

Expanded phenotype of new DOCK4-related neurodevelopmental disease in patient with pituitary stalk interruption syndrome and septo-optic dysplasia

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Case Report

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Abstract

Dedicator of Cytokinesis 4 (DOCK4) is increasingly recognized as being involved in human neurodevelopmental disorders. Because only a few cases have been reported, the full phenotypic spectrum remains poorly defined. We report a 17-year-old female patient with heterozygous truncating *DOCK4* *de novo* variant NM_001363540.2:c.4651C > T (p.Arg1551*). She presented with global developmental delay, mild intellectual disability, microcephaly, ataxia and hypopituitarism. Brain magnetic resonance imaging showed pituitary stalk interruption syndrome (PSIS), features of septo-optic dysplasia (SOD) and polymicrogyria. Whole-exome sequencing identified the *de novo DOCK4* variant, which is predicted to undergo nonsense-mediated mRNA decay and fulfilled PVS1 „very strong” criteria using the ClinGen/AutoPVS1 framework. Given the established role of *DOCK4* in RAC1-mediated neurodevelopmental pathways, the identified loss-of-function variant is likely to contribute to the observed neurodevelopmental phenotype and may represent a candidate explanation for the associated structural brain abnormalities. This report expands the phenotypic spectrum of *DOCK4*-related neurodevelopmental disorder and raises the possibility that SOD and PSIS may represent previously unrecognized manifestations of *DOCK4* deficiency.

Introduction

DOCK4 encodes one of the 11 members of the DOCK protein family and activates RAC1, thereby regulating actin-dependent neuronal migration, axonal growth, and synaptic organization (Boland et al., 2023; Laurin and Côté, 2014).

Emerging evidence suggests that *DOCK4* variants may cause a distinct neurodevelopmental disorder. **In 2024, Herbst et al.** described seven individuals with neurodevelopmental disorders carrying heterozygous *DOCK4* variants, as well as a fetus with compound-heterozygous variants and a severe phenotype characterized by rhombencephalosynapsis and microlissencephaly. Experimental evidence that *DOCK4* regulates RAC1-dependent neuronal development provides a plausible mechanism linking *DOCK4* deficiency to structural brain abnormalities (Huang et al. 2020).

Here, we describe a patient with a *de novo* heterozygous truncating *DOCK4* variant who presented with a neurodevelopmental disorder, pituitary stalk interruption syndrome (PSIS), and septo-optic dysplasia (SOD), potentially expanding the phenotypic spectrum associated with *DOCK4* variant.

Clinical report

The patient is a 17-year-old girl born to healthy, non-consanguineous Caucasian parents. She presented with developmental delay, mild intellectual disability, microcephaly, ataxia, optic nerve hypoplasia, GH, ACTH and arginine vasopressin (AVP) deficiency. Brain MRI revealed PSIS, SOD features, and polymicrogyria.

She was born at 41 weeks by vaginal delivery with a birth weight of 3200 g, length of 57 cm, occipito-frontal circumference (OFC) of 33 cm (– 1 SDS), and an Apgar score of 10. At 3 months, evaluation for absent visual responsiveness revealed absence of the septum pellucidum (SP) on transfontanelle ultrasound. At 5 months, MRI confirmed absent SP, corpus callosum (CC) hypoplasia, and suspected optic nerve hypoplasia. Fundoscopy showed bilaterally small, pale optic discs with pigmentary rims. She underwent right strabismus surgery at 12 years. At 17 years, visual field testing showed no response in the right eye and concentric constriction to 10–20° in the left eye. She sat at 18 months and walked and spoke her first words at 2.5 years, when her OFC was 46 cm (– 2.04 SDS). At 7 years, emotional dysregulation and attention difficulties affecting school performance were treated briefly with risperidone, followed by biofeedback therapy.

At 6 years, she was referred for short stature (100 cm; –3.37 SDS) and diagnosed with severe GH deficiency. GH therapy was administered from ages 8 to 14 years. Levothyroxine was started at 9 years because of increased requirements during GH treatment. AVP and partial ACTH deficiency were diagnosed at 10.4 and 12.6 years, respectively. Menarche occurred at 12 years.

At 8 years, pituitary MRI showed anterior pituitary hypoplasia, a thin stalk, and an absent posterior pituitary bright spot, consistent with PSIS. Additional findings included absent septum pellucidum, optic chiasm hypoplasia, and suspected bilateral frontoparietal polymicrogyria, confirmed by high-resolution MRI at 12 years.

At age 17, she underwent whole-exome sequencing (WES) as part of a PSIS research study. Ophthalmological examination revealed nystagmus and complete loss of vision in the right eye. Neurological findings included ataxic dysarthria, intention tremor, dysdiadochokinesia, and a broad-based, unsteady gait with impaired tandem walking. She had mild intellectual disability and recurrent smiling in emotionally incongruent situations. Final height is 152.7 cm and OFC 52.5 cm (– 2.0 SDS).

Genetic tests

Karyotype was 46,XX. Trio WES (proband and parents) identified a de novo heterozygous nonsense variant in *DOCK4*, NM_001363540.2.4651C > T (p.Arg1551*). Variant annotation using GeneBe classified the variant as a variant of uncertain significance (VUS; PM2). The variant (rs1191324504) is absent from ClinVar submissions and is extremely rare in the general population (gnomAD v4 allele frequency 1.4×10^{-6} , no homozygous carriers). It is predicted to result in a stop-gain, affects a highly conserved residue (PhyloP100 = 8.08), and multiple in silico tools support a deleterious effect. (Stawiński and Płoski, 2024). AutoPVS1 analysis (ClinGen PVS1 framework) demonstrated that the variant is located in exon 44 of 53, is predicted to undergo nonsense-mediated mRNA decay (NMD), and fulfilled the PVS1 Very Strong criterion, supporting a loss-of-function mechanism consistent with *DOCK4* haploinsufficiency. Although *DOCK4* has not yet undergone formal ClinGen gene curation, previously reported loss-of-function variants in patients with neurodevelopmental disorders further support this disease mechanism (Fig. 1)

(Herbst et al., 2024). WES detected additional heterozygous, mostly intronic variants classified as benign. A heterozygous *DUOX1* VUS was also identified but was considered unrelated to the phenotype.

Discussion

Our patient's developmental delay, intellectual disability, ataxia, and microcephaly overlap with previously reported *DOCK4*-related phenotypes. Her persistently positive mood may also reflect the neurodevelopmental disorder. Neuroanatomical abnormalities reported in seven patients by Herbst et al. were generally nonspecific. Only one patient had CC thinning and unilateral multiregional white matter loss. Clinical features of our patient and previously reported cases are summarized in Table 1.

Importantly, the identified variant, p.Arg1551*, represents the most distal truncating *DOCK4* variant reported to date in association with neurodevelopmental disease (Fig. 1). Previously reported loss-of-function variants included p.Arg298*, p.Arg924* and p.Asp1304Thrfs*27, all of which were associated with neurodevelopmental phenotypes. The location of p.Arg1551* within the DOCKER/DHR2 region, which mediates RAC1 activation, supports the functional relevance of the variant and is consistent with a loss-of-function disease. *Dock4*-knockout mice show behavioral, synaptic, and hippocampal microstructural abnormalities, although brain malformations have not been systematically assessed (Guo et al. 2021; Huang et al. 2020). Polymicrogyria is associated with disrupted neuronal migration and cytoskeletal regulation, including activating *RAC1* variants (Banka et al. 2022). Thus, *DOCK4* haploinsufficiency could impair RAC1-dependent cortical development, providing a plausible explanation for polymicrogyria in our patient.

DECIPHER reports multiple copy-number variants encompassing *DOCK4*, associated with intellectual disability, developmental delay, autism, CC hypoplasia, and optic disc hypoplasia. The coexistence of optic nerve hypoplasia and pituitary stalk hypoplasia may indicate a broader disturbance of neuroectodermal and midline forebrain development.

The posterior pituitary T1-hyperintense signal likely reflects vasopressin-containing neurosecretory granules. *DOCK4* disruption could theoretically impair their storage or release through altered RAC1-dependent actin dynamics. This hypothesis is supported by experimental evidence indicating that the actin cytoskeleton contributes to vasopressin release from supraoptic nucleus neurons (Tobin and Ludwig, 2007).

The *DOCK4* variant likely explains the neurodevelopmental phenotype and may contribute to the hypothalamic–pituitary abnormalities. PSIS, SOD, and arginine vasopressin deficiency may expand the *DOCK4*-related phenotype, although a coincidental association cannot be excluded.

Figure 1. Distribution of published and current *DOCK4* variants along the canonical protein.

Schematic representation of the canonical *DOCK4* protein (Q8N1I0; 1966 amino acids) showing the SH3, C2 DOCK-type and DOCKER/DHR2 domains according to UniProt annotations. Variants reported by

Herbst et al. are shown in blue, while the de novo variant identified in the present patient, p.Arg1551*, is shown in red. The patient-specific variant lies within the DOCKER/DHR2 region, which mediates RAC1 activation.

Table 1 The clinical characteristics of the presented patient and those reported in the literature.

Symptoms	Proband	Herbst et al. 2024
Intellectual disability	Yes (mild)	67% (4/6)
Motor developmental delay	Yes	86% (6/7)
Speech delay	Yes	71% (5/7)
Microcephaly	Yes	40% (2/5)
Coordination or gait abnormalities	Ataxia	71% (5/7) \ including ataxia 29% (2/7)
Seizures/epilepsy	No	50% (3/6)
Behavioral problems	A persistently positive mood attention difficulties	Autism-like behavior 29% (2/7)
Dysmorphic feature	Yes, but expressed mildly	67% (4/6)
Ophthalmologic abnormalities	Optic nerve hypoplasia Strabismus	57% (4/7) (Strabismus, Amblyopia, Myopia)
Brain MRI abnormalities	The pituitary-hypothalamic MRI -absent septum pellucidum -optic chiasm hypoplasia -hypoplastic anterior pituitary -absence of the posterior pituitary -pituitary stalk hypoplasia -polymicrogyria	67% (4/6) 1. mild cerebellar ectopia 2. corpus callosum thinning/ multiregional white matter loss with basal ganglia/brainstem involvement 3. cerebral hemispheric white matter volume loss and gliosis 4. mild diffuse cerebral atrophy

Declarations

Patient Consent Statement

Written informed consent was obtained from the patient's parents for genetic testing and for the publication of this case report.

Ethics Approval Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Ethics Committee of Wroclaw Medical University, Poland (Nr KB 277/2025)

Conflicts of Interest

The authors declare no conflict of interest. The corresponding author made all authors aware of the journal's conflict of interest policy.

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Author Contribution

J.Ch .P.K, M.S., M.D. P.Ch , MP wrote the main manuscript text and prepared figures 1 and table 1 . All authors reviewed the manuscript

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Figures

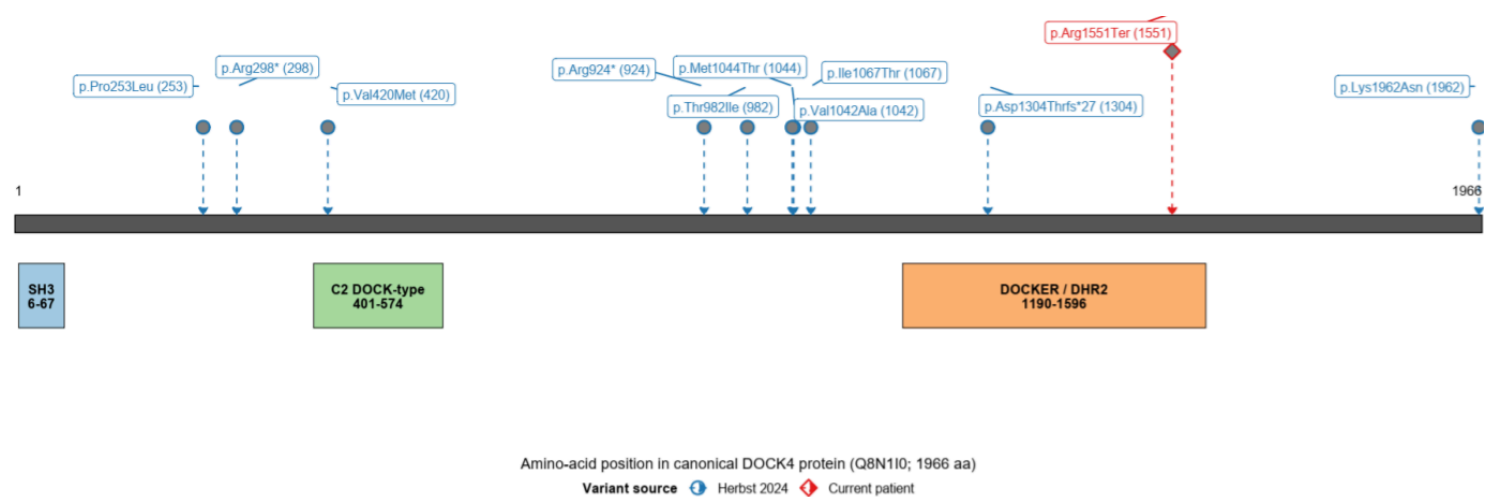


Figure 1

Distribution of published and current *DOCK4* variants along the canonical protein.

Schematic representation of the canonical DOCK4 protein (Q8N1I0; 1966 amino acids) showing the SH3, C2 DOCK-type and DOCKER/DHR2 domains according to UniProt annotations. Variants reported by Herbst et al. are shown in blue, while the de novo variant identified in the present patient, p.Arg1551*, is shown in red. The patient-specific variant lies within the DOCKER/DHR2 region, which mediates RAC1 activation.