Exploring the genetic basis of inherited retinal disease in West Yorkshire

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Background

Inherited retinal diseases (IRDs) are a group of clinically heterogeneous conditions leading to visual impairment and affecting quality of life, independent living and lifestyle choices.(1) The IRD genotypes differ by disease and across populations. Understanding the genetic basis can help clinicians provide an accurate diagnosis and genetic counselling and may also help identify personalised treatment strategies in the future. In the UK, 25,000 individuals are affected by IRD, however comprehensive data on the most prevalent IRD genes is limited, particularly in ethnic minority groups.(2)

This study aimed to identify and analyse the most frequent genes associated with IRD in West Yorkshire, with a focus on differences according to diagnosis, ethnicity and inheritance.

Aims

1. To review genetic test results of patients with IRD across West Yorkshire.
2. To identify the most common IRD-associated genes in the local population, stratified by diagnosis, ethnicity and predicted pattern of inheritance .

Methods

This retrospective cohort study reviewed the clinical diagnoses, inheritance patterns, ethnicities and genetic test results of West Yorkshire patients with IRD and a confirmatory genetic testing. All patients attending local clinics and with a positive genetic test result, obtained either through a research laboratory or NHS diagnostic service, were included. Electronic medical records and local databases were used to collect relevant information. Data analysis was performed using descriptive statistics to investigate associations between genotype and diagnosis, ethnicity and predicted inheritance pattern prior to testing.

Results

The total number of patients in this data set was **633**. This included 464 Caucasian, 187 South Asian, and 12 patients of other ethnicities. The majority (92.9%) had acquired and progressive disease, while 7.1% had congenital and stationary conditions.

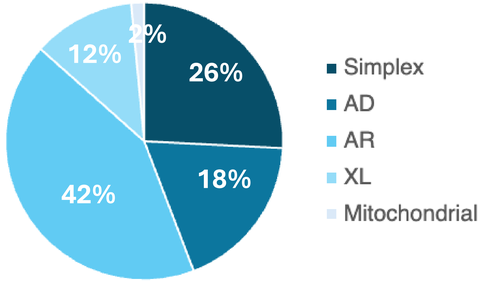


Figure 1. Pie chart to show the predicted inheritance pattern

There were **103** different IRD-causing genes in the cohort, with variants in 13 genes causing congenital and stationary diseases, and in 90 genes causing acquired and progressive diseases. Only **<1%** of the genes were mitochondrial.

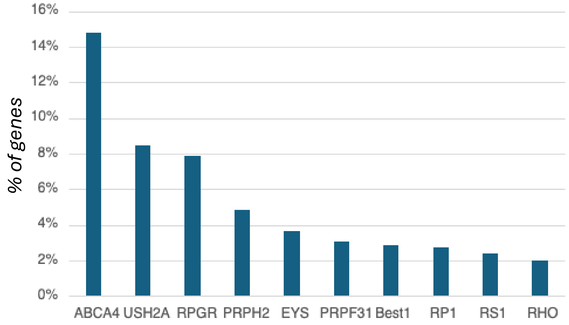


Figure 2. Graph to show the percentage of 10 most common genes causing IRD in this cohort from West Yorkshire

Caucasian patients exhibited greater genetic heterogeneity than South Asian patients (83 vs 63 genes). Variants in RPGR, and PRPH2 were less common in South Asian patients, while ABCA4 variants were more prevalent.

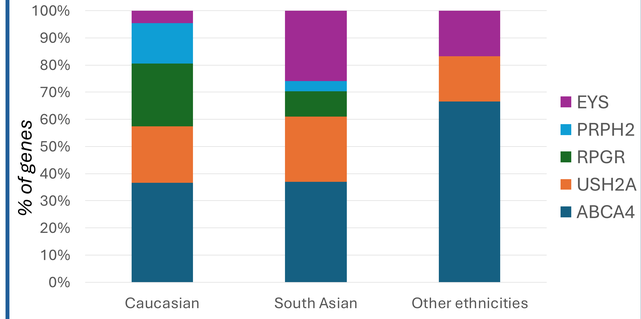


Figure 3. Bar chart to show the relative frequency of the 5 most common IRD-associated genes by ethnicity

A limited number of genes were responsible for most diagnoses, while the majority affecting less than 1% of the patients across disease types and ethnicities.

Diagnostic group	Gene	% of group
Congenital and stationary disease	CNGB3	19
	CNGA3	17
	TRPM1	11
Macular dystrophies	ABCA4	42
	PRPH2	16
	BEST1	9
Generalised retinal dystrophy (non syndromic)	RGPR	14
	USH2A	8
	EYS	7
Generalised retinal dystrophy (syndromic)	USH2A	43
	MYO7A	11
	USH1C	3

Figure 4. Table showing IRD diagnostic groups and the most common disease-causing genes

Conclusion

This study highlights the diversity of genes associated with IRD in West Yorkshire. Most patients with a positive genetic test results had non-syndromic, progressive macular or generalised retinal dystrophies and the most common predicted pattern of inheritance was autosomal recessive. Pathogenic variants in the ABCA4, RPGR and USH2A genes together accounted for more than 31% of all IRD cases. These were the most implicated genes in autosomal recessive (ABCA4, USH2A), simplex (ABCA4, USH2A), and X-linked (RPGR) inheritance, respectively. Knowledge of the most common diagnoses, inheritance patterns and genotypes in the local population can guide clinical decision making, genetic counselling and the interpretation of genetic test results.

Discussion

This is the first study to explore the most common IRD-causing genes in West Yorkshire by diagnosis, ethnicity, and inheritance pattern. While the findings align with larger studies from Moorfields Eye Hospital(3) , the smaller sample size and underrepresentation of non-Caucasian/Asian groups (1.8%) in our study population may limit generalisability.(3) This emphasises the importance of creating more inclusive genetic databases that accurately reflect the diversity of ethnic minority groups. Further research into factors such as consanguinity may help explain the high rate of autosomal recessive inheritance. Despite limitations, this study may support prognosis and guide future gene therapy research. Knowledge of gene prevalence can support earlier diagnosis and enable prioritisation for genetic testing panels tailored to local populations.

References:

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