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Case Report

A case report of Chung-Jansen syndrome

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ABSTRACT

Global developmental delay (GDD) has a wide range of underlying causes, and advances in genetic testing, particularly whole exome sequencing (WES), have improved diagnostic accuracy. Chung–Jansen syndrome is a rare neurodevelopmental disorder caused by variants in the PHIP gene and is characterized by developmental delay, intellectual disability, hypotonia, and behavioural abnormalities. We report a 6-year-old girl with global developmental delay, hypotonia, and inattention. She had delayed motor and speech milestones along with progressive cognitive decline. Examination revealed generalized hypotonia, mild distal weakness, bilateral ptosis, and refractive error. WES identified a heterozygous missense variant in the PHIP gene, classified as a variant of uncertain significance (VUS). The clinical presentation showed partial overlap with Chung–Jansen syndrome. The child is on multidisciplinary supportive therapy. Genetic counselling and parental testing were advised. This case highlights the importance of WES in unexplained GDD and the need for clinic genetic correlation when interpreting VUS.

Keywords: Global developmental delay, PHIP gene, Chung-Jansen syndrome, Whole exome sequencing

INTRODUCTION

Global developmental delay (GDD) refers to significant delay in two or more developmental domains in children younger than five years and often progresses to intellectual disability later in childhood. The prevalence of GDD and intellectual disability is estimated to be approximately 1-3% worldwide.[1] The etiological spectrum is broad and includes chromosomal abnormalities, metabolic disorders, congenital infections, structural brain abnormalities, and single-gene disorders.[2] With the introduction of next-generation sequencing techniques such as whole exome sequencing (WES), the diagnostic yield in children with unexplained developmental delay has significantly increased.[3] These techniques enable identification of rare genetic variants responsible for neurodevelopmental disorders that were previously difficult to diagnose. The PHIP gene, located on chromosome 6q14.1, encodes Pleckstrin Homology Domain Interacting Protein, which plays an important role in insulin signalling, cell proliferation and neuronal development.[4] Pathogenic variants in this gene are associated with Chung-Jansen syndrome, a rare neurodevelopmental disorder first described in 2016.[5] The syndrome is characterized by developmental delay, intellectual disability, hypotonia, obesity, behavioural

abnormalities and distinctive facial features.[5] Here we present a case of a 6-year-old girl with global developmental delay and hypotonia in whom whole exome sequencing revealed a heterozygous missense variant in the PHIP gene. The clinical features demonstrated overlap with the phenotype described in Chung-Jansen syndrome.

CASE REPORT

A 6-year-old girl presented for evaluation of global developmental delay and learning difficulties. She was born to non-consanguineous parents and was the first child of the family. There was no history of similar neurological disorders in the family.

Table 1: Sequence variant analysis identified a heterozygous missense variant in the PHIP gene.

Gene* (transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
PHIP (-) (ENST00000275034.5)	Exon 15	c.1394A>G (p.His465Arg)	Heterozygous	Chung-Jansen syndrome (OMIM#617991)	Autosomal dominant	Uncertain significance (PM2, PP3)

The antenatal period was complicated by maternal pre-eclampsia. The child was born late preterm with a birth weight of 2.5kg. Baby did not cry soon after birth and required neonatal resuscitation. The baby was admitted in the neonatal intensive care unit (NICU) admission for seven days following birth for respiratory distress. No major neonatal complications were documented. There was no history of feeding problems in infancy and no history of hearing loss. The child exhibited delayed developmental milestones across multiple domains. Parents reported delayed motor and speech development with echolalia. There was no history of seizures. As the child grew older, cognitive difficulties became more evident with poor academic performance and reduced adaptive functioning suggestive of evolving intellectual disability.

Clinical examination

General examination revealed a cooperative child with mild developmental delay. Neurological examination showed generalized hypotonia with mild distal muscle weakness. Deep tendon reflexes were preserved (2+). The child had a weight of 35.6 kg which was above the 97th percentile with bilateral ptosis, refractive error, inattention and behavioral concerns. She also has a hypopigmented patch over the lower back measuring approximately 5×2 cm. No major dysmorphic features or organomegaly were noted. No similar neurodevelopmental conditions were reported among other family members.

Investigations

The absence of phenotypical features of well-known syndromes causing developmental delay and considering neuromuscular involvement in the child the possibility of myopathies and mitochondrial disorders was kept; to diagnose and rule out other syndromes, whole exome sequencing combined with whole mitochondrial genome sequencing was performed using peripheral blood samples. This gene is associated with Chung-Jansen syndrome, which follows an autosomal dominant pattern of inheritance but most of the reported cases are de novo mutations.[5] According to American College of Medical Genetics and Genomics (ACMG) guidelines, the variant was classified as a Variant of Uncertain Significance (VUS) based on criteria including rarity in population.[6]

Clinical correlation

The identified variant results in a missense change where arginine is substituted by histidine at codon 465 in the PHIP protein. Variants affecting the PHIP gene have been implicated in Chung-Jansen syndrome, a condition characterized by developmental delay, intellectual disability, hypotonia, behavioral abnormalities, and obesity. Some patients may also exhibit facial dysmorphism, ocular abnormalities, and feeding difficulties.[5] In the present case, several clinical features overlap with those described in Chung–Jansen syndrome, including global developmental delay, intellectual disability, hypotonia, and behavioral issues such as inattention. Although the detected variant is classified as a variant of uncertain significance, the clinical phenotype demonstrates partial concordance with previously reported cases of PHIP-related neurodevelopmental disorder. Children presenting with global developmental delay require evaluation for multiple possible etiologies. In this case, the differential diagnoses considered included chromosomal abnormalities such as microdeletion or microduplication syndromes, inborn errors of metabolism, mitochondrial disorders, structural brain abnormalities, and neuromuscular disorders. The absence of significant findings in mitochondrial genome analysis and copy number variant analysis, along with the presence of a potentially relevant PHIP variant, suggested a possible PHIP-related neurodevelopmental disorder.

Management and follow-up

Management of children with genetic neurodevelopmental disorders is primarily supportive and multidisciplinary. The child is currently undergoing

developmental therapy, exercises and weight training, speech and language therapy, occupational therapy, behavioral interventions, ophthalmologic evaluation with correction of refractive error, and regular neurological follow-up. Genetic counseling was recommended for the family. Parental testing for the identified PHIP variant was advised to clarify its clinical significance and assess recurrence risk.

DISCUSSION

Chung-Jansen syndrome is a rare genetic disorder caused by pathogenic variants in the PHIP gene. The syndrome was first described in 2016 and has since been reported in several individuals with neurodevelopmental delay and distinctive clinical features.[5] The PHIP gene encodes Pleckstrin Homology Domain Interacting Protein, which functions in cellular signaling pathways including insulin receptor signaling and transcriptional regulation. Disruption of PHIP function is believed to affect neuronal development and metabolic pathways, leading to neurodevelopmental abnormalities. The clinical phenotype associated with PHIP variants is variable but typically includes developmental delay, intellectual disability, hypotonia, and behavioral abnormalities such as attention deficits or autism spectrum features.[5] Obesity is also frequently reported in older children and adolescents with this condition. Our patient exhibited several clinical features consistent with PHIP-related neurodevelopmental disorder, including developmental delay, hypotonia, and behavioral concerns. However, the absence of distinctive dysmorphic features highlights the phenotypic variability associated with this condition. The identified variant was classified as a variant of uncertain significance. Interpretation of such variants requires careful correlation with clinical findings, segregation analysis, and accumulation of additional evidence from future studies. As genomic databases expand, variants currently classified as uncertain may later be reclassified as pathogenic or benign. This case underscores the utility of whole exome sequencing in the evaluation of unexplained developmental delay. Early genetic diagnosis can help guide management, inform prognosis, and facilitate appropriate genetic counseling for possible family expansion.[7]

CONCLUSION

We report a case of a 6-year-old girl with global developmental delay, hypotonia, and behavioral concerns in whom whole exome sequencing identified a heterozygous missense variant in the PHIP gene. Although currently classified as a variant of uncertain significance, the clinical phenotype demonstrates overlap with features of Chung-Jansen syndrome. Further studies, including parental segregation analysis and accumulation of additional case reports, are necessary to clarify the pathogenicity of this variant. This case highlights the importance of integrating clinical evaluation with genomic testing in children with unexplained developmental delay.

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