Letter to the Editor

Crouzon syndrome and Bent bone dysplasia associated with mutations at the same Tyr-381 residue in FGFR2 gene

To the Editor:

We report the identification of novel p.Tyr381Asn (c.1141T>A) mutation in FGFR2 gene in a family affected by Crouzon syndrome (MIM:123500). This mutation is located at the same residue than the mutation (p.Tyr381Asp, c.1141T>G) recently described in the perinatal lethal Bent bone dysplasia (BBD) (1). Crouzon syndrome was suspected in the proband at the age of 3 years. Birth parameters were weight: 2940 g, length: 46 cm, and head circumference: 37 cm. At the age of 3 years, he presented with a scaphocephaly with bilateral exophthalmos, parrot-beaked nose and frontal bossing (Fig. 1). A pronounced nasal obstruction with septal deviation and a malocclusion was observed. A skull computed tomography (CT) examination performed at the age of 5 years confirmed the closure of the sagittal suture (Fig. 1). A mild descent of the cerebellar tonsils was found at brain magnetic resonance (MR) imaging (Fig. 1); whereas the proband presented a typical Crouzon syndrome, the other family members (father and sister) displayed a milder phenotype with exophthalmos, hypertelorism and facial retrusion (Fig. 1). The father (28 years old) showed also an asymmetric dolichocephaly and moderated malocclusion. The sister (30 months old) was not dolichocephalic. However, in both cases, the CT examination showed the fusion of the sagittal suture (Fig. 1). No anomalies of the appendicular skeleton were found on X-ray examinations.

As usually described in Crouzon syndrome (2), an important clinical variability and high penetrance were

Fig. 1. Proband: computed tomography (CT) skull 3D reconstructions (a), sagittal T2-weighted magnetic resonance imaging (b), and frontal and lateral photography (c). CT examination of the sister (d) and father (e) of the proband. Frontal and lateral photography of the sister (f) and father (g) of the proband. Note the absence of sagittal suture and the mild craniofacial asymmetry of the father.
found in this family. All three members harboring the mutation p.Tyr381Asn presented a craniosynostosis with hypertelorism and exophthalmos but the typical facial dysmorphism (2) was only observed in the proband. His phenotype worsened in time, as usually observed in Crouzon syndrome, being only slightly visible at birth.

The p.Tyr381Asn (c.1141T>A) mutation was the only variant detected after the sequencing analysis of FGFR2 (IIIc spliceform) coding exons and adjacent intronic regions (cDNA reference sequence NM_000141.4) (Figure S1, Supporting Information). The variant was not found in 200 control chromosomes and not featured on the Exome Variant Server of over 13,000 alleles. The change is located in the transmembrane domain of FGFR2 and replaces a highly conserved hydrophobic residue with a polar uncharged amino acid (Alamut Software®), considered as probably damaging with the use of sequence homology-based program, Polymorphism Phenotype (PolyPhen) with a maximal score of 1. The transmembrane domain is conserved among mammalian fibroblast growth factor receptors (FGFR) (1–3) and the Tyr residue in 381 is common between FGFR (1–3) human and between the two major isoforms of FGFR2.

The majority of the mutations responsible for Crouzon syndrome are located in the exons 8 (IIIA) and 10 (IIIC) of FGFR2 corresponding to immunoglobulin domain. In the exactly same region of FGFR2, mutation may lead to other craniosynostosis syndromes, such as Apert (MIM:101200) or Pfeiffer (MIM:101600) syndrome, which may have overlapping features with Crouzon syndrome (3). Other regions of FGFR2 namely tyrosine kinase or immunoglobulin II domains have been rarely implicated in Crouzon syndrome (3). In transmembrane domain or in the C-terminal end of the linker region, mutations have been associated with the severe and rare Beare–Stevenson syndrome (MIM:1273790) and very recently to the perinatal lethal BBD (1) (MIM:614592). The fetus showing the BBD displayed a hypertelorism, micrognathia, micros- tomeia, low-set posteriorly rotated ears and a flattened midface, reduced mineralization of the calvaria, coronal craniosynostosis, hypoplastic clavicle, Bent long bones in the lower extremities and hypoplastic pubis and abnormal phalanges. Compared to that description, the phenotype in our three cases is milder. Interestingly, none of them presented lower limb, claviculae or hand anomalies.

Also, the p.Tyr381Asp mutation responsible for the BBD abolished the FGFR2 transmembrane topology (1) at the difference of Asn change which had no impact by using transmembrane prediction based on hidden Markov models (TMHMM) online prediction software. Besides, the difference of the negatively charged carboxyl groups on aspartic acid and the polar uncharged side chains of Asparagine in transmembrane domain could modify differently the ligand-independent activation of the dimer or its stabilization (4). Consequently, the two mutations could lead to a different level of the phosphorylation of the tyrosine kinase domain (5) and may affect the severity of the phenotype.

Supporting Information
The following Supporting information is available for this article:

Figure S1: Chromatogram showing the FGFR2 missense mutation p.Tyr381Asn (c.1141T>A) in heterozygous state in proband of his father and his sister.

Additional Supporting information may be found in the online version of this article.

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References

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