Buccal Anomalies, Cephalometric Analysis and Genetic Study of Two Sisters With Orofaciodigital Syndrome Type I

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Orofaciodigital syndromes have many clinical and cephalometric anomalies, including facial irregularities, oral cavity abnormalities, and malformations of fingers and toes. In this case of twin girls, buccal exploration, cephalometric examination, and genetic analysis were performed to diagnose Orofaciodigital I or Orofaciodigital II syndrome. Clinically, the twins had several dental and skeletal irregularities. Genetic analysis revealed a DNA segment abnormality corresponding to exon 3 and presence of nucleotide change, 243C>G, leading to the missense mutation H81Q. This causative mutation associated with the OFD1 gene has not been reported previously. Both patients were diagnosed as having Orofaciodigital I syndrome.

KEY WORDS: *OFD syndrome; Papillon-Léage syndrome*

The orofaciodigital (OFD) syndromes are a group of disorders that consist of facial anomalies, abnormalities of the oral cavity and malformations of fingers and toes (Tüysüz et al., 1999). Although Torriello (1993) divided OFD syndromes into nine subgroups, OFD classification for many years has been based solely on clinical findings and inheritance patterns (Franceschini et al., 1995). Although clinical variability in OFD syndromes may reflect genetic heterogeneity, there is some overlap among these groups, and misdiagnosis may account for some variability in overlapping manifestations (Hsieh and Hou, 1999). Molecular testing for OFD type I has been available for close to 5 years (Ferrante et al., 2001).

Papillon-Léage and Psaume syndrome (OFD I) has a reported frequency of 1/50,000 births (Martinot et al., 1994). It was described first by Papillon-Léage and Psaume (1954) and is characterized by facial deformities including frontal bossing, hypoplastic mandible ramus and zygoma, broad nasal root, and pseudocleft of mid–upper lip. Internal oral/maxillofacial irregularities include a cleft or defect of hard palate, a palate divided by frenula behind cuspid teeth, a cleft tongue with hamartomas between lobes, ankyloglossia, absence of lower lateral incisors, thick fibrous bands (frenula) in upper and lower mucobuccal fold, malposition of teeth, and supernumerary teeth. Skeletal deformities may include syndactyly, clinodactyly, brachydactyly, short tubular hand and foot bones, and hypoplasia of the second to fifth toes and the hallux often bent in a tubular direction. Mental retardation also has been described (Melnick and Shields, 1975; Gorlin et al., 1978; Jones and Smith, 1988; Gunbay et al., 1996; King and Sanares, 2002; Driva et al., 2004).

First described by Mohr (1941), Mohr syndrome or OFD type II (OFD II), has a frequency of 1/330,000 births (Martinot et al., 1994) and is characterized by oral/maxiofacial deformities such as low nasal bridge, broad nasal tip sometimes slightly bifid, hypertelorism, nodules on tongue, midline cleft of lip, high arched or cleft palate, hypertrophy of usual frenula, hypoplasia of zygomatic arch and maxilla, and micrognathia. Other abnormalities include partial reduplication of hallux, brachydactyly, syndactyly, polydactyly, and conductive hearing loss. Although normal intelligence is common, in some cases mental deficiency has been reported (Gorlin et al., 1978; Jones and Smith, 1988; Prpic et al., 1995; Hosalkar et al., 1999). Cerebellar anomalies (Annerén et al., 1990) and forking of the metacarpals (Annerén et al., 1984; Hsieh and Hou, 1999) also have been described.

Malposition of teeth is a consistent finding. The canines occasionally are separated from the incisors or premolars by a gap resulting from a hypertrophied frenulum (Townes et al., 1976; Martinot et al., 1994). Goldstein and Ledesma reported two cases with agenesis, supernumerary teeth, delayed eruption, microdontia, talonism, supernumerary cusps, and abnormal root morphology (Goldstein and Ledesma, 1974), and natal teeth also have been reported using prenatal diagnosis (Balci et al., 1999).

Differential diagnosis between OFD II and OFD I can be difficult and no argument is absolute. Many authors recognize the importance of bilateral bifidity of the big toe (Gorlin et al., 1978; Baraister, 1986). This is characteristic of type II, but is not pathognomonic, because it can also be found in type I (Townes et al., 1976; Martinot et al., 1994). Cutaneous anom-

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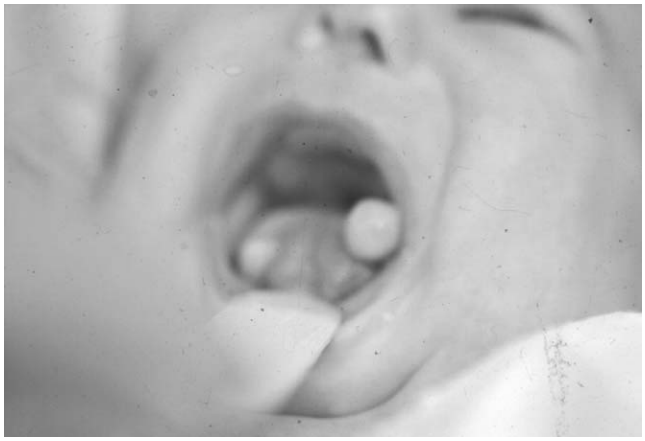

FIGURE 1 Fibromas and bifid tongue.

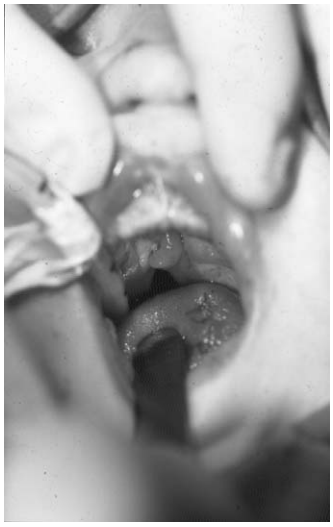

FIGURE 2 Cleft soft palate and cleft of the mid–upper lip.

alies suggest type I (Gorlin et al., 1978; Martinot et al., 1994). Facial anomalies are not discriminatory (Martinot et al., 1994). An absence of lower lateral incisors is typical of OFD I syndrome, whereas the absence of lower median incisors suggests type II. Inherited deafness is characteristic of type II (Baraister, 1986) and polycystic kidneys are seen in type I (Donnai et al., 1987). An irregular mineralization of the phalanxes of the hands and feet has been noted in OFD I, but not in OFD II (Annerén et al., 1984). This distinguishing anomaly, however, has been contradicted in one case (Lipp and Lubit, 1990).

Differential diagnosis of OFD I versus OFD II is important in that it allows appropriate genetic advice to be given, because the mode of inheritance of these two syndromes is different. OFD I syndrome is X-linked dominant and of variable expression, whereas OFD II syndrome is autosomal recessive (Rimoin and Edgerton, 1967). In OFD I, only women and girls are affected, and even if the mother presents a mild expression of the syndrome, she will transmit it to only half of her daughters. However, because OFD I causes almost certain mortality in boys, all living sons will not have the disorder. In OFD II the risk of producing a second affected child is 25% (Cotton et al., 1979). A healthy sibling of an affected child has two chances in three of being a healthy heterozygote carrier of the syndrome (Martinot et al., 1994). The gene responsible for OFD I was identified through a positional candidate gene approach in 2001 and the gene named OFD1 (Ferrante et al., 2001) Therefore, OFD I molecular testing can be carried out.

The therapeutic approach involves a multidisciplinary course of action involving surgeons, pediatricians, genetic experts, orthodontists, orthophonists, and psychologists. The following abnormalities must be operated on: lingual tumors and bifidity, ankyloglossia, cleft palate, polydactyly, and syndactyly. The need for surgery is more relative for abnormalities concerning the external ear, median cleft of the upper lip, vestibular frenulum, and deviation of nasal bridge. Ridging of the metopic sutures is not normally operated on except in cases of trigonocephaly that require surgical correction for morphological reasons (Martinot et al., 1994).

PATIENTS

Two twin sisters (Spanish, white, 7 years 8 months of age) were referred from the Craniofacial Unit at the 12 de Octubre Hospital in Madrid. Both had been diagnosed with OFC syndrome, although it was unclear whether they had OFD I (Papillon-Léage) or OFD II (Mohr).

According to their medical records, the placenta was monocorial biamniotic and birth occurred by cesarean section. Both weighed 2340 g, with a height of 44.5 cm. Both had a normal 46,XX karyotype.

Abnormal features common to both were essential severe valgus, flat feet with mobile subastragals, mild shortened Achilles' tendon, and blepharofimosis. Both girls also presented central nervous system alterations such as multi-partitioned interhemispheric cysts. These were excised surgically when the girls were 1 year old, leaving them with a cyst-peritoneal derivation and a Dandy-Walker malformation.

In reference to the tongue, both girls presented a bifid tongue, ankyloglossia, and multiple fibromas (Fig. 1). Fibromas were removed when the girls were 6 months old and at the same time, surgery to correct the bifid tongue and the ankyloglossia was performed. Both girls presented a cleft soft palate and a cleft of the mid–upper lip (Fig. 2).

When they were 16 months old, the girls underwent an intra-alveolar veloplasty with minimal Langenbeck discharge to treat the cleft, whereas at the lip an enlargement of the vestibulum and a reconstruction of the muscles and Cupid arch were performed.

At the age of 5 years, both girls developed an oronasal fistula that required surgical closure. Both presented brachydactyly, more evident in digits 2 and 3 and more obvious on the inferior extremities (Fig. 3). Neither presented clinodactyly or polydactyly. They also presented an irregular pattern of radiolucency and a spicule-like formation in the phalanges and metacarpals of the second, third, and fourth fingers but in a very mild way (Fig. 4), as described by Annerén et al. (1984).

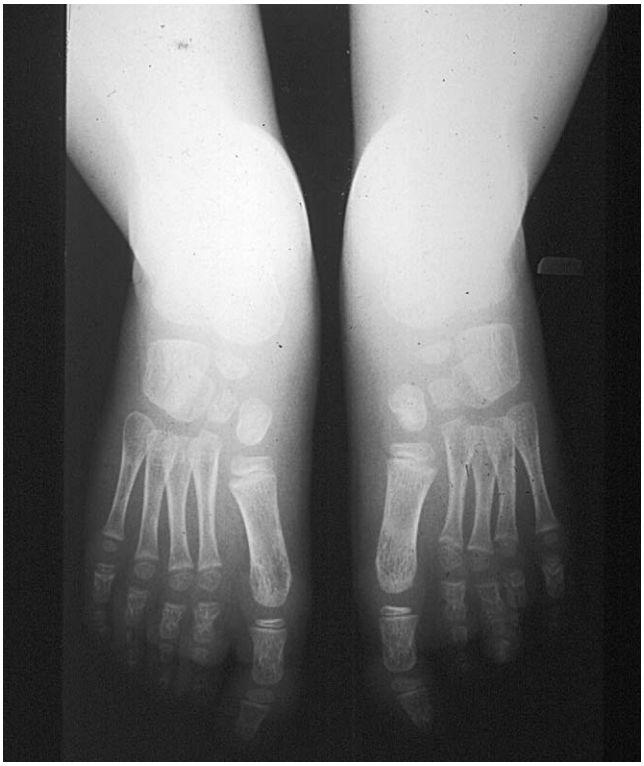

FIGURE 3 Brachydactyly in the toes.

Each also presented a nasal deformity, including a low nasal bridge and a broad nasal tip; these were operated on some time after the girls were 8 years of age. Dissection of the alar and triangular cartilages, resection of a fragment of the nasal spine, filing of the dorsum and glabella, and the insertion of a graft from the septal cartilage in dorsum and columella were performed.

The two girls had some differing buccal characteristics, which are described below.

Case 1

At a buccal level, a marked hypertrophy of the frenulum was observed, as well as agenesis of the permanent teeth (lower lateral incisors, second lower bicuspids, and second lower left molar), a second lower deciduous molar agenesis, microdontia, and a bizarre crown morphology (Figs. 5 and 6).

The malocclusion consisted of a dental class II, a crossbite on the left side, an anterior open bite, and arched palate vault (Fig. 7).

Case 2

At a buccal level, a marked hypertrophy of the frenulum was observed, as well as agenesis of the permanent teeth (lower lateral incisors, lower cuspids, lower second bicuspids, and first and second lower right molars), agenesis of some primary teeth (lower right second molar and lower left cuspid), microdontia, and a bizarre crown morphology (Figs. 8 and 9).

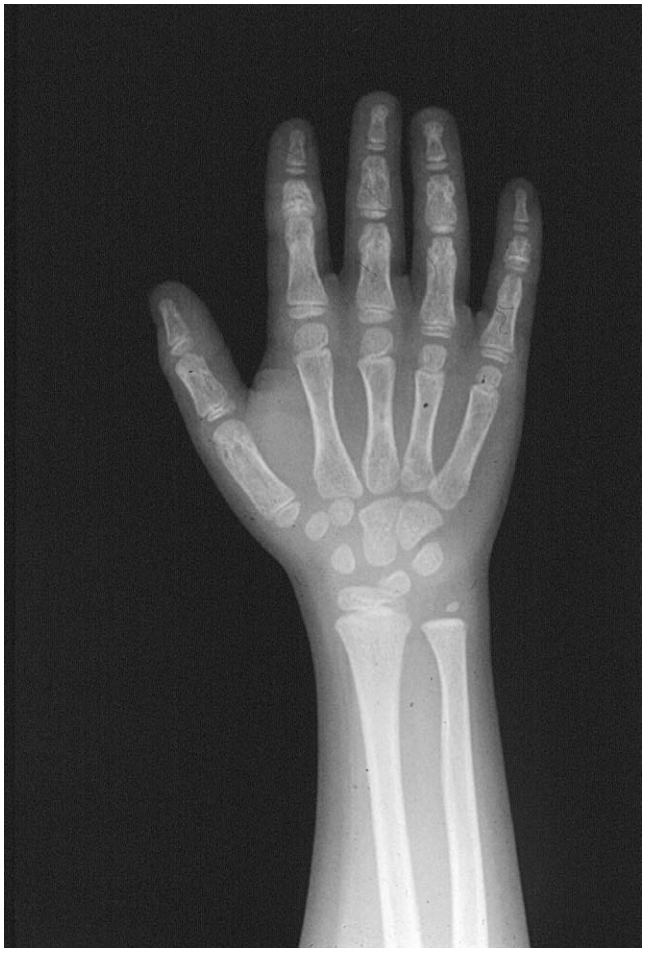

FIGURE 4 Brachydactyly in the fingers.

Her malocclusion consisted of a dental class II, a crossbite on the right side, an anterior open bite, and a highly arched palate vault (Fig. 10).

Both sisters had an apparent dolichocephaly and a leptoprosopic face, a skeletal open bite, and a bimaxillary retrognathism (Figs. 11 and 12).

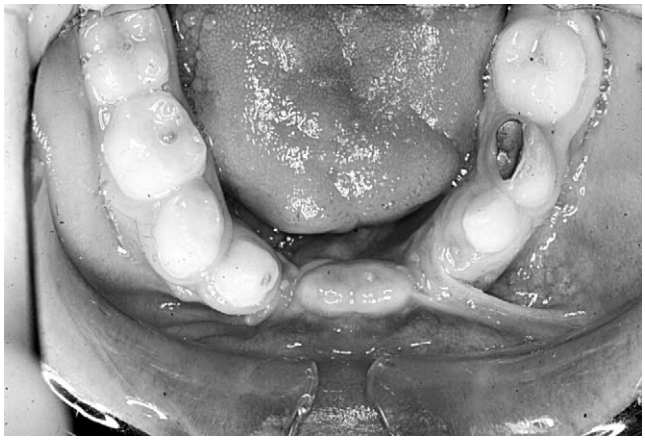

FIGURE 5 Lower arch. Agenesis of lower lateral incisors and frenulum hypertrophy.

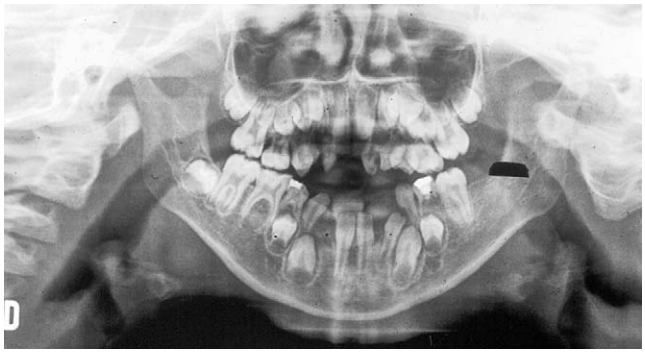

FIGURE 6 Panoramic x-ray. Agenesis and bizarre crown morphology.

Molecular Analysis of the OFD1 Gene

In order to test the possible involvement of the OFD1 gene, we studied total genomic DNA from Case 1 through a denaturing high performance liquid chromatography (DHPLC) analysis on the 23 coding exons codifing for the OFD1 transcript. Our analysis revealed an abnormality in the pattern of Case 1 in the DNA segment corresponding to exon 3. The corresponding polymerase chain reaction (PCR) product was analyzed by direct sequencing on both the forward and the reverse strand. Our analysis revealed the presence of a nucleotide change, 243C>G, leading to the missense mutation H81Q. This has not been described before in OFD I patients.

DNA from Case 2 was analyzed and the same mutation was identified. Interestingly, the histidine in position 81 is conserved between *Homo sapiens*, *Mus musculus*, *Xenopus laevis*, *Fugu rubripres*, and *Danio rerio*, thus suggesting that this amino acid is important for OFD1 protein biological function. To exclude the possibility of a polymorphism 200, normal X chromosomes were analyzed and the 243C>G nucleotide change was not identified in the normal controls. In addition, DNA from both parents was analyzed and no mutations were identified, suggesting that the abnormality identified is a *de novo* mutation that occurred in the monocorial biamniotic twins, although the possibility of a mosaicism cannot be ruled out. Together these data indicate that the H81Q mutation identified in both patients is the causative mutation underlying their OFD syndrome.

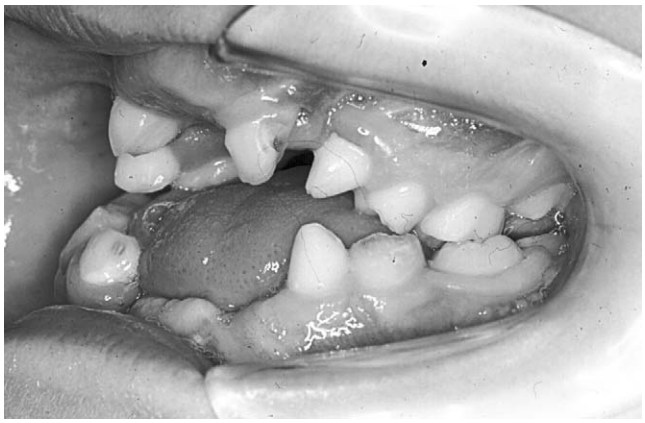

FIGURE 7 Class II, anterior open bite.

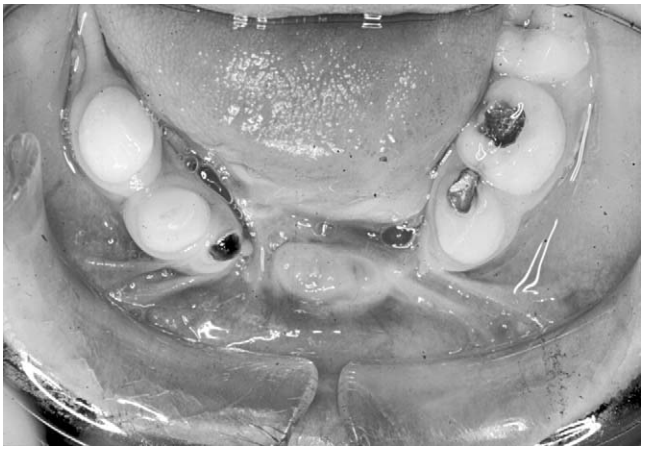

FIGURE 8 Lower arch. Agenesis of lower lateral incisors and frenulum hypertrophy.

Primers and conditions used for mutation analysis already have been described (Ferrante et al., 2001, 2003). Polymerase chain reactions were carried out on genomic DNA extracted from peripheral blood leukocytes using the Capture Column Kit (Gentra Systems, Inc., Minneapolis, MN). The PCR products were checked on agarose gel and then sequenced on both strands using the ABI Prism Big Dye Terminator Cycle Sequencing Kit (Perkin Elmer, Waltham, MA) and an ABI 377 automated DNA sequencer (Applied Biosystems, Foster City, CA). One hundred normal white individuals were analyzed for exon 3. Mutation analysis on patients and controls were performed by DHPLC using the Wave DNA fragment analysis system (Transgenomic, Inc., Omaha, NE) according to the manufacturer's instructions. Mutation description follows standard nomenclature (Antonarakis, 1998). Patients and controls used in this study were white and full ethical approval was obtained for the study.

Discussion

Papillon-Léage syndrome (OFD I) and Mohr syndrome (OFD II) are well-defined conditions. There are very few ref-

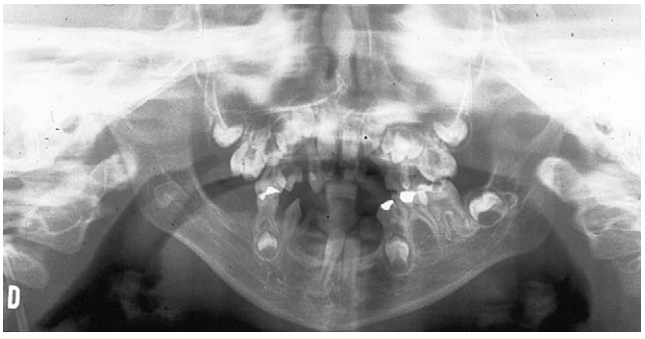

FIGURE 9 Panoramic x-ray. Agenesis in permanent and primary dentition.

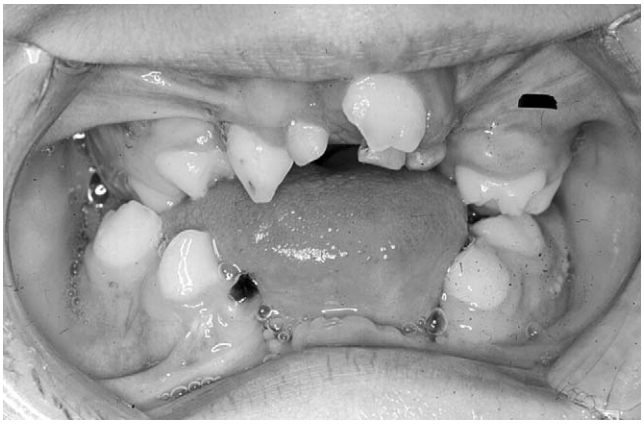

FIGURE 10 Frontal view. Class II, anterior open bite, crossbite on the right side.

erences to them in dental literature, although the first Papillon-Léage case study was published in a dental journal (Papillon-Léage and Psaume, 1954).

Some of the anomalies our patients presented and their presence or absence in OFD I and OFD II syndromes are presented in Table 1. The lingual alterations in these cases, as well as the cleft lip and palate the girls presented, did not allow us to clearly determine whether they had OFD I or II (Buyse, 1990), although the lower lateral incisors agenesis is more characteristic in the Papillon-Léage syndrome (Buyse, 1990). It is noteworthy that all agenesis was localized in the lower arch and also that the patients presented agenesis of primary teeth, as previously reported by Salinas et al. (1991).

Other alterations such as frenula hypertrophy; the presence of a gap which, in Case 1 was between the cuspids and incisors and in Case 2 between the cuspids and bicuspids; the microdontia; and the bizarre crown morphology are characteristic in OFD II but also can be seen in OFD I (Goldstein and Ledesma, 1974; Townes et al., 1976; Martinot et al., 1994; Driva et al., 2004).

The neurological alterations present in these patients also have been described in OFD II; the arachnoid cysts have been reported by Reardon et al. (1989) and Balci et al. (1999), and the corpus callosum agenesis also has been reported by Wahrman et al. (1966) and Balci et al. (1999). The Dandy-Walker malformation has been reported by several authors (Haumont and Pelce, 1983; Gillerot and Koulischer, 1988; Balci et al., 1999).

The nasal alterations and the brachydactyly these patients presented may appear in both OFD I and OFD II, however, the absence of renal lesions in our patients (polycystic kidneys may appear in OFD I [Donnai et al., 1987; Salinas et al., 1991]), as well as the presence of conduction deafness, indicated OFD II.

From an orthodontic point of view, only one cephalometric analysis has been published on a patient with OFD syndrome (King and Sanares, 2002). The cephalometric analysis performed on this case of twin girls confirmed the maxillary hy-

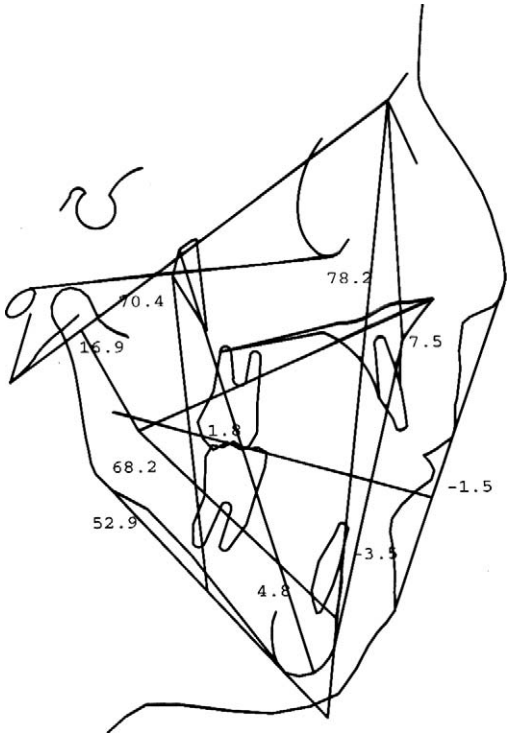

FIGURE 11 Lateral cephalometry, Case 1. Apparent dolichocephaly, skeletal open bite, and bimaxillary retrognathism.

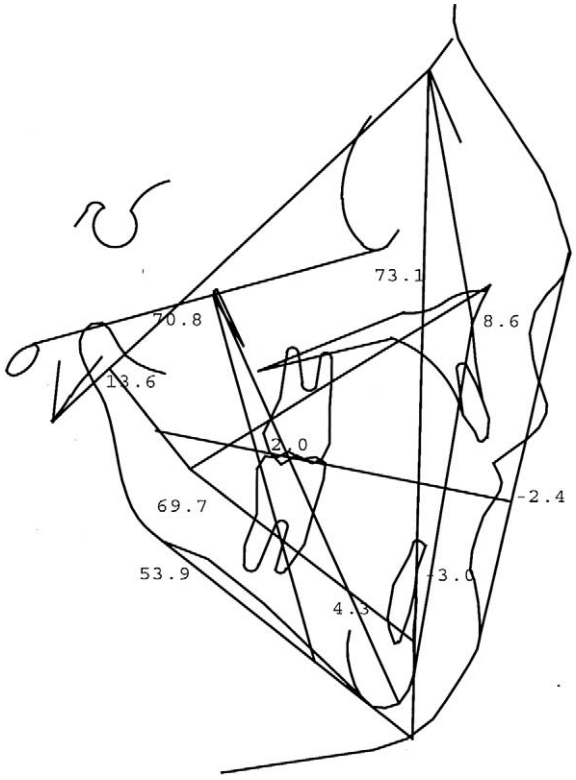

FIGURE 12 Lateral cephalometry, Case 2. Apparent dolichocephaly, skeletal open bite, and bimaxillary retrognathism.

TABLE 1 Anomalies Presented by Our Patients and Their Presence or Absence in OFD I and OFD II Syndromes

	Sex	*Hyperplastic Frenula*	*Broad Nasal Root*	*Digital Anomalies*	*Hypodontia*	*Pseudocleft of the Upper Lip*	*Tongue Nodules*	*Gap Between Teeth*	*Microdontia*	*Renal Lesions*
OFD1	Female	yes	yes	yes	lower lateral incisors	yes	yes	sometimes	sometimes	yes
OFD2	Female and male	yes	yes	sometimes	lower medial incisors	yes	yes	characteristic	characteristic	no
Our patients	Female	yes	yes	yes	lower lateral incisors	yes	yes	yes	yes	yes

poplasia as well as the micrognatia previously described by other authors (Gorlin et al., 1978; Jones and Smith, 1988).

OFD II syndrome is 6.5 times less frequent than OFD I (Ruess et al., 1962), but in both cases and due to their very low incidence, dental literature is very rare. However, Lyons (1939) published a case that most likely indicated OFDS II syndrome 2 years before Mohr (1941) published his article with the first description of the syndrome.

The previously unreported H81Q mutation we identified in these twin sisters falls within exon 3, which is one of the exons most frequently associated with mutations in OFD type I patients (Rakkolainen et al., 2002; Thauvin-Robinet et al., 2006). Interestingly, these patients also presented with mild mental retardation, which also has been frequently associated with mutation in exon 3 (Thauvin-Robinet et al., 2006).

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