U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Li C, Slavotinek A. *FREM1* Autosomal Recessive Disorders. 2008 Jul 9 [Updated 2019 May 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

FREM1 Autosomal Recessive Disorders

Chumei Li, MD, PhD, FRCPC, FCCMG[1] and Anne Slavotinek, MBBS, PhD[2]

Created: July 9, 2008; Updated: May 9, 2019.

Summary

Clinical characteristics

FREM1 autosomal recessive disorders include Manitoba oculotrichoanal (MOTA) syndrome, *b*ifid *n*ose with or without *a*norectal and *r*enal anomalies (BNAR syndrome), and isolated *c*ongenital *a*nomalies of *k*idney and *u*rinary *t*ract (CAKUT).

- MOTA syndrome is characterized by an aberrant hairline (unilateral or bilateral wedge-shaped extension of the anterior hairline from the temple region to the ipsilateral eye) and anomalies of the eyes (widely spaced eyes, anophthalmia/microphthalmia and/or cryptophthalmos, colobomas of the upper eyelid, and corneopalpebral synechiae), nose (bifid or broad nasal tip), abdominal wall (omphalocele or umbilical hernia), and anus (stenosis and/or anterior displacement of the anal opening). The manifestations and degree of severity vary even among affected members of the same family. Growth and psychomotor development are normal.
- BNAR syndrome is characterized by a bifid or wide nasal tip, anorectal anomalies, and renal malformations (e.g., renal agenesis, renal dysplasia). Typically the eye manifestations of MOTA syndrome are absent.
- *FREM1*-CAKUT was identified in one individual with bilateral vesicoureteral reflux (VUR) and a second individual with VUR and renal hypodysplasia.

Diagnosis/testing

The diagnosis of a *FREM1* autosomal recessive disorder is established in a proband by identification of biallelic pathogenic variants in *FREM1* on molecular genetic testing.

Management

Treatment of manifestations:

Author Affiliations: 1 Director, Clinical Genetics Program, McMaster Children's Hospital, Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada; Email: chumeili@hotmail.com. 2 Department of Pediatrics, Division of Genetics, University of California, San Francisco, San Francisco, California; Email: anne.slavotinek@ucsf.edu.

- Intensive ocular lubrication to avoid exposure keratopathy before surgery is performed; release of synechiae between the eyelid and cornea; surgical intervention and/or prostheses for anophthalmia/microphthalmia and cryptophthalmos if warranted; supportive care for those with visual impairment
- Rhinoplasty for notched ala nasi or bifid nose
- Surgical closure of omphalocele; surgical or conservative management of umbilical hernia
- Dilation for anal stenosis
- Supportive treatment to preserve renal functions and electrolyte balance; dialysis and transplant if indicated in individuals with renal failure
- Psychosocial support

Genetic counseling

MOTA, BNAR syndrome, and *FREM1*-CAKUT are inherited in an autosomal recessive manner. At conception, each full sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *FREM1* 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

FREM1 Autosomal Recessive Disorders: Included Phenotypes [1, 2]
• Manitoba oculotrichoanal (MOTA) syndrome • Bifid nose with or without anorectal and renal anomalies (BNAR syndrome) • *FREM1* congenital anomalies of kidney and urinary tract (CAKUT)

1. For other genetic causes of these phenotypes, see Differential Diagnosis.
2. Nonsyndromic metopic craniosynostosis (OMIM 614485) due to heterozygous pathogenic variants in *FREM1* is not included in the scope of this chapter (see Genetically Related Disorders).

Suggestive Findings

A *FREM1* autosomal recessive disorder **should be suspected** in an individual with features of Manitoba oculotrichoanal (MOTA) syndrome, *b*ifid *n*ose with or without *a*norectal and *r*enal anomalies (BNAR syndrome), and *c*ongenital *a*nomalies of *k*idney and *u*rinary *t*ract (CAKUT).

MOTA syndrome

- Widely spaced eyes
- Aberrant anterior hairline extending to the ipsilateral eye (unilateral or bilateral); often wedge-shaped, but may also resemble a thin stripe or appear tongue-shaped
- Ocular abnormalities including ipsilateral colobomas of the upper eyelid (sometimes referred to as a Tessier number 10 cleft by surgeons), corneopalpebral synechiae (i.e., adhesions between the eyelids and the cornea), and microphthalmia/anophthalmia and/or cryptophthalmos. Corneal clouding was described in one individual. The upper eyelid colobomas and cryptophthalmos are part of a spectrum of anomalies ranging from colobomas of the lid to eyelid coloboma plus corneopalpebral synechiae (also known as abortive cryptophthalmos) to complete cryptophthalmos [Nouby 2002]. Anomalies may be unilateral or bilateral; the severity may differ between the two eyes.
- Absent or interrupted eyebrow ipsilateral to the eye defect
- A bifid nose, a notch at the nasal tip, or a broad nose
- Anal stenosis and/or anteriorly placed anus
- Omphalocele or umbilical hernia
- Family history consistent with autosomal recessive inheritance

- Ethnic origin of aboriginal Oji-Cree

_B_ifid _n_ose with or without _a_norectal and _r_enal anomalies (BNAR syndrome)

- Median nose cleft or notch, or wide bulbous nasal tip
- Anorectal anomalies (e.g., anal stenosis, anteriorly placed anus)
- Renal malformations (e.g., renal agenesis, renal dysplasia)
- Eye manifestations of MOTA syndrome typically absent

***FREM1* congenital anomalies of kidney and urinary tract (CAKUT).** Renal malformations (e.g., vesicoureteral reflux, renal hypodysplasia) [Kohl et al 2014]

Establishing the Diagnosis

The diagnosis of a *FREM1* autosomal recessive disorder **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *FREM1* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *FREM1* variants of uncertain significance (or of one known *FREM1* pathogenic variant and one *FREM1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *FREM1* autosomal recessive disorders is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of a *FREM1* autosomal recessive disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of a *FREM1* autosomal recessive disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing**
  - In individuals with **Oji-Cree ancestry**, gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications of *FREM1* may be considered first. If only one or no pathogenic variant is found, sequence analysis of *FREM1* can be performed.
  - In individuals of **other ethnicities**, sequence analysis of *FREM1* that detects small intragenic deletions/insertions and missense, nonsense, and splice site variants can be performed first. If only one or no pathogenic variant is found, deletion/duplication analysis of *FREM1* can be performed.
- **A multigene panel** that includes *FREM1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of a *FREM1* autosomal recessive disorder is not considered because an individual has an atypical phenotype, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 *FREM1* Autosomal Recessive Disorders

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
FREM1	Sequence analysis [3]	~80%-90% [4]
	Gene-targeted deletion/duplication analysis [5]	7 persons [6]

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. 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.
4. Alazami et al [2009], Slavotinek et al [2011], Nathanson et al [2013]
5. 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 or duplications.
6. A deletion of exons 8 to 23 (c.824+627_c.3840-1311del) was identified in six individuals of Oji-Cree ancestry [Slavotinek et al 2011]. An upstream deletion in compound heterozygous form in an individual with isolated congenital diaphragmatic hernia was reported by Beck et al [2013].

Clinical Characteristics

Clinical Description

Manitoba Oculotrichoanal (MOTA) Syndrome

Ocular abnormalities include ipsilateral colobomas of the upper eyelid (sometimes referred to as a Tessier number 10 cleft by surgeons), corneopalpebral synechiae (i.e., adhesions between the eyelids and the cornea, also known as abortive cryptophthalmos), and microphthalmia/anophthalmia and/or cryptophthalmos. Anomalies may be unilateral or bilateral; the severity may differ between the two eyes.

Visual impairment may result directly from the ocular malformations or indirectly from exposure keratopathy. The long-term visual outcome depends on the severity of the ocular malformations and is poor for individuals

with bilateral complete cryptophthalmos. In those with milder ocular malformations, such as upper eyelid colobomas, vision is typically intact.

Corneal clouding was described in one individual.

Anal anomalies include anal stenosis and/or anteriorly placed anus. No associated anomalies of the sacrum, vertebrae, or tethered cord have been reported. No affected individuals have had refractory constipation, fecal incontinence, or procedure-related stenosis or fistula.

Characteristic facial features include widely spaced eyes; an aberrant anterior hairline extending to the ipsilateral eye (unilateral or bilateral) that is often wedge-shaped but may also resemble a thin stripe or appear tongue-shaped; ipsilateral absent or interrupted eyebrow; and a broad nose or notched or bifid nasal tip.

Omphalocele or umbilical hernia has been reported in approximately one third of affected individuals. Conservative management or surgical intervention for omphalocele or umbilical hernia is usually well tolerated and outcomes are excellent. Long-term intestinal complications have not been described.

Other. Additional findings have been reported: renal pelviectasis, renal dysplasia, hydrometrocolpos and vaginal atresia, cutaneous syndactyly, and additional dysmorphic features (e.g., high forehead with a frontal upsweep of hair, dysplastic ears, maxillary hypoplasia, underdeveloped ala nasi, short philtrum, thin upper lip, and relative microstomia) [Slavotinek et al 2011, Mitter et al 2012, Nathanson et al 2013].

Growth and development. Individuals with MOTA syndrome assessed at various ages appear generally healthy with age-appropriate growth and cognition. Motor, social, and speech and language skills are typically normal, although development may be influenced by the presence of severe eye defects that lead to visual impairment.

The manifestations and degree of severity vary even among affected members of the same family.

*B*ifid *N*ose with or without *A*norectal and *R*enal Anomalies (BNAR) Syndrome

BNAR syndrome was described by Al-Gazali et al [2002] and Alazami et al [2009] in ten individuals from three consanguineous families of Egyptian, Afghani, and Pakistani origin.

- **Craniofacial features.** Broad and/or bifid nose (100%), widely spaced eyes, short and thick oral frenula
- **Renal malformations** (e.g., bilateral renal agenesis, unilateral renal agenesis) in 6/9 individuals evaluated
- **Anorectal malformations** (e.g., anteriorly placed anus, anal stenosis) in 2/9 individuals evaluated
- **Airway malformations** in 2/8 individuals evaluated

FREM1 Congenital *A*nomalies of *K*idney and *U*rinary *T*ract (CAKUT)

FREM1-CAKUT phenotype has been reported in an individual with bilateral vesicoureteral reflux (VUR) grade III and in another individual with right-sided VUR grade V in conjunction with right-sided renal hypodysplasia [Kohl et al 2014].

Other Phenotypes

The following other phenotypes have been reported in individuals with biallelic *FREM1* pathogenic variants:

- One individual with isolated congenital diaphragmatic hernia [Beck et al 2013]
- One fetus with severe hydrocephalus and shortened limbs associated with novel *FREM1* pathogenic variants [Yang et al 2017]

Genotype-Phenotype Correlations

Genotype-phenotype correlations have not been possible to date given the rarity of the condition and limited number of pathogenic variants described.

Prevalence

The prevalence of *FREM1* autosomal recessive disorders are unknown. To date, the authors are aware of 27 published individuals with MOTA syndrome.

Based on the number of individuals identified to date in the aboriginal Oji-Cree community of the Island Lake region of northern Manitoba, Canada, which had a population of 4,685 in 1996 and 2,020 in 2001 [First Nation Profiles 2004], the incidence of MOTA syndrome in that population is estimated at 2:1,000-6:1,000 births; however, this may be an underestimate in this population, as a few presumably affected individuals have also been identified through family histories of affected individuals, and some milder cases may not have come to medical attention. All affected individuals from the Island Lake region identified to date are presumed to be related.

Genetically Related (Allelic) Disorders

Heterozygous *FREM1* pathogenic variants have been reported in individuals with nonsyndromic metopic craniosynostosis (OMIM 614485) [Vissers et al 2011].

Larger deletions of chromosome 9p22.3 encompassing part or all of the *FREM1* gene have been reported in individuals with metopic craniosynostosis [Swinkels et al 2008]. Additional clinical features associated with 9p22.3 deletion may include developmental delay, short stature, and congenital cardiac defect (e.g., pulmonary stenosis, ventricular septal defect).

Differential Diagnosis

The following disorders should be considered in the differential diagnosis of Manitoba oculotrichoanal (MOTA) syndrome and *b*ifid *n*ose with or without *a*norectal and *r*enal anomalies (BNAR) syndrome (Table 2).

Table 2. Disorders to Consider in the Differential Diagnosis of MOTA Syndrome and BNAR Syndrome

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/MOTA &/or BNAR syndrome	Distinguishing from MOTA & BNAR syndromes
Fraser syndrome (OMIM PS219000)	*FRAS1* *REM2* *GRIP1*	AR	• Anophthalmia/ microphthalmia, cryptophthalmos, eyelid colobomas, widely spaced eyes • Wedge-shaped lateral anterior hairline • Bifid nasal tip / notched ala nasi • Anal stenosis or imperforate anus [1]	• Cognitive impairment • Often early mortality
Frontonasal dysplasia (FND) (OMIM PS136760)	*ALX1* *ALX3* *ALX4*	AR	• Widely spaced eyes • Broad forehead • Widow's peak • Range from notched ala nasi to bifid nose [2]	• Cranium bifidum [3] • Absence of omphalocele & anorectal abnormalities

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/MOTA &/or BNAR syndrome	Distinguishing from MOTA & BNAR syndromes
Craniofrontonasal dysplasia (CFND) (OMIM 304110)	*EFNB1*	XL	In females w/CFND: [4] • Widely spaced eyes • Broad nasal bridge, bifid nasal tip	• Craniosynostosis • Cranium bifidum • Absence of omphalocele & anorectal abnormalities
Oculoauriculofrontonasal syndrome (OMIM 601452)	Unknown	Unknown	• Upper eyelid colobomas, widely spaced eyes • Notched ala nasi or bifid nose • Normal intelligence	• Hemifacial microsomia • Ear malformations, preauricular tags • Epibulbar dermoids • Abnormalities of the frontal bone
FG syndrome type 1 (See *MED12*-Related Disorders.)	*MED12*	XL	In a male infant: • Widely spaced eyes • Anteriorly placed anus, anal stenosis	Often, additional findings such as: • Thumb anomalies • Vertebral abnormalities
Townes-Brocks syndrome	*SALL1*	AD	Anteriorly placed anus, anal stenosis	
VACTERL (OMIM 192350)	Unknown	Unknown		
Donnai-Barrow syndrome	*LRP2*	AR	• Widely spaced eyes • Omphalocele	• Agenesis of the corpus callosum • Sensorineural hearing loss • Diaphragmatic hernia

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance; VACTERL = *v*ertebral abnormalities, *a*nal abnormalities, *c*ardiac defects, *t*racheo*e*sophageal fistula, *r*enal and/or *r*adial ray abnormalities, and *l*imb anomalies; XL = X-linked

1. Slavotinek & Tifft [2002], McGregor et al [2003], Vrontou et al [2003]

2. Jones [2006]

3. Cranium bifidum is a midline defect of the frontal bone detected on skull x-rays.

4. CFND is inherited in a unique X-linked manner that paradoxically shows greater severity in heterozygous females than in hemizygous males. Typically, females have FND, craniofacial asymmetry, craniosynostosis, a bifid nasal tip, and grooved nails; they may also have skeletal abnormalities. In contrast, males typically show only widely spaced eyes [Twigg et al 2004, Wieland et al 2004].

***FREM1* congenital anomalies of kidney and urinary tract (CAKUT).** Isolated CAKUT has been associated with more than 20 genes to date and may be inherited in an autosomal dominant, autosomal recessive, or multifactorial manner [Nicolaou et al 2015]. The genetic etiology in most individuals with isolated CAKUT is unknown [Kohl et al 2014].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *FREM1* autosomal recessive disorder, the evaluations summarized in Table 3, Table 4, or Table 5 (depending on the phenotype) are recommended if they have not already been performed as part of the evaluation that led to the diagnosis:

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with MOTA Syndrome

System/Concern	Evaluation	Comment
Ocular	Ophthalmologic eval	For coloboma &/or keratopathy
Gastrointestinal	Referral to surgeon	For omphalocele, umbilical hernia, &/or anal anomalies if present
ENT	Eval for bifid nose / notched ala nasi	Referral to plastic surgeon as needed
Other	Consultation w/clinical geneticist &/or genetic counselor	

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with BNAR Syndrome

System/Concern	Evaluation	Comment
Renal	Renal imaging & renal functional analysis	
Gastrointestinal	Referral to surgeon	For omphalocele, umbilical hernia, &/or anal anomalies if present
Respiratory	• ENT eval for bifid or notched nose • Eval of the airway	Referral to plastic surgeon as needed
Other	Consultation w/clinical geneticist &/or genetic counselor	

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *FREM1*-CAKUT

System/Concern	Evaluation
Genitourinary	Clinical exam, imaging & surgical eval
Other	Consultation w/clinical geneticist &/or genetic counselor

Treatment of Manifestations

Treatment of *FREM1* autosomal recessive disorders consists primarily of surgical intervention with procedures tailored to the specific needs of the individual. A multidisciplinary team comprising a clinical geneticist, general surgeon, ophthalmologist, otolaryngologist, plastic surgeon, and social worker is preferred for optimal management.

Table 6. Treatment of Manifestations in Individuals with *FREM1* Autosomal Recessive Disorders

Manifestation/ Concern	Treatment	Considerations/Other
Colobomas of upper eyelids & synechiae	• Managed conservatively w/intensive ocular lubrication • Surgical release of synechiae	To avoid exposure keratopathy before surgery is performed
Anophthalmia/microphthalmia & cryptophthalmos	May warrant surgical intervention & insertion of prostheses	To facilitate development of ocular region [1]
Visual impairment (e.g., refractive errors)	Per ophthalmologist	May be assoc w/colobomas & corneopalpebral synechiae
Notched ala nasi or bifid nose	Rhinoplasty	May be performed for cosmetic purposes
Omphalocele & umbilical hernia	May be managed conservatively or surgically	To date, all persons w/a *FREM1* AR disorder managed surgically have tolerated the procedure w/out complications.
Anal stenosis	Serial dilations	
Anteriorly placed anus	Managed conservatively or w/surgical intervention	As determined on an individual basis

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Renal malformations	• Supportive treatment to preserve renal function & electrolyte balance • Surgical correction when indicated	Dialysis & transplant may be indicated in persons w/renal failure.
Psychosocial stressors	Psychosocial support	May be indicated for parents & affected child

AR = autosomal recessive
1. Seah et al [2002]

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

Manitoba oculotrichoanal (MOTA) syndrome, *b*ifid *n*ose with or without *a*norectal and *r*enal anomalies (BNAR syndrome), and *FREM1* congenital anomalies of kidney and urinary tract (CAKUT) are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *FREM1* pathogenic variant).
- Heterozygotes (carriers) are not affected with MOTA, BNAR, or *FREM1*-CAKUT. To date, heterozygous parents of individuals with MOTA, BNAR, or *FREM1*-CAKUT have not been reported to have *FREM1* trigonocephaly (see Genetically Related Disorders).

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are not affected with MOTA, BNAR, or *FREM1*-CAKUT. To date, heterozygous sibs of individuals with MOTA, BNAR, or *FREM1*-CAKUT have not been reported to have *FREM1* trigonocephaly (see Genetically Related Disorders).

Offspring of a proband. The offspring of an individual with a *FREM1* autosomal recessive disorder are obligate heterozygotes (carriers) for a *FREM1* pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *FREM1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FREM1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *FREM1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Pregnancies at high a priori risk. Ultrasound examination may be diagnostic of Manitoba oculotrichoanal (MOTA) syndrome if findings such as omphalocele, cryptophthalmos, anophthalmia/microphthalmia, widely spaced eyes, and/or a wide nose are detected. However, mild findings may be difficult to detect on prenatal imaging.

Pregnancies at low a priori risk. Chromosome analysis and possibly DNA-based testing for other specific disorders with findings similar to MOTA syndrome should be considered when omphalocele and craniofacial features associated with MOTA syndrome are identified on fetal ultrasound examination in a pregnancy not known to be at risk for MOTA syndrome.

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.

- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.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. FREM1 Autosomal Recessive Disorders : Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FREM1	9p22.3	FRAS1-related extracellular matrix protein 1	FREM1 database	FREM1	FREM1

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 FREM1 Autosomal Recessive Disorders (View All in OMIM)

248450	MANITOBA OCULOTRICHOANAL SYNDROME; MOTA
608944	FRAS1-RELATED EXTRACELLULAR MATRIX PROTEIN 1; FREM1
608980	BIFID NOSE WITH OR WITHOUT ANORECTAL AND RENAL ANOMALIES; BNAR

Molecular Pathogenesis

The FREM1 protein is a member of the FRAS1/FREM family of extracellular matrix proteins that are located in the sublamina densa of epithelial basement membranes during embryogenesis [Pavlakis et al 2011]. FREM1 forms a ternary complex with FRAS1, FREM2, and FREM3, which have similar functional domains and structures [Pavlakis et al 2011]. The ternary complex is critical for maintenance of epithelial-mesenchymal cohesion during embryonic development in mammals [Pavlakis et al 2011]. *FREM1* pathogenic variants in humans are predicted to disturb the interactions with the proteins in this complex, although the levels of FRAS1 and FREM2 are not decreased [Vissers et al 2011]. Loss or disruption of the ternary complex is thought to reduce epithelial-mesenchymal adhesion during development, with subsequent generation of the characteristic clinical findings associated with Fraser syndrome and the *FREM1* autosomal recessive disorders [Chacon-Camacho et al 2017].

Mechanism of disease causation. All pathogenic variants reported to date in *FREM1* are hypothesized to result in loss of function.

Table 7. Notable *FREM1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_144966.5 NP_659403.4	c.824+627_3840-1311del (IVS7+631_IVS23-1311 del; del8-23 exon)	p.385_1327del	Common deletion assoc w/MOTA in Oji-Cree [Slavotinek et al 2011]
	c.3971T>G	p.Leu1324Arg	Observed in 1 person w/MOTA & features of Fraser syndrome [Mitter et al 2012]
	c.4629delC	p.Phe1544SerfsTer62	
	c.2721delG	p.Val908SerfsTer17	Observed homozygous in persons w/ BNAR [Alazami et al 2009]
	c.1945C>T	p.Arg649Trp	
	c.4318G>A	p.Gly1440Ser	

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_144966.5	c.5334+1G>A/~86-kb deletion upstream *FREM1*	--	Complex deletion assoc w/isolated CDH [Beck et al 2013]
NM_144966.5 NP_659403.4	c.4879G>T	p.Ala1627Ser	Observed in persons w/CAKUT [Kohl et al 2014]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

Author History

Albert E Chudley, MD, FRCPC, FCCMG; University of Manitoba (2011-2019)
Chumei Li, MD, PhD, FRCPC, FCCMG (2008-present)
Anne Slavotinek, MBBS, PhD (2011-present)

Revision History

- 9 May 2019 (sw) Comprehensive update posted live
- 13 October 2011 (me) Comprehensive update posted live
- 9 July 2008 (me) Review posted live
- 16 May 2008 (cl) Original submission

References

Literature Cited

Alazami AM, Shaheen R, Alzahrani F, Snape K, Saggar A, Brinkmann B, Bavi P, Al-Gazali LI, Alkuraya FS. FREM1 mutations cause bifid nose, renal agenesis, and anorectal malformations syndrome. Am J Hum Genet. 2009;85:414–8. PubMed PMID: 19732862.

Al-Gazali LI, Bakir M, Hamud OA, Gerami S. An autosomal recessive syndrome of nasal anomalies associated with renal and anorectal malformations. Clin Dysmorphol. 2002;11:33–8. PubMed PMID: 11822703.

Beck TF, Veenma D, Shchelochkov OA, Yu Z, Kim BJ, Zaveri HP, van Bever Y, Choi S, Douben H, Bertin TK, Patel PI, Lee B, Tibboel D, de Klein A, Stockton DW, Justice MJ, Scott DA. Deficiency of FRAS1-related extracellular matrix 1 (FREM1) causes congenital diaphragmatic hernia in humans and mice. Hum Mol Genet. 2013;22:1026–38. PubMed PMID: 23221805.

Chacon-Camacho OF, Zenker M, Schanze D, Ledesma-Gil J, Zenteno JC. Novel FREM1 mutations in a patient with MOTA syndrome: clinical findings, mutation update and review of FREM1-related disorders literature. Eur J Med Genet. 2017;60:190–4. PubMed PMID: 28111185.

First Nation Profiles. Indigenous and Northern Affairs Canada website. 2004. Accessed 5-23-23.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Jones KL. Frontonasal dysplasia sequence. In: *Smith's Recognizable Patterns of Human Malformation*. 6 ed. Philadelphia, PA: Elsevier Saunders; 2006:1268-9

Kohl S, Hwang DY, Dworschak GC, Hilger AC, Saisawat P, Vivante A, Stajic N, Bogdanovic R, Reutter HM, Kehinde EO, Tasic V, Hildebrandt F. Mild recessive mutations in six Fraser syndrome-related genes cause isolated congenital anomalies of the kidney and urinary tract. J Am Soc Nephrol. 2014;25:1917–22. PubMed PMID: 24700879.

McGregor L, Makela V, Darling SM, Vrontou S, Chalepakis G, Roberts C, Smart N, Rutland P, Prescott N, Hopkins J, Bentley E, Shaw A, Roberts E, Mueller R, Jadeja S, Philip N, Nelson J, Francannet C, Perez AA, Megarband A, Kerr B, Wainwright B, Woolf AS, Winter RM, Scambler PJ. Fraser syndrome and mouse blebbed phenotype caused by mutations in FRAS1/Fras1 encoding a putative extracellular matrix protein. Nat Genet. 2003;34:203–8. PubMed PMID: 12766769.

Mitter D, Schanze D, Sterker I, Müller D, Till H, Zenker M. MOTA syndrome: molecular genetic confirmation of the diagnosis in a newborn with previously unreported clinical features. Mol Syndromol. 2012;3:136–9. PubMed PMID: 23112756.

Nathanson J, Swarr DT, Singer A, Liu M, Chinn A, Jones W, Hurst J, Khalek N, Zackai E, Slavotinek A. Novel FREM1 mutations expand the phenotypic spectrum associated with Manitoba-oculo-tricho-anal (MOTA) syndrome and bifid nose renal agenesis anorectal malformations (BNAR) syndrome. Am J Med Genet A. 2013;161A:473–8. PubMed PMID: 23401257.

Nicolaou N, Renkema KY, Bongers EM, Giles RH, Knoers NV. Genetic, environmental, and epigenetic factors involved in CAKUT. Nat Rev Nephrol. 2015;11:720–31. PubMed PMID: 26281895.

Nouby G. Congenital upper eyelid coloboma and cryptophthalmos. Ophthal Plast Reconstr Surg. 2002;18:373–7.

Pavlakis E, Chiotaki R, Chalepakis G. The role of Fras1/Frem proteins in the structure and function of the basement membrane. Int J Biochem Cell Biol. 2011;43:487–95. PubMed PMID: 21182980.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Seah LL, Choo CT, Fong KS. Congenital upper lid colobomas: management and visual outcome. Ophthal Plast Reconstr Surg. 2002;18:190–5.

Slavotinek AM, Baranzini SE, Schanze D, Labelle-Dumais C, Short KM, Chao R, Yahyavi M, Bijlsma EK, Chu C, Musone S, Wheatley A, Kwok PY, Marles S, Fryns JP, Maga AM, Hassan MG, Gould DB, Madireddy L, Li C, Cox TC, Smyth I, Chudley AE, Zenker M. Manitoba-oculo-tricho-anal (MOTA) syndrome is caused by mutations in FREM1. J Med Genet. 2011;48:375–82. PubMed PMID: 21507892.

Slavotinek AM, Tifft CJ. Fraser syndrome and cryptophthalmos: review of the diagnostic criteria and evidence for phenotypic modules in complex malformation syndromes. J Med Genet. 2002;39:623–33. PubMed PMID: 12205104.

Swinkels ME, Simons A, Smeets DF, Vissers LE, Veltman JA, Pfundt R, de Vries BB, Faas BH, Schrander-Stumpel CT, McCann E, Sweeney E, May P, Draaisma JM, Knoers NV, van Kessel AG, van Ravenswaaij-Arts CM. Clinical and cytogenetic characterization of 13 Dutch patients with deletion 9p syndrome: delineation of the critical region for a consensus phenotype. Am J Med Genet A. 2008;146A:1430–8. PubMed PMID: 18452192.

Twigg SRF, Kan R, Babbs C, Bochukova EG, Robertson SP, Wall SA, Morriss-Kay GM, Wilkie AOM. Mutations of ephrin-B1 (EFNB1), a marker of tissue boundary formation, cause craniofrontonasal syndrome. Proc Nat Acad Sci. 2004;101:8652–7. PubMed PMID: 15166289.

Vissers LE, Cox TC, Maga AM, Short KM, Wiradjaja F, Janssen IM, Jehee F, Bertola D, Liu J, Yagnik G, Sekiguchi K, Kiyozumi D, van Bokhoven H, Marcelis C, Cunningham ML, Anderson PJ, Boyadjiev SA, Passos-Bueno MR, Veltman JA, Smyth I, Buckley MF, Roscioli T. Heterozygous mutations of FREM1 are

associated with an increased risk of isolated metopic craniosynostosis in humans and mice. PLoS Genet. 2011;7:e1002278. PubMed PMID: 21931569.

Vrontou S, Petrou P, Meyer BI, Galanopoulos VK, Imai K, Yanagi M, Chowdhury K, Scambler PJ, Chalepakis G. Fras1 deficiency results in cryptophthalmos, renal agenesis and blebbed phenotype in mice. Nat Genet. 2003;34:209–14. PubMed PMID: 12766770.

Wieland I, Jakubiczka S, Muschke P, Cohen M, Thiele H, Gerlach KL, Adams RH, Wieacker P. Mutations of the ephrin-B1 gene cause craniofrontonasal syndrome. Am J Hum Genet. 2004;74:1209–15. PubMed PMID: 15124102.

Yang YD, Huang LY, Yan JM, Han J, Zhang Y, Li DZ. Novel FREM1 mutations are associated with severe hydrocephalus and shortened limbs in a prenatal case. Eur J Obstet Gynecol Reprod Biol. 2017;215:262–4. PubMed PMID: 28622873.

License