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A New Case of Syndromic Craniosynostosis With Cryptic 19p13.2–p13.13 Deletion

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TO THE EDITOR:

Syndromic craniosynostosis is associated with various manifestations primarily involving osseous defects and neurological impairment. Up to 180 distinct syndromes have been associated with craniosynostosis and the identification of underlying genetic defects is continually improving [Kimonis et al., 2007]. Mutations in genes of the FGFR family are most common and account for various clinical conditions [Arlt, 2007; Wilkie et al., 2007], while other well-characterized mutations involving TWIST1 [El Ghouzzi et al., 1997], RAB23 [Jenkins et al., 2007], EFNBI [Wieland et al., 2004], or MSX2 genes [Jabs et al., 1993] have been described. In these cases, one single gene mutation can generate various clinical phenotypes, or inversely, a single phenotype (e.g., craniosynostosis) can correspond to several gene mutations. Additionally, a large number of chromosomal deletions or duplications have been related to syndromic craniosynostosis, including del(7p) [Chotai et al., 1994], del(9p) [Alfi et al., 1976], del(11q) [Lewanda et al., 1995], del(15q) [Hiraki et al., 2008], and dup(5q) [Breslau-Siderius et al., 1993]. However, the clinical significance of these large chromosomal aberrations is often difficult to extrapolate due to variability in the size of the genetic region involved and in the corresponding clinical presentation. Here, we describe for the first time an interstitial 19p13.2–p13.13 deletion associated with complex craniosynostosis, developmental delay, and malformations.

The present case is the fourth child of unrelated healthy parents and the only affected child. Family history is unremarkable except for one miscarriage and one vanishing twin during propositus’ pregnancy. The antenatal period was characterized by a third trimester ultrasound showing nuchal translucency at 80th centile and intrauterine growth retardation associated with umbilical arterial thrombosis. Ultrasound was otherwise normal. The patient was delivered by cesarean at 36 weeks 6/7, weighing 1,800 g and measuring 43 cm (both below −2 SD); the head circumference was 30.5 cm (−2 SD). She was admitted to the neonatal care center for respiratory distress. Clinical examination revealed general hypotonia and anomalies, including hypoplasia of the left orbit and a prominent frontal bone bulge (Fig. 1A), hypertelorism, proptosis, strabismus, small nose with low nasal bridge, low set ears with underfolded superior helix (Fig. 1B–D), deep skin folds on the hands and feet, arthrogryposis of the lower limbs, and clinodactyly of the fifth finger and third toe (Fig. 1E,F) with an increased space between the first and second toe. Chest examination revealed a systolic murmur and an atrial septal defect was diagnosed by echocardiogram. Cerebral three-dimensional computed tomography scan showed a complex craniosynostosis with fusion of the left coronal, lambdoid, and parieto-temporal sutures together with left sphenoid-orbital dysplasia (Fig. 1II). Moderate ventriculomegaly was noted on cerebral magnetic resonance imaging. Retinal inspection was normal but neurophysiological examination revealed a hearing threshold of 60 dB in both ears, while electroencephalography showed a too large proportion of slow elements. At 4 months, facial asymmetry increased with deformation of the left hemi-mandible and orbit. The patient’s psycho-motor development was delayed at 6 months with a lack of visual contact.

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FIG. 1. Photographs and skull imaging of the patient. I: Appearance of the face (A, frontal view) and the right ear horn (B) of the propositus at birth. Aspect of the head (C, frontal view; D, right profile) and of the right hand (E, dorsal face) at 1 year old. Medial side of left foot at 3 years old (F). II: Cerebral three-dimensional computed tomography scan showing skull deformation on the left side with left orbitary hypoplasia and left posterior plagiocephaly. Craniosynostosis was remarked at the level of left coronal, parieto-temporal and lambdoid sutures. Partial craniosynostosis could also be identified at the level of left sphenosquamous and sphenofrontal sutures. Digitiform imprints were noticed in the left parieto-temporal region. Pictures show front (A), back (B), left (C), and right (D) views of the skull.
FIG. 2. Interstitial deletion from 19p13.2 to 19p13.13 detected by aCGH and FISH. A: Representation of normalized aCGH data for the whole chromosome 19 (I). Only probes with a copy number ratio $\geq 0.5$ are represented by green dots (negative copy number ratio) or red dots (positive copy number ratio). Positive regions were considered only with more than three consecutive abnormal dots. The moving average (purple line) based on the Cy3:Cy5 ratio of fluorescence intensity of each probe shows a leftward deviation from the central axis at 19p13.2–p13.13 bands, revealing the interstitial deletion. Identical representation with enlargement of the deleted segment (II). B: FISH analysis of the 19p13.13–p13.2 deletion. Spectrum-green labeled BAC clones RP11-91021 (I) and RP11-19I2 (II), mapped on 19p13.2, were hybridized with a spectrum-orange labeled T19q subtelomeric probe used for identification of chromosomes 19. Arrow points to the green signal on normal chromosome 19 and arrowhead indicates the absence of green signal on chromosome del(19)(p13.13p13.2), confirming aCGH results.
and weight and head circumference remaining at −2 SD. Furthermore, she had a considerable degree of kyphosis. At 1 year, she underwent surgery for correction of the craniosynostosis by opening of the prematurely fused sutures. Following surgery, the craniofacial manifestations improved rapidly but neurological skills did not evolve similarly. The patient was able to sit at the age of 15 months and stood with help at 33 months. Currently, at 3 years and 8 months of age, the patient still has no language acquisition. She weighs 12.3 kg (−3.4 SD), is 104 cm in height (−0.9 SD) and has a head circumference of 49 cm (−0.7 SD).

Neurofibromatosis type 1 was excluded by absence of the NF1 gene mutation. Testing was negative for TWIST1 and FGFR3 craniosynostosis gene mutations. Testing for a TWIST-1 gene defect by MLPA was negative and no mutation (P250R) in exon 7 of the FGFR3 gene was detected. The presence of a constitutional chromosomal abnormality was investigated by conventional G-banding karyotype but was apparently normal (46 XX; 550-band resolution). We then performed an array comparative genomic hybridization (aCGH) analysis on Agilent 44K-array following the manufacturer’s instructions and the data were analyzed with their Feature Extraction 9.1 software. Data were then processed with the Agilent CGH Analytics 3.4 software using the z-score statistical algorithm (sensitivity threshold set at 2.5 and moving average window at 2.0 Mb). A 3-Mbp interstitial deletion was detected on chromosomal bands 19p13.2–19p13.13 (NCBI Build 36.1), with the distal breakpoint between chr19:10,246,651 and 10,256,871 bp and the proximal breakpoint between chr19:13,188,698 and 13,280,203 bp (Fig. 2A). The deleted sequences were carefully analyzed for segmental duplications using the website from Toronto University (http://projects.tcag.ca), which found no evidence that this region is located within duplicons that allow recombination (duplication/deletion) events. This chromosomal region contains 114 genes/ESTs between the ICAM1 and CACNA1A genes.

To validate this observation, fluorescent in situ hybridization (FISH) analysis was carried out using 19p13.2-mapped BAC probes following standard labeling and hybridization protocols. The fluorescent signal of BACs was absent on one of the two FISH signals on one of the two metaphases. 

ICAM1 and CACNA1A genes represent a critical etiology in this particular phenotype. To our knowledge, craniosynostosis has never been reported in association with chromosome 19 imbalances. However, the lack of distinguishable traits of these patients in these studies present common traits with two other cases reported without craniosynostosis [Hurgouiu and Suciu, 1984; Archer et al., 2005].

The chromosomal segment detected in our patient contains the DAND5 and CALR genes, both involved in the metabolism of bone morphogenesis or osteoblastic cells, suggesting that one or both are potentially involved in the craniosynostosis. In particular, the DAND5 gene encodes a member of the BMP (bone morphogenic protein) antagonist family and has been shown to regulate tissue differentiation [Asavian–Kretchmer and Hsueh, 2004; Marques et al., 2004]. The CALR (calreticulin) gene encodes a chaperone protein mediating the attenuating effect of glucocorticoids in Wnt signaling in osteoblastic cells, thereby plays an important role in controlling osteoblastogenesis [Oikku and Mahonen, 2009]. However, because our case represents a currently isolated report of copy number variation in the 19p13.2p13.1 region associated with craniosynostosis, it is possible that this phenotype occurred by chance or is due to a multi-gene effect associated with several of the numerous genes included in the deletion. Moreover, the lack of craniosynostosis in two other patients carrying the commonly deleted region might also be due to lower penetrance of the same hemizygote gene.

In the syndromic forms of craniosynostosis, gene mutations account for ~25% of cases [Wilkie et al., 2007] and, using karyotyping and molecular genetic techniques, causative chromosomal imbalances have recently been detected in 19/45 patients (42%) [Jehee et al., 2008]. These results indicate that genetic anomalies represent a critical etiology in this particular phenotype. To our knowledge, craniosynostosis has never been reported in association with chromosome 19 imbalances. However, the lack of distinguishable bands on this chromosome may have prevented the detection of aberrations in previous karyotyping studies. Using aCGH, we were able to show an interstitial 19p13.2–p13.13 deletion for the first time associated with syndromic craniosynostosis, pointing to an important new craniosynostosis locus.

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