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Enlarged Parietal Foramina

Synonym: Symmetric Parietal Foramina

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.

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 diagnosis of a pregnancy at increased risk and preimplantation genetic diagnosis 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 symmetrical across the midline, and 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, as above, 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 disorders (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 at the most reasonable cost 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 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 This Gene | Proportion of Pathogenic Variants ³ Detectable by This Method | |
|----------------------|---|--|--|
| | | Sequence analysis ⁴ | Gene-targeted deletion/duplication analysis ⁵ |
| <i>ALX4</i> | ~70% | ~90% ⁶ | ~10% ⁶ |
| <i>MSX2</i> | ~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. 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: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: 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 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 one in 15,000 to one in 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 |
|-------------|---|-----|---|
| <i>ALX4</i> | <i>ALX4</i> -related frontonasal dysplasia ¹ [OMIM 613451] | AR | <ul style="list-style-type: none"> Median facial malformations of the frontonasal dysplasia type with enlarged parietal foramina Craniosynostosis, alopecia, cryptorchidism, brain abnormalities, & intellectual disability |
| <i>MSX2</i> | Parietal foramina with cleidocranial dysplasia ² [OMIM 168550] | AD | <ul style="list-style-type: none"> 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 |
|-------------|---|-----------------------------|
| <i>ALX4</i> | <i>ALX4</i> -related craniosynostosis ¹ | OMIM 615529 |
| <i>MSX2</i> | <i>MSX2</i> -related craniosynostosis ² | OMIM 604757 |
| | <i>MSX2</i> -related classic cleidocranial dysplasia ³ | |

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 non-coding 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 | See Genetically Related Disorders |
| MSX2-related cleidocranial dysplasia [OMIM 168550] | MSX2 | See Genetically Related Disorders |
| Saethre-Chotzen syndrome [OMIM 101400] | TWIST1 | <ul style="list-style-type: none"> • Craniosynostosis syndrome characterized by coronal synostosis, facial asymmetry, ptosis, & a distinctive appearance of the ear • Syndactyly of digits 2 & 3 of the hand is variably present • Enlarged parietal foramina are a less common manifestation |
| Acromelic frontonasal dysostosis [OMIM 603671] | ZSWIM6 | <ul style="list-style-type: none"> • 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 evaluations summarized in this section (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 www.ClinicalTrialsRegister.eu in Europe for 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, 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.—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. Though 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 has 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 theoretical 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, his or her family members 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 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 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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

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 diagnosis 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 Sivriköz 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, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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](#).

AboutFace International

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

Children's Craniofacial Association (CCA)

13140 Coit Road
Suite 517
Dallas TX 75240
Phone: 800-535-3643 (toll-free)
Email: contactCCA@ccakids.com
www.ccakids.org

Molecular Genetics

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 | MUSCLE SEGMENT HOMEBOX, DROSOPHILA, HOMOLOG OF, 2; MSX2 |
|------------------------|---|

| | |
|------------------------|--|
| 168500 | PARIETAL FORAMINA 1; PFM1 |
| 605420 | ARISTALESS-LIKE 4, MOUSE, HOMOLOG OF; 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 (Allelic) Disorders). The *MSX2* missense variants in craniosynostosis involve a particular homeodomain residue; there is evidence that these stabilize DNA binding (Ma et al 1996).

Table 5. Enlarged Parietal Foramina: Gene-Specific Laboratory Technical Considerations

| Gene ¹ | Considerations |
|-------------------|---|
| <i>ALX4</i> | None |
| <i>MSX2</i> | A processed pseudogene of <i>MSX2</i> , <i>MSX2P1</i> , resides on human chromosome 17q22, within an intron of the gene, <i>OR4D1</i> |

1. Genes in alphabetic order.

Table 6. Enlarged Parietal Foramina: Notable Pathogenic Variants by Gene

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

Variants listed in the table have been provided by the author(s). *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 in alphabetic order.

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Chapter Notes

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