Clinical Vignette

First Report of Bainbridge-Ropers Syndrome in an Indian Individual

Shreya Chauhan[1], Veronica Arora[2], Samarth Kulshrestha[2], Praveen Suman[3], Imran Mushtaq[3], Praveen Kumar[4]

1 Department of Pediatrics , Sir Ganga Ram Hospital, New Delhi 2 Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi 3 Child Development Clinic, Institute of Child Health Sir Ganga Ram Hospital, New Delhi 4 Pediatric Neurology, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi
Correspondence to: Dr Veronica Arora, Email: veronicaarora@gmail.com

Abstract

Bainbridge-Ropers syndrome (BRS; OMIM #615485), a rare syndromic entity is caused by heterozygous de novo pathogenic variants in the *ASXL3* gene (Additional sex-combs like 3). First described by Bainbridge et al, fewer than 50 cases have been reported so far worldwide, and none from India. The clinical features have a significant phenotypic overlap with Bohring- Opitz syndrome (OMIM *612990, BOS). We describe the first case of Bainbridge-Ropers syndrome from India with a four base-pair heterozygous duplication; NM_030632.12:c.3746_3749dup (p.Lys 1250AsnfsTer2) in *ASXL3* resulting in a frameshift and premature truncation of the protein two amino-acids downstream. We also propose the potential role of the gene of interest in cardiac development.

Keywords: Bainbridge-Ropers syndrome, ventricular septal defect, *ASXL3*, cardiac phenotype, frameshift mutation

Introduction

Bainbridge-Ropers syndrome is known to be caused by a loss-of-function variant in the *ASXL3* gene (OMIM: 615115) on the long arm of chromosome 18 (Bainbridge et al., 2013). The clinical manifestations include psychomotor retardation, speech delay, feeding problems, hypotonia and facial dysmorphism (Dinwiddie et al., 2013, Srivastava et al., 2016). To date, all *ASXL3* gene variants reported in literature are either truncating or splice site variants. *ASXL3* is a transcriptional regulator gene belonging to ASXL family members which are known to have a role in epigenetic regulation and are implicated in hereditary neurological disorders and malignancies. Truncating variants in *ASXL1* are associated with Bohring-Opitz syndrome which has a clinical overlap with BRS (Hori et al., 2016). We report a 2 years old boy with BRS and describe an incidental phenotype of ventricular septal defect. We also discuss differential diagnosis and present a thorough comparative analysis of all the described cases for an easier syndrome identification.

Clinical details

A 2 years old male child, first born of a 5th degree consanguineous couple was brought with the concerns of global developmental delay and hypotonia. The mother had a history of two first trimester miscarriages. After an uneventful antenatal period, the proband was born via Caesarean section at term in view of fetal distress. The birth weight was 2.07 kg (< 3rd percentile), head circumference was 33 cm (50th percentile), birth length was 46cm (5th percentile) and he cried immediately after birth. The perinatal period was uneventful. Overtime, the parents noticed that developmental milestones were delayed. Neck holding was achieved at the age of 7 months. The child was able to sit without support at the age of 1 year and stand without support at the age of 2 years. There was significant delay in cognition and there was no eye contact. Dentition was also delayed. He was able to speak only monosyllables. The mother also noticed that he was slipping from her lap sometimes and felt very loose. There was no history of seizures, recurrent infections, feeding difficulties and sleep disturbances.

The child was consumed in self, restless and did not show any to and fro interaction. Anthropometric parameters were - weight of 9.5 kg (< 3rd percentile), length of 82 cm (5th percentile) and head circumference of 46 cm (5th percentile). Facial dysmorphism was noted including synophrys, prominent ears and pointed chin as shown in **Figure 1**. Neurological examination revealed generalised hypotonia with brisk reflexes. There was no hepato splenomegaly. Examination of the genitalia showed right sided undescended testis. Rest of the systemic examination was normal. In view of global developmental delay, autistic features, undescended testis and facial dysmorphism, a genetic cause was suspected.

Complete blood counts revealed anaemia (Hb-10.5 g/dl). Thyroid function tests, liver function tests, renal function tests, ammonia, lactate, and

Figure 1 Facial features of the patient showing prominent forehead, synophrys, thick eyebrows, depressed nasal ridge, large prominent anteriorly rotated ears and pointed chin.

homocysteine levels were all within normal limits. Vitamin D level was low (16.8 ng/ml). Abdominal ultrasound was normal. Ultrasound scrotum confirmed right sided undescended testis. Methylation-based PCR for Fragile X syndrome was normal. Magnetic resonance imaging of the brain and brainstem-evoked response audiometry were normal. 2D echocardiography

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WILD TYPE: ctgct ata tcg gga gca att aaa gaa cat ccc ttt gtg
             A   I   S   G   A   I   K   E   H   P   F   V

MUTATED:   ctgct ata tcg gga gca att aat taa
             A   I   S   G   A   I   N   *
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Figure 2 b Wild type sequence represents the original sequence along with the amino acids sequence. Variant sequence represents a duplication of 4 nucleotides (in bold) which results in a frameshift and termination of amino acid chain. *Represents the stop codon.

revealed a ventricular septal defect of 2 cm with no pulmonary arterial hypertension. After a normal chromosomal microarray and fragile X testing, whole exome sequencing was ordered for identification of a genetic etiology. It revealed a four base-pair heterozygous duplication in *ASXL3*; NM_030632.12(*ASXL3*):c.3746_3749dup(p.Lys1250AsnfsTer2) resulting in a frameshift and premature truncation of the protein two amino-acids downstream shown in **Figure 2a, 2b**. This variant is novel. It has not been reported in the population databases: 1000 Genomes, gnomAD and GenomeAsia. Further segregation and Sanger validation of this variant in the parents confirmed its denovo nature. Based on the 2015 classification guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP), this variant has been classified as "Pathogenic" (PVS1+PM2+PP4).

Discussion

Bainbridge-Ropers syndrome is phenotypically characterized by feeding difficulty, failure to thrive, speech delay, global developmental delay, intellectual disability, generalised

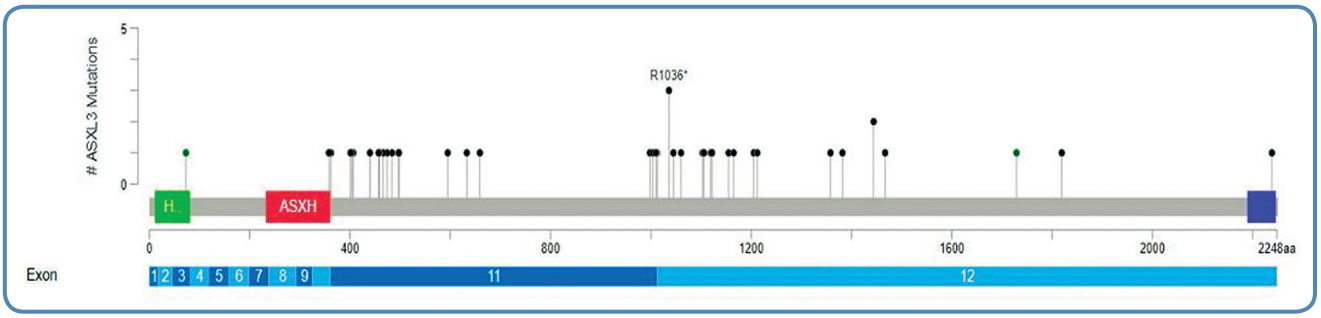

Figure 2 a Variant plot for the *ASXL3* gene. R1036Ter is a recurrent mutation. It is evident that majority of the previously identified mutations lies in either exon11 or exon12 and are of truncating nature. Variant categories: missense-2, truncating-39, splice-01, others-01.

hypotonia and distinctive cranio-facial features. The salient features identified in our patient included developmental delay, autistic features, undescended testis, hypotonia and facial dysmorphism in the form of low set prominent ears, pointed chin and synophrys. These features overlap with many other dysmorphic syndromes like Fragile X syndrome which is characterised by large prominent ears, prominent jaw, speech delay and intellectual disability. Presence of developmental delay, undescended testis, hypotonia with intellectual disability and prominent large ears make Kabuki syndrome, a close differential here. Furthermore, deciphering the clinical spectrum, one cannot rule out Cornelia de Lange syndrome as well which is characterised by intellectual disability, synophrys, low set large ears, anteverted nares and autistic traits. Given the complex phenotypic overlap between these syndromes, it becomes almost impossible to ascertain the final diagnosis clinically.

An extensive review of literature and comparison of clinical features of previously reported cases of Bainbridge-Ropers syndrome are provided in **Supplementary Table 1**(http://iamg.in/Bainbridge_Ropers_syndrome_Supplementary_Table_Oct_Dec_2022.docx). We can infer that majority of cases presented with symptoms like psychomotor delay, intellectual disability, speech delay, feeding difficulties, facial dysmorphism, generalised hypotonia, failure to thrive and skeletal abnormalities. Less prominent features are autism, microcephaly, short stature and somatic manifestations. Behavioural abnormalities noted in most of the patients are in the form of autistic traits, sleep disturbances, stereotypic movements and increased agitation/ aggressiveness. Further analysing the cohort for cranio-facial features revealed that arched eyebrows, long face and prominent ears are the most common presentation that point towards the diagnosis. Autistic traits were seen in 35-40% of the cases. Genotypically, majority of the cases had frameshift mutation leading to premature truncation (85%). Rest includes missense and splice site mutations.

Cardiac involvement has not been described in BRS till date. In our patient, 2D echocardiography was done as a part of general work up and revealed a ventricular septal defect of 2cm. Cardiology reference was sought and as the patient was asymptomatic, no intervention was required. The gene is known to be expressed in the brain, eyes, digestive tract, ovaries, testis, liver, kidneys, bone marrow and heart. Fu et al reported that compound heterozygous mutation in the *ASXL3* gene causes congenital heart disease reflecting a possible role of *ASXL3* in cardiac development by regulating expressions of mRNA associated with cell apoptosis and cell proliferation (Fu et al., 2021). A potential role of *ASXL3* in cardiac development has been recently reported (McGrath et al., 2022). They studied results of *ASXL3* frameshift variation in a mouse model and human embryonic stem cell lines and found that the biallelic genetic inactivation of *ASXL3* leads to alteration in cardiac development in both the species, thus highlighting the role of the interested gene in extracellular matrix gene programs via cardiac fibroblasts during cardiomyocyte development. But since BRS is associated with haplo-insufficiency, we can only speculate about the role of *ASXL3* in cardiac development as of now and further research is warranted to achieve concrete results on the same.

In conclusion, we report the first case of BRS from India with an incidental finding of ventricular septal defect. We also highlight the need of careful cardiac evaluation in every patient. The differential diagnosis is discussed and extensive review of literature available so far to help in better syndromic description.

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Conflicts of interest: There are no conflicts of interest.

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