Case Report

Joubert Syndrome with Homozygous Duplication in Exon 7 of SMN2 Gene and c.746G>A (p.R249H) Variant of Uncertain Significance in TRPV4 Gene: A Case Report

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Abstract

The case report presents 5 years old male proband with Joubert syndrome (JS) referred to the Institute with the complaint of developmental delay. Mutation analysis in the proband by MLPA showed homozygous duplication in exon 7 of SMN2 gene. Further, next generation sequencing (NGS) based gene panel study showed one copy of c.746G>A (p.R249H) variant of uncertain significance in exon 5 of TRPV4 gene in heterozygous condition. The same variant was identified in the probands father. Prenatal diagnosis in proband's mother who was pregnant, revealed heterozygous missense variants of uncertain significance at c.578C>G (p. Thr193Arg) in exon 4 of PNPLA8 gene and c.862C>T (p. Arg288Cys) in exon 6 of KCNH1 gene in the developing foetus. Thus, the advanced genetic analysis along with clinical findings and typical imaging will help in appropriate diagnosis and management of the Joubert syndrome.

Keywords: Joubert Syndrome; SMN2; TRPV4; Autosomal Recessive; Duplication

1. Introduction

Joubert Syndrome (JS) is a rare autosomal recessive disorder, inherited heterogeneously. The prevalence of Joubert syndrome is less than 1 in 100,000. Clinical features include ataxia, abnormal eye movements, hyperpnea episodes, hypotonia, respiratory anomalies, mental retardation, and growth retardation [1]. Molar tooth sign finding in the imaging, is the distinctive feature of Joubert syndrome, which emerges in the form of midbrain-hindbrain anomalies. Till date mutations in 34 genes are causal in Joubert syndrome, of which 33 are autosomal recessive and one X-linked. The case report presents Joubert syndrome with homozygous duplication in exon 7 of SMN2 gene and c.746G>A (p.R249H) variant of uncertain significance in TRPV4 gene.

2. Case Presentation

A 5-year-old boy with developmental delay was referred to Institute of Genetics and Hospital for Genetic Diseases. The parents of the proband were healthy and married with no consanguinity. The family members of both sides did not have developmental delay, mental retardation, or other nervous system abnormalities, including Joubert syndrome and JSRD. The proband was suspected for Spino-muscular disorder / Neuro muscular disorder / Joubert Syndrome based on clinical examination. 2D Echo of the proband showed flow across the valves with mild TR flow and normal pulmonary flow. EEG examination showed normal study. PET-CT scan showed severe hypometabolic bilateral medical temporal cortices and cerebellar hemispheres, moderate hypometabolic bilateral thalami and lateral temporal cortices with mild anti-cingulate gyri. However, ultrasound scan of the abdomen showed normal study. Mutation analysis in the proband was carried out by multiplex ligation probe dependent amplification (MLPA, MRC Holland) using SALSA MLPA probe mix P060-B2 SMA for SMN1 and SMN2 genes. Homozygous duplication in exon 7 of SMN2 gene was identified without any variation in SMN1 gene.

Further, molecular testing of the proband based on gene panel next generation sequencing (NGS) revealed one copy of c.746G>A (p.R249H) variant of uncertain significance in exon 5 of TRPV4 gene in heterozygous condition, which was also confirmed by Sanger sequencing. Further, the gene analysis was also carried out in parents of the proband, where in similar c.746G>A (p.R249H) variant was observed in the probands father in heterozygous condition. The probands mother did not reveal any such variation. As the probands mother was 4 months pregnant, taking the clinical history of the proband into consideration, prenatal screening for neuromuscular disorder was advised to the couple. Amniotic fluid was obtained by amniocentesis for prenatal screening. The prenatal diagnosis test results showed heterozygous variants of uncertain significance at c.578C>G (p. Thr193Arg) in exon 4 of PNPLA8 (transcript NM_015723.4) gene on Chr7:108155358 and c.862C>T (p. Arg288Cys) in exon 6 of KCNH1 (transcript NM_172362.2) gene on Chr1:211192295. Both the missense variants have not been reported previously as a pathogenic variant nor as a benign variant, to our knowledge.

3. Discussion

Joubert syndrome at the neuropathological level was caused due to hypoplasia and dysplasia of the cerebellar vermis and of pontine and medullary structures, and the absence of decussation of the superior cerebellar peduncles and the pyramidal tracts [2]. Survival motor neuron 1 (SMN1) gene on chromosome 5q 13.2 is highly conserved and a single copy is present in the genome of all eukaryotic organisms. However, in humans a genomic duplication has given rise to a second gene, SMN2. SMN2 modulate the disease

severity through variation in its copy number [3]. SMN protein has several key regulatory cellular functions in neuronal cells, including roles in RNA processing and transport, impairment in these processes leads to loss of SMN protein, resulting in altered motor neuron function and progressive death of motor neurons [4]. In the present report, homozygous duplication in exon 7 of SMN2 gene was identified in the proband, which may result in altered neuronal development and Joubert syndrome.

Transient receptor potential vanilloid 4 channels (TRPV4) is a calcium permeable non-selective cation channel expressed in various tissues and cell types. TRPV4gene is located on chromosome 12q23-q24.1 and composed of 15 exons coding 5 different splice variants. TRPV4 is involved in osmo and mechanotransduction, which is important for several functions, one of them is regulation of ciliary beat frequency [5]. In peripheral nervous system TRPV4 expression was exhibited in the skin sensory receptors, dorsal root ganglia and to a lesser proportion in the motor neurons [6]. The exact role of TRPV4 in neurons have not yet fully explained. However, dominant mutations in TRPV4 have been described in peripheral nervous system and skeletal diseases. One copy of c.746G>A (p.R249H) variant of uncertain significance in exon 5 of TRPV4 gene in heterozygous condition identified in the proband may hinder the nervous development and may lead to the features of Joubert syndrome.

The prenatal diagnosis of the foetus in the present case showed heterozygous variants of uncertain significance at c.578C>G (p. Thr193Arg) in exon 4 of PNPLA8 gene and c.862C>T (p. Arg288Cys) in exon 6 of KCNH1 gene, which may also have a significant role in the developmental process. The p.T193R variant in PNPLA8 gene is observed in 10/29,936 (0.0334%) alleles from individuals of South Asian background in genome AD Exomes and 1/978 (0.1022%) alleles from individuals of South Asian background in 1000 Genomes. A large physicochemical difference between arginine and cysteine, in missense variant p.R288C in KCNH1 gene, is likely to impact secondary protein structure. Both the variants p.T193R and p.R288C are predicted to be damaging by both SIFT and PolyPhen2 and conserved by GERP++ and PhyloP across 100 vertebrates and have been classified as uncertain significance.

4. Conclusion

Thus, advanced genetic testing such as Next-generation sequencing, microarray etc has enabled the identification and characterization of several genes involved in various genetic syndromes at the pathophysiological level. Thus, the report presents a rare case of Joubert syndrome based on advanced genetic diagnostics, which include multi gene panel study besides clinical history and MRI findings and helps in prenatal diagnosis and offer appropriate genetic counselling and decision making for future pregnancies.

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Conflict of Interest

None to declare.

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