Biallelic UNC80 mutations caused infantile hypotonia with psychomotor retardation and characteristic facies 2 in two Chinese patients with variable phenotypes

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ARTICLE INFO

Keywords:
UNC80
Developmental delay
Whole exome sequencing

ABSTRACT

Biallelic UNC80 mutations cause infantile hypotonia with psychomotor retardation and characteristic facies 2 (IHPRF2), which is characterized by hypotonia, developmental delay (DD)/intellectual disability (ID), intrauterine growth retardation, postnatal growth retardation and characteristic facial features. We report two unrelated Chinese patients with compound heterozygous UNC80 mutations inherited from their parents, as identified by whole-exome sequencing (WES). Mutations c.3719G > A (p.W1240*)/c.4926_4937del (p.N1643_L1646del) and c.4963C > T (p.R1655C)/c.8385C > G (p.Y2795*) were identified in patient 1 and patient 2, respectively. Although both patients presented with DD/ID and hypotonia, different manifestations also occurred. Patient 1 presented with infantile hypotonia, epilepsy and hyperactivity without growth retardation, whereas patient 2 presented with persistent hypotonia, growth retardation and self-injury without epilepsy. Furthermore, we herein summarize the genotypes and phenotypes of patients with UNC80 mutations reported in the literature, revealing that IHPRF2 is a phenotypically heterogeneous disease. Common facial dysmorphisms include a thin upper lip, a tented upper lip, a triangular face, strabismus and microcephaly. To some extent, the manifestations of IHPRF2 mimic those of Angelman syndrome (AS)-like syndromes.

1. Introduction

Infantile hypotonia with psychomotor retardation and characteristic facies 2 (IHPRF2; OMIM 616801) is a severe autosomal recessive neurodevelopmental disorder caused by biallelic mutations in the UNC80 gene (OMIM 612636), which was first described by Perez et al. (2016). This disorder is characterized by hypotonia, psychomotor retardation, facial dysmorphias, intrauterine growth retardation and postnatal growth retardation. There exists a different subtype of this disorder, infantile hypotonia with psychomotor retardation and characteristic facies 1 (IHPRF1), caused by NALCN (OMIM 611549) mutations. We report two Chinese patients with compound heterozygous UNC80 mutations whose characteristics are consistent with IHPRF2, with the exception of lack of postnatal growth retardation in one patient. Both patients exhibited hypotonia and developmental delay (DD)/intellectual disability (ID), but different manifestations occurred. Patient 1’s manifestations mimic those observed in Angelman syndrome (AS) patients. In addition, we summarize common clinical characteristics of IHPRF2 and compare IHPRF2 with IHPRF1 and AS-like syndromes.

2. Materials and methods

2.1. Clinical reports

Patient 1 (Fig. 1A–B) was a 9.5-year-old boy who was the only child of healthy and non-consanguineous parents with no family history of DD/ID. He was born via cesarean section following an uneventful and full-term pregnancy. His birth weight and body length were 3.35 kg (0SD) and 50 cm (0SD), respectively. He experienced physiologic jaundice one week after birth. Hypotonia and psychomotor retardation were observed. He could raise his head at the age of one year and sit by himself when he was two years of age; he ambulated when he was three years old. At approximately five years of age, he could use only simple speech. He also exhibited poor balance and displayed hyperactive
behavior and a happy and excitable disposition with frequent smiling and laughing. In addition, he suffered from constipation. Seizures occurred when he was two years old and were effectively treated with valproate and levetiracetam. When he was referred to our clinic at 6 years and 5 months of age, his height and weight were 120 cm (0 SD) and 20 kg (0 SD), respectively. When followed up at the age of 9.5 years, his height, weight and head circumference were 135 cm (−0.5 SD), 25 kg (−1.3 SD) and 51 cm (−0.5 SD), respectively. His facial features included frontal bossing, strabismus, a tented upper lip, a broad nasal bridge, and a short, smooth philtrum. He had long, slender fingers (Fig. 1C). An electroencephalograph (EEG) revealed excessively slow background. AS was initially suspected, but methylation-specific multiplex ligation-dependent probe amplification revealed no abnormalities in the 15q11-q13 region. Chromosomal microarray tests also showed no pathogenic copy number variations.

Patient 2 (Fig. 1D-F) was born in a healthy, non-consanguineous Chinese family after a full-term pregnancy. Her mother had no history of exposure to teratogenic pathogens or drugs during gestation. Her mother's first pregnancy (II-1 in Fig. 1F) terminated during the first trimester due to an unknown cause. The patient was referred to our department for DD and failure to thrive without feeding difficulty at approximately three years of age. She could speak only simple words such as “baba” and “mama” and could not walk. A physical examination revealed hypotonia. Her head circumference was 44 cm (−3.7 SD). Her facial dysmorphisms included a triangular face; light, sparse hair; frontal bossing; strabismus; a thin upper lip; and micrognathia. Echo-cardiographic examination, brain magnetic resonance imaging (MRI) and an EEG revealed no abnormalities. Metabolic screening and assessments of the patient's thyroid function at age three produced normal results. At the age of five, she could stand with support but remained unable to ambulate or speak. She suffered from sleep disturbance and a tendency toward self-injury behaviors, such as hitting her head with her hands or bumping her head. Follow-up when the patient was 5 years and 9 months old showed that she could not walk or speak. At that time, her body length was 100 cm (−3.4 SD), and she weighed 11 kg (−4 SD). Chromosomal microarray tests revealed no pathogenic copy number variations. According to clinical records, the proband's younger brother (II-3 in Fig. 1F) presented similar phenotypes such as hypotonia and DD. He died at the age of one year due to severe pneumonia. He was diagnosed as IHPRE2 clinically. However, no genetic analysis was performed, as DNA was unavailable.

Informed consent was provided by the parents of both patients for DNA study and the publication of clinical features. The study protocol was approved by the Ethical Review Board of Xin Hua Hospital (XHEC-D-2014-044).

2.2. Next-generation sequencing

Genomic DNA was extracted from peripheral whole blood using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA), following standard procedures. Whole exome sequencing (WES) was performed as previously described (Sun et al., 2017). We excluded variants from the candidate variant list that were observed with a frequency of > 1% in the 1000 Genomes Project, Exome Aggregation Consortium (ExAC), or Exome Variant Server (EVS) database or a frequency of > 5% in a local database containing 150 exomes. Variants of patient 1 were subsequently screened using autosomal recessive and autosomal dominant/de novo inheritance patterns. Variants of patient 2 were filtered using an autosomal recessive inheritance pattern based on the pedigree.

2.3. Sanger sequencing

Candidate variants were confirmed using Sanger sequencing. PCR primer sequences and protocols are available upon request. Amplified
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