

# A rare case of SRD5A3-CDG in a patient with ataxia and telangiectasia: A case report

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## Abstract

SRD5A3-CDG (MIM 612379) is an extremely rare congenital disease, with only 38 cases having been reported. Common manifestations are developmental delay, intellectual disability, ophthalmological abnormalities, cerebellar abnormalities, ataxia, and hypotonia. Here, we discuss a seven-year-old boy with SRD5A3-CDG (homozygous variant c.57G>A [p.Trp19Ter]), featuring the unprecedented finding of telangiectasia.

## A rare case of SRD5A3-CDG in a patient with ataxia and telangiectasia: A case report

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## A rare case of SRD5A3-CDG in a patient with ataxia and telangiectasia: A case report

### Abstract

SRD5A3-CDG (MIM 612379) is an extremely rare congenital disease, with only 38 cases having been reported. Common manifestations are developmental delay, intellectual disability, ophthalmological abnormalities, cerebellar abnormalities, ataxia, and hypotonia. Here, we discuss a seven-year-old boy with SRD5A3-CDG (homozygous variant c.57G>A [p.Trp19Ter]), featuring the unprecedented finding of telangiectasia.

**Keywords:** Allergy and immunology; Genetics; Paediatrics; SRD5A3-CDG

### Key Clinical Message

Genetic disorders such as SRD5A3-CDG must not be overlooked when a child presents with ataxia and telangiectasia. Whole-exome sequencing should be requested in cases that do not fit the typical clinical picture of ataxia-telangiectasia.

### Introduction

SRD5A3-CDG (MIM 612379) is an extremely rare congenital disease, common manifestations of which are global development delay, intellectual disability, ophthalmological abnormalities (retinitis pigmentosa/retinal dystrophy, optic nerve hypoplasia), cerebellar abnormalities, and hypotonia (1). Only 38 cases of this disease have been reported worldwide, presenting with a highly variable phenotype. While ataxia is mentioned in just under half of these cases, telangiectasia is yet to be reported (2, 3).

Ataxia and telangiectasia are clinical signs that characterize a neurodegenerative disorder known as ataxia-telangiectasia, but can also be seen in other genetic disorders like congenital disorders of glycosylation (CDG) (4). Classically, ataxia-telangiectasia involves multiple organ systems, particularly the nervous and immune systems. From early childhood, those who inherit this autosomal recessive disease develop ataxia: a disability in movement coordination (5). This manifests as problems with walking, balance, and hand coordination, as well as chorea, myoclonus, and neuropathy; a wheelchair is usually needed by adolescence. Patients also suffer from oculomotor apraxia, a condition where looking from one side to the other is difficult. Slurred speech is also prominent. Telangiectasia is one of the two major components of this condition, where enlarged blood vessels are seen in the eyes and skin.

An important note for physicians is that alternative genetic disorders must not be overlooked when a child presents with ataxia and telangiectasia. In this case report, we discuss a seven-year-old boy with a delayed diagnosis of SRD5A3-CDG (MIM 612379; homozygous variant c.57G>A [p.Trp19Ter]), where a diagnosis of ataxia-telangiectasia had been presumed.

## Case presentation

A seven-year-old boy, presumed case of ataxia-telangiectasia, was referred to our pediatric immunology clinic by a pediatric neurologist for further workup due to ocular involvement. He was born from non-consanguineous parents, gravid four, with a history of developmental delay in the previous child but no history of abortion or death. The proband weighed 3.5 kg at birth (full-term), at which time asphyxia did not occur. At the age of eight months, the parents became concerned about a delay in sitting and standing, but neuroimaging was normal without any evidence of cerebellar or vermian hypoplasia or other anomalies. He developed telangiectasia in the eyes at 15 months of age, at which time vision problems also manifested. He had a delay in global development and speaking; by four years, he could only correctly say one or two words. The convulsion history was negative. Due to his attention disorder, methylphenidate and risperidone were prescribed for him at the age of five.

At seven years of age, he had a weight of 29 kg (+2 standard deviations [SD]), a height of 120 cm (-1 to 0 SD), with a head circumference of 52 cm (-1 SD). Our physical examination revealed slight facial coarseness, mildly deep-set eyes, round nasal tip, full cheeks and thick lips (Fig. 1), central hypotonia, and ataxia. Deafness, ichthyosis, and hand stereotypes were not noted.

Our ophthalmologic consultant reported pigmentary retinopathy with optic disc paleness on examination of the fundus. Telangiectasia and nystagmus were also reported, though ocular coloboma was not seen. The visual-evoked potential demonstrated an extinguished response.

On laboratory workup, routine hematology and biochemical tests (renal/hepatic function) were normal, as were the essential metabolic screening, arterial lactate, and blood ammonia. Interestingly, the insulin-like growth factor (IGF)-1 level was normal. Other normal tests included an electroencephalogram, the brainstem-evoked potential, a karyotype study, and chromosomal microarray.

Considering the patient's clinical manifestations (pigmentary retinopathy, hypotonia, ataxia, and telangiectasia), we suspected congenital disorders of glycosylation (CDG) and requested serum isoelectric focusing and whole-exome sequencing. Exome sequencing identified the presence of homozygous pathogenic variant c.57G>A (p.Trp19Ter) in the *SRD5A3* gene. The mutation was confirmed by Sanger sequencing, and the diagnosis of SRD5A3-CDG was established.

## Discussion

The *SRD5A3* gene, at its 4q12 locus, encodes a protein that plays a role in testosterone production. This protein is a member of the polyprenol reductase subfamily within the steroid 5-alpha reductase family. To achieve N-linked glycosylation of proteins, androgen 5-alpha dihydrotestosterone (DHT) must convert polyprenol to dolichol, with this process being hindered in the SRD5A3-CDG disease (6). Congenital defects in type Iq glycosylation are linked with mutations in the *SRD5A3* gene; products of this gene expressed in the hippocampus and cerebellum are essential for brain development (7).

SRD5A3-CDG (MIM 612379) is an extremely rare congenital, multisystem disease that manifests with a highly variable phenotype (8). The main disease characteristics include ocular abnormalities (optic nerve hypoplasia/atrophy, iris and optic nerve coloboma, congenital cataract, or glaucoma), intellectual disability, nystagmus, hypotonia, ataxia, and/or ichthyosiform skin lesions (9). Cerebellar or vermian hypoplasia is seen in roughly fifty percent of cases; liver enzyme and coagulation abnormalities, and microcytic anemia, kyphosis, congenital heart defects, hypertrichosis, and retinitis pigmentosa have also been reported (1, 3). Recent years have witnessed a rise in the number of detected cases considering the emergence of next-generation sequencing (2). In the literature, only 38 cases of SRD5A3-CDG have been described (3). Our patient is the first confirmed case of SRD5A3-CDG to be reported from Iran, though some familial cases have been described in nearby countries including Turkey and Pakistan (2).

Although the phenotype of SRD5A3-CDG is highly variable (9), our case fits in with the literature in terms of features such as developmental delay, hypotonia, ataxia, pigmentary retinopathy, and nystagmus. However, an unprecedented finding is telangiectasia, which is yet to be reported in cases of SRD5A3-CDG. In fact, this clinical manifestation moved our colleagues toward presuming a diagnosis of ataxia-telangiectasia. This, coupled with the gradual emergence of the manifestations and the lack of prior access to whole-exome sequencing, led to a seven-year delay in arriving at the final diagnosis. When the patient was referred to us, we suspected congenital disorders of glycosylation (CDG) due to manifestations such as pigmentary retinopathy, hypotonia, ataxia, and telangiectasia, and requested the related diagnostic tests. A diagnostic challenge was that the insulin-like growth factor (IGF)-1 level was normal, which is unexpected in CDG. The final diagnosis of SRD5A3-CDG was achieved quite late, stressing the importance of increased understanding of this disorder.

Our report highlights the significance of carefully evaluating children who present with developmental delay alongside manifestations such as ataxia and telangiectasia. Further reports are needed to improve our understanding of SRD5A3-CDG, with the hope of achieving better management strategies and patient outcomes.

## Author Contributions

SHH: Study concept, study design, manuscript revising

RN: Study design, data collection, manuscript writing

LJ: Data collection, manuscript writing & revising

SAH: Data collection, manuscript writing & revising

HE: Data collection, manuscript writing & revising

SSA: Data collection, manuscript writing & revising

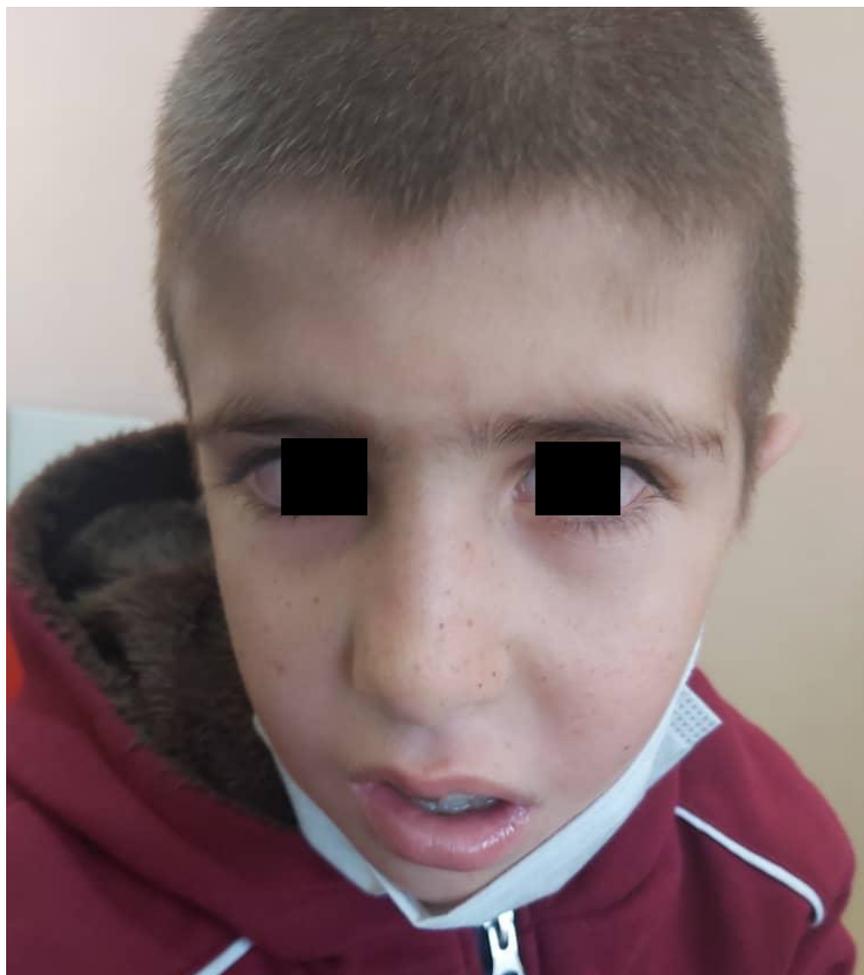
All authors read and approved the final manuscript and accept accountability for this work.

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## Figures & Legends



**Fig. 1.** Slight facial coarseness, mildly deep-set eyes, round nasal tip, full cheeks, and thick lips.