CASE REPORT

Novel Nonsense Mutation in *ASXL3* causing Bainbridge-Ropers Syndrome

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Background: Bainbridge-Ropers syndrome is a rare autosomal dominant genetic disorder. **Case characteristics:** A 26-day-old neonate presented with feeding difficulties, excessive sleeping, and hirsutism over forehead and lumbosacral skin. **Outcome:** Whole-exome sequencing identified a novel nonsense mutation. **Message:** We report a novel mutation in a Chinese neonate with Bainbridge-Ropers syndrome.

Keywords: *Hypersomnia, Mutation, Whole-exome sequencing.*

Bainbridge-Ropers syndrome (BRPS, OMIM: 615485), first identified in 2013, is caused by a loss-of-function mutation in the *ASXL3* gene (OMIM: 615115). The clinical features of the condition are severe psychomotor retardation, speech disorders, feeding difficulties, hypotonia, and distinctive craniofacial features.

To date, almost all *ASXL3* gene variants reported in the literature are nonsense mutations and frameshift mutations, except for one splice site mutation (c.3039+1G>A) [1]. We report a novel nonsense mutation in *ASXL3*.

Case Report

The patient was a 26-day-old female neonate with failure to thrive, excessive sleeping and hypotonia. She was the only daughter of a healthy, non-consanguineous Chinese couple. Mother's pregnancy was normal with spontaneous birth in the 39th week of gestation. She suffered from embryonic developmental arrest at day 58 during the first pregnancy, and spontaneous abortion during the second pregnancy. The birth weight was 2.6 kg and length was 50 cm. The patient was hypersomnic and breastfeeding frequency was low. She had a loud cry, but used to sleep around 22 hours per day. Her weight at presentation was 2.51 kg (<3rd percentile), length was 51 cm (3rd-10th percentile), and head circumference was 34 cm (3rd percentile). She had slightly wide and flat nose bridge, hirsute forehead and lumbosacral skin, and hypotonia. Rooting reflex, sucking reflex, Moro reflex, grasp reflex, and bilateral knee reflex were normal. Liver function tests blood gas analysis, blood ammonia, lactate levels, blood tandem mass spectrometry and urinary organic acid analyses were normal. Her brain and lumbo-sacral magnetic resonance imaging showed no gross abnormalities. The result of karyotype analysis were 46, XX.

At the age of 6 months, her weight was 4.6 kg (<3rd percentile), length 63.5 cm (3rd-10th percentile), and OFC head circumference 40.6 cm (3rd-10th percentile). Her developmental milestones were delayed. She barely had steady head control, was not able to rollover or sitting up unaided. She had little facial expression, and barely made eye contact with people around (even with parents). However, she could follow sounds and objects, and had not suffered from any seizures. She maintained a daily sleep time of 20-22 hours. Craniofacial features gradually became more prominent (***Fig.* 1**).

Whole-exome sequencing revealed a heterozygous mutation c.3464C>A in exon 12 of *ASXL3* gene, resulting in the amino acid change p.S1155X. No variation was present at this site in her parents. Sanger sequencing of family members validated this analysis, suggesting a *de novo* mutation (***Web Fig.* 1**). The predicted results of both SIFT and PolyPhen-2 were unknown.

Discussion

In addition to the typical symptoms of craniofacial features, hypotonia, and ulnar deviation of both wrists, there were other manifestations (hypersomnia, hirsutism) that have not been reported in BRPS cases available in the literature. The decreased feeding frequency was probably related to longer

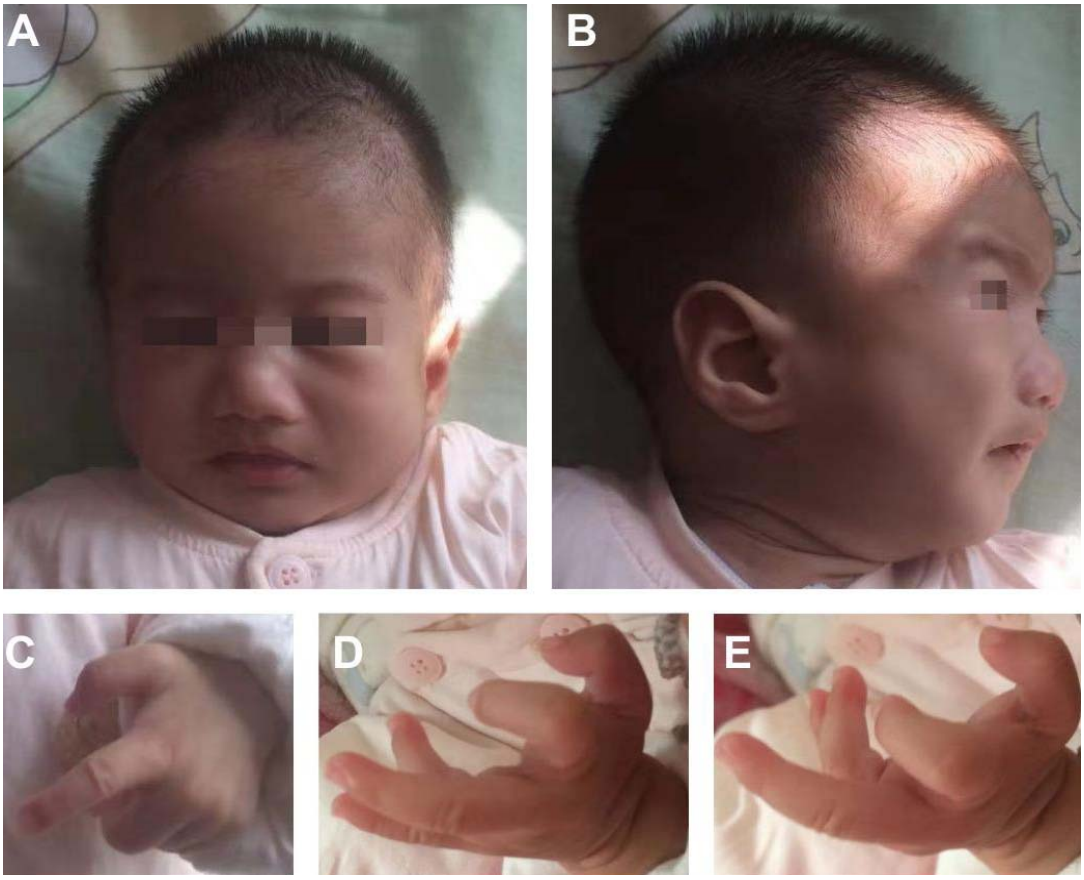

FIG 1. *Facial phenotypes and hands of patient at age 6 months: (a) long face, arched eyebrows, wide nose bridge, and downturned corners of the mouth; (c-e) prominent forehead, short nose bridge, and high-arched palate; her fingers and thumbs were in bent position and the phalangeal joints were stiff, with ulnar deviation of both wrists.*

sleep time. Due to limited knowledge of the disease and lack of specific features in early infancy, early diagnosis of this syndrome is very challenging. In our case, the variant is predicted to cause a stop-gain at amino acid 1155 (NM_030632;exon12: c.3464C>A, p.S1155X), resulting in truncate ~50% of the encoded protein. According to the 2015 ACMG Guidelines [2], the c.3464C>A mutation was defined to be pathogenic.

The clinical phenotype of BRPS is complex, and differs even in patients with the same gene variant [3,4]. We speculate that the clinical heterogeneity of patients with BRPS may relate to the following two factors. Firstly, it is likely that *ASXL3* gene mutation occurs after fertilization or during early embryonic development, resulting in the formation of chimeras with different presentations or incomplete phenotypes [5]. Secondly, the expression of the *ASXL3* gene varies in different tissues, higher in testis, ovary, and brain tissue. Therefore, the probability of *ASXL3* gene mutation may increase significantly during fertilization and embryonic brain development.

Bainbridge-Ropers syndrome has an autosomal dominant inheritance pattern. Kuechler, *et al*. [6] reported that the elder twin sister of a patient were healthy and did not carry a mutation in the *ASXL3* gene, indicating that the *ASXL3* gene mutation in that patient was a *de novo* mutation. On the other hand, the twin sisters described by Koboldt, *et al*. [7] were both diagnosed with Bainbridge-Ropers, and both had the same gene mutation, suggesting possible germline mosaicism in one parent. In this case, the patient's mother had been pregnant three times, with embryonic arrest occurring on day 58 of the first pregnancy, spontaneous abortion ending the second pregnancy during the first trimester, and the third pregnancy resulting in the normal birth of the patient. We speculate that the mutation in *ASXL3* gene might have played a role in the early loss of the first two pregnancies. In addition, the currently reported pathogenic mutation of the *ASXL3* gene is generally a *de novo* mutation, which includes the possibility of a germline chimera. Early genetic counseling should be performed for families desiring another child to avoid the birth of more children with the same disease.

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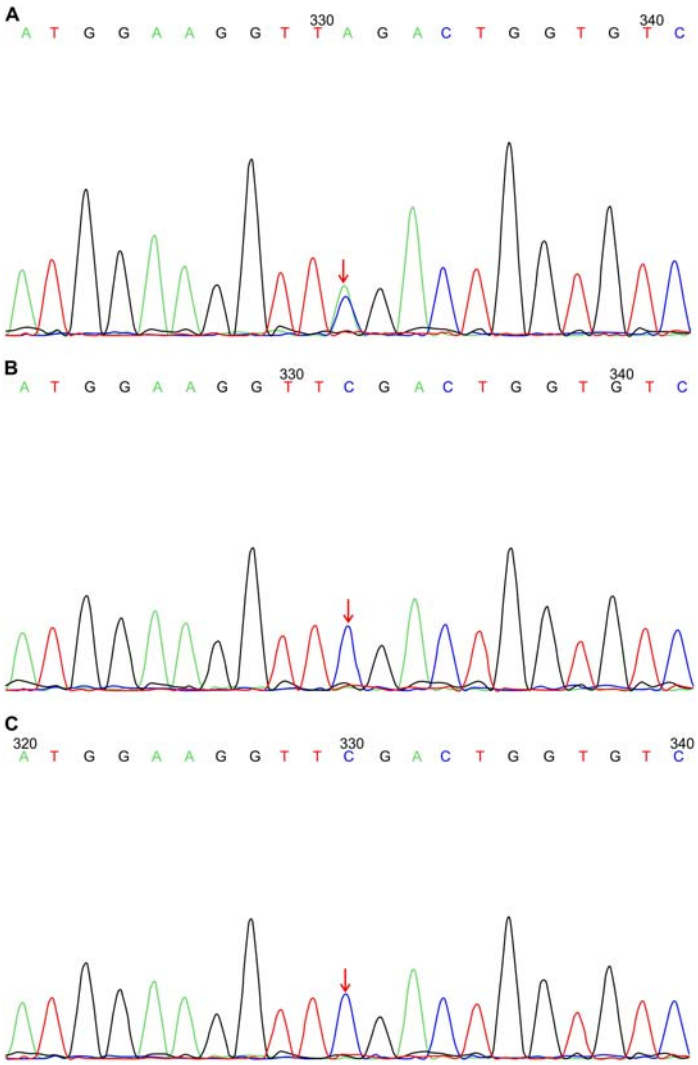

WEB FIG. 1 *Sanger sequencing of the ASXL3 mutation in patient and her parents. A: A heterozygous mutation (c.3464C>A) in patient. B: not found in her father. C: not found in her mother. Arrow indicates location of mutation.*