LETTER TO JMG

Heterozygous P250L mutation of fibroblast growth factor receptor 3 in a case of isolated craniosynostosis

S Schindler, M Friedrich, H Wagener, B Lorenz, M N Preising

Craniosynostoses are caused by premature fusion of one or more sutures of the infant’s skull with an incidence between 1:1000 and 1:10 000. Isolated and syndromic forms can be differentiated and are involved in over 150 genetic disorders. Syndromic forms tend to be inherited and include variable other malformations of the extremities, the backbone, and the face. Isolated forms of craniosynostoses are often non-hereditary with closure of a single cranial suture. In most cases of syndromic craniosynostoses, multiple sutures are closed and often hydrocephalus and intracranial hyper-tension occurs. Mutations in the genes for fibroblast growth factor receptors (FGFR) 1, 2, and 3 have been associated with syndromic craniosynostoses in a variety of clinical phenotypes (table 1).

Muenke syndrome has been reported as syndromic craniosynostosis with unilateral or bilateral coronal synostosis, and minimal non-facial features. Muenke syndrome has been diagnosed in patients ascribed to different clinical entities, such as Saethre-Chotzen, Pfeiffer, Crouzon, and Jackson-Weiss syndromes. In these cases, a specific single mutation P250R (749C→G) was found in the FGFR3 gene, first described by Bellus et al. Patients show variable abnormalities on radiographs of the hands and feet, including thimble-like middle phalanges, coned epiphyses, and carpal and tarsal fusions, and in some cases brachydactyly. Sensorineural hearing loss has been described in approximately 30% of cases and developmental delay has rarely been found.

The P250R mutation is located in the linker region between the second and third extracellular Ig-like domains of the FGFR3 protein. The corresponding residues are mutated in two other FGFRs involved in craniosynostoses syndromes, FGFR1 (P252R, Pfeiffer syndrome4) and FGFR2 (P253R, Apert syndrome5). Moloney et al.6 stated that this mutation is due to somatic mosaics. Bone samples were stored at –80°C. For DNA preparation, the bone samples were deep frozen in liquid nitrogen and crushed in a mortar. The powder was extracted from bone samples obtained at suture surgery (fronto-orbital advancement) to avoid false negative results.
disclosed bilateral sectorial hypopigmentation of the upper show any abnormalities. Ophthalmoscopy at the same age of 4 because of the molecular genetic diagnosis but did not ing 15.2 cm from right to left and 17.5 cm from left to right. Asymmetry of the skull was obvious with diagonals measured circumference was 52 cm (slightly above the 97th centile). performed at the age of 3 years. At this age the patient's head plagiocephaly (fig 2A). A fronto-orbital advancement was with a minor blunt optic disc. Neuroimaging showed a unilat- the right inferior oblique eye muscle was diagnosed together ophthalmological examination, a V pattern and overactivity of tropia associated with a vertical deviation. On neuro-

was referred to the University of Regensburg because of exo-

forehead on the right side was diagnosed. At 18 months she months. A frontal bossing of the left side and flattened intracranial pressure had been found. On examination, she showed a prominent and large forehead, a slightly smaller right side of the face, and a slight facial scoliosis to the right (fig 2B). The ophthalmological examination showed an exophoria at near distances (~12.5). Radiographs of the hands and feet did not show any abnormalities.

DISCUSSION
The phenotype in the patient and her mother resembles the milder forms of Muenke syndrome. The mutation (P250L) affects a known mutation hot spot (749C) in FGFR3 and rein-
forces the conclusion of Moloney et al \(^1\) that 749C is a frequently mutated nucleotide of FGFR3 in craniosynostoses. The novel finding in this regard is that in addition to the well known P250R mutation, which underlies a separate entity of craniosynostoses called Muenke syndrome, \(^1\) the substitution of proline 250 by leucine causes a similar phenotype. Therefore, we agree that patients carrying mutations at P250 in FGFR3 should be considered as affected by Muenke syndrome. Expressivity may be mild (as in the index patient) or even minimal (as in the mother). Patients with isolated craniosynostosis should therefore be screened for mutations in the FGFR3 gene.

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