Bilateral Foramina Parietalia Permagna – A Calvarial Defect Caused by Haploinsufficiency of the Msh Homeobox 2 Gene: A Case Report and Current Literature Review

Niklas Kahl[1] Natalia Lüsebrink[1] Susanne Schubert-Bast[1] Thomas M. Freiman[2] Matthias Kieslich[1]

[1] Division of Neurology, Neurometabolics and Prevention, Department of Pediatrics, Goethe University Frankfurt, Frankfurt, Germany
[2] Department of Neurosurgery, Rostock University Medical Center, Rostock, Germany

Address for correspondence Niklas Kahl, BSc, Hengstbachstraße 3, 63303 Dreieich, Germany (e-mail: niklaskahl@stud.uni-frankfurt.de).

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Abstract

Foramina parietalia permagna (FPP) is a rare anatomical defect that affects the parietal bones of the human skull. FPP is characterized by symmetric perforations on either side of the skull, which are caused by insufficient ossification during embryogenesis. These openings are typically abnormally large and can range from a few millimeters to several centimeters in diameter. Enlarged foramina are often discovered incidentally during anatomical or radiological examinations and in most cases left untreated unless symptoms develop. Although this calvarial defect is usually asymptomatic, it may be accompanied by neurological or vascular conditions that can have clinical significance in certain cases. FPP is an inherited disorder and arises due to mutations in either Msh homeobox 2 (*MSX2*) or aristaless-like homeobox 4 (*ALX4*) genes. In almost all cases, one parent is affected. Clinical findings and diagnostic imaging typically contribute to determine the diagnosis.

Keywords
- foramina parietalia permagna
- MSX2
- parietal bones
- calvarial defect

Introduction

Foramina parietalia permagna (FPP) represents a rare and variable osseous defect of the posterior parietal bones that is caused by deficient ossification within the calvaria. These symmetric, oval-shaped openings are located bilaterally to the sagittal suture and are typically separated by a narrow midsagittal osseous bridge.[1,2] In normal conditions, the parietal bones are usually ossified by the fifth month of fetal development.[3] However, newborns with FPP exhibit enlarged foramina that progressively reduce in size during early childhood but frequently remain open.[3] In rare cases, these cranial defects may ossify completely.[4] Parietal foramina occur in various sizes with diameters ranging from a few millimeters to single-digit centimeters.[5] Small parietal foramina are considered normal variants, prevalent in about 60% of the population.[5,6] In contrast, enlarged parietal foramina represent a rare developmental ossification disorder with an estimated prevalence of 1 in 15,000 to 1 in 25,000.[5,7] To differentiate between small and enlarged parietal foramina, Reddy et al (2000) proposed a diagnostic reference value of 5 mm in diameter.[5] The inheritable trait of FPP was first indicated by Goldsmith (1922), who observed an increased occurrence of enlarged parietal foramina in the Catlin family.[8] And indeed, FPP is an autosomal dominant inherited disorder with high but incomplete penetrance, occurring in two primary forms: parietal foramina 1 (PFM1; OMIM #168500) and parietal foramina 2 (PFM2; OMIM #609597).[5,9] Both types exhibit similar prevalence and identical phenotypes—thus, they can only be distinguished at the

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Georg Thieme Verlag KG,
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molecular genetic level.[9] Enlarged parietal foramina result from heterozygous mutations either in Msh homeobox 2 (*MSX2*) or aristaless-like homeobox 4 (*ALX4*) genes, which encode for transcription factors that are crucial in the regulation of skeletal development.[9] Specifically, pathogenic variants in the *MSX2* locus on chromosome 5q35.2 are associated with PFM1, while PFM2 is linked to variants in the *ALX4* gene on chromosome 11p11.2.[9,10] A potential third PFM locus (PFM3; OMIM #609566) was reported by Chen et al (2003), caused by mutations in the PFM3 locus on chromosome 4q21-q23.[11] In terms of clinical characteristics, FPP is usually asymptomatic but occasionally accompanied by craniofacial, cerebrovascular, meningeal, or skeletal anomalies.[5] Rare manifestations include vomiting and seizures as well as severe headache and pain upon soft pressure application to the unprotected area.[3,7] To establish a definitive diagnosis of FPP, a thorough differential diagnosis is essential to exclude similar syndromes such as the Potocki–Shaffer's syndrome (OMIM #601224), MSX2-related cleidocranial dysplasia (OMIM #168550), or ALX4-related frontonasal dysplasia (OMIM #136760).[12–14] Additionally, a comprehensive evaluation should also consider other etiologies, including head injuries, infections, local trauma, and tumors.[5,7]

Case Report

We report the case of a female infant presenting cranial malformation and facial asymmetry after birth. The delivery succeeded in the 39th week of gestation, following a normal pregnancy. The presence of craniofacial abnormalities was accompanied by an occipital cephalhematoma resulting from vacuum-assisted delivery. No indications of intracerebral hemorrhages or cerebral dysplasia were recorded. At the age of 4 weeks, enlarged bilateral openings of the parietal bones were initially observed and documented during a routine pediatric examination. These symmetric cranial defects were identified proximate to the lambda and on either side of the sagittal suture. Additionally, focal protrusions of brain parenchyma were palpable, with only the scalp providing coverage and protection. At that time, the cranial oval openings measured 18 and 14 mm in diameter on the right and left sides, respectively. Initially, the clinical diagnosis suspected a bilateral diastasis of the lambdoid suture with prolapsing encephalocele. However, despite the severe symmetrical cranial dilations and focal protrusions, the patient's health condition appeared unremarkable, and neurodevelopmental deficits or additional malfunctions were not shown. None of the patient's parents and siblings exhibited clinical signs of cranial bone defects. Neither neurological disorders nor osseous abnormalities are registered in the patient's family history. In neuropediatric follow-up examinations, the posterior bilateral openings were constantly monitored and measured. At 17 weeks old, conducted sonographic imaging showed an increase in the size of the biparietal bone perforations, measuring 19 mm × 18 mm on the left side and 25 mm on the right side. Yet, the patient's health condition remained unaffected, and even a progressive decline of the bulges was noticed. At the age of 6 months, the parents agreed to further diagnostic imaging. Computed tomography imaging of the skull revealed that the biparietal openings had merged with the sagittal suture (►**Fig. 1A**). These findings provided additional evidence of insufficient ossification of the skull and indicated the presence of bilateral FPP. Subsequent molecular genetic testing confirmed the diagnosis of PFM1 by identifying a heterozygous missense mutation (c.515G > C, p.R172H) in exon 2 of the *MSX2* gene.

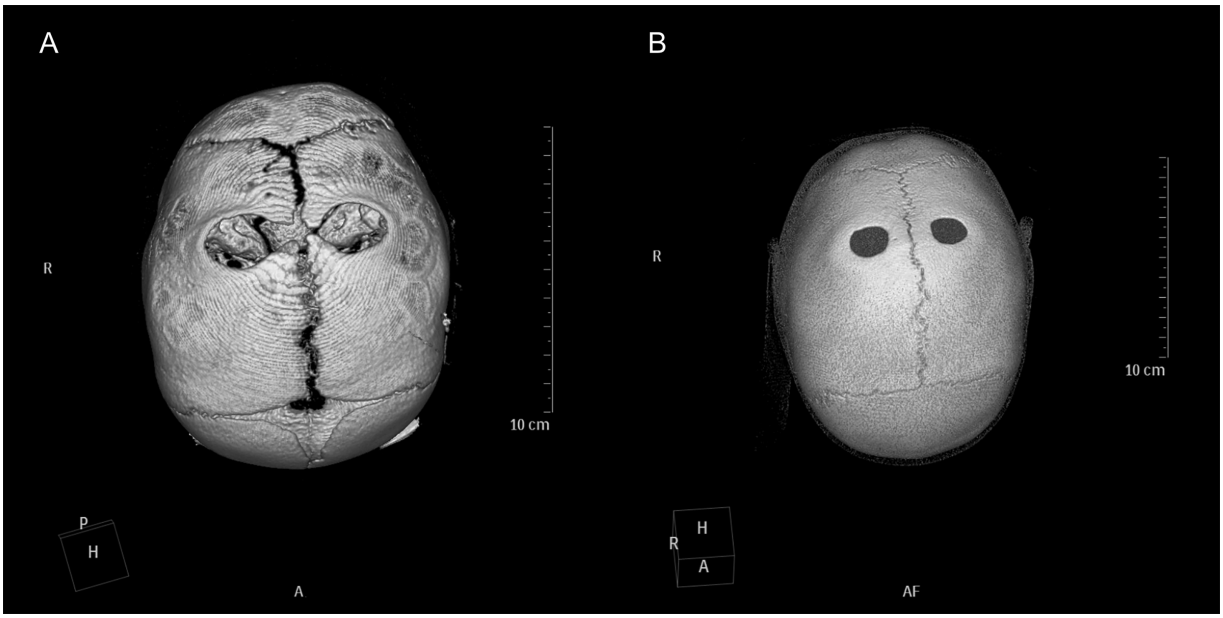

Fig. 1 Dorsal three-dimensional computed tomography images of the calvaria. (**A**) The initial image of bilateral enlarged parietal foramina. The foramina are merged with the sagittal suture. Coronal, lambdoidal, and sagittal sutures are not closed. The imaging was conducted at 6 months of age and the openings measured 32 and 28 mm on the right and left side, respectively. (**B**) Progressive ossification of the openings at age of 2 and half years with symmetrical size of 18 mm in diameter.

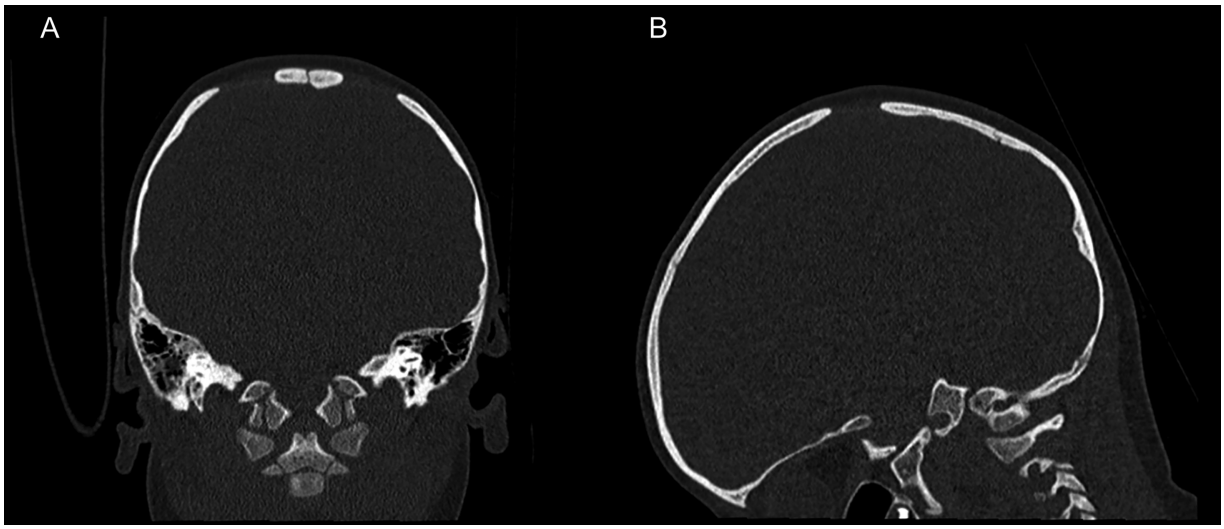

Fig. 2 Computed tomography images of the defective calvaria showing biparietal perforations at the age of 2 and half years. (**A**) Coronal view depicting the symmetrical voids that approach the midsagittal suture. (**B**) Sagittal image illustrating the posterior opening in the parietal bone measuring 16 mm in diameter.

Paternal genetic testing revealed that the father also possesses a pathogenic variant of the *MSX2* gene. In follow-up examinations, radiological studies showed a progressive decline of the biparietal openings and an age-appropriate growth of the calvaria (►**Figs. 1B** and **2**). Over a 20-month observation period, the patient's head circumference was regularly measured. It stabilized between the 10th and 25th percentiles of the growth curve, after initially ranging between the 3rd and 10th percentiles from birth to 17 weeks of age (►**Supplementary Fig. S1**, available in the online version). The patient remained asymptomatic with age-appropriate neurodevelopment. Clinical intervention was not necessary, and regular pediatric surveillance was arranged.

Discussion

FPP is a rare but well-recognized intramembranous ossification defect of the parietal bones in the human skull. Although most cases of FPP are asymptomatic and benign, it can have clinical significance in rare cases. Enlarged foramina may become symptomatic or be associated with other craniofacial anomalies and malformations of the surrounding tissue.[3,5] FPP is typically diagnosed in early childhood or during pregnancy by prenatal examinations.[3,15] In this context, physical and radiological examinations are decisive diagnostic tests to evaluate the degree of this osseous defect. Clinical observations determine clinical severity and contribute to discussion about medical interventions. During physical examinations, prolapsing areas and borders of the perforations are commonly palpable, while radiological studies assess the presence of defect-associated anomalies. Despite rare disease presentations, enlarged perforations in the skull should prompt clinicians to consider a differential diagnosis based on clinical and radiographic examinations. Moreover, it is important to recognize the genetic characteristics of FPP. A thorough understanding of molecular traits and adequate evaluation of clinical and radiological findings are essential for accurate diagnosis and prevention of intracerebral damage. In this report, we presented the case of a newborn girl with FPP, attributed to a known mutation in the *MSX2* gene.[10] Reduced levels of MSX2 due to loss-of-function mutations in the homeodomain affect craniofacial morphogenesis and contribute to FPP pathogenesis.[9,10] Given the hereditary nature of FPP, genetic analysis is advised for precise clinical diagnosis. In cases of unremarkable family history, physical examination of the patient's relatives with the possible addition of radiological imaging should be contemplated. The management of FPP is typically conservative.[3] However, surgical treatment may be necessary in severe cases of symptomatic patients or those with significantly enlarged and persistent foramina.[4] For instance, enlarged foramina with encephalocele can cause intracranial hypertension that may lead to focal vascular impairments and cerebral herniation.[4] High and persistent intracranial pressure may also impair and prevent ossification processes during early development. Surgical closure may be warranted in patients with an increased risk of intracranial injury. These include active and impulsive children or those who experience defect-associated symptoms such as seizures and epilepsy.[3,4] Therefore, it is crucial to evaluate each case individually to prevent malformations and neurological injuries, including secondary pressure lesions. In need of surgical intervention, cranioplasty is advocated using autologous or alloplastic bone grafts to correct cranial defects and minimize the risk of brain damage.[4,5]

Conclusion

Overall, clinical reports about FPP play a crucial role in establishing certain criteria for more precise clinical assessments and further contribute to enhance our understanding of this condition. The present case report emphasizes that conspicuously enlarged perforations in the skull may be associated with FPP, which can have clinical relevance in rare cases.

Conflict of Interest
None declared.

References

1 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(01): 45–47
2 Mupparapu M, Binder RE, Duarte F. Hereditary cranium bifidum persisting as enlarged parietal foramina (Catlin marks) on cephalometric radiographs. Am J Orthod Dentofacial Orthop 2006;129 (06):825–828
3 Griessenauer CJ, Veith P, Mortazavi MM, et al. Enlarged parietal foramina: a review of genetics, prognosis, radiology, and treatment. Childs Nerv Syst 2013;29(04):543–547
4 Kortesis B, Richards T, David L, Glazier S, Argenta L. Surgical management of foramina parietalia permagna. J Craniofac Surg 2003;14(04):538–544
5 Reddy AT, Hedlund GL, Percy AK. Enlarged parietal foramina: association with cerebral venous and cortical anomalies. Neurology 2000;54(05):1175–1178
6 Fein JM, Brinker RA. Evolution and significance of giant parietal foramina. Report of five cases in one family. J Neurosurg 1972;37 (04):487–492
7 Lodge T. Developmental defects in the cranial vault. Br J Radiol 1975;48(570):421–434
8 Goldsmith WM. "THE CATLIN MARK": the inheritance of an unusual opening in the parietal bones. J Hered 1922;13(02): 69–71
9 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(02):151–158
10 Wilkie AOM, Tang Z, Elanko N, et al. Functional haploinsufficiency of the human homeobox gene MSX2 causes defects in skull ossification. Nat Genet 2000;24(04):387–390
11 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 (08):420–424
12 Swarr DT, Bloom D, Lewis RA, et al. Potocki-Shaffer syndrome: comprehensive clinical assessment, review of the literature, and proposals for medical management. Am J Med Genet A 2010;152A (03):565–572
13 Garcia-Miñaur S, Mavrogiannis LA, Rannan-Eliya SV, et al. Parietal foramina with cleidocranial dysplasia is caused by mutation in MSX2. Eur J Hum Genet 2003;11(11):892–895
14 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(01):236–244
15 Chung HYB, 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(04):521–522

