Malformation of Cortical and Vascular Development in One Family with Parietal Foramina Determined by an ALX4 Homeobox Gene Mutation

Marcelo Valente, Kette D. Valente, Sofia S. M. Sugayama and Chong Ae Kim

http://www.ajnr.org/content/25/10/1836
Malformation of Cortical and Vascular Development in One Family with Parietal Foramina Determined by an ALX4 Homeobox Gene Mutation

Marcelo Valente, Kette D. Valente, Sofia S. M. Sugayama, Chong Ae Kim

Summary: Vascular and cortical anomalies have been found in a family with parietal foramina type 2 (PFM2), which is determined by the ALX4 gene. It is believed that ALX4 has a bone-restricted expression. We report a case of PFM with age-related size variation in a 4-year-old boy, as well as in his mother, aunt and grandfather. MR imaging of the child demonstrates prominent malformations of cortical (polymicrogyric cortex with an unusual infolding pattern) and vascular development (persistent median prosencephalic vein), associated with high tentorial incisure perialtrial white matter changes.

Parietal foramina (PFM; Online Mendelian Inheritance in Man accession number 168500) is a skull ossification disorder with symmetrical oval defects in the parietal bones separated by a narrow bone bridge. The size of the parietal foramina decreases with age, and intrafamilial variability is observed (1, 2). Heterozygous mutations of MSX2 homeobox gene (5q34–35; 3) and ALX4 homeobox gene (11p11–12; 4, 5) determine classification as PFM type 1 (PFM1) or PFM type 2 (PFM2). These mutations result in functional haploinsufficiency critical for human skull ossification, and to date PFM is known as a normal skull variant, not related to other abnormalities.

We describe malformations of vascular and cortical development with distinct degrees of severity in one affected family of PFM2 with an identified ALX4 homeodomain transcription factor mutation (653G→A encoding Arg218Gln). Molecular studies of this family were previously reported by Mavrogiannis et al (6).

Received December 22, 2003; accepted after revision March 5, 2004.

Author’s contributions: Study concept and design (M.V. and K.D.V.); data acquisition (M.V., K.D.V., and S.S.M.S.); data analysis and interpretation (M.V. and C.A.K.); drafting of the manuscript (K.D.V., M.V., C.A.K.); critical revision of the manuscript for important intellectual content (M.V. and C.A.K.); study supervision (M.V. and C.A.K.).

From the Pediatric Neuroradiology Division (M.V.) and Clinical Genetic Unit (S.S.M.S., C.A.K.), Department of Pediatrics; Division of Neuroradiology (M.V.), Department of Radiology; and Laboratory of Clinical Neurophysiology (M.D.V.), Department of Psychiatry, University of São Paulo School of Medicine, São Paulo, Brazil.

Address correspondence to Dr. Marcelo Valente, Rua Jesuino Arruda, 901, São Paulo, SP, Brazil CEP, 04532-082.

© American Society of Neuroradiology
Discussion

This study demonstrated the coexistence of vascular and cortical anomalies in three relatives with PFM2. The presence of very similar anomalies were previously documented by Reedy et al (7) and Sener (8), which corroborates the assumption that these are not incidental findings, but rather were identified because of neuroimaging advances. The study of three generations of one family and the determination of the type of PFM on genetic bases, not previously done by others (7, 8), are major aspects that may provide a better comprehension of the mechanisms that determine the presence and severity of these anomalies in patients with PFM. First, the occurrence of more severe clinical pictures with thrombosis, excessive bleeding during surgical procedures, and epilepsy in some cases of PFM may be explained by the generation-related gravity observed in this study, because the child was the most affected mem-

Fig 1. Pedigree of the affected family.

Fig 2. Neuroimaging studies of the affected family (III-2, II-4, and I-2). CT scan of the head with 3D cranial vault reformatations (CT3D); axial plane MR imaging without contrast enhancement (T1-weighted MR imaging) and MR venography (MRv).
ber of this family. In view of the genetic mechanism, recent observations suggested that *Alx4* and *Mx2* (ALX4 and MSX2 murine homologs) may play similar, but not identical, roles in transcriptional activation, leading to intramembranous ossification of the skull vault (10). To date, there is no evidence of a phenotype-genotype correlation based on published cases (3, 6, 10), although neuroimaging and electrophysiological studies of families with *MSX2* mutations (PFM1) would be of interest to clarify whether these neuroimaging and neurophysiological abnormalities are more frequent or restricted to PFM2.

It may be postulated that a mesenchymal disturbance could be the primary cause for these tentorial, vascular, and bone abnormalities. It is known that each parietal bone ossifies in a membranous pathway from two ossification centers that make their appearance during the 8th and 9th weeks of fetal life. One of these centers is located adjacent to the upper end of the sigmoid bend of the transverse sinus, close to the tentorial incisura. The tentorium is formed from a coalescence of left and right tentorial membranes that fuse in the midline at 3 months of intrauterine life (8). The falcine sinus, also developed from mesenchyme, is an embryonic vascular channel, originating at the level of the mesencephalic flexure, usually defined as a straight sinus precursor. It tends to close after birth but can be found later in life, and persistence has been associated with an underdeveloped straight sinus and dysplastic tentorium cerebri. Moreover, primitive veins of the posterior fossa have an ascending course in early stages of development. At 12 weeks of gestation, the straight sinus is relatively highly located and, with the increasing volume of the telencephalon, the area where the straight sinus joins the superior sagittal sinus gradually descends. The measurement of the base torcular angle by using fetal MR imaging showed that this angle gradually increases with gestational age (11).

What needs to be addressed is the inter-relationship between these anomalies and the malformation of cortical development in the occipital lobes, adjacent to these structures, as well as the role that *ALX4* plays in affecting this chain of events. Our current understanding is malformations of cortical development result from a multifactorial complex pathogenesis with interaction of genetic and environmental factors (12). The inconsistent overlap between cortical abnormalities and the vascular territories of the extrinsic vessels has always argued against a hemodynamic failure. In our case, there is a clear relationship between the abnormal cortex and the vascular abnormality. Thus, an interruption of blood supply during the embryonic period is feasible, although presumably influenced by genetic factors. These theories (vascular and genetic) are not necessarily contradictory, but might be additive. It is possible that the common pathogenetic mechanism is a genetic disorder of perfusion with varying penetration.

Size reduction, illustrated in III-2 and reported extensively in the literature, can be explained by a mechanical or disclosure type defect alone; however, the more prominent intracranial phenotype in the youngest generation, which suggests a generation-modulated expression of intracranial anomaly, is beyond this explanation.

It is known that mutations in mouse *Alx-4* affects the craniofacial mesenchyme during embryogenesis and is involved in skull development (10), substantiating the hypothesis that mesenchyme maturity is in some way disturbed when this gene is affected. It is possible that this specific timing and anatomic setting may link the *ALX4* homeobox to other clinical situations, especially those involving disorders of the skull vault ossification and vascular and cortical abnormalities. These mechanisms might be further considered.

---

**Fig 3.** CT3D - Patient III-2. Regressive size of the bone defects in time. CT scans at the ages of 3 months and at 2 years of age.
in other distinct syndromes in which pathogenic processes remain unclear.

Acknowledgments
We wish to thank Dr. Susan Baser for reviewing this manuscript and making valuable suggestions.

References