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TXNL4A-Related Craniofacial Disorders

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Summary

Clinical characteristics

TXNL4A-related craniofacial disorders comprise a range of phenotypes that includes: isolated choanal atresia; choanal atresia with minor anomalies; and Burn-McKeown syndrome (BMKS), which is characterized by typical craniofacial features (bilateral choanal atresia/stenosis, short palpebral fissures, coloboma of the lower eyelids, prominent nasal bridge with widely spaced eyes, short philtrum, thin vermilion of the upper lip, and prominent ears). Hearing loss is common and cardiac defects and short stature have been reported. Intellectual disability is rare.

Diagnosis/testing

The diagnosis of a *TXNL4A*-related craniofacial disorder is established in a proband with suggestive findings and biallelic pathogenic variants in *TXNL4A* identified by molecular genetic testing. All probands described to date have had at least one copy of one of the two partially overlapping 34-bp deletions in the *TXNL4A* promoter.

Management

Treatment of manifestations: Neonates with airway compromise at delivery may require intubation or surgical correction of choanal stenosis/atresia. Defects of the lower eyelids that can result in corneal exposure require care by an ophthalmologist to reduce the risk of corneal scarring. Treatment of hearing loss is individualized and may involve hearing aids. Treatment of craniofacial manifestations (e.g., cleft lip and/or palate, preauricular tags, prominent ears) is individualized and managed by a multidisciplinary team. Cardiac defects are managed in a routine manner.

Surveillance: Monitoring by an ophthalmologist, audiologist, and craniofacial team is recommended.

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Genetic counseling

TXNL4A-related craniofacial disorders are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance inheriting neither of the familial *TXNL4A* pathogenic variants. Once the *TXNL4A* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

GeneReview Scope

TXNL4A-Related Craniofacial Disorders: Included Phenotypes [1]
• Burn-McKeown Syndrome (BMKS) • Choanal atresia with minor anomalies • Isolated choanal atresia

For synonyms and outdated names, see Nomenclature.
1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

Suggestive Findings

A *TXNL4A*-related craniofacial disorder **should be suspected** in individuals with the following clinical findings and family history.

Clinical findings. Bilateral choanal atresia/stenosis WITH OR WITHOUT:

- Distinctive facies (Figure 1):
  - Short palpebral fissures (i.e., distance between inner canthus and outer canthus)
  - Lower eyelid defects including coloboma and thick eyelashes
  - Prominent nasal bridge and widely spaced eyes, leading to a typical facial profile
  - Short philtrum, thin vermilion of the upper lip, thick vermilion of the lower lip, and reduced opening of the mouth
- Normal intellect

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of a *TXNL4A*-related craniofacial disorder **is established** in a proband with suggestive findings and biallelic pathogenic variants in *TXNL4A* identified by molecular genetic testing (see Table 1).

All probands described to date have had at least one copy of a 34-bp deletion in the promoter of *TXNL4A*. Two partially overlapping 34-bp deletions have been described:

- Type 1: chr18:g. 77,748,581_77,748,614del [GRCh37/hg19]
- Type 2: chr18:g.77,748,604_77,748,637del [GRCh37/hg19]

The majority of reported probands have a type 1 promoter deletion on one allele and a loss-of-function pathogenic variant on the other.

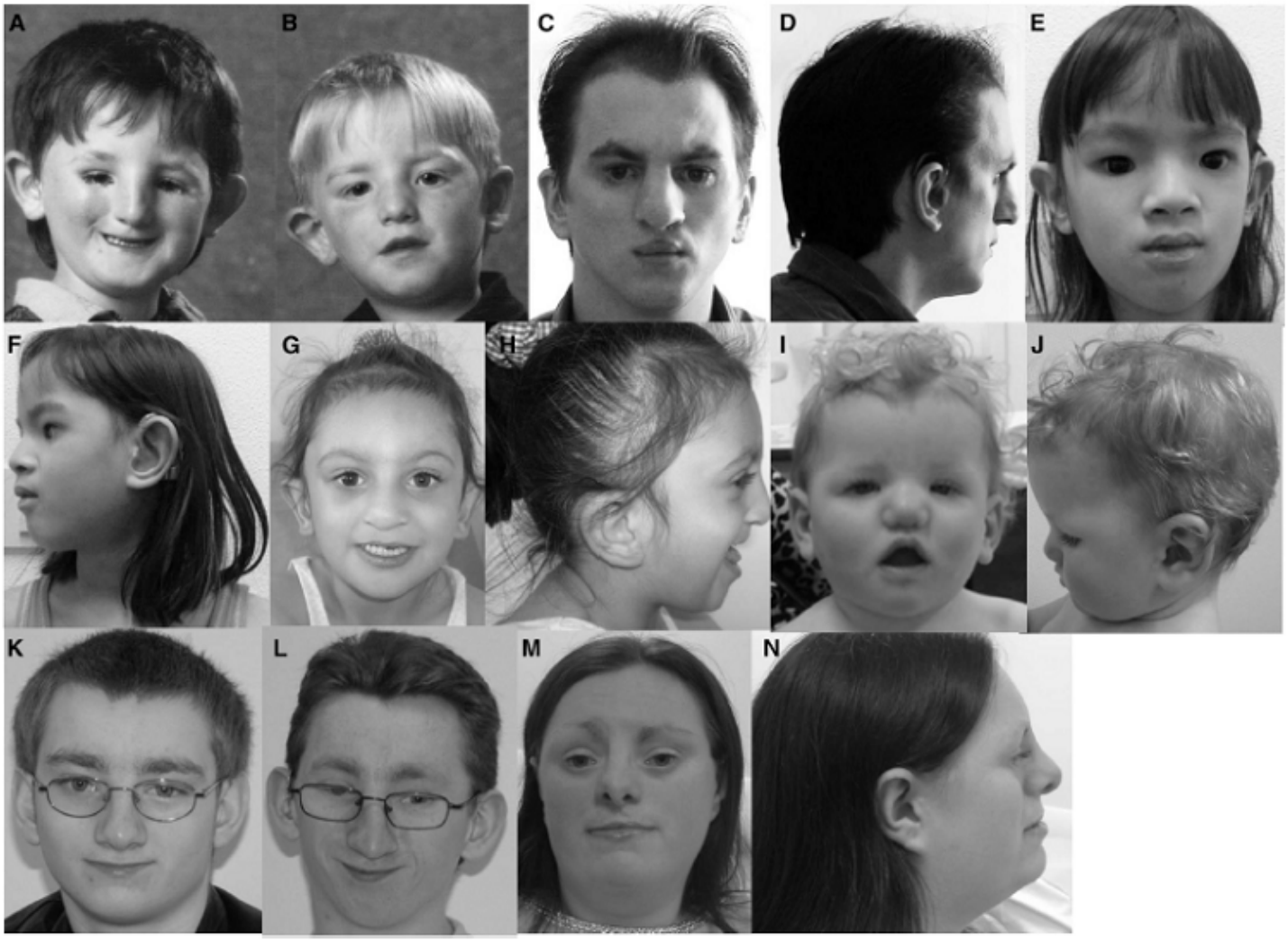

Figure 1. Craniofacial phenotype in individuals with a *TXNL4A*-related craniofacial disorder. Note short palpebral fissures (i.e., the distance between inner and outer canthi), prominent nasal bridge, large and (to some extent) protruding ears, and short philtrum.

From Wieczorek et al [2014]; republished with permission from Elsevier, Inc

Note: Identification of biallelic *TXNL4A* variants of uncertain significance (or identification of one known *TXNL4A* pathogenic variant and one *TXNL4A* variant of uncertain significance) does not establish or rule out a diagnosis of this disorder.

Molecular genetic testing approaches can include **targeted assay to detect promoter deletions**, **single-gene testing**, **chromosomal microarray analysis (CMA)**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Recommended Testing

Tier 1 testing. Targeted assay to detect the type 1 and type 2 promoter deletions (e.g., PCR and sequence analysis of the *TXNL4A* promoter, allele-specific PCR, or other targeted assay) is performed first.

Note: If a deletion that includes *TXNL4A* was previously detected by CMA, detection of one copy of the type 1 or type 2 promoter deletion establishes the diagnosis of a *TXNL4A*-related craniofacial disorder.

Tier 2 testing. If Tier 1 testing detects one copy of a type 1 or type 2 promoter deletion, additional studies to detect a second variant can include:

- **Sequence analysis** of *TXNL4A* to test for loss-of-function variants;
- **Chromosomal microarray analysis (CMA)** to identify larger deletions in 18q23, which cannot be detected by either sequence analysis or gene-targeted deletion/duplication analysis;
- **Gene-targeted deletion/duplication analysis** of *TXNL4A* to test for whole-exon deletions or duplications.

Other Testing to Consider

A multigene panel that includes promoter deletion assays of *TXNL4A* and testing of other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing does not require the clinician to determine which gene is most likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible and is the genomic testing method recommended for individuals with a suspected *TNXL4A*-related craniofacial disorder as it can detect pathogenic variants in both coding and noncoding regions associated with *TNXL4A*.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *TXNL4A*-Related Craniofacial Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
TXNL4A	Promoter deletion assays [3]	17/17 [4]
	Sequence analysis [5]	7/17 [6]
	Gene-targeted deletion/duplication analysis [7]	4/17 [8]
	CMA [9]	4/17 [8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. The two reported 34-bp promoter deletions can be detected and distinguished by targeted assays (e.g., PCR and subsequent sequence analysis of PCR products).
4. Wieczorek et al [2014], Goos et al [2017], Narayanan et al [2020], Wood et al [2022]. Of note, homozygous promoter deletions were reported in two families with isolated choanal atresia [Goos et al 2017].
5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
6. Wieczorek et al [2014], Goos et al [2017], Wood et al [2022]
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions. To date, no partial or complete *TXNL4A* duplications have been identified.
8. Wieczorek et al [2014]
9. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *TXNL4A*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 18q23 region. CMA designs in current clinical use target the 18q23 region.

Clinical Characteristics

Clinical Description

TXNL4A-related craniofacial disorders range from isolated choanal atresia to choanal atresia with minor anomalies to Burn-McKeown syndrome (BMKS), which is characterized by typical craniofacial features (bilateral choanal atresia/stenosis, short palpebral fissures, coloboma of the lower eyelids, prominent nasal bridge with widely spaced eyes, short philtrum, thin vermilion of the upper lip, and prominent ears). Hearing loss is common and cardiac defects and short stature have been reported. Intellectual disability is rare [Wieczorek et al 2014].

To date, 20 individuals with biallelic pathogenic variants in *TXNL4A* have been identified [Wieczorek et al 2014, Goos et al 2017, Narayanan et al 2020, Wood et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *TXNL4A*-Related Craniofacial Disorders: Frequency of Select Features

Feature	# of Persons w/Feature / # Assessed	Comment
Bilateral choanal stenosis/atresia	20/20	3 persons have had isolated choanal atresia [Goos et al 2017].
Short palpebral fissures	11/19	
Defects of lower eyelids	12/20	
Hypertelorism	12/17	
Prominent nasal bridge	17/18	
Short philtrum	14/17	
Thin vermilion of the upper lip	10/17	
Prominent ears	13/17	
Preauricular tags	10/16	
Hearing loss	12/19	
Micrognathia	12/19	
Submucous cleft palate or cleft lip/palate	10/20	
Cardiac defect	5/16	
Short stature	3/17	
Normal intellect	16/18	

Bilateral choanal stenosis/atresia is potentially life threatening.

Defects of lower eyelids can result in corneal exposure and, hence, drying.

Hearing loss. Detailed clinical information regarding the severity and course of hearing loss has not been reported.

Cleft lip/palate. Submucous cleft palate and uni-/bilateral cleft lip/palate have been described.

Cardiac defects include persistent ductus arteriosus and patent foramen ovale.

Short stature is proportionate and mild.

Intellectual disability. One female had mild learning disabilities and another had severe intellectual disability [Strang-Karlsson et al 2017].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

Initially described as a distinct entity in a highly consanguineous Alaskan family by Hing et al [2006], oculootofacial dysplasia (OOFD) was reclassified as Burn-McKeown syndrome (BMKS) when Wieczorek et al [2014] identified homozygous type 2 *TXNL4A* promoter deletions in affected members of this family.

Prevalence

The prevalence of *TXNL4A*-related craniofacial disorders has not been established. To date 20 individuals with a *TXNL4A*-related craniofacial disorder have been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TXNL4A*.

Differential Diagnosis

Table 3. Genetic Disorders with Choanal Atresia/Stenosis in the Differential Diagnosis of *TXNL4A*-Related Craniofacial Disorders

Gene(s)	DiffDx Disorder	MOI	Key Features of DiffDx Disorder	Comment / Distinguishing Features
CHD7	CHARGE syndrome (See *CHD7* Disorder.)	AD	Intraocular coloboma, heart defects, choanal atresia, growth deficiency, DD, genital hypoplasia, & ear anomalies	While some overlap exists between CHARGE syndrome & *TXNL4A*-related craniofacial disorders, esp choanal atresia, the CHARGE syndrome phenotype comprises clinical findings (intraocular coloboma, genital anomalies, & specific ear anomalies) not seen in *TXNL4A*-related craniofacial disorders. Note: The coloboma assoc w/*TXNL4A*-related craniofacial disorders involves the eyelid only & not intraocular structures.
EFTUD2	Mandibulofacial dysostosis with microcephaly (MFDM)	AD	Mandibulofacial dysostosis (e.g., upslanting palpebral fissures, micrognathia, & ear anomalies), prenatal (usually progressive) microcephaly, & moderate-to-severe ID	While some overlap exists between MFDM & *TXNL4A*-related craniofacial disorders, severe microcephaly & moderate ID in MFDM & distinctive facial phenotypes help to clinically distinguish the 2 disorders.
POLR1B *POLR1C* *POLR1D* *TCOF1*	Treacher Collins syndrome (TCS)	AD AR [1]	Mandibulofacial dysostosis w/ variable expressivity. Anomalies (usually restricted to craniofacial region) incl: downslanted palpebral fissures, hypoplasia of the zygomatic bones, lower-eyelid coloboma, microtia, & micrognathia.	Downslanted palpebral fissures, hypoplasia of the zygomatic bones, & microtia have not been reported in *TXNL4A*-related craniofacial disorders. Cardiac defects & short stature are uncommon in TCS.

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance

1. Autosomal dominant TCS is caused by a heterozygous pathogenic variant in *TCOF1*, *POLR1D*, or *POLR1B*; autosomal recessive TCS is caused by biallelic pathogenic variants in *POLR1C* or *POLR1D*.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *TXNL4A*-related craniofacial disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with a *TXNL4A*-Related Craniofacial Disorder

System/Concern	Evaluation	Comment
Choanal stenosis/atresia	Airway assessment for evidence of upper-airway obstruction	Esp important in newborns
Lower eyelid defects	Ophthalmology assessment for possible corneal issues	
Hearing loss	Audiology assessment	
Submucous cleft palate or cleft lip/palate	Cleft palate team assessment	
Structural cardiac defects	Cardiology assessment	Incl echocardiography
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of a *TXNL4A*-related craniofacial disorder to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with a *TXNL4A*-Related Craniofacial Disorder

Manifestation/Concern	Treatment
Choanal stenosis/atresia	Intubation &/or surgical correction
Lower eyelid defects	Care directed by ophthalmologist to ↓ risk of corneal scarring
Hearing loss	Hearing aids as needed
Craniofacial manifestations	Individualized & managed by multidisciplinary team [1]
Cardiac defects	As directed by cardiologist

1. The team may include a oromaxillofacial surgeon, plastic surgeon, otolaryngologist, dentist/orthodontist, and speech-language therapist.

Surveillance

Table 6. Recommended Surveillance for Individuals with a *TXNL4A*-Related Craniofacial Disorder

System/Concern	Evaluation	Frequency
Lower eyelid defects	Ophthalmology eval w/focus on cornea	Per ophthalmologist
Hearing loss	Hearing assessment	Shortly after birth & then per audiologist
Craniofacial manifestations	Regular visits to craniofacial team	Per craniofacial team

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

TXNL4A-related craniofacial disorders are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *TXNL4A* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *TXNL4A* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *TXNL4A* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *TXNL4A* pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with a *TXNL4A*-related craniofacial disorder are obligate heterozygotes (carriers) for a pathogenic variant in *TXNL4A*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TXNL4A* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *TXNL4A* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TXNL4A* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  babyhearing.org

- **Face Equality International**

  United Kingdom

  faceequalityinternational.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. TXNL4A-Related Craniofacial Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
TXNL4A	18q23	Thioredoxin-like protein 4A	TXNL4A	TXNL4A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for TXNL4A-Related Craniofacial Disorders (View All in OMIM)

608572	BURN-MCKEOWN SYNDROME; BMKS
611595	THIOREDOXIN-LIKE 4A; TXNL4A

Molecular Pathogenesis

TXNL4A encodes a highly conserved component of the U5 spliceosomal complex that is essential for U4/U6·U5 tri-snRNP assembly and cell cycle progression. While complete loss of *TXNL4A* is hypothesized to be lethal, reduced *TXNL4A* function results in a *TXNL4A*-related craniofacial disorder.

Two 34-bp deletions (type 1 and type 2) in the promoter region of *TXNL4A* have been described. The type 1 and type 2 promoter deletions partially overlap and occur at a fairly high frequency in the general population. Among 3,343 healthy individuals, 45 were heterozygous and one was homozygous for the type 1 promoter deletion; one individual was heterozygous for the type 2 promoter deletion [Wieczorek et al 2014].

Probands identified to date are compound heterozygous for the type 1 promoter deletion and a loss-of-function allele, or homozygous for the type 2 promoter deletion, or more rarely, homozygous for the type 1 promoter deletion [Goos et al 2017].

Mechanism of disease causation. The type 1 and type 2 promoter deletions result in reduced promoter activity and reduced *TXNL4A* expression [Wieczorek et al 2014]. They must therefore be considered hypomorphic alleles. Of note, the type 2 promoter deletion results in significantly lower transcription than the type 1 promoter deletion.

In yeast, homozygous null variants of the orthologous gene *DIB1* are lethal [Liu et al 2006]. Thus, homozygous loss-of-function *TXNL4A* variants in humans may be lethal as well. This is compatible with findings in individuals with a *TXNL4A*-related craniofacial disorder described to date.

***TXNL4A*-specific laboratory technical considerations.** The ability of a clinical molecular genetic laboratory to detect one or two deletions in the promoter region of *TXNL4A* is important for diagnosis of *TXNL4A*-related craniofacial disorders. Confirmation of clinical diagnosis is possible in every molecular laboratory that offers Sanger sequencing, multiplex ligation-dependent probe amplification, and chromosomal microarray analysis. Genome sequencing also allows detection of the promoter deletions, larger deletions, and loss-of-function pathogenic variants.

Chapter Notes

Author Notes

Dagmar Wieczorek has longstanding expertise in syndromic entities, especially those with intellectual disability (ID) and craniofacial malformations. She was principal investigator in the German Mental Retardation Network, funded by NGFNplus, and in the CRANIRARE, FACE, and Chromatin-Net consortia, all funded by the BMBF. She has published many papers on gene identification in individuals with ID and with craniofacial anomalies

(e.g., Treacher Collins syndrome, Burn-McKeown syndrome, and acrofacial dysostosis, Cincinnati type), as well as papers on the clinical spectrum of new entities with special emphasis on the facial phenotype.

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