TIMP3 c.319C>T, p.(Arg107Cys): Novel Sequence Variant In Sorsby Fundus Dystrophy

Rozaliya Hristova[1,2], Nevyana Veleva[1,2], Alexander Oscar[1,2], Svetoslav Slavchev[1,2], Yani Zdravkov[1,2]

[1]Department of Ophthalmology, University Hospital Alexandrovska, Sofia, Bulgaria
[2]Department of Ophthalmology, Medical University Sofia, Sofia, Bulgaria

ABSTRACT

Introduction: Sorsby fundus dystrophy is a rare autosomal dominant inherited retinal disease. The purpose of this case report is providing evidence to link the novel variant TIMP3 c.319C>T, p.(Arg107Cys), classified as variant of uncertain significance, to the clinical phenotype and to consider assignment of pathogenicity.

Case: Thorough history and comprehensive ophthalmological exam of a 51-year old female with presenile cataract and difficulty in night vision were conducted. Visual acuity was 0.15 logMAR and 0.05 logMAR in the right and left eye, respectively.

Observations: The examination was remarkable for pseudophakia in the left eye and bilateral drusenoid deposits. Visual fields demonstrated reduced retinal sensitivity. Optical coherence tomography showed drusen in the periphery. Fundus autofluorescence demonstrated corresponding hyper-autofluorescence. Electroretinography depicted reduced bioelectrical activity for scotopic conditions. Genetic testing identified a heterozygous missense, splice region variant TIMP3 c.319C>T, p.(Arg107Cys), which is a variant of uncertain significance and no other possible disease causing mutations.

Conclusion: Based on our findings we propose assignment of pathogenicity to the novel variant TIMP3 c.319C>T, p.(Arg107Cys) as likely pathogenic in Sorsby Fundus Dystrophy.

Key words: Genetic mutation; inherited retinal disease; sorsby fundus dystrophy; TIMP3.

Financial Interest : Nil
Conflict of Interest : Nil

Received : 22.10.2023
Accepted : 25.12.2023

Corresponding Author
Rozaliya Hristova
Email: alleta@abv.bg

Access this article online
Website: www.nepjol.info/index.php/NEPJOPH
DOI: https://doi.org/10.3126/nepjoph.v16i1.63004

ISSN: 2072-6805, **E-ISSN:** 2091-0320

INTRODUCTION

Sorsby fundus dystrophy is a rare disease with an approximate prevalence of 1 in 220,000 (Anand-Apte et al., 2019). It is characterized by changes similar to age-related macular degeneration seen in a younger age group (around 40-60 years). Symptoms usually begin with night blindness, abnormal dark adaptation, central scotomata, and abnormal color vision. Fundoscopic examination demonstrates drusenoid deposits in the posterior pole along the vascular arcades, as well as reticular pseudo-drusen. Later in the course of the disease, choroidal neovascularization develops simultaneously or followed by chorioretinal geographic atrophy.

Sorsby fundus dystrophy is a monogenic, albeit genetically heterogeneous disease with 16 known mutations in the *TIMP3* gene (Dewing et al., 2019) (tissue inhibitors of metalloproteinase 3) inherited in autosomal dominant manner. Mutations in *TIMP3* lead to both excessive amounts of protein with reduced metabolism, as well as loss of function – reduced inhibition of matrix metalloproteinases. Most of the disease-associated variants are in the C-terminal region and involve the gain of a cysteine residue.

This case report is aimed at providing evidence to link the novel variant *TIMP3* c.319C>T, p.(Arg107Cys), classified as variant of uncertain significance, to the clinical phenotype and to consider assignment of pathogenicity.

CASE REPORT

This case report meets international norms and the terms of Declaration of Helsinki. Approval from the institutional/ethical review board and informed consent from the subject have been obtained.

A 51-year old female with presenile cataract complained of reduced clarity of vision and difficulty in night driving. Her family history was unremarkable. She has 2 healthy children.

At clinical examination at 1300 lux of room illumination the best corrected visual acuity was 0.15 logMAR in her right eye and 0.05 log MAR in her left eye at distance (tested on 4m). Near best corrected visual acuity was 0.1 logMAR in her right eye and 0.05 logMAR in her left eye. Retinoscopy following cycloplegia did not reveal significant refractive error: right eye: -0.50/−1.0 × 10° and left eye: -1.00/−0.50 × 120°.

Anterior segments were unremarkable except for pseudophakia in the left eye (LE) and nuclear opacification in the right eye (RE). Fundus examination demonstrated bilateral drusenoid deposits along the vascular arcades extending to the mid-periphery.

Humphry visual field Analyzer 3 (Carl Zeiss AG, Jena, Germany) static 30-2 SITA Standard perimetry evidenced slightly reduced retinal sensitivity within the central 30° (Figure 1).

Central foveal thickness analyzed by optical coherence tomography (3D OST-1 Maestro2, Topcon Healthcare, Oakland, NJ, USA) measured 248 microns in the right eye and 251 microns in the left eye, with normal macular morphology. Both macular and peripapillary RNFL were normal. Scans of the drusenoid deposits revealed irregularity of the RPE with homogeneous hyperreflective elevations consistent with drusen. (Figure 2).

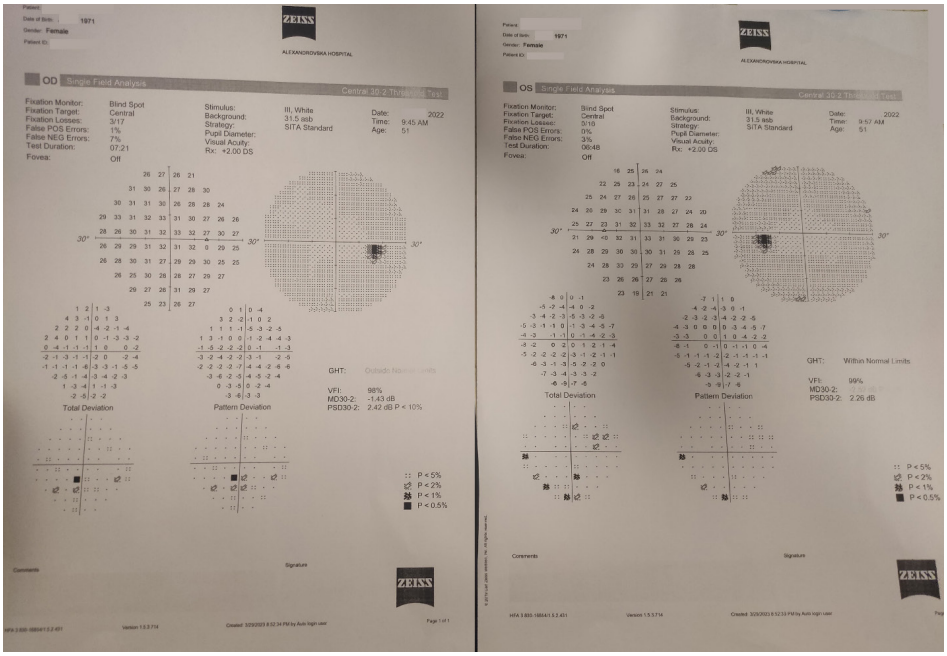

Figure 1. Standard automated perimetry demonstrating slightly reduced retinal sensitivity within the central 30°.

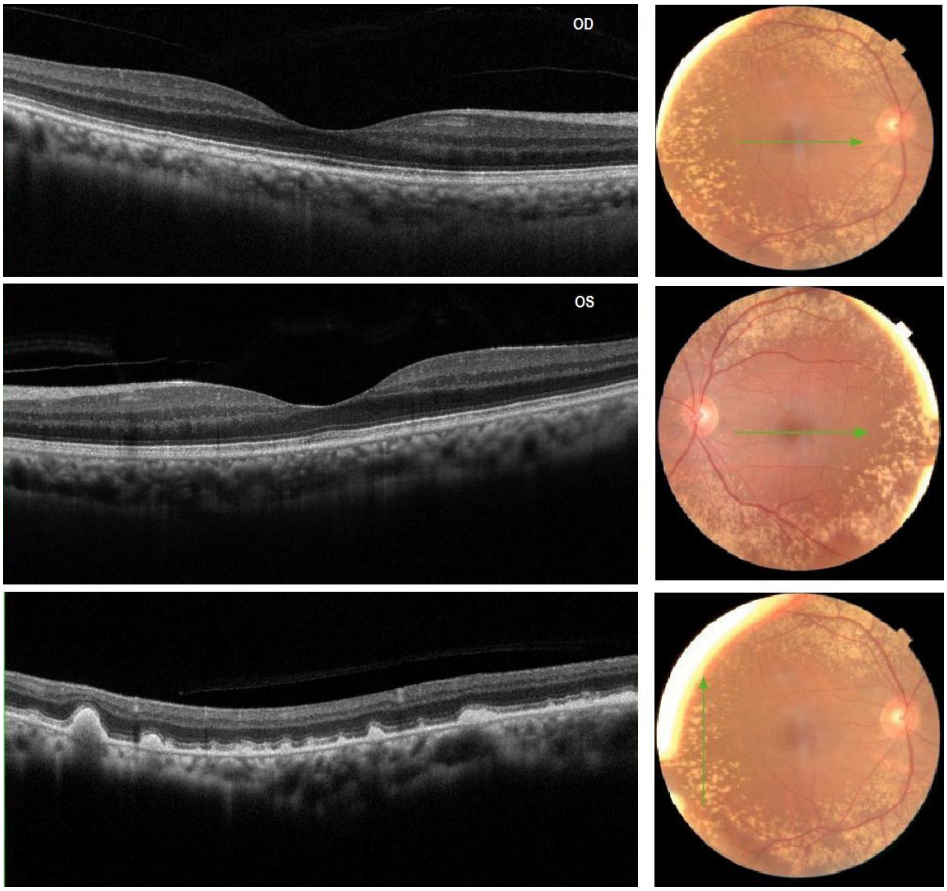

Figure 2. Optical coherence tomography showing normal macular structure with fundus view in the right (OD) and left (OS) eye and a b-scan through the drusen in the periphery of the right eye (bottom).

Fundus autofluorescence demonstrated patchy hyperautofluorescence in the periphery corresponding to the drusenoid deposits (Figure 3).

Electrophysiological testing (Roland Consult RETI-port/scan 21, Roland Consult Stasche & Finger GmbH–German Engineering, Brandenburg an der Havel, Germany) according to ISCEV standards was performed. Full-field electroretinography (ERG) depicted reduced bioelectrical activity more pronounced for scotopic conditions with delayed explicit times bilaterally. Multifocal ERG demonstrated bilateral signs of slightly reduced voltage (RE 55.29μV/47ms; LE 48.93 μV /47ms) with preserved morphology of the macular peak in the right eye (Figure 4).

A buccal swab from the patient was collected and sent to Blueprint Genetics Laboratory, Espoo, Finland. The Blueprint Genetics Retinal Dystrophy Panel (version 6, 2020, Feb 22) identified a heterozygous missense, splice region variant *TIMP3* c.319C>T, p.(Arg107Cys), which is a variant of uncertain significance (VUS) through Plus sequence and copy number variation analysis, as well as heterozygous *RDH5* c.218C>T, p.(Ser73Phe), which is likely pathogenic, *KATNIP* c.808del, p.(Ser270Valfs*28), also likely pathogenic.

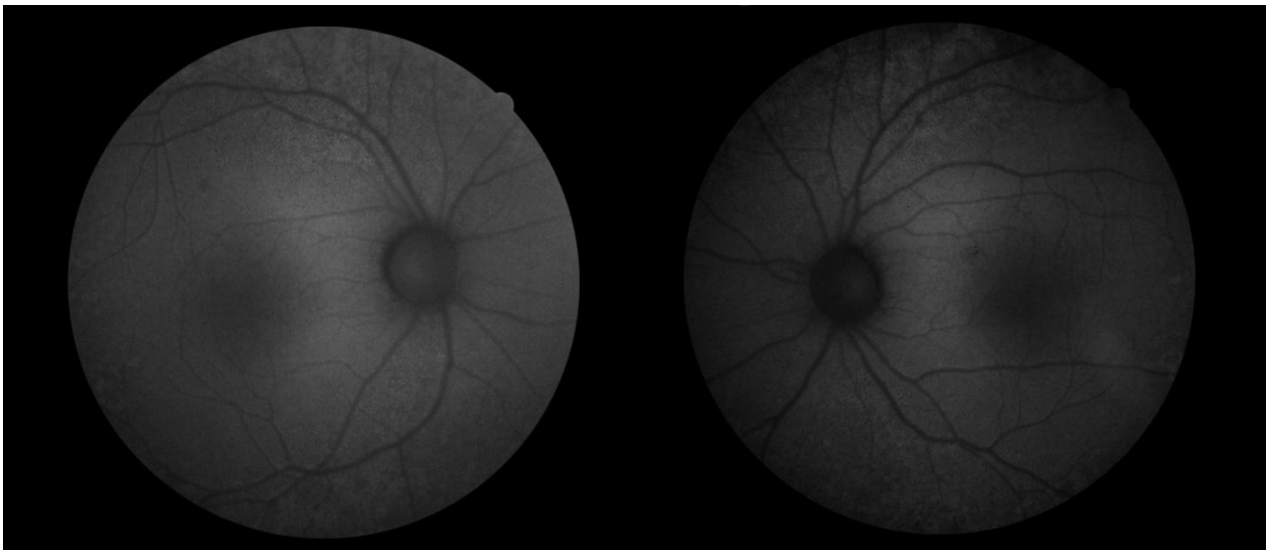

Figure 3. Fundus autofluorescence demonstrating patchy hyperautofluorescence corresponding to the drusenoid deposits.

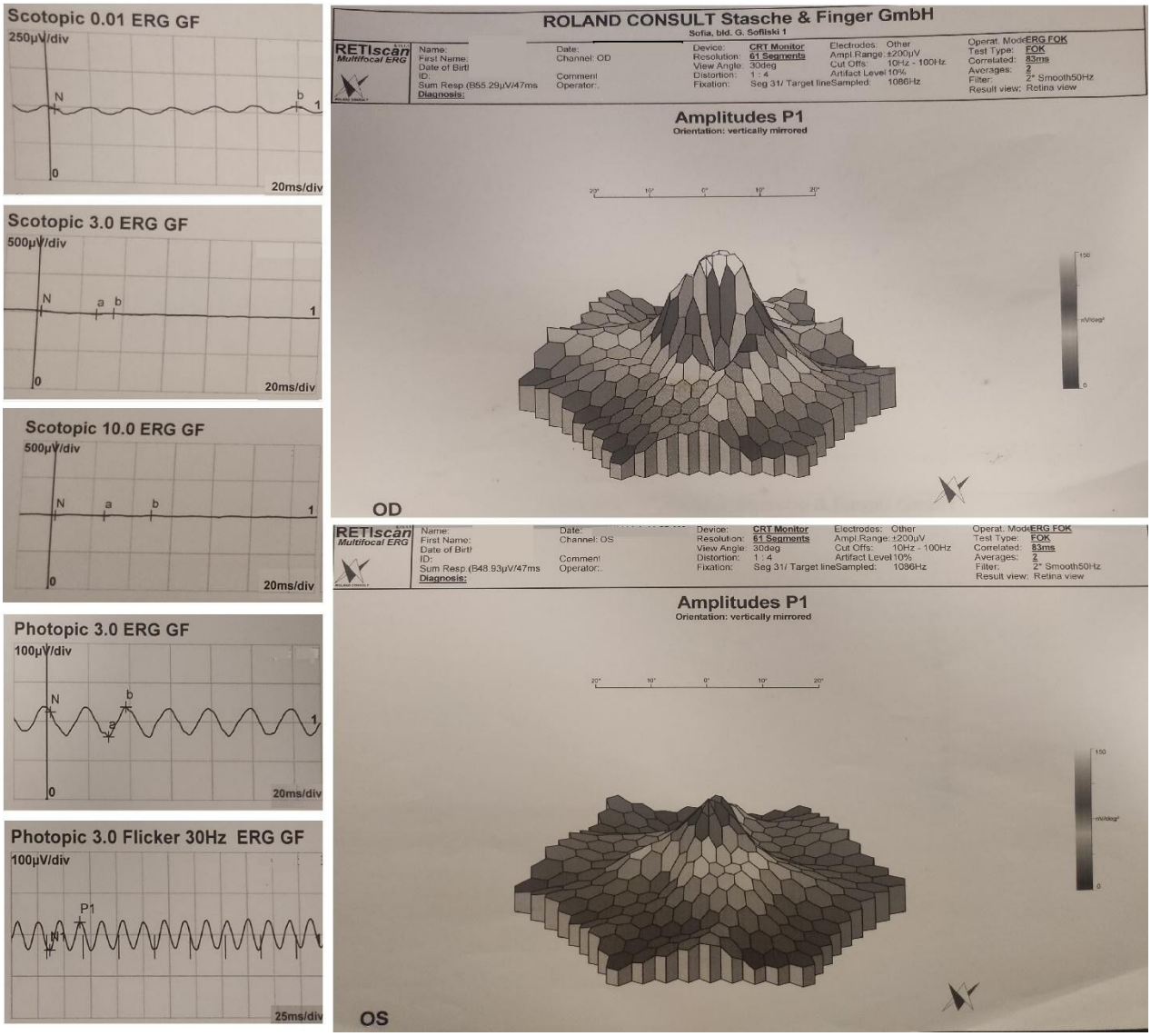

Figure 4. Electrophysiological testing. Left: Full-field ERG demonstrating reduced bioelectrical activity for scotopic conditions. Right: Multifocal ERG demonstrated bilateral signs of slightly reduced voltage with preserved morphology of the macular peak in the right eye.

DISCUSSION

The TIMP family of proteins has a highly conserved tertiary structure comprising six intramolecular disulfide bonds forming between 12 cysteine residues. Pathogenic variants in *TIMP3* are causative for autosomal dominant Sorsby fundus dystrophy. Drusen-like deposits are frequent characteristics of early disease (Christensen et al, 2017). Our patient demonstrated typical drusen-like deposits in the periphery, but no macular pathology.

Weber et al. (1994) first described *TIMP3* missense variants c.572A>G, p.(Tyr191Cys) and c.610A>T,p.(Ser204Cys) in two families

with autosomal dominant Sorsby fundus dystrophy. Since then, multiple additional missense variants in *TIMP3* have been reported in association with Sorsby fundus dystrophy (Christensen et al, 2017, Wang et al, 2017).

Our patient was diagnosed with *TIMP3* c.319C>T, p.(Arg107Cys) variant, which is absent in the large reference database "The Genome Aggregation Database" (gnomAD). After thorough research, we found that this variant has not been reported in the medical literature or on disease-related variation database "The Human Gene Mutation Database" HGMD. Although termed variant of uncertain significance (VUS), *TIMP3* c.319C>T, p.(Arg107Cys) is (1) absent in population databases and (2) detected in a pathogenic phenotype, which can be classified as moderate evidence of pathogenicity (Richards et al, 2015). Further determinants include, (1) multiple computational evidence (Muttaster, PolyPhen, and Sift in-silico tools) supporting its deleterious effect, affecting a highly conserved amino acid within the netrin domain of the protein, (2) a pathological phenotype for the disease is caused by missense variants, which are rarely benign, and (3) patient phenotype is highly specific for a disease with a single genetic etiology (Figure 2). These findings fulfill the supporting pathogenic criteria (Richards et al, 2015). In general, based on the combination of 2 moderate and ≥2 supporting criteria the variant TIMP3 c.319C>T, p.(Arg107Cys) could be reclassified as likely pathogenic.

RDH5 c.218C>T, p.(Ser73Phe), which is likely pathogenic, is linked to fundus albipunctatus (Y), a condition characterized by impaired night vision and whitish-yellow flecks in the retina. Our patient had impaired night vision, but the whitish-yellow flecks in the retina were found to be drusen. Since *RDH5*-related disease is autosomal recessive and no second potentially disease-causing variant in *RDH5* was detected in the patient, this heterozygous variant is not expected to be related to the patient's clinical presentation.

The patient was found to be heterozygous for a likely pathogenic variant *KATNIP* c.808delp. (Ser270Valfs*28), which has been associated with Joubert syndrome (Brancati et al, 2010). To the best of our knowledge, this variant has not been described in the medical literature or reported in disease-related variation databases.

CONCLUSION

In accordance with a thorough literature research this is the first report of *TIMP3* c.319C>T, p.(Arg107Cys) associated with a clinical manifestation of Sorsby fundus dystrophy. Therefore, we conclude that the variant *TIMP3* c.319C>T, p.(Arg107Cys) contributed to the pathologic phenotype, clearly demonstrating its significance in the presented case, and should be reclassified according to the criteria of evidence as likely pathogenic.

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