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SHORT REPORT

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A novel mutation in the *MSX2* homeobox gene of a family with foramina parietalia permagna, headache and vascular anomaly

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Enlarged parietal foramina (PFM, MIM 168500) are secondary to an ossification default of the parietal fontanelles. They are bilateral, situated on both sides of the sagittal suture. They can be more than 2 cm in diameter and are occasionally seen on a routine skull radiograph. They are of no pathological significance, but are clinically associated with headache, scalp defects and structural or vascular malformation of the brain [4, 5]. A surgical intervention is sometimes required. PFM is caused by haploinsufficiency of the *ALX*4 gene, being part of the DEFECT 11 syndrome (MIM 601224) [2] or due to mutations in *MSX*2 on *5q34-q35*. *MSX2* is an *MSX* homeobox transcription factor. *MSX*2 has been shown to be involved in craniofacial development. Msx2-deficient mice show defects of skull ossification and persistent calvarial foramen. Altogether, nine *MSX*2 loss-of-function mutations have been reported [1, 3, 6, 7].

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We studied a family with eight affected members showing cranial foramina associated with flash headaches and venous malformation (Fig. 1). Clinical examination and skull X-rays detected the presence of two symmetrical parietal foramen on each side of the sagittal suture in individuals VP-1, 3, 30, 31, 32 and 310. Moreover, VP-310 had a dilated vein on the right parietal part of the skull, arising from a right swelling of the vertex. Mild flash headaches from the right hole, often heat-dependent, were noted in individuals VP-1 and 3. VP-31 presented occasional painless flashes. Clinical examination of VP-11, 32, 311, 312, 313 and 314 did not show a foramen.

*MSX*2 screening revealed a 17-nucleotide duplication (CCTGGAGCGCAAGTTCC) in exon 2 for all affected individuals (Fig. 1). The *c.468-485dup* mutation occurs in helix I at the 21st amino acid of the DNA-binding domain of *MSX*2. It changes the open reading frame by abolishing 105 amino acids. In addition, it creates 23 new amino acids, followed by a premature stop codon. Co-segregation of the mutation was verified for all family members. It was not observed in 100 control alleles. This duplication results in protein-truncation and is consistent with *MSX*2 haploinsufficiency. Two protein-truncating duplications were previously identified. In one family, PFM was associated with cleidocranial dysplasia (PFMCCD, MIM168550) [1]. In the other, one individual had ventricular septal defect [3].

Interestingly, this is the first time that a mutation in the *MSX*2 gene is responsible for PFM associated with headache and venous anomaly, although the latter has been reported twice in clinical PFM cases [4, 5]. The presence of a venous anomaly underlying a skull defect raises the question whether *MSX*2 is directly linked to craniovascular development or whether the loss of parietal bone permits abnormal vascular morphogenesis. We need to identify the downstream targets of *MSX*2 and to characterise the associated cellular processes, including proliferation, apoptosis and cell adhesion, before we can understand how *MSX*2 dosage effect alters cranial bony and vascular development. Studying additional families is also important to evaluate the phenotype/genotype correlation.

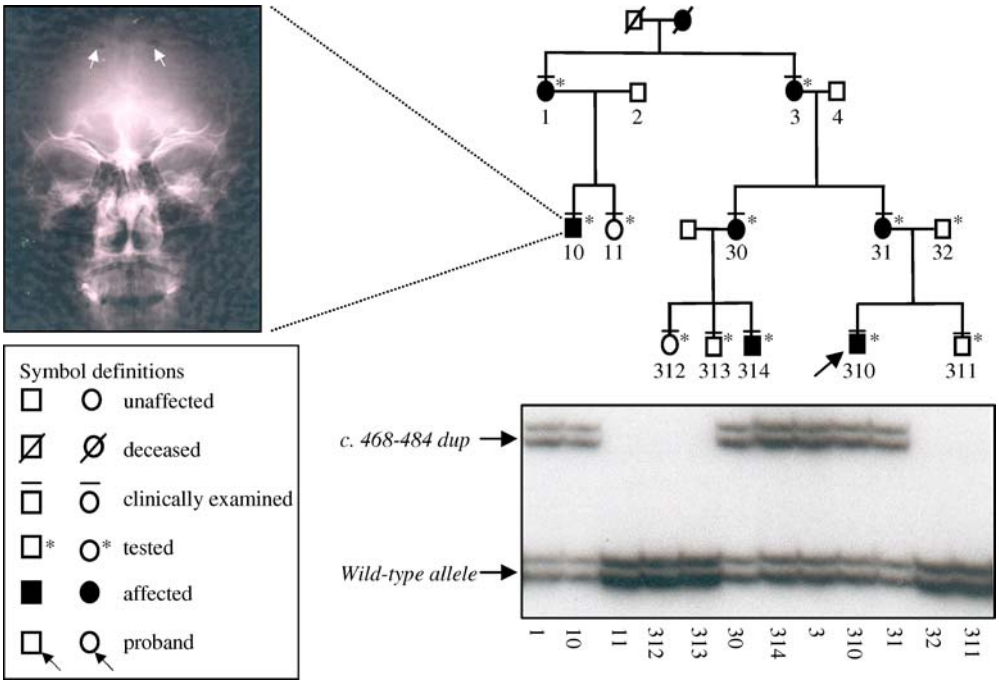

Fig. 1 Pedigree of the VP family with inherited foramina parietalia. Photograph of acrylamide gel showing segregation of allele harbouring duplication. Skull X-ray for individual VP-10 illustrates the presence of PFM (*arrows*)

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