The ROYAL COLLEGE of OPHTHALMOLOGISTS

focus

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Genomic Medicine in Ophthalmology

Mr Jay Self BM FRCOphth PhD
Consultant ophthalmologist and Associate Professor
University of Southampton
University Hospital Southampton

Dr Mariya Moosajee MBBS BSc PhD FRCOphth
Consultant ophthalmologist and Associate Professor
Moorfields Eye Hospital NHS Foundation Trust
Great Ormond Street Hospital for Children NHS Foundation Trust
UCL Institute of Ophthalmology, London

What is genomic medicine?

Genetics is the study of certain parts of an individual's DNA, usually a limited number of genes or parts of genes. In contrast, genomics is the study of the entirety of an individual's DNA (approximately 3 billion nucleotides and over 20,000 genes) or a significant proportion of it. Genomics is a relatively new term as it has only been made possible by recent advances in technology which allow massive amounts of DNA to be sequenced in parallel and data to be analysed using high-performance computing and mathematical techniques known as bioinformatics.

Genomic medicine is an emerging medical discipline/approach that involves using genomic information about an individual as part of their clinical care (e.g. for diagnostic or therapeutic decision-making) and is increasingly being recognised as having a major impact on healthcare systems and individualised medical care.

How is genomic medicine impacting ophthalmology?

Genomic medicine is central to the move towards precision medicine, which is a key priority for the NHS as part of its '5 year forward view'. For some time, genetic testing has been available for certain rare ophthalmic conditions but with the advent of modern sequencing techniques and better pipelines for interpreting results, genomic information is now part of 'best practice' management for many ophthalmic conditions and helping to tailor treatments and diagnostic workflows in most ophthalmic specialties. Many novel therapies, such as gene and stem cell therapies, have relied for some time on genomic information to select patients which may respond to treatment but pharmacogenomics (the study of how an individual's genomic makeup dictates their response to specific medicines) is now starting to show promise for more common conditions such as glaucoma and AMD. Even when genomic studies do not direct the ophthalmologist to a specific treatment, they can help ophthalmologists to plan future screening for the individual, provide more informed prognostic information and provide genetic counselling to families and risk stratification for relatives. Additionally, in some cases excluding or identifying conditions which require ongoing systemic management is becoming a key role and leads to earlier diagnosis, access to treatments or the correct specialists to reduce co-morbidity and in many cases significantly fewer diagnostic investigations.

Why is genetic testing important?

Despite the improvement in genetic testing in ophthalmology in recent years, and the numerous reasons for its importance, it is still sometimes considered to be of limited value or of 'research interest' only. In the table below, we outline some of the most common ways in which pursuing a genetic diagnosis can help patients, clinicians and the NHS more broadly in the context of busy ophthalmic practice.

Outcome	Benefits
Identification of associated/ potential systemic features	Hastening medical care for associated pathologies and reducing co-morbidity
Exclusion of more significant genetic disorders	Reducing investigations and screening costs and providing life-long information to patients
Identification of whether the condition is progressive or non-progressive	Providing information allowing patients to plan their futures. Allowing clinicians to plan future care/screening and typically reduce costs and investigation burden
Identification of the likely mode of inheritance	Facilitating genetic counselling and family planning
	Permitting targeted screening of family members – increasing early diagnosis and reducing unnecessary screening in some cases
Identification of genetic aetiologies for which established genetic therapies or clinical trials are currently recruiting	Permitting access to current clinical trials or established genetic therapies for specific disorders
Identification of specific disorders for which targeted medical or surgical therapies exist	Permitting early treatments which would not otherwise have been considered
Identification of the specific disorder *per se*	Patients value simply knowing what their condition is. This is often underappreciated

Example 1

Lisa is a 9 year old girl who is healthy, has no previous medical history and takes no medications. She reported blurring of her vision, which had progressed over the previous year (no previous ophthalmic examinations) and was found to have bilateral cataracts, visual acuities of 0.6 LogMAR in either eye and an otherwise normal ocular examination (see Figure 1).

At the time of cataract surgery, a congenital cataract gene exome sequencing panel was sent, which identified a homozygous, known disease-causing variant in the CYP27A1 gene suggesting a diagnosis of autosomal recessive cerebrotendinous xanthomatosis (CTX). Subsequent segregation in her parents and cholestanol studies confirm the diagnosis, which triggered a prompt referral to the regional metabolic service.

CTX is a multisystem disorder and oral bile acid replacement therapy can halt disease progression and prevent symptoms entirely in asymptomatic individuals. Therefore, early diagnosis and treatment is extremely important in order to prevent the significant systemic complications of this condition including: seizures, ataxia, dementia, cholestatic liver disease and cardiovascular disease. In this case, ophthalmic panel testing, in a girl with a seemingly isolated ophthalmic disorder, was key to this patient's life-long medical care and provided targeted screening for family members.

Example 2

Jasper was born with poor vision and was diagnosed with Leber congenital amaurosis (LCA) (see Figure 2). Genomic testing became available on the NHS when he was 4 years old. This demonstrated that he had a mutation in RPE65, which is a gene expressed in the RPE working to convert all-trans retinal back to 11-cis retinal as part of the visual cycle. When faulty, it leads to an excess of all-trans retinal build-up within the RPE that leads to severe visual impairment beginning very early in life. In September 2019, NICE recommended the first licensed gene therapy for vision loss caused by RPE65-mediated retinal dystrophy called voretigene neparvovec (also called Luxturna made by Novartis Pharmaceuticals UK). Jasper now has the option to receive a targeted gene therapy that may slow his retinal degeneration or even halt disease progression. This is delivered through vitrectomy and subretinal injection.

Do all ophthalmologists need to become genomics experts?

No. However, as genomics is taking up a more central role in ophthalmology, there is currently a focus on how services can integrate genomics and what roles non-specialist ophthalmologists will take. However, broadly, there is a move away from the previous model by which only a few major centres were involved in genomic testing and the well recognised inconsistencies in management due to postcode lottery. The rapid changes in how genomic tests are ordered, who can order them and how they are funded (soon to be centrally funded through a National Genomic Medicine Service (NGMS)) mean that every ophthalmologist will be involved in genomics to some degree, perhaps from time-to-time and perhaps purely in staying abreast of which patients may benefit from genomic testing and referring on. In order to prepare for these changes the RCOphth is acting now to make changes to the Ophthalmic Specialist Training (OST) curriculum and provide additional CPD courses in order to develop a broad, genomics literate workforce. The United Kingdom Eye Genetics Group (UKEGG) have an education page that provides free access to a range of teaching material and CPD/CME courses: **https://ukegg.com/education/**

How do clinicians find the best genetic test for individual patients?

In the UK there is an advisory organisation called the UK Genetic Testing Network (UKGTN) that aims to promote high quality, equitable laboratory services for patients and their families who require genetic advice, diagnosis and management. It has a membership of diagnostic laboratories that meet a wide range of professional criteria including quality assurance and accreditation for molecular genetics services. Clinicians can access this site (**https://ukgtn.nhs.uk**) to identify which laboratories provide particular genetic tests, providing information on cost and turnaround time. In most instances an established system will be in place for most conditions and currently local services often have bespoke arrangements, although there are plans to standardise these clinical networks through the NGMS. It is important that clinicians ensure that patients know what conditions are being tested for and are counselled appropriately (consider a retinal gene panel with circa 200 genes, some of which cause significant or even life limiting conditions).

Summary

The role of genomic medicine is rapidly embedding in ophthalmology due to precision medicine/genomics being central to the mission of the NHS. Similarly, the benefits to patients, clinicians and the NHS more broadly are now being recognised and valued more than ever before. Consequently, changes are happening very quickly in regards to centralised NHS funding, laboratory services and the establishment of a National Genomic Medicine Service. It is imperative that ophthalmology in the UK reacts to these changes, and in broad terms, moves towards a genomics-literate workforce in the interest of our patients.

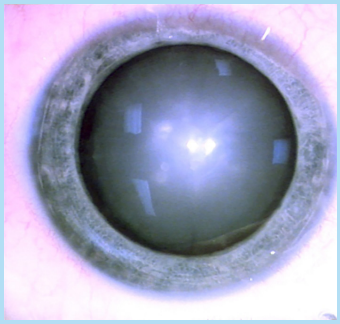

Figure 1. Mixed layer congenital cataract

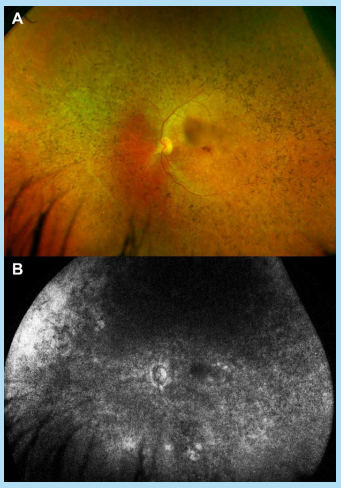

Figure 2. *RPE65* retinopathy (A) widefield fundus image and (B) corresponding autofluorescence

Andrew Tatham Editor, Focus