Genetic pathology: what is it, what does it involve and what happens in the lab

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Genetic pathology is one of the newest disciplines in pathology. Even amongst medical colleagues, describing myself as a genetic pathology trainee is often met with much confusion. In this post, I want to dispel some misconceptions about what happens in a genetic testing laboratory, outline what genetic pathology training involves, and try valiantly to predict what the future may hold for this field.

What is genetic testing?

Genetic pathology registrars work in genetic testing laboratories, performing, interpreting, and reporting genetic tests that help to diagnose or manage patients with genetic disorders.

The range of tests performed in a typical genetic laboratory can be broad and often straddle many different areas of medicine, including paediatric, adult, and obstetric medicine. It can include testing for a single recurrent genetic variant (e.g. JAK2 V617F), a panel of multiple recurrent variants (e.g. cystic fibrosis), or sequencing of all protein-coding nucleotides (e.g. BRCA1 and BRCA2 testing).

On a larger scale, karyotyping or Fluorescent In-Situ Hybridisation (FISH) can identify numerical and structural chromosomal abnormalities, and chromosomal microarray can identify deletions or duplications within the genome. Laboratories may even perform whole genome sequencing, which interrogates all 3.2 billion bases in the human genome; a feat that only at the beginning of the millennium cost 2.7 billion dollars and 13 years to achieve (see: the cost of sequencing a human genome), but can now be done within a week.

The benefits of genetic pathology

For many genetic tests, there is often no cure or even a treatment for the disorder that is diagnosed, and you could be led to believe that there is little clinical utility in testing for them. But this is far from the truth, and genetic test results can have a wide range of implications. For example, diagnosing a child with an autosomal recessive genetic disorder may help in preventing the birth of another affected child. Identifying a de novo genetic variant (a new variant that has not been inherited from parents) in an affected child can help counsel couples about the low risk of recurrence in future offspring. Even the simple fact of having a diagnosis or a name to describe their child’s condition can make a world of difference to families.

There are other benefits as well; genetic test results can confirm diagnoses in clinically borderline cases, offer clues about prognosis, or allow cascade testing in other family members who may also be at risk of a disorder. It may even be able to predict adult-onset disease in currently asymptomatic individuals, thus allowing preventive or
surveillance measures. Detection of somatic genetic variants in a tumour biopsy sample may predict treatment response or resistance.

Pharmacogenetic testing may be able to predict whether a drug will cause side effects or be ineffective, and spare the individual of both by using a reduced dose or an alternative drug. Non-invasive prenatal testing (NIPT) can identify fetal chromosomal abnormalities through a mother's blood sample, significantly increasing the sensitivity of prenatal screening and reducing the number of invasive diagnostic procedures required. Couples can be screened for carrier status prior to conception, which in turn can facilitate pre-implantation genetic diagnosis. Rapid whole genome sequencing with a turnaround time of 50 hours has also been reported in the literature, and has been used to diagnose and manage critically ill neonates in the intensive care setting (see: rapid whole-genome sequencing for genetic disease in NICU).

The list of clinical applications for genetic testing, and demand for those with skills and expertise in these areas, is growing day by day.

Day-to-day responsibilities of a Genetic Pathology Registrar

The day-to-day responsibilities of a genetic pathology registrar involve analysing genetic testing data, interpreting the clinical significance of the data for a patient and family in their clinical context, reporting test findings, and liaising with clinicians for complex or clinically urgent results. While reports can be standardised in many instances, rare genetic variants or specific clinical contexts can warrant extensive searches in the literature and databases for relevant evidence.

This can be one of the most interesting parts of the job, with the need to integrate knowledge of basic genomic sciences, the testing technology used and its limitations, and clinical phenotypes in order to form a professional opinion. Despite the enormous body of genetic literature, uncertainty and ambiguity nevertheless go hand-in-hand with genetic testing; the vastness of the genome and its many possible permutations means that the clinical significance of a particular variant can often remain unclear.

The risks of genetic testing and interpretation

Genetic testing and interpretation is not without significant risk, and making the wrong call or making a mistake in the laboratory can potentially have a devastating impact on patients and families. It may mean the difference between having a second affected child in the family, or of mistakenly terminating an unaffected normal pregnancy. Or, being told that you have a high chance of developing breast cancer in the future, and undergoing an irreversible medical procedure on the basis of an incorrect test result. Results also often have implications not just for the tested individual, but also their family members, reproductive partner, and future offspring.

New disease-associated genes are identified and new testing techniques are invented every day. It’s therefore common for laboratories and their registrars to be perpetually involved in the validation of new tests, which involves establishing that the test works the way it should, that the results correlate with a specific phenotype, and that the
results have utility in a clinical setting. Seeing an assay that you have designed and validated go ‘live’, and provide real answers for patients and their families, is one of the most satisfying parts of the role.

The pros and cons of genetic pathology as a career

Like any job, there are a few downsides. There are few training positions available, and training outside of your home state may be necessary. The small number of trainees means that training can be an isolated affair. More broadly, genetic testing is becoming ubiquitous across many pathology fields, and the role of a genetic pathologist may need to evolve in response to this. There is zero patient contact, and it may be difficult to realise the impact that your work has on a patient or their families.

But contrary to popular belief, it’s not a career for those wishing to shirk social interaction; being able to lead, understand, and communicate with teams of highly trained scientists is an essential part of being a genetic pathologist. This for me is one of the most attractive parts of the job, where a medical practitioner is not merely a solo practitioner, but works closely with a group of individuals over time, and has the opportunity to direct resources, develop processes and work cultures, educate and develop careers, and initiate organisational change and innovation. This for me more than makes up for the lack of patient contact, and arguably gives you the opportunity to affect many more patients than you would as an individual practitioner.

Conclusion

Genetic pathology is an exciting, dynamic field of pathology. It will suit individuals with an analytical mind, who can integrate scientific data within a clinical context, who want to be at the forefront of laboratory and information technology, and are prepared to undertake self-directed learning throughout their career. The types of tests performed, the clinical applications of various tests, and even the role of the genetic pathologist are all likely to evolve in the near future.

What will remain unchanged, however, is the need for individuals who can interpret genetic testing data within a medical context, in a manner that is clinically safe and evidence-based. For those who are interested in this field, I encourage you to read what is available on the website of the Royal College of Pathologists Australia, and speak to laboratory directors and current genetic pathology trainees. It is certainly a road less travelled, but one well worth exploring.

References
