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

NLM Citation: Mavrogiannis LA, Wilkie AOM. Enlarged Parietal Foramina. 2004 Mar 30 [Updated 2019 Nov 27]. 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/

Enlarged Parietal Foramina

Synonym: Symmetric Parietal Foramina

Lampros A Mavrogiannis, MSc, DPhil[1] and Andrew OM Wilkie, MA, DM, FRCP[2]

Created: March 30, 2004; Updated: November 27, 2019.

Summary

Clinical characteristics

Enlarged parietal foramina are characteristic symmetric, paired radiolucencies of the parietal bones, located close to the intersection of the sagittal and lambdoid sutures, caused by deficient ossification around the parietal notch, which is normally obliterated by the fifth month of fetal development. Enlarged parietal foramina are usually asymptomatic. Meningeal, cortical, and vascular malformations of the posterior fossa occasionally accompany the bone defects and may predispose to epilepsy. In a minority of individuals, headaches, vomiting, or intense local pain are sometimes associated with the defects, especially on application of mild pressure to the unprotected cerebral cortex.

Diagnosis/testing

Typically oval or round, enlarged parietal foramina resemble a "pair of spectacles" on postero-anterior skull radiographs. They may be less apparent on lateral skull radiographs because the lucencies are projected obliquely through normal bone. In young children, the disorder may present as a persistently enlarged posterior fontanelle caused by a single large central parietal bone defect (cranium bifidum). 3D CT scanning using bone windows clearly reveals the defect. MRI is useful in defining associated intracranial anatomic changes. Heterozygous pathogenic variants in either *ALX4* or *MSX2* are established causes.

Management

Treatment of manifestations: Treatment is generally conservative. Persistent cranium bifidum may warrant operative closure. Associated headaches or seizures should be treated appropriately. The risk for penetrating injury to the brain is small but may cause anxiety; education of parents, teachers, and the affected child to avoid risky behaviors that could result in injury suffices in most circumstances.

Agents/circumstances to avoid: Contact sports in those with a persistent midline bony defect.

Author Affiliations: 1 Genetics Laboratory St James University Hospital Leeds, United Kingdom; Email: lampros.mavrogiannis@nhs.net. 2 University of Oxford Oxford, United Kingdom; Email: andrew.wilkie@imm.ox.ac.uk.

Genetic counseling

Enlarged parietal foramina are inherited in an autosomal dominant manner with high, but not complete, penetrance. Most individuals diagnosed with enlarged parietal foramina have an affected parent. The proportion of cases caused by *de novo* pathogenic variants appears to be small. Each child of an individual with enlarged parietal foramina has a 50% chance of inheriting the pathogenic variant. Detailed fetal ultrasound examination at 18 to 20 weeks' gestation can usually detect the defects in a fetus at risk; fetal MRI is also an option. When the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Enlarged parietal foramina **should be suspected** in individuals with the following clinical and imaging findings.

Clinical Findings

A flattened region behind the apex of the skull is apparent. The defects are often palpable as soft areas on physical examination, tending to be symmetric across the midline; the bony border may be palpable.

Imaging Findings

Radiographic findings. Enlarged parietal foramina are symmetric, paired radiolucencies of the parietal bones, located close to the intersection of the sagittal and lambdoid sutures. They are caused by deficient ossification around the parietal notch, which is normally obliterated by the fifth month during fetal development [Currarino 1976]. Typically oval or round, they resemble a "pair of spectacles" on postero-anterior skull radiographs. They may be less apparent on lateral skull radiographs because the lucencies are projected obliquely through normal bone.

3D CT scan. In young children, the disorder may present as a persistently enlarged posterior fontanelle caused by a single large central parietal bone defect (cranium bifidum). This tends to give a less characteristic appearance on plain skull radiography, especially in neonates, but 3D CT scanning using bone windows clearly reveals the defect.

MRI scan. Although less satisfactory than CT scanning for visualizing the bone defect, cranial MRI is superior for demonstrating localized and often subtle changes in the meningeal, vascular, and cortical structures.

Establishing the Diagnosis

The diagnosis of enlarged parietal foramina **is established** in a proband with compatible clinical and imaging findings, and on identification of a heterozygous pathogenic variant in *ALX4* or *MSX2* by molecular genetic testing (see Table 1), which can assist with identification of disorders that are either allelic (see Table 2) or in the differential diagnosis (Table 4).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) (Option 1) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) (Option 2). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

Option 1

When the **phenotypic and imaging findings suggest the diagnosis** of enlarged parietal foramina, a **multigene panel for craniofacial conditions** that includes *ALX4* and *MSX2* 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 [Lee et al 2018]. While a panel that is restricted to *ALX4* and *MSX2* could be used, broader testing may be clinically relevant. 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 panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the **diagnosis of enlarged parietal foramina is not considered** because an individual has atypical clinical and/or imaging findings, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used [Farwell et al 2015, Meng et al 2017]; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **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 Enlarged Parietal Foramina

Gene [1, 2]	Proportion of Enlarged Parietal Foramina Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ALX4	~70%	~90% [6]	~10% [6]
MSX2	~30%	~90% [6]	~10% [6]
Unknown [7]		NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. 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.
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. Excluding syndromic cases, sequence-level changes comprise the majority of pathogenic variants [Wilkie et al 2000; Wuyts et al 2000a; Wuyts et al 2000b; Mavrogiannis et al 2001; Spruijt et al 2005; Ghassibé et al 2006; Mavrogiannis et al 2006; Altunoglu et al 2014; Farwell et al 2015; Meng et al 2017; Lee et al 2018; T Lester & H Lord, unpublished data].
7. Very limited evidence for additional genetic heterogeneity exists (OMIM 609566) [Chen et al 2003].

Clinical Characteristics

Clinical Description

Isolated enlarged parietal foramina caused by a heterozygous *ALX4* or *MSX2* pathogenic variant are primary osseous defects that are usually asymptomatic. Enlarged parietal foramina / cranium bifidum may present as an unexpected finding on prenatal ultrasound examination, as a large posterior fontanelle in infancy, or as a coincidental finding on skull radiography in children or adults.

Cranium bifidum tends to resolve into distinct enlarged parietal foramina over the first few years of life through the midline ossification of a central bridge of bone bisecting the defect [Pang & Lin 1982, Little et al 1990]. A minor suture, perpendicular to the sagittal suture, often connects the two foramina, which tend to decrease in size with age but may persist throughout life.

Meningeal, cortical, and vascular malformations of the posterior fossa occasionally accompany the bone defects and may predispose to epilepsy [Preis et al 1995, Wuyts et al 2000b, Mavrogiannis et al 2001, Valente et al 2004, Valente & Valente 2004]. In a minority of individuals, headaches, vomiting, or intense local pain are sometimes associated with the defects, especially on application of mild pressure to the unprotected cerebral cortex [Pang & Lin 1982, Ghassibé et al 2006].

Scalp defects have been reported [Preis et al 1995, Wuyts et al 2000b].

A risk from direct trauma exists and skull fracture has been reported [Edwards et al 2012].

Features of the frontonasal dysplasia spectrum, ranging from almost inconspicuous to mild, may manifest in individuals with heterozygous *ALX4* pathogenic variants [Bertola et al 2013, Altunoglu et al 2014].

Genotype-Phenotype Correlations

With respect to the skull defects, no significant phenotypic differences exist between parietal foramina 1 and parietal foramina 2. Enlarged parietal foramina caused by *MSX2* and *ALX4* pathogenic variants are usually of similar size and clinically indistinguishable [Mavrogiannis et al 2006].

MSX2. No prominent genotype-phenotype correlation exists between different *MSX2* pathogenic loss-of-function variants causing enlarged parietal foramina. However, unique pathogenic variants in single families have been associated with aplasia cutis congenita [Preis et al 1995, Wuyts et al 2000b] and clavicular hypoplasia [Garcia-Miñaur et al 2003], possibly suggesting subtle dominant-negative effects.

ALX4. Heterozygous missense variants that tend to affect residues of the homeodomain or other complex pathogenic variants with potential for dominant-negative effects have been associated with clinical features in addition to parietal foramina, such as hypertelorism, nasal clefting and broad columella, sparse hair, thumb/hallux broadening, and genital abnormalities [Bertola et al 2013; Altunoglu et al 2014; A Fryer & T Lester, unpublished observations]. Although secondary and only documented in a few reports, these abnormalities suggest genuine overlap with *ALX4*-related frontonasal dysplasia, which is typically caused by biallelic pathogenic variants.

Penetrance

Penetrance for either an *MSX2* or *ALX4* heterozygous pathogenic variant is age related (as the relative width of the defects decreases with age) and high, but reduced (several individuals with a documented pathogenic variant showed no radiographic evidence of enlarged parietal foramina [Wilkie et al 2000, Mavrogiannis et al 2001, Mavrogiannis et al 2006]).

Nomenclature

Enlarged parietal foramina have been referred to using the obsolete eponymous label "Catlin mark." Other terms that may be encountered are "foramina parietalia permagna," "fenestrae parietales symmetricae," and "giant parietal foramina."

Prevalence

The prevalence of enlarged parietal foramina is in the range of 1:15,000 to 1:50,000 according to old surveys [Moore 1949, Lodge 1975].

Genetically Related (Allelic) Disorders

Contiguous gene deletions. Proximal 11p deletion syndrome (P11pDS) (Potocki-Shaffer syndrome [PSS]) is a rare contiguous gene deletion syndrome with enlarged parietal foramina and multiple exostoses as defining clinical features; intellectual disability and craniofacial dysmorphism are also frequently present (OMIM 601224) [Swarr et al 2010, Kim et al 2012]. Deletion events invariably remove *ALX4* and the adjacent gene, *EXT2* (see Hereditary Multiple Exostoses); *PHF21A*, which is variably deleted, is highly likely to account for the intellectual disability and facial dysmorphism.

Other phenotypes associated with germline pathogenic variants in *ALX4* and *MSX2* are summarized in Tables 2 and 3. Disorders included in Table 2 are associated with enlarged parietal foramina in addition to other clinical features and should be considered in the differential diagnosis.

Table 2. Allelic Disorders with Enlarged Parietal Foramina to Consider in the Differential Diagnosis

Gene	Disorder	MOI	Major Clinical Features
ALX4	*ALX4*-related frontonasal dysplasia [1] (OMIM 613451)	AR	• Median facial malformations of the frontonasal dysplasia type w/enlarged parietal foramina • Craniosynostosis, alopecia, cryptorchidism, brain abnormalities, & intellectual disability
MSX2	Parietal foramina w/cleidocranial dysplasia [2] (OMIM 168550)	AD	• Parietal foramina • Hypoplastic clavicles

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Reported mostly in consanguineous families with probands who are autozygous for nonsense or missense pathogenic variants [Kayserili et al 2009, Kayserili et al 2012, El-Ruby et al 2018]
2. Associated with an *MSX2* pathogenic variant in a single family [Garcia-Miñaur et al 2003]

Table 3. Other Allelic Disorders (not in the Differential Diagnosis)

Gene	Disorder	Reference
ALX4	*ALX4*-related craniosynostosis [1]	OMIM 615529
MSX2	*MSX2*-related craniosynostosis [2]	OMIM 604757
	MSX2-related classic cleidocranial dysplasia [3]	Ott et al [2012]

1. Single report of *ALX4* variants with postulated link to craniosynostosis susceptibility [Yagnik et al 2012]
2. Caused by specific missense pathogenic variants [Jabs et al 1993, Janssen et al 2013] and also associated with an additional copy of *MSX2* as a result of gross structural abnormalities [Kariminejad et al 2009]
3. Classic cleidocranial dysplasia associated with microduplications in noncoding regions upstream of *MSX2* [Ott et al 2012]

Differential Diagnosis

Isolated enlarged parietal foramina need to be distinguished from other causes of defective skull ossification including meningoencephalocele, ventricular, or arachnoid cyst; ectopic glial tissue; tumors; scalp defects; craniolacunae; osteoporosis; local inflammation; injury; and infections [Lodge 1975, Currarino 1976, Pang & Lin 1982].

Additionally, isolated enlarged parietal foramina need to be distinguished from unequivocal syndromic associations including those described in Table 4.

Table 4. Autosomal Dominant Syndromes with Enlarged Parietal Foramina to Consider in the Differential Diagnosis of Isolated Enlarged Parietal Foramina

Disorder	Gene(s) / Genetic Mechanism	Clinical Features
Potocki-Shaffer syndrome (OMIM 601224)	Proximal 11p deletion	See Genetically Related Disorders.
ALX4-related frontonasal dysplasia (OMIM 613451)	*ALX4*	
MSX2-related cleidocranial dysplasia (OMIM 168550)	*MSX2*	
Saethre-Chotzen syndrome	*TWIST1*	• Craniosynostosis syndrome characterized by coronal synostosis, facial asymmetry, ptosis, & distinctive appearance of the ear • Syndactyly of digits 2 & 3 of the hand variably present • Enlarged parietal foramina are a less common manifestation.
Acromelic frontonasal dysostosis (OMIM 603671)	*ZSWIM6*	• Severe frontonasal dysplasia & cranium bifidum / enlarged parietal foramina • Preaxial polydactyly • Cryptorchidism in males

CDAGS syndrome (craniofacial dysplasia with genitourinary and skin abnormalities; OMIM 603116) may also be considered. Consensus features of this rare autosomal recessive syndrome are coronal synostosis, wide fontanelles and enlarged parietal foramina, hypoplasia of the clavicles, imperforate anus, and skin eruptions. The respective locus has been mapped to chromosome 22q12-q13.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with enlarged parietal foramina / cranium bifidum, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Plain skull radiography
- 3D CT scan of the head with bone windows
- Brain imaging using CT or MRI scanning, if appropriate
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The management of enlarged parietal foramina is generally conservative. Although surgical closure of parietal bone defects has been advocated and performed [Kortesis et al 2003], its role is controversial. The procedure is

not likely to be routinely clinically indicated, given the benign natural history of the skull defects, their tendency to reduce in size with age, and uncertainty as to whether symptoms such as headaches are improved. However, persistent cranium bifidum may warrant operative closure [Perlyn et al 2005].

Associated headaches or seizures should be treated symptomatically.

The risk of penetrating injury to the brain is small but may cause anxiety. Education of parents, teachers, and the affected child to avoid risky behaviors suffices in most circumstances.

Agents/Circumstances to Avoid

Contact sports should be avoided if a midline bony defect persists.

Evaluation of Relatives at Risk

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

Pregnancy Management

When large skull defects are identified prenatally, consideration should be given to the planning of the delivery (e.g., review of indications to use scalp electrodes, forceps, and/or vacuum extraction). Elective cesarean section may reduce the theoretic risk for traumatic birth injury.

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

Isolated enlarged parietal foramina are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with enlarged parietal foramina have an affected parent.
- A proband with enlarged parietal foramina may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by *de novo* pathogenic variants appears to be small.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include physical examination, skull radiography, and molecular genetic testing if an *MSX2* or *ALX4* variant has been identified in the proband.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. While theoretically possible, no instances of germline mosaicism have been reported.

- The family history of some individuals diagnosed with enlarged parietal foramina may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and molecular genetic testing have been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *MSX2* or *ALX4* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *MSX2* or *ALX4* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *MSX2* or *ALX4* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for enlarged parietal foramina because of the possibility of reduced penetrance in a parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with enlarged parietal foramina has a 50% chance of inheriting the enlarged parietal foramina-related pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is either affected or has the pathogenic variant identified in the proband, other members of the parent's family are at risk.

Related Genetic Counseling Issues

When enlarged parietal foramina are ascertained in families with a background of consanguinity or endogamy, the risk for severe multiple malformations from homozygous *ALX4* (and theoretically *MSX2*) pathogenic variants should be considered (see Genetically Related Disorders).

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 or at risk.

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).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the enlarged parietal foramina-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic

testing are possible. However, given the usually benign prognosis, such requests are expected to be very infrequent.

Fetal imaging. Detailed fetal ultrasound examination at 18 to 20 weeks' gestation usually detects enlarged parietal foramina in a fetus at 50% prior risk; fetal MRI is also an option [Chung et al 2010, Saraç Sivrikoz et al 2016]. This information may be useful for delivery planning (see Pregnancy Management).

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. Enlarged Parietal Foramina: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ALX4	11p11.2	Homeobox protein aristaless-like 4	ALX4 database	ALX4	ALX4
MSX2	5q35.2	Homeobox protein MSX-2	MSX2 database	MSX2	MSX2

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 Enlarged Parietal Foramina (View All in OMIM)

123101	MSH HOMEOBOX 2; MSX2
168500	PARIETAL FORAMINA 1; PFM1
605420	ARISTALESS HOMEOBOX 4; ALX4
609597	PARIETAL FORAMINA 2; PFM2

Molecular Pathogenesis

ALX4 and *MSX2* encode members of the Alx and Msx homeodomain protein families required for diverse developmental processes. In humans, the skull appears to be particularly sensitive to their dosage. In the absence of *ALX4*, median facial development, hair follicle growth, and genital development are also affected.

Mechanism of disease causation. For both *ALX4* and *MSX2*, heterozygous whole-gene deletions, frameshift or nonsense variants anywhere in the coding region, and, to a degree, missense variants within the homeodomain are likely to result predominantly in loss of function and cause enlarged parietal foramina because of haploinsufficiency. Certain missense variants within the homeodomain or other complex changes, particularly in *ALX4*, may also have dominant-negative effects that could explain the broader phenotypes in heterozygosity (see Genetically Related Disorders). The *MSX2* missense variants in craniosynostosis involve a particular homeodomain residue; there is evidence that these stabilize DNA binding [Ma et al 1996].

Laboratory-specific technical considerations: *MSX2*. A processed pseudogene of *MSX2*, *MSX2P1*, resides on human chromosome 17q22, within an intron of the gene *OR4D1*.

Table 5. Enlarged Parietal Foramina: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
ALX4	NM_021926.4	c.646C>G	p.Arg216Gly	Assoc w/mild nasal clefting [Altunoglu et al 2014]
MSX2	NM_002449.4	c.443C>A	p.Pro148His	Assoc w/craniosynostosis [Jabs et al 1993]
		c.443C>T	p.Pro148Leu	Assoc w/craniosynostosis [Florisson et al 2013, Janssen et al 2013]

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. Genes are in alphabetic order.

Chapter Notes

Acknowledgments

We are grateful to Tracy Lester and Helen Lord at the Oxford Medical Genetics Laboratories for collating and providing clinical testing service data.

Revision History

- 27 November 2019 (bp) Comprehensive update posted live
- 8 November 2012 (me) Comprehensive update posted live
- 30 March 2010 (me) Comprehensive update posted live
- 25 May 2006 (me) Comprehensive update posted live
- 26 May 2004 (aw) Revision: prenatal testing availability
- 30 March 2004 (ca/me) Review posted live
- 13 January 2004 (aw) Original submission

References

Literature Cited

Altunoglu U, Satkın B, Uyguner ZO, Kayserili H. Mild nasal clefting may be predictive for ALX4 heterozygotes. Am J Med Genet A. 2014;164A:2054–8. PubMed PMID: 24764194.

Bertola DR, Rodrigues MG, Quaio CR, Kim CA, Passos-Bueno MR. Vertical transmission of a frontonasal phenotype caused by a novel ALX4 mutation. Am J Med Genet A. 2013;161A:600–4. PubMed PMID: 23401352.

Chen G, Zhang D, Feng G, Liu W, He L. A novel locus for parietal foramina maps to chromosome 4q21-q23. J Hum Genet. 2003;48:420–4. PubMed PMID: 12905082.

Chung HY, Uster-Friedberg T, Pentaz S, Blaser S, Murphy K, Chitayat D. Enlarged parietal foramina: findings on prenatal ultrasound and magnetic resonance imaging. Ultrasound Obstet Gynecol. 2010;36:521–2. PubMed PMID: 20586040.

Currarino G. Normal variants and congenital anomalies in the region of the obelion. AJR Am J Roentgenol. 1976;127:487–94. PubMed PMID: 183538.

Edwards LS, Sachs JR, Elster AD. Skull fractures through parietal foramina: report of two cases. J Comput Assist Tomogr. 2012;36:308–9. PubMed PMID: 22592614.

El-Ruby M, El-Din Fayez A, El-Dessouky SH, Aglan MS, Mazen I, Ismail N, Afifi HH, Eid MM, Mostafa MI, Mehrez MI, Khalil Y, Zaki MS, Gaber KR, Abdel-Hamid MS, Abdel-Salam GMH. Identification of a novel homozygous ALX4 mutation in two unrelated patients with frontonasal dysplasia type-2. Am J Med Genet A. 2018;176:1190–4. PubMed PMID: 29681084.

Farwell KD, Shahmirzadi L, El-Khechen D, Powis Z, Chao EC, Tippin Davis B, Baxter RM, Zeng W, Mroske C, Parra MC, Gandomi SK, Lu I, Li X, Lu H, Lu HM, Salvador D, Ruble D, Lao M, Fischbach S, Wen J, Lee S, Elliott A, Dunlop CL, Tang S. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genet Med. 2015;17:578–86. PubMed PMID: 25356970.

Florisson JM, Verkerk AJ, Huigh D, Hoogeboom AJ, Swagemakers S, Kremer A, Heijsman D, Lequin MH, Mathijssen IM, van der Spek PJ. Boston type craniosynostosis: report of a second mutation in MSX2. Am J Med Genet A. 2013;161A:2626–33. PubMed PMID: 23949913.

Garcia-Miñaur S, Mavrogiannis LA, Rannan-Eliya SV, Hendry MA, Liston WA, Porteous ME, Wilkie AO. Parietal foramina with cleidocranial dysplasia is caused by mutation in MSX2. Eur J Hum Genet. 2003;11:892–5. PubMed PMID: 14571277.

Ghassibé M, Bernier V, Boon LM, Vikkula M. A novel mutation in the MSX2 homeobox gene of a family with foramina parietalia permagna, headache and vascular anomaly. Eur J Pediatr. 2006;165:734–5. PubMed PMID: 16642368.

Jabs EW, Muller U, Li X, Ma L, Luo W, Haworth IS, Klisak I, Sparkes R, Warman ML, Mulliken JB, Snead ML, Maxsone R. A mutation in the homeodomain of the human MSX2 gene in a family affected with autosomal dominant craniosynostosis. Cell. 1993;75:443–50. PubMed PMID: 8106171.

Janssen A, Hosen MJ, Jeannin P, Coucke PJ, De Paepe A, Vanakker OM. Second family with the Boston-type craniosynostosis syndrome: novel mutation and expansion of the clinical spectrum. Am J Med Genet A. 2013;161A:2352–7. PubMed PMID: 23918290.

Kariminejad A, Kariminejad R, Tzschach A, Ullmann R, Ahmed A, Asghari-Roodsari A, Salehpour S, Afroozan F, Ropers HH, Kariminejad MH. Craniosynostosis in a patient with 2q37.3 deletion 5q34 duplication:

association of extra copy of MSX2 with craniosynostosis. Am J Med Genet A. 2009;149A:1544–9. PubMed PMID: 19533795.

Kayserili H, Altunoglu U, Ozgur H, Basaran S, Uyguner ZO. Mild nasal malformations and parietal foramina caused by homozygous ALX4 mutations. Am J Med Genet A. 2012;158A:236–44. PubMed PMID: 22140057.

Kayserili H, Uz E, Niessen C, Vargel I, Alanay Y, Tuncbilek G, Yigit G, Uyguner O, Candan S, Okur H, Kaygin S, Balci S, Mavili E, Alikasifoglu M, Haase I, Wollnik B, Akarsu NA. ALX4 dysfunction disrupts craniofacial and epidermal development. Hum Mol Genet. 2009;18:4357–66. PubMed PMID: 19692347.

Kim HG, Kim HT, Leach NT, Lan F, Ullmann R, Silahtaroglu A, Kurth I, Nowka A, Seong IS, Shen Y, Talkowski ME, Ruderfer D, Lee JH, Glotzbach C, Ha K, Kjaergaard S, Levin AV, Romeike BF, Kleefstra T, Bartsch O, Elsea SH, Jabs EW, Macdonald ME, Harris DJ, Quade BJ, Ropers HH, Shaffer LG, Kutsche K, Layman LC, Tommerup N, Kalscheuer VM, Shi Y, Morton CC, Kim CH, Gusella JF. Translocations disrupting PHF21A in the Potocki-Shaffer-syndrome region are associated with intellectual disability and craniofacial anomalies. Am J Hum Genet. 2012;91:56–72. PubMed PMID: 22770980.

Kortesis B, Richards T, David L, Glazier S, Argenta L. Surgical management of foramina parietalia permagna. J Craniofac Surg. 2003;14:538–44. PubMed PMID: 12867871.

Lee E, Le T, Zhu Y, Elakis G, Turner A, Lo W, Venselaar H, Verrenkamp CA, Snow N, Mowat D, Kirk EP, Sachdev R, Smith J, Brown NJ, Wallis M, Barnett C, McKenzie F, Freckmann ML, Collins F, Chopra M, Gregersen N, Hayes I, Rajagopalan S, Tan TY, Stark Z, Savarirayan R, Yeung A, Adès L, Gattas M, Gibson K, Gabbett M, Amor DJ, Lattanzi W, Boyd S, Haan E, Gianoutsos M, Cox TC, Buckley MF, Roscioli T. A craniosynostosis massively parallel sequencing panel study in 309 Australian and New Zealand patients: findings and recommendations. Genet Med. 2018;20:1061–8. PubMed PMID: 29215649.

Little BB, Knoll KA, Klein VR, Heller KB. Hereditary cranium bifidum and symmetric parietal foramina are the same entity. Am J Med Genet. 1990;35:453–8. PubMed PMID: 2185629.

Lodge T. Developmental defects in the cranial vault. Br J Radiol. 1975;48:421–34. PubMed PMID: 776315.

Ma L, Golden S, Wu L, Maxson R. The molecular basis of Boston-type craniosynostosis: the Pro148-->His mutation in the N-terminal arm of the MSX2 homeodomain stabilizes DNA binding without altering nucleotide sequence preferences. Hum Mol Genet. 1996;5:1915–20. PubMed PMID: 8968743.

Mavrogiannis LA, Antonopoulou I, Baxova A, Kutilek S, Kim CA, Sugayama SM, Salamanca A, Wall SA, Morriss-Kay GM, Wilkie AO. Haploinsufficiency of the human homeobox gene ALX4 causes skull ossification defects. Nat Genet. 2001;27:17–8. PubMed PMID: 11137991.

Mavrogiannis LA, Taylor IB, Davies SJ, Ramos FJ, Olivares JL, Wilkie AOM. Enlarged parietal foramina caused by mutations in the homeobox genes ALX4 and MSX2: from genotype to phenotype. Eur J Hum Genet. 2006;14:151–8. PubMed PMID: 16319823.

Meng L, Pammi M, Saronwala A, Magoulas P, Ghazi AR, Vetrini F, Zhang J, He W, Dharmadhikari AV, Qu C, Ward P, Braxton A, Narayanan S, Ge X, Tokita MJ, Santiago-Sim T, Dai H, Chiang T, Smith H, Azamian MS, Robak L, Bostwick BL, Schaaf CP, Potocki L, Scaglia F, Bacino CA, Hanchard NA, Wangler MF, Scott D, Brown C, Hu J, Belmont J, Burrage LC, Graham BH, Sutton VR, Craigen WJ, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, Muzny DM, Miller MJ, Wang X, Leduc MS, Xiao R, Liu P, Shaw C, Walkiewicz M, Bi W, Xia F, Lee B, Eng CM, Yang Y, Lalani SR. Use of exome sequencing for infants in intensive care units: ascertainment of severe single-gene disorders and effect on medical management. JAMA Pediatr. 2017;171:e173438. PubMed PMID: 28973083.

Moore S. On the Catlin mark. Am Antiquity. 1949;14:225–6.

Ott CE, Hein H, Lohan S, Hoogeboom J, Foulds N, Grünhagen J, Stricker S, Villavicencio-Lorini P, Klopocki E, Mundlos S. Microduplications upstream of MSX2 are associated with a phenocopy of cleidocranial dysplasia. J Med Genet. 2012;49:437–41. PubMed PMID: 22717651.

Pang D, Lin A. Symptomatic large parietal foramina. Neurosurgery. 1982;11:33–7. PubMed PMID: 7110564.

Perlyn CA, Schmelzer R, Govier D, Marsh JL. Congenital scalp and calvarial deficiencies: principles for classification and surgical management. Plast Reconstr Surg. 2005;115:1129–41. PubMed PMID: 15793456.

Preis S, Engelbrecht V, Lenard HG. Aplasia cutis congenita and enlarged parietal foramina (Catlin marks) in a family. Acta Paediatr. 1995;84:701–2. PubMed PMID: 7670261.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Saraç Sivrikoz T, Altunoglu U, Kalelioglu İH, Yüksel A, Uyguner OZ, Has R, Kayserili H. ALX4 related parietal foramina mimicking encephalocele in prenatal period. Prenat Diagn. 2016;36:591–3. PubMed PMID: 27080046.

Spruijt L, Verdyck P, Van Hul W, Wuyts W, de Die-Smulders C. A novel mutation in the MSX2 gene in a family with foramina parietalia permagna (FPP). Am J Med Genet A. 2005;139:45–7. PubMed PMID: 16222674.

Swarr DT, Bloom D, Lewis RA, Elenberg E, Friedman EM, Glotzbach C, Wissman SD, Shaffer LG, Potocki L. Potocki–Shaffer syndrome: comprehensive clinical assessment, review of the literature, and proposals for medical management. Am J Med Genet A. 2010;152A:565–72. PubMed PMID: 20140962.

Valente KD, Valente M. Epilepsy in one family with parietal foramina: an incidental finding? J Neurol Neurosurg Psychiatry. 2004;75:1648–9. PubMed PMID: 15489411.

Valente M, Valente KD, Sugayama SS, Kim CA. Malformation of cortical and vascular development in one family with parietal foramina determined by an ALX4 homeobox gene mutation. AJNR Am J Neuroradiol. 2004;25:1836–9. PubMed PMID: 15569759.

Wilkie AOM, Tang Z, Elanko N, Walsh S, Twigg SR, Hurst JA, Wall SA, Chrzanowska KH, Maxson RE Jr. Functional haploinsufficiency of the human homeobox gene MSX2 causes defects in skull ossification. Nat Genet. 2000;24:387–90. PubMed PMID: 10742103.

Wuyts W, Cleiren E, Homfray T, Rasore-Quartino A, Vanhoenacker F, Van Hul W. The ALX4 homeobox gene is mutated in patients with ossification defects of the skull (foramina parietalia permagna, OMIM 168500). J Med Genet. 2000a;37:916–20. PubMed PMID: 11106354.

Wuyts W, Reardon W, Preis S, Homfray T, Rasore-Quartino A, Christians H, Willems PJ, Van Hul W. Identification of mutations in the MSX2 homeobox gene in families affected with foramina parietalia permagna. Hum Mol Genet. 2000b;9:1251–5. PubMed PMID: 10767351.

Yagnik G, Ghuman A, Kim S, Stevens CG, Kimonis V, Stoler J, Sanchez-Lara PA, Bernstein JA, Naydenov C, Drissi H, Cunningham ML, Kim J, Boyadjiev SA. ALX4 gain-of-function mutations in nonsyndromic craniosynostosis. Hum Mutat. 2012; 2012;33:1626–9. PubMed PMID: 22829454.

License