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Nonsyndromic Retinitis Pigmentosa in the Ashkenazi Jewish Population

Genetic and Clinical Aspects

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Purpose: To analyze the genetic and clinical findings in retinitis pigmentosa (RP) patients of Ashkenazi Jewish (AJ) descent, aiming to identify genotype–phenotype correlations.

Design: Cohort study.

Participants: Retinitis pigmentosa patients from 230 families of AJ origin.

Methods: Sanger sequencing was performed to detect specific founder mutations known to be prevalent in the AJ population. Ophthalmologic analysis included a comprehensive clinical examination, visual acuity (VA), visual fields, electroretinography, color vision testing, and retinal imaging by OCT, pseudocolor, and autofluorescence fundus photography.

Main Outcome Measures: Inheritance pattern and causative mutation; retinal function as assessed by VA, visual fields, and electroretinography results; and retinal structural changes observed on clinical funduscopy as well as by pseudocolor, autofluorescence, and OCT imaging.

Results: The causative mutation was identified in 37% of families. The most prevalent RP-causing mutations are the Alu insertion (c.1297_8ins353, p.K433Rins31*) in the male germ cell-associated kinase (*MAK*) gene (39% of families with a known genetic cause for RP) and c.124A>G, p.K42E in dehydrodolichol diphosphate synthase (*DHDDS*) (33%). Additionally, disease-causing mutations were identified in 11 other genes. Analysis of clinical parameters of patients with mutations in the 2 most common RP-causing genes revealed that *MAK* patients had better VA and visual fields at relatively older ages in comparison with *DHDDS* patients. Funduscopic findings of *DHDDS* patients matched those of *MAK* patients who were 20 to 30 years older. Patients with *DHDDS* mutations were referred for electrophysiologic evaluation at earlier ages, and their cone responses became nondetectable at a much younger age than *MAK* patients.

Conclusions: Our AJ cohort of RP patients is the largest reported to date and showed a substantial difference in the genetic causes of RP compared with cohorts of other populations, mainly a high rate of autosomal recessive inheritance and a unique composition of causative genes. The most common RP-causing genes in our cohort, *MAK* and *DHDDS*, were not described as major causative genes in other populations. The clinical data show that in general, patients with biallelic *MAK* mutations had a later age of onset and a milder retinal phenotype compared with patients with biallelic *DHDDS* mutations. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

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The Ashkenazi Jewish (AJ) population comprises individuals with a recent ancestry in Central and Eastern Europe. As with all other Jewish diaspora groups, Ashkenazi Jews trace their ancestry to the Middle East, beginning approximately 2000 to 3000 years ago. Between the 13th and 15th centuries, after expulsions from Western Europe, the communities expanded eastward, especially to Poland, Lithuania, and then Russia. The AJ population lived in closed communities, developed a unique language, Yiddish, and married within their community.[1,2] The AJ population started as a small community and expanded from 10% of the world's Jewish population in the 12th century to 90% in the 1930s. After the Holocaust, during which approximately 6 million AJ individuals were murdered, the AJ population size dropped drastically and most of the survivors immigrated out of Europe, mainly to the United States and the emerging state of Israel. The largest Jewish populations worldwide reside in Israel (44% of all Jews) and the United States (39%). The AJ population comprises 50% of the Jewish population in Israel and approximately 90% of

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the Jewish population in the United States.[1] The third largest Jewish population resides in France (3.5% of all Jews) and is mainly of North African origin (Morocco, Algeria, Libya, and Tunisia), with approximately 40% individuals of AJ origin.

The genetics of the AJ population have been studied in great detail.[3] Because of a history of narrow bottleneck events followed by rapid population expansion, the AJ population shows distinctive genetic characteristics.[4,5] Founder effects and possibly selection[6] resulted in a relatively high prevalence of Mendelian conditions in the AJ population, including, for example, a high frequency of autosomal recessive (AR) diseases[7] and a high carrier frequency of susceptibility alleles to breast and ovarian cancers.[8]

Nonsyndromic retinitis pigmentosa (RP; Mendelian Inheritance in Man identifier, 268000) is the most common inherited retinal degeneration, and its prevalence is estimated at 1:5000 in Europe and the United States.[9–11] Lately, the prevalence of nonsyndromic RP among Jews in the vicinity of Jerusalem was estimated at approximately 1:2230 because of extremely high prevalence of consanguinity or intracommunity marriage.[12] Retinitis pigmentosa is characterized by initial gradual degeneration of the rod photoreceptors in the retina leading to night blindness, followed by degeneration of cone photoreceptors leading to loss of central vision, often deteriorating to legal blindness.[13] Retinitis pigmentosa can be transmitted in all Mendelian modes of inheritance and is highly heterogeneous, with more than 60 genes reported to cause the disease when mutated (RetNet database; available at https://sph.uth.edu/retnet/; accessed November 1, 2017). The phenotypic heterogeneity is also high, with a large range of severity of symptoms, even between members of the same family.[13]

Founder mutations in 2 genes have been described as relatively common causes of RP in the AJ population: an Alu insertion (c.1297_8ins353, p.K433Rins31*) in exon 9 of the male germ cell-associated kinase (*MAK*)[14,15] and a missense mutation (c.124A>G, p.K42E) in dehydrodolichol diphosphate synthase (*DHDDS*).[16,17] Follow-up analysis of these 2 mutations in a cohort of RP patients from North America verified that these mutations are unique to the AJ population and did not reveal any significant clinical differences between patients who were homozygous for the *MAK* mutation versus those homozygous for the *DHDDS* mutation.[18] However, this study examined a relatively small number of patients (*MAK*, n = 14; *DHDDS*, n = 5) with a limited range of ages (from 29 to 64 years).

The *MAK* gene encodes a serine and threonine protein kinase, which was shown to be expressed in the testis[19] and in the retina.[15,20] MAK was shown to regulate retinal photoreceptor ciliary length and subcompartmentalization.[21] Haplotype analyses revealed that the *MAK* mutation was an AJ founder mutation.[18] The clinical phenotype of patients who were homozygous for the Alu insertion in *MAK* showed some resemblance to patterns described in autosomal dominant (AD) RP, with prolonged preservation of the central retina and good visual acuity.[14] In an additional 11 patients, other missense and nonsense mutations in the *MAK* gene also were reported to be associated with a relatively mild phenotype.[22]

DHDDS encodes an evolutionarily conserved enzyme involved in the biosynthesis of dolichol, which plays a major role in N-linked protein glycosylation.[23] In humans, dolichols mainly consist of dolichol-17 (containing 17 isoprene units), dolichol-18, dolichol-19, and dolichol-20, with dolichol-19 being the more common form.[24,25] Individuals who are homozygous for p.K42E have a different and shortened dolichol pattern.[26] Haplotype analyses revealed that the p.K42E mutation was an AJ founder mutation.[16] *DHDDS* was shown to be a common causative gene in a cohort of RP patients in the vicinity of Jerusalem.[12] The clinical phenotype of patients who are homozygous for the p.K42E mutation generally is within the spectrum often described in AR RP.[16–18] In addition to the above-mentioned founder mutations, we previously reported a few rare RP-causing mutations in AJ patients (each responsible for disease in 1–2 families) in *FAM161A*,[27] *BBS2*,[28] *CNGB1*,[29] and *HGSNAT*.[30] In this study, we performed comprehensive genetic and clinical characterization of a large cohort of AJ patients with RP and performed genotype–phenotype correlation analysis in patients with the 2 major causative genes found in this cohort, *MAK* and *DHDDS*.

Methods

Patients and Clinical Evaluation

All participants in the study signed an informed consent that adhered to the tenets of the Declaration of Helsinki before a blood sample for molecular analysis was drawn. Ethical approval for this study was obtained from the local institutional review board committees at the Hadassah-Hebrew University Medical Center and at Rambam Medical Center.

Clinical evaluation included a full ophthalmic examination; determination of best-corrected visual acuity (BCVA) using an Early Treatment Diabetic Retinopathy chart; full-field electroretinography performed according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards; electrooculography; Goldmann perimetry; color vision testing using the Farnsworth D-15 panel and Ishihara tests; OCT, color fundus photography, infrared and fundus autofluoresence imaging; and fluorescein angiography, as detailed previously.[31] Best-corrected visual acuity (Early Treatment Diabetic Retinopathy decimal scores) was measured at each visit of the patient to the clinic, and the average between 2 eyes was taken. In case the patient underwent cataract surgery and his or her BCVA improved in the operated eye, measurements before surgery that were lower in this eye were corrected to the measurement after surgery with the thought that this better represents retinal function at that time. To provide numerical values for low BCVAs, the following conversions were made: no light perception, 0; light perception, 0.0001; hand movements, 0.001; and counting fingers, 0.01.

Genetic Analysis

DNA was extracted from the index patient, as well as from other affected and unaffected family members, with the FlexiGene DNA kit (QIAGEN) or by the Maxwell 16 Blood DNA purification kit (AS1010; Promega, Madison, WI) using the Maxwell 16 instrument (Promega).