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A nationwide genetic analysis of inherited retinal diseases in Israel as assessed by the Israeli inherited retinal disease consortium (IIRDC)

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Abstract

Inherited retinal diseases (IRDs) cause visual loss due to dysfunction or progressive degeneration of photoreceptors. These diseases show marked phenotypic and genetic heterogeneity. The Israeli IRD consortium (IIRDC) was established in 2013 with the goal of performing clinical and genetic mapping of the majority of Israeli IRD patients. To date, we recruited 2,420 families including 3,413 individuals with IRDs. On the basis of our estimation, these patients represent approximately 40% of Israeli IRD patients. To the best of our knowledge, this is, by far, the largest reported IRD cohort, and one of the first studies addressing the genetic analysis of IRD patients on a nationwide scale. The most common inheritance pattern in our cohort is autosomal recessive (60% of families). The most common retinal phenotype is retinitis pigmentosa (43%), followed by Stargardt disease and cone/cone–rod dystrophy.

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We identified the cause of disease in 56% of the families. Overall, 605 distinct mutations were identified, of which 12% represent prevalent founder mutations. The most frequently mutated genes were *ABCA4*, *USH2A*, *FAM161A*, *CNGA3*, and *EYS*. The results of this study have important implications for molecular diagnosis, genetic screening, and counseling, as well as for the development of new therapeutic strategies for retinal diseases.

KEYWORDS
genetic analysis, inherited retinal diseases, Israel, mutations, retina, retinitis pigmentosa

1 | INTRODUCTION

Inherited retinal diseases (IRDs) are a clinically and genetically heterogeneous group of diseases, which cause visual loss due to improper development or premature death of the retinal photoreceptors (Duncan et al., 2018). The most common form of IRD is retinitis pigmentosa (RP; also known as rod-cone degeneration), with a worldwide prevalence of approximately 1/4,000 individuals. RP symptoms include night blindness and peripheral visual field loss (Derby, 1886; Verbakel et al., 2018). In cone–rod dystrophy (CRD), cone involvement initially exceeds that of rods, and thus reduced visual acuity, photophobia, and impaired color vision are prominent early symptoms (Hittner, Murphree, Garcia, Justice, & Chokshi, 1975; Thiadens et al., 2012). Leber congenital amaurosis (LCA) is the most severe form of IRD, in which both rods and cones are nonfunctional at birth, or are lost within the first years of life (Kumaran, Moore, Weleber, & Michaelides, 2017; Leber, 1869). Other subtypes of IRDs, such as Best vitelliform macular dystrophy (Best, 1905; Johnson et al., 2017) and Stargardt disease (STGD; Stargardt, 1909; Tanna, Strauss, Fujinami, & Michaelides, 2017), affect primarily the macula and thus are associated with central vision loss. In addition to degenerative retinal dystrophies, IRDs also include nondegenerative phenotypes which do not progress over time, such as congenital stationary night blindness (CSNB; Cunier, 1838; Zeitz, Robson, & Audo, 2015) and achromatopsia (rod monochromatism; Holm & Lodberg, 1940; Tsang & Sharma, 2018). However, these heterogeneous clinical entities lie along a spectrum, and in some cases, the diagnostic boundaries between them are not distinct. Although in most cases of IRD, the disease involves only ophthalmic manifestations (nonsyndromic), over 70 forms of syndromic IRD have been described (Werdich, Place, & Pierce, 2014; OMIM, https://www.ncbi.nlm.nih.gov/omim). The most common one is Usher syndrome (USH), characterized by the combination of RP and hearing loss (Tsang, Aycinena, & Sharma, 2018; Usher, 1914).

IRD is one of the most genetically heterogeneous groups of disorders in humans. It can be inherited as autosomal recessive (AR), autosomal dominant (AD), or X-linked (XL). Mitochondrial and digenic patterns of inheritance have also been described. To date, over 260 genes have been implicated in the etiology of IRD (RetNet, Retinal Information Network, https://sph.uth.edu/Retnet/). However, the contribution of each of these genes to the overall prevalence of the disease is relatively small, and for many of them, pathogenic mutations have been reported in only a few families worldwide. Moreover, in approximately 30% of IRD patients, the underlying genes are yet to be found. These factors make the genetics of IRD very challenging (Duncan et al., 2018).

Israel has an estimated population of 8.97 million people. This population resides in a relatively small geographic region, and is highly heterogeneous, including Jews (74% of the population), Arab Muslims (19.5%), Arab Christians (1.5%), Druze (1.6%), and others (data are based on the Israeli Central Bureau of Statistics as of 2018). Some ethnic groups have high rates of consanguinity and a high number of siblings per family, leading to an increased rate of recessively-inherited diseases. Indeed, whereas the prevalence of nonsyndromic RP in Europe and the United States is approximately 1/5,000 (Bunker, Berson, Bromley, Hayes, & Roderick, 1984; Haim, 1992; Rosenberg, Haim, Hauch, & Parving, 1997), a much higher prevalence of 1/2,100 was found for nonsyndromic RP in the Jerusalem area, both in the Jewish and in the Arab Muslim populations (Sharon & Banin, 2015). Due to its unique genetic makeup, many of the genetic alterations identified in the Israeli population are novel. In the Jewish population, specific founder mutations are characteristic of specific ethnic groups (e.g., Ashkenazi Jews, North African Jews, Yemenite Jews, etc.). Such mutations are frequent among affected individuals from the same ethnic group. The Arab population is characterized by a high rate of consanguinity, leading to increased homozygosity of rare mutant alleles in specific families and villages (Hanany et al., 2018; Zlotogora, 2002).

Aiming to fully map IRDs in the Israeli population, we established the Israeli IRD consortium (IIRDC), including ophthalmologists, visual electrophysiologists, and geneticists from all over the country, as well as an expert in bioinformatics. Our aim was to recruit and genetically diagnose the vast majority of Israeli IRD patients.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

The tenets of the Declaration of Helsinki were followed, the study was approved by institutional review boards in participating Medical Centers, and written informed consent was obtained from all participants or their parents.

2.2 | Clinical evaluation

The clinical diagnosis was based on an ophthalmic examination, including measurement of best-corrected visual acuity, visual field testing, slit lamp examination, ophthalmoscopic examination after pharmacologic pupillary dilatation, and retinal imaging including color fundus photography and spectral-domain optical coherence tomography. The electrophysiological assessment was performed according to the discretion of the retinal specialist and included full-field electroretinography (ERG), multifocal ERG and measurement of flash visually evoked potentials.

2.3 | Genetic analyses

Genomic DNA was extracted from venous blood samples using a high-salt solution according to a standard protocol (Grimberg et al., 1989). Haplotype analysis was performed as previously described (Auslender et al., 2007). Homozygosity mapping was performed using whole-genome single-nucleotide polymorphism microarrays (Illumina and Affymetrix). Homozygous regions were calculated using HomozygosityMapper (Seelow, Schuelke, Hildebrandt, & Nurnberg, 2009). Targeted next-generation sequencing (T-NGS) of 108 known IRD genes was performed using the molecular inversion probes technique (Weisschuh et al., 2018). Whole-exome sequencing (WES) and whole-genome sequencing (WGS) were performed as previously described (Khateb et al., 2018; Tatour et al., 2019). Variant filtering was based on both external databases (including gnomAD, https://gnomad.broadinstitute.org/), which includes data on the Ashkenazi Jewish population, and the 1000 Genomes Project (http://www.internationalgenome.org/), as well as our internal database of approximately 1,450 samples analyzed by NGS. Copy number variation (CNV) analysis was performed using several methods, including the arrEYE customized microarray of 106 known IRD genes (van Cauwenbergh et al., 2017), array-based comparative genomic hybridization targeted for *PRPF31* (GeneDx), Fragment analysis Multiplex Ligation-dependent Probe Amplification of the *PRPF31* gene (MRC-Holland), and in-house coverage analysis of NGS data (Khateb et al., 2016).

Testing for founder mutations, screening specific genes and verification of identified mutations were performed by polymerase chain reaction 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). Variants nomenclature is based on hg19 genome version, as verified by Mutalyzer (http://www.lovd.nl/mutalyzer/) and Position Converter (https://mutalyzer.nl/position-converter). All variants have been submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/).

3 | RESULTS

3.1 | Characteristics of the Israeli IRD cohort

A total of 3,413 Israeli IRD patients from 2,420 families were recruited between the years 1999 and 2018. These patients reside all over the country (Figure 1a,b). The most common phenotype is nonsyndromic RP (43%), followed by STGD, CD/CRD, and USH (8% each). USH is the most common type of syndromic IRD (60% of syndromic families), followed by Bardet–Biedl syndrome (1.6% of total families; 13% of syndromic families; Figure 1c). Thirty-seven percent of the recruited families are consanguineous. Arab Muslims constitute the largest ethnic group in our cohort (25%), followed by Ashkenazi Jews (20%; Figure 1d).

As mentioned above, nonsyndromic RP patients constitute 43% of our cohort, which includes all types of IRDs. Since the prevalence of nonsyndromic RP in the Jerusalem area is about 1:2,000 (Sharon & Banin, 2015), and assuming that this prevalence is not different in the rest of the country, the overall IRD prevalence in Israel is expected to be higher than 1:1,000. On the basis of this prevalence and on the size of the Israeli population (8.97 million), the expected number of IRD patients in Israel is approximately 9,000. Consequently, we estimate that the 3,413 patients described here constitute 38% of all Israeli IRD patients.

3.2 | The process of genetic analysis

The process of genetic analysis in our IRD cohort is presented in Figures 2 and 3. This process was changed over the years, following the implementation of novel genetic techniques. The relatively high proportion of founder mutations in the Israeli population allowed us to perform a quick and efficient mutation screening, based on the relevant phenotype, ethnic background, and/or place of residence. A variant was considered as a founder mutation if it appeared in at least three families of the same ethnic group. This strategy led to the identification of the causative mutations in 21% of the families (37% of the solved families). In specific cases, when patients were affected by a phenotype known to be caused by one major candidate gene, composed of up to 15 exons, the entire gene was sequenced. Representative examples are the Best disease gene (*BEST1*) with 10 coding exons and the retinoschisis gene (*RS1*) with six coding exons. This led to the identification of the causative mutations in 10% of the families (19% of the solved families). Until the year 2008, families were studied by linkage analysis with microsatellite repeat markers linked to all relevant IRD loci and genes (Auslender et al., 2007; Nevet, Shalev, Zlotogora, Mazzawi, & Ben-Yosef, 2010). This led to the identification of the causative mutations in 1% of the families (2% of the solved families). Between the years 2009 and 2012, homozygosity mapping was used mainly in consanguineous families with at least two affected individuals (Beryozkin et al., 2014). This led to identification of numerous novel IRD genes by members of the IIRDC, including *CDH3*, *ADAM9*, *FAM161A*, *PDE6G*, *C2ORF71*, *IMPG2*, *DHDDS*, *C8ORF37*, and *RAB28* (Bandah-Rozenfeld, Collin, et al., 2010, Bandah-Rozenfeld, Mizrahi-Meissonnier, et al. 2010; Collin et al., 2010; Dvir et al., 2010; Estrada-Cuzcano et al., 2012; Parry et al., 2009; Roosing et al., 2013; Sprecher et al., 2001; Zelinger et al., 2011; Table S1). In total, 1% of the families were solved using this approach (2% of solved families). Since 2012, patients' DNAs were subjected to NGS, using either T-NGS and/or WES. Novel IRD

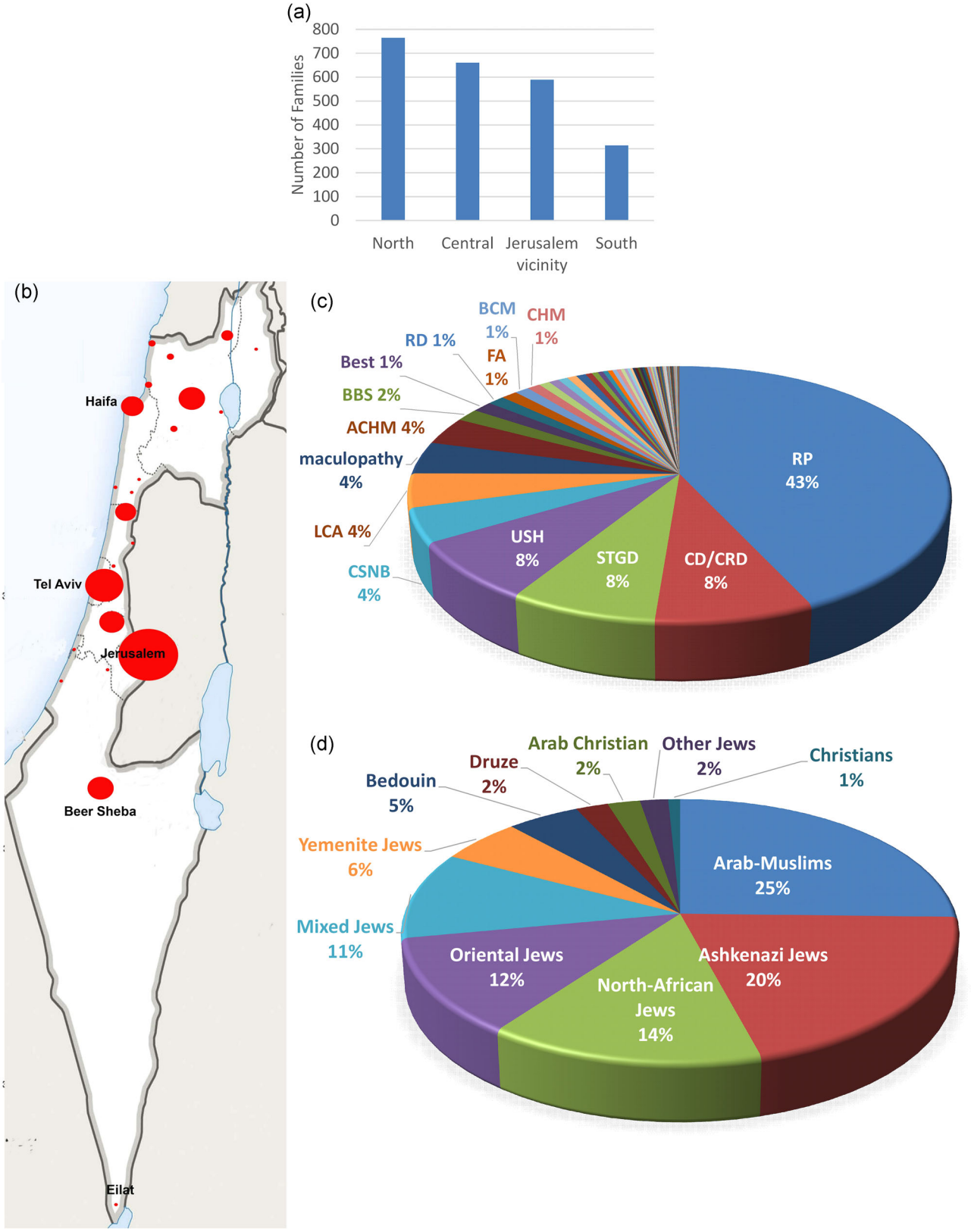

FIGURE 1 Characteristics of the Israeli IRD cohort. (a) Geographic distribution of Israeli IRD patients included in this study. The numbers on the *Y*-axis represent the number of families recruited in each region. (b) Shown is a map of the state of Israel. Red dots represent places of residence of IRD patients. Dot size is proportional to the number of patients residing in each location. (c) Phenotypic distribution of the Israeli IRD cohort. (d) Ethnic distribution of the Israeli IRD cohort. ACHM, achromatopsia; BBS, Bardet–Biedl syndrome; BCM, blue cone monochromacy; Best, Best disease; CD/CRD, cone/cone–rod dystrophy; CHM, chorioderemia; CSNB, congenital stationary night blindness; FA, fundus albipunctata; LCA, Leber congenital amaurosis; RD, retinal dystrophy; RP, retinitis pigmentosa; STGD, Stargardt disease; USH, Usher syndrome

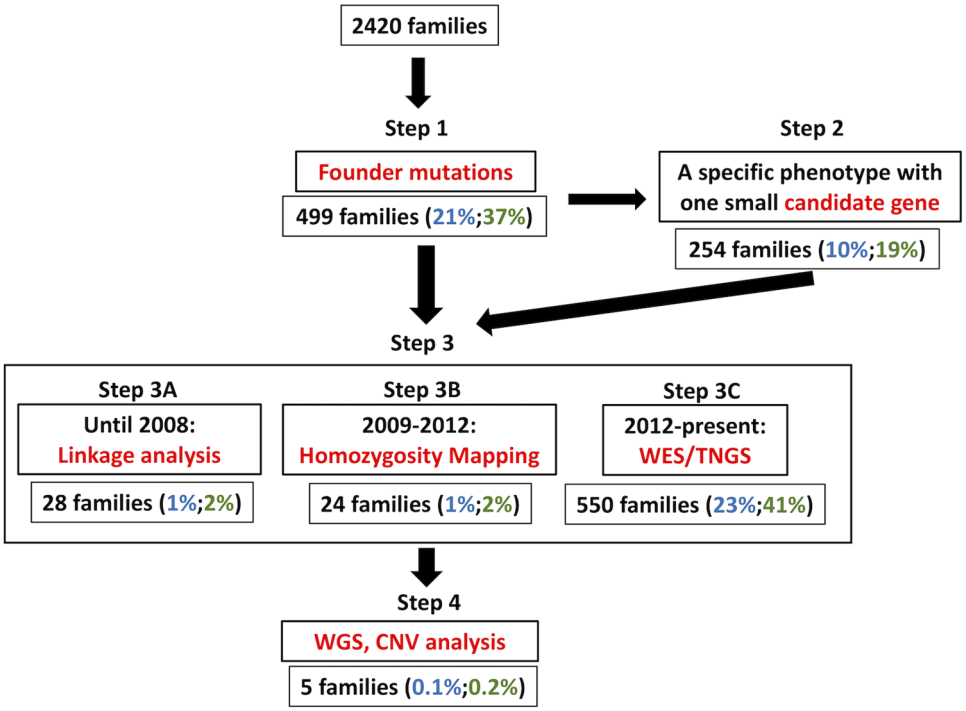

FIGURE 2 The process of genetic analysis. For each step, numbers in blue represent the percentage of solved families out of the total families in the cohort (solved and unsolved), whereas numbers in green represent the percentage of solved families out of the total solved families. Step 1: Founder mutation screening, based on the relevant phenotype, ethnic background and/or place of residence. Step 2: Candidate gene approach. When patients were affected by a phenotype known to be caused by one major candidate gene, composed of up to 15 exons, the entire gene was sequenced (coding exons and exon/intron boundaries). Step 3A: Until the year 2008, families were studied by linkage analysis with microsatellite repeat markers linked to all relevant IRD loci and genes. When cosegregation of a certain haplotype with the disease was identified, the linked gene was screened by direct sequencing. Step 3B: Between the years 2009 and 2012, homozygosity mapping was used mainly in consanguineous families with at least two affected individuals. Known IRD genes located within shared regions of homozygosity were screened by direct sequencing. When known IRD genes were not present in homozygous regions, candidate genes located within these regions were screened for mutations. Step 3C: Since 2012, patients' DNAs were subjected to next-generation sequencing (NGS), using either T-NGS and/or WES. When WES was performed, the initial analysis step focused on mutations in known IRD genes. If negative, the data was further analyzed, to search for causative variants in novel IRD genes. Step 4: Some patients who remained unsolved following steps 1–3, were subjected to further analyses, including WGS and CNV analyses. CNV, copy number variation; IRD, inherited retinal diseases; T-NGS, targeted next-generation sequencing; WES, whole-exome sequencing, WGS, whole-genome sequencing

genes identified by IIRDC members using this approach include *MAK*, *ARL2BP*, *CEP250*, *CEP78*, *IDH3A*, *SCAPER*, *ARMC9*, and *ARSG* (Davidson et al., 2013; Khateb et al., 2014, 2018; Namburi et al., 2016; Özgül et al., 2011; Pierrache et al., 2017; Tatour et al., 2017; van de Weghe et al., 2017; Table S1). In total, 23% of the families were solved using this approach (41% of solved families). Some patients who remained unsolved were subjected to further analyses, including WGS and CNV analyses. To date, only five families (0.1%) were solved using these approaches (0.2% of solved families).

3.3 | Genetic findings

Following the process of genetic analysis described above, we were able to identify the genetic basis for disease in 56% of families (1,369/2,420). In 137 additional families with AR inheritance (6%), only one heterozygous recessive allele which is relevant to the observed phenotype was discovered. However, it should be noted that the described cohort includes patients that were recruited up to December 2018, and some of these patients have not been fully analyzed yet. Among the unsolved index cases, 39% underwent T-NGS, 17% underwent WES, and only 0.5% underwent WGS. Among the 1,696 families recruited up to December 2015, in whom genetic analysis was more comprehensive, 1,078 (64%) were fully solved.

Before genetic analysis, most cases in our cohort (48%) were defined as isolate cases (single affected, no positive family history, and no consanguinity). This distribution changed postgenetic analysis, since a specific inheritance pattern was assigned to many of the isolated cases. Most of these turned to be AR. The current distribution shows that the most common mode of inheritance is AR (60%), followed by isolated cases (26%), AD (8%), and XL (6%; Figure 4a).

The five most common mutated genes in our cohort are *ABCA4*, *USH2A*, *FAM161A*, *CNGA3*, and *EYS* (Figure 4b). In total, 605 distinct pathogenic variants in 129 distinct genes were identified (Table S2). These included missense (46%), nonsense (18%), frameshift (17%), and splice-site mutations (12%), large deletions (5%), and more

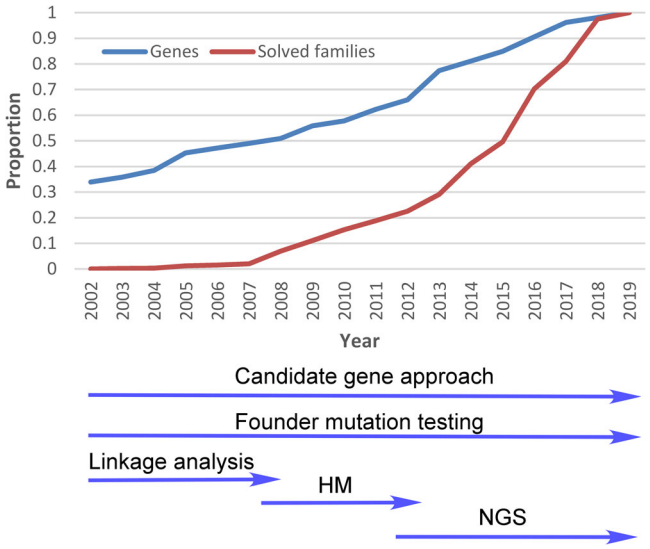

FIGURE 3 The relationship between the rate of genetic diagnosis, the rate of inherited retinal disease gene discovery, and the various diagnostic approaches used over the years. The red curve corresponds to the proportion of families with molecular diagnoses out of 1,369 families. The blue curve corresponds to the proportion of identified genes out of 129 genes in which mutations were detected. The used diagnostic approaches are indicated below the chart. HM, homozygosity mapping; NGS, next-generation sequencing

(Figure 4c). Only one case of a de novo mutation was identified. However, for many of the patients, parental DNA was not available, and therefore, this issue could not be addressed. Twelve percent of the identified mutations were founder mutations, which were identified in at least three unrelated families. The most common founder mutation was *ABCA4*: p.(Gly1961Glu). Although this mutation is common in diverse populations all over the world, most of the prevalent founder mutations in our cohort are unique to specific ethnic groups which are highly represented within the Israeli population. These include *CLRN1*: p.(Asn48Lys), *DHDDS*: p.(Lys42-Glu), and *MAK*: p.(Lys433Argfs*31; highly prevalent among Ashkenazi Jews); *EYS*: p.(Thr135Leufs*26), *FAM161A*: p.(Arg523*), and *RPE65*: c.95–2A>T (highly prevalent among North African Jews); *ABCA4*: p.(Ala1794Pro), *PRCD*: p.(Arg22*), and *TRPM1*: p.(Lys294*; highly prevalent among Arab Muslims), among others (Figure 4d).

4 | DISCUSSION

IRD is a highly heterogenous group of diseases, both clinically and genetically. Though genetic analysis in IRD patients is a challenging task, it has nonetheless become the benchmark for the diagnosis and management of patients with these debilitating conditions. Mapping of the genetic alterations underlying the retinal disease etiology is highly important for several reasons: (a) It complements the clinical findings and facilitates an accurate clinical diagnosis; (b) it leads to reduction in disease prevalence, by genetic screening and counseling in high-risk populations; (c) it allows the establishment of genotype–phenotype correlations, which enable the clinicians to more accurately inform their patients regarding the expected prognosis; (d) it enables identification of novel disease genes and mechanisms; and (e) it allows fast identification of patients who might benefit from emerging gene-based therapeutic modalities that are most effective in an early stage of the disease. Although no effective treatment currently exists for most forms of IRDs, this field has been undergoing dramatic changes over the last decade, mainly due to the development of novel therapeutic modalities that are either gene-based (gene therapy and targeted pharmacological agents) or non-gene-based (regenerative medicine and retinal implants; Kannabiran & Mariappan, 2018). The recent success of gene therapy for *RPE65* deficiency (voretigene neparvovec-rzyl, i.e., Luxturna) has led to a large number of ongoing gene therapy clinical trials targeting additional IRD-related genes (Miraldi Utz, Coussa, Antaki, & Traboulsi, 2018; Ong, Pennesi, Birch, Lam, & Tsang, 2019). Moreover, due to the marked genetic and etiologic heterogeneity of IRDs, both gene-based and non-gene-based therapies have to be tested on sets of patients with a known genetic diagnosis to prove their efficiency. Such cohorts of patients can be efficiently identified in a nationwide set-up as described in the current study.

Here, we describe a cohort of 3,413 Israeli IRD patients recruited since the year 1999. Though genetic analyses in large cohorts of IRD patients have been previously reported (ranging from 722 to 1000 patients; Carss et al., 2017; Dockery et al., 2017; Stone et al., 2017), to the best of our knowledge this is by far the largest IRD cohort reported to date. In 2017, Dockery et al. reported partial results of genetic analysis among 750 individuals, as part of the Target 5000 project, a national effort aimed to genetically characterize IRDs in the Irish population. They estimated that their cohort represented 15% of the Irish IRD population. Our ongoing study includes a much larger cohort, encompassing approximately 40% of the Israeli IRD population, and is, therefore, one of the first studies which report genetic analysis of IRD patients on a nationwide scale. Recruitment and analysis of such a large cohort became possible due to a joint nationwide effort. The IIRDC was established in 2013, to improve and enhance the genetic analysis of IRD patients in Israel. This is a unique consortium, consisting of five genetic centers, four electrophysiological laboratories, 11 ophthalmologists with expertise in IRD, and a bioinformatics expert, giving the IIRDC the needed nationwide spread, and the availability for testing populations from all backgrounds. Indeed, since the establishment of the IIRDC, we were able to scale-up the rate of subject recruitment and genetic analysis.

Overall, we succeeded to identify the genetic basis of disease in 56% of the recruited families (64% among families recruited up to December 2015). This percentage is within the range of diagnostic rates reported recently in other large cohorts of IRD patients (Carss et al., 2017; Dockery et al., 2017; Haer-Wigman et al., 2017; Stone et al., 2017). It should be noted that of the unsolved families, only 17% have undergone WES and only 0.5% have undergone WGS. Applying additional genetic tests on these patients, and mainly WGS will certainly identify the genetic cause for disease in additional families, as demonstrated previously (Carss et al., 2017).

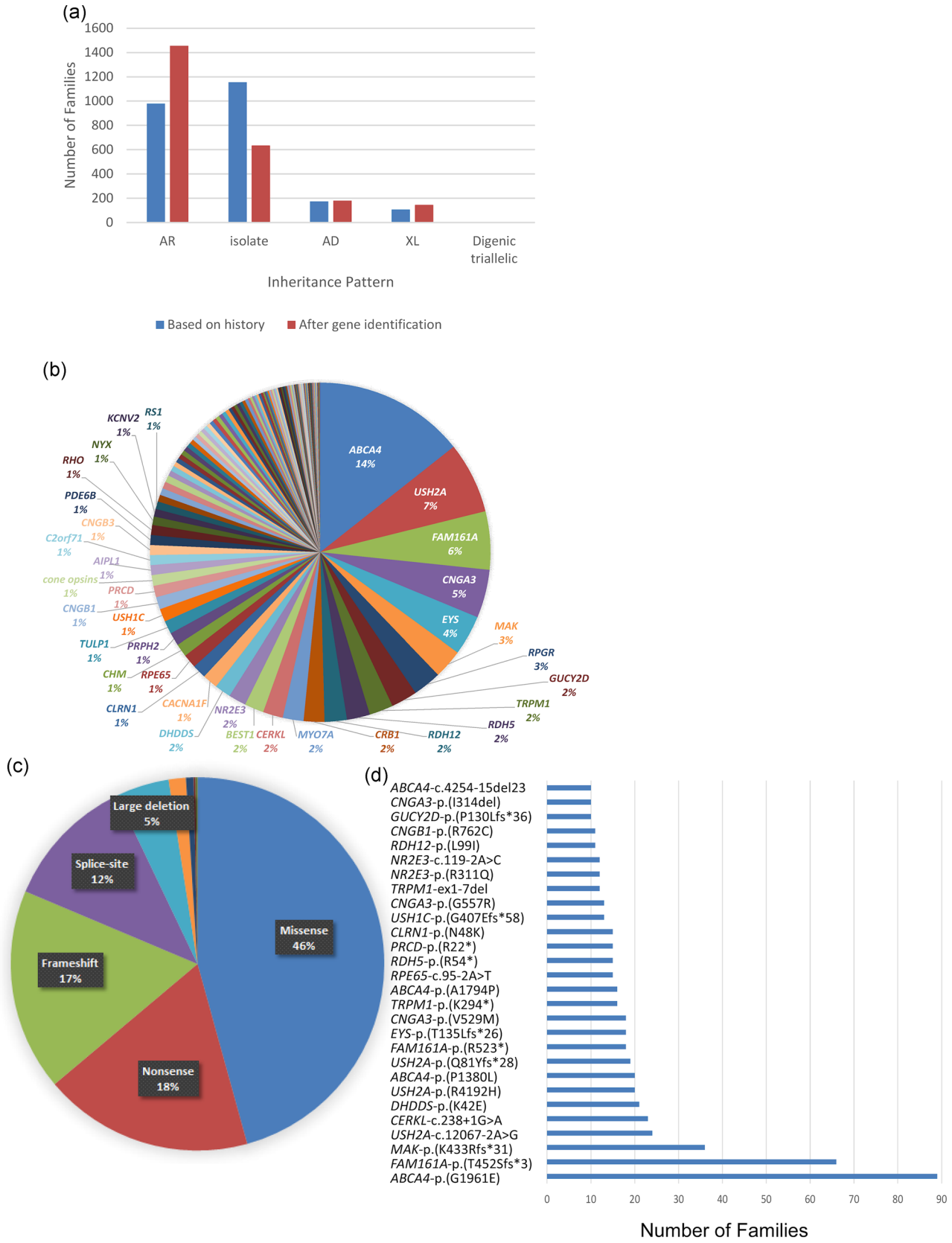

FIGURE 4 Genetic findings in the Israeli inherited retinal disease consortium (IIRDC) cohort. (a) Distribution of inheritance modes before and after genetic analysis. (b) Distribution of mutated genes in the IIRDC cohort. (c) Distribution of mutation types in the IIRDC cohort. (d) The most common mutations identified in the IIRDC cohort. AD, autosomal dominant; AR, autosomal recessive; XL X-linked

Though the proportion of solved families steadily increased over the years, it was significantly enhanced in two time points: 2008 and 2013 (Figure 3). The increased rate of mutation identification between the years 2008 and 2013 can be attributed to two main factors: (a) A shift to the homozygosity mapping approach, which enabled genetic analysis in relatively small consanguineous families; and (b) discovery of new IRD genes: 20% of the 129 mutated genes listed in Table S2 were discovered between these years. The increased rate of mutation identification between the years 2013 and 2019 is attributed mainly to the use of NGS. Of all solved families, 77% were solved between these years, whereas only 10% of the mutated genes were discovered during this period. This trend indicates that in recent years, improved diagnostic rates are achieved mainly by technological advances, which enable better identification of mutations in known IRD genes. A similar trend was observed by Ellingford et al. (2016).

In 6% of the families, only one heterozygous recessive allele which is relevant to the observed phenotype was discovered. In most of these families, the single identified allele is probably causative, and the second allele has been missed due to technical reasons (lack of coverage, inaccurate annotation, nonexonic localization, inability to pick up the genetic defect, or inaccurate interpretation). However, it should be noted that some IRD causative mutations have a very high carrier frequency in the Israeli population, and therefore, IRD patients may be coincidental carriers of these mutations, in addition to the mutations which are actually causing their disease (Hanany et al., 2018). It is therefore not surprising that in 6% (79/1,368) of solved families, we identified a heterozygous disease-causing mutation in another IRD gene.

Our cohort includes a large fraction of IRD patients in Israel, and the obtained data provide an epidemiological overview of IRD distribution and etiology in the Israeli population. The most prevalent phenotype is nonsyndromic RP, the most prevalent type of syndromic IRD is USH, and the most prevalent mode of inheritance is AR. The two most frequently mutated genes in the Israeli IRD cohort are *ABCA4* (14%) and *USH2A* (7%). These findings are similar to those found in large IRD cohorts from other populations (Carss et al., 2017; Dockery et al., 2017; Haer-Wigman et al., 2017; Stone et al., 2017). However, some of our findings are unique. For example, the third and fourth most common mutated genes in the Israeli cohort are *FAM161A* (6%) and *CNGA3* (5%). In contrast, mutations in each of these two genes affect <1% of the cohorts described by Carss et al. (2017)—mainly representing the UK population, and by Stone et al. (2017)—mainly representing the US population. The significant contribution of these two genes to IRDs in Israel is due to frequent founder mutations: Two *FAM161A* mutations, p.(Arg523*) and p.(Thr452Serfs*3), and three *CNGA3* mutations, p.(Val529Met), p.(Gly557Arg), and p.(Ile314del), are among the most common founder mutations in the Israeli population.

Interestingly, Arab Muslims constitute the largest ethnic group in our cohort (25%). Their representation in the IRD cohort is higher than their share in the Israeli population (19.5%). This is due to the very high rate of consanguinity in the Arab Muslim population. Among Israeli Arabs, 45% of the marriages are between related spouses; half of whom are first cousins. Most of the Israeli Arab population has been living in small, relatively isolated localities, which were originally settled by a small number of founders. Most of the genetic diseases frequent among Israeli Arabs are due to founder effects (Zlotogora, 2002).

Over the years, IIRDC members have identified numerous novel IRD causative genes (Table S1). For most of these genes, the original publication by IIRDC members was followed by reports of additional patients of various ethnicities with mutations in the same gene, and some of them turned out to be major contributors to IRD worldwide. For some of the genes, additional associated phenotypes have been reported over the years (Table S1). In addition to novel genes, a large number of founder mutations segregating in various ethnic groups were discovered (Auslender et al., 2007, 2008; Khateb et al., 2012, 2018; Tatour et al., 2019; Zelinger et al., 2011). Many of these findings have already been implemented into the clinical practice in Israel enhancing our ability for molecular diagnosis and genetic counseling to IRD patients and their relatives.

The main expected long-term outcome of this collaborative project is a significant reduction of IRD load in Israel. We hope to achieve this goal by prevention of the disease, using genetic screening and counseling in high-risk populations. Furthermore, the study should facilitate treatment of IRD patients, via identification of patient groups with shared genetic diagnoses, who can be treated accordingly.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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