Patient impact of genetic testing in inherited retinal dystrophy

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Introduction

Inherited retinal diseases (IRDs) are a clinically heterogeneous group of rare disorders, characterised by photoreceptor dysfunction.

Recent advances in genetics and molecular biology have led to improved gene identification (NGS, whole exome sequencing). Over 270 genes have been characterized so far, accounting for >90% of cases.

Gene therapy for biallelic *RPE-65* mutation is already approved with other novel therapies on the horizon. [1]

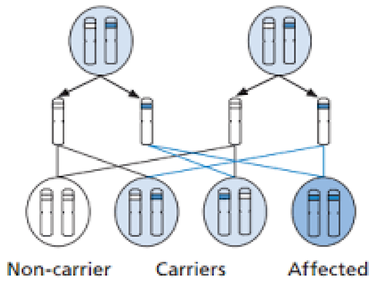

Fig.1: *Autosomal recessive inheritance pattern when both parents are carriers.*

Autosomal recessive carrier offspring have a 1/4 chance of being affected if both parents are carriers.

Incidence of genetic errors also increases in consanguineous families

Patient ZC has two heterozygous autosomal recessive pathogenic mutations and would have benefited from pre-conception counselling.

BMEC is now providing a regional retinal genetics service with three specialists in the department.

Clinical case

Ms. ZC, a 40-year-old Pakistani female was referred to our genetics clinic with an IRD.

She had genetic testing done aged 12, with a negative result at the time.

Family history: she was 1st cousins with her husband and had 1 miscarriage.

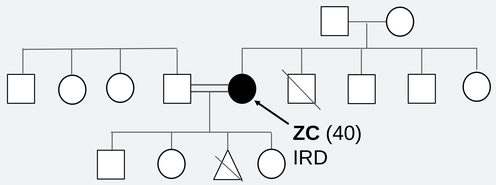

Fig. 2: Patient ZC's family tree

Her HAD score (Depression=11, Anxiety=9), PSQI score (5) and Time Trade-Off score (0.875) indicate the significant impact of her disease on her mood, sleep and quality of life.

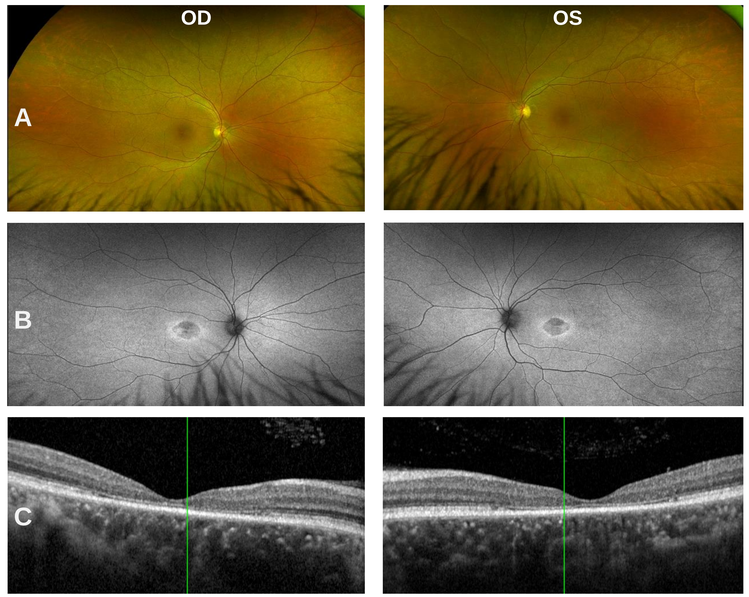

Fig. 3: Images show, from top to bottom, the patient's: (**A**) Fundus Optos image right (OD) and left eye (OS) (**B**) Autofluorescence showing characteristic hypofluorescent area and hyperfluorescent ring (**C**) Macular OCT, showing central loss of the photoreceptor layers

This time, repeat genetic testing (whole exome sequencing of 199 genes) showed:
- Homozygous TTLL5 mutation
- Heterozygous AHI1 and Heterozygous BEST-1

Biallelic AHI1 can cause Joubert Syndrome, a severe multisystem congenital disorder causing nervous system malformations, and biallelic BEST1 causes Bestrophinopathy.

Outcome

Although this patient's mutation was not suitable for gene therapy or current clinical trials, she was able to obtain a diagnosis, access genetic counselling and will be able to access future trials when available.

Key Takeaway Points:

A good family history is paramount to identify inheritance patterns where IRD is suspected.

Even if there was a past negative result, recent advances in genetics mean it is worth repeating genetic testing with whole exome or whole genome sequencing.

Genetic testing helps patients with:
- Providing a diagnosis
- Relieving anxiety and depression
- Family planning
- Identifying risk for children and family members
- Accessing available treatments
- Accessing current and future clinical trials

References

1. Thompson et al, 2020. Advancing Clinical Trials for Inherited Retinal Diseases. Translational Vision Science & Technology, 9(7), p.2.

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