CASE REPORT

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A Case Report of Family with Pathogenic Variants in SIX6 and TTC8 Genes Indicating Bardet-Biedl syndrome 8

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Abstract

Bardet Biedl Syndrome (BBS) is genetically heterogeneous and pleiotropic in nature which includes obesity, polydactyly, retinal degeneration, and renal anomalies. Whole-exome sequencing of the proband and parents revealed pathogenic homozygous single base pair deletion (c.188del) in exon 1 of SIX6 gene and another pathogenic heterozygous single base pair deletion (c.793del) in exon 10 of TTC8 gene which resulted in the causation of Bardet-Biedl syndrome 8 and Retinitis pigmentosa 51 in the proband.

Keywords: Bardet Biedl Syndrome, SIX6, TTC8, Retinal Degeneration.

INTRODUCTION

Bardet Biedl Syndrome (BBS) is a rare genetic disorder with autosomal recessive pattern of inheritance. BBS is genetically heterogeneous and pleiotropic in nature which includes obesity, polydactyly, retinal degeneration, and renal anomalies [1]. There are 21 genes associated as causative mutations leading to BBS. These 21 genes can be divided into three subclasses based on their association with a complex known as the BB Some; BB Some associated (BBS1–5, 7–9, 14, 17, 18), BB Some chaperonin (BBS6, 10, 12), otherwise non-BB Some associated (BBS11, 13, 15, 16, 19–21). BB Some is a complex made up of eight BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, and BBS18), and plays an important role in intracellular trafficking and protein trafficking within the cilium. SIX6 gene is located on chromosome 14q23.1 that encodes a member of the sine coulis homeobox (SIX) transcription factor family, which plays a role in eye development. Mutations in SIX6 gene might cause microphthalmia with cataract type 2 (MCOPCT2). The present case report describes a family with pathogenic variants in SIX6 and TTC8 genes indicating Bardet-Biedl syndrome 8.

CASE REPORT

33-year-old pregnant women with 24 weeks of gestation and 43-year-old male affected with polio referred to the Institute for clinical diagnosis and genetic counseling. Pedigree information was obtained and presented in Figure-1. The couple had third degree consanguineous marriage with a marital life of 13years. The couple's reproductive history includes first male child (IV-1) succumbed within 10 hours of birth due to respiratory distress, congenital heart defect and undescended testis. The second male child (IV-2) expired within 30 days due to congenital diaphragmatic hernia. While, the third female child (IV-3) was found to be affected with clinical indications of unilateral cleft lip, bilateral microphthalmia, microcornea, iris coloboma, and broad nose with normal karyotype of 46, XX chromosomal constitution. Now, the couple has come for genetic counselling for the fourth pregnancy (IV-4).

The family history of the pregnant women showed that her younger sister (III-8) died at the age of 26 from renal failure and also had intellectual disability, postaxial polydactyly of feet, and was operated for uterovaginal abnormality. She was suspected for Bardet-Biedl syndrome. While her younger brother (III-9) had speech delay and expired at the age of 1year due to chickenpox.

Whole-exome sequencing was carried out for the 5 years old, third female child (IV-3) of the couple. The report showed two pathogenic variants in SIX6 and TTC8 genes respectively. In SIX6 gene (ENST00000327720.6) homozygous single base pair deletion (c.188del) in exon 1 revealed in a frameshift change those results in premature truncation of the protein 53amino acid downstream to codon 63(p.His63profsTer53) leading to optic disc anomalies with retinal and macular dystrophy. While, the second pathogenic variant in TTC8 gene (ENST00000614125.4) was heterozygous single base pair deletion (c.793del) in exon 10, which results in a frameshift, and premature truncation of protein 4 amino acids downstream to codon 265 (p.Lys265AsnfsTer4:) and is responsible to cause Bardet-Biedl syndrome 8 and Retinitis pigmentosa 51. The pattern of inheritance for both the variants was autosomal recessive.

Clinical exome was also carried out for the couple for carrier detection and identified same pathogenic variants in the both the parents as detected in the 5 years old female child of the couple in SIX6 (exon 1-c.188del) and TTC8 (exon 10-c.793del) genes in heterozygous condition.

Prenatal sanger variant analysis was carried out in the fetus for SIX6 and TTC8 genes. The results identified c.188del in exon 1 of SIX6 gene in homozygous condition, as reported in the 5 year old female child. However, no variants were identified in TTC8 gene. The Chromosomal Microarray was also performed for the fetus which did not show any significant copy number variation.

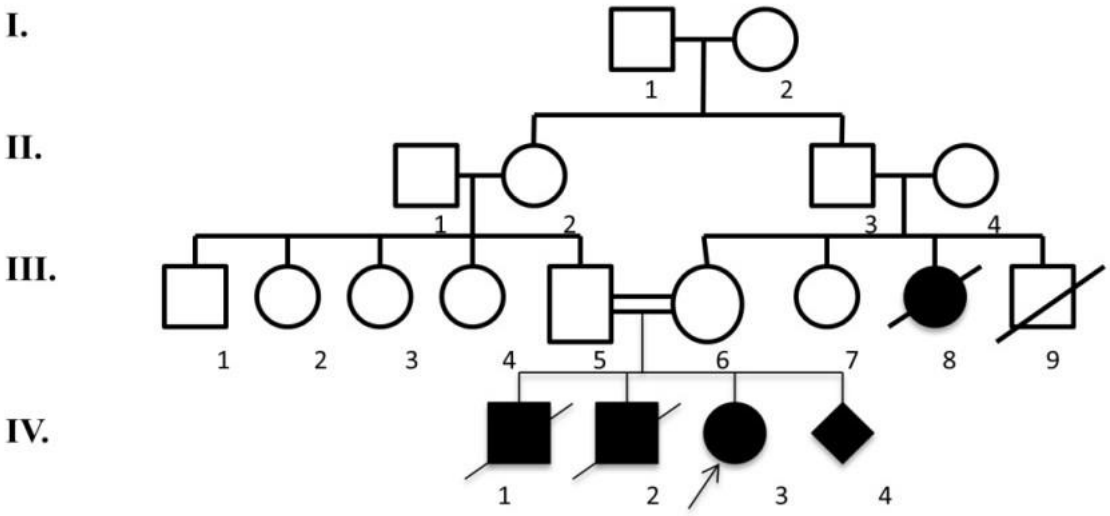

Figure 1: Pedigree chart of the family

DISCUSSION

Bardet-Biedl syndrome (BBS) is caused due to the impairment of primary cilia and belongs to a wide group of disorders known as ciliopathies, and characterizes a hallmark exemplar with a highly variable clinical presentation, possibly due to second-site modification of primary causal loci [2-4]. TTC8 (tetratricopeptide repeat protein having eight domains) is the gene responsible for BBS8 and it is located on chromosome 14q32.1. TTC8 gene contains 15 exons and encodes a protein of 531 amino acids. TTC8 mutations are associated with BBS type 8, and its gene frequency is 1% in people with BBS [5]. TTC8 mutations are mostly seen in affected individuals of Middle Eastern or North African descent. Though rarely reported, TTC8 is also a causative gene for no syndromic autosomal recessive retinitis pigmentosa [6]. Gene sequencing in an African-American identified two heterozygous variants, one in the CEP290 gene (c.4393 C>T) and another variant in the TTC8 gene (c.1021 C>T), two mutations extremely indicative of BBS [5]. The present case report identified two pathogenic variants in SIX6 and TTC8 genes in a family. In SIX6 gene homozygous single base pair deletion (c.188del) in exon 1 revealed in a frameshift change those results in premature truncation of the protein 53 amino acid downstream to codon 63 (p.His63profsTer53) leading to optic disc anomalies with retinal and macular dystrophy. While, the second pathogenic variant in TTC8 gene was heterozygous single base pair deletion (c.793del) in exon 10, which results in a frameshift, and premature truncation of protein 4 amino acids downstream to codon 265 (p.Lys265AsnfsTer4:) and is responsible to cause Bardet-Biedl syndrome 8 and Retinitis pigmentosa 51. The pattern of inheritance for both the variants was autosomal recessive.

According to Abigail *et al* (2011) loss of BBS8 results in dramatic and variable reduction in cilia, the important signalling platform for olfaction, which alters the homogeneity of responses in population of olfactory sensory neurons (OSNs) expressing the same receptor, thus causative to the observed axon-targeting defects [7]. Homozygosity mapping identified a single base deletion of c.299delC (p. Ser100Leufs*24) in exon 4, a novel

protein truncating mutation of the BBS9 gene in a consanguineous Pakistani family with Bardet Biedl syndrome [8]. Compound heterozygous *SCLT1* mutations were identified in two unrelated Japanese patients with clinical diagnosis of BBS [9]. Two brothers with an atypical phenotype of Bardet-Biedl Syndrome were homozygous positive for the presence of a c.1169T > G (p. Met390Arg) mutation in BBS1 [10]. Next-generation sequencing identified novel homozygous variants in BBS9 gene in each patient, c.2014C>T, p. Gln672Ter and c.673_674insAA, p. Gln225GlnfsX10 causing Bardet Biedl syndrome in two Iranian consanguineous families [11]. Whole-exome sequencing identified a novel homozygous variant c.1114C>T (p.Q372X) in the BBS9 of the two siblings in a Chinese family [12]. A case report by Fossa *et al* (2021) described an individual with BBS caused by a rare recurrent variant in *BBS12* (NM_152618.3: c.1063C>T; p. Arg355*) [4].

CONCLUSION

In conclusion the present case report reveals pathogenic variants in SIX6 and TTC8 genes indicating Bardet-Biedl syndrome 8. To our knowledge, this is the first report from India to identify TTC8 variant with BBS8, which will further help in identifying the unknown variants of TTC8 in spectrum of BBS8, and helps in prenatal diagnosis and genetic counselling.

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Authors Contribution

Concept design and data acquisition was done by Ayushi Gupta. Dr. Shahnaz Sultana has drafted the manuscript. Dr. Sunitha Tella has done the diagnosis of the family and provided relevant clinical history. Dr. Venkateshwara Anantapur has approved the final version to be published.

Conflict of Interest

None declared.

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