

The genetic counseling in a patient affected by choroideremia solved with the whole-exome sequencing approach

Bedia Sahin, Erik Burton¹, Okkes Kuybu¹,
Yavuz Sahin², John Brinkley³

Key words: *CHM*, choroideremia, genetic counseling, whole-genome sequencing

Choroideremia (*CHM*, MIM 303100) is a rare X-linked recessive disease characterized by the progressive chorioretinal atrophy field.^[1] Choroideremia is caused by pathogenic variants in the *CHM* gene and is estimated to affect 1 in 50,000 to 100,000 males. The *CHM* gene encodes Rab escort protein-1 (REP-1), which prenylated Rab GTPases to play a role in the intra-cellular trafficking.^[2] Most of the pathogenic variants identified in the *CHM* gene are loss-of-function variants. Generally, female carriers are asymptomatic; affected males suffer night blindness in late childhood along with retinal pigment epithelium mottling in the peripheral fundus.^[3] Progressive atrophy of the peripheral choroid and outer retina with relative preservation of the central macula is typical. Here, we report a patient with *CHM* arising from a hemizygous variant in the *CHM* gene.

A 17-year-old male sought ophthalmologic evaluation after his sister disclosed his complaint of night blindness during preconception counseling. The affected male had experienced poor night vision at an early age and decreased visual acuity and was initially diagnosed as retinitis pigmentosa (RP) in previous eye examinations. A detailed ophthalmological exam showed the best-corrected visual acuity of 20/20 in both the eyes with patchy loss of the mid-peripheral visual fields.

The funduscopic exam showed a slight loss of retinal pigment epithelium (RPE) and retinal atrophy. Spectral-domain optical coherence tomography (OCT) imaging of the macula

shows atrophy of the peri-foveal RPE, the outer retina along with the presence of outer retinal tubulations, and choroidal atrophy in the right eye [Fig. 1a] and left eye [Fig. 1b]. The sub-foveal ellipsoid zone is faintly preserved in both the eyes. After 4 years of follow-up evaluation, the patient showed progressive loss of his peripheral vision and increased choroidal atrophy. The patient's parents were unrelated [Fig. 1c], of Turkish ethnicity, and healthy with no other affected family members. To provide an accurate diagnosis, correct healthcare support for the patient, and appropriate genetic counseling, it may be increasingly useful to consider extensive genetic testing through an extended clinical panel or whole-exome sequencing (WES).

Consents were obtained from the patient, his sister, and brother-in-law for genomic DNA testing from peripheral blood according to standard protocols. Samples for the male proband underwent WES by the MGISEQ-2000 platform. WES generated about 10.5 Gb of sequence data for the tested individual II-1. The raw paired-end reads were in the form of a FASTQ file which underwent several programs such as Bowtie, BWA, SAMtools, Picard, and GATK to create a variant call format (VCF) file, sequentially. Later, we analyzed the VCF file using ANNOVAR. After filtering, a hemizygous c.969T>A, (p.Tyr323*) variant on NM_000390.3 transcription of the *CHM* gene was identified. The variant was confirmed by Sanger sequencing in the patient as hemizygous [Fig. 1d]. His sister was also a carrier, but no variant was identified in her husband [Fig. 1d] at the *CHM* gene. This variant has not been reported in a hemizygous or homozygous state in publicly available databases such as the gnomAD, ExAC, and the 1000 Genome Project or the in-house Turkish exome database which contains 1286 samples. Prediction analysis within silico algorithms, such as Mutation Taster, Polyphen-2, and Combined Annotation-Dependent Depletion (CADD), showed this alteration to be pathogenic and disease-causing. The variant was reported as pathogenic in ClinVar (rs886041180). From the genetic data and clinical findings, the diagnosis was corrected to choroideremia.

Discussion

Choroideremia is a rare X-linked recessive disease of the outer retina because of variants of the *CHM* gene which encodes REP-1, an essential protein for intra-cellular vesicular trafficking. Progressive chorioretinal degeneration will occur when unprenylated proteins accumulate in the cytosol because of the loss of REP-1 functions.^[4,5] Choroideremia is the second leading cause of hereditary and progressive bilateral night blindness after retinitis pigmentosa and occurs in approximately 4% of the blind

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Department of Ophthalmology, Karaman State Hospital, Karaman, Turkey, ¹Department of Neurology, LSU Health Shreveport, Shreveport, LA, USA, ²Genoks Genetic Diseases Diagnostic Center, Ankara, Turkey, ³Department of Ophthalmology, LSU Health Shreveport, Shreveport, LA, USA

Correspondence to: Dr. John Brinkley, Department of Ophthalmology, LSU Health Shreveport, 1501 Kings Highway, Shreveport - 71130, USA. E-mail: jbrin2@lsuhsc.edu

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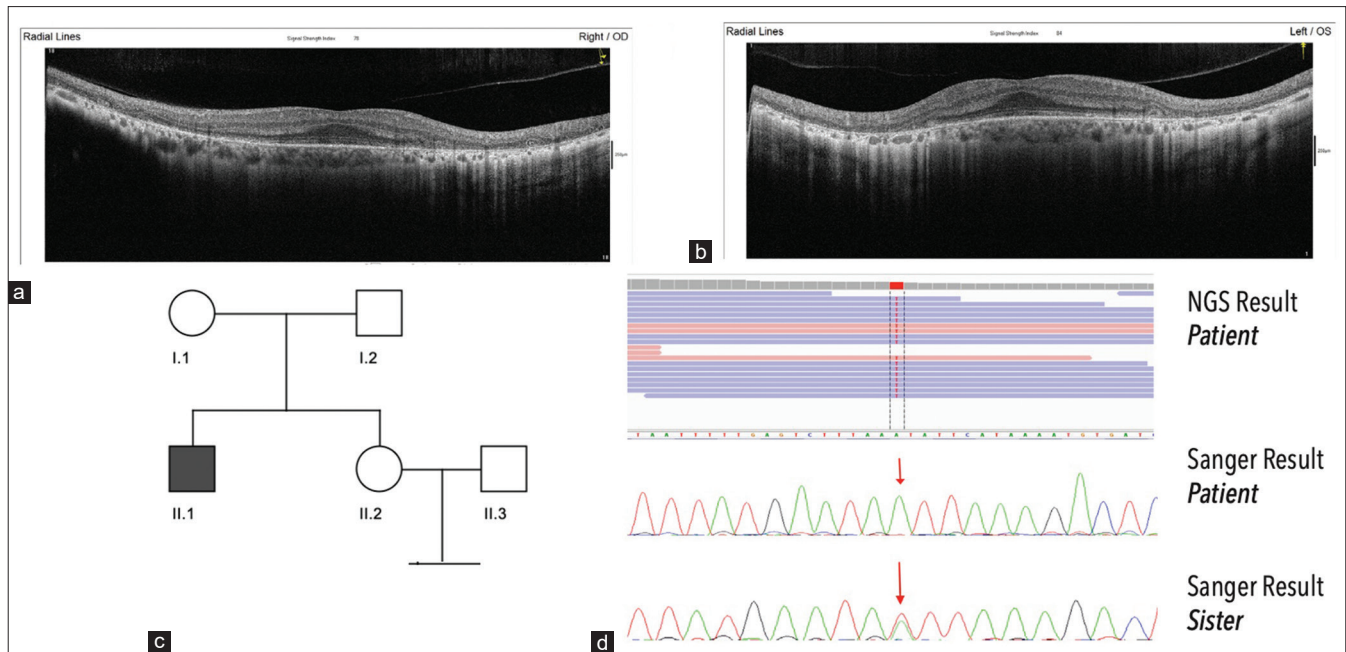


Figure 1: (a and b) Optical coherence tomography (OCT) imaging of the maculas. (c) Pedigree of the family. The black arrow shows the index patient. (d) Next-generation sequencing (NGS) revealed the hemizygous variant at the index patient. Sanger sequencing confirmed the NGS result and showed the sister as a carrier

population.^[6] More than 300 pathogenic variants of *CHM* have been described, and the loss-of-function variant is the most common pathogenic variant as shown in our case.^[7] This variant caused a non-sense-mediated mRNA decay with specific degradation of transcripts with a pre-mature stop codon. Here, we report a non-sense variant in the *CHM* gene in a Turkish man with choroideremia, c.969T>A, (p.Tyr323*). According to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) 2015 guidelines, this variant is classified as a likely pathogenic variant based on one very strong piece of evidence (PVS1) and one moderate piece of evidence (PM2).

The differential diagnosis for choroideremia includes other inherited retinal disorders such as gyrate atrophy and retinitis pigmentosa.^[8,9] WES may be useful when a genetic syndrome is suspected during pre-conception counseling. Genetic counseling may be given once exome sequencing and clinical findings support a hereditary disorder. WES may be useful in overlapping phenotype-related retinal disorders because it promises shorter turnaround times and/or higher diagnostic yields.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

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