Clinical Brief

Novel *CHD7* and *FBN1* Mutations in an Infant with Multiple Congenital Anamolies

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ABSTRACT

The first case of an infant with a dual genetic diagnosis of CHARGE and Marfan syndrome is reported here. The patient had multiple congenital anamolies, many of them consistent with CHARGE syndrome and genetic testing identified a heterozygous mutation c.3806_11del6insA in the CHD7 gene. In addition, his father had physical features consistent with Marfan syndrome. Fibrillin-1 (FBN1) mutation screening identified a heterozygous c.3990insC mutation in both father and the patient. **[Indian J Pediatr 2010; 77 (2) : 208-209]** *Email: pankaj.agrawal@childrens.harvard.edu*

Key words: *CHARGE syndrome; CHD7; FBN1; Marfan syndrome*

CHARGE syndrome (MIM 214800) is characterized by a constellation of clinical findings that include coloboma, choanal atresia, cranial nerve dysfunction, ear abnormalities, genital hypoplasia, cardiovascular malformations, growth deficiency and tracheoesophageal fistula.[1] The syndrome was first reported in 1979. Since then, clinical findings associated with this syndrome have been extensively described and in 2004, heterozygous mutations in the *CHD7* gene were identified *CHD7* mutations are responsible for about 60% of the cases with CHARGE syndrome. *FBN1* is the only gene known to be associated with Marfan syndrome (MS) and mutations of this gene are responsible for 70-93% of the cases.[3] Here is reported the first case of an infant with multiple congenital anamolies carrying heterozygous mutations of both the *CHD7* and *FBN1* genes.

REPORT OF CASE

The male patient was born at 37 wk gestation. The pregnancy was complicated by polyhydramnios and fetal growth restriction. At birth, he was noted to have multiple congenital anomalies that included crumpled ears, left facial palsy, micropenis, and long fingers and toes (Fig. 1a-c). Birth weight was 2.035 kg, height 43 cm and head circumference 31 cm. Excessive oral secretions and inability to pass a nasogastric tube in stomach raised suspicion for esophageal atresia (EA). Radiographic findings were consistent with EA and tracheoesophageal fistula (TEF). His echocardiogram revealed bicuspid aortic valves, atrial septal defect, patent ductus arteriosus, and a left-sided aortic arch with an aberrant right subclavian artery. He underwent repair of EA/TEF on day of life (DoL) 2.

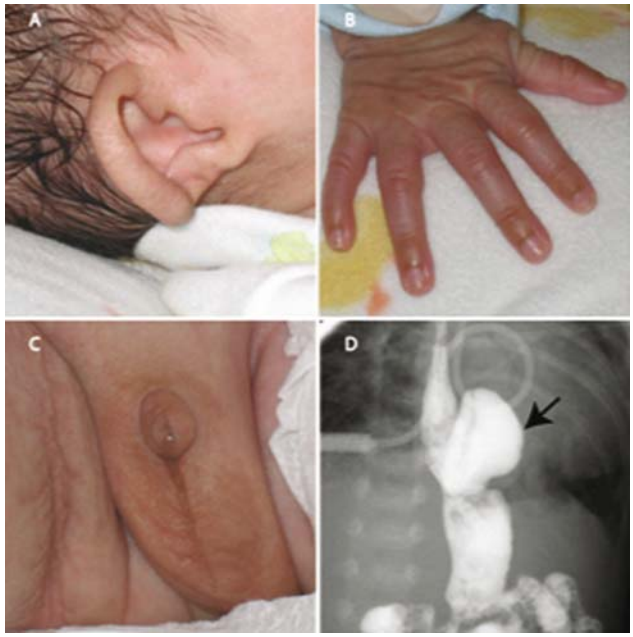

Fig. 1. Phenotypic features and upper gastrointestinal (UGI) radiographic study of the patient. His facial features included crumpled ears (Panel A). He had long, slender fingers (Panel B). Genital hypoplasia was also present (Panel C) with stretched penile length of 2 cm. Panel D demonstrates intrathoracic stomach (arrow) on UGI study.

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His hospital course was further complicated by development of recurrent lobar collapse and respiratory difficulty needing periods of mechanical ventilation and continuous positive airway pressure (CPAP), patent ductus arteriosus needing ligation and a large sliding type congenital hiatal hernia (Fig. 1d) associated with severe gastroesophageal reflux needing repair along with gastrostomy tube placement. He was discharged home on supplemental oxygen and gastrostomy feeds.

Additional diagnoses included bronchomalacia, laryngeal cleft, bilateral hydronephrosis, severe vesicoureteral reflux, and hypogonadotropic hypogonadism. No colobomas were visualized on eye examination and he passed the hearing screen in one ear. The magnetic resonance imaging of the brain and karyotype (46,XY) were normal.

The clinical diagnosis of CHARGE syndrome was made based on 2 major (characteristic external ear abnormalities and cranial nerve dysfunction) and several minor criteria (genital hypoplasia, cardiovascular malformations, tracheoesophageal fistula and characteristic face).[4] *CHD7* mutation testing identified a heterozygous mutation c.3806_11del6insA in exon 16 of the gene. This mutation causes a single base insertion of A following a 6 base deletion of TTAAAG, which leads to a premature stop codon denoted as p.P269X at the protein level. The mutation may lead to nonsense mediated mRNA decay or a truncated protein with loss of normal function.

The patient's father was noted to be unusually tall for his predicted genetic background (both parents of the father were relatively very short), with long fingers and a disproportionate arm span. On further questioning, he reported that he had aortic root dilatation and had been diagnosed with MS, but had never undergone genetic testing. The patient was also noted to have long toes and fingers and congenital hiatus hernia, findings described with MS in neonates per few case reports. Echocardiograms done in our patient at one year of age and later showed significant aortic root dilatation associated with MS. On screening for *FBN1* mutation known to be responsible for majority of MS cases, the patient and his father carried a heterozygous c.3990ins.C change in exon 32 that caused frameshift and therefore, a premature stop codon downstream of the mutation site.

DISCUSSION

Most of our patient's congenital anomalies were attributable to the *CHD7* mutation, including cardiac findings, ear anomalies, genital hypoplasia, and facial palsy. Some of his other clinical findings, such as the long fingers and toes and congenital hiatus hernia may be attributed to the *FBN1* mutation. The association of congenital hiatus hernia in neonates and MS has been described in the past. In 1997, Parida et al. described an infant with a hiatal/paraesophageal hernia who was diagnosed to have MS based on skeletal, cardiovascular findings and strong family history.[5] In 2003, Petersons *et al*. reported two neonates with congenital hiatus hernia, mothers of whom were diagnosed with MS.[6] Neither of these case reports mention a molecular diagnosis of MS based on identification of a *FBN1* mutation on chromosome 15. It is important to consider a diagnosis of MS in patients born with hiatus hernia whether or not there is a family history since about 25% of *FBN1* mutations are *de nov*o.

A severe and rapidly progressive form of MS that presents very early in life and is sometimes referred to as "neonatal MS" has been described. Neonatal MS is associated with mutations in exons 24-27 and 31-32 of *FBN1* gene. Our patient's mutation was present in exon 32 but he did not show any typical manifestations of neonatal MS.

It will be important to follow his growth since CHARGE syndrome makes him a candidate for growth delay and MS is associated with excessive linear growth of the long bones. To the best of our knowledge, our patient's *FBN1* and *CHD7* mutations have not been previously described.

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