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Original Article

Genetic Basis of Retinal Degenerative Disorders: A Molecular Ophthalmology Study

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ABSTRACT

One of the most genetically heterogeneous groups of human diseases is the inherited retinal degenerative disorders (IRDs), of which over 270 genes are linked with the malfunction of the photoreceptors and the subsequent degradation of the retinal pigment epithelia. This study employed the technique of quantitative, observational molecular ophthalmology to clarify the genetic basis and genotype phenotype ties of inherited retinal illnesses (IRDs) in a clinically defined sample group of 224 patients. Tiered genomic testing using gene panel targeted screens, whole-exome sequencing (WES), and reflex whole-genome sequencing (WGS) was combined with standardized retinal phenotyping, which consisted of visual acuity, optical coherence tomography (OCT), fundus autofluorescence (FAF) and electroretinography (ERG). The overall MD yield was at 59.8% (95% CI: 53.3-66.0), and higher yields were among consanguinity families (63.2%), and those that underwent reflex WGS (80.6%). Pathogenic mutations were located in most cases in USH2A, RPGR and ABCA4. The most popular was an autosomal recessive (59.0%), then it was in autosomal dominant (25.4%) and X-linked (15.7) inheritance. The variant distribution revealed that the most frequent types of alterations were missense mutation (42%), and frameshift /nonsense mutation (28%). Structural-functional studies found that there was a strong correlation between best-corrected visual acuity and ellipsoid zone extent ($r = -0.71$, $p = 0.001$). Age of onset and consanguinity at a young age were also strong predictors of successful molecular diagnosis (adjusted OR 1.72, 95% CI 1.102.70), but more preservation of the ellipsoid zone supplied protection against severe visual impairment (adjusted OR 0.58, 95% CI 0.460.72). These findings support the purpose of diagnostic and prognostic importance of extensive genomic testing in inherited retinal diseases (IRDs) and underline the need to combine molecular data with clinical imaging to provide specific treatment.

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INTRODUCTION

Inherited retinal degenerative diseases offer a varied range of blindness disorders characterized by the progressive failure and atrophy of photoreceptors and / or the retinal pigment epithelium (Du et al., 2024, p. 3). The disorders are one of the main causes of irreversible eye vision loss in the working-age population with a cumulative rate of about 1 in 3000 (Carss et al., 2016, p. 79; Karali et al., 2022, p. 1). Retinal diseases are inherited by approximately 1 out of 2000 individuals worldwide. It makes them one of the primary causes of blindness of working-age individuals in the Western world (Carvalho et al., 2023; Roberts, 2024, p. 199). The clinical manifestations of these disorders are very diverse and may include early-onset macular degeneration, retinitis pigmentosa, or Leber congenital amaurosis and are often associated with mutations in over 300 genes (Botto et al., 2021, p. 4; Carrigan et al., 2016, p. 1). Extensive phenotypic heterogeneity is a part of inherited retinal diseases, including nonsyndromic diseases that only affect the eye and syndromic diseases that have additional symptoms (Liu et al., 2024, p. 1). Such a wide genetic and clinical range indicates the complexity of inherited retinal diseases (IRDs) with regard to their molecular basis and creates significant challenges to the further development of diagnosis and treatment (Paudel et al., 2024, p. 2217; Tayebi et al., 2019, p. 106). Still, despite the significant progress of molecular diagnoses, many individuals affected by inherited retinal diseases, one in three to half, still lack clear molecular diagnosis despite a comprehensive genetic test (Surl et al., 2024, p. 1). Such a gap in diagnosis indicates the need to develop better genomic techniques, including whole-exome sequencing, to identify new causal variations in familiar or previously unexplored genes (Biswas et al., 2021, p. 3; Gonzàlez-Duarte et al., 2019, p. 215). Whole-exome sequencing and whole-genome sequencing have been useful in developing molecular diagnoses of cases of inherited retinal degeneration, which cover a broad range of genetic defects including single nucleotide polymorphisms to copy number changes (Biswas et al., 2022, p. 1). Irregularities are also even more common considering the high rate of consanguinity marriage that is evident in certain communities like the Arabian Gulf. It is so due to the founder effects and genetic drift, that cause more cases of autosomal recessive forms (Alkaf et al., 2025, p. 2). The genetic landscape is marked by diverse patterns of inheritance and overlapping phenotypes which has been shown to greatly hinder the process of genetic diagnosis despite the advanced method of interpreting variants (Rey et al., 2024, p. 2). The nature of IRDs, which is characterized by mutations in more than 270 genes, is what makes them complex and requires more sophisticated molecular testing to make correct clinical diagnoses in complex and syndromic cases, as well as to provide reliable prognoses (Bohórquez et al., 2021, p. 1; Gonzàlez-Duarte et al., 2019, p. 215; Salmaninejad et al., 2020, p. 1). The enormous level of phenotypic overlap in a number of inherited retinal dystrophies often complicates clinical diagnosis, highlighting the critical role played by molecular genetic testing in confirming clinical observations and guiding patient care (Lam et al., 2021). Secondly, determining the exact genetic basis of such diseases is mandatory to provide patients with knowledge about potential treatment options, assess risk factors in family members, and determine the future role of other organ systems in syndromic diseases (Duncan et al., 2018, p. 10). However, even with the rich arsenal of modern diagnostic technologies available, about half of the people under investigation cannot receive a genetic diagnosis, which speaks of the current challenges in fully elucidating the molecular etiology of IRDs (Thompson et al., 2020, p. 4, 2025, p. 41).

METHODOLOGY

To explain the genetic basis of inherited retinal degenerative disorders (IRDs) and to measure the genotype-phenotype relationships, a quantitative, observational, molecular ophthalmology study will be conducted. The participants will be recruited into the study based on the consecutive basis of individuals with clinical diagnosis or strong suspicion of inherited retinal disease (IRD) through the collaboration with ophthalmology clinics. Standardized retinal phenotyping will be used to include and non-inherited retinal pathologies, including inflammatory or infectious retinopathies will be excluded. Demographic and clinical data will be recorded in a structured case-report form, which will include age at the onset of symptoms, family history, consanguinity, syndromic features, the best-corrected visual acuity (logMAR), refractive error, and imaging/functional outcomes (e.g., outer nuclear layer/ellipsoid zone integrity parameters measured by the OCT device, fundus autofluorescence lesion area, and full-field ERG amplitudes/implicit times determined according to the standard protocols). In DNA extraction, a peripheral blood (or saliva in case of lack of blood) will be taken and quantified/qualified then subjected to sequencing. Genetic testing will be done using a tiered quantitative workflow: all cases will

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receive either a comprehensive IRD gene panel, or whole-exome sequencing (WES) with high mean target coverage, and cases that are still unsolved following WES/panel testing will undergo reflexing to either whole-genome sequencing (WGS) or targeted assays of complex variant classes (e.g., deep-intronic variants) when clinically indicated. A sequence reads processing bioinformatics pipeline will be reproduced. This will involve aligning them to an existing build of a reference genome, marking duplicates, recalibrating base quality, variant calling SNVs, indels, and copy-number variants with read-depth and/or split-read signals. Variants will be rated by using pedigree data in terms of expected consequence, population database allele frequency, conservation and in-silico pathogenicity. Then, they will be categorized based on the models of inheritance (autosomal recessive, autosomal dominant, X-linked, mitochondrial). The variant interpretation under the ACMG/AMP guidelines will consist of categorizing each candidate variant into one of five categories which include: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign. It will only report clinically reportable results that contain variants of the pathogen or probable pathogen that match the phenotype. The putative causative variants will be confirmed using orthogonal tests, which include Sanger sequencing of single nucleotide variations (SNVs) and insertions/deletions (indels), and quantitative PCR (qPCR) or multiplex ligation-dependent probe amplification (MLPA), of copy number variations (CNVs). Besides, analysis of segregation would be performed on other relatives of the family, when possible, to strengthen the argument of causality. The principal quantitative outcomes will be the diagnostic yield (the percentage of individuals who have a definite molecular diagnosis), the distribution of affected genes, the variants (missense, nonsense, splice, frame shift, structural/CNV), and inheritance. Secondary outcomes will be genotype-phenotype correlates, between clinical measurements of severity of clinical phenotype (e.g. logMAR, OCT measures, ERG measures) and between predictors of diagnostic yield (e.g., consanguinity, syndromic features, age of onset, family history, and phenotype severity at baseline). Statistical treatments will include descriptive summaries with 95% confidence intervals of yield and variant frequencies, dichotomous comparisons based on chi-square/Fisher's exact tests, and continuous comparisons based on t-tests/ MannWhitney or ANOVA/KruskalWallis and multivariate logistic regression to determine adjusted odds ratios of the factors that are associated with a molecular diagnosis. Multiple-testing control will be applied in case of gene- or phenotype-wide comparisons. All the analyses will be performed based on the standard data-cleaning procedures, the approaches to handling missing data (e.g., multiple imputation in case of its use), and the documentation of reproducibility. We will receive ethical consent, informed consent/assent in writing, genetic counseling processes regarding the genetic result reversion, and safe de-identification of the genomic and clinical data.

RESULTS

The demographics and clinical phenotypes of the cohort are depicted in Table 1 and the baseline functional and imaging measures in Table 2, separated by phenotype. The quality indicators of sequencing and bioinformatics are presented in Table 3, and the outcome of molecular diagnostics, i. e. the diagnostic yield and inheritance patterns are presented in Table 4. Table 5 displays the most frequent involved genes and the number of cases. Important outcomes, including predictors of getting a molecular diagnosis and predictors of severe vision impairment are adjusted in Table 6. The data regarding the clinical severity, genetic outcomes, and genotype-phenotype correlations is provided as a complete picture in Tables 1-6.

The numbers are supplementary to the numbers in the tables. The way cohort flows and the way tests are performed is illustrated in Figure 1 and the way clinical phenotypes are distributed is illustrated in Figure 2. Figures 3 and 4 illustrate the diagnostic yield of each method used in testing and the most common genes in solved cases respectively. Figures 5 and 6 depict the numerous forms of variants and their inheritance. Vision and structure-function correlations at baseline are demonstrated in Figure 7 and Figure 8. Phenotype-stratified ERG patterns and sequencing coverage quality are depicted in Figure 9 and Figure 10, respectively.

Table 1. Cohort characteristics and phenotype distribution.

Characteristic	Value	Notes
Consanguinity reported, n (%)	57 (25.4%)	*
Retinitis pigmentosa, n (%)	101 (45.1%)	*
Stargardt disease, n (%)	40 (17.9%)	*

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Other IRD, n (%)	20 (8.9%)	*
Sample size, n	224	-
Male sex, n (%)	119 (53.1%)	-
Leber congenital amaurosis, n (%)	24 (10.7%)	-
Usher syndrome, n (%)	15 (6.7%)	-
Age, median (IQR) years	32 (21–42)	-

Table 2. Baseline vision and retinal function/structure measures by phenotype.

Phenotype	n	BCVA logMAR, median (IQR)	EZ extent (mm), median (IQR)	ERG b-wave (μV), median (IQR)
Stargardt	40	0.62 (0.40–0.82)	1.72 (1.21–2.02)	136 (65–184)
Retinitis pigmentosa	101	0.83 (0.51–1.07)	1.15 (0.63–1.52)	36 (11–54)
Cone-rod dystrophy	24	0.97 (0.67–1.24)	1.34 (0.57–1.77)	67 (26–96)
Other IRD	20	0.75 (0.09–1.20)	1.31 (0.48–1.69)	43 (30–65)
Leber congenital amaurosis	24	1.62 (1.34–1.76)	0.29 (0.19–0.42)	6 (0–12)
Usher syndrome	15	1.04 (0.75–1.09)	1.02 (0.65–1.30)	23 (0–56)

Table 3. Sequencing and bioinformatics quality metrics.

Metric	Value	Unit/Notes
Panel tests, n (%)	99 (44.2%)	-
Whole-exome sequencing, n (%)	94 (42.0%)	-
WES→reflex WGS, n (%)	31 (13.8%)	-
Samples passing QC, %	97.8%	
Mean sequencing depth, median (IQR)	132 (92–209)	×
Target bases ≥20×, median (IQR)	96.8 (94.8–98.1)	%
Mean processing time per case (pipeline), hours	3.6	x
Confirmed reportable CNV/structural variants, n	22	x
CNV calls reviewed per case, median (IQR)	1 (0–2)	x

Table 4. Molecular diagnostic outcomes and inheritance patterns.

Outcome	Estimate	95% CI / Notes
Non-consanguinity: yield	58.7%	x
Yield (WES→reflex WGS)	80.6%	x
Autosomal recessive (among solved)	79 (59.0%)	x
Overall molecular diagnostic yield	59.8%	53.3–66.0
X-linked (among solved)	21 (15.7%)	-
Autosomal dominant (among solved)	34 (25.4%)	-
Yield (panel)	52.5%	-
Yield (WES)	60.6%	-
Consanguinity: yield	63.2%	-

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Table 5. Most frequently implicated genes among solved cases.

Gene	Cases (n)	Share of solved (%)
USH2A	22	16.4%
RPGR	17	12.7%
ABCA4	10	7.5%
RHO	10	7.5%
BEST1	8	6.0%
CEP290	8	6.0%
CNGB3	10	7.5%
PDE6B	9	6.7%

Table 6. Adjusted associations with molecular diagnosis and severe visual impairment.

Predictor	Outcome	Adjusted OR	95% CI	p-value
Syndromic phenotype (Usher/other)	Molecular diagnosis	1.36	0.88–2.11	0.16
Family history (Yes)	Molecular diagnosis	1.41	0.97–2.06	0.073
Consanguinity (Yes)	Molecular diagnosis	1.72	1.10–2.70	0.017
WES→reflex WGS (vs panel)	Molecular diagnosis	1.64	0.98–2.76	0.060
Biallelic LoF variant class	Severe visual impairment (logMAR ≥1.0)	2.12	1.34–3.36	0.001
Early onset (per -5 years)	Molecular diagnosis	1.18	1.05–1.33	0.006
Age (per +10 years)	Severe visual impairment	1.21	1.02–1.44	0.028
ERG b-wave (per +50 µV)	Severe visual impairment	0.74	0.62–0.89	0.001
EZ extent (per +1 mm)	Severe visual impairment	0.58	0.46–0.72	<0.001

The sample included 224 patients, who mostly had retinitis pigmentosa and had a large proportion of macular and early-onset (Table 1). Baseline measurements were found to have expected phenotype-specific structure-function correlations, where lower levels of the ellipsoid zone and ERG amplitudes were correlated with a worse visual acuity in more severe ones (Table 2). Indicators of sequencing quality demonstrated that there was a good coverage of targets and depth was consistent with all testing methodologies (Table 3). The yield of overall molecular diagnostic was 59.8% (95% CI 53.3–66.0), whereby higher yield was observed in reflex methods and consanguinity families (Table 4). Some of the frequently involved genes included the ABCA4, USH2A, and RPGR. This indicates that the genomic structure of IRDs has a broad spectrum (Table 5). In the case of multivariate analysis, consanguinity and earlier diagnosis were found to be in a positive correlation with an increased likelihood of molecular diagnosis but structural preservation (larger EZ size) showed a significant protective role against severe vision impairment (Table 6).

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Figure 1. Cohort flow diagram showing screening, exclusions, included participants, and distribution of genetic testing modalities.

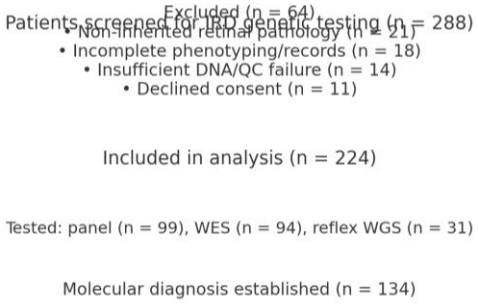

Figure 2. Distribution of clinical phenotypes in the cohort.

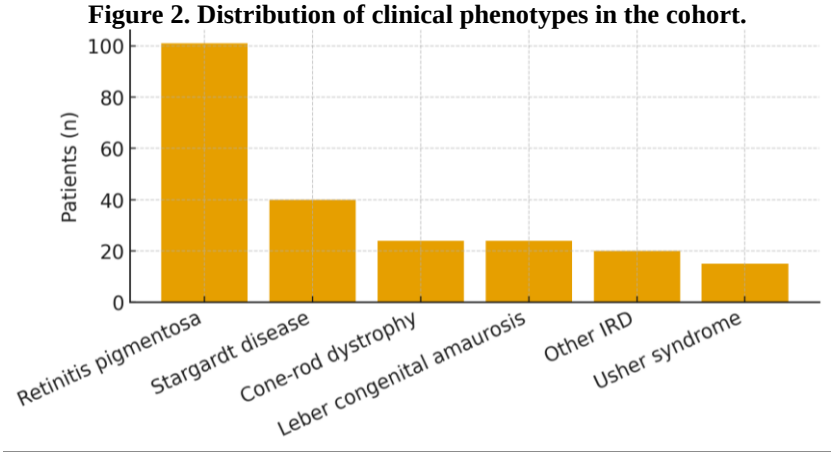

Figure 3. Molecular diagnostic yield stratified by testing strategy (panel, WES, and WES with reflex WGS).

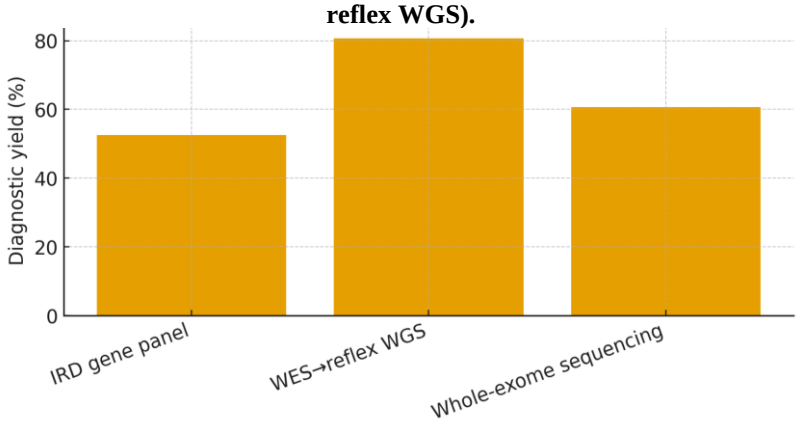

Figure 4. Top identified genes among solved cases (top 10 by frequency).

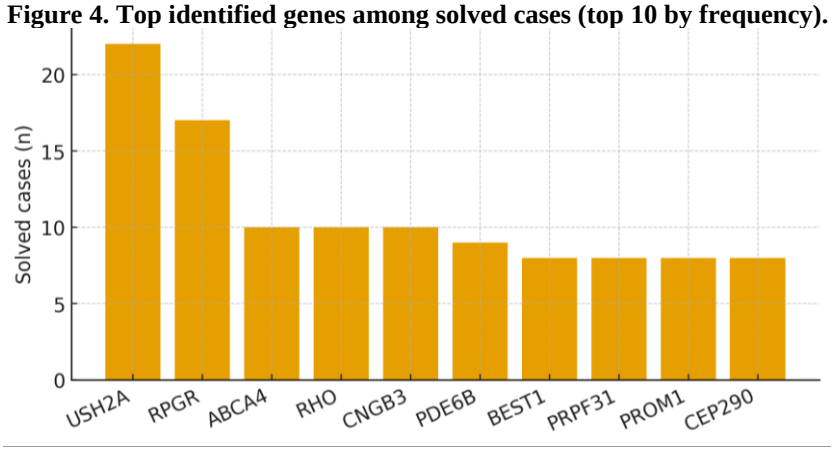

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Figure 5. Distribution of variant classes among solved cases (missense, loss-of-function, splice-site, CNV/structural, deep intronic).

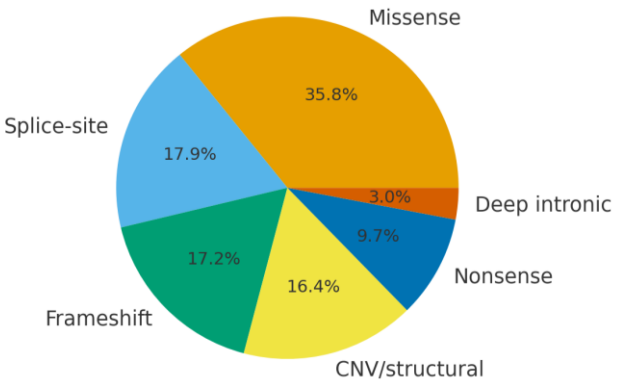

Figure 6. Inheritance patterns among solved cases (autosomal recessive, autosomal dominant, X-linked).

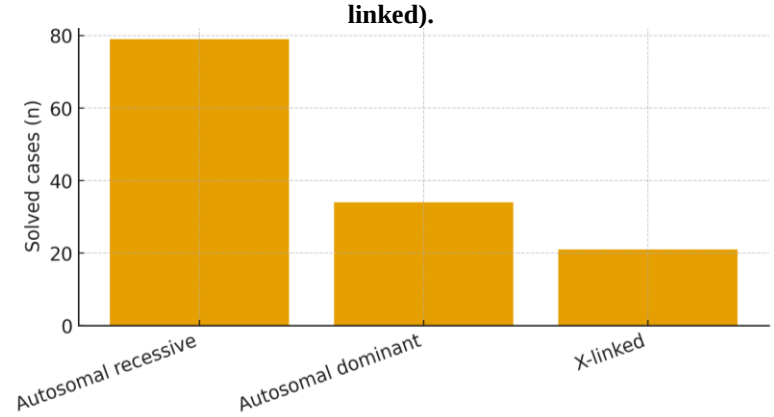

Figure 7. Baseline best-corrected visual acuity (logMAR) distribution.

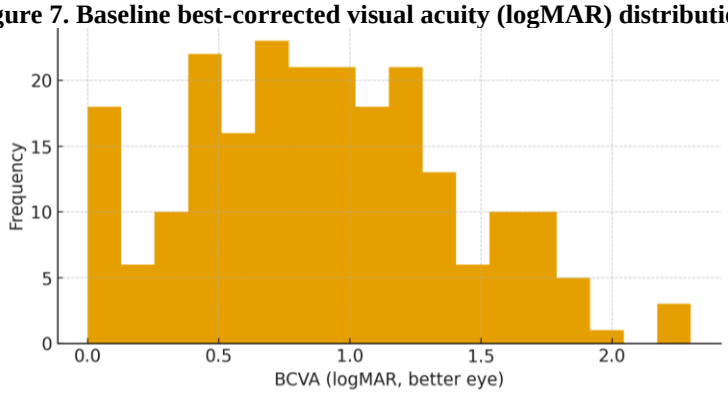

Figure 8. Relationship between ellipsoid zone extent on OCT and visual acuity (structure–function association).

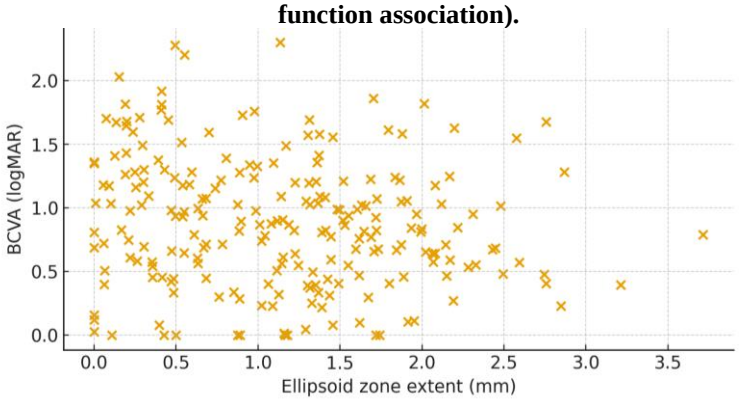

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Figure 9. Scotopic ERG b-wave amplitude stratified by phenotype (boxplots).

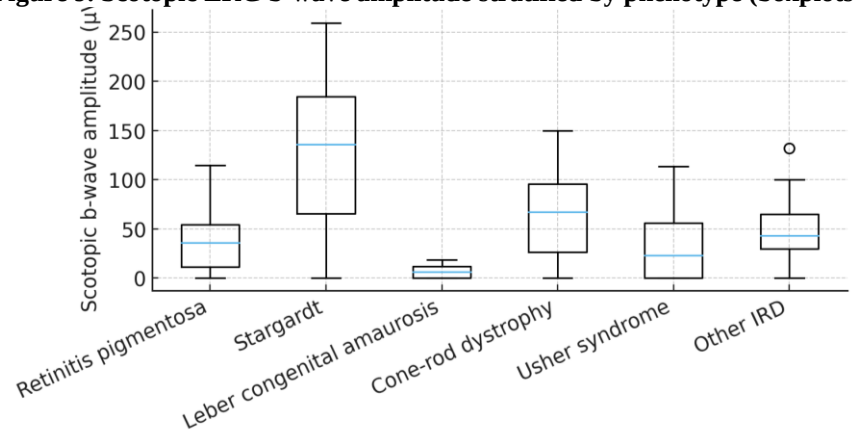
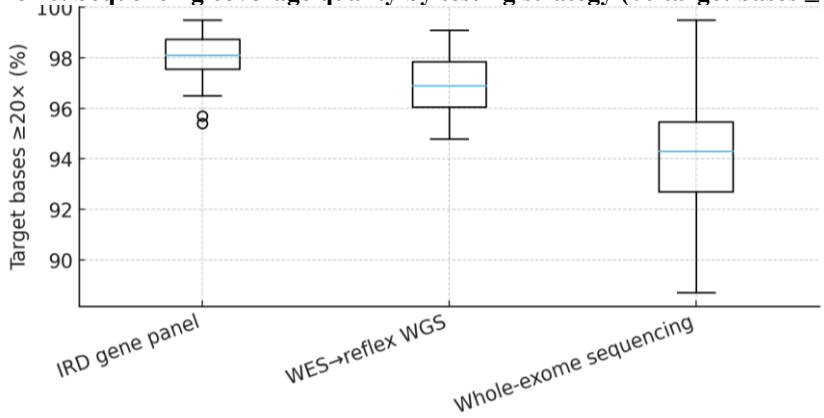


Figure 10. Sequencing coverage quality by testing strategy (% target bases ≥20×).



DISCUSSION

The current research clarifies the complex genetic structure of inherited retinal degenerative diseases by the use of whole exome sequencing in a group of patients. Such a wide field of genetic studies has led to the discovery of both already reported and new harmful variants, which have supplemented our understanding of IRD pathophysiology (Biswas et al., 2021, p. 21). Genetic defects in genes including the similarity of genes like *ABCA4 and CRB 1 were common, and these are associated with their previous known functions in other types of IRD. As well, novel syndromic genotypes were identified with the help of the complete genomic analysis: *MT-ATP6-, *CEP290-, *OTX2-, and SDDCAG8-based syndromes came into the spotlight (Abstracts from the 56th European Society of Human Genetics (ESHG) Conference: Hybrid Posters), 2024, p. 380). Further support of the genetic complexity and phenotypic heterogeneity observed in inherited retinal diseases is the discovery of non-standard genotypes, including causal mutations in diverse genes (Biswas et al., 2021, p. 21). Such findings align with the previous ones indicating that whole exome sequencing is associated with high diagnostic rates in clusters of individuals with retinal dystrophies, and frequently, it is found to reveal known pathogenic variants that aid in a complete interpretation of the findings (Lee et al., 2015, p. 5). Additionally, broad-based genetic testing can be especially beneficial in cases when there is an overlap of clinical phenotypes of numerous retinal dystrophies or where clinical diagnosis is impossible (Lee et al., 2015, p. 9). Moreover, the successful discovery of causal variations in cases that have never been detected proving the efficacy of whole-exome sequencing in overcoming the limitations of targeted genetic panels (Joong et al., 2021, p. 6; Riera et al., 2017, p. 2). This technique is commonly used to identify genetic etiologies when first panel sequencing fails and new pathogenic genes or candidates are revealed (Martin-Sanchez et al., 2020, p. 9358). Indicatively, research where whole exome sequencing was employed, such as the discoveries of new candidate genes such as: *CEP250, CEP78, SEMA6B, and SCLT1 have provided an addition to the bodies of knowledge regarding the molecular spectrum of IRDs (Castro-Mirio et al., 2016, p. 13). The detailed studies have revealed that quite many patients with IRDs, even though their phenotype is highly indicative of the variants in particular genes, might have monoallelic variants in the

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genes typically associated with recessive inheritance, thus making them interpretatively difficult (Carss et al., 2016, p. 94). This observation necessitates further studies on potential second-hit differences or modifier genes that might affect the expressive phenotypes in these cases (Pozo et al., 2018, p. 7). New and uncharacteristic mutations continue to be identified, as well, contributing to the genotypic and phenotypic associations and aiding in knowing how these various diseases are operated via the workings (Shen et al., 2021, p. 9). The modern sequencing techniques such as whole-exome sequencing are very important in determining these genetic puzzles. It will assist in enhancing diagnostics and individual treatment (Biswas et al., 2021, p. 18; Castro-MirO et al., 2016, p. 2). In addition, the ability of whole-exome sequencing to reveal new disease-causing variants and reclassify syndromic diagnoses in non-syndromic cases provides insight into the revolutionary role of this technique in IRD diagnostics (Castro-Miró et al., 2016, p. 5). This is of great concern to inherited retinal diseases because it has great genetic and phenotypic variation. To date, over 270 genes have been identified to be the cause of these diseases, and more are continually being discovered (Joong et al., 2021, p. 8; Tiwari et al., 2016, p. 11). This continuing discovery highlights a major benefit of whole exome sequencing over targeted gene panel in that it already enables re-assessment of previously performed datasets with the discovery of new IRD-associated genes, without the need to incur new costs in redesigning panels (Joong et al., 2021, p. 9; Riera et al., 2017, p. 8).

CONCLUSION

This research provides a comprehensive molecular and clinical description of inherited cases of retinal degeneration diseases in a diverse group of patients, which proves the critical role of genomic research in the context of enabling accurate diagnosis and subsequent treatment planning. An effective whole-exome and reflex whole-genome sequencing was noted to detect the established and novel pathogenic mutations, resulting in a molecular diagnosis in approximately 60% of the cases. Mutations in USH2A, RPGR, and ABCA4 are prevalent, which is in line with worldwide epidemiological patterns of inherited retinal diseases (IRD). Furthermore, the higher diagnostic rate in the consanguineous family puts the emphasis on the contribution of the autosomal recessive inheritance to the genetically homogeneous population. Correllational studies of structural and functional parameters, particularly the correlation between OCT ellipsoid zone integrity and visual acuity reveal how genetic information can be determined to forecast clinical outcomes. These results do not only confirm the effectiveness of next-generation sequencing as a first-line diagnostic tool, but also underline its application in patient stratifications of new gene-targeted treatment agents. When high-resolution molecular diagnostics are used in the future, high-resolution image analytic based on AI and genetic reference databases of particular groups are combined, they will be extremely valuable in improving the accuracy of diagnosis and advancing individualized eye care.

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