Nonsyndromic retinitis pigmentosa is highly prevalent in the Jerusalem region with a high frequency of founder mutations

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Purpose: Nonsyndromic retinitis pigmentosa (RP) is the most common inherited retinal degeneration, and prevalence of the disease has been reported in populations of American and European origin with a relatively low consanguinity rate. Our aim was to determine the prevalence of nonsyndromic RP in the Jerusalem region, which has a population of about 1 million individuals with a high rate of consanguinity.

Methods: The patients' clinical data included eye exam findings (visual acuity, anterior segment, and funduscopy) as well as electroretinographic (ERG) testing results under scotopic and photopic conditions. Mutation analysis on a subgroup of patients was performed mainly with candidate gene analysis and homozygosity mapping.

Results: We evaluated the medical records of patients with degenerative retinal diseases residing in the Jerusalem region who were examined over the past 20 years in a large tertiary medical center. A total of 453 individuals affected with nonsyndromic RP were diagnosed at our center, according to funduscopic findings and ERG testing. Based on the estimated population size of 945,000 individuals who reside in the vicinity of Jerusalem, the prevalence of nonsyndromic RP in this region is 1:2,086. The prevalence of RP was higher among Arab Muslims (1:1,798) compared to Jews (1:2,230), mainly due to consanguineous marriages that are more common in the Arab Muslim population. To identify the genetic causes of RP in our cohort, we recruited 383 patients from 183 different families for genetic analysis: 70 with autosomal recessive (AR) inheritance, 15 with autosomal dominant, 86 isolate cases, and 12 with an X-linked inheritance pattern. In 64 (35%) of the families, we identified the genetic cause of the disease, and we revised the inheritance pattern of 20 isolate cases to the AR pattern; 49% of the families in our cohort had AR inheritance. Interestingly, in 42 (66%) of the genetically identified families, the cause of disease was a founder mutation.

Conclusions: Previous studies showed an approximate prevalence of 1:5,260 on average for nonsyndromic RP in American and European populations. We show that the prevalence in the vicinity of Jerusalem is two-and-a-half times higher due to a high rate of consanguinity and highly prevalent founder mutations within the historically semi-isolated subpopulations we serve.

Hereditary retinal diseases (HRDs) are heterogeneous disorders that cause incurable visual loss mainly due to the dysfunction or degeneration of rod and cone photoreceptor cells in the retina. Although a wide and sometimes overlapping spectrum of phenotypes exists, HRDs that mainly affect photoreceptors and/or RPE cells can be roughly divided into three main categories based on the predominant cell type affected and the pattern of disease progression: rod-dominated diseases in which pronounced, widespread rod photoreceptor loss precedes cone involvement (retinitis pigmentosa [RP], the most common form of inherited retinal degeneration, classically follows this pattern), cone-dominated diseases with more pronounced cone photoreceptor loss, and regional degeneration in which a specific retinal region (e.g., the macula) is affected. The total number of genes responsible for these heterogeneous diseases is still unknown but is estimated to be more than 200. Numerous manuscripts and many excellent reviews have been published on the genetic and clinical aspects of inherited retinal diseases [1-7].

The Israeli population contains several different ethnic groups including Jews of various origins (75% of the population), Arab Muslims (17%), Bedouins (2.8%), Arab Christians (2%), and Druze (1.6%; data are based on the Israeli Central Bureau of Statistics as of 2010). Consanguinity has been reported to be high in various ethnic groups in Israel for many generations, stemming from historic, ethnic, religious, and cultural causes [8,9]. Genetic analysis of Israeli families with various inherited diseases was and is actively pursued, and has led to the identification of the disease-causing genes (including novel ones) in many cases (data are available online in the Israeli National Genetic Database).

The Jewish population originated in the Middle East but during the course of history (spanning thousands of years) was divided into isolated ethnic groups separated geographically throughout practically the entire world. Within these semi-isolated ethnic groups, the need and desire to maintain

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religion and culture led to relatively high levels of intracommunity marriages. Over the past 150 years, and more prominently following the establishment of the state of Israel in 1948, many returned to their homeland, and in recent history, a lower rate of consanguinity and an elevated rate of interethnic marriages are already evident [8]. The largest Jewish ethnic group is the Ashkenazi Jewish population, which comprises about 55% of Israeli Jews, followed by North African Jews (about 25%), and Eastern Jews (from Iran, Iraq, etc., about 20%). Genetic analyses of Ashkenazi Jewish families aided in the identification and characterization of many genes in which founder mutations cause common inherited diseases in this ethnic group (see [10] for review), including Tay-Sachs [11], Gaucher [12], and Usher syndrome [13,14] and several genes that cause recessive RP [15-17]. An intense scientific effort was directed during the past 15 years using different genetic tools and markers to genetically analyze the different Israeli subpopulations. These studies led to better

classification of the different ethnic groups and shed light on the common origin of most of these populations [18-23].

Individuals of Arab Muslim origin tend to live in villages that were founded a few generations ago by a small number of individuals. In accordance with the customs of the Arab population throughout the Middle East [24,25], consanguineous marriages are common among Israeli Arabs, with a preference for first-cousin marriages [25,26]. This is one of the reasons for the high rate of occurrence of autosomal recessive diseases in this population, with more than 200 diseases described thus far [27].

The Bedouin population is unique in its structure, which is tribal, and exhibits an extremely high level of consanguinity. Studying the genetics of Bedouin Israeli families was a key factor in the discovery of many disease-causing genes, including those causing Bardet-Biedl syndrome, such as *BBS1* (GeneID 582, OMIM: 209901), [28], *BBS2* (GeneID 583, OMIM: 606151) [29], *ARL6* (GeneID 84100, MIM: 608845) [30], and *TRIM32* (GeneID 22954, OMIM: 602290) [31].
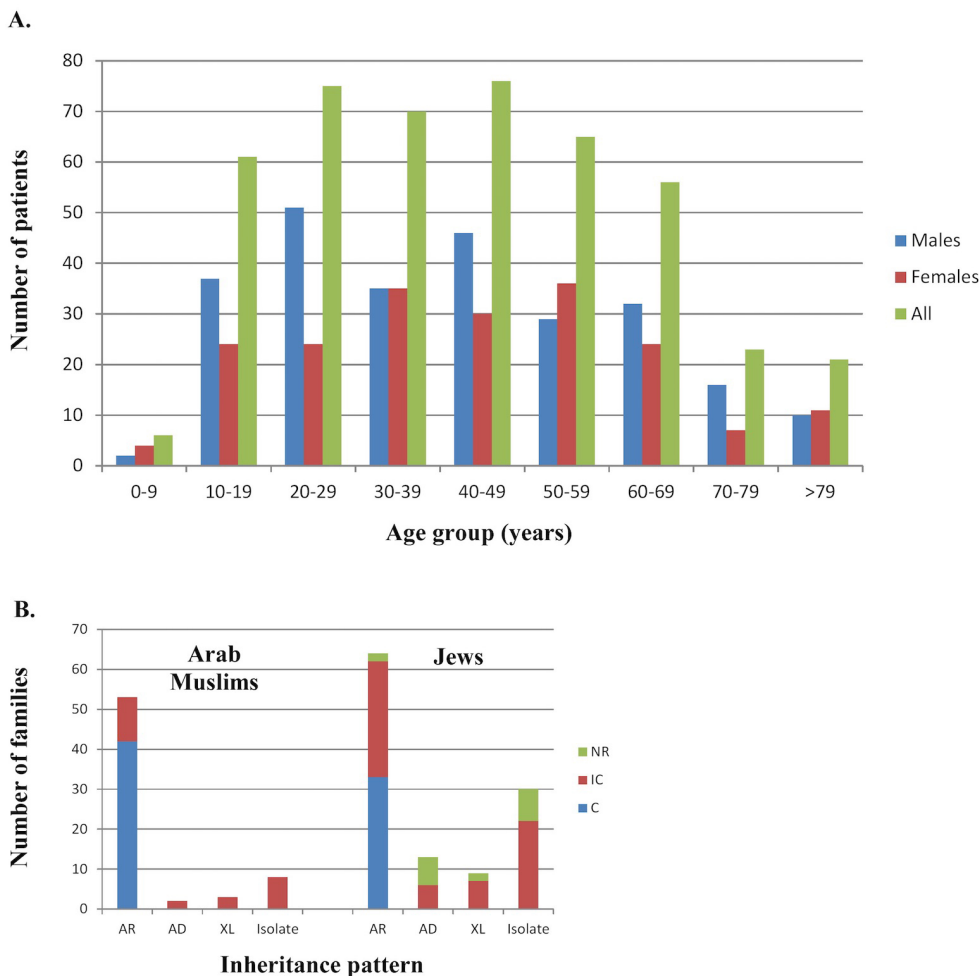
A.

B.

Figure 1. Distribution of patients with RP by age, origin, consanguinity, and inheritance type. **A**: The distribution of the studied set of patients by age. Each bar represents the number of patients within each specific age group, divided into 10-year intervals. Data are presented for all patients (green), men only (blue), and women only (red). **B**: The distribution of the cohort of recruited families by origin, inheritance type, and parental relatedness. For each origin (Arab Muslims and Jews), families are presented by inheritance pattern and relatedness. AR=autosomal recessive and consanguineous isolate cases; AD=autosomal dominant; XL=X-linked; NR=parents are not related; IC=intracommunity marriages; C=consanguineous marriages.

Analyzed cohort	No. of recruited families (No. of patients)**	AR	Isolate cases, from consanguineous families	AD	XL	Isolate cases
Based on family history*	183 (383)	70 (38%)	32 (17%)	15 (8%)	12 (7%)	54 (30%)
Updated following genetic evaluation*	183 (383)	90 (49%)	26 (14%)	15 (8%)	12 (7%)	40 (22%)
Arab Muslims	66 (151)	36 (55%)	17 (26%)	2 (3%)	3 (4%)	8 (12%)
Jews	116 (227)	54 (46%)	10 (9%)	13 (11%)	8 (7%)	31 (27%)

TABLE 1. MODE OF INHERITANCE PATTERNS IN THE STUDIED SET OF PATIENTS.

*The inheritance pattern in each family was initially determined by the family history (first row- "Based on family history"). Following the genetic diagnosis (in 35% of cases), the inheritance pattern was revised based on the identified gene and mutation (second row- "Updated following genetic evaluation"), resulting in more accurate values. **- The total number of patients (383) includes mainly patients of Arab-Muslim origin (151) and Jewish origin (227), as well as 5 patients (who belong to the same family) of Bedouin origin.

To date, the prevalence of inherited retinal diseases has been estimated in studies that were performed mainly in North America or Europe. Nonsyndromic RP [MIM # 268000] is the most common inherited retinal degeneration with an estimated prevalence of 1:5,193 in Maine [32], 1:6,134 in Denmark [33], and 1:4,440 in Norway [34]. Similarly, the total prevalence of RP (including syndromic as well as nonsyndromic forms) was estimated at 1:4,756 in Maine [32], 1:4,869 in Birmingham [35], 1:3,937 in Denmark [33], and 1:3,784 in China [36].

No accurate data are currently available on the prevalence of RP in the Israeli and Palestinian population. Merin and Auerbach [37] estimated that the prevalence of RP in Israel, and autosomal recessive RP in particular, is higher than that reported in other countries because of the high rate of consanguineous marriages. In a survey that was performed to roughly estimate the prevalence of RP in the Israeli Jewish population, 341,175 files of individuals (ages 17–20 years) were evaluated [38]. In this survey, the best-corrected visual acuity (VA) was determined, and those who had acuity of less than 20/25 were further examined by an ophthalmologist. The prevalence in this study was estimated at 1:4,610, which was predicted to be an underestimation since many patients with RP in this age group have relatively preserved visual acuities and would not have been identified with the VA screening parameter used. The purpose of the current study was to determine the prevalence of nonsyndromic RP in the Jerusalem region and to compare prevalence data of the two major subpopulations residing in this region, namely, Jews and Arab Muslims.

METHODS

Subjects: Ethical approval for this study was obtained from the Hadassah Medical Center Institutional Review Board (IRB). All participants in the genetic research signed an informed consent that adhered to the tenets of the Declaration of Helsinki. Subsequently, venous blood samples were collected and processed immediately. Genomic DNA was extracted using FlexiGene DNA kit (Qiagen, Venlo, The Netherlands).

Clinical evaluation: The ocular diagnosis was determined mainly using a full ophthalmologic exam and full-field electroretinography (FFERG). In many cases, additional supportive functional and structural data was available, including combinations of electro-oculography (EOG), color vision testing using the Panel D-15 test, Humphrey and/or Goldmann perimetry, optical coherence tomography (OCT), color, infrared and fundus autofluorescence (FAF) imaging, and fluorescein angiography (FA).

Genetic analyses: Various genetic analyses were used to identify the cause of disease, including homozygosity mapping followed by Sanger sequencing of candidate genes, mutation analysis of founder mutations, and whole exome sequencing as detailed elsewhere [16,39,40].

RESULTS

Aiming to estimate the prevalence of nonsyndromic RP in the vicinity of Jerusalem, we created a database of patients who were examined with ERG at our unit, were clinically examined at our ophthalmology clinic, or participated in the ophthalmic genetic study. For the prevalence calculation, we included only individuals who were diagnosed with nonsyndromic RP and reside in the vicinity of Jerusalem. We identified 453 patients with RP in a region that is estimated

TABLE 2. DISEASE-CAUSING MUTATIONS IDENTIFIED IN RP PATIENTS FROM THE VICINITY OF JERUSALEM.

Gene Name	Mutation name	# of Families (# of alleles)	% of the total number of alleles	Origin
ADAM9	c.1087T>A (p.C363S)	2 (4)	3.4%	Iraqi Jewish
BBS1	c.479G>A (p.R160Q)	1 (2)	1.7%	Arab-Muslim
CDHR1	c.1381C>T (p.Gln461*)	1 (2)	1.7%	Arab-Muslim
	c.2087_2090del4 (p.D696Afs*3)	1 (2)	1.7%	Arab-Muslim
CNGB1	c.2284C>T (p.R762C)	2 (4)	3.4%	Buchara Jewish
CRB1	c.1148G>A (p.C383Y)	1 (2)	1.7%	Kurdish Jewish
	c.2498G>A (p.G833D)	2 (4)	3.4%	Iraqi Jewish
	c.3306G>A (p.G1103R)	2 (4)	3.4%	Arab-Muslim
c2orf71	c.2950C>T (p.R984*)	1 (1)	0.8%	Turkey Jewish
	c.3289C>T (p.Q1097*)	1 (1)	0.8%	Iranian Jewish
C8orf37	c.529C>T (p.R177W)	1 (2)	1.7%	Arab-Muslim
DHDDS	c.124A>G (p.K42E)	8 (16)	13.8%	Ashkenazi Jewish
EYS	c.403delA,c.406G>T,c.del410_424 (p.T135Lfs*25)	5 (9)	7.7%	North-African Jewish
	c.1211_1212insA (p.N404Kfs*2)	1 (2)	1.7%	North-African Jewish
	c.8218_8219delCA (p.H2740Yfs*27)	1 (1)	0.8%	Iraqi Jewish
	c.9286_95del10 (p.V3096Lfs*28)	1 (2)	1.7%	Ashkenazi Jewish
FAM161A	c.1355_6delCA (p.T452Sfs*3)	6 (12)	10.3%	North-African Jewish
	c.1567C>T (p.R523*)	1 (2)	1.7%	Syrian Jewish
MAK	c.1296_7ins353 (Alu insertion)	2 (4)	3.4%	Ashkenazi Jewish
NR2E3	c.119−2A>C (IVS1−2A>C)	2 (2)	1.7%	Arab-Muslim
	c.932G>A (p.R311Q)	2 (2)	1.7%	Ashkenazi Jewish
	c.747+1G>C (IVS5+1G>C)	1 (1)	0.8%	Ashkenazi Jewish
	c.194−202del9bp (p.N65-C67del)	1 (1)	0.8%	Ashkenazi Jewish
PDE6A	c.1960C>T (p.Q654*)	1 (2)	1.7%	Arab-Muslim
RDH12	c.295C>A (p.L99I)	2 (4)	3.4%	North-African Jewish
	c.377C>T (p.A126V)	2 (4)	1.7%	Arab-Muslim
	c.658G>A (IVS5+1G>A)	1 (2)	1.7%	Arab-Muslim
	c.740T>C (p.L274P)	1 (2)	3.4%	Arab-Muslim

Gene Name	Mutation name	# of Families (# of alleles)	% of the total number of alleles	Origin
RPGR	c.259G>T (p.E87*)	1 (1)	0.8%	Bedouin Arab-Muslim
	c.592G>A (p.G198R)	2 (2)	1.7%	Ashkenazi Jewish
	c.2964_5delGG (p.G998Gfs*88)	1 (1)	0.8%	Ashkenazi Jewish
	c.2797delG (p.E943Kfs*155)	1 (1)	0.8%	Ashkenazi Jewish
	c.2405_6delAG (p.E802Gfs*31)	1 (1)	0.8%	
RP2	c.530_531delTT (p.F177Yfs*40)	1 (1)	0.8%	Ashkenazi Jewish
SPATA7	c.288T>A (p.C96*)	1 (2)	1.7%	Arab-Muslim
USH1C	c.1220delG (p.G407Efs*56)	3 (6)	5.2%	Yemenite Jewish
USH2A	c.377delG (p.S126Ifs*18)	1 (1)	0.8%	Arab-Muslim
	c.3959C>T (p.P1320L)	1 (1)	0.8%	Arab-Muslim
	c.6937G>T (p.G2313C)	1 (1)	0.8%	Arab-Muslim
	c.12052G>A (p.A4018T)	1 (1)	0.8%	Arab-Muslim

to be populated by 945,000 individuals (data collected from the Israeli Bureau of Statistics), resulting in an estimated prevalence of 1:2,086 individuals. There was a higher number of affected men (258, 57%), probably due to the contribution of the X-linked (XL) RP cases. We then estimated the prevalence of nonsyndromic RP in the two major subpopulations residing in the Jerusalem area: Jews (about 65% of the population) and Arab Muslims (35%). The prevalence of RP was higher among Arab Muslims (1:1,798) compared to Jews (1:2,230). The distribution of each disease by age group is shown in Figure 1A. As expected, RP is mainly prevalent from age 10 and on, as it is often not diagnosed earlier.

To identify the genetic causes of RP in our cohort, we recruited for genetic analysis 383 patients from 183 different families: Based on the family tree structure, 70 families showed an autosomal recessive (AR) inheritance pattern, 15 were suggestive of autosomal dominant (AD) inheritance,

32 cases were isolate with consanguinity (indicative of AR inheritance), 54 were non-consanguineous isolate cases, and 12 families showed an X-linked inheritance pattern (Table 1). A distribution analysis by mode of inheritance and parental relatedness (Figure 1B) shows an extremely high contribution of consanguinity (blue bar) and intracommunity (brown bar) marriages to AR inheritance in Arab Muslims and Jews. This is likely to be the major reason for the relatively high proportion of families with AR in our cohort and the relatively high disease prevalence.

In 64 (35%) of the families, we identified the genetic cause of disease and thus revised the inheritance pattern of 14 nonconsanguineous and six consanguineous isolate cases to an AR pattern; at least 49% of the families in our cohort had AR inheritance (Table 1). Moreover, since almost all consanguineous isolate cases are expected to be due to AR genes, our cohort is likely to contain at least 63% families
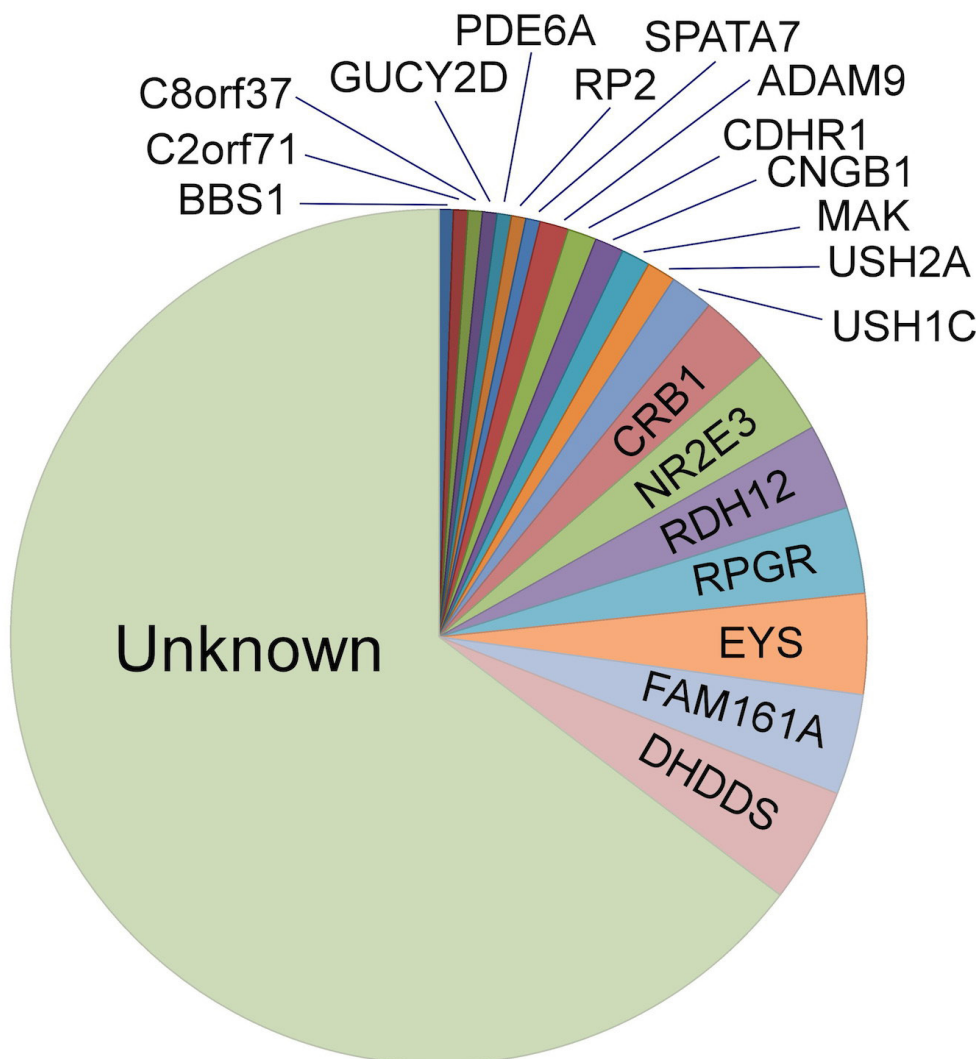

Figure 2. Pie chart showing the distribution of disease-causing genes in the vicinity of Jerusalem. Please note that most families (65%) have not been genetically diagnosed ("Unknown").
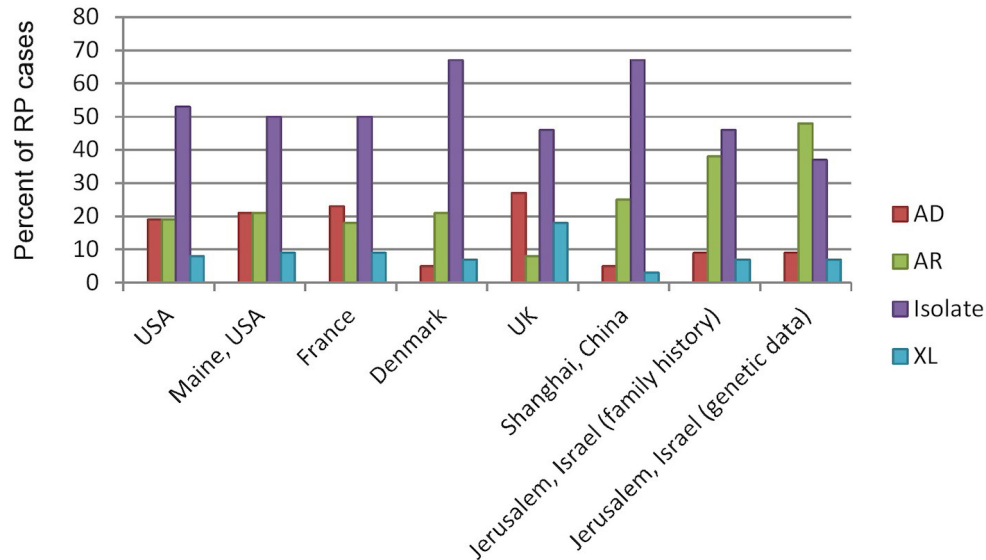
Figure 3. Distribution of RP inheritance patterns in different countries. The data are based on the following publications: the United States [45], Maine (the United States) [32], France [46], Denmark [33], the United Kingdom [47], and Shanghai (China) [48]. In some reports, the inheritance pattern could not be clearly established for some of the families, and we therefore corrected the percentage data accordingly. The data of the current study are presented based on family history as well as a revised distribution following results obtained in the genetic analysis.

with AR inheritance pattern. This high level of AR cases is more prominent in the Arab Muslim cohort, which has a combined AR inheritance of at least 81% (Table 1, clear AR inheritance in 55% of cases and consanguineous isolate in 26% of cases). Interestingly, in 42 (66%) of the genetically identified families, the cause of disease was a founder mutation within the studied population, identified in the following genes: *ADAM9* (GeneID 8754, OMIM: 602713), *CNGB1* (GeneID 1258, OMIM: 600724), *CRB1* (GeneID 23418, OMIM: 604210), *DHDDS* (GeneID 79947, OMIM: 608172), *EYS* (GeneID 346007, OMIM: 612424), *FAM161A* (GeneID 84140, OMIM: 613596), *MAK* (GeneID 4117, OMIM: 154235), *NR2E3* (GeneID 10002, OMIM: 604485), *RDH12* (GeneID 145226, OMIM: 608830), *RPGR* (GeneID 6103, OMIM: 312610), and *USH1C* (GeneID 10083, OMIM: 605242; Table 2 and Figure 2). The most common disease-causing allele in the vicinity of Jerusalem is the p.K42E missense mutation in *DHDDS* found in this study in 13.8% of the identified alleles (Table 2), followed by the c.1355_6delCA frameshift mutation in the *FAM161A* gene (10.3% of identified alleles). Similarly, the most common RP-causing genes were *DHDDS* (13.8% of identified alleles), *FAM161A* (12%), and *EYS* (11.9%).

DISCUSSION

Autosomal recessive retinal diseases are predicted to be more common in populations in which consanguineous and intra-community marriages are common. Consanguinity levels in different Israeli subpopulations have been reported to be relatively high [8,9,41], and this fact was appreciated even earlier by others who predicted a high prevalence of AR diseases, including nonsyndromic RP [37].

To date, few studies have estimated the prevalence of nonsyndromic RP, and these studies were performed in populations with a relatively low level of consanguinity including the state of Maine (USA), Denmark, and Norway [32-34]. Taken together, these studies suggested a prevalence rate of 1:5,256 individuals on average. We provide evidence that substantiates for the first time Merin and Auerbach's hypothesis regarding the prevalence of nonsyndromic RP in our population, which in the vicinity of Jerusalem is two-and-a-half to three times higher than that previously reported in other populations. This high prevalence is likely to be due to the high frequency of consanguineous marriages in the studied population in association with founder mutations. We showed that the proportion of families with the AR inheritance pattern is much higher than that reported in other populations (Figure 3). The rate of AR inheritance presented is probably an underestimate in all populations, as the yet-unidentified isolate cases, which constitute a large group in all the studies, are likely to represent mainly AR as well as XL cases. Once the causative gene is identified in these cases, the proportion is likely to shift toward an even higher rate of AR cases (Figure 3, family tree versus genetic data bars).

Founder mutations identified in the Israeli Jewish population, and mainly in Ashkenazi Jews, were also reported to be prevalent among non-Israeli Jews residing in North America [17,42-44]. This can greatly facilitate mutation analysis of Ashkenazi Jewish patients with RP. The most common disease-causing alleles found in this study are *DHDDS* p.K42E and *FAM161A* c.1355_6delCA, and the most common RP-causing genes are *DHDDS*, *FAM161A*, and *EYS*. This distribution is different from that reported in other

populations in which other genes such as *USH2A* (GeneID 7399, OMIM: 608400), *ABCA4* (GeneID 24, OMIM: 601691), and *RHO* (GeneID 6010, OMIM: 180380) are the major RP-causing genes when mutated [4]. In summary, we present evidence for the relatively high prevalence of nonsyndromic RP in the vicinity of Jerusalem, and we predict that this high prevalence reflects similar rates throughout the country and many other countries in the Middle East in which consanguineous marriages and founder mutations are not rare.

ACKNOWLEDGMENTS

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