Frontofacionasal Dysplasia in a Newborn with a De Novo Duplication of 7p15.2-p15.1

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Abstract

We report a new case of frontofacionasal dysplasia or dysostosis (FFND) with a 1.5 Mb duplication in the region of 7p15.2-p15.1, and provide a review of the literature to understand the underlying pathogenesis better.

Keywords

- baby
- frontofacionasal dysplasia
- duplication
- malformation

Genetic Background

Frontofacionasal dysplasia or dysostosis (FFND; online Mendelian inheritance in man [OMIM] 229400) is a rare craniofacial anomaly that was first described by Gollop.[1] History of consanguinity or affection of siblings was reported in at least five families suggesting an autosomal mode of inheritance.[1–4] However, our case adds up to a list of six sporadic cases previously reported as well.[3,5–8] FFND shows extreme variability in the combination and severity of abnormalities which include blepharophimosis, lower lid lagophthalmos, primary telecanthus, s-shaped palpebral fissures, facial hypoplasia, eyelid coloboma, widow peak, cranium bifidum occultum, anterior encephalocele, frontal lipoma, nasal hypoplasia, deformed nostrils, bifid nose, and cleft of lip, premaxilla, palate, and uvula.[1,2,5–8]

Clinical Report

A full-term baby girl of European descent was born to nonconsanguineous parents by normal spontaneous vaginal delivery. The mother is 27 years having a history of early abortion and another full-term normal pregnancy. The mother denied use of alcohol, tobacco, or illicit drugs during the pregnancy. However, the pregnancy was complicated by first trimester urinary tract infection, gestational diabetes, and postpartum depression. Prenatal medications included glyburide for diabetes, prenatal vitamins, Zofran (GlaxoSmithKline, Philadelphia, PA) and Reglan (Baxter International Inc., Deerfield, Illinois) for morning sickness and albuterol for asthma. The father is 33 years and denied any medications or infectious diseases. The mother has a cousin diagnosed with Goldenhar syndrome (OMIM 164210), another craniofacial syndrome known to be associated with eyelid coloboma.

The proposita was noticed at birth to have a nasopalpebral soft tissue mass extending toward the inner canthi with apparent microphthalmia (►**Fig. 1**). Her facies shows small anterior fontanelle and midfacial hypoplasia with ocular hypertelorism and telecanthus. The eyes have bilateral colobomas of the upper eyelids but no choroidal colobomas. Palpebral fissures have a characteristic s-shape with absent eyelashes. There are lower lids lagophthalmos and incomplete closure of the eyes. There are micrognathia and short philtrum. The nasal root is broad and the nose appears somewhat hypoplastic without hypoplasia of the

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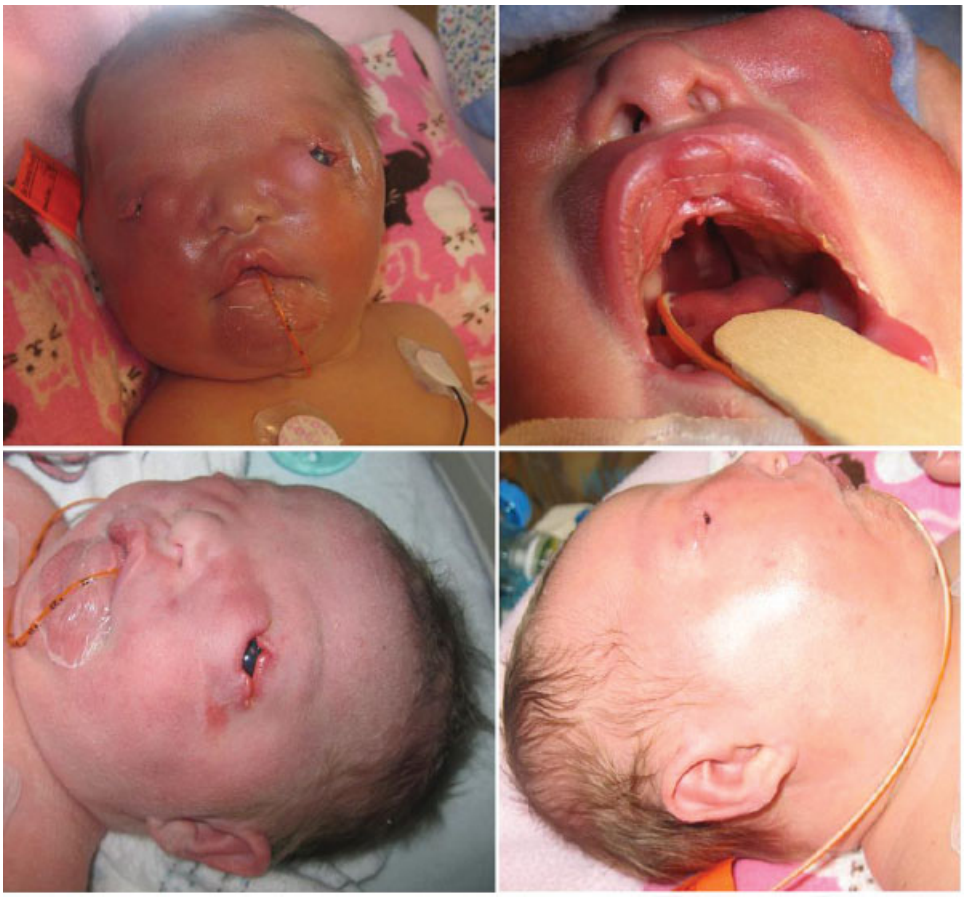

Fig. 1 Photographs for the patient's face and oral cavity.

ala nasi. Examination of the oral cavity shows complete cleft of the hard and soft palate as well as a cleft uvula (►**Fig. 1**). All four proximal and distal extremities were normal. Parental consent was obtained for publication of the case report and using the baby's pictures.

Results

Radiological Investigations

Magnetic resonance imaging (MRI) of the face and brain shows normal brain anatomy (►**Fig. 2**). The corpus callosum

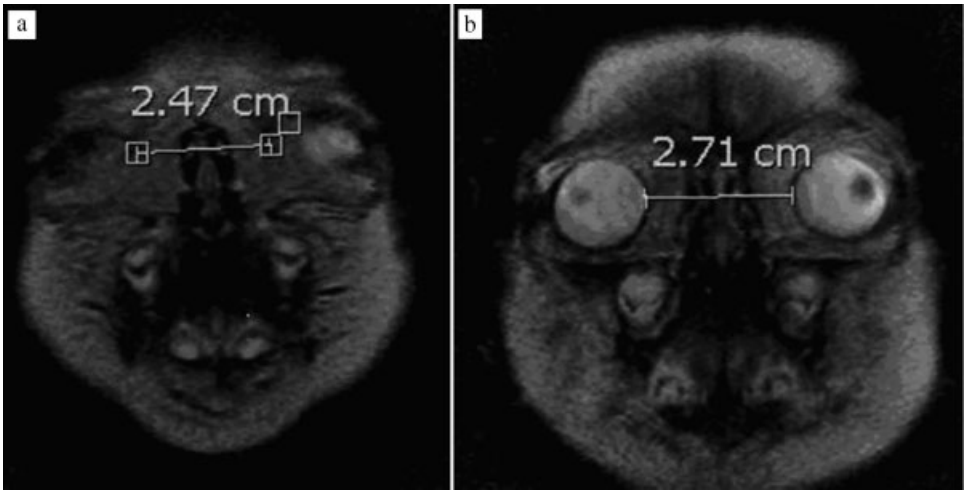

Fig. 2 MRI-coronal section of the head demonstrating the intercanthal folds (a) and the bony interorbital distance from the medial globes (b). MRI, magnetic resonance imaging.

is present and the falx cerebri is normal in appearance. The interorbital distance is increased as measured by the intercanthal folds (2.47cm; ►**Fig. 2a**) and the bony interorbital distance from the medial globes (2.71cm; ►**Fig. 2b**). No anterior encephaloceles are evident. MRI of the face is consistent with a frontal lipoma.

Abdominal Ultrasound and Echocardiogram

No abnormalities of the gut or heart were detected.

Single Nucleotide Polymorphism Chromosomal Microarray

Analysis with the Affymetrix CytoScan HD single nucleotide polymorphism (SNP) array with NetAffx 32.2 hg19 array revealed a copy number gain of 1,964 probes in the region of 7p15.2-p15.1 (►**Fig. 3**). This is classified as duplication and is estimated to be of a minimum size of 1.5 Mb extending from nucleotides 27,203,536 to 28,736,104 (UCSC Freeze Feb. 2009, hg19). This segment starts in *CREB5* (centromeric end) and ends in *HOXA9* (telomeric end). The duplication includes the following RefSeq genes: *JAZF1*, *TAX1BP1*, *HIBADH*, *EVX1*, *HOXA13*, *HOXA11*, and *HOXA10* (see Supplementary Table 1 in the online version of the article). In addition there are at least five noncoding RNA genes: *JAZF1-AS1*, *HOTTIP*, *HOXA11-AS1*, *MIR196B*, and *HOXA-AS4*. Parental SNP chromosomal microarray studies were done and have confirmed this finding to be de novo and not inherited.

Discussion

The constellation of features seen in this case report is most consistent with frontofacionasal dysplasia.[1,2,5–8] This baby did not have cranium bifidum occultum or encephalocele but did have a nasopalpebral lipoma. Gollop's first case also did not have a cranium bifidum occultum or encephalocele.[1] The second case of Gollop and the case presented by White did not have an encephalocele but rather had frontal lipomas similar to our case.[1,6] The midline clefting in the patient extends to include soft and hard palates and the uvula but does not involve the premaxilla or the lip. The mild hypoplasia of the nose in this patient represents the mildest presentation ever reported in cases of FFND.

The important differential diagnosis of FFND includes syndromes with facionasal dysplasia; frontonasal dysplasia (FND; OMIM 136760, 613451, 613456), acromelic FND (AFND; OMIM 603671), acrofrontofacionasal dysostosis syndromes (AFFND; OMIM 201180, 239710), craniofrontonasal syndrome (CFNS; OMIM 304110), FND with alar clefts (OMIM 203000), oculoauriculofrontonasal syndrome (OAFNS; OMIM 601452). The patient in this report has none of the extracranial defects seen in FND (e.g., congenital heart defect and mental retardation),[9–12] AFND (e.g., central nervous system malformations and limb defects),[13] AFFND (e.g., mental retardation, short stature, and digital, limb, and foot anomalies),[14] and CFNS (e.g., grooved nails, digital anomalies, and abnormalities of the thoracic skeleton).[15] Severe palpebral fissure abnormalities are not expected in FND or FND with alar clefts. In addition, the patient lacked coronal synostosis found in CFNS[15] and lacked the microtia, skin tags, and ocular dermoids seen with OAFNS.[16]

There is a high similarity in our case with the features of nasopalpebral lipoma–coloboma syndrome (OMIM 167730). Both are characterized by congenital nasopalpebral lipomas,

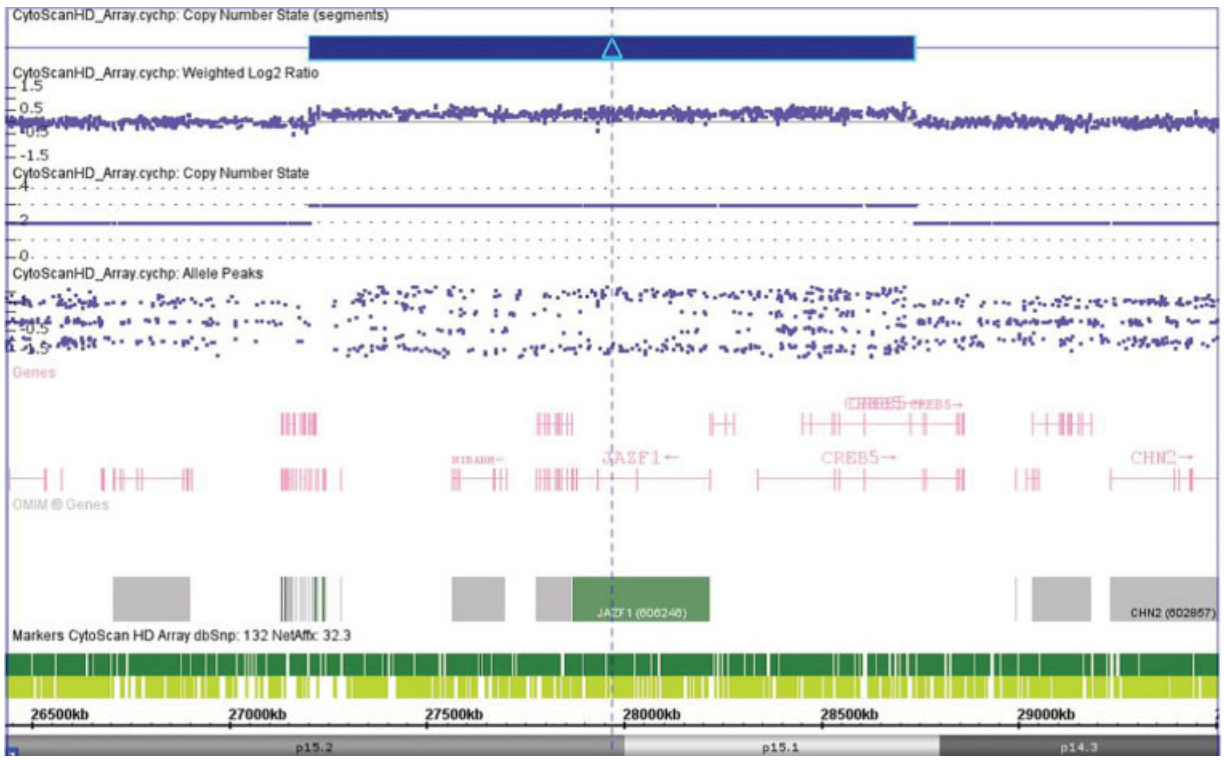

Fig. 3 Chromosomal microarray using Affymetrix (Santa Clara, CA) CytoScan HD (NetAffx 32.2) revealed a duplication of 7p15.2p15.1 (arr[hg19] 7p15.2p15.1[27,203,536–28,736,104] × 3).

eyelid colobomas, lagophthalmos, and telecanthus.[17–21] The true hypertelorism with increased bony intraorbital distance, clefting, and absent eye lashes are distinctive to our case. Other syndromes associated with eyelid coloboma include Goldenhar syndrome, Treacher Collins syndrome, Delleman syndrome, as well as FND. In spite of family history, Goldenhar syndrome (OMIM 164210) was ruled out by the absence of facial asymmetry, ear deformities, and vertebral anomalies.[22] The missing diagnostic features of Treacher Collins syndrome (OMIM 154500, 613717, and 248390) include downward slanting of the palpebral fissures, hypoplasia of the facial bones, and ear deformities.[23] Delleman syndrome (OMIM 164180) is characterized by orbital cysts, cerebral malformations, and focal dermal lesions.[24,25] None of these features were seen in this patient.

The craniofacial midline is seen as a developmental field and is not just a sagittal plane. Frontonasal malformations results from arrest in the embryogenesis of the frontonasal process causing failure of nasal capsule to develop normally.[26,27] FFND was thought to be a specific subtype of the FND developmental field.[6] Two factors affect the severity of the facial changes; the onset and the cause of the embryological defect. The morphokinetic arrest starts between embryonic days 21 and 70 with more severe malformations on earlier onset. The classical eliciting pathology is a frontal encephalocele with anterior cranium bifidum causing typical ocular hypertelorism, and nasal deformities involving both the dorsum and the tip of the nose.[27,28] Orofacial clefting has been associated with hypertelorism as a part of the developmental field defect, but the specific mechanism is unknown.[28,29] Frontal lipoma is a less common cause of facial dysplasia, however; it was associated with more variability of malformations.[1,6,28] In our case, we expect that the lipoma developed late giving enough time for almost normal development of the nose. The nasopalpebral position might explain the severity of the ocular manifestations and the phenotypic similarities with of nasopalpebral lipoma–coloboma syndrome. Our results suggest that the lipoma impaired the craniofacial midline developmental field and caused true ocular hypertelorism with associated oral clefting.

To our knowledge, this report is the first to associate FFND with a duplication of 7p15.2-p15.1. However, an interstitial deletion at chromosome 7p15.1–21.1 was previously reported with a case of facial dysgenesis.[30] This 1.5 Mb duplication has not been reported as a common variant in DGV[31] (►**Supplementary Fig. 1** available in the online version of the article) or CAGdb (CAGdb.org), although a 1.35 Mb duplication (chr7:27433518–28790162) was reported in Database of Genomic Variation and Phenotype in Humans Using Ensembl Resources (DECIPHER)[32,33] in a patient with unknown diagnosis. Autosomal recessive mode of inheritance was suggested in FFND because of recurrence in siblings and history of consanguinity in multiple cases.[1–4] However, other cases did not show such supportive history.[3,5–8] Habecker-Green et al 2000 identified a rare de novo balanced translocation involving chromosomes 8 and 12 (t[8;12] [q22;q21]) in a case of FFND. They proposed four possible explanations which still apply to our case. First, being an irrelevant coincidence which might be supported in our patient by having none of the genes in the duplicated area associated before with impaired craniofacial development. For example, while the duplication region involves a large segment of the HOXA cluster which is known to be crucial for embryonic development,[34] the genes in this duplication were shown to be coordinately regulated in distal limb and genital bud development, not craniofacial development.[35] Second, having an autosomal recessive mode of inheritance where the child received a recessive allele of the disease from one parent, and the acquired genetic event distorted the other parent's gene. This explanation might be unlikely in our patient because loss-of-function is not expected in genetic duplications, unless it occurred at the break point of inverted tandem duplications or secondary to interstitial deletions. Third, if genetic heterogeneity underlies the pathogenesis of FFND, and this de novo genetic rearrangement presents an autosomal dominant form of the disease. Two of the noncoding RNA genes involved in the duplication are known to be involved in complex genomic regulation and could be valid candidates. HOTTIP is a long noncoding RNA that epigenetically regulates homeotic gene expression.[36] MIR196B, a microRNA found in the duplication region, alters the expression of *Hox* genes and impairs the axial patterning in zebrafish and chicken.[37,38] Dosage increase of either genes might be responsible for our case. The last proposed mechanism is the interaction between a combination of environmental factors and the acquired genetic insult.[6] The differential diagnosis as discussed above may be a phenotypic variation of a single entity. Future studies in animal models will be required to distinguish between these possibilities.

Acknowledgments

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