Two specific mutations are prevalent causes of recessive retinitis pigmentosa in North American patients of Jewish ancestry

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INTRODUCTION

Retinitis pigmentosa (RP) is a hereditary degenerative disease of the retina that affects approximately 1 in 4,000 individuals worldwide. Rod photoreceptors are predominantly affected, and typically patients first experience visual problems under moonlight or starlight conditions. As the disease evolves, cone photoreceptors also degenerate, peripheral vision deteriorates, and patients develop tunnel vision that ultimately progresses to result in legal or complete blindness. The age of onset of the disease varies, but often affected individuals seek medical attention during their second decade of life. RP is a genetically heterogeneous disease for which all Mendelian forms of inheritance are known. In particular, recessively inherited RP is caused by mutations in more than 30 genes and loci (RetNet database; https://sph.uth.edu/retnet/), most of which account for only a small percentage of cases.¹ Affected people have been reported in diverse ethnic groups worldwide.²⁻⁶ Recently, mutations in two genes, MAK⁷⁻⁸ and DHDDS⁹⁻¹⁰ were found to cause autosomal recessive RP (arRP) in patients of Ashkenazi Jewish ancestry, i.e., in descendents of Israelites who migrated from the Middle East to Central and Eastern Europe during the Middle Ages.

The male germ cell–associated kinase (MAK) is a highly conserved serine/threonine protein kinase, the expression of which is limited to testis and retina.¹¹ Four alternative MAK isoforms are present in humans; the longer isoform, containing an alternative 75-bp exon between exons 11 and 12, has a photoreceptor-specific expression.⁷,⁸ In mice, Mak regulates photoreceptor ciliary length and is crucial for photoreceptor long-term survival; for these reasons, Mak⁻/⁻ animals develop progressive retinal degeneration.⁹ A homozygous 353-bp Alu insertion in exon 9 of MAK was originally reported in one isolated RP patient of Jewish ancestry and in 20 probands from a cohort of 1,798 unrelated arRP cases of mixed ethnicity (~1%). Interestingly, all carriers of the mutation reported Jewish ancestry.⁷ A screen of 1,207 healthy individuals of Ashkenazi descent also revealed the presence at a relatively high frequency of this Alu insertion in a heterozygous state.¹⁴ The mutation results in the insertion of 31 incorrect amino acids, followed by a premature termination codon; in retinal cells derived from patient fibroblasts, this mutation prevents the expression of the photoreceptor-specific isoform.⁷ Clinical manifestations in individuals harboring this pathogenic DNA change resemble those of autosomal dominant forms of RP linked to RP1 mutations; prolonged preservation of the central retina with good visual acuity is also a typical feature in these patients.¹⁴

DHDDS encodes dehydrodolichyl diphosphate synthase, an evolutionarily conserved enzyme participating in the
biosynthesis of dolichol, an essential lipid serving as glycosyl moiety carrier for protein N-glycosylation.\textsuperscript{15} Dolichol is ubiquitously present in human tissues.\textsuperscript{15,16} In the retina, DHDDS is expressed in the inner segment of photoreceptors, where dolichol biosynthesis is predicted to happen.\textsuperscript{9} Recently, a missense mutation of a conserved residue (p.Lys42Glu) in DHDDS was associated with arRP in a non-consanguineous pedigree of Jewish ancestry,\textsuperscript{10} as well as in 15 other unrelated families of Ashkenazi descent, corresponding to a prevalence of \textasciitilde 10\% in the latter ethnic group.\textsuperscript{9} Clinically, patients presented with the classical form of the disease, with symptoms starting during the second decade of life. Unlike patients with the MAK mutation, acuity was reduced to 20/200 in young adulthood. In most cases, computerized electroretinography (ERG) responses were reported as not detectable as tested.\textsuperscript{9} The p.Lys42Glu mutation has been reported to be an Ashkenazi-specific founder mutation, and it is very rare in other populations.\textsuperscript{9}

In this study, we ascertained the prevalence of these MAK and DHDDS mutations in a cohort of North American patients of Jewish ancestry and compared it with that from cases of mixed ethnicity. Clinical findings are also described.

**MATERIALS AND METHODS**

**Patients**

This research was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional review boards of the University of Lausanne and of Harvard Medical School and the Massachusetts Eye and Ear Infirmary, where the blood was collected and the patients were followed. Written informed consent was obtained from patients who participated in the study before they donated 10–30 ml of their blood for research. Ancestry/ethnic origins of patients were self-reported.

DNA from peripheral blood leukocytes was extracted from 35 unrelated North American RP patients of Jewish ancestry and from 240 North American RP patients of mixed ethnicity. These patients had a family history indicative of a recessive form of inheritance and they were previously screened for a variety of known RP genes. Patients were clinically evaluated with an ophthalmologic examination, including Goldmann visual field testing and ERGs.\textsuperscript{17}

**Genetic analyses**

Mutational screening was performed by PCR, followed by Sanger sequencing. Primer sequences were either designed using Primer3 software or selected from previous literature.\textsuperscript{8} Primer sequences were: 5′-TACCGCCCATTTTGTCTTACAT-3′ (MAK intron 8, forward); 5′-ACTGAGAATCTGTACTGAG-3′ (MAK intron 9, reverse); 5′-TCCCTGAAGAATATGAGACCTGT-3′ (DHDDS exon 2, forward); and 5′-CAAACCTAGGCCTTGTTTCTCTA-3′ (DHDDS exon 2, reverse). PCR amplification was performed in a 25-μl reaction containing 20 ng genomic DNA, 1x GoTaq buffer, 1.2 mM MgCl\textsubscript{2}, 0.1 mM dNTPs, 0.4 μM of each primer, and 0.01 U/μl of GoTaq polymerase (Promega, Madison, WI). Amplification conditions

Table 1 Polymorphic markers used for haplotype analysis of patients harboring the Alu insertion in MAK

| SNP ID  | Chromosomal position | 002-211 | 002-216 | 121-270 | 121-400 | 121-122 | 002-213 | 002-280 | 121-147 | 121-164 | 121-184 | 121-190 | 121-197 |
|---------|----------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| rs114668723 | 6:10687602 | CT | TT | TT | TT | TT | TT | TT | CT | TT | TT | TT | TT |
| rs1045911 | 6:10723499 | AC | CC | CC | CC | CC | CC | AC | CC | CC | CC | CC | CC |
| rs518954 | 6:10745066 | AA | AA | AA | AA | AA | AA | AA | AA | AA | AA | AA | AA |
| rs116734564 | 6:10753038 | CC | CC | CC | CC | CC | CC | CC | CC | CC | CC | CC | CC |
| rs518954, in bold, is the SNP that is closest to the mutation. The shared haplotype is highlighted in gray. | | | | | | | | | | | | | | |
| ID     | Genotype | Ancestry          | Age | NB   | VFL  | Sex | Visual acuity OD | Visual acuity OS | Visual field OD | Visual field OS | Dark adaptation | 0.5 Hz ERG OD | 0.5 Hz ERG OS | 30 Hz ERG OD | 30 Hz ERG OS | Lens OD | Lens OS | Macula OD and OS | Periphery OD and OS |
|--------|----------|-------------------|-----|------|------|-----|------------------|------------------|-----------------|-----------------|----------------|---------------|---------------|---------------|---------------|-----------|---------|------------------|--------------------|
| 003-321| M/M      | Hungarian/Austrian/black/Russian | 29  | 18   | 18   | F   | 20/30           | 20/25            | 5401            | 5877            | 2.0            | 5.80          | 2.10          | 0.53          | 0.76          |          |         |                  |                    |
| 121–216| M/M      | Jewish            | 31  | 19   | 17   | M   | 20/30           | 20/30            | 2497            | 6684            | NA             | 1.50          | 3.70          | 0.41          | 0.94          |          |         |                  |                    |
| 121–410| M/M      | Russian/Polish/English | 31  | 25   | 25   | F   | 20/20           | 20/20            | 5898            | 6102            | 1.0            | 7.00          | 6.00          | 0.98          | 0.87          |          |         |                  |                    |
| 003-370| M/M      | Polish/Israeli     | 35  | 25   | 25   | M   | 20/80           | 20/70            | 2593            | 1920            | 3.5            | 5.50          | 4.00          | 0.40          | 0.47          |          |         |                  |                    |
| 121–122| M/M      | Jewish            | 42  | 25   | 30   | M   | 20/25           | 20/30            | 9381            | 9140            | NA             | 1.40          | 1.00          | 2.11          | 0.88          |          |         |                  |                    |
| 003-213| M/M      | Hungarian/Russian  | 42  | 29   | 29   | F   | 20/20           | 20/20            | 11835           | 10735           | 2.5            | 22.00         | 19.00         | 7.31          | 8.43          |          |         |                  |                    |
| 003-033| M/M      | Jewish            | 43  | 40   | 40   | M   | 20/20           | 20/20            | 6566            | 7412            | NA             | 28.00         | 25.50         | 13.99         | 12.76         |          |         |                  |                    |
| 121–184| M/M      | Jewish            | 44  | 35   | 38   | M   | 20/30           | 20/20            | 679             | 1447            | NA             | 2.30          | 3.20          | 0.41          | 0.51          |          |         |                  |                    |
| 121–147| M/M      | Jewish            | 46  | 18   | 12   | M   | 20/30           | 20/40            | 2163            | 3354            | NA             | 2.00          | 1.30          | 0.40          | 0.90          |          |         |                  |                    |
| 121–265| M/M      | Lithuanian/Polish  | 47  | 40   | 40   | M   | 20/25           | 20/25            | 7694            | 3290            | 0.70           | 1.60          | 0.37          | 0.51          |          |         |                  |                    |
| 121–470| M/M      | Jewish            | 54  | 41   | 51   | M   | 20/40           | 20/30            | 5934            | 4811            | 3.0            | 4.20          | NA            | 1.75          | 0.63          |          |         |                  |                    |
| 121–283| M/M      | Jewish            | 55  | 20   | 30   | M   | 20/80           | 20/80            | 1665            | 1415            | 4.5            | NA            | 0.20          | 0.36          | 0.36          |          |          |                  |                    |
| 121–847| M/M      | Jewish            | 63  | 30   | 30   | M   | 20/60           | 20/40            | 264             | 253             | 3.0            | NA            | NA            | 0.09          | 0.08          |          |         | Aphakia          | Aphakia            |
| 003-287| M/M      | Russian/Romanian  | 64  | 35   | 35   | M   | 20/30           | 20/40            | 277             | 255             | 4.0            | NA            | NA            | 0.19          | 0.19          |          |         |                  |                    |
| 121–544| D/D      | Eastern European/Russian | 33  | 32   | 32   | F   | 20/25           | 20/25            | 4720            | 4234            | NA             | 17.70         | 16.30         | 9.99          | 5.64          |          |         |                  |                    |
| 121–217| D/D      | Jewish/Russian    | 39  | 21   | 30   | F   | 20/50           | 20/30            | 395             | 285             | NA             | 2.60          | 1.40          | 0.21          | 0.25          |          |         |                  |                    |
| 121–463| D/D      | Jewish/Russian    | 44  | 30   | 33   | M   | 20/20           | 20/20            | 4847            | 4832            | 0.5            | 47.00         | 44.10         | 3.17          | 2.41          |          |         |                  |                    |
| 003-110| D/D      | Romanian/Russian  | 46  | 30   | 16   | M   | 20/100          | 20/30            | 709             | 510             | 1.5            | 5.20          | 4.20          | 0.28          | 0.73          |          |         | Pseudophakia     | Pseudophakia        |
| 003-015| D/D      | Jewish/Russian    | 38  | 26   | 32   | F   | 20/30           | 20/30            | 4922            | 5157            | NA             | 36.90         | 32.40         | 0.84          | 1.05          |          |         |                  |                    |

ID, Berman-Gund Laboratory patient ID; M, Alu insertion in MAK; D, p.Lys42Glu mutation in DHDDS; Age, age at first visit (years); NB, age of onset of night blindness, self-reported (years); VFL, age of onset of visual field loss, self-reported (years); OD, right eye; OS, left eye. Visual acuity, best corrected Snellen visual acuity; Visual field, Goldmann total field area to V-4e white test light (lower norm = 11,399 degrees squared); Dark adaptation, final threshold in log units above normal to an 11 degree white test light after 45 minutes of dark adaptation; ERG, full field ERG amplitudes in microvolts to white light single 0.5 Hz flash (lower norm = 11,399 degrees squared); 30 Hz white light (lower norm = 50); Lens, clear lens; central posterior subcapsular cataract +; Macula, within normal limits – granular +; Periphery, bone spicule or pigment in one or more quadrants: + present, - absent; NA, data not available.
were as follows: an initial step at 95 °C for 2 minutes, followed by 35 cycles of denaturation at 94 °C for 30 seconds, annealing at 56 °C (MAK) or 58 °C (DHDDS) for 30 seconds, and extension at 72 °C for 1 minute. Before the end of the reaction, a final extension step at 72 °C for 5 minutes was performed. After purification of the PCR product (ExoSAP-IT, USB, Santa Clara, CA), the sequencing reaction was performed by Sanger sequencing using 3.2 µM of sequencing primers (5′-CACTGAGTCATAAAAAGTGGT-3′ MAK and 5′-TCCCTGAAGAATATGAGACCTGT-3′ DHDDS) and 0.5 µl of BigDye Terminator v1.1 (Applied Biosystems, Foster City, CA). The sequencing products were then run on an ABI-3130 XLS sequencer (Applied Biosystems).

Because the PCR protocol to detect the Alu insertion in MAK could lead to the preferential amplification of one allele, we designed additional primers spanning the Alu insertion site for the wild-type and the mutant allele (5′-CGAAATGGAGAATCTTTTTTCCT-3′ wild-type and 5′-GAAAAAAGGAGGCCGCGCGGT-3′ mutant). Nested PCR was performed using primers for the wild-type or mutant allele in combination with primers used for amplification of exon 9. PCR conditions were the same as reported here, except that amplification cycles were reduced to 13 or to 15, respectively.

Haplotype analysis of patients harboring the Alu insertion in MAK was performed by sequencing eight polymorphic single-nucleotide polymorphisms (SNPs) with minor allele frequency of 0.01 to 0.30 and encompassing the insertion site. All patients harboring the insertion shared a homozygous haplotype for five markers around the mutation, confirming that the mutation was the result of a founder effect (Table 1).

After the screening of the same cohort of 275 patients for p.Lys42Glu in DHDDS, we found five patients carrying the mutation in a homozygous state. Three reported Jewish ancestry (prevalence = 3/35, or 8.6%), whereas two reported Russian or Eastern European ancestry, which again was compatible with a possible Ashkenazi Jewish origin. One patient (121−423) carried p.Lys42Glu heterozygously.

Investigation of mitochondrial DNA haplotypes revealed that three patients harboring the MAK insertion (003-033, 121−847, and 121−470) and one patient with the DHDDS mutation (121−463) belonged to the mitochondrial haplogroup K1a1b1a (markers 16224, 16234, 16311, 16519, 73, 114, 263). One MAK-positive patient (003−321) and one DHDDS-positive patient

**RESULTS**

Genetic analysis

Screening of 275 unrelated patients revealed the presence of 14 cases harboring the Alu insertion in exon 9 of MAK in a homozygous state. Of these, nine belonged to a subgroup of 35 arRP patients of Jewish ancestry, which corresponds to a prevalence of 25.7% within this ethnic group. The remaining five belonged to a subgroup of arRP patients of mixed ethnicity (prevalence = 5/240, or 2.1%). However, the latter positive individuals all reported East European origin and therefore were compatible with a possible Ashkenazi Jewish descent. No heterozygotes were found.

We ascertained the haplotype associated with the Alu insertion by sequencing eight polymorphic markers around the insertion site using PCR conditions reported in previous literature (5′-TCAATGGGCTGTCCCTGTAAG-3′ and 5′-GGGTGATGGTGGCCCGTCTA-3′) and identical PCR conditions as reported here, except that amplification of the primers was performed at 65°C. Sanger sequencing was performed using 3.2 µM of sequencing primers 5′-TCAAATGGGCTGTCCCTGTAAG-3′ and 5′-CTGTATCCGACATCTGGTTCCT-3′.

**Figure 1** Fundus photos of left eyes of patients with either MAK (top) or DHDDS (bottom) mutations.
tions were indeed of Ashkenazi descent, we sequenced the two mutations in patients carrying one of the two mutations to investigate whether patients carrying the Alu insertion in MAK had ancestors from this ethnic group. To further support this notion, we used Haplotype analysis in patients carrying the Alu insertion in MAK, which showed intraretinal pigment in a bone spicule configuration in the periphery, typical of RP. In conclusion, we found that six patients carried the K1a1b1a and N1b2 haplogroups, which are both enriched in Ashkenazi Jews but are very rare in other populations. The presence of the N1b2 genotype in a patient reporting mixed ethnicity (003-321) provides an additional level of support to the notion that homozoygosity of MAK mutations is attributable to a founder effect.

From a clinical standpoint, all patients had signs of typical RP and no significant differences could be noted in general between patients with MAK vs. DHDDS mutations. However, three individuals with the MAK mutation presented ocular manifestations that differed from the average of all other patients. Patient 121–184 showed more severe loss of retinal function with a substantial reduction of visual field and almost unrecordable cone responses. By contrast, patients 003–213 and 003–033 had ages comparable to that of patient 121–184 but had milder clinical features, with more preserved visual field and larger cone ERGs. A possible explanation is that these patients harbor additional variants that, added to the effect of the mutation, can modulate the overall phenotype. Because of the degree of variability in retinal function detected by visual field and ERGs in patients of comparable age with the DHDDS mutation, the same explanation could apply for this mutation as well.

In conclusion, we found that a 353-bp Alu insertion in MAK and the p.Lys42Glu mutation in DHDDS are common causes of arRP in North American patients of Jewish ancestry. More specifically, these two mutations alone account for approximately one-third of such recessive or isolate cases and therefore should be considered primary targets for molecular diagnosis of RP in patients within this ethnic group.

**DISCUSSION**

There is a growing list of genes that have been shown to be responsible for a high percentage of cases of recessive retinal degenerations in individuals of Ashkenazi descent (e.g., CLRN1 and PCDH15). In our screen of North American arRP patients of Jewish ancestry, we found a prevalence of ~26% for the Alu insertion in MAK, and of ~9% for the missense mutation in DHDDS. Despite all known retinal degeneration genes can now be collectively queried by DNA capture panels and next-generation sequencing (NGS), these elevated prevalence figures may justifi the screening of these two mutations in patients of Jewish ancestry, particularly for time-sensitive cases or for individuals whose health insurance does not cover large-scale tests. Furthermore, the Alu insertion in MAK may not be recognizable by NGS techniques, highlighting the value of simple PCR-based procedures to detect this mutation, either as a prescreening test or to retrospectively query samples that are seemingly negative to NGS approaches.

Haplotype analysis in patients carrying the Alu insertion in MAK showed a shared homozygous region of five polymorphic markers, suggesting that this is a founder mutation in the Jewish population. This also indicates that, most likely, the individuals reporting mixed ethnicity who were also found to harbor the mutation had ancestors from this ethnic group. To further investigate whether patients carrying one of the two mutations were indeed of Ashkenazi descent, we sequenced the two hypervariable regions of the mitochondrial genome. We found that six patients carried the K1a1b1a and N1b2 haplogroups, which are both enriched in Ashkenazi Jews but are very rare in other populations. The presence of the N1b2 genotype in a patient reporting mixed ethnicity (003-321) provides an additional level of support to the notion that homozoygosity of MAK mutations is attributable to a founder effect.

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**SUPPLEMENTARY MATERIAL**

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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**DISCLOSURE**

The authors declare no conflict of interest.

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