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

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**Purpose:** Retinitis pigmentosa is a Mendelian disease with a very elevated genetic heterogeneity. Most mutations are responsible for less than 1% of cases, making molecular diagnosis a multigene screening procedure. In this study, we assessed whether direct testing of specific alleles could be a valuable screening approach in cases characterized by prevalent founder mutations.

**Methods:** We screened 275 North American patients with recessive/isolate retinitis pigmentosa for two mutations: an Alu insertion in the *MAK* gene and the p.Lys42Glu missense in the *DHDDS* gene. All patients were unrelated; 35 reported Jewish ancestry and the remainder reported mixed ethnicity.

**Results:** We identified the *MAK* and *DHDDS* mutations homozygously in only 2.1% and 0.8%, respectively, of patients of mixed

ethnicity, but in 25.7% and 8.6%, respectively, of cases reporting Jewish ancestry. Haplotype analyses revealed that inheritance of the *MAK* mutation was attributable to a founder effect.

**Conclusion:** In contrast to most mutations associated with retinitis pigmentosa—which are, in general, extremely rare—the two alleles investigated here cause disease in approximately one-third of North American patients reporting Jewish ancestry. Therefore, their screening constitutes an alternative procedure to large-scale tests for patients belonging to this ethnic group, especially in time-sensitive situations.

*Genet Med* advance online publication 25 September 2014

**Key Words:** Ashkenazi; *DHDDS*; *MAK*; retinal degeneration; retinitis pigmentosa

## 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.<sup>1</sup> Affected people have been reported in diverse ethnic groups worldwide.<sup>2–6</sup> Recently, mutations in two genes, *MAK*<sup>7,8</sup> and *DHDDS*,<sup>9,10</sup> were found to cause autosomal recessive RP (arRP) in patients of Ashkenazi Jewish ancestry, i.e., in descendants 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<sup>11</sup> and retina.<sup>12</sup> 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.<sup>7,8,13</sup> In mice, *Mak* regulates photoreceptor ciliary length and is crucial for photoreceptor long-term survival; for these reasons, *Mak*<sup>-/-</sup> animals develop progressive retinal degeneration.<sup>13</sup> 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.<sup>7</sup> 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.<sup>14</sup> 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.<sup>7</sup> 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.<sup>14</sup>

*DHDDS* encodes dehydrodolichyl diphosphate synthase, an evolutionarily conserved enzyme participating in the

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Submitted 22 May 2014; accepted 19 August 2014; advance online publication 25 September 2014. doi:[10.1038/gim.2014.132](https://doi.org/10.1038/gim.2014.132)

biosynthesis of dolichol, an essential lipid serving as glycosyl moiety carrier for protein N-glycosylation.<sup>15</sup> Dolichol is ubiquitously present in human tissues.<sup>15,16</sup> In the retina, *DHDDS* is expressed in the inner segment of photoreceptors, where dolichol biosynthesis is predicted to happen.<sup>9</sup> Recently, a missense mutation of a conserved residue (p.Lys42Glu) in *DHDDS* was associated with arRP in a non-consanguineous pedigree of Jewish ancestry,<sup>10</sup> as well as in 15 other unrelated families of Ashkenazi descent, corresponding to a prevalence of ~10% in the latter ethnic group.<sup>9</sup> 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.<sup>9</sup> The p.Lys42Glu mutation has been reported to be an Ashkenazi-specific founder mutation, and it is very rare in other populations.<sup>9</sup>

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.<sup>17</sup>

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.<sup>9</sup> Primer sequences were: 5'-TACCGCCCATTTTGTTCAT-3' (*MAK* intron 8, forward); 5'-ACTGAGAAGTGTACTGTGAG-3' (*MAK* intron 9, reverse); 5'-TCCCTGAAGAATATGAGACCTGT-3' (*DHDDS* exon 2 forward); and 5'-CAAACCTCAGAGCCTGGTTTTCTA-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<sub>2</sub>, 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

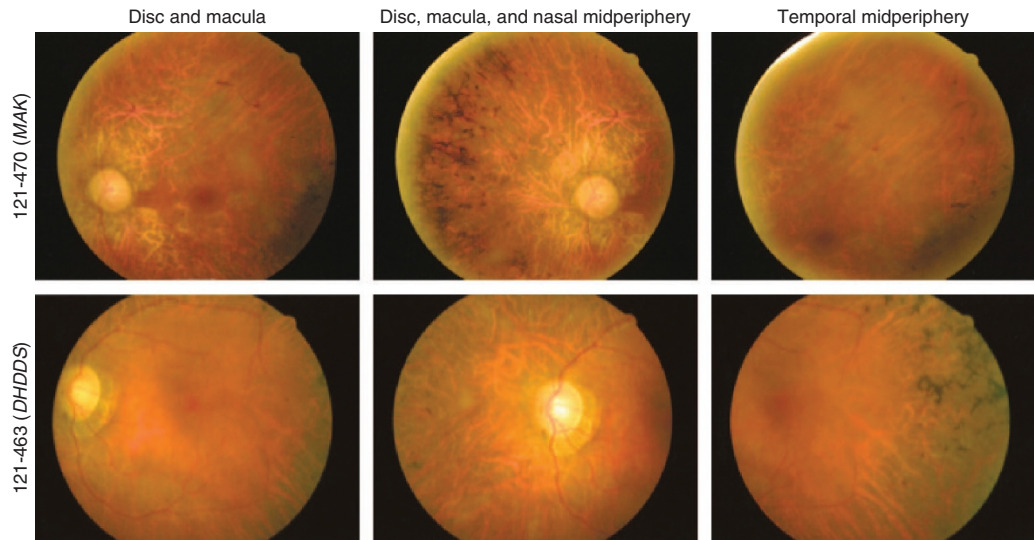
SNP ID	Chromosomal position	003-321	121-216	121-410	003-370	121-122	003-213	003-033	121-184	121-147	121-265	121-470	121-283	121-847	003-287
rs111468923	6:10687602	CT	TT	TT	TT	TT	TT	TT	CT	CT	TT	TT	TT	TT	TT
rs1045911	6:10723449	AC	CC	CC	CC	CC	CC	CC	CC	AC	CC	CC	CC	CC	CC
rs545019	6:10745066	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA
rs116734564	6:10753038	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC
<b>rs518954</b>	6:10791859	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG
rs7766477	6:10792427	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC	CC
rs9357021	6:10906154	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG	GG
rs12215477	6:10919736	GG	AA	GG	AG	GG	GG	GG	GG	GG	GG	GG	AG	GG	GG

rs518954, in bold, is the SNP that is closest to the mutation. The shared haplotype is highlighted in gray.

**Table 2** Clinical summary of first visits of patients with mutations in MAK or DHDDS

ID	Geno-type	Ancestry	Age	NB	VFL	Sex	Visual acuity		Visual field OD	Visual field OS	Dark adaptation	0.5 Hz		30 Hz		Lens OD	Lens OS	Macula OD and OS		Periphery OD and OS	
							OD	OS				ERG OD	ERG OS	ERG OD	ERG OS			ERG OD	ERG OS	OS	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	NA	NA	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	20/25	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	NA	NA	0.20	0.13	+	+	+	+	+	+
121-265	M/M	Jewish/Lithuanian/Polish	47	40	40	M	20/25	20/25	7694	3290	NA	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	NA	0.20	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	5.99	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	Pseudo-phakia	Pseudo-phakia	-	-	-	+
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 = 350), 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.



**Figure 1** Fundus photos of left eyes of patients with either *MAK* (top) or *DHDDS* (bottom) mutations.

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'-CACTGAGTCATAAAAGTGGT-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'-CGAAATGGAGAATCTTTTTCCT-3' wild-type and 5'-GAAAAAAGGAGGCCGGCGCGGT-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 markers around the insertion site using PCR conditions reported here and primer pairs listed in **Supplementary Table S1** online.

Sequencing of the two hypervariable regions in mitochondrial DNA of patients carrying either the *DHDDS* or the *MAK* mutation was accomplished by PCR amplification followed by Sanger sequencing using primers reported in previous literature<sup>18</sup> (5'-TCAAATGGGCCTGTCCTTGTAG-3' and 5'-GGGTGATGTGAGCCCGTCTA-3') and identical PCR conditions as reported here, except that annealing of the primers was

performed at 65 °C. Sanger sequencing was performed using 3.2 μM of sequencing primers 5'-TCAAATGGGCCTGTCCTTGTAG-3' and 5'-CTGTATCCGACATCTGGTTCCT-3'.

## 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 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

(003-015) belonged to the haplogroup N1b2 (markers 16145, 16176A, 16223, 16390, 16519, 73, 152, 263).

### Clinical assessment

The self-reported mean age of onset of night blindness in patients with the Alu insertion in *MAK* was 29 years ( $n = 14$ ; range, 18–41 years at first visit), and age of onset of visual field loss was 30 years ( $n = 14$ ; range, 12–51 years) (Table 2). In agreement with what was previously observed by Stone et al.,<sup>14</sup> patients carrying the Alu insertion in *MAK* had preserved visual acuity in at least one eye at their initial visit. In half of these patients visual field areas were reduced by 50% or more compared with lower normal values. Most had 30-Hz cone ERGs that were reduced 95% below normal.

Self-reported mean age of onset of night blindness in patients with the *DHDDS* mutation was 28 years ( $n = 5$ ; range, 21–32 years at first visit), and onset of visual field loss was 29 years ( $n = 5$ ; range, 16–33 years at first visit) (Table 2). In their mid 30s, most had visual field areas reduced by 50% or more compared with control individuals. Their 30-Hz cone ERGs were reduced more than 90% below normal. These patients were not examined later in life to ascertain whether visual acuity was retained.

Patients with either *MAK* or *DHDDS* mutations in practically all cases presented with posterior subcapsular cataracts, and all showed intraretinal pigment in a bone spicule configuration in the periphery, typical of RP (Figure 1).

## 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*<sup>19</sup> and *PCDH15*<sup>20</sup>). 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 justify 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,<sup>7</sup> 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.<sup>21–23</sup> The remainder had haplogroups that were compatible with, but not exclusive of, Ashkenazi descent. The presence of the N1b2 genotype in a patient reporting mixed ethnicity (003-321) provides an additional level of support to the notion that homozygosity 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 (Table 2). 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.

### SUPPLEMENTARY MATERIAL

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

### ACKNOWLEDGMENTS

This work was supported by the Swiss National Science Foundation (grant 310030-138346), the Gebert R uf Foundation, Switzerland (Rare Diseases—New Technologies grant), and a Center Grant to the Berman-Gund Laboratory for the Study of Retinal Degenerations, Harvard Medical School (to E.L.B.), from the Foundation Fighting Blindness, Columbia, MD.

### DISCLOSURE

The authors declare no conflict of interest.

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