# Original Article

# Review of *SRD5A3* Disease-Causing Sequence Variants and Ocular Findings in Steroid 5α-Reductase Type 3 Congenital Disorder of Glycosylation, and a Detailed New Case

(retinal dystrophy / SRD5A3-CDG / *SRD5A3* / novel variant)

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**Abstract. Steroid 5α-reductase type 3 congenital disorder of glycosylation (SRD5A3-CDG) is a severe metabolic disease manifesting as muscle hypotonia, developmental delay, cerebellar ataxia and ocular symptoms; typically, nystagmus and optic disc pallor. Recently, early onset retinal dystrophy has been reported as an additional feature. In this study, we summarize ocular phenotypes and *SRD5A3* variants reported to be associated with SRD5A3-CDG. We also describe in detail the ophthalmic findings in a 12-year-old Czech child harbouring a novel homozygous variant, c.436G>A, p.(Glu146Lys) in *SRD5A3*. The patient was reviewed for congenital nystagmus and bilateral optic neuropathy diagnosed at 13 months of age. Examination by spectral domain optical coherence tomography and fundus autofluorescence imaging showed clear signs of retinal dystrophy not recognized until our investigation. Best corrected visual acuity was decreased to 0.15 and 0.16 in the right and left eye, respectively, with a myopic refractive error of –3.0 dioptre sphere (DS) / –2.5 dioptre cylinder (DC) in the right and –3.0 DS / –3.0 DC in the left eye. The proband also had optic head nerve drusen, which have not been previously observed in this syndrome.**

## Introduction

Congenital disorders of glycosylation (CDG) are a group of metabolic disorders caused by deficient glycosylation of proteins and/or lipids. Detection of CDG has been traditionally performed by isoelectric focusing (IEF) of serum transferrin (Jaeken et al., 1984; Guillard et al., 2011).

Steroid 5α-reductase type 3 congenital disorder of glycosylation (SRD5A3-CDG) (OMIM 612379) is a rare autosomal recessive disorder. In addition to muscle hypotonia, intellectual disability, and cerebellar ataxia, patients with SRD5A3-CDG have variably associated hepatic, cardiac, skeletal, coagulation and ophthalmic abnormalities. Ocular manifestations include microphthalmia, cataract, chorioretinal coloboma, glaucoma, optic nerve hypoplasia/atrophy, and nystagmus (Cantagrel et al., 2010; Morava et al., 2010; Taylor et al., 2017). Recently, a case series of 10 individuals showed that early-onset severe retinal dystrophy (EOSRD) is also a feature of this condition (Al-Sarraj et al., 2014; Taylor et al., 2017; Gupta et al., 2018; Khan, 2018).

SRD5A3-CDG is caused by pathogenic variants in *SRD5A3*, encoding an enzyme responsible for dolichol synthesis, and when defective, leading to impaired

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Abbreviations: BCVA – best corrected visual acuity, CDG – congenital disorders of glycosylation, DC – dioptre cylinder, DS – dioptre sphere, EOSRD – early-onset severe retinal dystrophy, FAF – fundus autofluorescence, IEF – isoelectric focusing, IQ – intelligence quotient, SD-OCT – spectral domain optical coherence tomography, SRD5A3-CDG – steroid 5α-reductase type 3 congenital disorder of glycosylation.

N-glycan biosynthesis in the endoplasmic reticulum (Morava et al., 2010).

In this study, we report clinical and molecular genetic findings in a 12-year-old child harbouring a novel *SRD5A3* homozygous variant. We particularly focus on her ocular phenotype. We also summarize all disease-causing variants identified in *SRD5A3* to date and ocular phenotype observations in patients with genetically confirmed SRD5A3-CDG.

## Material and Methods

The study was approved by the Ethics Committee of the General University Hospital in Prague and adhered to the Declaration of Helsinki.

### *Clinical examination*

A child investigated since birth for a CDG metabolic defect, which was later proved to be SRD5A3-CDG, at the age of 12 years underwent ocular examination that included spectral domain optical coherence tomography (SD-OCT) and BluePeak blue laser fundus autofluorescence (FAF) imaging (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany).

### *Molecular genetic analysis*

DNA from the proband and her parents was extracted from peripheral leucocytes using the salting-out method. Targeted sequencing of 79 CDG-related genes (Table 1) was performed in the patient in a SOLiDTM 4 System (Life Technologies, ThermoFisher Scientific, Foster City, CA) using a custom SeqCap Enrichment kit according to the manufacturer's protocol. Sequence reads were aligned to the reference genome (hg19) using NovoalignCS version 1.08 (Novocraft, Selangor, Malaysia) with default parameters. Conversion of SAM format to BAM, duplicate removal and sequence variants were identified using the SAMtools (http://www.htslib.org/) package version 0.1.12. The high confidence variant list was annotated with the ANNOVAR (http://annovar.openbioinformatics.org/) tool (hg19). For further analysis, sequence variants with a minor allele frequency < 0.005 as per the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/) were prioritized. Conventional Sanger sequencing was used to verify the presence of the identified variant considered pathogenic and for targeted screening in first-degree relatives. The detected variant considered likely pathogenic was subjected to *in silico* analysis using six different tools (Table 2).

### *Analysis of pathogenic variants in SRD5A3 and ocular phenotypes associated with SRD5A3-CDG*

Sequence variants in *SRD5A3* previously reported as causing SRD5A3-CDG were searched for in the literature, manually curated and aligned to the reference sequence NM_024592.4. The population frequency of the

*Table 1. Genes implicated in congenital disorders of glycosylation screened by next-generation sequencing in the proband*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *ALG1* | *B3GALTL* | *DK1* | *GALE* | *CHST6* | *MAN2B2* | *PIGN* | *SLC35A2* |
| *ALG11* | *B3GAT3* | *DPAGT1* | *GALK1* | *CHSY1* | *MAN2C1* | *PIGO* | *SLC35C1* |
| *ALG12* | *B4GALT1* | *DPM1* | *GALNT12* | *ISPD* | *MGAT2* | *PIGV* | *SLC35D1* |
| *ALG13* | *B4GALT7* | *DPM2* | *GALNT3* | *LARGE* | *MPDU1* | *PMM2* | *SRD5A3* |
| *ALG2* | *COG5* | *DPM3* | *GALT* | *LFNG* | *MPI* | *POMGNT1* | *ST3GAL3* |
| *ALG3* | *COG7* | *EXT1* | *GCS1* | *MAGT1* | *NGLY1* | *POMT1* | *ST3GAL5* |
| *ALG6* | *COG8* | *EXT2* | *GFPT1* | *MAN1A1* | *PGAP2* | *POMT2* | *TMEM165* |
| *ALG8* | *COSMC* | *FKRP* | *GNE* | *MAN1B1* | *PIGA* | *RFT1* | *TUSC3* |
| *ALG9* | *DDOST* | *FKTN* | *CHST14* | *MAN1C1* | *PIGL* | *SEC23B* | *XGPT1* |
| *ATP6V0A2* | *DHDDS* | *G6PC3* | *CHST3* | *MAN2A2* | *PIGM* | *SLC35A1* | |

*Table 2. In silico analysis of SRD5A3 homozygous missense variant identified in the proband. Six different algorithms were used to predict the effect of c.436G>A; p.(Glu146Lys) (reference sequence NM_024592.4).*

| **Prediction algorithm** | | | | | |
|---|---|---|---|---|---|
| **SIFT** | **PolyPhen2** | **MutPred2** | **MutationTaster** | **SNPs&GO** | **PROVEAN** |
| Damaging | Probably damaging* | Probably disease-causing | Disease causing | Disease | Deleterious |

*overall score > 0.5

Web Resources:

SIFT (Sorting Intolerant From Tolerant), http://sift.jcvi.org/

PolyPhen2 (Polymorphism Phenotyping v2), http://genetics.bwh.harvard.edu/pph2/

MutPred2, http://mutpred.mutdb.org/

MutationTaster, http://www.mutationtaster.org/

SNPs&GO, http://snps.biofold.org/snps-and-go/

PROVEAN (Protein Variation Effect Analyzer), http://provean.jcvi.org/

variants was retrieved from gnomAD, providing sequencing data from more than 138,000 unrelated individuals of various ethnic backgrounds, and 4,528 Czech control chromosomes available through the projects of the National Centre for Medical Genomics (https://ncmg.cz/en/). The associated phenotypic features were reviewed.

## Results

### *Systemic findings*

A child born to a consanguineous white Czech family was investigated at six weeks of age because of muscle hypotonia, nystagmus, irritability and developmental delay. She was also documented at the age of 19 months to have antithrombin III, factor XI and protein C deficiency. The coagulopathy dramatically worsened during acute infections in preschool years accompanied by a mild stroke-like episode resolving within 72 h at 2.5 years of age. Thereafter, she had recurrent hepatic vein thrombosis and elevation of liver enzymes requiring administration of anticoagulants. Pubertal development was normal. There were no signs of cardiomyopathy, facial dysmorphism, dermatitis or marphanoid habitus. At the last examination at 12 years of age, she had non-progressive cerebellar ataxia with stereotypic movements, mild intellectual disability (IQ = 64), obesity, kyphoscoliosis and genua valga. Mild liver dysfunction and coagulopathy persisted. The patient had never experienced seizures.

### *Sequence variant analysis*

An N-glycosylation metabolic defect was suspected based on the presence of neurological symptomatology, hepatopathy and coagulopathy, and confirmed at the age of two years by isoelectric focusing of serum transferrin. The definitive diagnosis was made when the patient was 7.5 years old by next-generation sequencing. The homozygous variant c.436G>A, p.(Glu146Lys) in *SRD5A3* (NCBI reference sequence NM_024592.4, https://www.ncbi.nlm.nih.gov/) was identified and predicted to be pathogenic (Fig. 1, Table 2).

### *Ocular examination*

The proband had congenital nystagmus from birth. Review of the clinical notes documented temporal pallor of the optic discs at 13 months of age. Right exotropia and amblyopia were documented at two years, requiring strabismus surgery at the ages of six and eight

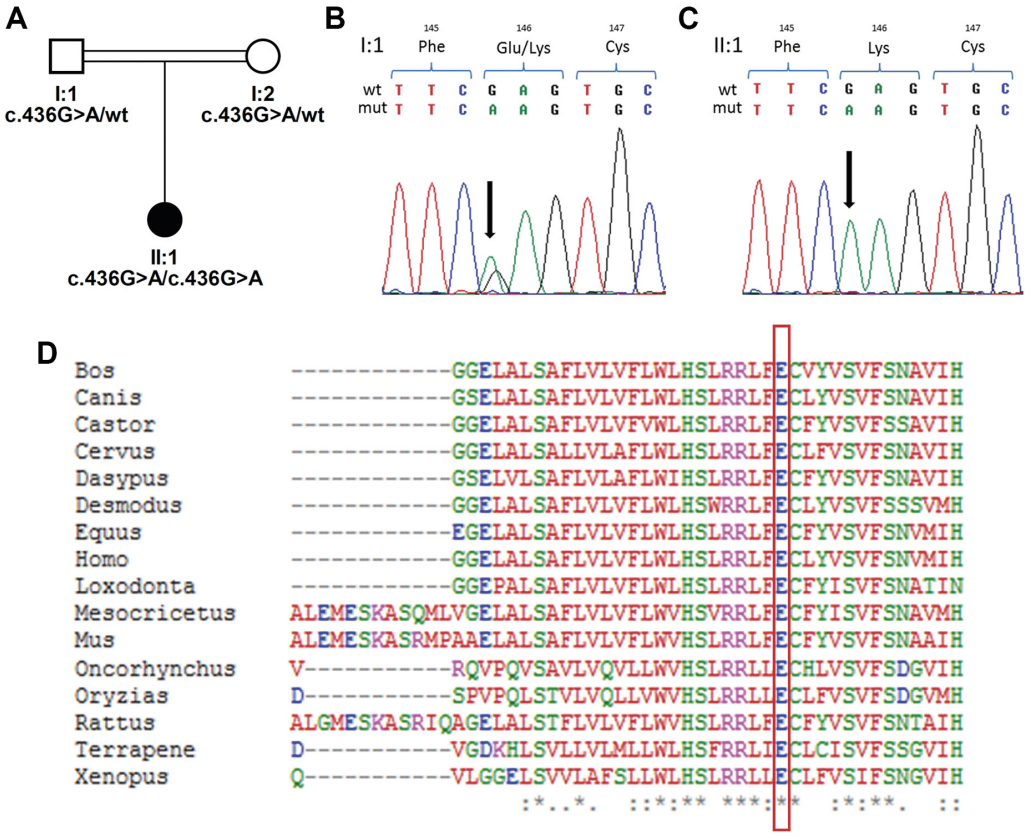


*Fig. 1*. Pedigree and segregation of the identified variant in *SRD5A3*
The affected individual is homozygous, while her parents are heterozygous carriers (**A**). Sequence chromatograms showing c.436G>A in a heterozygous (**B**) and homozygous state (**C**). T-Coffee (https://www.ebi.ac.uk/Tools/msa/tcoffee/) multiple sequence alignment of the SRD5A3 protein; amino acid at position 146 in the human SRD5A3 protein sequence is indicated by a rectangle; high degree of evolutionary conservation is observed (**D**).

years. At the age of seven years, documented decimal best corrected visual acuity (BCVA) was 0.33 in both eyes and at the age of 12 years, 0.15 in the right and 0.16 in the left eye, with a refractive error of –3.0 dioptre sphere (DS) / –2.5 dioptre cylinder (DC) in the right and –3.0 DS / –3.0 DC in the left eye.

Retinopathy had not been suspected until 12 years of age, when dilated fundus examination was performed. Tilted optic discs with temporal pallor and subtle mottling of the retinal pigment epithelium in the retinal periphery were observed (Fig. 2A, B, E). Retinal atrophy with photoreceptor degeneration was evident in SD-OCT imaging (Fig. 2C, D). FAF in the right eye identified a perimacular ring of increased signal (Fig. 1F); in the left eye, it was not possible to obtain an image due to limited compliance. In addition, superficial drusen at the optic disc margin were observed bilaterally (Fig. 2A, B, F). Perimetry, retinal nerve fibre layer measurements and ocular electrophysiology could not be performed.

### *Review of pathogenic variants in SRD5A3*

Including this study, only 15 pathogenic variants observed in 25 families with SRD5A3-CDG have been identified (Table 2). Eleven variants were not present in the gnomAD dataset, and the remaining four had a very low minor allele frequency (< 0.00003), in keeping with being pathogenic in an autosomal recessive disorder. Most cases had variants in a homozygous state and were from consanguineous families or endogamous populations. Only two probands were compound heterozygotes. Eleven variants were predicted to introduce premature stop codons, consequently leading either to truncation of

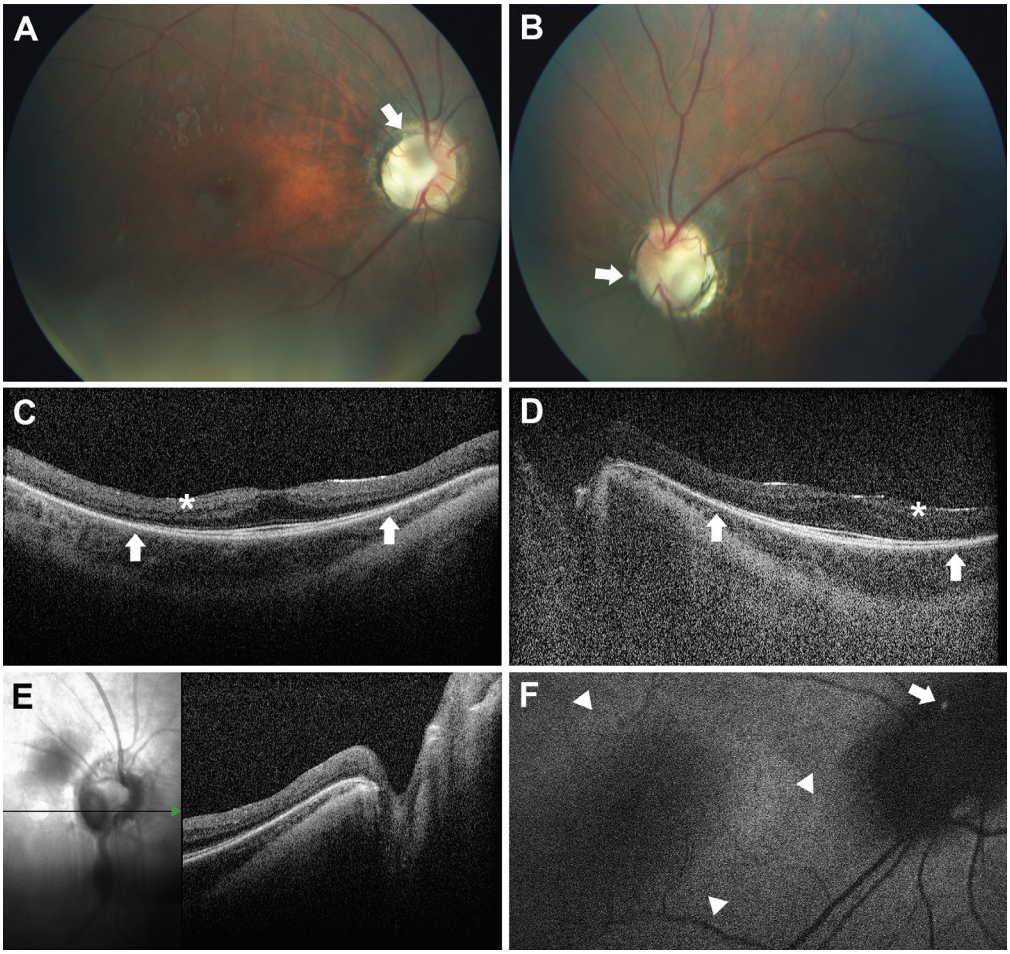


Fig. 2. Ocular findings in a 12-year-old patient with steroid 5α-reductase type 3 congenital disorder of glycosylation
Fundus photographs of the right (**A**) and left (**B**) eye showing fine granularity of the retinal pigment epithelium in the retinal periphery, temporal optic disc pallor and small superficial drusen at the optic disc margin (arrow). Horizontal SD-OCT macular scans in the right eye (**C**) and left eye (**D**). Note widespread loss of outer retinal lamination in the macular periphery including lack of the external limiting membrane, ellipsoid zone or interdigitation zone with relative preservation at the central macula. White arrows indicate borders of intact layers (1,975 µm nasally and 2,423 µm temporally and 1,940 µm nasally and 1,948 µm temporally from the fovea, in the right and left eye, respectively). Asterisks indicate loss of retinal ganglion cells. (**E**) Horizontal SD-OCT papillary scan in the right eye documenting tilted optic disc. Fundus autofluorescence imaging of the right eye (**F**) detects a hyperautofluorescent ring around the macula (demarcated by triangles) and small superficial drusen at the optic disc margin (arrow). The quality of the retinal imaging was limited by compliance and nystagmus.

*Table 3. Summary of SRD5A3 pathogenic variants reported in patients with steroid 5α-reductase type 3 congenital disorder of glycosylation. All variants were manually curated and are listed according to the reference sequence NM_024592.4.*

| DNA level | Protein level | gnomAD frequency | No. of affected | No. of families | Origin | Zygosity | Consanguinity | Reference |
|---|---|---|---|---|---|---|---|---|
| c.29C>A | p.(Ser10*) | 0 | 1 | 1 | Turkish | HOM | Y | (Cantagrel et al., 2010) (Morava et al., 2010) |
| c.57G>A | p.(Trp19*) | 0.0001251 | 14 | 10 | Turkish Pakistani Indian | HOM | Y/7 N/3 | (Assmann et al., 2001) (Prietsch et al., 2002) (Grundahl et al., 2012) (Kara et al., 2014) (Wheeler et al., 2016)† (Taylor et al., 2017)(Gupta et al., 2018) |
| c.204dup§ | p.(Phe69Leufs*2) | 0 | 3 | 1 | Iranian | HOM | Y | (Kahrizi et al., 2011) |
| c.286_288delinsTGAGTAAGGC | p.(Gln96*) | 0 | 5 | 3 | Baluchi | HOM | Y/2 N/1 | (Al-Gazali et al., 2008) (Khan, 2018) |
| c.292_293del | p.(Leu98Valfs*121) | 0 | 2 | 1 | Polish | HOM | Y | (Cantagrel et al., 2010) (Morava et al., 2010) |
| c.320G>A | p.(Trp107*) | 0 | 2 | 2 | Turkish | HOM | Y | (Cantagrel et al., 2010) (Morava et al., 2010) (Tuysuz et al., 2016) |
| c.424C>T | p.(Arg142*) | 0 | 1 | 1 | Polish | Compound HET | N | (Cantagrel et al., 2010) (Morava et al., 2010) |
| c.489C>A | p.(Tyr163*) | 0 | | | | | | |
| c.436G>A | p.(Glu146Lys) | 0.00001443 | 1 | 1 | Czech | HOM | Y | Current study |
| c.530_531del | p.(Val177Alafs*42) | 0 | 1 | 1 | Turkish | HOM | Y | (Kasapkara et al., 2012) |
| c.562+3del | p.? | 0.00002844 | 2 | 1 | Western European | Compound HET | N | (Wheeler et al., 2016) |
| c.920C>G‡ | p.(Pro307Arg) | 0.000007224 | | | | | | |
| c.603G>A | p.(Trp201*) | 0 | 2 | 1 | Puerto Rico | HOM | N | (Wheeler et al., 2016) |
| c.744T>G | p.(Phe248Leu) | 0 | 2 | 1 | Quatari | HOM | Y | (Al-Sarraj et al., 2014) |
| Complex rearrangement in exon 5 | p.? | 0 | 1 | 1 | Turkish | HOM | Y | (Cantagrel et al., 2010) (Morava et al., 2010) |

HOM = homozygous, HET = heterozygous, Y = yes, N = no
† origin not reported
§ previously reported as c.203dupC
‡ previously reported as c.921C>G

the encoded protein, or degradation of aberrant transcripts by nonsense-mediated mRNA decay. One variant was a large deletion completely disrupting gene transcription, and only three variants, including the novel variant reported herein, were predicted to be missense.

### *Summary of ocular phenotypes and their correlation with the detected genotypes*

Including this study, ocular examination has been reported for 37 patients with molecularly confirmed SRD5A3-CDG (summarized in Table 4). Nystagmus, in keeping with severe early onset visual impairment, was the most common clinical manifestation, and was noted in 34 patients. The second most common reported ocular pathology was optic disc pallor, atrophy or hypoplasia, found in 24 individuals. EOSRD was documented in 10 patients, and three further patients had severe retinal dystrophy described later in their life (Al-Sarraj et al., 2014; Kara et al., 2014; Wheeler et al., 2016; Taylor et al., 2017; Gupta et al., 2018; Khan, 2018). Childhood-onset cataract was less frequently documented (six individuals) (Kahrizi et al., 2009; Cantagrel et al., 2010; Wheeler et al., 2016). Retinal and/or optic disc colobomas were present only in nine patients (Al-Gazali et al., 2008; Kahrizi et al., 2009; Cantagrel et al., 2010; Kasapkara et al., 2012; Tuysuz et al., 2016; Wheeler et al., 2016).

## Discussion

Awareness of the presence of EOSRD in systemic disorders is important for establishing a timely diagnosis and as such, paediatric ophthalmologists/retina specialists play an essential role in this process (Morava et al., 2010; Wheeler et al., 2016; Taylor et al., 2017; Gupta et al., 2018; Khan, 2018). The case described here further supports the observations that EOSRD is a feature

*Table 4. Summary of ocular phenotypes reported in patients with genetically confirmed steroid 5α-reductase type 3 congenital disorder of glycosylation. All findings related to the eye structure and visual functions as stated in the original report have been entered.*

| No. | Age* | Ocular findings† | BCVA | | Reference |
|---|---|---|---|---|---|
| | | | RE | LE | |
| 1 | 9 y | Nystagmus, strabismus, astigmatisms, hyperopia, no RP (ERG not done) | NA | NA | (Assmann et al., 2001) |
| 2 | 6 y | Nystagmus | NA | NA | (Grundahl et al., 2012) |
| 3 | 38 y | Horizontal nystagmus, posterior subcapsular cataract, optic nerve hypoplasia/atrophy, RP | CF | CF | (Kara et al., 2014) |
| 4 | 40 y | Horizontal nystagmus, posterior subcapsular cataract, optic nerve hypoplasia/atrophy, RP | HM | HM | |
| 5 | 12.5 y | Horizontal nystagmus, wide-set eyes, optic nerve hypoplasia/atrophy (noticed at 4 m), no coloboma, no cataract, no RP | NA | NA | (Wheeler et al., 2016) |
| 6 | 11 y | Horizontal nystagmus, rolling eyes up frequently, RE iris coloboma, LE ovoid shape of the pupil, optic disc coloboma, no cataract, no RP | NA | NA | |
| 7 | 11 y | Horizontal nystagmus, optic nerve hypoplasia/atrophy, no cataract, no RP | NA | NA | |
| 8 | 34 y | Nystagmus, optic nerve hypoplasia/atrophy (diagnosed in childhood), deep-set eyes, no coloboma, no cataract, no nystagmus, no RP | ≤ 0.1 | ≤ 0.1 | |
| 9 | 33 y | Nystagmus, optic nerve hypoplasia/atrophy, cataract (diagnosed in childhood), no coloboma, RP (diagnosed in proband's 20's) | NA | NA | |
| 10 | 17 m | Horizontal nystagmus, lack of ocular fixation at 4 m, strabismus convergens alternans, optic nerve hypoplasia/atrophy | NA | NA | (Prietsch et al., 2002) |
| 11 | 20 y | Multiplanar nystagmus, nyctalopia from 6 y, mild myopia (SE −1.0 RE/−1.25 LE), optic disc pallor, foveal hypoplasia, granular appearance of peripheral retina, attenuated retinal vasculature, hyperfluorescent ring, ERG – rod-cone impairment | 0.03 | 0.03 | (Taylor et al., 2017) |
| 12 | 13 y | Multiplanar nystagmus, strabismus, progressive myopia from 2 m, (SE −5.0 RE/ −6.0 LE by 3 y), nyctalopia from 7 y, temporal optic disc pallor, attenuated retinal arterioles, hyperfluorescent ring | 0.05 | 0.06 | |
| 13 | 18.5 y | Nystagmus, strabismus, myopia from 18 m (SE −4.75 RE/−5.5 LE), tilted optic disc with temporal pallor and peripapillary atrophy, attenuated retinal vasculature, hyperfluorescent ring, OCT – widespread loss of outer retinal structures with relative preservation of foveal structures, including photoreceptors | 0.125 | 0.160 | |
| 14 | 14.5 y | Nystagmus, roving eye movements from 3 m, nyctalopia, photophobia, high myopia (SE −7.25 BE), tilted optic discs, attenuated retinal vasculature, subtle mottling in the retinal periphery, hyperfluorescent ring, OCT – widespread loss of outer retinal structures with relative preservation of foveal structures | 0.1 | 0.16 | |

to be continued ▶

| | | | | | |
|---|---|---|---|---|---|
| 15 | 16 y | Roving eye movements and nyctalopia from <1 y, exotropia from 16 y, high myopia (SE −15.5 RE/ −13.5 LE), tilted optic discs, attenuated retinal vasculature, subtle mottling in the retinal periphery, OCT – widespread loss of outer retinal structures and complete absence of the photoreceptor layer | NA | NA | (Taylor et al., 2017) |
| 16 | 14 y | Roving eye movements from 2–3 y, nyctalopia, high myopia (SE −8.75 RE/ −7.0 LE), exophoria, tilted optic discs, attenuated retinal vasculature, subtle mottling in the retinal periphery, hyperfluorescent ring, OCT – widespread loss of outer retinal structures with relative preservation of foveal structures | NA | NA | |
| 17 | 24 y | Nystagmus, high myopia (SE −7.25 LE/−7.5 RE), optic disc pallor, attenuated retinal vasculature, hyperfluorescent ring, OCT – widespread loss of outer retinal structures with relative preservation of foveal structures, ERG – profoundly electronegative, grossly delayed cone-specific responses | 0.1 | 0.1 | |
| 18 | 4 y | Nystagmus, mild optic disc pallor, RP | NA | NA | (Gupta et al., 2018) |
| 19 | 13 y | Pendular nystagmus, exotropia, −1.25 BE, attenuated vessels, RP, CME, hyperfluorescent ring | 0.13 | 0.13 | (Khan, 2018) |
| 20 | 0–3 m | Nystagmus, optic nerve hypoplasia/atrophy, iris and chorioretinal coloboma | NA | NA | (Al-Gazali et al., 2008) |
| 21 | 4.5 y | Nystagmus, optic nerve hypoplasia/atrophy, LE chorioretinal coloboma | NA | NA | |
| 22 | 2 y | Nystagmus, iris and chorioretinal coloboma, optic nerve hypoplasia/atrophy | NA | NA | |
| 23 | 5 y | Nystagmus, LE strabismus, optic nerve hypoplasia/atrophy, LE microphthalmia | NA | NA | |
| 24 | 8 y | Nystagmus, optic nerve hypoplasia/atrophy | < 0.5 | < 0.5 | (Morava et al., 2009) |
| 25 | 5 y | Nystagmus, optic nerve hypoplasia/atrophy | NA | NA | |
| 26 | 2 y | Nystagmus, strabismus, glaucoma | NA | NA | |
| 27 | NA | Nystagmus, optic nerve hypoplasia/atrophy | NA | NA | (Cantagrel et al., 2010) |
| 28 | NA | Nystagmus, iris and chorioretinal coloboma, microphthalmia, cataract | NA | NA | |
| 29 | NA | Nystagmus, optic nerve hypoplasia/atrophy, cataract | NA | NA | |
| 30 | 4 m | Nystagmus, iris coloboma, glaucoma, corneal clouding | NA | NA | (Tuysuz et al., 2016) |
| 31 | 3.5 y | Nystagmus, convergent strabismus, optic nerve atrophy/hypoplasia, RE iris, chorioretinal and optic disc coloboma, chorioretinal atrophy | NA | NA | (Kasapkara et al., 2012) |
| 32 | 12 y | Nystagmus, optic nerve hypoplasia, myopia, visual impairment | NA | NA | (Al-Sarraj et al., 2014) |
| 33 | 5 y | Nystagmus, optic nerve atrophy, ERG – diffuse retinal dystrophy | NA | NA | |
| 34 | 45 y | LE iris coloboma, cataract (documented since adolescence) | NA | NA | (Kahrizi et al., 2009) |
| 35 | 42 y | Cataract (documented since adolescence) | NA | NA | |
| 36 | 40 y | Iris coloboma, cataract (documented since adolescence) | NA | NA | |
| 37 | 12 y | Nystagmus, tilted optic discs, optic nerve hypoplasia/atrophy, subtle peripheral mottling of the retinal pigment epithelium, myopia (SE −4.25 RE/ −4.5 LE), OCT – widespread loss of outer retinal structures with relative preservation of foveal structures | 0.15 | 0.16 | Current study |

Best corrected visual acuity is extrapolated to decimal values. Abnormality of the optic disc is denoted due to insufficient consensus between the individual reports as hypoplasia/atrophy.

* Age at examination

† Unless specified, clinical findings are assumed to be bilateral.

y = years, m = months, NA = not available, ERG = electroretinography, RP = retinitis pigmentosa (pigmentary retinopathy), RE = right eye, LE = left eye, SE = spherical equivalent, OCT = optical coherence tomography, BE = both eyes, CME = cystoid macular oedema, BCVA = best corrected visual acuity, CF = counting fingers, HM = hand movement

of SRD5A3-CDG (Taylor et al., 2017; Gupta et al., 2018; Khan, 2018). We also report the finding of optic head nerve drusen in this syndrome, which to the best of our knowledge has not been previously observed.

The reason why retinopathy in patients with SRD5A3-CDG has not been recognized until recently is likely due to several factors. In most cases, nystagmus and poor visual behaviour could have been attributed to optic disc pallor, which is found in the majority of patients, and thereby visual failure is incorrectly considered to be due to optic nerve hypoplasia/atrophy (current evidence is insufficient to determine which of the two terms is correct) (Morava et al., 2010; Taylor et al., 2017). In addition, ophthalmic evaluation in individuals with SRD5A3-CDG is often not comprehensive due to the significant learning difficulties present in the vast majority of patients (Kahrizi et al., 2009, 2011; Wheeler et al., 2016). As fundus examination may not reveal typical pigmentary changes in the early stages and patients may not be able to undergo perimetry or ocular electrophysiology, SD-OCT and FAF examination are particularly valuable methods to de-

tect retinal abnormalities in these subjects (Taylor et al., 2017; Khan, 2018).

In summary, patients with SRD5A3-CDG are unique in that they develop abnormal ocular phenotypes including EOSRD, which can now be considered to be disease-delineating features. Description of more cases and long-term follow-up is necessary to better characterize the optic nerve and retinal pathology in SRD5A3-CDG.

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