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Clinical report

A novel heterozygous mutation of three consecutive nucleotides causing Apert syndrome in a Congolese family

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ABSTRACT

Apert syndrome (OMIM 101200) is a rare genetic condition characterized by craniosynostosis and syndactyly of hands and feet with clinical variability. Two single nucleotides mutations in the linker region between the immunoglobulin-like domains II and IIIa of the ectodomainin the Fibroblast Growth Factor Receptor 2 gene (*FGFR2*, OMIM 176943) are responsible of the vast majority of cases: c.755C > G; p.Ser252Trp (65%) and c.758C > G; p.Pro253Arg (34%. Three exceptional cases carry multiple substitutions of adjacent nucleotides in the linker region.

Here we present a Congolese male patient and his mother, both affected with Apert syndrome of variable severity, carrying a previously undescribed heterozygous mutation of three consecutive nucleotides (c.756_758delGCCinsCTT) in the IgII–IgIIIa linker region. This is the fourth live-born patient to carry a multiple nucleotide substitution in the linker region and is the second alternative amino acid substitutions of the Pro253. Remarkably, this novel mutation was detected in the first Central African patient ever to be tested molecularly for the Apert syndrome. To discriminate between a hitherto unreported mutation and an ethnic specific polymorphism, we tested 105 Congolese controls, and no variation was detected.

1. Introduction

Apert syndrome (OMIM 101200) is a rare genetic condition with an estimated prevalence of ~1 in 70,000 live births and presenting craniosynostosis (premature and antenatal fusion of skull sutures) associated with syndactyly of hands and feet [Bochukova et al., 2009; Ibrahimi et al., 2001]. The phenotype can be variable, both regarding to the severity of the acrocephalosyndactyly or to the presence of additional manifestations (such as cleft palate or intellectual disability) [Lajeunie et al., 1999; Mundhofir et al., 2013; Oldridge et al., 1997; Park et al., 1995]. However, this variability cannot readily be explained by the underlying causal mutations. Indeed, majority of patients present with single nucleotide substitution in the linker region between the immunoglobulin-like domains II and IIIa (IgII and IgIIIa) of the ectodomain of the Fibroblast Growth Factor Receptor 2 (*FGFR2*, OMIM 176943) [Lajeunie et al., 1999; Oldridge et al., 1997; Sakai et al., 2001; Wilkie et al., 1995]. Consistent with other paternal age effect mutations, those causing AS exclusively originate during spermatogenesis, have a gain-of-function (GOF) effect and exhibit a remarkable enrichment in spermatogonia with ageing due to a protein-driven selective advantage from the mutant protein [Bochukova et al., 2009; Goriely et al., 2005; Goriely and Wilkie, 2012; Ibrahimi et al., 2001; Risch et al., 1987]. As expected for any

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GOF mutation, the repertoire of mutations causing AS is limited. Two single nucleotide substitutions in the *FGFR2* gene, c.755C > G; p.Ser252Trp (65%) and c.758C > G; p.Pro253Arg (34%), are recurrent in Apert Syndrome [Lajeunie et al., 1999].

Besides the two canonical single nucleotide mutations, rare consecutive double nucleotide substitutions involving the CpG dinucleotide at position 755_756 and changing Ser252 into Phenylalanine (c.755_756delCGinsTT; p.Ser252Phe and c.755_756delCGinsTC; p.Ser252Phe) have been reported in Apert syndrome [Goriely et al., 2005; Lajeunie et al., 1999; Oldridge et al., 1997]. The rarity of p.Ser252Phe mutation is ascribed to the requirement that two consecutive nucleotides of the Serine at codon 252 need to be mutated [Goriely et al., 2005].

Oldridge et al. reported the only patient carrying consecutive triple nucleotide substitutions in the linker region (c.755_757delCGCinsTCT) resulting in the change in two consecutive amino acids (Ser252Phe and Pro253Ser). Although Ser252Phe substitution is known to cause Apert syndrome, the patient carrying both Ser252Phe and Pro253Ser substitutions presented with the less severe Pfeiffer syndrome [Kan et al., 2002; Oldridge et al., 1997].

Here we report a male patient and his mother, both affected with Apert syndrome, carrying a new heterozygous mutation and showing variable expression.

2. Clinical report

2.1. Case descriptions

A 42-day-old Congolese male infant was referred to genetic consultation at the University Hospitals, University of Kinshasa because of congenital malformations. He was the only child of unrelated parents and was born after an uneventful pregnancy and delivery. At birth, he presented with craniofacial and limb anomalies (Fig. 1). At the time of consultation, his weight was 7.7 kg (P90), length 68 cm (P97 = 67.5 cm) and OFC 41 cm (P75-90). Craniofacial anomalies included craniosynostosis, midfacial retrusion, mild proptosis, hypertelorism, strabismus and tented upper lip (Fig. 1A and B). The ears were mildly low set with overfolded helices. There was a bilateral symmetric type 2 hand syndactyly, according to the classification by Cohen and Kreiborg [1995], and bilateral post-axial polydactyly. His feet showed bilateral and symmetrical type 1 feet syndactyly [Cohen and Kreiborg, 1995]. The palate was normal.

The 44-year-old father, unavailable for clinical examination, was reported to have normal development and to be free of obvious malformations. The index's mother was born from a 49 years old father and was 33 years old when she gave birth to the index. She had mild intellectual disability, OFC of 53 cm (P10), length of 176 cm

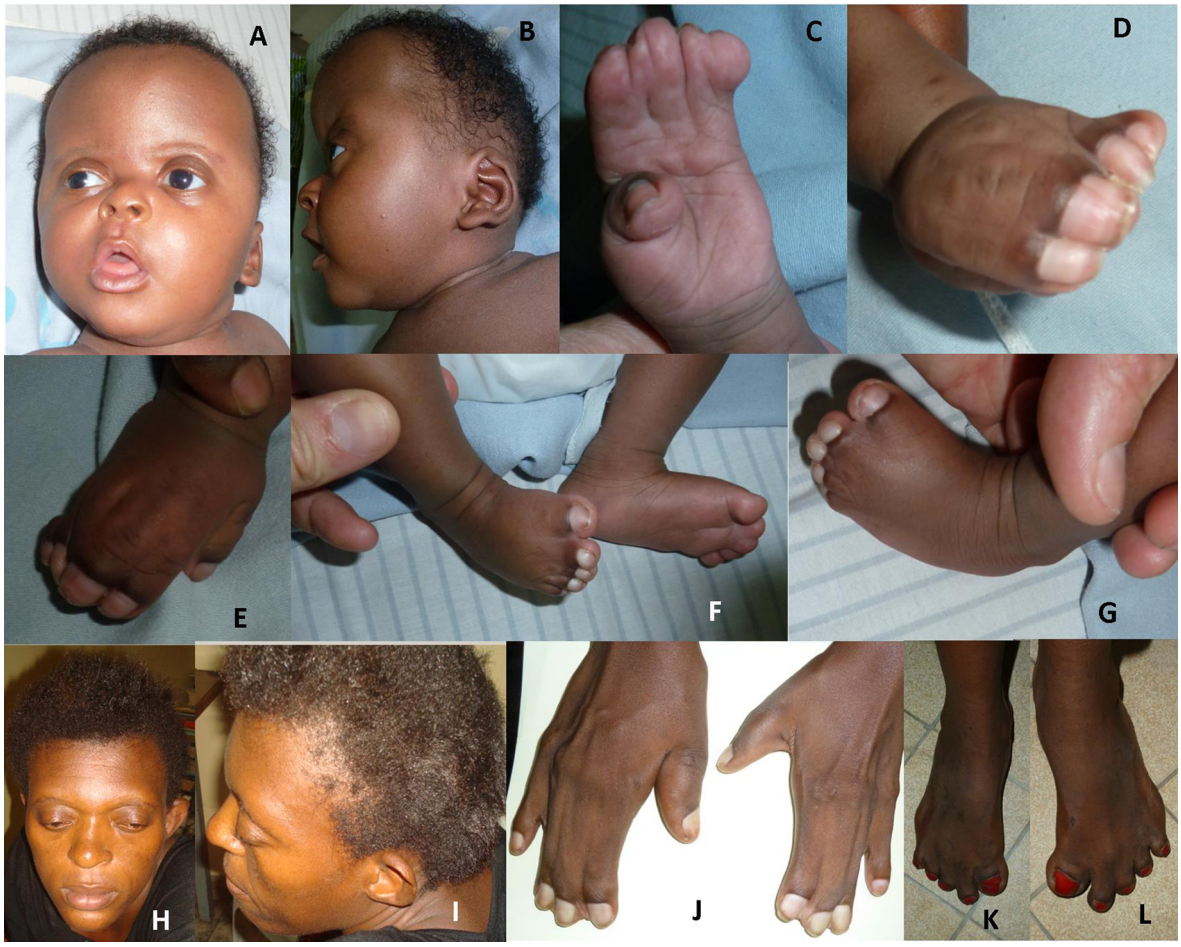

Fig. 1. Photographs of patients. Legend: **A**–**G**: index. **A** & **B**: Frontal and lateral view of the index: note prominent front, depressed midface, exophthalmos, hypertelorism, strabismus, overfolded helix, anteriorly rotated lobule and low set ears, tented upper lip, oxycephalic skull; **C, D** & **E**: Index's hands. Note abnormal position of the thumb and syndactyly of fingers II–IV; **F&G**: index's feet with bilateral syndactyly of toes; **H**–**L**: index's mother. **H&I**: frontal and lateral view of the mother's head. No major skull malformations observed. Note exophthalmos, protruding ears with unfolded helix; **J**: bilateral syndactyly of fingers II–V; **K&L**: toe syndactyly on right and left foot.