GENEReviews

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Manitoba Oculotrichoanal Syndrome

[*Marles Syndrome, MOTA Syndrome*]

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Summary

Disease characteristics. Manitoba oculotrichoanal (MOTA) syndrome is characterized by congenital anomalies affecting the anterior hairline (unilateral or bilateral wedge-shaped extension of the anterior hairline from the temple region to the ipsilateral eye); eyes (ocular hypertelorism, microphthalmia, cryptophthalmos, colobomata of the upper eyelid, and corneopalpebral synechiae); nose (bifid or wide with a notched 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.

Diagnosis/testing. Diagnosis is based on clinical findings and family history, and in many cases ethnicity is taken into account. The causative gene has not been mapped and is not known.

Management. *Treatment of manifestations:* Treatment consists primarily of surgical repair as needed, including closure of an omphalocele, dilatation for anal stenosis, release of synechiae between the eyelid and cornea, and craniofacial surgery for bifid nose.

Genetic counseling. MOTA syndrome is presumed to be 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 an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Molecular genetic testing is not available because the causative gene is not known.

Diagnosis

Clinical Diagnosis

Diagnosis of Manitoba oculotrichoanal (MOTA) syndrome is based on the following [Marles et al 1992, Li et al 2007]:

Clinical features

- Ocular hypertelorism (seen in 100% of affected individuals)
- Aberrant anterior hairline extending to the ipsilateral eye. May be unilateral or bilateral; often wedge-shaped, but may also be a thin stripe or tongue-shaped (seen in 85%).
- Wide nares, notched nares, or bifid nose (seen in 71%)

- Ipsilateral absent or interrupted eyebrow
- Ocular abnormalities including ipsilateral coloboma of the upper eyelid, corneopalpebral synechiae (i.e., adhesion between the eyelid and the cornea), microphthalmia, and/or cryptophthalmos. It is believed that upper-eyelid coloboma and cryptophthalmos are part of a spectrum of anomalies ranging from colobomata 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; severity may differ between the two eyes.
- Omphalocele or umbilical hernia (present in approximately 20% of affected individuals)
- Anal stenosis or anteriorly placed anus

Minimum diagnostic criteria should include ocular hypertelorism plus **either**:

- At least two additional features

  or

- One additional feature plus a previously affected full sib, parental consanguinity, or Island Lake aboriginal ethnicity.

Family history

- A positive family history consistent with autosomal recessive inheritance (i.e., an affected full sib and/or consanguinity) is helpful, but not necessary, for the diagnosis.
- Ethnic origin of aboriginal Oji-Cree. To date, most (not all) affected individuals have been Oji-Cree, descended from the highly inbred population living in the Island Lake region of northern Manitoba, Canada.

Testing

Gene. The causative gene is not known; it has not been mapped.

Clinical Description

Natural History

Manitoba oculotrichoanal (MOTA) syndrome is characterized by the findings present at birth detailed in Diagnosis. The manifestations and degree of severity vary even among affected members of the same family. Not all features are observed in all affected individuals.

Pregnancy of an affected infant is usually uneventful and birth weight, length, and head circumference are appropriate for gestational age.

Visual impairment may result directly from ocular malformation or indirectly from exposure keratopathy. The long-term visual outcome has not been determined, as many of these individuals are lost to follow-up.

Conservative or surgical intervention for omphalocele or umbilical hernia is usually well tolerated and outcomes are excellent. Long-term intestinal complications are not known.

Anteriorly displaced anus and anal stenosis are not associated with anomalies of the sacrum, vertebrae, or tethered cord. No affected individuals have had refractory constipation, fecal incontinence, or procedure-related stenosis or fistula.

Individuals with MOTA syndrome assessed at various ages appear generally healthy with age-appropriate growth, cognition, and motor, social, and speech and language skills.

Individuals with MOTA syndrome have not had malformations of the limbs, spine, heart, lungs, kidneys, genitalia, or other internal organs. They have normal skull x-rays with no evidence of cranium bifidum, a midline defect in the frontal bone found in the related condition of frontonasal dysplasia (FND) sequence.

Genotype-Phenotype Correlations

Genotype-phenotype correlations are not possible given that the causative gene is unknown.

Prevalence

The prevalence in the general population is unknown, but it is likely that the condition is rare.

To date, 13 individuals from Manitoba and one Dutch individual have been reported [Marles et al 1992, Li et al 2007]. Similar clinical findings have been identified in one German individual [Slavotinek, personal communication] and several individuals in a Turkish kindred [Tukun, personal communication].

Based on the number of individuals identified so far in the aboriginal Ojibway-Cree community of the Island Lake region of northern Manitoba, Canada, which had a population of 4685 in 1996 and 2020 in 2001 [First Nation Profile Site 2004], the prevalence of MOTA syndrome in that population is estimated at 2:1000-6:1000 births; however, this may be an underestimate in this population, as a few presumed-affected individuals have 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 related.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Conditions with similar ocular findings, either on prenatal imaging or postnatal examination that may be confused with Manitoba oculotrichoanal (MOTA) syndrome include those with ocular hypertelorism, coloboma of the eyelids, microphthalmos, cryptophthalmos, and omphalocele.

Ocular hypertelorism occurs in more than 500 disorders [Dollfus & Verloes 2004].

The etiology of microphthalmia includes chromosomal, teratogenic, and monogenic disorders [Verma & FitzPatrick 2007]. More than 200 entries that include microphthalmia are listed in OMIM (see Anophthalmia/Microphthalmia Overview).

The following conditions need to be distinguished from MOTA syndrome:

- Fraser syndrome (also known as cryptophthalmos syndrome). Phenotypic overlap between Fraser syndrome [Slavotinek & Tifft 2002, McGregor et al 2003, Vrontou et al 2003] and MOTA syndrome includes cryptophthalmos, a wedge-shaped lateral anterior hairline, and notched nares. Both conditions are inherited in an autosomal recessive manner and are more likely in consanguineous unions because of their rarity in the general population. However, persons with MOTA syndrome do not have cognitive impairment, ear anomalies, limb anomalies, abnormal genitalia, or renal dysplasia, and they do not fulfill the clinical diagnostic criteria for Fraser syndrome [Slavotinek & Tifft 2002, van Haelst et al 2007]. Mutations in *FRAS1* (OMIM

607830) and *FREM2* (OMIM 608945) underlie Fraser syndrome [McGregor et al 2003, Jadeja et al 2005]. Mutations in *FRAS1* have not been found in individuals with MOTA syndrome [McGregor et al 2003; Slavotinek et al 2006; Tukun, personal communication]. No data concerning sequence analysis of *FREM2* in individuals with MOTA syndrome are available.

- FND sequence, also known as median cleft face syndrome, is characterized by a broad forehead, widow's peak, ocular hypertelorism, and nostrils that range from notched to completely divided [Jones 2006]. Cranium bifidum, a midline defect of the frontal bone detected on skull x-rays, is also a common feature. Craniofrontonasal dysplasia (CFND) shares the main craniofacial phenotype with FND sequence but also includes craniosynostosis. Ocular hypertelorism and nasal anomalies are observed in MOTA syndrome, FND sequence, and CFND; however, cranium bifidum is not observed in MOTA syndrome, and omphalocele and anal abnormalities are not known to be associated with FND sequence or CFND.

  The etiology of FND sequence is unknown and most cases have been simplex (i.e., a single occurrence in a family) [Ishmael et al 2002]. Of note, a 3H1 Br/Br mouse, thought to be a model for human FND sequence [McBratney et al 2003], shows the FND sequence phenotype when both mutant Br alleles are present, similar to autosomal recessive inheritance.

  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, bifid nasal tip, and grooved nails; they may also have skeletal abnormalities. In contrast, males typically show only ocular hypertelorism [Twigg et al 2004, Wieland et al 2004]. Mutations in *EFNB1* are causative.

- Omphalocele can be the result of complex etiologies including chromosomal abnormalities, environmental exposures, monogenic disorders such as Beckwith-Wiedemann syndrome [Cohen et al 2002, Barisic et al 2001, Stoll et al 2008], or malformation sequences of unknown cause including omphalocele, exstrophy of bladder, imperforate anus, spinal defect (OEIS) complex [Keppler-Noreuil 2001]. Omphalocele and ocular hypertelorism can be observed together in Donnai-Barrow syndrome (DBS) [Kantarci et al 2007], but the additional features of DBS, including agenesis of the corpus callosum, sensorineural hearing loss, ocular coloboma, and diaphragmatic hernia, distinguish it from MOTA syndrome.

- Anteriorly placed anus and anal stenosis can be seen in a number of genetic conditions, both chromosomal and monogenic [Cho et al 2001]. In a male infant with ocular hypertelorism, FG syndrome may need to be considered (see MED12-related Disorders, which includes FG syndrome type 1) [Risheg et al 2007]. But FG syndrome and other disorders associated with anal anomalies (e.g., Townes-Brocks syndrome or VACTER [**v**ertebral abnormalities, **a**nal abnormalities, **c**ardiac defects, **t**racheo**e**sophageal fistula, and **r**enal and/or **r**adial ray abnormalities]) often have findings such as thumb anomalies, vertebral abnormalities, and/or abnormal genitalia that distinguish them from MOTA syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Manitoba oculotrichoanal (MOTA) syndrome, the following are recommended:

- Ophthalmologic evaluation

- Surgical evaluation for severity of omphalocele and umbilical hernia, if present, and for evidence of anal abnormalities
- ENT (ear-nose-throat) evaluation
- Plastic surgery evaluation

Treatment of Manifestations

A multidisciplinary team comprising a medical geneticist, general surgeon, ophthalmologist, otolaryngologist, plastic surgeon, and social worker is preferred for optimal management of a patient with MOTA syndrome.

Treatment consists primarily of surgical intervention with procedures tailored to the specific needs of the individual.

Eye anomalies

- Coloboma of the upper eyelids and synechiae are managed conservatively with intensive ocular lubrication to avoid exposure keratopathy before surgery is performed.
- Microphthalmia and cryptophthalmos may warrant surgical intervention to facilitate the development of the ocular region [Seah et al 2002].
- Visual impairment, such as refractive errors, may be associated with coloboma and corneopalpebral synechiae.

Notched or bifid nose. Rhinoplasty may be performed for cosmetic purpose.

Omphalocele and umbilical hernia may be managed conservatively or by surgery. All patients with MOTA syndrome who have been managed surgically tolerated the procedure well without procedure-related complications.

Anal stenosis is generally managed by serial dilatations.

Anteriorly placed anus is managed conservatively or with surgical intervention, as determined on a case-by-case basis.

Psychosocial support may be indicated for the parents and the affected child.

Testing 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 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Manitoba oculotrichoanal (MOTA) syndrome is presumed to be inherited in an autosomal recessive manner.

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is not available. —ED.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one mutant allele).
- Heterozygotes (carriers) have been asymptomatic to date.

Sibs of a proband

- 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 of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with MOTA syndrome are obligate heterozygotes (carriers) for a disease-causing mutation.

Carrier Detection

Carrier status can be ascertained in some instances by pedigree analysis. However, carrier testing by molecular genetic testing is not possible because the gene is not mapped or identified.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk 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, carriers, or at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes,

mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the gene(s) in which disease-causing mutations occur has/have not been identified. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Because the gene(s) in which disease-causing mutations occur has/have not been identified, prenatal testing using molecular genetic testing is not available.

Pregnancies at high a priori risk. Ultrasound examination may be diagnostic of MOTA syndrome if findings such as omphalocele, cryptophthalmos, microphthalmos, ocular hypertelorism, 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.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

The gene for this condition has not been identified.

Table A. OMIM Entries for Manitoba Oculotrichoanal Syndrome

248450	MANITOBA OCULOTRICHOANAL SYNDROME; MOTA

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

AboutFace International
123 Edward Street Suite 1003
Toronto ON M5G 1E2
Canada
Phone: 800-665-FACE (800-665-3223); 416-597-2229
Fax: 416-597-8494
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

Children's Craniofacial Association
13140 Coit Road Suite 517
Dallas TX 75240
Phone: 800-535-3643; 214-570-9099
Fax: 214-570-8811
Email: contactCCA@ccakids.com
www.ccakids.com

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Barisic I, Clementi M, Hausler M, Gjergia R, Kern J, Stoll C. Evaluation of prenatal ultrasound diagnosis of fetal abdominal wall defects by 19 European registries. *Ultrasound Obstet Gynecol* 2001;18:350–6.

Cho S, Moore SP, Fangman T. One hybdred three consecutive patients with anorectal malformations and their associated anomalies. *Arch Pediatr Adolesc Med* 2001;155:587–91. [PubMed: 11343503]

Cohen MM Jr, Neri G, Weksberg R (2002) Overgrowth syndromes. Oxford University Press, New York

Dollfus H, Verloes A. Dysmorphology and the orbital region: a practical clinical approach. *Survey Ophthal* 2004;49:547–61. [PubMed: 15530943]

First Nation Profile Site (2004) Indian and Northern Affairs Canada Web site (sdiprod2.inac.gc.ca/fnprofiles). Accessed 7-2-08.

Ishmael HA, Begleiter ML, Regier EJ, Butler M. Oculoauriculofrontosasal syndrome in a nine-month old male. *Am J Med Genet* 2002;107:169–73. [PubMed: 11807893]

Jadeja S, Smyth I, Pitera JE, Taylor MS, van Haelst M, Bentley E, McGregor L, Hopkins J, Chalepakis G, Philip N, Perez Aytes A, Watt FM, Darling SM, Jackson I, Woolf AS, Scambler PJ. Identification of a new gene mutated in Fraser syndrome and mouse myelencephalic blebs. *Nature Genet* 2005;37:520–5. [PubMed: 15838507]

Jones KL (2006) Frontonasal dysplasia sequence. In: Smith's Recognizable Patterns of Human Malformation, 6 ed. Elsevier Saunders, Philadelphia, pp 268-9

Kantarci S, Al-Gazali L, Hill RS, Donnai D, Black GC, Bieth E, Chassaing N, Lacombe D, Devriendt K, Teebi A, Loscertales M, Robson C, Liu T, MacLaughlin DT, Noonan KM, Russell MK, Walsh CA, Donahoe PK, Pober BR. Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico-renal syndromes. *Nat Genet* 2007;39:957–9. [PubMed: 17632512]

Keppler-Noreuil KM. OEIS (Omphalocele- Exstrophy of bladder -Imperforate anus - Spinal defect): a review of 14 cases. *Am J Med Genet* A 2001;99:271–9.

Li C, Marles SL, Greenberg CR, Chodriker BN, van de Kamp J, Slavotinek A, Chudley AE. Manitoba Oculotrichoanal (MOTA) Syndrome: Report of Eight New Cases. *Am J Med Genet Part A* 2007;143A:853–7.

Marles SL, Greenberg CR, Persaud TV, Shuckett EP, Chudley AE. New Familial syndrome of unilateral upper eyelid coloboma, aberrant anterior hairline pattern, and anal anomalies in Manitoba Indians. *Am J Med Genet* 1992;42:793–9. [PubMed: 1554017]

McBratney BM, Margaryan E, Ma W, Urban Z, Lozanoff S. Frontonasal dysplasia in 3H1 Br/Br mice. *Anat Rec* 2003;271A:291–302.

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: 12766769]

Nouby G. Congenital upper eyelid coloboma and cryptophthalmos. *Ophthal Plast Reconstr Surg* 2002;18:373–7. [PubMed: 12352825]

Risheg H, Graham JM, Clark RD, Rogers RC, Opitz JM, Moeschler JB, Peiffer AP, May M, Joseph SM, Jones JR, Stevenson RE, Schwartz CE, Friez MJ. A recurrent mutation in MED12 leading to R961W causes Opitz-Kaveggia syndrome. *Nature Genet* 2007;39:451–3. [PubMed: 17334363]

Seah LL, Choo CT, Fong KS. Congenital upper lid colobomas: management and visual outcome. *Ophthal Plast Reconstr Surg* 2002;18:190–5. [PubMed: 12021649]

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: 12205104]

Slavotinek A, Li C, Sherr EH, Chudley AE. Mutation analysis of the FRAS1 gene demonstrates new mutations in a propositus with Fraser syndrome. *Am J Med Genet Part A* 2006;140A:1909–14.

Stoll C, Alembik Y, Dott B, Roth MP. Omphalocele and gastroschisis and associated malformations. *Am J Med Genet A* 2008;146:1280–5.

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: 15166289]

van Haelst MM, Scambler PJ. Fraser syndrome: a clinical study of 59 cases and evaluation of diagnostic criteria. *Am J Med Genet A* 2007;143A:3194–203. [PubMed: 18000968]

Verma AS, FitzPatrick DR. Anophthalmia and microphthalmia. *Orphanet J Rare Dis* 2007;2:47. [PubMed: 18039390]

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: 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: 15124102]

Chapter Notes

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