DOI: 10.4274/forbes.galenos.2025.77045
Forbes J Med 2025;6(3):299-302

Case Report / Olgu Sunumu

Horizontal Gaze Palsy with Progressive Scoliosis (HGPPS) in a Consanguineous Family: A Case Report

Akraba Evliliği Olan Bir Ailede Horizontal Bakış Paralizisi ve Progresif Skolyoz: Bir Olgu Sunumu

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Cite as: Toprak DE, Tekel GM, Doğan YC, Işık E, Horizontal gaze palsy with progressive scoliosis (HGPPS) in a consanguineous family: a case report. 2025;6(3):299-302

ABSTRACT

Horizontal gaze palsy with progressive scoliosis is a rare autosomal recessive disorder caused by biallelic variants in *ROBO3*, a gene essential for commissural axon crossing in the hindbrain and spinal cord. It is characterized by the congenital absence of horizontal eye movements and progressive scoliosis, typically presenting in childhood or adolescence.

Keywords: Horizontal gaze palsy with progressive scoliosis, HGPPS, *ROBO3*, brainstem, malformation

ÖZ

Horizontal bakış paralizisi ve ilerleyici skolyoz, beyin sapı ve omurilikte komissural akson geçişi için gerekli olan *ROBO3* genindeki bialelik varyantlardan kaynaklanan nadir bir otozomal resesif bozukluktur. Doğumsal horizontal göz hareketlerinin yokluğu ve genellikle çocukluk veya ergenlik döneminde ortaya çıkan ilerleyici skolyoz ile karakterizedir.

Anahtar Kelimeler: Horizontal bakış paralizisi ve ilerleyici skolyoz, HGPPS, *ROBO3*, beyin sapı, malformasyon

Received/Geliş: 14.09.2025
Accepted/Kabul: 28.11.2025
Publication Date/ Yayınlanma Tarihi: 05.12.2025

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INTRODUCTION

Horizontal gaze palsy with progressive scoliosis (HGPPS) is a rare autosomal recessive disorder first described in 1974.[1] It is characterized by a congenital absence of horizontal eye movements and progressive scoliosis, both of which usually become apparent during childhood or adolescence. The condition is caused by biallelic pathogenic variants in the Roundabout homolog 3 *(ROBO3)* gene, which encodes a receptor essential for commissural axon crossing within the hindbrain and spinal cord.[2] Impaired *ROBO3*-mediated signaling results in defective horizontal gaze control and abnormal spinal cord circuitry underlying scoliosis progression. To date, almost 100 patients with HGPPS have been reported and 55 *ROBO3* mutations have been identified, most of them occurring in consanguineous families.[3] We present a 17-year-old male with genetically confirmed HGPPS, highlighting the clinical, radiological, and genetic findings and intrafamilial recurrence.

CASE REPORT

A 17-year-old male was referred for evaluation of impaired horizontal eye movements, scoliosis, and decreased vision. His parents were consanguineous (first cousins). The family history revealed an older brother with a similar clinical phenotype, including limitation of horizontal gaze and scoliosis requiring surgical correction, whereas another brother was healthy. Both parents were unaffected. Segregation analysis could not be performed in the parents or the affected brother due to technical limitations; however, the same variant was presumed to be present in the affected brother.

The patient's medical history included congenital torticollis identified during infancy, along with horizontal gaze restriction observed in early childhood. Cervicothoracic and thoracolumbar scoliosis progressed with advancing age. Despite these findings, his cognitive and motor developmental milestones were appropriate for his chronological age.

Neurological examination revealed complete restriction of horizontal eye movements, with preserved upward and downward gaze. The remainder of the cranial nerve examination was normal, with no facial asymmetry. Examinations of the pyramidal and extrapyramidal systems were unremarkable. Ophthalmological evaluation showed bilateral optic atrophy, and the patient required corrective lenses. Spinal evaluation identified an S-shaped scoliosis, characterized by a left-convex curve at the cervical and upper thoracic levels and a right-convex curve at the lower thoracic and upper lumbar regions.

Cranial magnetic resonance imaging (MRI) demonstrated mild hypoplasia of the medulla oblongata and pons within the posterior fossa, along with a midline cleft extending to the floor of the fourth ventricle and involving the midsagittal planes of both structures (Figure 1). Spinal MRI demonstrated scoliosis, with a Cobb angle of 12°, showing left convexity at the cervical and upper thoracic levels and right convexity at the lower thoracic and upper lumbar levels (Figure 2). A long-segment syrinx measuring up to 3 mm was observed within the thoracic spinal cord at the level of the T8-9 disc. Additionally, minor central protrusions were noted at the C4-5 and C6-7 disc levels. The transverse processes of the L5 vertebra were sacralized. At the L4-5 disc level, degenerative signal loss and mild annular bulging were present. Genetic testing using a

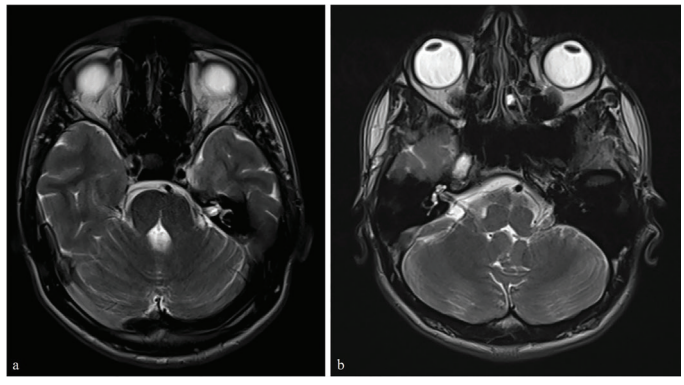

Figure 1. Axial T2-weighted cranial magnetic resonance imaging demonstrates a fissure extending from the posterior midsagittal aspects of the pons (a) and the medulla oblongata (b) to the floor of the fourth ventricle

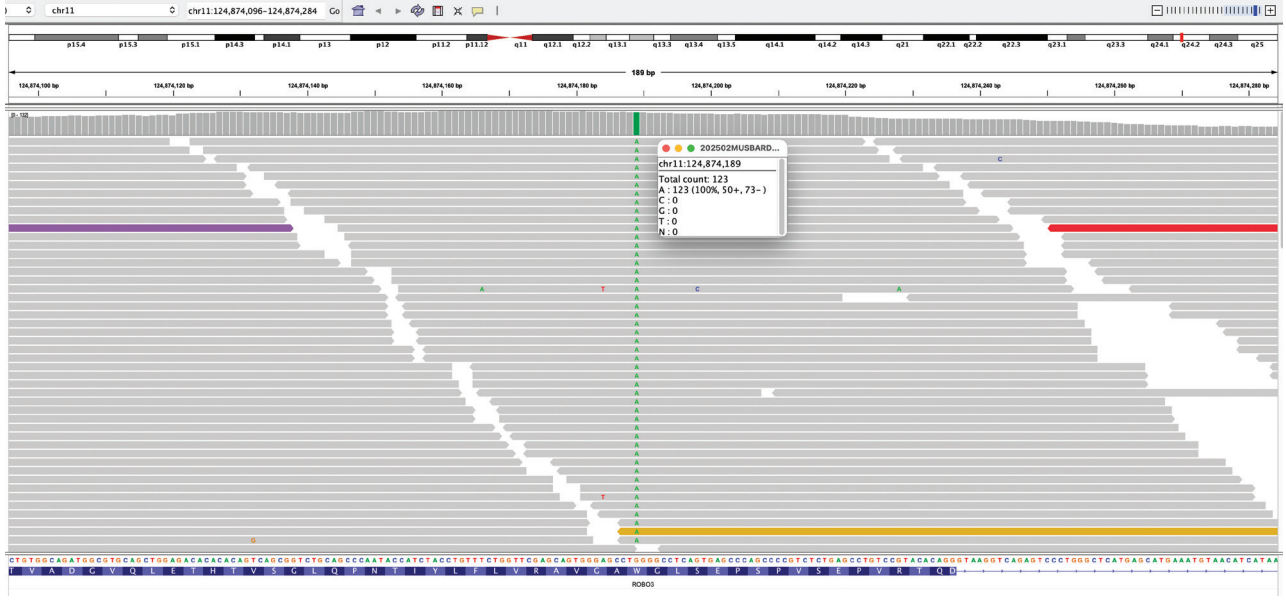

Figure 2. Integrative genomics viewer screenshot showing the homozygous c.1904G>A variant in *ROBO3*

skeletal dysplasia gene panel identified a homozygous, likely pathogenic variant in *ROBO3* (c.1904G>A, p.Trp635*), a gene previously associated with HGPPS (Figure 2). Based on these clinical and radiological findings, a diagnosis of HGPPS was considered. Notably, the homozygous c.1904G>A (p.Trp635*) variant identified in our patient has not been previously reported in the literature.

DISCUSSION

HGPPS is a distinct clinical entity that should be suspected in patients presenting with congenital horizontal gaze palsy and progressive scoliosis, particularly in the setting of consanguinity.[4] Our patient exhibited the classical clinical features, including absence of horizontal eye movements, torticollis in infancy, and progressive scoliosis in adolescence. The presence of an affected sibling in the family further supported the autosomal recessive inheritance pattern.

At initial evaluation, the differential diagnosis encompassed a broad spectrum of genetic and mitochondrial disorders, including Duane retraction syndrome, Moebius syndrome, congenital fibrosis of the extraocular muscles, congenital oculomotor apraxia, and polymerase gamma-related mitochondrial disease, because of the combination of ophthalmological and neurological manifestations.[5] However, the characteristic brain MRI findings-hypoplasia of the pons and medulla with a midline cleft extending into the floor of the fourth ventricle-together with progressive scoliosis were pivotal in narrowing the differential diagnosis. These features strongly suggested HGPPS, enabling us to establish a targeted genetic hypothesis and reach a definitive diagnosis more rapidly.

Neuroimaging abnormalities are highly suggestive of HGPPS and reflect impaired axonal guidance in the hindbrain resulting from ROBO3 dysfunction.[6] The identification of a homozygous likely pathogenic *ROBO3* variant (c.1904G>A) in our patient provided molecular confirmation of the diagnosis. Although segregation testing could not be performed, the affected brother is highly likely to carry the same variant, further supporting its pathogenic role. This variant has not been previously reported in any published case, representing a novel addition to the *ROBO3* mutational spectrum. This truncating variant introduces a premature stop codon predicted to result in loss of function, which aligns with the established disease mechanism. In the limited number of cases reported to date, loss-of-function variants have consistently been implicated in HGPPS, further reinforcing the pathogenicity of the truncating variant observed in our patient. Our case also highlights an unusual feature-bilateral optic atrophy-which has not been consistently reported in HGPPS and may represent either a coincidental finding or an expansion of the phenotype. Longitudinal follow-up is necessary to clarify its clinical relevance.

Management of HGPPS remains supportive, primarily consisting of ophthalmological monitoring and orthopedic interventions for scoliosis.[7] Early recognition is important not only to anticipate complications but also to guide genetic counseling and to avoid unnecessary investigations for other neurogenetic or mitochondrial disorders.

CONCLUSION

We report a consanguineous family with two affected siblings who present with the classical features of HGPPS and who carry a homozygous, likely pathogenic ROBO3 variant. This case underlines the importance of considering HGPPS in patients with congenital horizontal gaze palsy and progressive scoliosis, and emphasizes the diagnostic utility of brain MRI and genetic testing. In our patient, the characteristic MRI findings, together with scoliosis, were the key diagnostic clues that directed us toward HGPPS and enabled earlier genetic confirmation, thereby avoiding extensive investigations for other mitochondrial or neurogenetic disorders. Recognition of this rare disorder is essential for timely counseling, surveillance, and supportive management.

Ethics

Informed Consent: The authors confirm that written informed consent was obtained from the patient (and/or the patient's legal guardian) for publication of the clinical details and accompanying images in this report.

Footnotes

Authorship Contributions

Concept: G.M.T., Data Collection or Processing: D.E.T., G.M.T., Y.C.D., E.I., A.H.Ç., Analysis or Interpretation: D.E.T., G.M.T., Y.C.D., E.I., A.H.Ç., Literature Search: D.E.T., G.M.T., Writing: D.E.T., G.M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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