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Ophthalmology and genomics

Dr Jiten Morarji[1]
Prof Graeme Black[2,3]

Contact

[1]Manchester Royal Eye Hospital
Central Manchester University Hospitals

[2]Centre for Genomic Medicine,
Central Manchester University Hospitals

[3]Faculty of Medical and Human Sciences
University of Manchester

In addition to visual impairment, ophthalmic genetic conditions can have significant systemic implications and affect both the young and old. Integration of genomic information into clinical care will help to refine the delivery of personalised medicine for patients with inherited ophthalmic disorders. These powerful new tools will enable ophthalmologists to provide bespoke healthcare, improving disease prevention, prediction, diagnosis and treatment.

Advances in genetic technology have the potential to improve disease diagnoses and management. This, coupled with an increasing patient demand for genetic and genomic investigation is driving rapid change. Clinicians and allied professionals working in ophthalmology need to understand the opportunities for genomic medicine and feel confident in their skills to deliver personalised care effectively and compassionately.

Making a detailed diagnosis

Precision of diagnosis, including the identification of disease subtypes, directly influences optimal care and treatment. This requires an understanding of pathology at a molecular level, which is now made possible by rapid, affordable sequencing of human genetic code. Pathogenic genetic variants ('mutations') can now be identified, improving the accuracy of diagnosis thereby informing prognosis, facilitating genetic counselling and guiding treatment, especially as potential novel therapies become available. Defects in specific genes can result in malfunction and abnormal development of the eye and may be associated with important systemic anomalies that can be otherwise clinically difficult to diagnose (example 1).

Advances in ophthalmology are now being made by utilising rapid high throughput gene panel sequencing, for example in children with retinal dystrophies and cataract. The samples of DNA are gathered and by testing multiple genes in parallel, this vastly reduces time and expense. Almost 200 genes for inherited retinal diseases can now be tested for with next generation sequence (NGS) panel based testing.

Rare genetic diseases

Rare diseases, 80% of which are genetic in origin, collectively affect 1 in 17 people in the UK population and make up a proportion of the clinical caseload in all specialties. Genetic disease in ophthalmology is a major cause of blindness among children and working-age adults. 20.2% of blind registrations in the working age group in England and Wales are attributed to inherited retinal disorders.

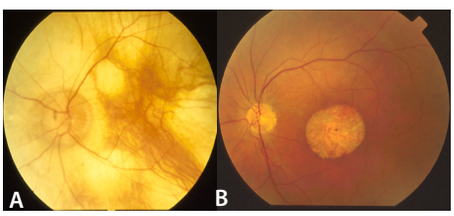
Figure 1. Systemic complications are seen in some patients with Leber congenital amaurosis

Fundus photographs of patient with Leber congenital amaurosis (LCA) subsequently found to have a mutation in the CRB1 *gene (note characteristic pigment distribution). Diagnosis reasssures that there is no risk of renal problems.*

Example 1: LCA

For patients with Leber congenital amaurosis (LCA), unlike the patient pictured who has a homozygous mutation in *CRB1*, genomic analysis may reveal mutations in genes such as *IQCB1* and *IFT140* whose presence may be associated with the development of the progressive renal disease nephronophthisis. Recognition of this allows improved screening and management of renal complications. Interpretation of genomic results in the context of ocular phenotyping is now becoming an important part of ophthalmic practice, allowing diagnoses to be made earlier.

Figure 2:



Fundus photographs showing: ***A****: Choroideremia,* ***B****: Cone-rod dystrophy*

Example 2:

Advances in genetic knowledge and sequencing have led to the development of new genetic tests for rare monogenic diseases. Examples of such conditions affecting the eye in isolation include mutations in the *REP1* gene (choroideremia), *TIMP3* (Sorsby's retinal dystrophy) and *RB1* (retinoblastoma) genes. More recently genomic testing can be applied to conditions such as cone rod dystrophy that can be caused by mutations in many genes.

Genetic testing can now be used effectively to diagnose many single gene (monogenic) conditions in ophthalmology (example and figure 2). New genomic based testing is particularly useful in conditions such as retinitis pigmentosa or congenital cataract where the causal mutation for an individual may be in one of many different genes (genetic heterogeneity). With older technologies, such tests were expensive and time-consuming.

It is likely that clinicians across multiple specialties will have access to these tests, and eventually to tests for all genes or even the whole genome. The UKGTN website (see further information and resources) provides information on genetic tests that are currently listed on the NHS directory of genetic tests. Genomic test development has revolutionised the way rare conditions are being detected, enabling diagnosis at an earlier stage of investigation.

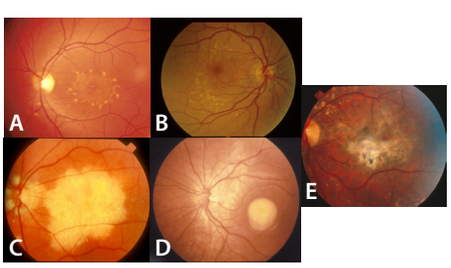
Use of genetic testing will be supported by clinical guidelines, published testing criteria and educational resources (useful contact details for support are provided at the end of this document). However, it is recognised that expert support will still be required to help with interpreting the results from gene panel or genomic sequencing, as there is a greater risk of finding genetic changes that are of uncertain significance. Complex ethical issues involving family members may also need to be addressed.

Genetics of common complex diseases

As well as contributing to a greater understanding of pathways involved in disease mechanisms (which are potential targets for drug development), investigation of rare cases of 'genetic' disease has been important for understanding more common diseases (figure 3).

Common diseases such as age related macular degeneration (ARMD) are complex in aetiology, caused by a combination of environmental risk factors and an underlying genetic susceptibility. Recent advances in medical genetics through genome wide association studies have led to a more comprehensive understanding of the contribution of genetic factors and normal genetic variation between individuals in the pathogenesis of ARMD. For example, genomic testing has shown that a combination of variants in complement factor H and *ARMS2/HTRA1* genes confer up to 40 times increased susceptibility to developing ARMD.

Figure 3:



Monogenic macular dystrophies (with associated gene mutation): ***A****: Stargardt disease (ABCA4, ELOVL4),* ***B****: Pseudoxanthoma elasticum (ABCC6),* ***C****: Doyne honeycomb dystrophy (EFEMP1),* ***D****: Best Vitelliform macular dystrophy (VMD2),* ***E****: Sorsby's macular dystrophy (TIMP3)*

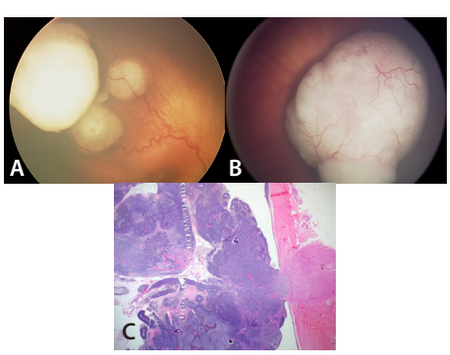
Pharmacogenetics and treatment

Even after taking into account disease sub-phenotypes, there is considerable variability in individual responses to medicines which can be due to differences in the way a drug is handled in the body (pharmacokinetics) and / or variation in the drug targets (*e.g.* receptors, enzymes, ion channels *etc.*). Knowledge of the genomic influences in these processes, when combined with clinical risk factors can provide insights into how a patient will respond in terms of efficacy to a given drug which may alter drug choice and / or dose. This information can also predict susceptibility to adverse drug reactions, including those at the more severe end of the spectrum (example 3).

Example 3:

Azathioprine is used in the treatment of sight threatening uveitis. A significant side effect of this immunosuppressive treatment is myelosuppression. Thiopurine methyl-transferase (TPMT) is an enzyme which metabolises the toxic by-products of azathioprine, but genetic variation in the *TPMT* gene can result in reduced levels of this enzyme. This increases the risk of developing azathioprine toxicity. Testing for homozygous gene mutations in *TPMT* can help to predict those who are enzyme deficient thus avoiding potentially fatal side effects of this medication.

Figure 4:



***A+B:** Fundus pictures of retinoblastoma, **C:** Histology showing a haematoxylin and eosin stain of a retinoblastoma (stained purple) attached to the optic nerve (stained in pink).*

With the development of rapid sequencing assays, and multiple gene panels, it is anticipated that testing for relevant genetic variants that influence both drug efficacy and drug safety will be increasingly used to aid both drug and dosage selection. Such information is being incorporated into the summary of product characteristics of individual drugs, and is reflected in the guidance provided by regulatory agencies such as the European Medicines Agency and the FDA.

Cancer

With over 330,000 new cases in the UK each year, cancer patients are diagnosed and cared for across all specialties within the healthcare service. Again, genomics is transforming care in this area. The detection of a tumour's genetic signature may be used to make a precise diagnosis, enabling a more accurate prognosis and better-tailored treatment.

Retinoblastoma is a malignant retinal tumour, which typically presents in children less than 6 years of age (figure 4). Loss of function in the *RB1* tumour suppressor gene during retinal development can result in the development of the tumour. Identifying the presence of these mutations is paramount in being able to plan follow-up and identify those at risk of developing malignant lesions.

Uveal melanoma is a condition that results in malignant transformation of the melanocytes in the uveal tract (iris, cilliary body, uvea) and is reported to metastasize in up to 50% of cases. Phenotypic characteristics, such as size and presence of lipofuscin pigment, are used as pathological prognostic predictors. Gene testing has shown that patients who possess a loss of chromosome 3 (monosomy 3) and a mutation that inactivates *BAP1* show increased propensity to metastatic spread.

These examples illustrate where identification of pathological mutations can help in deciding when and how often to offer screening to patients and their relatives.

Personalised prevention using genomics

Personalised prevention recognises that people differ in their risk of disease and in their likely response to preventive interventions. Genetic differences account for some of this variation. Testing may be used to identify individuals with rare mutations associated with a high risk of disease, to whom different preventive measures may be offered. Currently, such individuals are usually identified through clinical diagnosis or cascade testing within families. However, the wider availability of genome-wide testing may soon mean that patients learn about these risks unexpectedly when tested for other clinical reasons. It is also anticipated that testing for a range of genetic susceptibility variants for common diseases will become routinely feasible and such data could be incorporated into risk assessment tools, allowing individuals to be more accurately placed into different risk groups within the population.

Further Information and Resources

The Eye Genetic Group UK is an open discussion forum for clinicians and scientists. It encourages research collaboration and provides updates of current research and support on strategic initiatives in the field of ophthalmic genetics. The content of this resource is endorsed by the UK EGG.
www.ukegg.com

HEE Genomics Education Programme
Health Education England
Information on genomics education including HEE sponsored MSc., Diploma, PG Certificate and CPPD genomics courses
0121 695 2374
genomicseducation@wm.hee.nhs.uk
www.genomicseducation.hee.nhs.uk

Online module, St George's, University of London, The Genomics Era: the future of genetics in medicine
www.futurelearn.com/courses/the-genomics-era

UK Genetic Testing Network (UKGTN)
0203 350 4999
SECSU.UKGTN@nhs.net
ukgtn.nhs.uk

UK Pharmacogenetics and Stratified Medicine network.
www.uk-pgx-stratmed.co.uk

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Ethical, legal, social and organisational implications

There are a number of broader challenges that will influence the use of genomic medicine. These include:

- Developing skills and expertise in genomics within the wider health professional workforce
- Issues relating to patient communication, privacy and consent (particularly for genomic testing in children)
- Handling uncertain, unexpected or incidental findings from genomic tests in clinical practice
- Implications of significant results for other family members
- Bioinformatics provision and secure genomic data storage and access within the health service
- Impact of genomics on current healthcare services, resources and patient pathways (including equity of access to genomic tests)
- Developing intelligent decision support systems that allow the use of genomic and clinical information to aid in the prescribing of drugs at the right dose
- Clarifying risks and benefits associated with using genomic tests for opportunistic screening

The future

The last two decades have seen unprecedented investment in life sciences in the UK. Advanced technologies are now available to sequence the entire genome at a cost of a few thousand pounds, and it is envisaged that this cost will fall considerably over the next few years. Achieving the benefits of these technologies will depend on the ability of clinicians to use them effectively, efficiently and responsibly, for the population as a whole. Genomics can no longer be left to specialists and enthusiasts, but must be grasped by every clinician throughout the NHS.

Through the 'Clinical Champions' network, the Royal College of Physicians aims to promote education and training in genomics within every specialty. This will ensure that clinicians of the future are ready to capitalise on all of these new developments to provide personalised care for their patients.

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