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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 lq32-41 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 Iq32-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; Sertie 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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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-ll) 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 (1-2) 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.

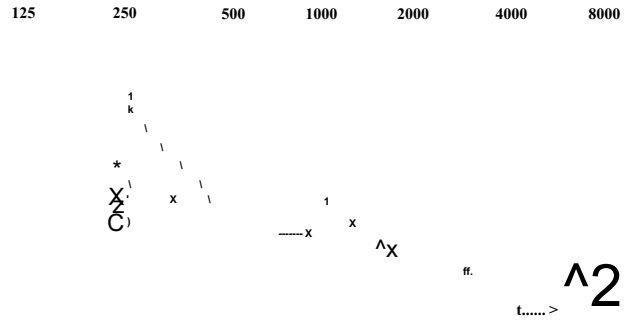

Fig. 3. Audiogram of patient 3, showing sensorineural hearing loss.

a

Flourescence In Situ Hybridization (FISH)

Two bacterial artificial chromosome (BAC) clones, 501İ21 and 564al7, were used in this study. Clone 501İ21 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 lq32 of chromosomes 1 from patient 5, indicating that there is no visible deletion at lq32 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 lq32 region in our patient.

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