American Journal of Medical Genetics 86:269–273 (1999)

Discordance of Oral–Facial–Digital Syndrome Type 1 in Monozygotic Twin Girls

Vorasuk Shotelersuk,[1] Cynthia J. Tifft,[2] Scott Vacha,[3] Kathryn F. Peters,[4] and Leslie G. Biesecker[3]*

[1]*Heritable Disorders Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland*

[2]*Department of Medical Genetics, Children's National Medical Center, Washington, DC*

[3]*Genetic Disease Research Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland*

[4]*Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland*

The oral–facial–digital syndrome type 1 (OFD1) includes limb, facial, intraoral malformations and the gene for the disorder was recently mapped to Xp22.3-p22.2. We report on monozygotic twin girls discordant for OFD1. Monozygosity is supported by placental pathology (monochorionic diamniotic) and molecular studies with probability of dizygosity $<1 \times 10^{-6}$. The affected twin has oral cavity abnormalities including median cleft lip, cleft palate, lobulated hamartomatous tongue, aberrant hyperplastic oral frenula, alveolar notches, and absent lateral incisors. Facial manifestations include telecanthus, hypoplastic alae nasi, and transient neonatal facial milia. The patient also has short and deviated fingers with partial cutaneous syndactyly. At 10 years, she has not had central nervous system or kidney problems. X-inactivation study revealed similar X-inactivation patterns in the lymphoblasts of both twins. We conclude that skewed X-inactivation is an unlikely cause for the discordance, which is more likely due to a postzygotic mutation in the affected twin. Am. J. Med. Genet. 86:269–273, 1999.

© 1999 Wiley-Liss, Inc.

KEY WORDS: oral–facial–digital syndrome type 1 (OFD1); discordant MZ twins; postzygotic mutation; X-inactivation

INTRODUCTION

The oral–facial–digital syndrome type 1 (OFD1: OMIM 311200) is thought to be a single gene malformation syndrome inherited in an X-linked dominant pattern. The gene for the disorder was mapped to Xp22.3-p22.2 [Feather et al., 1997] and the critical region was recently narrowed to 12 Mb [Gedeon et al., 1999]. Here we report on monozygotic twin girls discordant for OFD1 most likely caused by a postzygotic mutation.

CLINICAL REPORT

Twin girls were born to a 23-year-old, G2P1 Caucasian mother and a 34-year-old, nonconsanguineous Caucasian father. The pregnancy was complicated by maternal hyperemesis gravidarum treated with intravenous hydration and promethazine hydrochloride. There was no history of fever, spotting, tobacco, alcohol, or illicit drug use or X-ray exposure. Prenatal tests including maternal serum alpha-fetoprotein and four ultrasound studies were reportedly normal (The existence of twinning was noted.) Due to the risk of fetal erythroblastosis, their mother received Rh (D) immunoglobulin during the pregnancy. Maternal weight gain was 14 kg with normal fetal activity. The labor lasted 6 hr and was followed by Caesarean section at 36 weeks of gestation because of previous Caesarean section. APGAR scores of both twins were 8 and 9 at 1 and 5 min, respectively. The twins birth weights were 2350 g and 2490 g (both normal), and birth lengths 45.7 cm and 47.0 cm (both normal), for Twins A and B, respectively. The placenta was diamniotic and monochorionic.

Twin A had no physical anomalies. However, Twin B was noted to have dysmorphic features of the face, oral cavity, and limbs. Both twins went home with an apnea monitor, however, Twin B was readmitted at the age of 6 weeks due to apnea. A sepsis evaluation was negative. She was discharged after 2 days on theophylline without further episodes of apnea. Twin B had multiple ear infections, requiring the insertion of four sets of

*Correspondence to: Leslie G. Biesecker, M.D., National Institutes of Health, National Human Genome Research Institute, 49 Convent Drive, Room 4A80, Bethesda, MD 20892–4472. Email: leslieb@helix.nih.gov

Received 15 December 1998; Accepted 24 May 1999

© 1999 Wiley-Liss, Inc.

tympanostomy tubes. The median cleft lip and the cleft palate were repaired at the ages of 4 months and 11 months, respectively. She also had an esotropia requiring eye patching. Besides these operations, frequent otitis media, and the esotropia, she has been in good health. Twin A was healthy with the exception of exercise-induced asthma.

At the age of 10 years twin B weighed 56.5 kg (>95th centile for age), and was 141.2 cm tall (50th–75th centile). Her hair was sparse anteriorly with normal texture and hairline. The forehead was normal and the palpebral fissures were neutral. She had telecanthus (inner canthal distance of 3.6 cm (>+2 *SD*), but no hypertelorism (interpupillary distance of 5.6 cm (between 75th and 97th centile)) (Fig. 1A,B). The ears were normal in position, configuration, and size. Her alae nasi were hypoplastic with a prominent columella. There was a well-healed surgical scar from a median cleft lip repair. The mouth was downturned and there was thinning of the lateral vermilion border. The palate was repaired. There were alveolar notches on both sides of upper and lower alveolar ridges. There were several frenula joining the alveolar ridges and the buccal mucosa (Fig. 2A). The lateral incisors were missing and the tongue had a longitudinal groove on the left side. There was a hamartoma on the left posterior part of the tongue (Fig. 2B). The neck was mildly shortened. No chest deformities were noted. Cardiac and abdomi-

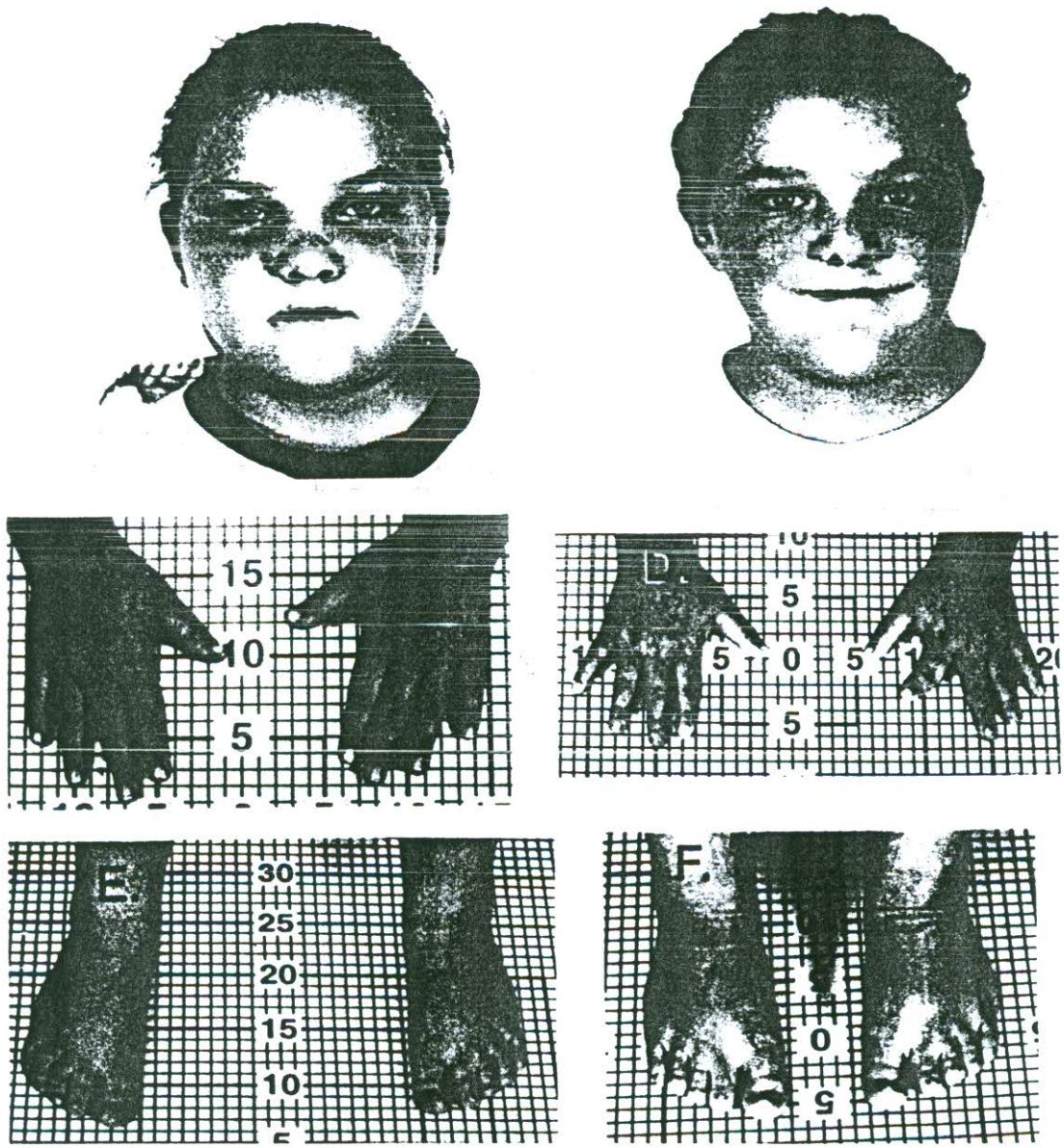

Fig. 1. Faces **(A, B)**, hands **(C, D)**, and feet **(E, F)** of Twin A (A, C, E) and Twin B (B, D, F) at 10 years of age. Note telecanthus, hypoplastic alae nasi, repaired median cleft lip, and thinning of the lateral border of vermilion border (B); brachydactyly, clinodactyly, and partial cutaneous syndactyly of third and fourth fingers of the left hand (D); partial cutaneous syndactyly of the second and third toes bilaterally, mildly hypoplastic toenails, and everted first toenails (F) present in Twin B but not in Twin A.

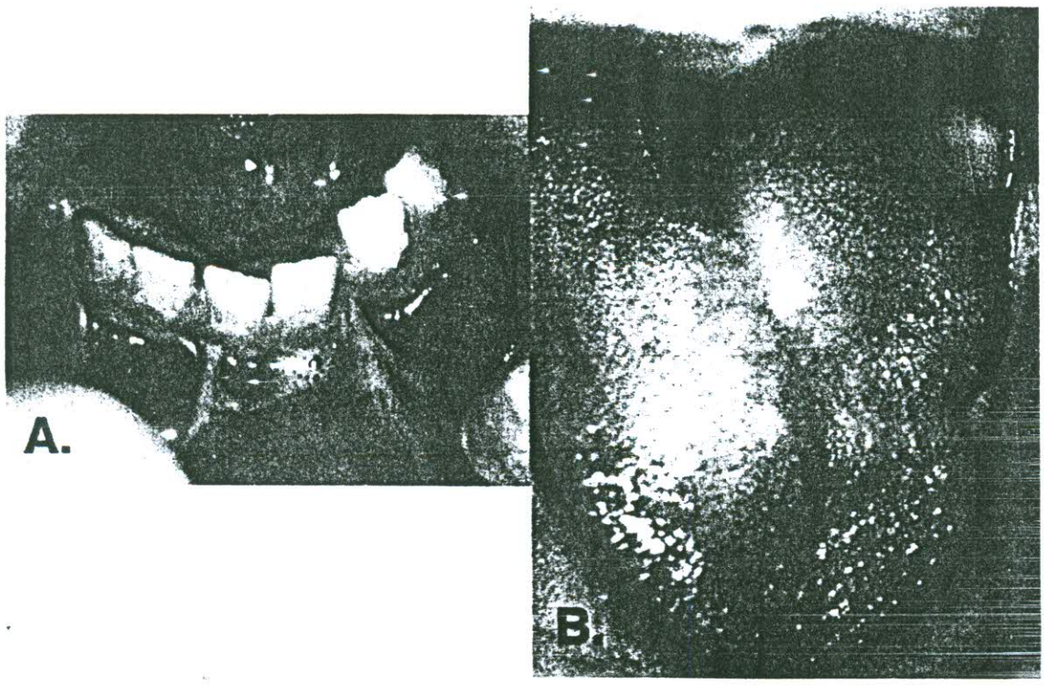

Fig. 2. Oral abnormalities in Twin B: (A) alveolar notches on both sides of the lower alveolar ridges, several frenula between the alveolar ridges and buccal mucosa, and missing of the lateral incisors; (B) lobulated hamartomatous tongue.

nal findings were normal. The breasts were Tanner stage III and the genitalia were Tanner stage II. Her neurologic examination was normal. The hand lengths were 9.2 cm (75th centile for age), middle finger lengths were 5.6 cm on the right (~3rd centile) and 5.4 cm on the left (<3rd centile). She had short left second proximal and middle phalanges (Fig. 1C,D). The left index and right middle finger had radial deviation and the right index finger had mild ulnar deviation. There was a partial cutaneous syndactyly of the third and fourth fingers of the left hand. Dermatoglyphic patterns on all fingertips were whorl except arch/loop on the left middle finger. The foot lengths were 22 cm (~50th centile). Both halluces had medial deviation (Fig. 1E,F). There was partial cutaneous syndactyly of the second and third toes bilaterally. All toenails were hypoplastic and the hallucal nails were everted.

Radiographs of the hands of twin B (Fig. 3) showed short proximal and middle phalanges of the second digit of the left hand. Pattern profile analysis was performed as described [Poznanski, 1984] (Fig. 4). Monozygosity was confirmed by typing 37 short tandem repeat polymorphic markers on the twins as described previously [Biesecker et al., 1995]. Eighteen markers were interpretable and were identical in the twins and 17 of those markers were heterozygous. The heterozygous markers were used to estimate the probability of dizygosity to be less than 1.4×10^{-6} [Bridge, 1997]. An X-inactivation study of peripheral blood lymphocytes was performed as previously described [Trejo et al., 1994] and showed that both twins had a skewed X-inactivation pattern and no difference in the degree of skewing was detectable (data not shown).

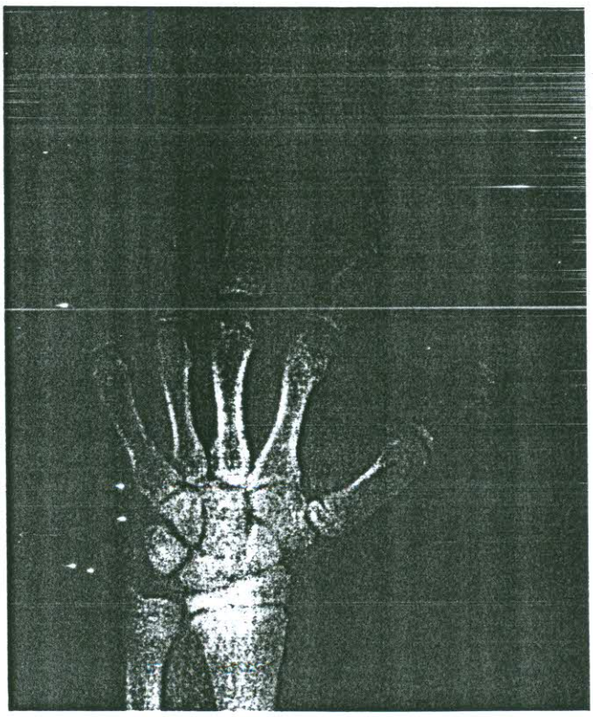

Fig. 3. Radiograph of the hand of Twin B showing brachydactyly and clinodactyly.

[illegible] hyperplastic oral frenula, alveolar notches, and missing lateral incisors. Her facial manifestations include telecanthus, hypoplastic alae nasi, and transient milia, and her limb malformations include short and deviated fingers with partial cutaneous syndactyly. A pattern profile analysis of the hands showed very short left second proximal and middle phalanges. These manifestations are consistent with OFD1. OFD Types 2–8 can be ruled out due to the absence of neurological deficit, tibial defects, hydronephrosis, or polydactyly. Of note, we do not observe the irregular mineralization of the bones of the hands and feet suggested to be pathognomonic for OFD1 [Anneren et al., 1984]. Neither Twin A nor the parents have clinical manifestations of OFD1 and we conclude that Twin B is a sporadic case.

[illegible] (Richards et al., 1990), red–green color blindness [Jorgensen et al., 1992], and Hunter disease [Winchester et al., 1992]. However, the twins reported here had similar X-inactivation patterns and we conclude that discrepant X-inactivation is an unlikely cause for the phenotypic discordance. We conclude that a postzygotic, posttwinning, somatic mutation is the most likely explanation for the discrepant phenotype in these twins.

ACKNOWLEDGMENTS

The authors thank the family for their participation in the study. Acknowledgment is also made to Dr. Harvey Stern, who made the initial diagnosis of OFD1 in this child.

REFERENCES

Anneren G, Arvidson B, Gustavson KH, Jorulf H, Carlsson G. 1984. Oro–facio–digital syndromes 1 and 2: radiological methods for diagnosis and the clinical variations. Clin Genet 26:178–186.

Biesecker LG, Rosenberg M, Dziadzio L, Lædbetter DH, Ning Y, Sarneso C, Rosenbaum K. 1995. Detection of a subtle rearrangement of chromosome 22 using molecular techniques. Am J Med Genet 58:389–394.

Bridge PJ. 1997. The calculation of genetic risks: worked examples in DNA diagnostics. Baltimore: Johns Hopkins University Press. p 181–184.

Feather SA, Woolf AS, Donnai D, Malcolm S, Winter RM. 1997. The oral-facial-digital syndrome type 1 (OFD1), a cause of polycystic kidney disease and associated malformations, maps to Xp22.2-Xp22.3. Hum Mol Genet 6:1163–1167.

Gedeon AK, Oley C, Nelson J, Turner G, Mulley JC. 1999. Gene localization for oral–facial–digital syndrome type 1 (OFD1:MIM311200) proximal to *DXS85*. Am J Med Genet 82:352–354.

Jorgensen AL, Philip J, Raskind WH, Matsushita M, Christensen B, Dreyer V, Motulsky AG. 1992. Different patterns of × inactivation in MZ twins discordant for red–green color-vision deficiency. Am J Hum Genet 51:291–298.

Machin GA. 1996. Some causes of genotypic and phenotypic discordance on monozygotic twin pairs. Am J Med Genet 61:216–228.

Monteiro J, Derom C, Vlietinck R, Kohn N, Lesser M, Gregersen PK. 1998. Commitment to X-inactivation precedes the twinning event in monochorionic MZ twins. Am J Hum Genet 63:339–346.

Poznanski AK. 1984. The hand in radiologic diagnosis. Philadelphia: Saunders. p 31–96.

Richards CS, Watkins SC, Hoffman EP, Schneider NR, Milsark IW, Katz KS, Cook JD, Kunkel LM, Cortada JM. 1990. Skewed × inactivation in a female MZ twin results in Duchenne muscular dystrophy. Am J Hum Genet 46:672–681.

Thienen MNV, Auwera BJVD. 1994. Monozygotic twins discordant for Spondylocostal dysostosis. Am J Med Genet 52:483–486.

Trejo V, Derom C, Vlietinck R, Ollier W, Silman A, Ebers G, Derom R, Gregersen PK. 1994. X- chromosome inactivation patterns correlate with fetal-placental anatomy in monozygotic twin pairs: implications for immune relatedness and concordance for autoimmunity. Mol Med 1:62–70.

Winchester B, Young E, Geddes S, Genet S, Hurst J, Middelton-Price H, Williams N, Webb M, Habel A, Malcolm S. 1992. Female twin with Hunter disease due to nonrandom inactivation of the X-chromosome: a consequence of twinning. Am J Med Genet 44:834–838.