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A novel CHD7 mutation in a Chinese patient with CHARGE syndrome

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ABSTRACT

In Genetics Out-patient Department of Shanghai Children's Medical Center, we consulted a 3-year-old boy with multiple anomaly syndrome (congenital heart disease, cryptorchidism, congenital deafness, mental retardation, exophthalmos, laryngeal cartilage dysplasia and high arched palate). We ruled out the possibility of multiple deformities caused by genomic imbalances. The patient was then clinically considered to have CHARGE syndrome, an autosomal dominant multi-system disorder involving defects in multiple organs, and *CHD7* is the only known gene associated with the syndrome. Sequencing analysis of *CHD7* of the proband identified a *de novo* heterogeneous mutation (c.2916_2917del, p.Gln972HisfsX22), a two-nucleotide deletion causing reading frame shift and resulting in a truncated CHD7 protein. Computational structure analysis suggests that the truncated protein only contains the chromo-domains of CHD7, but lacks the SWI2/SNF2-like ATPase/helicase domain and the DNA binding domain, which are indispensable for the proper function of the protein, especially on chromatin remodeling. The patient then received follow up treatment in different clinical departments in a long period. To our best knowledge, this is the first CHARGE syndrome in Chinese patients diagnosed by gene analysis. In summary, the clinical symptoms and the description of treatment in the present case, combined with genetic test and functional prediction of CHD7, are helpful for further understanding and genetic counseling of the CHARGE syndrome.

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Introduction

CHARGE syndrome is an autosomal dominant multi-system disorder involving coloboma, heart defects, choanal atresia, retarded growth and development, genital hypoplasia, ear anomalies and/or deafness (Jongmans et al., 2006). In 1998, Blake et al. established reformative diagnostic criteria for CHARGE syndrome comprising of major and minor criteria. Major criteria include coloboma, choanal atresia, ear anomalies/deafness and cranial nerve dysfunction; while minor criteria include heart defects, genital hypoplasia, growth deficiency, developmental delay, tracheoesophageal fistula, orofacial cleft, and distinctive facial appearance (Blake and Prasad, 2006).

CHD7 gene, located at chromosome 8 (8q12) and starting at 61.59 Mb from the p-arm telomere, has a genomic size of 188 kb and consists of 38 exons. It encodes for the chromodomain helicase DNA binding protein, a member of the chromodomain family. In human neural crest cells, CHD7 forms a protein complex with PBAF (polybromo- and BRG1-associated factor-containing complex) that regulates chromatin structure, gene expression and embryonic development (Bajpai et al., 2010; Hargreaves and Crabtree, 2011). Currently, *CHD7* is the only gene known to be associated with the CHARGE syndrome (Lalani et al., 2006); both heterozygous mutations and deletions of *CHD7* could result in CHARGE syndrome. Up to date, several types of mutations within the *CHD7* coding region have been identified, including nonsense mutations (44%), frame shift causing deletions or insertions (34%), splice sites (11%), missense mutations (8%), larger deletions and duplication (2%), translocations (<1%) and small in-frame deletions (<1%) (Janssen et al., 2012).

In the present study, we consulted and followed up a Chinese boy with multiple deformities and clinically diagnosed with CHARGE syndrome. Molecular genetic analysis identified a new frame-shift-causing deletion of *CHD7*, resulting in a truncated form of CHD7 protein. The clinical symptoms and the description of treatment in the present case, combined with genetic test and functional prediction of CHD7, are helpful for further understanding and genetic counseling of the CHARGE syndrome.

Materials and methods

Clinical information and follow-up

A 3-year-old little boy was the first child born by non-consanguineous Chinese healthy parents with an unremarkable family history, after uncomplicated pregnancy and delivery. After birth, the infant had been suffering from recurrent respiratory tract infections and thus admitted to hospital frequently. Subsequent examinations revealed multiple malformations such as unique facial features, atrial septal defect (ASD), bilateral ear anomalies, and micropenis. Based on the above observations, he was suspected to have CHARGE syndrome. The clinical features, laboratory results and follow-up treatment of the patient were investigated and recorded in detail.

The study was approved by the Ethnics Committee of Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine. Informed consents were obtained from the parents.

Genetic analysis

Genomic DNA was extracted from peripheral blood of the patient and his parents using QIAamp DNA Blood Mini Kit (Qiagen GMBH, Hilden, Germany). Chromosomal Microarray Analysis was applied to detect large structural variants (SVs) using CytoScanHD chip (Affymetrix, Santa Clara, CA).

Then all of the 38 exons and exon-intron boundaries of the CHD7 (GenBank accession number NM_017780.2) were amplified by polymerase chain reaction (PCR) using 76 primers. The primer sequences, PCR mixture components and cycling conditions were available upon request. The amplified products were purified by QIAquick Gel Extraction Kit (Qiagen GMBH, Hilden, Germany) and then sequenced via ABI3730XL sequencer (Applied Biosystems, Foster City, CA).