Letter to the Editor

Identification of two novel splice-site mutations in CHD7 gene in two patients with classical and atypical CHARGE syndrome phenotype

To the Editor:

CHARGE syndrome (CS) is an autosomal dominant disorder with involvement of several organs and systems (central nervous system, eye, ear, nose and mediastinal organs).

Two sets of consensus criteria, that do not fully overlap, were proposed by Blake and Verloes, respectively (1).

The causative gene for CS is CHD7 (located on chromosome 8q12.1), mutated in 60% of case series; splice-site mutations are detected in 11% of patients (2).

We describe two patients, sharing some features of CHARGE phenotypic spectrum, with new, de novo, intronic mutations in CHD7.

Patient 1, a male, born from first cousins parents. Clinical features included: left optic nerve coloboma, gum-chello-palate clefting, sensorineural hearing loss, pulmonar stenosis, esophageal atresia with tracheoesophageal fistula, psychomotor delay (Griffiths developmental quotient – DQ of 40), scoliosis and congenital fusion of lumbar vertebrae. A genetic evaluation, performed at 2 years of age, revealed dysmorphic ear, square-shaped face with asymmetry and short stature (Fig. 1a). Renal ultrasound and brain magnetic resonance imaging were normal.

According to Blake and Verloes criteria, a diagnosis of CS (3/4 major and 3/7 minor criteria) and atypical CS (1/3 major and 4/5 minor signs) was hypothesized, respectively.

Patient 2, a female, born from non-consanguineous parents. Clinical features included: atrio-ventricular septal defect and aortic coarctation, chorioretinal atrophy, bilateral progressive sensorineural hearing loss, and left kidney agenesis. Choanal atresia/stenosis (mild or unilateral type included) was excluded. Wechsler Intelligence Scale for Children (WISC-III) test revealed a DQ of 83. Clinical genetic examination detected: prominent nasal bridge, squared-shaped asymmetric face, crowded teeth, external ear anomalies (Fig. 1b). This patient shared two major and two minor criteria according to Blake, and three minor criteria using Verloes’ score, not sufficient for a CS diagnosis; atypical CS might be hypothesized if inner ear malformations would have been found. Nevertheless, CS diagnosis was supposed based on clinical gestalt.

Although relevant for a CS diagnosis (3), both patients’ parents refused to execute temporal bone CT or skull X-ray.

Array-comparative genomic hybridization (CGH) showed normal data for patient 1 and partial chromosome 11q22.1 monosomy considered as a benign variant in patient 2.

Mutation analysis of CHD7 gene was performed. In patient 1, a A→G transversion at intron 18 donor splice site (c.4353+3A>G) was identified; the mutation was not detected in the unaffected parents. The analysis of the patient’s mRNA detected a shortened transcript.

Fig. 1. (a) Clinical features of patient 1: note squared asymmetric face, broad nasal bridge, small mouth and V-shaped upper lip, antverted nostrils, and short neck. (b) Clinical features of patient 2: note squared asymmetric face, narrow bifrontal diameter, low set and cup shape of outer ears.
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with exon 18 skipping (p.Ala1396_Gly1451del; RefProtNP_060250.2). A significantly altered protein, lacking part of the elicase c-terminus domain, would be unlikely to retain any normal function.

In patient 2, the c.8077-10T>A variant at intron 37 was demonstrated. The mutation was not detected in the unaffected parents. This variant causes an alternative splicing site in intron 37, yielding an insertion of eight bases in exon 38. The insertion causes a frameshift with a premature stop codon (p. Gly2693TyrfsX19; RefProtNP_060250.2). The mutation identified in patient 2 is expected to lead to a truncated protein that lacks the last 304 amino acids. According to recent paper by Bergman et al., variants leading to a truncating CHD7 protein are considered pathogenic (4).

This is the first description of a CS patient carrying a deletion of exon 18 in CHD7 gene. One patient carrying a different mutation in IVS18+1G>T and showing a phenotype partially overlapping with our case has been reported (2).

Few previously described patients with mutations in the last exons show an atypical phenotype (5). Another mutation (c.8077-1G>A) in intron 37 has been reported, but clinical data were not available (www.CHD7.org). Pathogenic mutations in the intron 37 might support the existence of an unknown functional domain in last exon. Chorioretinal atrophy in patient 2 could be included among the ocular features of CS.

This study describes two new intronic CHD7 mutations associated with CHARGE phenotype, broadening the number of currently pathogenic ones.

The patient 2 is an interesting demonstration of the wide variability of the phenotypic consequences of CHD7 mutations, which may go beyond the limits posed by classical clinical diagnostic criteria. This confirms that CHD7 analysis is recommended even for patients with an incomplete CS phenotype.

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