Genetic causes of inherited retinal diseases among Israeli Jews of Ethiopian ancestry

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Purpose: This study sought to describe the phenotype frequency and genetic basis of inherited retinal diseases (IRDs) among a nationwide cohort of Israeli Jewish patients of Ethiopian ancestry.
Methods: Patients' data—including demographic, clinical, and genetic information—were obtained through members of the Israeli Inherited Retinal Disease Consortium (IIRDC). Genetic analysis was performed by either Sanger sequencing for founder mutations or next-generation sequencing (targeted next-generation sequencing or whole-exome sequencing).
Results: Forty-two patients (58% female) from 36 families were included, and their ages ranged from one year to 82 years. Their most common phenotypes were Stargardt disease (36%) and nonsyndromic retinitis pigmentosa (33%), while their most common mode of inheritance was autosomal recessive inheritance. Genetic diagnoses were ascertained for 72% of genetically analyzed patients. The most frequent gene involved was *ABCA4*. Overall, 16 distinct IRD mutations were identified, nine of which are novel. One of them, *ABCA4*-c.6077delT, is likely a founder mutation among the studied population.
Conclusions: This study is the first to describe IRDs' phenotypic and molecular characteristics in the Ethiopian Jewish community. Most of the identified variants are rare. Our findings can help caregivers with clinical and molecular diagnosis and, we hope, enable adequate therapy in the near future.

Inherited retinal diseases (IRDs) are a clinically and genetically heterogeneous group of diseases that cause vision loss due to abnormal development, dysfunction, or the progressive degeneration of photoreceptors or the retinal pigment epithelium (RPE). Irreversible progression toward low vision and blindness significantly affects patients' quality of life. Moreover, IRDs lead to reduced mobility and independence, and they pose a considerable psychological and economic burden. These diseases can be inherited via autosomal recessive (AR), autosomal dominant (AD), or X-linked (XL) inheritance. Digenic and mitochondrial inheritance patterns have also been reported [1].

The most common form of IRD is retinitis pigmentosa (RP; also known as rod-cone dystrophy), which is characterized by night blindness and the loss of the peripheral visual field [2]. While RP's prevalence in Europe and the United States is approximately 1:5,000, a much higher prevalence of approximately 1:2,000 has been found among the Israeli population [3,4]. For patients with cone-rod dystrophy (CRD), cone involvement initially exceeds, or is equal to, rod involvement. CRD symptoms include reduced visual acuity, impaired color vision, and photophobia [5]. Leber congenital amaurosis (LCA) is the most severe form of nonsyndromic IRD; in this condition, both rods and cones are nonfunctional at birth or lost within a patient's first year of life [6]. Some IRD subtypes, such as Stargardt disease (STGD) [7,8], affect primarily the macular region (macular dystrophies [MD]). Most IRD types are progressive, but some—such as achromatopsia (rod monochromatism) [9]—are non-degenerative and do not progress over time. While, in most IRD cases, the disease

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involves only ophthalmic manifestations (nonsyndromic), over 70 forms of syndromic IRDs have been described [10].

Due to the unique Jewish history of the Diaspora, characterized by intracommunity marriages and relatively small geographical regions, certain founder mutations that underlie a variety of Mendelian diseases are characteristic of specific Jewish sub-populations (e.g., Ashkenazi Jews, Yemenite Jews, and North African Jews) [11]. Israel's population is an estimated 9.3 million people. The Ethiopian Jewish community in the country represents a unique sector. As of December 2020, approximately 159,500 Jews of Ethiopian origin were living in Israel (1.7% of the Israeli population), 55% of whom had been born in Ethiopia and 45% of whom had been born in Israel (Central Bureau of Statistics, 2022). In 2018, 87% of Ethiopian Jews married partners of the same ethnicity. The Ethiopian Jewish population avoids consanguineous marriages by tracking familial ancestral records for up to seven generations.

Ethiopian Jews used to live in small villages across Ethiopia. They immigrated to Israel in waves from 1980 to 1992. Little is known about this community's origin and arrival in Ethiopia, and several studies have attempted to decipher this origin while shedding light on this ethnic group's history. Some researchers have claimed that Ethiopian Jews descend from Egyptian and Yemenite Jews [12]. A study by Litz Philipsborn et al. may support this claim, having found a common founder mutation for Meckel–Gruber syndrome among Jews of both Ethiopian and Yemenite origins [13]. Apart for the study by Litz Philipsborn et al., only a few studies, only a few studies on the genetic conditions that are frequent in the Ethiopian Jewish community, and their molecular causes, have been published [14,15]. We aimed to establish a nationwide cohort of Ethiopian Jewish patients living in Israel, estimate this population's IRD prevalence, and clinically characterize both this cohort's IRD types and genetic causes of disease.

METHODS

Subjects and clinical evaluation: Forty-two patients from 36 families were included in this study (Appendix 1). Prospective participants were identified by members of the Israeli Inherited Retinal Disease Consortium (IIRDC) [4], specifically from the following Israeli medical institutions: the inherited retinal degeneration clinic at Schneider Children's Medical Center of Israel; the Department of Ophthalmology at Rabin Medical Center; the Division of Ophthalmology at Hadassah-Hebrew University Medical Center; the Genetics Institute at Emek Medical Center; the Department of Ophthalmology on Rambam Health Care Campus; the Ophthalmology Department at Shamir Medical Center; the Goldschleger

Eye Institute at Sheba Medical Center; and the Division of Ophthalmology at Tel Aviv Sourasky Medical Center. The tenets of the Declaration of Helsinki were followed, the study was approved by institutional review boards, and written informed consent was obtained from all participants or their parents. Diagnoses were made based on complete ophthalmic examinations, which included best-corrected visual acuity, biomicroscopic examination, cycloplegic refraction, optical coherence tomography, and electroretinography testing for most participants.

Genetic analyses: Index patients from families 1, 2, 4, 5, 8, 9, 10, 11, 23, 32, and 33 were tested for specific, relatively common mutations, mainly in the *ABCA4* (NM_000350) gene. The mutations included c.5882G>A, c.4793C>A, and c.6077delT. Index patients from families 6, 7, 12, 14, 18, 19 were tested by Targeted Next Generation Sequencing (T-NGS) of 108 known IRD genes, using the Molecular Inversion Probes (MIPs) technique [16]. Index 78 patients from families 21, 25, and 31 were tested using the T-NGS of 113 known genes associated with RP and LCA using the MIPs technique [17]. Index patients from families 12 and 22 were tested with the T-NGS of 105 inherited MD and age-related MD-associated genes and noncoding or regulatory loci, known pseudo-exons, and the mitochondrial genome, using smMIPs [18]. Whole-exome sequencing (WES) was performed for index patients from families 16, 17, 26, 27, 29, and 30 at 3billion (Seoul, South Korea) using xGen Exome Research Panel, Version 2 (Integrated DNA Technologies, Coralville, IA). WES of the index patient from Family 18 was performed at Pronto Diagnostics (Tel Aviv, Israel) using a Nextera rapid exome-capture kit (Illumina, San Diego, CA). WES of the index patient from Family 14 was performed at Otogenetics Corporation (Norcross, GA) using a Roche NimbleGen, Version 2 (44.1 Mbp) paired-end sample-preparation kit (Roche NimbleGen, Madison, WI). WES of index patients from families 3 and 28 was performed at Variantyx Inc. (Framingham, MA) using SureSelectXT Human All Exon, Version 6 (Agilent Technologies, Santa Clara, CA). NGS reads were aligned to the reference human genome (GRCh37/hg19). Variants were called via the Franklin by Genoox web-based pipeline. Specific, relatively common mutations and verification of mutations that had been identified by NGS were tested by PCR amplification with specifically designed primers, followed by direct sequencing with the Big Dye terminator-cycle-sequencing kit on an ABI 3130xl Genetic Analyzer (PE Applied Biosystems, Foster City, CA). Bioinformatic analysis of amino acid conservation was performed with the ConSurf Server [19]. All pathogenic and likely pathogenic variants identified in this study were submitted to LOVD.
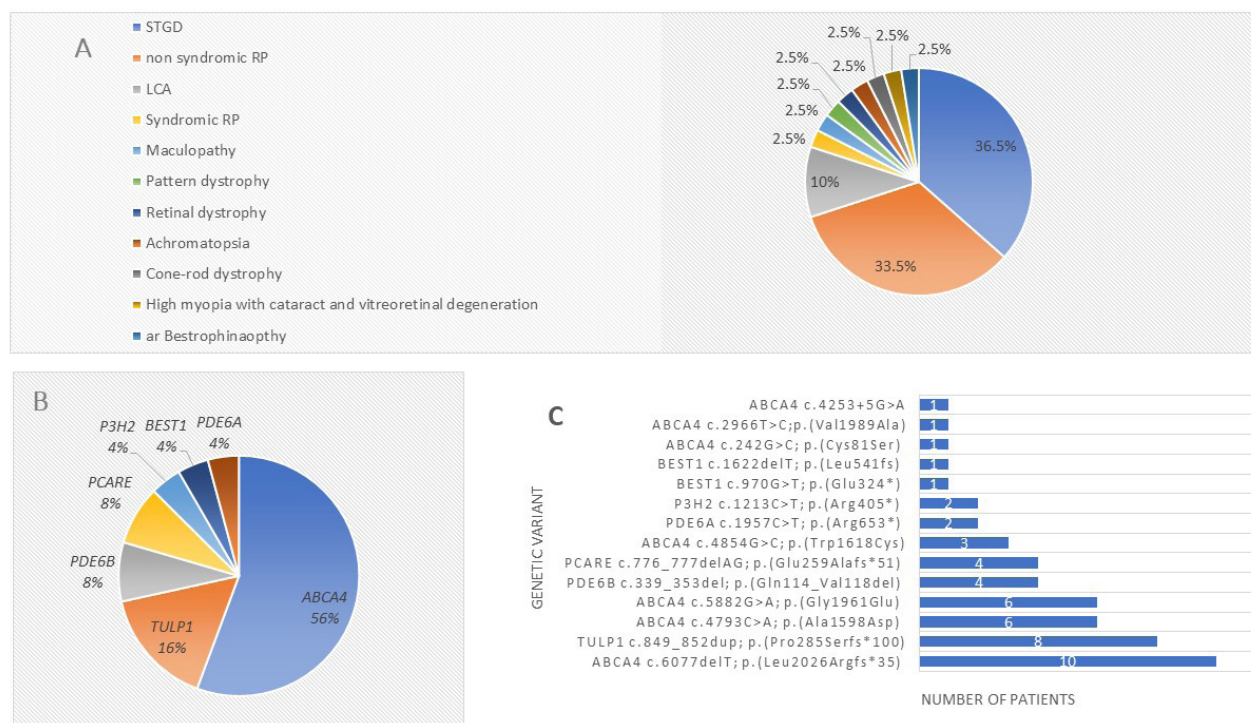
Figure 1. Phenotypic and genotypic findings for the study's cohort of Ethiopian Jewish patients with IRD. **A:** Phenotypic distribution. *RP* = retinitis pigmentosa; *STGD* = Stargardt disease; *LCA* = Leber congenital amaurosis; *ACHM* = achromatopsia; *CRD* = cone-rod dystrophy. **B:** Distribution of mutated genes. **C:** Distribution of variant types.

RESULTS

A total of 42 patients with IRD from 36 Israeli Jewish families of Ethiopian descent were recruited to this study (Appendix 1); therefore, the estimated IRD prevalence in this population is 1:1,899 (considering that about 50% of Israeli patients with IRD were recruited by the IIRDC) [4]. Twenty-three participants were female (55%). The patients' average age at diagnosis was 28 ±19 years (range: 1–82). The most common phenotypes were STGD (15 of 42 patients, 36%) and nonsyndromic RP (14 of 42, 33%), followed by LCA (4 of 42, 9.5%). Less common phenotypes that appeared in only a single family included syndromic IRD, achromatopsia, CRD, AR bestrophinopathy (ARB), Usher syndrome, pattern dystrophy, MD (non-STGD), and high myopia with vitreoretinal degeneration (Figure 1A and Appendix 2). The most common mode of inheritance was AR (25 of 36 families, 69%), followed by isolated cases (10 of 36 families, 28%).

For 33 of 36 families, thorough or partial genetic analysis was performed by NGS or founder-mutation testing, respectively, while three families have not been processed yet. In total, the results of 32 patients from 29 families were solved, possibly solved, or subjected to NGS and unsolved (Appendix 1). The underlying disease-causing variants were fully identified for 23 of these 32 patients; thus, the diagnostic rate was 72% (Appendix 1). All genetically diagnosed families had AR inheritance. Only three of all 36 families (8%) and two of the 20 genetically diagnosed families (10%) were consanguineous. Segregation analysis was performed whenever the DNA of additional relatives was available (Appendix 3).

Two families' results were defined as "possibly solved." For the patient from family 21, with a phenotypic combination of RP and hearing loss, two rare heterozygous variants in the *USH2A* gene were identified (Appendix 1). *USH2A* mutations are associated with Type 2 Usher syndrome (RP and hearing loss; 20), which aligns with this patient's observed phenotype. The identified variants were: c.784+14389G>T, a deep intronic mutation that had previously been shown to be splice-altering and classified as "pathogenic" (21; Table 1); and c.7951A>G;p.(Asn2651Asp), a rare missense variant. Asparagine at Position 2,651 was predicted to be functionally important (highly conserved and exposed; Figure 2B). Nevertheless, this variant was not predicted as deleterious using in silico prediction tools; therefore, it was categorized as a variant of unknown significance (VUS; Table 1). Similarly, for the patient from family 22, who had been diagnosed with

MD, a homozygous variant in the *RP1L1* gene was detected. This rare variant, c.194T>C;p.(Met65Thr), was predicted as pathogenic (Table 1), and it affects an amino acid (methionine 65), which was predicted to be structurally important (highly conserved and buried; Figure 2B). Moreover, *RP1L1* mutations have been associated with several phenotypes, including AR maculopathy [22]. Nevertheless, this variant was classified as a VUS.

For four patients with STGD from three families, only one heterozygous *ABCA4* mutant allele was found, and the second allele has yet to be identified. These families were defined as "monoallelic."

The most frequently involved gene was *ABCA4* (12 of 23 patients in the solved group, 52%), followed by *TULP1* (4 of 23, 17%), *PCARE* (2 of 23, 9%), *PDE6B* (2 of 23, 9%), *PDE6A*, *BEST1*, and *P3H2* (4% each; Figure 1B). In total, 16 distinct pathogenic or potentially pathogenic variants were identified, nine of which are novel (not previously reported in the literature; Table 1, Figure 1C, and Figure 2). Novel variants were considered causative, based on related phenotype, population frequency (Genome Aggregation Database [gnomAD; https://gnomad.broadinstitute.org/] minor allele frequency [MAF] ≤ 1% for AR variants), and the predicted effect on a protein product. Three of the variants were small deletions leading to a frameshift, and two were nonsense mutations; these variants were considered null mutations and classified as "pathogenic" or "likely pathogenic." One very rare mutation (not previously reported in the literature, ClinVar or gnomAD) in the *PDE6B* gene was a 15 bp deletion, leading to an in-frame loss of five amino acids in a non-repetitive protein region (c.339_353del;p.[Gln114_Val118del]). Three of the novel variants were missense variants. They are all rare and affect highly conserved amino acids (Figure 2B). The phenotypes of all patients who harbored novel mutations were similar to the reported phenotypes for patients with other mutations in the same genes (Table 1).

Seven distinct *ABCA4* mutations were found among 16 patients (12 patients in the solved group and four patients in the monoallelic group; Table 1 and Appendix 1). The most common mutation was c.6077delT (Figure 2), which appeared on 10 of 28 *ABCA4* mutant chromosomes (36%). We had originally reported this novel mutation in four of the families included in this paper as part of our report on the IIRDC's findings [4]. c.6077delT is a very rare mutation that is absent from public databases—including gnomAD, Trans-Omics for Precision Medicine (TOPMed) Bravo, The Greater Middle East (GME) Variome, and Exome Sequencing Project (ESP) 6500—and it is likely a unique founder mutation of the Ethiopian Jewish population.

The second most common *ABCA4* mutations were p.(Gly1961Glu) and p.(Ala1598Asp), each found on 6 of 28 chromosomes (21%). p.(Gly1961Glu) is the most prevalent mutation of *ABCA4* worldwide (present in ~20% of cases involving patients of European descent), and its frequency in the general population varies widely across ethnic groups, from 0.2% to 10% in European and East African populations, respectively [23-25]. Due to its high frequency in certain populations, this variant's pathogenicity has been subjected to controversy, especially concerning its presence among homozygous individuals. A recent study demonstrated that cis-acting modifiers in the *ABCA4* locus contribute to the penetrance of p.(Gly1961Glu), mainly the deep intronic c.769–784C>T variant, which was found in five of seven p.(Gly1961Glu) homozygous cases [26]. We, therefore, tested all patients with either one or two p.(Gly1961Glu) alleles for the presence of c.769–784C>T. None of them carried this allele. p.(Ala1598Asp) is a rare mutation that, based on the gnomAD database, is most frequent among Americans (0.0087%) and very rare among Africans (0%). It has been reported worldwide among patients of various ethnicities [27-30].

p.(Trp1618Cys), which was found on three of 28 chromosomes (11%; all within one family), is a very rare variant (gnomAD aggregated MAF = 0.0016%) that is more common among Americans (MAF = 0.0087%) and reaches a MAF of 0.4% among Mexicans. It was predicted as pathogenic by multiple prediction tools (Table 1), and it has been reported in the literature previously [31,32].

p.(Val1989Ala), c.4253+5G>A, and p.(Cys81Ser) were identified on only one chromosome each (4%). p.(Val1989Ala) and c.4253+5G>A are rare, were predicted as pathogenic, and have been reported previously in ClinVar and the literature (Table 1). We had originally reported p.(Cys81Ser) in the same family included in the current paper as part of our report on the IIRDC's findings [4]. This mutation is very rare and absent from public population databases. It affects a highly conserved amino acid and was predicted as pathogenic (Table 1 and Figure 2).

Two of this study's cases were especially interesting. The first case was that of Patient 17–1, who was heterozygous for two novel mutations in the *BEST1* gene. Both mutations were null (a nonsense and a frameshift; Table 1, and Appendix 1, Appendix 3). While some monoallelic heterozygous mutations in *BEST1* lead to AD Best vitelliform macular dystrophy, biallelic mutations in *BEST1* have been associated with ARB, as well as arRP [33-35]. ARB is characterized by multifocal, yellow subretinal deposits. In some cases, subretinal fibrous scars and cystoid macular intraretinal fluid may

TABLE 1. CAUSATIVE AND POSSIBLY-CAUSATIVE VARIANTS IDENTIFIED IN ETHIOPIAN JEWISH IRD PATIENTS.

Gene (Accession number)	Variant	ClinVar accession number	dbSNP ID	gnomAD aggregated MAF	In silico predictions [a]							ACMG classification	Phenotypes associated with this gene
					SIFT	Varity	Revel	Mutation-Taster	Splice AI	dbsc SNV Ada	dbsc SNV RF		
ABCA4 (NM_000350)	**c.242G>C; p.(Cys81Ser)** [b]	**RCV001002848.1**	**rs1570433137**	-	U	D	D	D	NA	NA	NA	**Likely Pathogenic**	**arSTGD1**, arMD, arRP, arFFM, **arCRD**
	c.2966T>C; p.(Val1989Ala)	RCV000085529.20	rs61749454	0.0003	U	D	D	D	NA	NA	NA	Pathogenic	
	c.4253+5G>A; p.Ile1377Hisfs*3	RCV000408462.3	rs61750138	0.000012	NA	NA	NA	NA	D	D	D	Likely Pathogenic	
	c.4793C>A; p.(Ala1598Asp)	RCV000085674.12	-	0.000024	U	D	D	D	NA	NA	NA	Pathogenic	
	c.4854G>C; p.(Trp1618Cys)	RCV001074894.1	rs61752439	0.000016	D	D	D	D	NA	NA	NA	Pathogenic	
	c.5882G>A; p.(Gly1961Glu)	RCV000078670.31	rs1800553	0.0046	U	D	D	D	NA	NA	NA	Pathogenic	
	c.6077delT; p.Leu2026 Argfs*35) [b]	**RCV001002808.1**	**rs1571245809**	-	NA	NA	NA	NA	NA	NA	NA	**Pathogenic**	
BEST1 (NM_004183)	**c.970G>T; p.(Glu324*)** [b]	-	-	-	NA	NA	NA	D	NA	NA	NA	**Likely Pathogenic**	adBest vitelliform MD, ad vitreoretinochoroidopathy, **ARB**, arRP, adRP
	c.1622delT; p.(Leu541 Argfs*68) [b]	**RCV002002203.3**	-	-	NA	NA	NA	NA	NA	NA	NA	**Pathogenic**	
P3H2 (*LEPREL1*) (NM_018192)	**c.1213C>T; p.(Arg405*)**	**RCV001809893.1**	**rs377600857**	**0.000024**	NA	NA	NA	D	NA	NA	NA	**Pathogenic**	ar high Myopia, with cataract and vitreo-retinal degeneration

Gene (Accession number)	Variant	ClinVar accession number	dbSNP ID	gnomAD aggregated MAF	In silico predictions [a]							ACMG classification	Phenotypes associated with this gene
					SIFT	Varity	Revel	Mutation-Taster	Splice AI	dbsc SNV Ada	dbsc SNV RF		
PCARE (NM_001029883)	**c.776_777delAG; p.(Glu259 Alafs*51)**	**RCV001268685.1**	**rs1572829514**	-	NA	NA	NA	NA	NA	NA	NA	**Pathogenic**	arRP
PDE6A (NM_000440)	c.1957C>T; p.(Arg653*)	RCV000627204.13	rs753942596	0.000028	NA	NA	NA	D	NA	NA	NA	Pathogenic	arRP
PDE6B (NM_000283)	**c.339_353del; p.(Gln114_Val118del)** [b]	-	-	-	-	-	-	-	NA	NA	NA	**VUS**	**arRP,** adCSNB
RP1L1 (NM_178857)	**c.194T>C; p.(Met65Thr)** [b]	**RCV001361602.2**	-	**0.0006**	U	**D**	**D**	**D**	NA	NA	NA	**VUS**	AD Occult MD, arRP, **arMD**
USH2A (NM_206933)	c.784+I4389G>T;p. Gly262Aspfs*26	-	-	0.00048	NA	NA	NA	NA	NA	NA	NA	Pathogenic	**arUSH2A,** arRP
	c.7951A>G; p.(Asn2651Asp)	**RCV001724132.3**	**rs141134147**	**0.000021**	**B**	**B**	**B**	**B**	NA	NA	NA	**VUS**	

[a]B, benign; D, deleterious; U, uncertain prediction[b] novel mutation ACMG, American College of Medical Genetics; ad, autosomal dominant; ar, autosomal recessive; ARB, autosomal recessive Bestrophinopathy; CRD, cone-rod dystrophy; CSNB, congenital stationary night blindness; FFM, fundus flavimaculatus; MAF, minor allele frequency; MD, macular dystrophy; NA, not applicable; RP, retinitis pigmentosa; STGD1, Type 1 Stargardt disease; USH2A, Type 2A Usher syndrome; VUS, variant of unknown significance
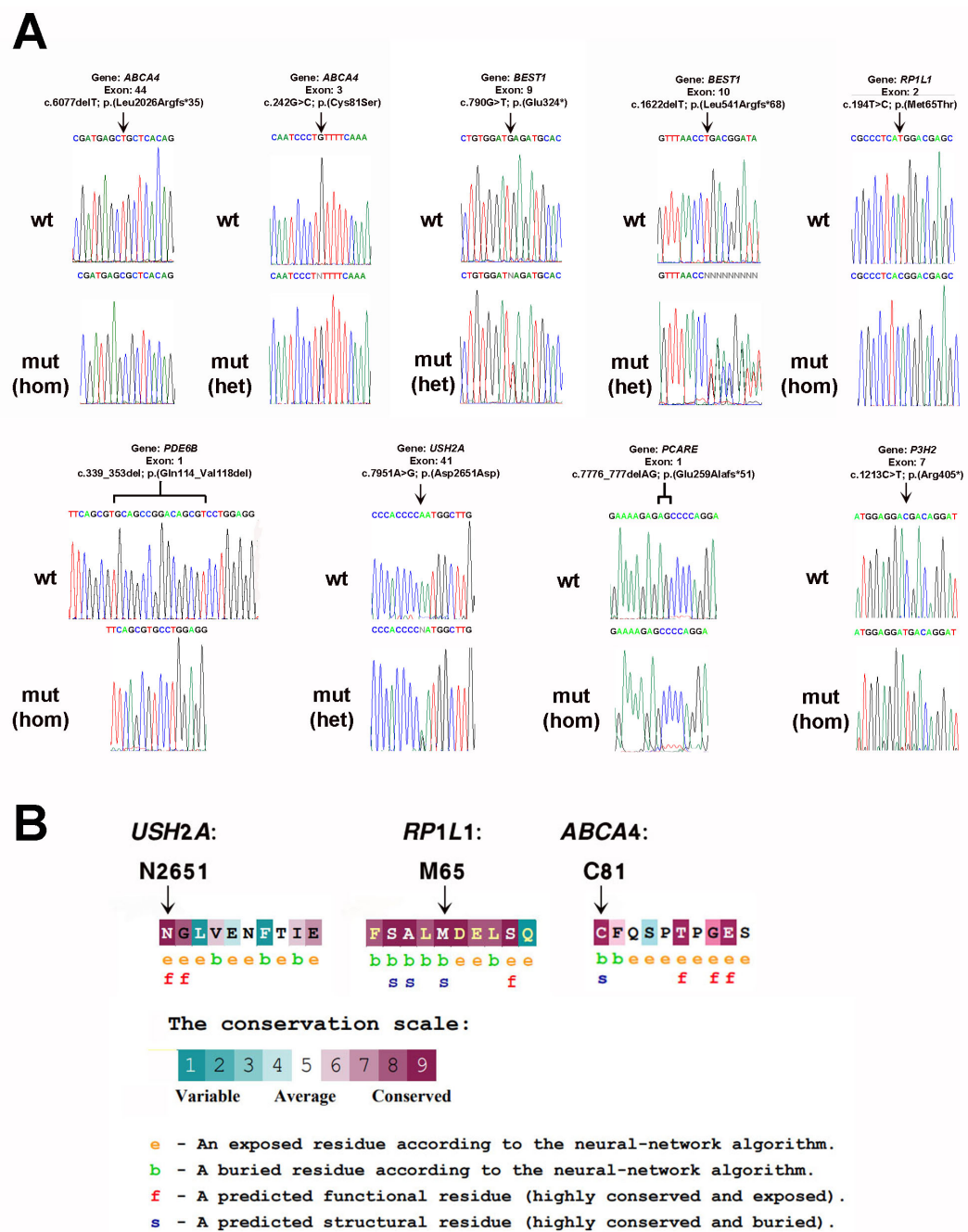
Figure 2. Novel variants identified in this study. **A**: Mutant (*mut*) and wild-type (*wt*) nucleotide sequence traces of the nine novel variants identified in this study. *hom* = homozygote; *het* = heterozygote. **B:** Evolutionary conservation of amino acids affected by three missense variants. Analysis performed with the ConSurf Server.

be found. Many ARB patients have hyperopia and shallow anterior chamber angles, with or without angle-closure glaucoma. For patients with this condition, electrooculogram (EOG) results and, in many cases, full-field electroretinogram (ERG) results are abnormal [36, 37]. Patient 17–1 was a 38-year-old woman who had been referred for poor vision and nyctalopia. Her best-corrected visual acuity was 20/300. Her ophthalmic examination revealed hyperopia (+3.00D), a normal-depth anterior chamber and normal intraocular pressure, a mild nuclear cataract, a pale optic nerve, and multiple yellow-white deposits in the macula and extramacular area, with patches of RPE atrophy in the periphery. Widefield

fundus autofluorescence showed marked autofluorescence changes at the posterior pole and in the mid periphery and hypo-autofluorescence signal corresponding to the patches of RPE atrophy. Macular optical coherence tomography (OCT) demonstrated intraretinal fluid and subretinal fluid with hyperreflective deposits. Her RPE layer was thickened and irregular (Appendix 4). Full-field ERG demonstrated moderately reduced rod and cone responses in scotopic and photopic conditions, respectively. According to the patient, her parents had good vision. She had five siblings, and only one sister had poor visual acuity and nyctalopia (Appendix 3). This sister of Patient 17–1 was unavailable for clinical or genetic testing.

Patient 18–1 was homozygous for a nonsense mutation in the *P3H2* (*LEPREL1*) gene (c.1213C>T; p.[Arg405*]). Biallelic mutations in this gene are rare and associated with AR high myopia with cataract and vitreoretinal degeneration [38]. Indeed, this patient had progressive pathologic myopia (RE −25D, LE −28D) with severely compromised visual acuity in childhood (counting fingers at 5 cm) and abnormal electroretinographic recordings. She had been diagnosed with LE rhegmatogenous retinal detachment (RRD) at 13 years of age, and she had undergone lens extraction, a pars-plana vitrectomy, endolaser treatment for retinal tears, and a perfluorocarbon liquid and silicone oil exchange. A few months later, she developed RRD in her right eye and underwent a similar surgical procedure. Unfortunately, her current visual acuity affords her no light perception in either eye due to her primary poor retinal condition and postoperative complications of corneal decompensation, rubeosis iridis, and elevated intra-ocular pressure.

DISCUSSION

Very little is known about the genetic basis for various Mendelian conditions in The Ethiopian Jewish population. The current study is the first to characterize the phenotypes and genetic causes of IRDs among a relatively large cohort of Ethiopian Jews. The most common phenotypes were nonsyndromic RP and STGD, and the most frequently mutated gene was *ABCA4*. While these findings are similar to IRD phenotypic and genotypic distribution in the general Israeli population [4] and other populations worldwide [1,39-42], the nature of the mutant alleles identified among Ethiopian Jewish IRD patients differs greatly from findings for other populations.

Over 2,200 disease-causing mutations of the *ABCA4* gene are known (The ABCA4 gene homepage – Global Variome shared LOVD). They cover all mutation types—missense, nonsense, small deletions or insertions, deep intronic, and splice-site variants [43]. Among Ethiopian Jews,

the most common *ABCA4* mutation was c.6077delT, which was diagnosed in a heterozygote state for eight patients and in a homozygote state for one patient. This allele was not found in other Israeli ethnic groups, either Jewish or non-Jewish, or in other populations worldwide. It appears to be a unique founder mutation of the Ethiopian Jewish population. Moreover, nine of 16 mutations identified among this study's cohort are novel, further demonstrating this population's unique genetic structure.

In 2020, we reported phenotypic and genotypic data on 3,413 IRD Israeli patients who had been identified by the IIRDC [4]. That publication's cohort included 20 patients of Ethiopian Jewish descent (0.58%). Notably, Ethiopian Jews constitute 1.7% of the Israeli population; therefore, patients of this ethnicity are underrepresented among total Israeli IRD patients ($p < 0.00001$ using Fisher's exact test). This underrepresentation contrasts with other Israeli ethnic groups, such as Muslim Arabs, who are significantly overrepresented in the Israeli IRD cohort, mainly due to a high prevalence of consanguineous unions [4]. A possible explanation for Ethiopian Jews' underrepresentation in the national cohort is this population's very low frequency of consanguinity. Nevertheless, additional socio-economic factors (including communication difficulties, traditional attitudes, and a tendency to be suspicious of the establishment) which influence the accessibility and awareness to medical services may also contribute to this trend.

In summary, this study is the first to describe the phenotypic and molecular characteristics of IRDs in the Ethiopian Jewish community. These data could help caregivers with clinical and molecular diagnosis and, we hope, facilitate adequate therapy (including gene-based and mutation-based therapy) in the near future.

APPENDIX 1. DEMOGRAPHIC AND GENETIC DATA OF STUDY PATIENTS.

To access the data, click or select the words "Appendix 1." [a] Family was reported in Sharon et al. [4] [b] Novel mutation [c] Family 8 appears twice in this table. Individual 1 (under solved families) is the mother of individuals 2 and 3 (under monoallelic families). All three are affected. Individual 1 is heterozygous for two different *ABCA4* variants. Her offspring (individuals 2 and 3) are heterozygotes for one *ABCA4* variant, and their second mutation is still to be found. [d] Families in which only one heterozygous mutant allele was identified, in a known IRD-causative gene which is inherited in an autosomal recessive mode. ACHM, achromatopsia; ar, autosomal recessive; ARB, autosomal recessive Bestrophinopathy; CRD, cone-rod dystrophy; F, female; het,

heterozygous; hemi, hemizygous; hom, homozygous; HL, hearing loss; i, isolated; LCA, Leber congenital amaurosis; M, male; MD, macular dystrophy; ND, not done; PD, pattern dystrophy; RD, retinal dystrophy; RP, retinitis pigmentosa; ss, short stature; STGD, Stargardt disease; T-NGS, targeted next generation sequencing; USH, Usher syndrome; WES, whole exome sequencing; XL, X-linked

APPENDIX 2. CLINICAL DATA OF STUDY PATIENTS.

To access the data, click or select the words "Appendix 2." ACHM, achromatopsia; ARB, autosomal recessive Bestrophinopathy; BAF- blue autofluoresence; BSP, bone spicule pigmentation; CF, counting fingers; CRD, cone-rod dystrophy; ERM, epiretinal membrane; F, female; FAF, fundus autofluorescence; HL, hearing loss; HM, hand motion; LCA, Leber congenital amaurosis; M, male; MD, macular dystrophy; MFERG: multifocal electroretinography; NA, not available; NLP, no light perception; OCT, optical coherence tomography; OD, right eye; OS, left eye; ON, optic nerve, OU, both eyes; PD, pattern dystrophy; RD, retinal dystrophy; RP, retinitis pigmentosa; RPE, retinal pigment epithelium, SS, short stature; STGD, Stargardt disease; VEP, visual evoked potentials; y, years [a]FFERG: full-field electro-retinogram; NR, non-recordable, WNR: within normal range, MiR: mildly reduced, MR: moderately reduced (1%–5% of normal range); SR, severely reduced (<1% of normal range); ND, non-detectable [b] Stargardt typing according to fundus autofluoresence distribution of pathologic findings [8][c] Type unknown since FAF is unavailable

APPENDIX 3. SEGREGATION ANALYSIS OF MUTATIONS IDENTIFIED IN SOME OF THE ETHIOPIAN JEWISH FAMILIES INCLUDED IN THIS PAPER.

To access the data, click or select the words "Appendix 3." Filled symbols represent affected individuals, whereas clear symbols represent unaffected individuals. Genotypes of family members are indicated below them (+, wt; m, mutant).

APPENDIX 4. MULTIMODAL RETINAL IMAGING FROM PATIENT 17 WITH ARB.

To access the data, click or select the words "Appendix 4." **A,B**: Optos widefield fundus photos of right and left eye respectively, showing multiple yellow-white deposits in the macula and extramacular area and patches of retinal pigment epithelium (RPE) atrophy in the periphery, **C, D**: Widefield fundus autofluorescence photos, showing autofluorescence changes at the macula and mid periphery and temporal peripheral hypo-autofluorescent patches corresponding to the RPE atrophic patches. **E, F**: Spectral-domain OCT images showing cystoid macular intraretinal fluid (narrow arrow) and subretinal fluid with hyperreflective deposits (wide arrow).

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