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REVIEW ARTICLE

Frontonasal dysplasia: a review

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ABSTRACT

Frontonasal dysplasia (FND) is a rare complex genetic facial malformation, mostly characterized by affecting the face and head regions of the body. Craniofacial defects can have a severe impact, revealing different types of clinical phenotypes, which are broadly grouped as FNDs. FNDs have been classified along with selected disorders on the genetic and molecular basis. FND is clinically diagnosed on the basis of at least two features including median facial cleft, broad nasal bridge, ocular hypertelorism, widened philtrum, median cleft upper lip, widow's peak frontal hairline, and missing or underdeveloped nasal tip. The three types of FNDs are caused by the *ALX* genes (*ALX1*, *ALX3*, and *ALX4*). Genes and pathways related to facial development are associated with direct or indirect expression of the FGF8, the Sonic hedgehog (SHH), and the BMP4. The present review provides a detail literature review on the FND phenotypes and mutation update of different genes involved that will help in proper classification, genetic counseling, and diagnosis of the affected families.

Keywords: Frontonasal dysplasia, FND, *ALX1*, *ALX3*, *ALX4*.

Introduction

Frontonasal dysplasia (FND; MIM 136760) or median facial crack syndrome or frontonasal malformation was first described in 1967 (1), characterized by a primary defect in the medial portion of the face (2). Phenotypic features associated with the FND include ocular hypertelorism; median facial cleft, disturbing the nose and/or upper lip, broadening of the base of the nose; unilateral or bilateral side cleft or base of the nose; absent nasal tip; widow's peak (frontal hairline) or V-shaped, ankyloglossia, and Poland's syndactyly (2–4). Features such as ocular changes, mild to severe intellectual disability, and profound deafness have also been reported (5). However, the patients might possess a normal range of intelligence, misanthropy, shyness, and also aggressiveness (6,7).

FND is inherited in an autosomal recessive or autosomal dominant fashion. It has been reported independently (non-syndromic) or associated with other severe abnormalities (syndromic) (8). Isolated clinical symptoms are required for the prevalence of the FND, fissures in the midline of the face are observed in 1/100,000 live births (9) while the congenital nasal anomalies are observed in 1/20,000 or 1/40,000 live births (10). In the syndromic FNDs, the overlapping phenotypes can also cause difficulty in the clinical diagnosis. T he present review provides a detail literature review on the three basic FNDs types along with few syndromic forms and providing mutation update, which will help in proper classification, m olecular d iagnosis, g enetic counseling, and might explain the pleiotropy phenomenon.

Previously, two classification systems (The DE Myer classification system and the Sedano Jirasek classification) were used to characterize FND (1,2; (Supplementary Table 1)). Both these classification systems have their own merits and demerits. While, in the nosology and classification of genetic skeletal disorders 2015, FNDs were placed in group 34 (Dysostoses with predominant craniofacial involvement) along with oral-facial-digital syndrome type I (OFD1), Weyers acrofacial (acrodental) dysostosis, Mandibulo-facial dysostosis, Miller syndrome, Acrofacial dysostosis, Nager type, and Mandibulofacial dysostosis with microcephaly (Supplementary Table 1). Since disease-causing genes have been identified for both syndromic and non-syndromic FNDs, thus genetic and clinical classifications are more important to further understand the etiology underline FND.

Genes and Associated Syndromes

As FND is a highly heterogeneous disorder, so the associated syndromes are genetically diverse. There are

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several genes assorted with FND causing severe facial dimorphism. There have been few FND cases reported to date and molecular diagnosis still remains an important issue. Different factors might be responsible for the etiology of FND, as both genetic and environmental factors are contributing elements in causing such phenotypes. In the present literature review, genetic and clinical presentation of different FND types have been presented including different genes involved, which might help in proper classification and revealing the molecular mechanisms involved. Understanding the developmental and clinical aspects of the FND spectrum disorders will unravel different interesting aspects of proper diagnosis and treatment of FND. FND has been classified into three types FND type 1, 2, and 3. Detailed clinical presentation of FND types has been presented in Table 1.

Frontonasal dysplasia type 1 or frontorhiny (FND1; OMIM 606014)

The gene responsible for causing FND type 1 is *ALX3* (Aristaless homeodomain 3; MIM 606014), located on chromosome 1p13.3. Twigg et al. (11) identified disease-causing homozygous variants in the *ALX3* gene in seven families, thus named as FND type 1 (11). FND1 is inherited in an autosomal recessive manner and associated features include broad nasal root, median cleft lip/palate, tetralogy of Fallot, hypoplastic frontal sinuses, cranium bifidum occultum, mild to severe mental retardation, microphthalmia, conductive hearing loss, and cranium bifidum occultum (defect in midline frontal bone) (Figure 1), (11). Recently, Ullah et al. (4), reported mild phenotypes in a Pakistani family having ocular hypertelorism, absent nasal tip, widened philtrum, broad nasal bridge, widely spaced teeth, and having no intellectual disability (4).

ALX3 gene comprises a total of four exons, which encode 343-amino acids long homeodomain protein functioning as a transcriptional regulator. The ALX3 protein comprises a homeodomain and three proline-rich domains (Pro1, 2, 3). The amino-terminus consists of the Pro 1 and the Pro 2 while the Pro 3 is located at the carboxyl-terminus of the protein. Up till now, all the mutations have been reported in the homeodomain of the ALX3 protein suggesting a greater role of this domain in the frontorhiny pathogenesis (Figure 2). The ALX3 protein is mostly expressing in the neural crest-derived craniofacial mesenchyme and developing limbs. The *alx3* knockout mice did not reveal any skeletal deformity; however, double mutant (*alx3/alx4*) mice exhibit severe craniofacial anomalies (12,13).

To date, eight pathogenic sequence variants have been reported in the *ALX3* gene associated with frontorhiny in families from different ethnic regions (Pakistan, Ireland, Morocco, Netherland, Turkey, Algeria, and India). These include four missense mutations (c.608A>G; p.Asn203Ser (Algeria), c.502C>G; p.Leu168Val (Ireland), c. 547C>T; p.Arg183Trp (Netherlands), c.586C>T; p.Arg196Trp (India)), two nonsense mutations (c.543T>A; p.Try181* (Netherlands), c.604C>T; p.Gln202* (Pakistan)), one splice acceptor site (c.595-2A>T (Morocco)), and one frameshift variant (c.578_581 delCTGA; p.Thr193ArgfsX137 (Turkey)) (4,11). Classification according to the ethnic groups has been presented in Table 2.

Frontonasal dysplasia type 2 or FND2 (OMIM 605420)

Pathogenic sequence variants in the *ALX4* (Aristaless homeodomain 4; MIM 605420) gene have been associated with FND2 (MIM 613451), having chromosomal location 11p11.2. FND2 is inherited in both autosomal recessive and autosomal dominant fashion with the identification of pathogenic *ALX4* homozygous or heterozygous variants in several families. FND2 is associated with features such as hypertelorism, small head, short palpebral fissures, depressed nasal bridge, cleft nasal alae, bifid nasal tip, short, broad columella, alopecia (in some patients), sparse eyebrows, craniosynostosis, and intellectual disability (craniosynostosis in some patients) (Figure 1).

To date, 21 pathogenic mutations have been reported in the *ALX4* gene including three homozygous mutations (c.793C>T; p.Arg265*, c.207delG, 2388bp incl ex. 4), causing FND2 (5,15) and 18 heterozygous mutations underlie parietal foramina permagna (OMIM 609597) including three nonsense (c.418C>T; p.Gln 140*, c.620C>A; p.Ser207*, c.736C>T; p.Gln246*) three missense (c.653G>A; p.Arg218Glu, c.815G>C; p.Arg272Pro, c.673C>G; p.Gln225Glu) three small deletions (c.385_394del10, c.504delT, c.291delG) one small insertion (c.343dupC) (16–22). Two pathogenic mutations have also been associated with non-syndromic craniosynostosis (c.19G>T; p.Val7Phe, c.631A>G; p.Lys211Glu) (23), a single small deletion causing skull defects, alopecia, and hypertelorism (c.503delC) (14), and an 11.9 Mb gross deletion causing parietal foramen, in Potocki Schaffer syndrome (24), (Supplementary Table 2).

Frontonasal dysplasia type 3 (FND3; OMIM 601527)

FND type 3 (FND3) is a highly severe form of the FND. The affected individual's exhibits complete failure of fusion between the frontonasal and maxillary arch-derived tissues, thus suffer from midfacial clefting (3,25). Loss of ALX1 (Aristaless homeodomain 1) function results in extreme bilateral microphthalmia, severe facial clefting, hypertelorism, disrupted palatal development, sparse eyelashes, absent eyebrows, mild mental retardation, and low-set posteriorly rotated ears (3,25; Figure 1). Both intragenic mutation and homozygous genomic deletion causing complete loss of function have been reported in the *ALX1* gene resulting in severe to a mild manifestation of FND3. Recently, a homozygous splice acceptor site mutation has been reported having milder features, which might produce a truncated ALX1 protein harboring residual activity (3).

Table 1. *Clinical presentation of different frontonasal dysplasias.*

Phenotype (gene)	Inheritance (OMIM)	Location	Craniofacial features	Integumentary	Musculoskeletal	CNS	Genitourinary
FND1 (*ALX3*)	AR (MIM136760)	1p13.3	Long philtrum with swelling in the peripheral region, midline notch in the upper lip and alveolus, ptosis of the upper eyelid	Widow's peak, Frontal cutaneous lipoma, Dermoid cyst in the Midline	Tetralogy of Fallot, Pectoral muscle hypoplasia/aplasia, Clinodactyly, Camptodactyly, Cleft palate	Lipoma of corpus callosum, Slight mental retardation, Cranium bifidum occultum, Maxillary hypoplasia	Not observed
FND2 (*ALX4*)	AR (MIM 613451)	11p11.2	Microphthalmia, Large skull defect, Blepharophimosis, Cleft alae nasi, Hypertelorism, Depressed nasal bridge, Craniosynostosis, Parietal formia	Sparse scalp hair or Total alopecia, Sparse eyebrows and eyelashes	Variable severity observed in different patients	Callosal anomaly with midline intracranial Lipoma, Mental retardation (few patients), Hypoplasia of corpus callosum, Cerebellar vermis hypoplasia	Hypospadias, Cryptorchidism
FND3 (*ALX1*)	AR/AD (MIM 613456)	12q21.31	Bilateral facial cleft, Microphthalmia in extreme form, Complete-mild cleft palate, Upper eyelid coloboma	Absence of Eyebrows, Sparse eyelashes	Not observed	Not observed	Not observed
Craniofrontonasal Syndrome (*EFNB1*)	XLD (MIM304110)	Xq13.1	Craniofacial asymmetry, Craniosynostosis, facial asymmetry, Widow's peak, Bifid nasal tip, Cleft palate/lip, Hypertelorism	Thick and wiry hair, low posterior hairline, Brittle and grooved nails	Dysplastic clavicles, Chest deformity Sprengel deformity, Broad halluces, Syndactyly, congenital diaphragmatic	Developmental delay, normal intelligence, hypotonia, hypoplasia	External genitalia, Hypospadias, and Cryptorchidism observed in males

(Continued)

Table 1. *Clinical presentation of different frontonasal dysplasias. (Continued)*

Phenotype (gene)	Inheritance (OMIM)	Location	Craniofacial features	Integumentary	Musculoskeletal	CNS	Genitourinary
Acromelic Frontonasal Dysostosis (*ZSWIM6*)	AD (MIM 603670)	5q12.1	Parietal foramina, Bifid nose, Broad nasal tip, Cleft palate, Brachycephaly, Hypertelorism, Telecanthus, Bifid nose and broad nasal tip, Brachycephaly, Cryptorchidism, Cranium bifidum (anterior)	Clubbed thick nails, Vertical creases of plantar surface	Hypoplastic patellae, Preaxial polydactyly, Syndactyly, Unilateral or bilateral hemimelia	Absent olfactory bulbs, Encephalocele, Enlarged sella turcica, Seizure, Callosal anomaly, hypopituitarism, Intellectual disability observed	Internal genitalia (Males). Cryptorchidism and Hypopituitarism observed in some patients
Oral facial digital syndrome type I (*CXORF5*)	XLD (MIM 311200)	Xp22.2	Frontal bossing, Facial Asymmetry, Microretrognathia, Pseudo-cleft of the upper lip, High-arched palate	Dry, rough, sparse hair (alopecia)	Short stature, cardiac anomalies, missing teeth, Buccal frenum, Syndactyly, Clinodactyly	Variable intellectual disability, absent corpus callosum, Hydrocephalus, Seizure, Porencephaly	Adult onset polycystic kidney, Ovarian cyst (female)
Acrofacial dysostosis type Nager (*SF3B4*)	AD (MIM 154400)	1q21.2	Micrognathia, Midface retrusion, Retrognathia, Cleft palate,	Partial absence of eyelashes	Deafness, High nasal bridge, Macrostomia, Tetralogy of Fallot, Syndactyly, Clinodactyly	Microcephaly, Hydrocephalus, Polymicrogyria, speech delay	Unilateral renal agenesis, duplicated calyx, Bicornuate uterus (Female)
Frontonasal Dysostosis (*SIX2*)	AD (MIM604994)	2p21	Craniosynostosis, Ptosis, Epicanthus inversus, High anterior hairline, Frontal bossing large anterior fontanelle, Parietal foramina	Not observed	Not observed	No intellectual disability observed	Not observed

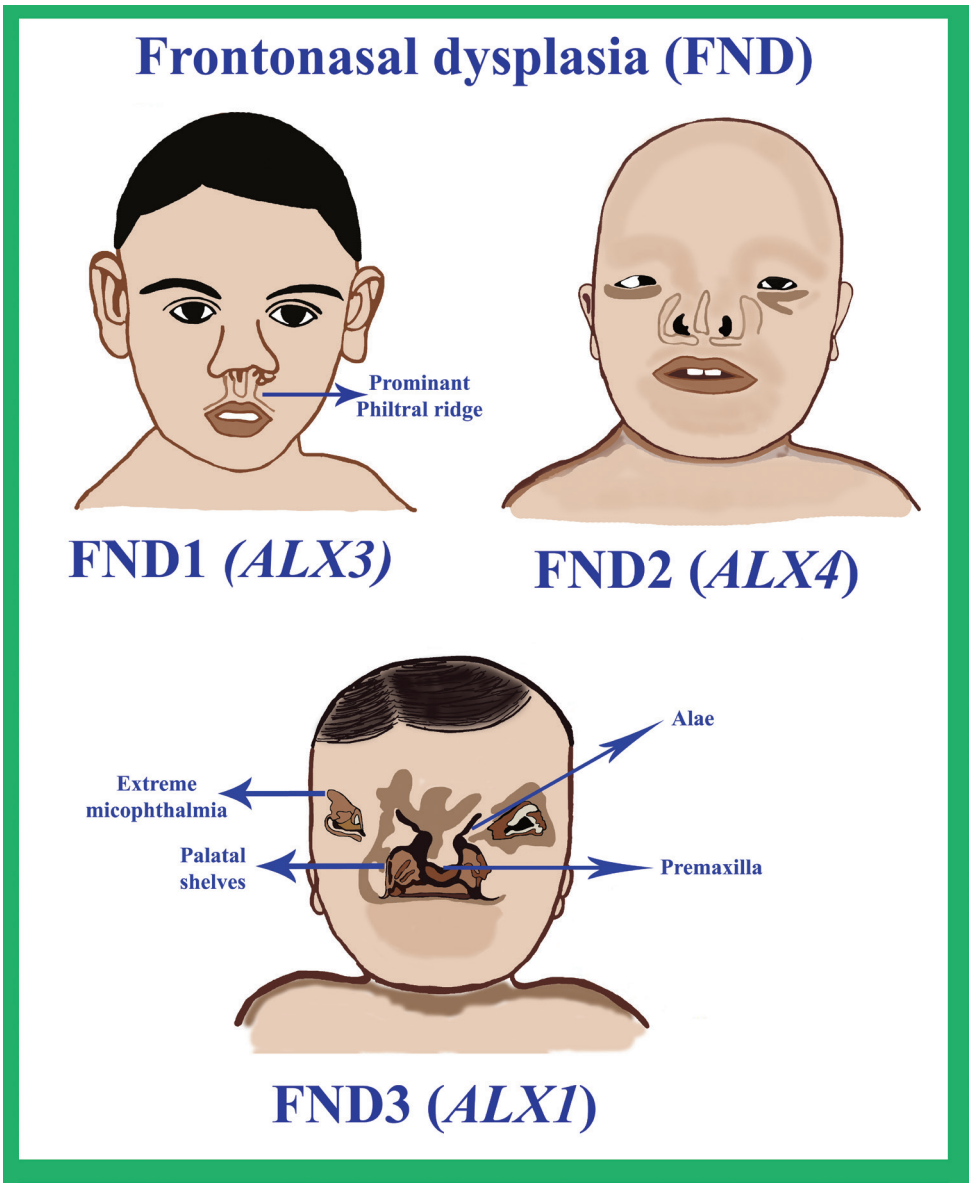

Figure 1. *Clinical presentation for Frontonasal dysplasia (FND) types 1, 2, and 3.*

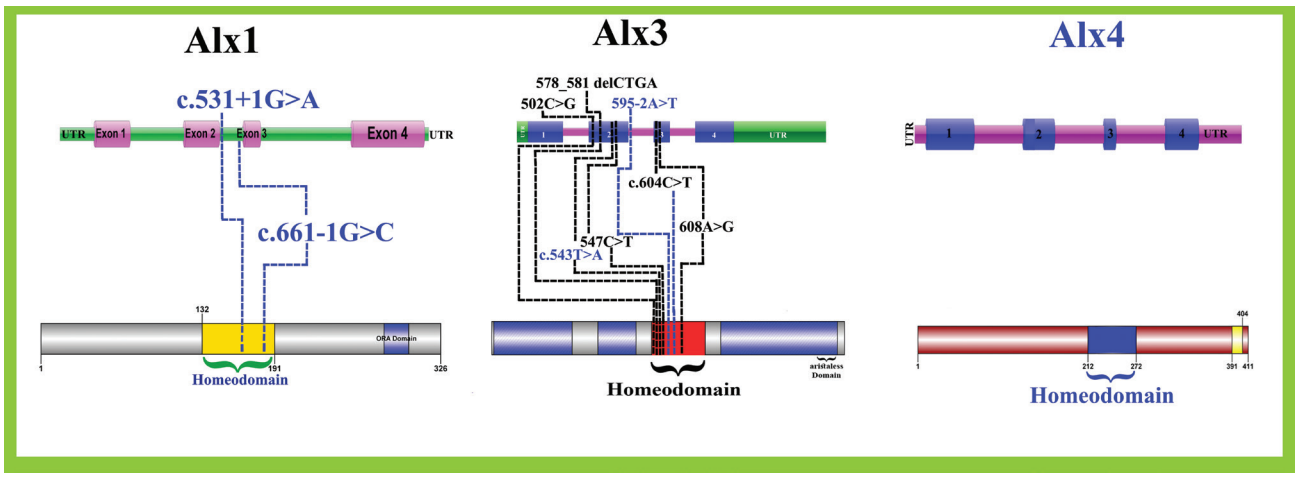

Figure 2. *Schematic representation of the ALX1, ALX3 and ALX4 gene and protein domains.*

Table 2. *FND1 classification according to mutations identified in different ethnic groups.*

Subject	Family	Sex	Country	Exon-Intron	Nucleotide change	Amino Acid change	References
1	1	Male	Morocco	-2	c.595-2A>T	*	11
2	1	Female	Morocco	-2	c.595-2A>T	*	11
3	2	Male	Algeria	3	c.608A>G	p.Asn203Ser	11
4	3	Male	Ireland	2	c.502C>G	p.Leu168Val	11
5	3	Female	Ireland	2	c.502C>G	p.Leu168Val	11
6	4	Female	Netherlands	2	c.547C>T	p.Arg183Trp	11
7	5	Female	Netherlands	2	c.543T>A	p.Try181X	11
8	5	Female	Netherlands	2	c.543T>A	p.Try181X	11
9	6	Male	Turkey	2	c.578_581delCTGA	p.Thr193Arg-fsX137	11
10	7	Female	India	2	c.586C>T	p.Arg196Trp	11
11	7	Male	India	2	c.586C>T	p.Arg196Trp	11
12	8	Female	Pakistan	3	c.604C>T	p.Gln202X	4
13	8	Male	Pakistan	3	c.604C>T	p.Gln202X	4
14	8	Male	Pakistan	3	c.604C>T	p.Gln202X	4
15	8	Female	Pakistan	3	c.604C>T	p.Gln202X	4

Abbreviations: *= Splice-site mutation, X = stop codon.

To date, only three mutations have been identified in the *ALX3* gene including a homozygous 3.7 Mb deletion, an intergenic splice donor site variant (c.531+1G>A) causing FND in two different Turkish families and a biallelic splice acceptor site variant (c.661-1G>C) in a Pakistani family presenting mild FND phenotypes (3).

The ALX genes

The *ALX* genes possess a conserved Aristaless domain that is closely related to homeodomain-containing transcription factors. The mouse *alx* genes (*alx1*, *alx3*, *and alx4*) are mostly expressed in the frontonasal prominence (FNP) mesenchyme spanning stages of the mouse embryos, during which cells of the cranial neural crest migrate into the facial primordia (26). FND spectrum disorders are caused by mutations in the *ALX* genes and occur throughout the protein but are most specifically found in the homeodomain. The homeodomain exhibits homology with different related family members (27). Pathogenic loss of function mutations in the homeodomain class transcription factors is associated with severe human anomalies while the missense mutations within the homeodomain might be associated with DNA-binding activity pathogenesis (16,23,28).

Mega or gross deletions in the homeodomain of the ALX4 protein have also been reported to cause the FND phenotype (14,29). The genes *alx1*, *alx3*, and *alx4* are expressed in the zebrafish facial mesenchyme cells; while the *alx1* is also expressed in the neural crest cells (30). In a zebrafish embryos, reduced *alx1* expression results in a severe phenotype such as severely hypoplastic facial skeleton, microphthalmia, and coloboma. While, the inhibition of *alx3* expression did not reveal any abnormal facial phenotypes (30), thus signifying substantial functional differences between the *alx* genes, as *alx1* expresses early relative to *alx3* and *alx4*. Thus, *alx1* has a greater role during the development of the zebrafish frontonasal structures. Loss of *alx1* in mice causes failure of neural tube closure (midbrain) development and consequent loss of the skull vault, thus result in severe exencephalic phenotypes (31).

Syndromes Involving Frontonasal Phenotypes

Craniofrontonasal syndrome (CFNS; MIM 304110)

CFNS is a severe craniofacial syndrome inherited in X-linked dominant condition; thus, females are mostly affected exhibiting FND phenotypes such as bifid or hypoplastic nasal tip, severe hypertelorism, coronal craniosynostosis, longitudinally grooved or split nails, clavicle malformations, woolly or thick hairs. As CFNS is inherited in an X-linked dominant condition, thus prior to causative gene identification, there might be a modifier gene or embryonic lethality involved in males (32–34). *EFNB1* (ephrin B1) mutations have been identified in affected females while male having the same mutations in the *EFNB1* gene presented milder phenotypes. The *EFNB1* gene (NM_004429; MIM 300035) is located on chromosomal location Xq13.1 and encodes a 346 amino acids ephrin-B1 (NP_004420) protein. EFNB1 is a membrane ligand for the Eph receptor, involved in

revolting signaling between individual cells (35). The X-chromosome inactivation phenomenon in the CFNS affected females is not observed, thus results in expression of either the wild-type or the mutant allele (35,36).

Features associated with *EFNB1* pathogenesis include short stature, brachycephaly, frontal bossing, eyes abnormalities including hypertelorism, telecanthus, strabismus and nystagmus, broad nasal root, hypoplastic nasal tip, cleft lip/palate, syndactyly, brittle nails, grooved nails, developmental delay, and hypotonia (37). To date, 108 mutations have been reported in the *EFNB1* gene including 105 mutations associated with the craniofrontonasal syndrome, two mutations associated with a diaphragmatic congenital hernia and single mutation causing hypertelorism (HGMD, 2017; http://www.hgmd.cf.ac.uk/ac/index.php).

Acromelic Frontonasal Dysostosis (AFND; MIM 603671)

AFND is a very severe disorder presenting severe craniofacial anomalies such as a median cleft face, widely spaced nasal alae, bifid nasal tip, hypertelorism, and parietal defects. It also includes several limb anomalies such as talipes equinovarus, underdeveloped tibia, and polydactyly. Features such as intellectual disability and brain malformations including corpus callosum agenesis, periventricular nodular heterotopia, interhemispheric lipoma, and hydrocephalus are also observed (38–40). Pathogenic heterozygous *de novo* variant (c.3487C>T) in the *ZSWIM6* gene (Zinc Finger SWIM-Type Containing 6; MIM 615951) has been reported as a cause of AFND (40,41). Deletions in the *ZSWIM6* gene region have been observed in individuals with unrelated phenotypes as well (41). *ZSWIM6* gene is located on chromosomal location 5q12.1, having 11 exons and encoding a 1,215 amino acids Zinc Finger SWIM-Type Containing six protein (42).

In a single family, a mild form of FND has been reported having a heterozygous deletion in the *SIX2* gene (SIX homeobox 2; member of SIX gene family; a transcription factor) (43). The affected individual had features such as hypertelorism, frontal bossing with a large anterior fontanelle, flat nasal bridge, ptosis, bilateral parietal foramina, broad nasal tip, macrocephaly, and complete sagittal synostosis. AFND involves malformation of the skull, which is not characteristically related with FNP developmental defects. The facial skeleton and the anterior skull are shaped from direct ossification of neural crest progenitors while mesodermal precursors through endochondral ossification give rise to the skull base. However, *Six2* mouse model involvement in the craniofacial development has demonstrated a relationship between these two independent structures (43).

Oral facial digital syndrome type I (OFD1; MIM 311200)

OFD1 is an X-linked dominant ciliopathy characterized by prominent features such as facial and oral malformations (oral clefts, cysts of the tongue, or hamartomas), and different types of digital anomalies (44). Abnormal dentition, polycystic kidney disease, thickened alveolar ridges, and absent lateral incisors are also observed in OFD1 patients. Although these features are easy to recognize in the affected individuals, and often lead to diagnosis in the early childhood.

Ferrante et al. (44) mapped several families to the critical region on Xp22 region and was able to identify pathogenic variants (a missense mutation, a 19-bp deletion, and a single basepair deletion leading to a frameshift in three families, a missense (de novo), a nonsense, a splice site, and a frameshift mutation in four sporadic patients) in the *OFD1* gene (MIM 300170; also known as *CXORF5*) locate on chromosomal location Xp22.2, encoding a centriole and centriolar satellite OFD1 protein (44). Since the *CXORF5* gene localizes to the basal body and centrosome of the primary cilia, OFD1 is considered as a ciliopathy disorder. Ferrante et al. (45) reported disturbance in the patterning process of the neural tube in the limb buds of mice lacking *Ofd1*, suggesting that *Ofd1* might have an important role beyond primary cilium assembly and organization (45).

Pathogenic mutations in the *CXORF5* gene have also been reported to cause Joubert syndrome-10 (JBTS10; MIM 300804), Simpson-Golabi-Behmel syndrome type 2 (GBS2; MIM 300209), and Retinitis pigmentosa 23 (MIM 300424). To date, 128 variants have been identified in the *OFD1* (*CXORF5*) gene and 117 have been reported to cause oral-facial-digital syndrome type I, seven with Joubert syndrome, two with the oral-facial-digital syndrome, and single variant associated with X-linked retinitis pigmentosa and Simpson-Golabi-Behmel syndrome (HGMD; http://www.hgmd.cf.ac.uk/ac/index.php).

Acrofacial dysostosis type Nager (SF3B4; MIM 154400)

Nager syndrome or acrofacial dysostosis (MIM 154400), first described by Nager and De Reynier in 1948, belongs to a severe disorder of craniofacial and limb malformations. Slingenberg (46) characterized Nager syndrome as a group of disorders known as acrofacial dysostoses. The limb deformities include radial elements of the upper limbs (radioulnar synostosis), absent radius, phocomelia of the upper limbs, and the absence or hypoplasia of the thumbs. Nager acrofacial dysostosis has been reported to follow both autosomal recessive and dominant pattern of inheritance. The major facial features include midface retrusion, down-slanted palpebral fissures, and micrognathia, which often require the placement of a tracheostomy in early childhood (46).

Using whole exome sequencing in patients having Nager type of acrofacial dysostosis, Bernier et al. (47) identified 18 pathogenic heterozygous variants within the *SF3B4* (splicing factor 3b subunit 4; MIM 605593) gene located on chromosome 1q21.2 (47). Another study also

identified seven heterozygous variants including four *de novo* variants in their 12 patient's analyzed (48). To date, 24 variants have been identified in the *SF3B4* gene associated with the Nager syndrome including seven small insertions, two missense, five nonsense, nine small deletions, and a single splice site variant (HGMD). *SF3B4* consists of six exons and encodes one of the four subunits of the splicing factor 3B protein having 424 amino acids.

Pathways Involved

Mechanisms such as patterning and growth of the facial primordia are associated with the expression of the FGF8 (fibroblast growth factor 8), the Sonic hedgehog (SHH), and the BMP4 (Bone morphogenetic protein 4). These key players have a vital role in patterning of the facial primordial, establishing growth, and any disturbance in these pathways might lead to severe facial clefting and FNP defects (49–52). The SHH and FGF8 expression domains in the frontonasal ectoderm form a signaling midpoint known as the frontonasal ectodermal zone that morphogenetically directs the outcome of FNP development (52,53). In the patterning and outgrowth of FNP, the Bmp signaling, especially the BMP4, have a key role (54,55). It has been observed that any blockage in the Bmp signaling results in down-regulation of SHH in FNP and decrease the SHH ability to induce its own expression (52,56). Similarly, along with the SHH and BMPS pathways, the FGF signaling is required for normal proliferation of FNP mesenchyme, and any blockage in FGF signaling results in facial clefts (57). The efficiency of these signaling pathways in the patterning systems must be tightly regulated three-dimensionally. Time-based gene expression regulation and the proper distribution of different genes serve as markers for the facial primordial allowing a fine-scale analysis of such severe developmental defects. The frontonasal ectodermal zone patterning has been well described using the chicken embryo, where a failure of mid face outgrowth is observed when the distribution of FGF8 and SHH is disturbed (53,58). Similarly, using mouse embryos, the mid and upper facial patterning issues have been observed when distribution/regulation SHH/FGF8 is disturbed (58).

Conclusion

FND is a highly severe genetic condition having prominent features affecting the mid-facial and the frontal cranial skeleton. Increase in craniofacial volume is a result of epicanthal distance and the expanded skull vault, a fundamental process responsible for the development of these structures responsible for the loss of skeletal precursors and their derivatives. These processes are involved in uniting the complex architecture of the craniofacial skeleton. The complex presentation of FND involve a wide range of other severe developmental issues, thus, animal models are a right choice for understanding the complex pathogenesis of FND related genes. The advent of massively parallel sequencing technology such as next-generation sequencing including whole genome sequencing and careful clinical phenotyping has resulted in a quick diagnosis, especially for rare genetic disorders, which resulted in the identification of many new disease-causing genes (59,60). Hopefully, knowledge of the developmental mechanisms with a combination of these new technologies will lead to proper molecular and genetic characterization of the FND group in coming future.

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