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Genetic Analysis of 252 Index Cases with Inherited Retinal Diseases Using a Panel of 351 Retinal Genes

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Abstract: Inherited retinal diseases (IRDs) are extremely heterogeneous with at least 350 causative genes, complicating the process of genetic diagnosis. We analyzed samples of 252 index cases with IRDs using the Blueprint Genetics panel for "Retinal Dystrophy" that includes 351 genes. The cause of disease could be identified in 55% of cases. A clear difference was obtained between newly-recruited cases (74% solved) and cases that were previously analyzed by panels or whole exome sequencing (26% solved). As for the mode of inheritance, 75% of solved cases were autosomal recessive (AR), 10% were X-linked, 8% were autosomal dominant, and 7% were mitochondrial. Interestingly, in 12% of solved cases, structural variants (SVs) were identified as the cause of disease. The most commonly identified genes were *ABCA4*, *EYS* and *USH2A*, and the most common mutations were *MAK*-c.1297_1298ins353 and *FAM161A*- c.1355_1356del. In line with our previous IRD carrier analysis, we identified heterozygous AR mutations that are not the cause of disease in 36% of cases. The studied IRD panel was found to be efficient in gene identification. Some variants were mis-interpreted by the pipeline and therefore multiple analysis tools are recommended to obtain more accurate annotation of potential disease-causing variant.

Keywords: consanguinity; gene panel; Inherited retinal diseases; retinal dystrophy; targeted next generation sequencing

1. Introduction

Inherited retinal diseases (IRDs) encompass a broad spectrum of retinal phenotypes characterized by extensive clinical variability and profound genetic heterogeneity [1,2]. Among IRDs, retinitis pigmentosa (RP) stands out as one of the most prevalent and heterogeneous conditions in humans, caused by disease-causing mutations in over 60 genes with inheritance patterns spanning autosomal dominant (AD), autosomal recessive (AR), digenic, mitochondrial and X-linked (XL) modes [1].

The advent of substantial sequencing breakthroughs over the past decades as well as improved bioinformatics and functional analyses has heralded a remarkable advancement in mutation detection methods as well as mutation characterization [3]. These include next-generation sequencing (NGS), whole exome sequencing (WES), whole genome sequencing (WGS), functional genomic techniques (such as CRISPR-Cas9 gene editing, RNA sequencing, and functional assays), bioinformatics analysis, single-cell genomics, epigenomic profiling techniques (including ChIP-seq and DNA methylation profiling), and multi-omics integration. Each of these modern methodologies offers unique advantages in elucidating the genetic underpinnings of various diseases.

From providing a comprehensive view of disease mechanisms to facilitating the identification of novel mutations and understanding complex diseases with heterogeneous genetic backgrounds, these techniques are often employed synergistically to enhance diagnostics, tailor personalized treatments, and refine disease management strategies.

However, the selection of an appropriate method is fraught with challenges due to several inherent limitations. These include cost considerations, the complexity of data analysis, the potential

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for false positives and false negatives, limitations in functional validation, incomplete genomic coverage, ethnic diversity, ethical and privacy concerns surrounding genomic data, and the intricacies of clinical utility and interpretation.

In light of these challenges, we endeavor to navigate the landscape of available methodologies, striving to identify the most suitable approach that aligns with our goal of providing comprehensive genetic insights to many patients. Our aim is to unveil all pertinent mutations contributing to the heterogeneity of IRDs.

Here we used a single gene panel to screen the DNA of 252 unsolved cases with IRDs. The analysis revealed the identification of the cause of disease in 55% of cases, with variability in detection rates between sub-groups.

2. Materials and Methods

2.1. Patient Recruitment

Blood and saliva samples were collected from 252 individuals diagnosed with IRDs, representing a diverse mix of newly recruited patients and those who remained unsolved following previous screening tests. The sample collection process adhered to ethical standards, receiving explicit approval from the Hadassah Hospital Institutional Review Board. Informed consent, obtained in writing, ensured compliance with all relevant ethical regulations and safeguarded the rights and privacy of participants.

2.2. DNA Extraction

Genomic DNA extraction was carried out from blood samples using the Promega kit and Promega Maxwell (Madison, WI) DNA extraction device. DNA extraction from buccal swab samples was conducted at the Blueprint Genetics company.

2.3. Next-Generation Sequencing (NGS)

The Retinal Dystrophy Panel (Blueprint Genetics; Espoo, Finland; test code OP0801: https://blueprintgenetics.com/tests/panels/ophthalmology/retinal-dystrophy-panel/), including 351 IRD genes, was used to analyze DNA of 252 IRD cases. A clinical grade NGS sequencing assay was employed allowing comprehensive coverage across various genomic IRD genes. The analysis included detection of single nucleotide variants, insertions, deletions, indels, and copy number variants (CNVs- deletions or duplications spanning at least a single exon). Sequencing depth at the nucleotide level was 174x at the nucleotide level, ensuring unparalleled sensitivity and accuracy in variant detection.

3. Results

3.1. Patient Demographics

A total of 252 index cases, selected from a cohort of over 2000 families, were enrolled to this study. Of these, 230 DNA samples were extracted from blood, with 98 undergone testing with a negative output. Additionally, 22 fresh saliva samples from newly recruited patients were shipped for analysis. Our cohort exhibited ethnic diversity, with 66% Jews (including 26% Ashkenazi Jews, 12% North African Jews, and 10% Moroccan Jews), 31% Arab Muslims (including 3% Bedouins), 2% Arab Christians, and other ethnicities with less than 1% each.

3.2. Efficiency of the Gene Panel

The genetic cause of disease (pathogenic or likely pathogenic mutation/s) was identified in 138 out of the 252 analyzed samples, a yield rate of 55% (Figure 1A, Table S1). Consequently, 114 cases remained unsolved (Figure 1A, Table S1). Further analysis revealed varying rates of gene identification between two distinct groups: newly recruited samples exhibited a 74% success rate,

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while previously analyzed samples with negative results (the analysis included genotyping of founder mutations, IRD gene panels, and WES) showed a 24% success rate (Figure 1B).

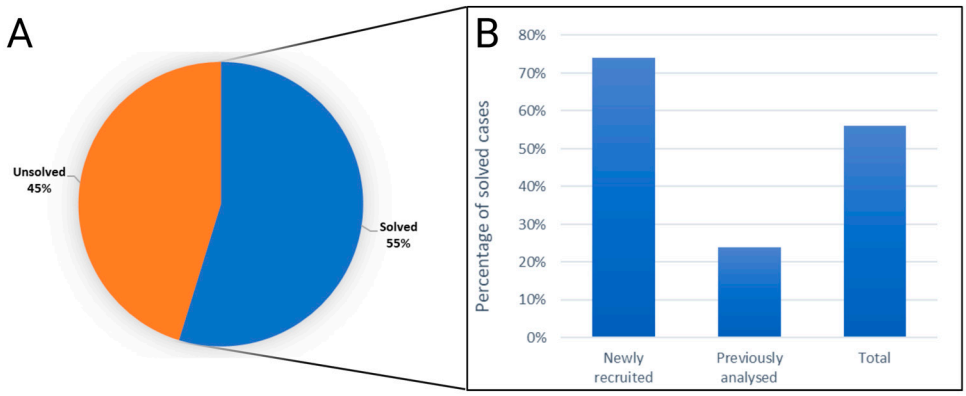

Figure 1. Insights into the effectiveness of the gene panel in different diagnosis histories. (A) A pie chart representing the distribution of solved and unsolved cases among a total of 252 samples analyzed using the Blueprint retinal dystrophy gene panel. (B) A bar chart that compares the success rates in comparison to two distinct groups: newly recruited samples and previously analyzed samples with negative results.

3.3. Types of Solved Cases and Gene Frequency Analysis

The majority of solved cases were attributed to autosomal recessive (AR) genes (75%), followed by X-linked (10%), autosomal dominant (AD) (8%), and mitochondrial genes (7%) (Figure 2A). The most frequently implicated genes were ABCA4 accounting for 8%, EYS with 7%, and USH2A with 6% (Figure 2B).

3.4. Frequency of the Most Common Mutations

Missense mutations constituted the most common variant type (38%), followed by frameshift mutations (17%), nonsense mutations (16%), structural variants (SVs) (12%), splice site mutations (10%), intronic mutations (4%), and in-frame mutations (3%) (Figure 3A). Notably, the most recurrent mutations identified were c.1297_1298ins353 in *MAK* and c.1355_1356del in *FAM161A* (Figure 3B).

3.5. KIF11 and Non-Syndromic Chorioretinopathy

The *KIF11* gene encodes a homo-tetrameric motor protein crucial for spindle polarity during mitosis. Variants in this ubiquitously expressed protein are typically de-novo and associated with various developmental syndromes, including impacts on retinal vasculature development. Considered rare, only one family in Israel is documented with a *KIF11* mutation [4]. Surprisingly, among the 142 cases solved in our study, *KIF11* emerged as the causal gene in two unrelated Ashkenazi Jewish patients.

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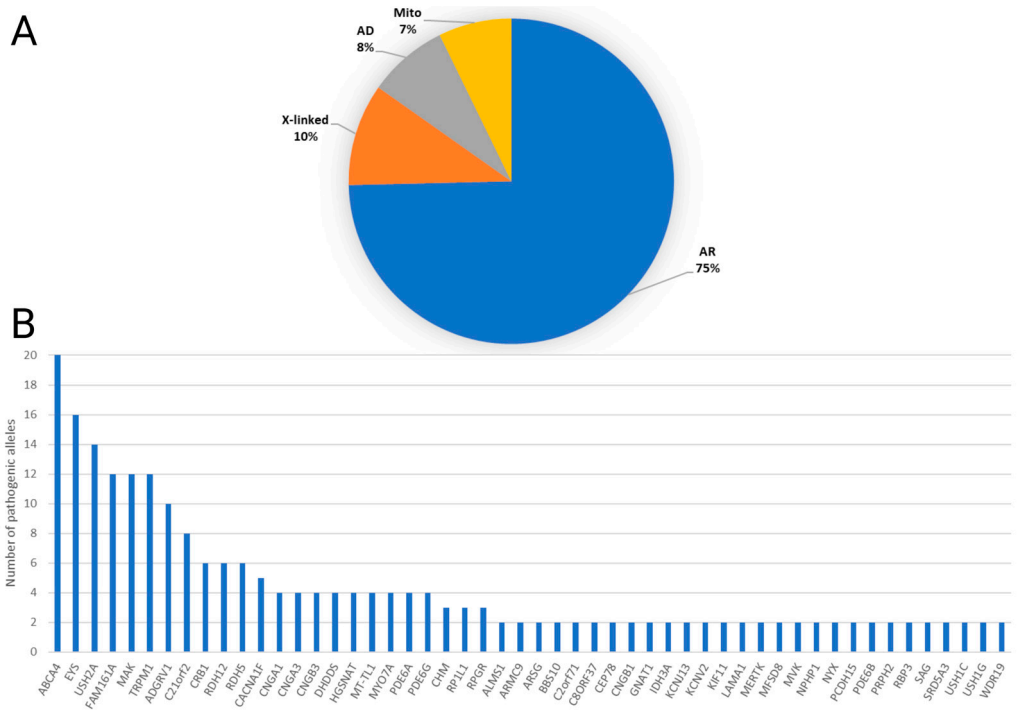

Figure 2. Overview of genetic mechanisms in inherited retinal diseases. (A) Pie chart illustrating the distribution of solved cases based on the mode of inheritance, including autosomal recessive (AR), X-linked, autosomal dominant (AD), and mitochondrial genes. Each segment represents the percentage of cases solved under each mode of inheritance. (B) Bar chart presenting the frequency of the most implicated genes in the cohort of 138 solved cases. The X-axis displays the frequently identified genes, while the Y-axis represents the number of alleles in families for which the gene was identified as the cause of their phenotype.

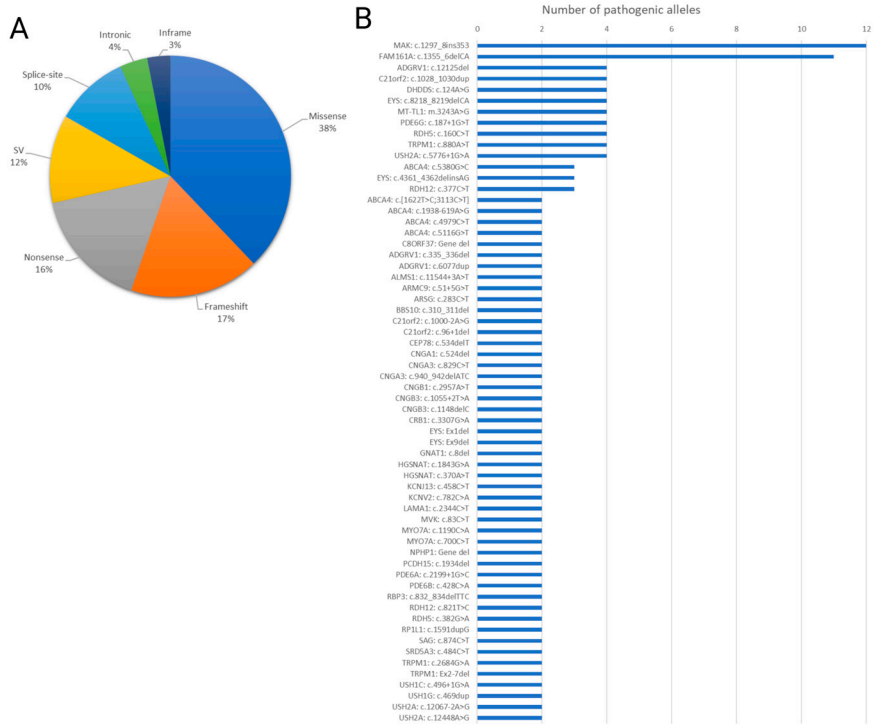

Figure 3. Spectrum of genetic alterations contributing to inherited retinal diseases. (A) Pie chart visually representing the distribution of various mutation types identified in the solved cases,

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including missense, frameshift, nonsense, structural variants (SVs), splice site, intronic, and in-frame mutations. Each segment depicts the percentage of cases attributed to a specific mutation type. (A) Bar chart depicting the number of alleles for each of the most recurrent mutations detected among the indexed cases. The X-axis displays the identified disease-causing variants and the Y-axis represents the number of alleles in families for which the mutation was identified as the cause of their phenotype.

Case MOL1984-1 was diagnosed at the age of 10 years with reduced visual acuity, mild myopia (-3 D), and photophobia. His Best-corrected visual acuity (BCVA) at the age of 16 was 0.6 / 0.5 in the right and left eye, respectively, and OCT showed a retinoschisis pattern. He has no family history of visual deficiencies. ERG at the age of 18 years revealed sub-normal responses, including cone flicker, mixed cone-rod b-wave and rod responses. Color vision was within normal range. Ophthalmic evaluation at the age of 19 years revealed atrophic chorioretinal patches next to the optic disc and the inferior arcade. The patient was therefore diagnosed with non-syndromic chorioretinopathy. Interestingly, gene panel analysis revealed a heterozygous frameshift mutation in *KIF11* (Table S1).

Case MOL2101-1 was diagnosed with a congenital retinal disease, including chorioretinal scars and retinoschisis. Visual acuity deteriorated and at the age of 11 reached 0.4 in the right eye and hand motion in the left eye with mild myopia (-3.5 D). Multiple electroretinography (ERG) examinations revealed non-progressive sub-normal ERG responses, including cone flicker, mixed cone-rod a and b-wave and rod responses. The patient was therefore diagnosed with non-syndromic chorioretinopathy. Interestingly, gene panel analysis revealed a heterozygous de-novo nonsense mutation in *KIF11* (Table S1).

3.6. An Elusive Coding Mutation

Further illustrating the complexities of genetic diagnostics, an intriguing and elusive nonsense pathogenic mutation in the *EYS* gene, was identified.

The index case, MOL2142-1, was diagnosed with ARRP due to extinguished ERG responses at the age of 55 years, fundus appearance that include typical signs of RP (bone-spicule pigmentation and attenuated blood vessels), and reduced BCVA of 0.25. Copy number variation (CNV) analysis of IRD genes, as part of the panel analysis, revealed a heterozygous deletion of a single *EYS* exon (#34), as well as two nucleotide changes (one synonymous and the other nonsynonymous), affecting neighboring nucleotides (c.4361C>A, p.S1454Y and c.4362C>G, p.S1454=). Interestingly, this combination of variants was identified in multiple cases with RP of Arab-Muslim origin, and confirmed to be in-cis. The combination of the two variant results in a nonsense mutation (c.4361_4362delinsAG, p.S1454*; Table S1). Such complex mutation can be oversighted in many NGS pipelines, highlighting the challenges of variant interpretation and the importance of comprehensive genetic panels.

3.7. Novel Genetic Discoveries in Israeli Patients: Unveiling Rare Variants and First Cases

Joubert syndrome, a recessive and genetically heterogeneous neurodevelopmental ciliopathy, is characterized by a distinctive brain malformation, often presenting with a complex phenotype that may include retinal dystrophy. In our study, we identified two cases, MOL2246-1 and MOL22151-1, marking the first documented instances in Israel of Joubert syndrome associated with mutations in the *ARMC9* and *LAMA1* genes, respectively. Notably, these genes are rare contributors to this syndrome; in the literature, only 19 cases of *ARMC9* mutations have been reported across five different articles from Japanese [5][6], Chinese [7], Turkish [8], and Indian [9] populations, while *LAMA1* mutations have been documented in just five cases from British [10] and Japanese [11] cohorts spanning two articles. This underscores the rarity and global diversity of genetic variants contributing to Joubert syndrome.

In addition to the aforementioned cases, our study unveiled several other rare variants, each representing the first documented instances in Israel. One such case is patient MOL1437-1, who exhibits a compound heterozygosity for missense mutations in the *WDR19* gene, resulting in non-syndromic retinitis pigmentosa (RP). Another noteworthy finding is a homozygous nonsense

 doi:10.20944/preprints202406.0581.v1

mutation in the SAG gene in patient MOL2008-1, leading to Oguchi disease. Lastly, patient MOL2079-1 was identified as homozygous for a nonsense mutation in the *SRD5A3* gene, which is associated with congenital disorder of glycosylation [12]. These five cases represent novel discoveries in the Israeli population, highlighting the significance of our study in expanding the understanding of rare genetic variants and their clinical implications.

4. Discussion

In the current study we used a single IRD gene panel to screen 252 IRD samples for mutations in 351 IRD-causing genes. Previous studies reported a yield of positive genetic results in 40-75% of analyzed cases and our study, with 55%, falls within this range, as expected [13–17]. Our cohort can be divided to newly-recruited cases who were not screened to any IRD-causing mutations and those who underwent genetic analysis (including genotyping founder mutations, IRD gene panels, and WES). The power of the current panel analysis can be appreciated by the much higher detection rate of 74% compare to only 26% of those previously analyzed. This high rate can partly be attributed to SV analysis performed on the NGS data. Improved recent NGS analysis pipelines include detection of both homozygous or heterozygous SVs, that assisted in the identification of such mutations on 10-15% of pathogenic alleles [18–20]. Switching to WGS is likely to increase this rate and improve overall detection rate of pathogenic alleles in IRDs.

Genetic analysis of newly diagnosed IRD cases depends on the phenotypic complexity and the available information on IRDs in the relevant population. The spectrum of IRD mutations in the Israeli population was studied comprehensively, mainly by a nationwide collaborative effort of the Israeli inherited retinal diseases consortium (IIRDC), leading to enriched information on disease prevalence of various IRD phenotypes [21], development of a NGS founder mutation gene panel [22], and identification of a large number of mutations in each sub-population [23–25]. This continuous effort allows in some cases to pinpoint the pathogenic mutation quickly, without the need of time-consuming and costly analyses. However, in the majority of cases, either due to the lack of known common founder mutations or challenging phenotyping, gene panels, such as the one used in the current study, can aid in the identification of the cause of disease in about 75% of cases.

Quick and reliable gene identification is important for a more efficient genetic counseling and disease prevention in the coming generations [26,27], participation in gene/mutation-specific clinical trials [1,28], or FDA-approved IRD therapies [29]. The analysis performed in this study, shows that gene panels can be highly efficient in identifying the cause of disease, and in some cases identifying also additional IRD-causing mutations that one out of three IRD patients carry by chance, as we previously reported [30]. Including the mitochondrial genome and performing SV analyses on the NGS data, further improves the yield of gene and mutation identification, and therefore such panels are highly recommended.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Table S1: identified gene and mutations in studied cases.

Author Contributions: Conceptualization, M.A.E. and D.S.; methodology, M.A.E., S.M., M.S., A.B, and S.K.; formal analysis, S.K. and E.B.; writing—original draft preparation, M.A.E. and D.S.; writing—review and editing, S.M., M.S., A.B, S.K., and E.B.; supervision, D.S. and E.B.; funding acquisition, D.S. and E.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethical approval was obtained from Hadassah University Medical Center Institutional Review Board (approval code 21-03.08.07, approved on 3 August 2007). The tenets of the Declaration of Helsinki were followed. Participants provided written informed consent after receiving an explanation about the study and its possible consequences and before donating blood samples.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data of this study are presented within the article and its Supplementary Materials. The authors are willing to share materials, data sets, and protocols used in the acquisition of data

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presented in this publication with other researchers upon request (contact Dror Sharon, E-mail: dror.sharon1@mail.huji.ac.il).

Conflicts of Interest: The authors declare no conflicts of interest.

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