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Report of a Novel Homozygous Intragenic *DCC* Duplication and a Review of Literature of Developmental Split-Brain Syndrome aka Horizontal Gaze Palsy with Progressive Scoliosis-2 with Impaired Intellectual Development Syndrome

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Established Facts

- Horizontal gaze palsy with progressive scoliosis-2 (HGPPS2, MIM 617542) with impaired intellectual development is a rare autosomal recessive disorder associated with biallelic pathogenic variants in the *DCC* gene.
- To date, four different pathogenic variants in the *DCC* gene have been reported in 7 patients with HGPPS2.

Novel Insights

- Our case demonstrates intragenic *DCC* duplications as a disease-mechanism causing HGPPS2 syndrome.
- This study expands the genotypic and phenotypic spectrum of HGPPS2 syndrome.

Keywords
HGPPS2 · DCC · Horizontal gaze palsy · Progressive scoliosis · Intellectual disability · Agenesis of corpus callosum · Duplication

Abstract
Introduction: Horizontal gaze palsy with progressive scoliosis-2 (HGPPS2, MIM 617542) with impaired intellectual development aka developmental split-brain

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syndrome is an ultra-rare congenital disorder caused by pathogenic biallelic variants in the deleted in colorectal cancer (*DCC*) gene. ***Case Presentation:*** We report the clinical and genetic characterization of a Syrian patient with a HGPPS2 phenotype and review the previously published cases of HGPPS2. The genetic screening was performed using exome sequencing on Illumina platform. Genetic analysis revealed a novel *DCC* c.(?_1912)_(2359_?) dup, p.(Ser788Tyrfs*4) variant segregating recessively in the family. This type of variant has not been described previously in the HGPPS2 patients. To date, including the case reported here, three different homozygous pathogenic frameshift variants, one homozygous missense variant, and an intragenic duplication in the *DCC* gene have been reported in 8 patients with the HGPPS2 syndrome. ***Conclusion:*** The analysis of duplications and deletions in the *DCC* should be included in the routine genetic diagnostic evaluation of patients with suspected HGPPS2. This report expands the knowledge of phenotypic and genotypic spectrum of pathogenic variants causing HGPPS2.

Introduction

Horizontal gaze palsy with progressive scoliosis-2 (HGPPS2, MIM 617542) with impaired intellectual development aka developmental split-brain syndrome is a rare congenital disorder characterized by absence of conjugate horizontal eye movements, progressive scoliosis developing in childhood, global developmental delay/intellectual disability, agenesis of corpus callosum, and absence of cerebral commissures. HGPPS2 was previously known as developmental split-brain syndrome. It has been demonstrated to be caused by biallelic, pathogenic predicted loss-of-function variants in the *DCC* gene [1].

The deleted in colorectal cancer (*DCC*) gene encodes the netrin-1 (NTN1) receptor DCC, a transmembrane protein required for the guidance of commissural axons, and known to be an evolutionarily conserved protein. Netrin-1/DCC guidance cue pathway plays a critical role in guidance growing axons toward the prefrontal cortex and in the maturational organization [2]. Pathogenic germline *DCC* variants disrupt the development in the central nervous system. Monoallelic, pathogenic missense and predicted loss-of-function *DCC* variants cause congenital mirror movements, isolated agenesis of corpus callosum, or both. However, the penetrance of heterozygous variants appears to be markedly reduced, and the clinical presentation of symptoms displays high inter- and intrafamilial variability [3–6].

To date, only four different homozygous pathogenic variants in the *DCC* gene have been identified in 8 patients with HGPPS2 phenotype [1, 7]. HGPPS2 phenotype caused by biallelic DCC variants appears to be fully penetrant and shows a similar clinical presentation including developmental delay, intellectual disability, neuromuscular scoliosis, horizontal gaze palsy, agenesis of corpus callosum, and the absence of cerebral commissures. We report here on the phenotype of a 9-year-old girl with HGPPS2 syndrome and a biallelic (homozygous) duplication of exons 13–15 of the *DCC* gene.

Case Report

The patient is a third child of consanguineous parents from Syria. She was born at term from an uneventful pregnancy by caesarean section. She has had significant failure to thrive, and her development has been remarkably delayed. She learned to roll from belly to back at the age of 2 years, crawl at the age of 5 years, and walk with mild support at the age of 8 years (online suppl. video 1; for all online suppl. material, see https://doi.org/10.1159/000534772). She was diagnosed with severe intellectual disability after moving to Finland at the age of 8 years. She needed help with everyday tasks including feeding and dressing up. Intermittent sleeping problems were noted. Polysomnography was normal. She had a medical history of progressive scoliosis; at the age of 9 years, she had a thoracal scoliosis with a Cobb angle of 62° and a thoracolumbar scoliosis with a Cobb angle of 67°, which was operated. A month after the operation, she had a residual thoracal scoliosis with a Cobb angle of 15° and a thoracolumbar scoliosis with a Cobb angle of 13° (Fig. 1).

In the clinical examination, she had short stature; at the age of 8 years, her height is 107 cm (−4.5 SD), weight 19 kg, body mass index 16.6 kg/m^2, and occipitofrontal circumference 48.7 cm (−2.5 SD). She understood simple speech, but she was not able to speak herself. She expressed herself with gestures. She had poor eye contact and stereotypic repetitive wringing hand movements, but no mirror movements were noted. Her gait was broad based and ataxic. She had small hands, tapering fingers, and planovalgus in her feet. She had bushy eyebrows, a broad mouth, short philtrum, and prognathia (Fig. 2).

Due to her intellectual disability and lack of communication skills, we were not able to perform full ophthalmological examination. The uncorrected binocular visual acuity was at least 0.05. Her vertical eye movements were full and conjugated, but she lacked all horizontal eye movements, even horizontal optokinetic nystagmus. Her direct and consensual pupillary reflexes were normal. Cycloplegic refraction showed mild hyperopia. The fundus examination was unremarkable (online suppl. videos 2, 3).

In the etiological investigations, array-CGH was normal. EEG was normal. Metabolic investigations including urine amino acids, organic acids and oligosaccharides, and plasma amino acids were normal. Her brain MRI showed complex abnormalities in the midline. In posterior fossa, pons was split in midline, and medulla

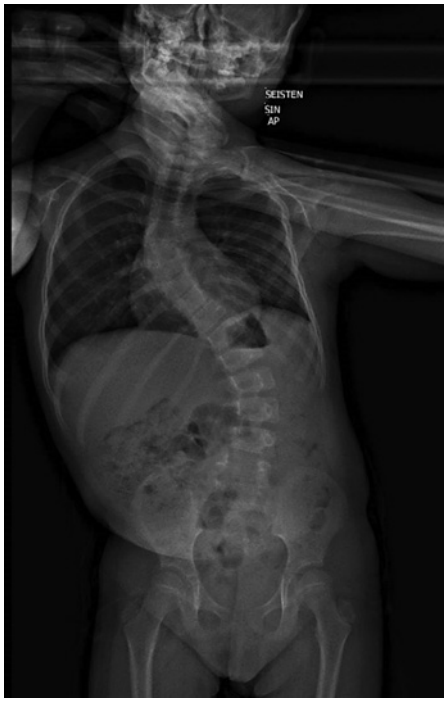

Fig. 1. X-ray of the scoliosis showing marked dextroscoliosis in the thoracal region and levoscoliosis in the thoracolumbar region.

oblongata showed a butterfly shape because of large midline cleft throughout the brainstem (Fig. 3). In supratentorial space, total agenesis of corpus callosum and other commissural tracts was evident. Widely spaced lateral ventricles, often called as racing car sign, could be seen. White matter myelination was normal.

Her parents and siblings were healthy and in the several visits, no mirror movements were noted in parents' normal behavior, but parents or siblings were not systematically examined. They did not have developmental delay or other neurological abnormalities.

We compared the clinical and radiological characteristics of the patient presented in this study and previously reported patients with HGPPS2 (Table 1). The clinical phenotype of the patient reported here and previously reported patients is recognizably similar. Consistent clinical features of horizontal gaze palsy, scoliosis, agenesis of corpus callosum, and absence of cerebral commissures were present in most the patients with biallelic pathogenic *DCC* variants.

Materials and Methods

The parents gave written informed consent. Genomic DNA was purified from peripheral blood samples of the patient and her parents using either phenol-chloroform extraction or MSM1 semi-automated extraction. Libraries were prepared using capture-based Custom Clinical Exome Solution by Sophia Genetics and sequenced with Illumina NextSeq 500 with a coverage of 50x in 98.7% of target regions. Variant filtering and annotation were performed with commercial Sophia DDM software (Sophia Genetics).

Results of Exome Sequencing

Exome sequencing revealed a homozygous apparently tandem duplication in the *DCC* (NM_005215.4):c.(?_1912)_(2359_?)dup, p.(Ser788Tyrfs*4); she has four copies of exons 13–15. The classification of the variant according to ACMG guidelines is PVS1, PM2, and PP4. Her parents are heterozygous carriers of this duplication confirming the recessive inheritance.

Review of the Literature

Clinical and genetic details of published patients with biallelic pathogenic *DCC* variants are summarized in Table 1. Original report described altogether 4 patients with biallelic *DCC* variants including an intragenic deletion and a missense variant in *DCC*, as well as a large genomic deletion including *DCC* [1]. Later, Zaka et al. [7] reported 3 patients with a homozygous single nucleotide duplication in *DCC* leading to a frameshift.

Including the patient presented in this report, altogether 8 patients with biallelic *DCC* pathogenic variants have been reported in the medical literature. The hallmarks of this syndrome are the horizontal gaze palsy ($N = 8/8$, 100%) and typical radiological features including a midline cleft in the brainstem, agenesis of corpus callosum, and absence of cerebral commissures present in all patients whose brain MRI result was available ($N = 7/7$, 100%). Common presenting features were global developmental delay, intellectual disability ($N = 5/8$, 63%), scoliosis ($N = 7/8$, 88%), short stature ($N = 3/5$, 60%), and behavioral problems ($N = 3/5$, 60%). Interestingly, occipitofrontal head circumference varied from microcephaly to macrocephaly.

To date, including the case presented in this study, altogether five different pathogenic variants causing HGPPS2 have been described in the medical literature [1, 7]. One patient with a homozygous *DCC* c.2071C>A p.(Gln691Lys) did not have intellectual disability suggesting that pathogenic missense variants may result in a milder phenotype. Most patients with pathogenic truncating *DCC* variants present with similarly severe phenotype. In the variant databases (e.g., HGMD, ClinVar), this type of genetic alteration described in our patient has not been reported previously.

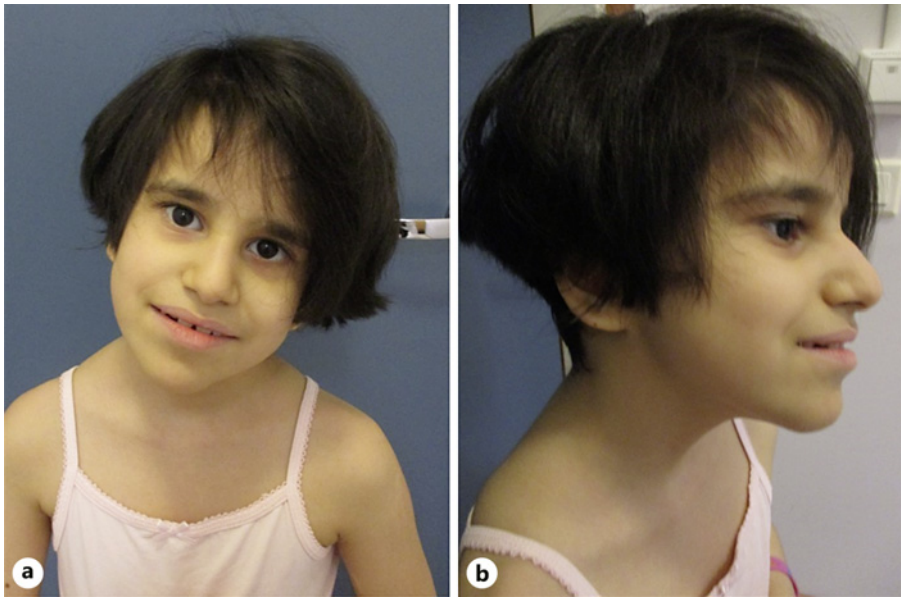

Fig. 2. a, **b** Facial photos demonstrates a long face, depressed nasal bridge, convex nasal ridge, low hanging columella, short philtrum, wide mouth, prognathia, and thick hair and eyebrows.

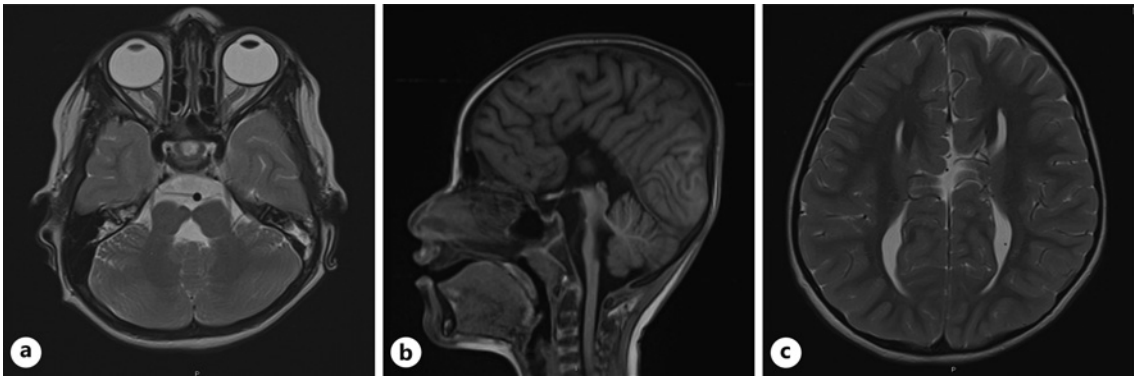

Fig. 3. a Axial T2-weighted image at the level of posterior fossa. Midline split in the pons and a butterfly appearance in the pons and medulla oblongata due to midline cleft in the brainstem. **b** Sagittal T1-weighted image in midline. Total agenesis of corpus callosum and other commissures between the hemispheres (see also the midline cleft of the pons and medulla oblongata). **c** Axial T2-weighted image at the level of centrum semiovale. Total agenesis of corpus callosum and other commissural tracts. Widely spaced lateral ventricles, often called as racing car sign.

Discussion

The first description of the clinical implications of *DCC* gene was reported around 1990 as its expression was greatly reduced in most colorectal carcinomas [8]. In the 2020, the first report by Srour et al. [9] described the association between heterozygous variant of *DCC* and mirror movements, which are contralateral involuntary movements that mirror voluntary ones. In 2017, Jamuar et al. [1] reported for the first time a novel human syndrome "developmental split-brain syndrome" caused by biallelic mutations in *DCC* gene.

DCC is a transmembrane glycoprotein, belonging to the immunoglobulin superfamily, and is highly expressed in brain and neural-crest-derived cells but can be found in low levels in almost all adult tissues. In the mature central nervous system, neurons express high levels of netrin-1 and its receptor DCC [10]. DCC and netrin-1 are highly expressed by midbrain dopaminergic neurons during neural development and in the mature brain [11–14]. CC null mice die within a few hours after birth [15].

Monoallelic *DCC* pathogenic frameshift variants are associated with reduced penetrance and predispose to mirror movements, agenesis of corpus callosum, and

Table 1. Pathogenic *DCC* variants and clinical characteristics of patients with HGPPS2 identified in the present study and previously published studies

	Jamuar et al. [1] (2017)	Jamuar et al. [1] (2017)	Jamuar et al. [1] (2017)	Zaka et al. [7] (2020)	This report	Frequency in all cases (%)
DCC variant [NM_005215.3)	7.7 kb homozygous deletion chr18: 49867185-49874867	7 bp homozygous deletion chr18: 50450167-50450173	Homozygous chr18: 50848434C>A; c.2071C>A	Homozygous c.2399dupA	Homozygous c.[?_1912)_[2359_?)dup	
Protein effect	p.[Pro11Thrfs*15)	p.[Val263Alafs*36)	p.[Gln691Lys)	p.[Asn800Lysfs*11)	p.[Ser788Tyrfs*4)	
Patients, *n*	*N* = 2	*N* = 1	*N* = 1	*N* = 3	1	8 patients
Intellectual disability	*N* = 2/2	Yes	No	*N* = 1/3	Yes	*N* = 5/8 (63)
Seizures	*N* = 0/2	No	Yes	NA	No	*N* = 1/5 (20)
Behavioral problems	*N* = 2/2	No	Yes	NA	No	*N* = 3/5 (60)
Horizontal gaze palsy	*N* = 2/2	Yes	Yes	*N* = 3/3	Yes	*N* = 8/8 (100)
Scoliosis	*N* = 2/2	Yes	No	*N* = 3/3	Yes, operated	*N* = 7/8 (88)
Mirror movements	*N* = 2/2	No	NA	*N* = 0/3	No	*N* = 2/7 (29)
Short stature	*N* = 1/2	No	Yes	NA	Yes [−3.7SD)	*N* = 3/5 (60)
Head circumference percentile	91st, 50th	Normal	91st	NA	<0.5th	
Agenesis of corpus callosum	*N* = 2/2	Yes	Yes	*N* = 3/3	Yes	*N* = 8/8 (100)
Absence of cerebral commissures	*N* = 2/2	Yes	NA	*N* = 3/3	Yes	*N* = 7/7 (100)
Midline cleft in the brainstem	*N* = 2/2	Yes	NA	*N* = 3/3	Yes	*N* = 7/7 (100)

reorganized corticomotor projections in transcranial magnetic stimulation [5]. These variants are predicted to result in haploinsuffiency via nonsense-mediated mRNA decay. This is supported by the gene's probability of being loss-of-function intolerant (pLI) score of 0.99 (http://gnomad.broadinstitute.org/). The effect of DCC haploinsufficiency seems to be critical in the time of brain development, specifically during axonal guidance and neuron migration. HGPPS2 is caused by fully penetrant biallelic *DCC* pathogenic frameshift variants resulting in complete loss of functional DCC protein. Our results confirm the previous speculations of dosage sensitivity of DCC.

We reviewed all the HGPPS2 cases reported in the literature to date; only 8 patients (including the patient presented in this paper) with biallelic *DCC* pathogenic variants causing the HGPPS2 have been described. We observed that 100% of the patients have horizontal gaze palsy and agenesis of corpus callosum. A total of 87.5% have scoliosis and 62.5% have intellectual development. The hallmarks of the syndrome were horizontal gaze palsy, scoliosis, and recognizable findings in the brain MRI including midline cleft in the brainstem and absence of corpus callosum and cerebral commissures, both anterior and posterior, demonstrating that normal function of DCC is necessary for the human embryonic development of midline structures in the CNS. This finding is consistent with animal models and functional studies demonstrating that DCC functions, together with NTN1, as a master regulator of midline crossing and commissural axon guidance in the CNS [15–17].

Commissural axons form connections between the left and right sides of the brain that are required for transfer and integration of information. The hallmarks of HGPPS2 include absence of all commissures including corpus callosum and brainstem defects. The horizontal gaze palsy may be caused by midline axon guidance defects in tracts in the hindbrain that control conjugated horizontal eye movements [18, 19]. The pathogenesis of progressive scoliosis in the disorder might arise from defective spinal commissural interneurons or paraspinal muscle activation imbalance [3, 7].

We report on here a rare case with a novel homozygous intragenic duplication in the *DCC* and a typical HGPPS2 syndrome phenotype. We speculate that this homozygous intragenic *DCC* duplication is located in tandem and breaks the reading frame and causes a preterm stop codon and due to loss of function causes the HGPPS2 phenotype in our patient. The phenotype of pathogenic DCC variants is so highly unique that even if we cannot be sure about the orientation nor the exact location of this duplication, we can certainly conclude that patient phenotype matches perfectly to that caused by pathogenic loss-of-function variants in DCC, so it is reasonable to presume that this variant is causal. This finding is unique as our patient is the only patient ever described with a partial duplication. Large exon-level duplication within the *DCC* has not been described earlier expanding the knowledge of genotypic spectrum of variants causing the HGPPS2 syndrome. The effect in protein of level of our exon-level duplication is based in interpretation of the genetic change and in silico software tools and has not been experimentally confirmed in vitro. This is a first report of the HGPPS2 in the Syrian population.

Our findings expand the genotypic and the phenotypic spectrum of the rare HGPPS2 syndrome caused by pathogenic biallelic variants in the *DCC* gene. Securing a diagnosis provides crucial information to the family for recurrence risk and allows the possibility to offer prenatal and preimplantation genetic diagnosis.

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Statement of Ethics

The study was performed according to the Declaration of Helsinki. Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images und videos. Ethical approval was not required for this study in accordance with national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Elisa Rahikkala and Maria K. Haanpää drafted the manuscript. Taneli Väisänen, Pia Pohjola, and Minna Toivonen were involved in genetic data analysis. Liisa Ojala was involved in the clinical management of the patient. Riitta Parkkola was responsible for the interpretation of radiological data. Maria K. Haanpää was involved in the clinical management of the patient and supervised the work. All authors critically revised the manuscript.

Data Availability Statement

Anonymized data not published in this article will be made available by request from the corresponding author.

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