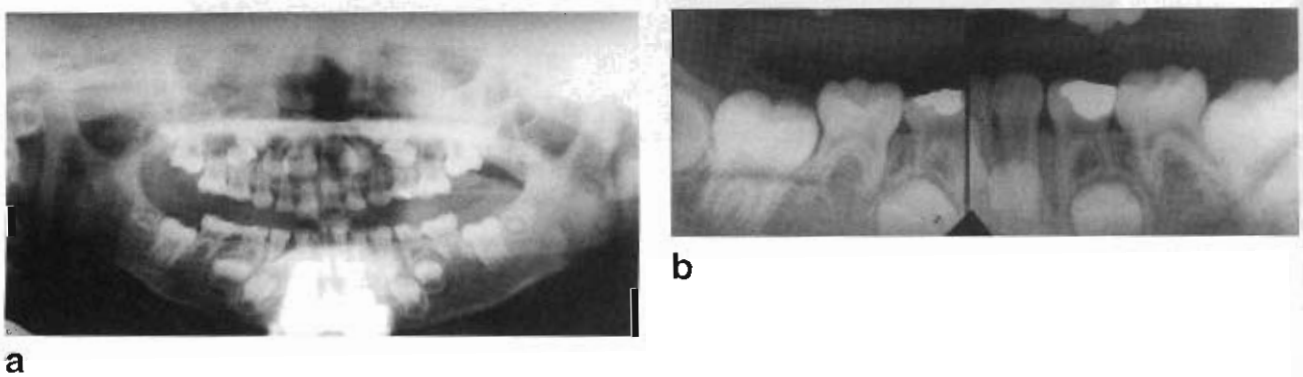
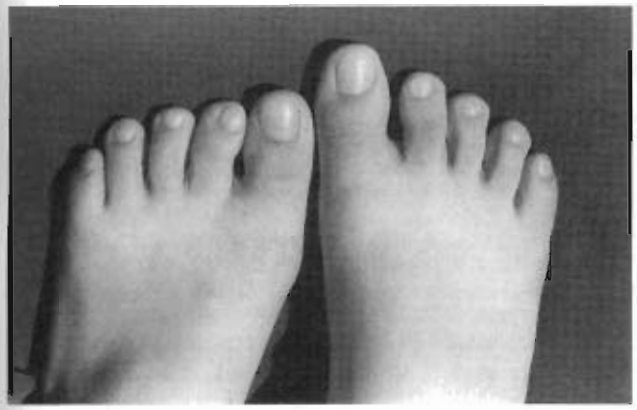


Fig. 4. **a:** Panoramic radiograph at age 7 6/12 years shows delayed dental development, congenital absence of second premolars, small deciduous molars, small coronoid processes. **b:** Periapical radiographs at age 8 6/12 years shows small deciduous molars. Roots of the second deciduous molars are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



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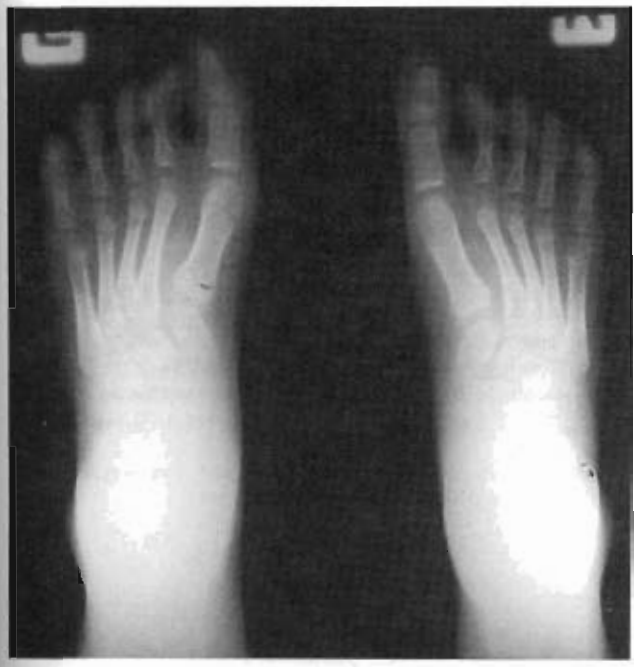

b

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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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

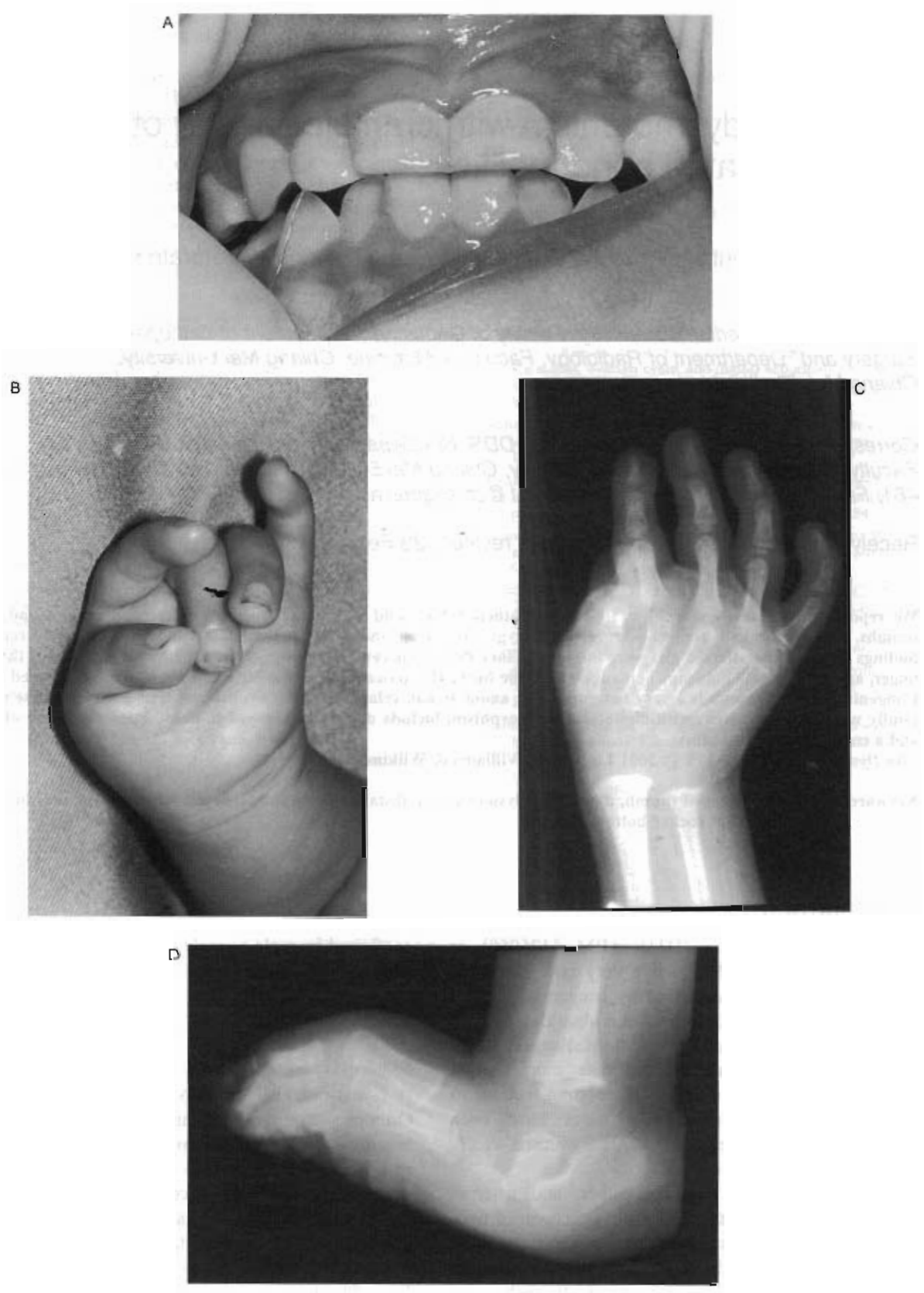

FIGURE 1. Patient 1 A) Large maxillary deciduous central incisors. B) Left clasped thumb with flexed third and fourth fingers. C) Medial dislocation of left cuboid bone. D) Vertical talius. The calcaneus is in equinus position.

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

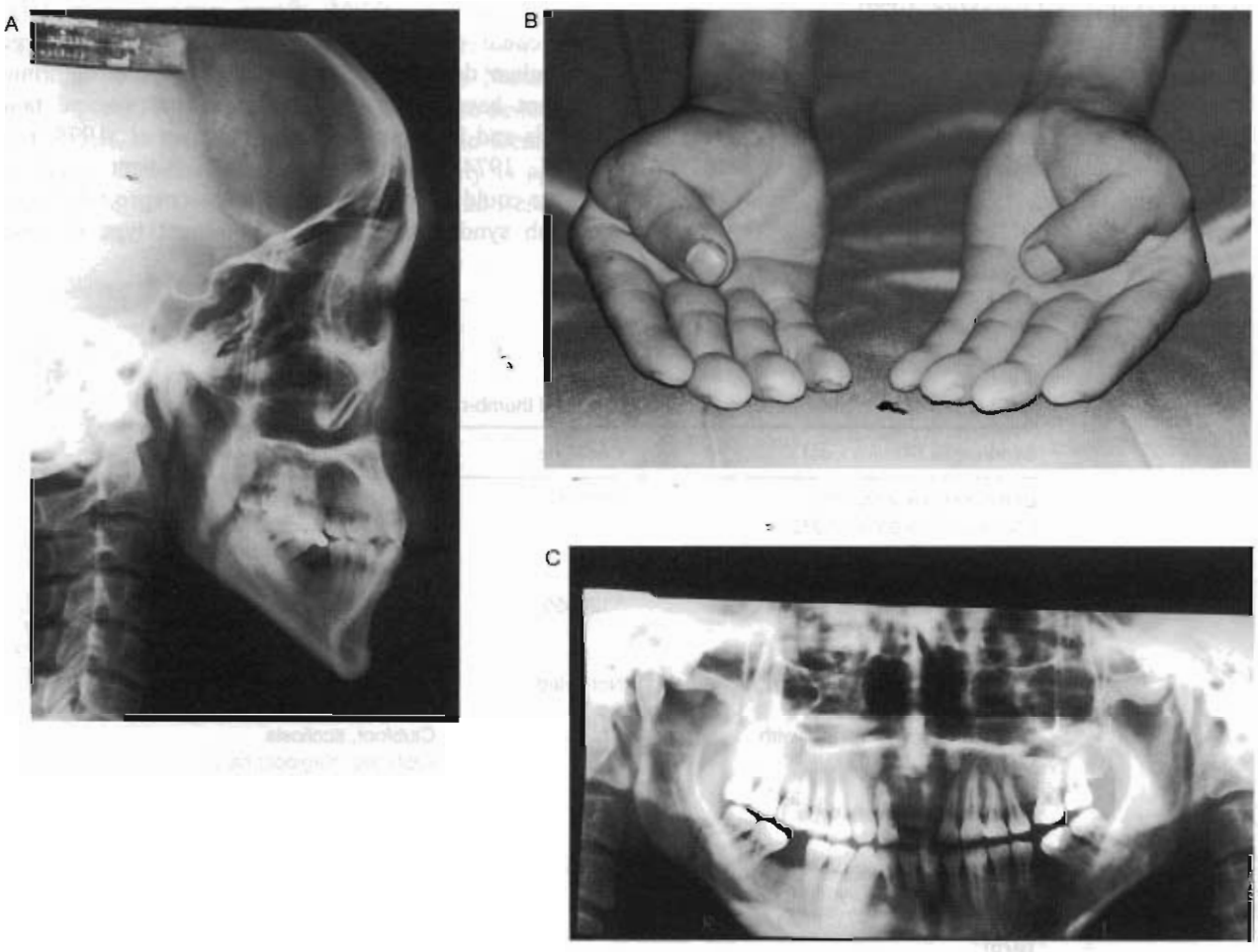

FIGURE 2. Patient 2. A) Lateral skull X-ray shows large posterior clinoid process and large opening of the sella turcica. B) Patient 2's hands. Thumbs are clasped at MCP joints with ulnar deviation of fingers. C) Panoramic radiograph reveals large left zygomatic arch and flat left condylar head.

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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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.

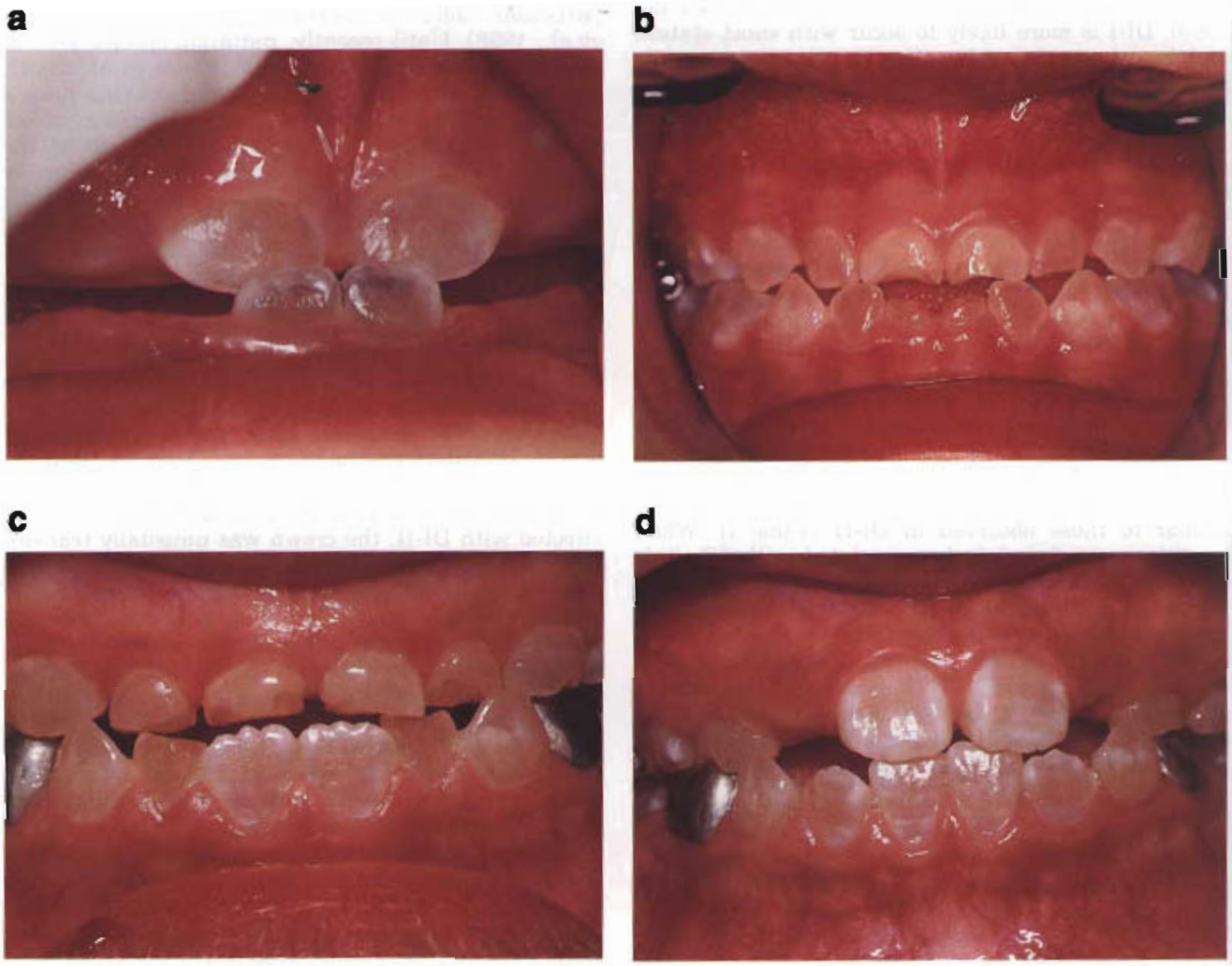

Fig. 1. **a:** At age nine months. Unusually translucent DI type II. **b:** Age four years. Note enamel wear and primary teeth became more opaque. **c:** Age six. Enamel wear and enamel fluorosis of the permanent incisor. **d:** Age eight. Permanent teeth are less translucent. Enamel fluorosis of all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

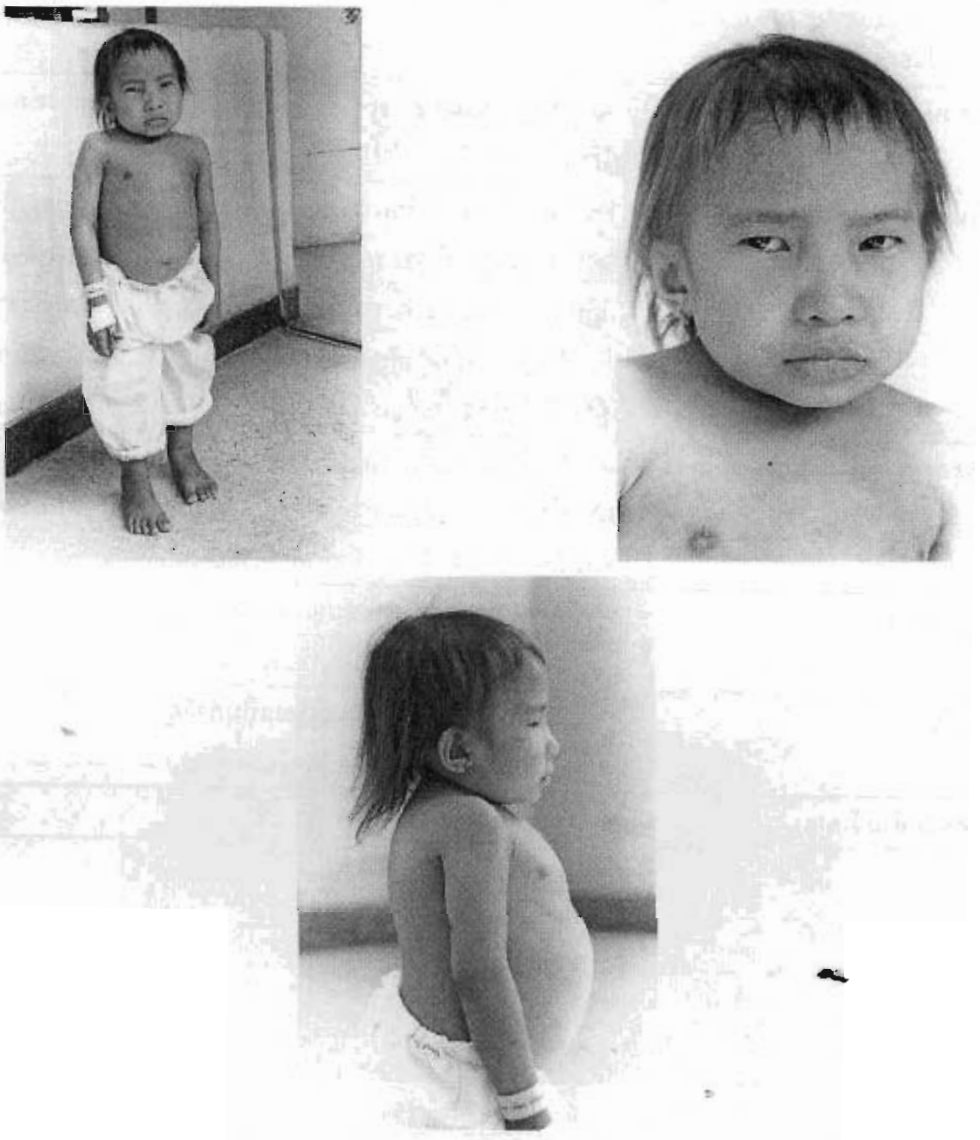

Fig 1. The girl has disproportionately short stature. Her neck is short and her nipples are widely spaced; in addition, she has a broad chest, protruding abdomen, and kyphosis. A broad, depressed nasal bridge also exists.

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

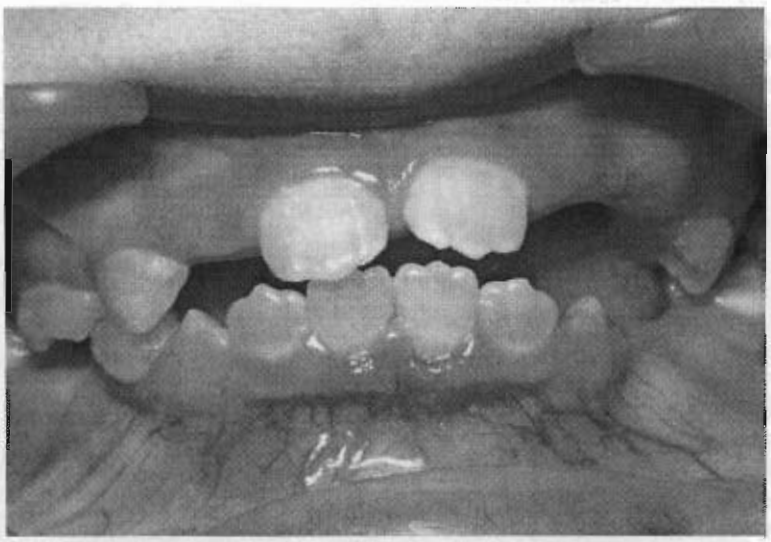

Fig 2. Opalescent teeth.

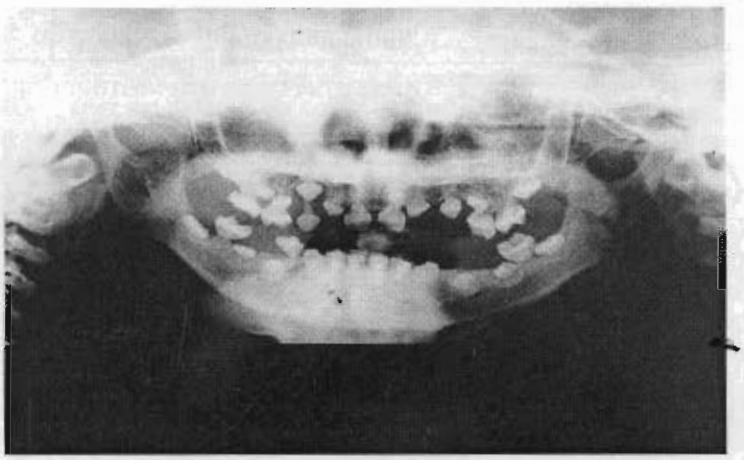

Fig 3. Panoramic radiograph shows small body of mandible, large inferior alveolar canal, and congenital absence of maxillary left first premolar. Some maxillary teeth have short and tapered roots. Most of the mandibular teeth do not have roots. Note obliterated coronal pulp chambers.

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

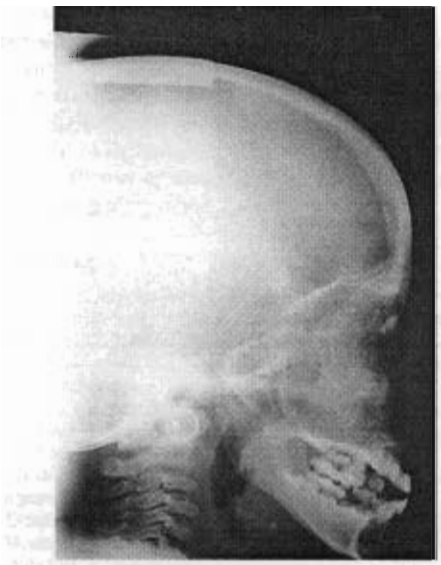

Fig 4. Large sella turcica and cervical platyspondyly.

(<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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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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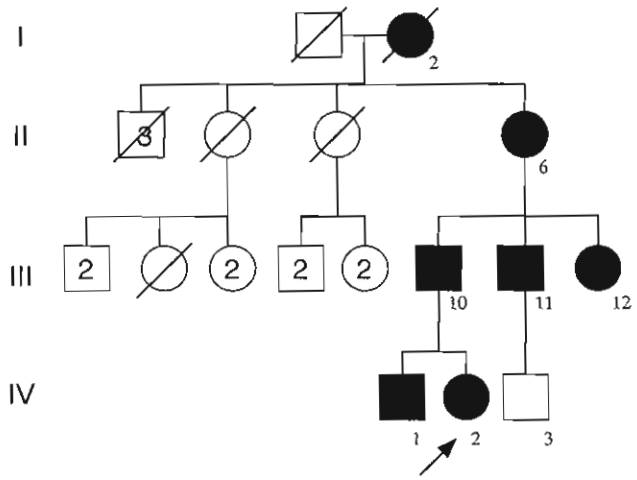

Fig. 1. Pedigree of the family. The closed circle and square depict patients with VWS, and the arrow shows the proband.

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.

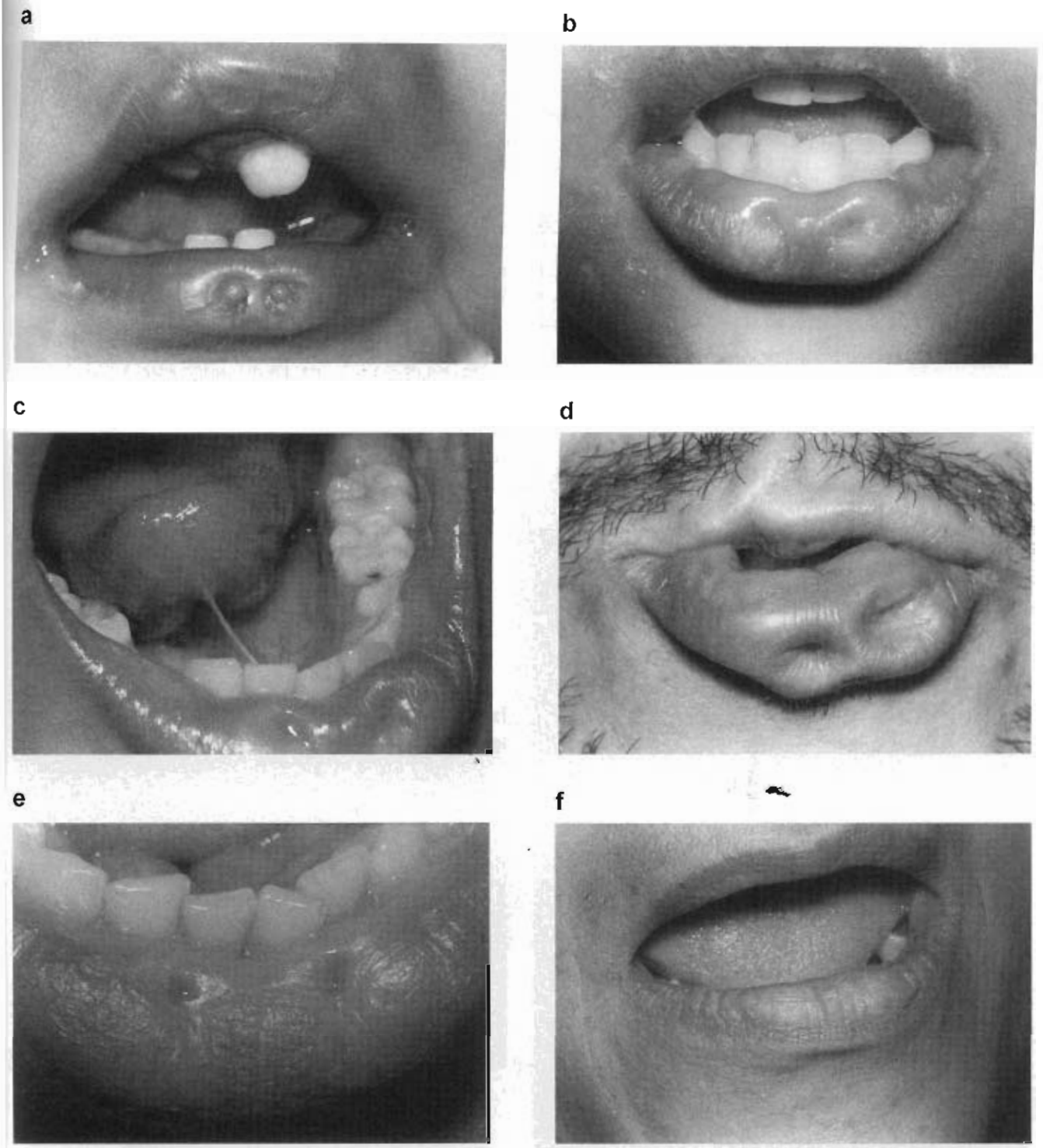

Fig. 2. Lip lesions in the patients. Bilateral lip pits in patient 1 (**a**), patient 2 (**b**), patient 3 (**d**), and patient 4 (**e**); lower lip depression in patient 6 (**f**); and ankyloglossia in patient 2 (**c**).

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.

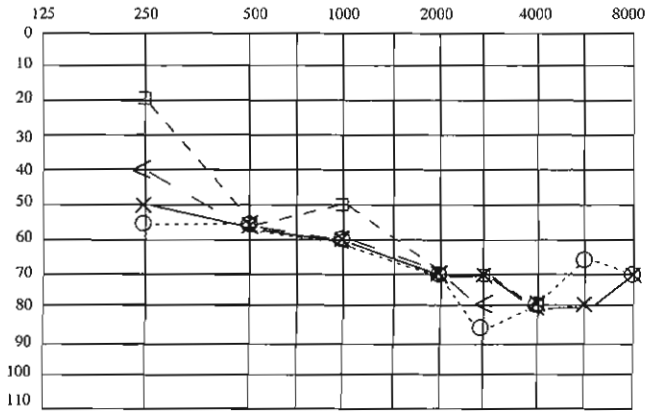

Fig. 3. Audiogram of patient 3, showing sensorineural hearing loss.

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;

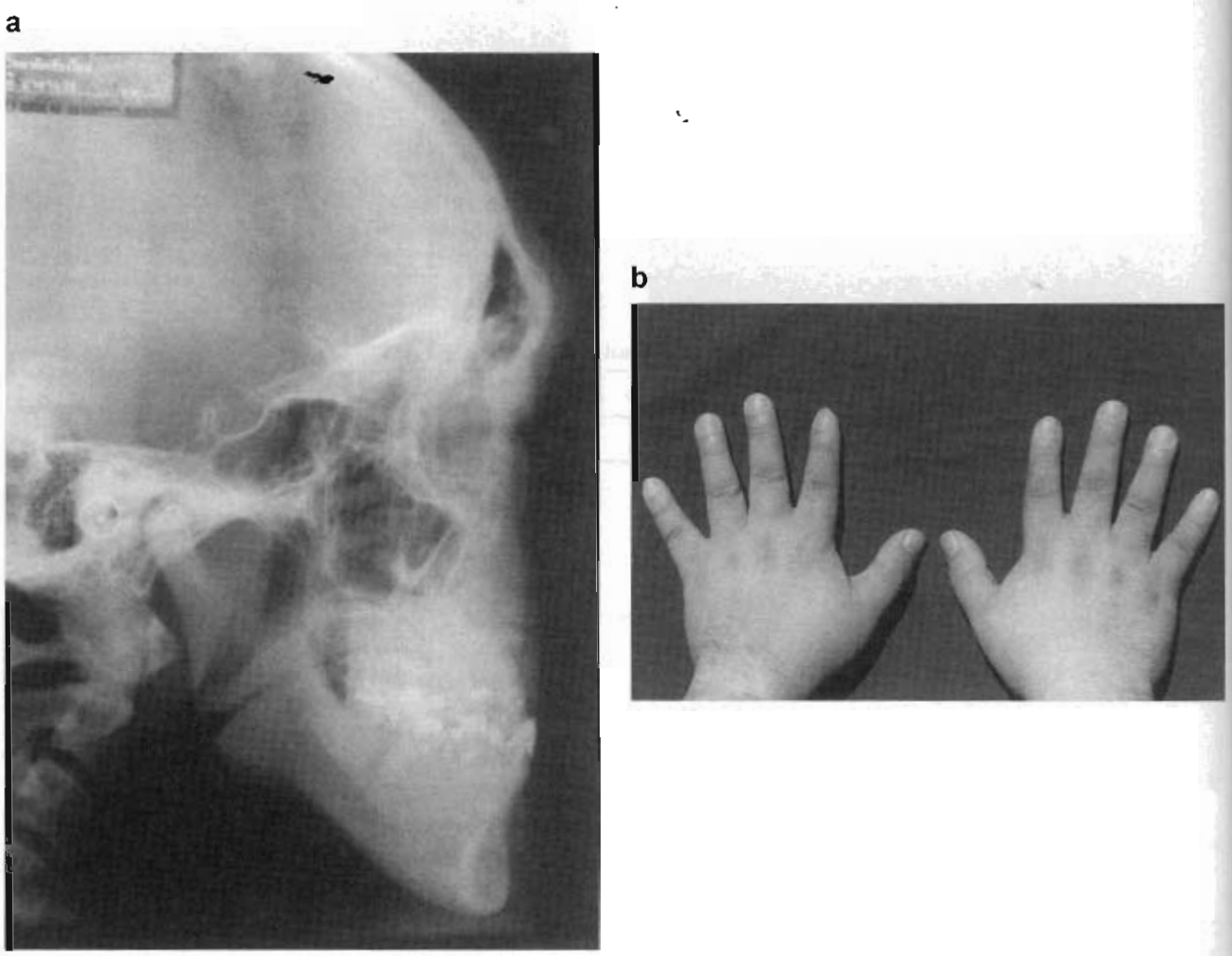

Fig. 4. Large frontal and sphenoidal sinuses and increased mastoid air cells in patient 3 (**a**), brachydactyly of fingers and thumbs in patient 3 (**b**), large frontal sinus in patients 4 (**c**) and 5 (**d**), and hypodontia of the mandibular second premolars in patient 6 (**e**).

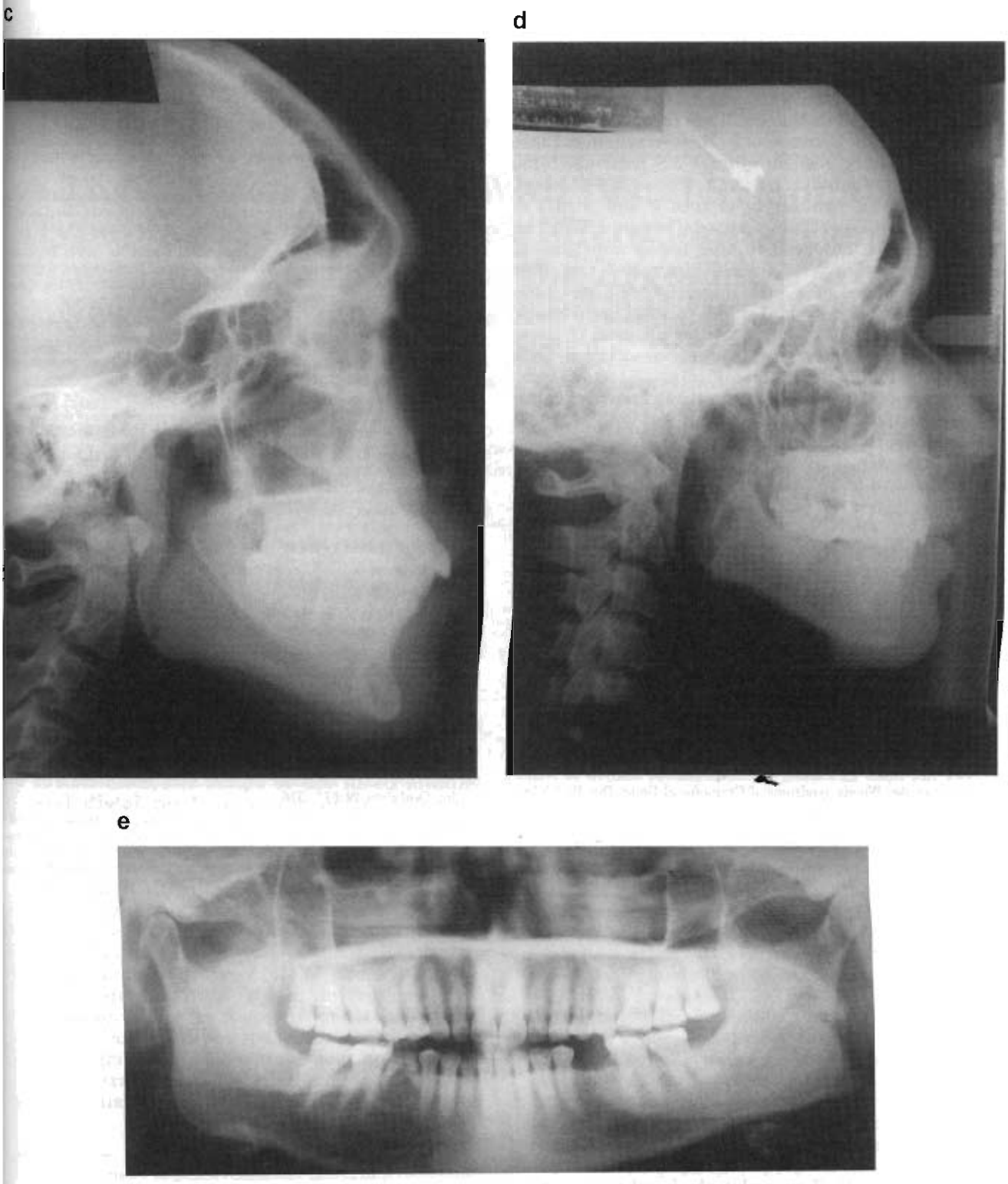

Fig. 4. (*Continued*)

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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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

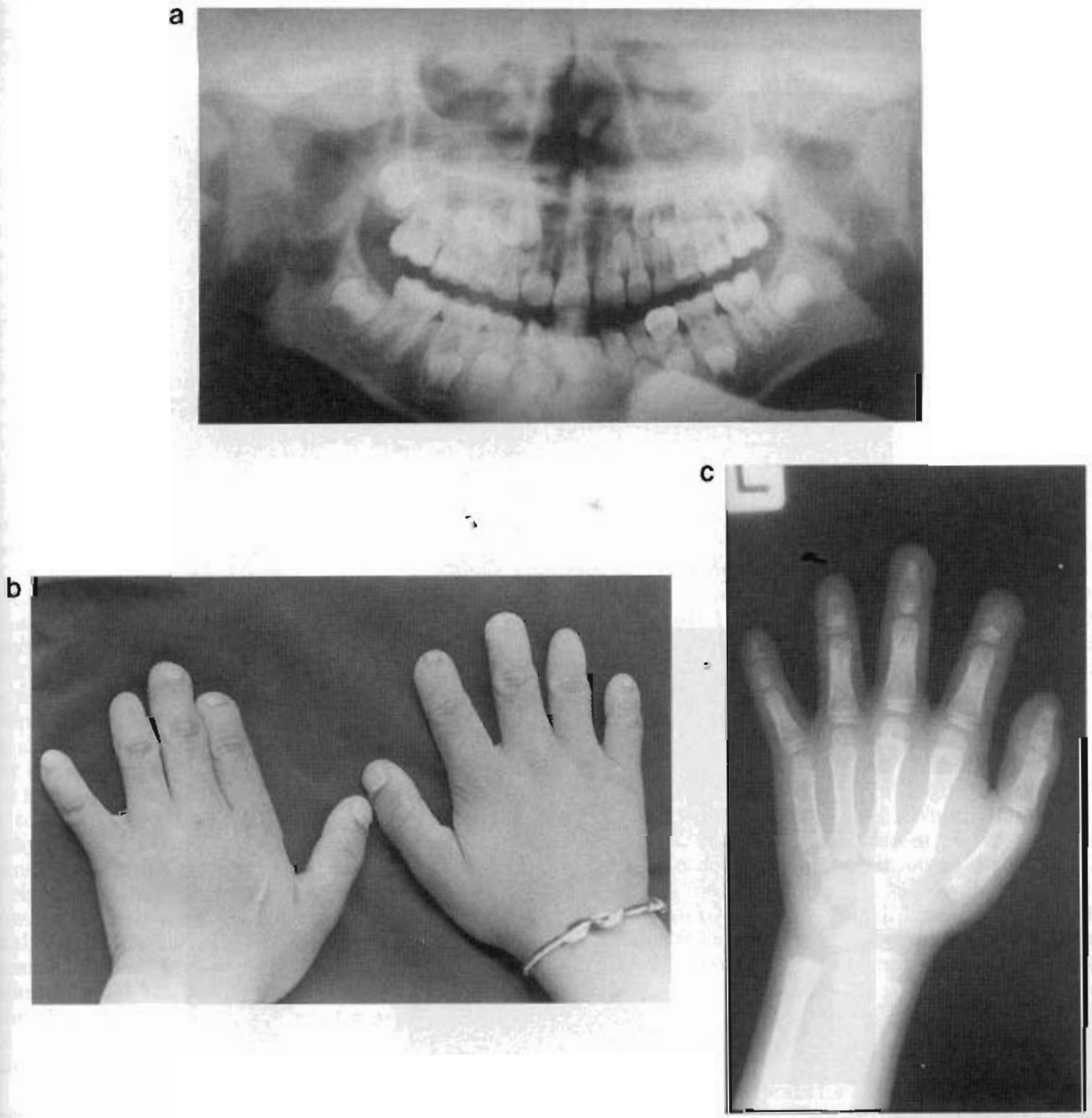

Fig. 1. Patient 1, having a narrowed left zygomatic arch and a dental pulp stone in the left maxillary first permanent molar (a); short fingers with absence of the right third and both fourth fingernails (b); absence of the fourth distal phalanx with fusion of the middle and distal phalanges 2 and 3, 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).

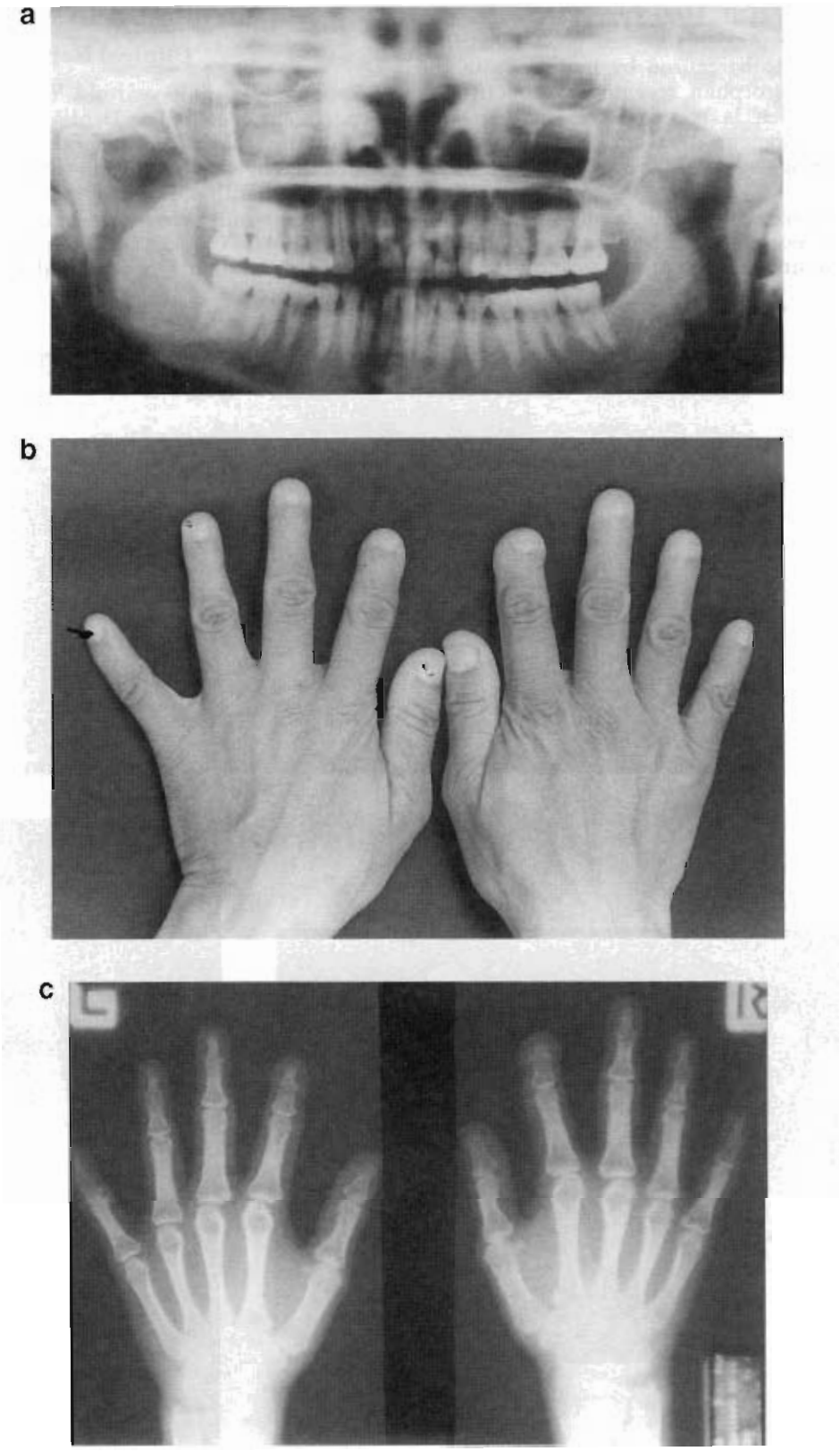

Fig. 2. Patient 2 (the mother), showing narrowing of the right zygomatic arch, and dental pulp stones in the first permanent molars (**a**), short finge with dysplastic fingernails and normal thumbs (**b**), and fusion of the middle and distal phalanges 2–5 (**c**).