Detection of regions of homozygosity in an unusual case of frontonasal dysplasia

César Paz-y-Miño1,2*,†, Ramón Miguel Vargas-Vera1,2*,†, Martha Verónica Placencia-Ibadango3, Kalid Stefano Vargas-Silva4, Juan Luis García-Hernández5, Thalía Balarezo-Díaz6 and Paola E. Leone7

Abstract
We present the case of a 7-year-old Ecuadorian mestizo girl with multiple orofacial malformations. The patient is the product of a first-degree relationship (father–daughter). A cytogenetic study revealed a normal karyotype. The genetic mapping array study identified 0.73 Gb of alterations, 727,087,295 bp involved in regions of homozygosity (ROH) in all chromosomes (25.2% of the genome) and 764,028 bp in gains in chromosomes 9 and 14. Genes from the TGFb, BMP, FGF, SHH and WNT families, among others, were identified in the ROH. They are related to craniofacial development and their protein products showed a strong association in the interactome analysis.

Keywords Frontonasal dysplasia, Genetic mapping array, Regions of homozygosity, Interactome

Background
Frontonasal dysplasia (DFN) is a malformation characterized by specific alterations at the craniofacial level that develop due to defects in the embryogenesis of the face. The aetiology of DFN is well known; it is a sporadic condition, that is, it manifests as an isolated condition without being related to any specific genetic disease; therefore, it is not transmissible. Since DFN has a strong relationship with the oral and maxillofacial region, understanding the mechanism of craniofacial, orbital and facial fissures, which are rare alterations that are often associated with cleft palate, is important. These alterations are usually associated with rudimentary forms, such as coloboma of the eyelids, fissures of the nasal passages, obstruction of the tear duct and mandibular hypoplasia [1, 2]. For this reason, Tessier classified facial fissures into 14 types of indentations [3] (Fig. 1).

For a proper understanding of the pathophysiology of DFN, it is imperative to remember that the human facies are formed from five embryonic prominences. Two of them are bilateral, the maxillary and mandibular prominences, whereas one is not, the frontonasal prominence. Craniofacial development is a complex process regulated by TGF-beta (TGF-B) growth factor genes, which are involved in embryonic development and are encoded by many genes, which, if altered, give rise to a variety of orofacial and craniofacial malformations [4].

We describe a patient who was the product of a first-degree relationship (father–daughter) with very severe and unusual frontonasal dysplasia. We used genetic...
techniques to analyse, the possible origin and the genes that could be involved in the phenotypic manifestations.

Case presentation

Newborn, the result of a first-degree relationship (father–daughter), mother of 12 years, father of 35 years, Ecuadorian origin and mestizo ethnicity. First pregnancy without prenatal care; caesarean delivery at 37 weeks of gestation with a weight of 2,450 g; multiple malformations; small eyes with sclerocornea and upper eyelid coloboma; bilateral cryptophthalmos; sparse scalp, frontal prominence; dolichocephaly; wide nasal root; depressed nasal bridge and tip upwards; cleft lip and palate that takes over the entire roof of the mouth; Tessier 1–5; retro-rotated and low-set ears; soft syndactyly between the second and third fingers; umbilical hernia; marble-like skin; and hyperplasic genitalia (Fig. 1).

The patient is currently 7 years old. The facial fissure was corrected at three years of age, and frontonasal and palate reconstruction are pending. Her blindness, moderate mental retardation, hyperactivity, and lack of sphincter control persisted (Fig. 3).

Complementary examinations such as echocardiogram, abdominal ultrasound, transfontanelar ultrasound, magnetic resonance imaging and facial computed axial tomography (CT) were also performed.

Cytogenetic and molecular studies were performed on peripheral blood samples from the patient according to standard techniques [5]. We used heparin for cytogenetic studies and EDTA for array analysis. One microgram of DNA was used, which was labelled and hybridized together with control DNA (Promega Corporation, Madison, WI) on the NimbleGen Human CGH 12x135 K array (Roche NimbleGen, Inc., Reykjavik, Iceland). The array was scanned on a NimbleGen MS 200 microarray scanner (Roche NimbleGen, Inc.). Image files from the MS 200 data collection program were imported into DEVA v1.2.1 (Roche NimbleGen Inc.) for analysis. The CGHweb21 program was used, and each genomic region showing a copy number change was examined via the USCS Genome Browser 22 to determine its location.

Additionally, a bioinformatic analysis was performed with the proteins involved in the genetic alterations found in the patient, along with other genes described in the literature [1–4], through the STRING23 program. A correlation was detected between the genotype obtained via bioinformatics analysis and the patient's genotype [6].

An echocardiogram revealed an atrial septal defect without haemodynamic repercussions and good biventricular systolic function. Abdominal ultrasound revealed no alterations: liver of normal size, homogeneous texture, regular and smooth contours without focal or diffuse lesions in the parenchyma; gallbladder: not assessable, intrahepatic vessels and pathways: no abnormalities; pancreas with homogeneous texture, normal size in all its segments; homogeneous spleen, measuring 29×18 mm without focal or diffuse lesions; and right kidney: measuring 32×17 mm.

Transfontanelar ultrasound revealed no alterations; magnetic resonance imaging revealed no alterations in the midline or eyeball (Fig. 4).

CT was used to evaluate the bone window, and the midline defect was evident at the level of the anterior segment of the face (Fig. 5).

A cytogenetic study revealed that the patient had a normal karyotype 46,XX.

The study of genetic mapping arrays revealed 0.73 Gb of alterations, 727,087,295 bp involved in regions of homozygosity (ROH) on all chromosomes and 764,028 bp involved in gains on chromosomes 9 and 14 [see Additional file 1] (Fig. 6).

The ROH ranged in size from 3.6 Mb to 93.2 Mb, with an average size of 18.2 Mb and a median of 12.3 Mb. In this situation, with large regions of homozygosity in all chromosomes, the percentage of the genome that is homozygous was estimated by the sum of all homozygous regions divided by the total genomic length (for GRCh37/hg19, it is approximately 2881 Mb) [7], which
was 25.2%. From the list of genes located in the regions of homozygosity, the function of each gene was sought in relation to the patient’s phenotype, generating a list of 27 genes to which the STRING bioinformatics analysis was applied [6] and ontogenetic (genotype–phenotype), with a correlation index of 0.527 (Table 1). Among the 27 genes in the ROH, 23 had interactions between their protein products (Fig. 7).

Discussion and conclusions
The medical literature has reported only the severe form of frontonasal dysplasia associated with bilateral Tessier clefts 1–5 [3]. The described patient presented with an asymmetrical oropalatina cleft with involvement of the skeletal system, with bilateral cryptophtalmos and bilateral anophthalmia. Given the consanguinity and phenotypic spectrum, a conventional cytogenetic study and a genetic mapping array were performed.

A cytogenetic study revealed a normal karyotype, and a genetic mapping array was used. A molecular study revealed gains of three copies at 9q21.11 and 14q32.33, with gains of the FXN and TJP2 genes MIR4507, MIR4538, MIR4537, MIR4539, FAM30A, ADAM6 and LINC00226, respectively. No association was found between the duplication of these genes and the patient’s phenotype; although duplication and overexpression of TJP2 and nonsyndromic hearing loss have been described [8], this patient does not have hearing problems.

However, 727,087,295 bp were also found in regions of homozygosity (ROH), which is consistent with the fact that the patient is the product of a relationship between first-degree relatives. The coefficient of consanguinity in the patient due to the first-degree relationship of her parents was 1/4, with expected regions of homozygosity of 716 Mb [7], and the patient presented 727 Mb.

ROH were detected on all chromosomes, except chromosome 19, involving 3,924 genes, of which GABRB3,
DLX2, MSX1, TBX1 and P63 encode transcription factors associated with isolated cleft lip and palate.

The GABRB3 gene (15q12) is associated with nonsyndromic orofacial clefts [9]. DLX2 (2q31.1) is important during the early steps of neural crest specification; it plays a role in craniofacial and forebrain development and in the terminal differentiation of bipolar cells in the retina [10, 11]. MSX1 (4p16.2) has roles in limb pattern formation and craniofacial development, particularly odontogenesis [12]. TBX1 (22q11.21) is involved in the development of craniofacial muscles [13]. Finally, P63 (3q28) plays a role in the regulation of epithelial morphogenesis. Alterations of this gene have been associated with ectrodactyly, syndactyly, dysplasia of fingernails and toenails, hypoplastic breasts and nipples, intensive freckles, atresia of the tear duct, frontal alopecia, primary hypodontia, and loss of permanent teeth [14].

Other genes were within the ROH, such as TGFBR1 (9q22.33), a receptor for the cytokine TGF beta that translates signals from the cell surface to the cytoplasm and thus regulates processes such as cell cycle arrest in epithelial cells and the control of mesenchymal cell proliferation and differentiation [15]. The TGFβ family is involved in the palatogenesis process [16], and within this family, there are also bone morphogenetic proteins (BMPs) that play important roles in embryogenesis and skeletal morphogenesis, among other biological processes.

Some BMPs were present in the ROH of this patient, such as BMP6 (6q24.6), which regulates the development of fat and bone; BMP4 (14q22.2), another TGF-beta ligand whose mutations are associated with orofacial clefts and abnormalities in eye formation from microphthalmia to anophthalmia; BMP2 (20p12.3), whose alterations are related to short stature, facial dysmorphism and skeletal abnormalities; and BMP7 (20q13.31), which is
important in some processes, such as embryogenesis and skeletal morphogenesis [9, 17, 18].

In vivo and in vitro studies have shown that MSX1 controls palate growth pathways involving BMPs and SHH (7q36.3), which encodes a fundamental protein in early embryo modelling. It has been implicated as the key inductive signal in the formation of the ventral neural tube, the anteroposterior axis of the extremities, and the ventral somites. Defects in this protein are the cause
of facial deformities [19]. All of these genes were in the patient’s ROH.

**Table 1** Gene Ontology functions of the proteins and genes associated with the phenotype of the patient.

| Function                                                                 | Genes                                                                 |
|-------------------------------------------------------------------------|----------------------------------------------------------------------|
| Formation of anatomical structures involved in morphogenesis            | ACVRZB, ALKAL2, ALX1, BMP2, BMP4, BMP6, BMP7, CHRD, COL2A1, EFNB1, FGFRIOP2, GREM2, IRF2, IRF2BP2, IRF4, MSX1, NBL1, RPE65, SHH, SOSTDC1, TBX1, TBX2, TCOF1, TGFB1, TGFBRI, WNT7A, and ZIC3 |
| Disease of anatomical entities                                           |                                                                      |
| Head development                                                         |                                                                      |
| Cleft palate isolated                                                    |                                                                      |
| Orofacial cleft                                                          |                                                                      |
| Synostosis                                                               |                                                                      |
| Coloboma                                                                |                                                                      |
| Dysostosis                                                               |                                                                      |
| Developmental bone disease                                               |                                                                      |
| Physical disorders                                                       |                                                                      |
| Embryonic morphogenesis                                                  |                                                                      |
| Morphogenesis of the salivary glands                                     |                                                                      |
| Morphogenesis of the middle ear                                         |                                                                      |
| Facial morphogenesis                                                     |                                                                      |
| Morphogenesis of the embryonic skeletal joint                           |                                                                      |
| Morphogenesis of the outer ear                                          |                                                                      |
| Morphogenesis of the embryonic cranial skeleton                         |                                                                      |
| Morphogenesis of sensory organs                                         |                                                                      |
| Morphogenesis of the cranial suture                                     |                                                                      |
| Regulation of odontogenesis in dentin-containing teeth                  |                                                                      |
| Enamel mineralization                                                    |                                                                      |
| Branching is involved in the morphogenesis of salivary glands           |                                                                      |
| Development of the secondary palate                                     |                                                                      |
| Development of the cranial skeletal system                               |                                                                      |
| Palate development                                                       |                                                                      |
| Development of the diencephalon                                         |                                                                      |
| Development of the pharyngeal system                                     |                                                                      |
| Ear development                                                          |                                                                      |
| Development of the inner ear                                             |                                                                      |
| Determination of left/right symmetry                                     |                                                                      |
| Development of sensory organs                                            |                                                                      |
| Ocular development                                                       |                                                                      |
| Camera-like eye morphology                                               |                                                                      |
| Uregulation of osteoblast and chondrocyte differentiation                |                                                                      |
| Front/rear shaft specification                                           |                                                                      |
| Symmetry specification                                                   |                                                                      |
| Regulation of neuroblast proliferation                                   |                                                                      |
| Segmentation                                                             |                                                                      |
| Shaft specification                                                      |                                                                      |
| Dorsal/ventral pattern formation                                         |                                                                      |
| Cell fate specification                                                  |                                                                      |
| Primary neural tube formation                                            |                                                                      |
| Cell regionalization                                                     |                                                                      |
| Development of the rhombencephalon                                      |                                                                      |
| Development of the telencephalon                                         |                                                                      |

The data were processed with STRING and included the following 27 genes of the interactome: ACVRZB, ALKAL2, ALX1, BMP2, BMP4, BMP6, BMP7, CHRD, COL2A1, EFNB1, FGFRIOP2, GREM2, IRF2, IRF2BP2, IRF4, MSX1, NBL1, RPE65, SHH, SOSTDC1, TBX1, TBX2, TCOF1, TGFB1, TGFBRI, WNT7A, and ZIC3

associated with other syndromes, such as Opitz syndrome, which is characterized by midline abnormalities such as cleft lip and laryngeal cleft. Related pathways include antiviral mechanisms involving IFN-stimulated genes and cytokine signalling in the immune system. The IRF2 (4q35.1), IRF2BP2 (1q42.3) and IRF4 (6p25.3) genes were also detected in the ROH [20].

Members of the WNT family, the expression of which is important in developing facial primordia, were also found in the ROH. WNT1 (12q13.12) functions in the induction of the midbrain and cerebellum; alterations in WNT10B (12q13.12) are associated with dental agenesis; and WNT7A (3p25.1) plays an important role in embryonic development [9].

Other genes associated with the ROH include TBX22 (Xq21.1), which encodes a transcription factor involved in the regulation of developmental processes. Mutations in this gene are associated with cleft palate and are thought to play an important role in human palatogenesis [21]. TCOF1 (5q32-q33.1) encodes an important protein involved in embryonic development of the head and face, and mutations in this gene alter craniofacial development [22]. COL2A1 (12q13.11) encodes a collagen specific to cartilage tissues, and ALKAL2 (2p25.3) is involved in the stimulation of ALK signalling, which is involved in neuronal development and is essential for normal embryonic development of the skeleton, linear growth and the ability of cartilage to resist compressive forces [9]. FGFRIOP2 (12p11.23) is a fibroblast growth factor 1 receptor associated with several craniofacial anomalies [23]. LHX4 (1q25.2) and LHX3 (9q34.3) encode transcription factors related to the development of the nervous system. ZIC3 (Xq26.3) is related to the transcriptional regulation of pluripotent stem cells and nervous system development. SIX3 (2p21) encodes a homeobox transcription factor related to eye development and holoprosencephaly, and EFNBI (Xq13.1) plays a role in the development and maintenance of the nervous system [9].

Many of the genes described in the ROH have been associated with frontonasal dysplasia [24] together with the ALXI gene (12q21.31). Mutations responsible for frontonasal dysplasia (DFN) type 3 have been described in ALXI, a gene associated with severe facial alterations, with an autosomal recessive inheritance pattern. This gene belongs to the homeobox family of proteins that regulate the expression of genes involved in the development of mesenchyme-derived craniofacial structures (9). A case from consanguineous parents with a phenotype similar to that of the patient under study from consanguineous parents has been reported, in which, by analysis with arrays, a region with a homozygous deletion of 3.7 Mb containing the ALXI gene was detected [25].

Cases with similar phenotypes resulting from consanguineous parents or from neighbouring localities suggest
a recessive aetiology for DFN. For the ALX1 gene, events such as mutations or homozygous deletions can cause complete loss of function of the ALX1 protein, which severely alters early craniofacial development.

The interactome and gene ontology analysis of the proteins produced by the genes in ROH confirmed the importance of these proteins and their respective interactions in the patients with craniofacial dysplasia.

Array technology identifies variations in the number of copies, and in this case, it has shown large regions of homozygosity in the patient, which is consistent with the family relationship between her parents.

In the regions of homozygosity, genes with important roles in craniofacial development were identified, and transcription factors; members of the TGFβ, BMP, FGF, SHH and WNT families; and associated genes, all with functions described in signalling pathways, which, owing to their homozygous state during craniofacial embryogenesis, explain the patient’s phenotype.

**Abbreviations**

- **ADAM** Disintegrin and metalloproteinase
- **ALKAL2** Alkaline phosphatase-like 2
- **ALX1** ALX homeobox 1
- **BMP2** Bone morphogenetic protein 2
- **BMP4** Bone morphogenetic protein 4
- **BMP6** Bone morphogenetic protein 6

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**Fig. 7** Interactome of proteins resulting from genes associated with craniofacial development in the ROH in the patient

The blue light lines represent interactions identified in selected databases; the pink lines represent experimentally determined interactions; the lines of other colours represent interactions predicted by gene neighbourhoods, gene fusions, and protein homology.
BMP7    Bone morphogenetic protein 7
BMPs    Bone morphogenetic proteins
COL2A1  Collagen type II alpha 1 chain
CT      Computed tomography
DFN     Frontonasal dysplasia
DLX2    Distalless homeobox 2
EDTA    Ethylenediaminetetraacetic acid
EFNB1   Ephrin-B1
FAM30A  Family with sequence similarity 30 member A
FGF     Fibroblast growth factor
FGFR1OP2 FGFR1 oncogene partner 2
FXN     Fratxin
GABRB3  Gamma-aminobutyric acid type A receptor beta 3 subunit
IFN     Interferon
IRF2    Interferon regulatory factor 2
IRF2BP2 Interferon regulatory factor 2 binding protein 2
IRF4    Interferon regulatory factor 4
LHX3    LIM homeobox 3
LHX4    LIM homeobox 4
LINC00226 Long intergenic nonprotein coding RNA 226
MID15   Midline 1, E3 ubiquitin protein ligase
MIR4507 MicroRNA 4507
MIR4537 MicroRNA 4537
MIR4538 MicroRNA 4538
MIR4539 MicroRNA 4539
MSX1    Msh homeobox 1
P63     Tumour protein p63
ROH     Regions of homozygosity
SHH     Sonic hedgehog
SIX3    SIX homeobox 3
TBX1    T-box transcription factor 1
TBX22   T-box transcription factor 22
TCOF1   Treacle ribosome biogenesis factor 1
TGF-B   Transforming growth factor beta
TGFBR1  Transforming growth factor beta receptor 1
TJP2    Tight junction protein 2
TRIM    Tripartite motif protein
WNT10B  Wingless-related integration site 10B
WNT1    Wingless-related integration site 1
WNT7A   Wingless-related integration site 7 A
WNT    Wingless-related integration site
ZIC3    Zinc finger protein of cebellum 3

Supplementary Information
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Author contributions
C PyM and RMVV carried out the clinical examination, cytogenetic studies, analysis of arrays and drafted the manuscript; MVPI and KSVS analysed the arrays and drafted the manuscript; ILGH performed studies with the microarrays, analysis of the arrays and drafted the manuscript; TBG performed case evaluation and drafted the manuscript; and PEL performed an analysis of the microarray results and drafted the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Human Research Ethics Committee (CISH) No. 2018-226E and Ministry of Public Health, No. MSP-DIS-2019-0283-O. For this research, we obtained informed consent from family members for their participation.

Consent for publication
For this research, we obtained informed consent from family members for publication.

Competing interests
The authors declare no competing interests.

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References
1. Eppley BL, van Aalst JA, Robey A, Havlik RJ, Sadove AM. The spectrum of orofacial clefting. Plast Reconstr Surg. 2005;115(7):e101–14. [https://doi.org/10.1097/01.pr.0000164495.98681.91]
2. Kalantar-Hormozi A, Abbaszadeh-Kasbi A, Goravanchi F, Davai NR. Prevalence of rare craniofacial clefts. J Craniofac Surg. 2017,28(5):e467–70. [https://doi.org/10.1097/SCS.0000000000003771]
3. Tressier F. Anatomical classification of facial, cranio-facial and latero-facial clefts. J Maxillofac Surg. 1976,469–72. [https://doi.org/10.1016/0301-0503(76)80013-6]
4. Singh S, Groves AK. The molecular basis of craniofacial placode development. Wiley Interdiscip Rev Dev Biol. 2016,5(3):363–76. [https://doi.org/10.1002/wdev.v22]
5. Paz-y-Miño C, Medranda C, Loaiza A, Ponce M, Leone PE. Rare pathology of rare craniofacial clefts. J Craniofac Surg. 2017,28(5):e467–70. [https://doi.org/10.1097/SCS.0000000000003771]
6. String Consortium 2023. Protein-protein interaction networks: Functional enrichment analysis. Version 12.0. [cited 2024 May 26]. Available in: [https://string-db.org/cgi/input?sessionId=bR EgW3EM4Ol&input_page_show_search=on]
7. Gonzales PR, Andersen EF, Brown TR, Horvitz J, Rehder CW, Rudy NL, Robin NH, Thorland EC, on behalf of the ACMG Laboratory Quality Assurance Committee. Interpretation and reporting of large regions of homozygosity and suspected consanguinity/uniparental disomy, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022,24(2):235–61. [https://doi.org/10.1038/s41436-021-00904-4]
8. Walsh T, Pierce SB, Lenz DR, Brownstein Z, Dagan-Rosenfeld O, Shahin H, Roeb W, McCarthy S, Nord AS, Gordon CR, Ben-Neriah Z, Sebat J, Kanaan M, Lee MK, Frydman M, King M, Avraham KB. Genomic duplication and overexpression of TJP2/ZO-2 leads to altered expression of apoptosis genes in progressive nonsyndromic hering loss DFNAS1. Am J Hum Genet. 2010,87:101–9. [https://doi.org/10.1016/j.ajhg.2010.05.011]
9. GeneCards. The Human Gene Database. Version S20-0 Available in: [https://www.genecards.org/]
10. Simões-Costa M, Bronner ME. Establishing neural crest identity: a gene regulatory mechanism. Development. 2015;142:242–57. [https://doi.org/10.1242/dev.105445]
11. Kim S, Margunova E, Naqvi S, Goovaerts S, Bader M, Koska M, Popov A, Luong C, Pogson A, Swigut T, Ciaes P, Tlapale J, Wysocka JA. DNA-guided transcription factor cooperativity shapes face and limb mesenchyme. Cell. 2024;187(3):692–711. [https://doi.org/10.1016/j.cell.2023.12.032]
12. Jezewski PA, Vieira AR, Nishimura C, Ludwig B, Johnson M, O’Brien SE, Daack-Hirsch S, Schultz RE, Weber A, Nepomuceno B, Romitti PA, Christiansen K, Orio IM, Castilla EE, Machida J, Natsume N, Murray J. Complete sequencing shows a role for MSX1 in non-syndromic cleft lip and palate. J Med Genet. 2003;40(6):399–407. [https://doi.org/10.1136/jmg.40.6.399]
13. Paylor R, Glaser B, Mupo A, Ataliotis P, Spencer C, Sobottka A, Sparks C, Choi C-H, Oghalai J, Curran S, Murphy KC, Monks S, Williams N, O’Donovan MC, Owen MJ, Scambler PJ, Lindsay E. Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. Proc Natl Acad Sci USA. 2006;103(20):7729–34. https://doi.org/10.1073/pnas.060206103

14. Corona-Rivera JR, Rios-Flores IM, Zenteno JC, Perla-Padilla C, Castillo-Reyes K, Bobadilla-Morales L, Corona-Rivera A, Acosta-Fernández E, Bruckman-Jiménez A. A family with EEC syndrome in the son and ADULT syndrome in his father caused by the c.797G > A (p.Arg266Gln) pathogenic variant in the TP63 gene. Mol Syndromol. 2024;15(1):51–7. https://doi.org/10.1159/000531934

15. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, Meyers J, De Bacquer J, Helleman J, Chen Y, Davis EC, Webb CL, Kress W, Coucke P, Rifkin DB, De Paepe AM, Dietz HC. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet. 2005;37(3):275–81. https://doi.org/10.1038/ng1511

16. Nawshad A, La Gamba D, Hay E. Transforming growth factor β (TGFβ) signaling in palatal growth, apoptosis and epithelial mesenchymal transformation (EMT). Arch Oral Biol. 2004;49:675–89. https://doi.org/10.1016/j.archoralbio.2004.05.007

17. Tan YT, GonzagaJauregui C, Bhoj EI, Strauss KA, Briggs K, Puffenberger E, Li D, Xie LQ, Das N, Skubas I, Deckelbaum RA, Hughes V, Brydges S, Hatsell S, Siao CJ, Dominguez MG, Economides A, Overton JD, Mayne V, Simm PJ, Jones BO, Eggers S, LeGuayader G, Pielaud F, Haack TB, Sturm M, Riess A, Walldmueller S, Hofbeck M, Steindl K, Josten P, Rauch A, Hakonarson H, Baker NL, Farlie PG. Monoallelic BMP2 variants predicted to result in haploinsufficiency cause craniofacial, skeletal, and cardiac features overlapping those of 20p12 deletions. Am J Hum Genet. 2017;101(6):985–94. https://doi.org/10.1016/j.ajhg.2017.10.006

18. Pachajoya H, Moreno F. Neural crest cells: evolution, embryonic basis and craniofacial development. Systematic review of the literature. [In Spanish]. Rev Estomatol. 2015;23(2):45–56. https://hdl.handle.net/10893/9142

19. Pegelow M, Peyrard-Janvid M, Zucchelli M, Fransson I, Larson O, Kure J, Larson C, Karlsten A. Familial non-syndromic cleft lip and palate-analysis of the IRF6 gene and clinical phenotypes. Eur J Orthod. 2008;30(2):169–75. https://doi.org/10.1093/ejo/cjm097

20. Zhang Z, Song Y, Zhao X, Zhang X, Fermin C, Chen Y. Rescue of cleft palate in Msx1- deficient mice by transgenic Bmp4 reveals a network of BMP and Shh signaling in the regulation of mammalian palatogenesis. Development. 2002;129(17):4135–46. PMID: 12163415. https://doi.org/10.1242/dev.129.17.4135

21. Slavec L, Geršak K, Eberlinc A, Hovnik-T, Lovrečič L, Minarin-Raščan I, Kuželički NK. A comprehensive genetic analysis of slovenian families with multiple cases of orofacial clefts reveals novel variants in the genes IRF6, GRHL3, and TBX22. Int J Mol Sci. 2023;24(5):4262. https://doi.org/10.3390/ijms24054262

22. Wise C, Chiang LC, Paznekas WA, Sharma M, Musy MM, Ashley JA, Lovett M, Jabs EW. TCOF1 gene encodes a putative nuclear phosphoprotein that exhibits mutations in Treacher Collins syndrome throughout its coding region. Proc Natl Acad Sci USA. 1997;94:3110–15. https://doi.org/10.1073/pnas.94.7.3110

23. Xie Y, Su N, Yang J, Tan Q, Huang S, Jin M, Ni Z, Zhang B, Zhang D, Luo F, Chen H, Sun X, Feng JQ, QI H, Chen L. FGF/FGFR signaling in health and disease. Sig Transduct Target Ther. 2020;5:181. https://doi.org/10.1038/s41392-020-00222-7

24. Tiol-Carrillo A. Displasia frontonasal: Revista ADM. 2023;83(3):145–50. https://doi.org/10.35366/111432

25. Uz E, Alanay Y, Aktas D, Vargel I, Gucer S, Tuncbilek G, von Eggeling F, Yilmaz E, Deren O, Posorski N, Ozdag H, Liehr T, Balci S, Akarsu NA. Disruption of ALX1 causes extreme microphthalmia and severe facial clefting: expanding the spectrum of autosomal-recessive ALX-related frontonasal dysplasia. Am J Hum Genet. 2010;86:789–96. https://doi.org/10.1016/j.ajhg.2010.04.002

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