

At medicine's frontier

A REVOLUTION IS TAKING PLACE IN THE FIELD OF GENETICS, AND GENETIC PATHOLOGISTS ARE UNIQUELY POSITIONED TO PLAY A LARGE PART IN IT, WRITES TONY JAMES.

PHOTOGRAPHER: MALCOLM FAIRCLOUGH + JAMES ALCOCK

Genetics is the “new kid on the block” for pathologists. Hereditary aspects of disease have been recognised for centuries, but knowledge about the mechanisms behind inheritance and the way that genes control normal and abnormal biological functions has increased exponentially in the past few decades.

Genetic pathologists are at the forefront of translating basic science into clinical practice that benefits patients. Some knowledge of genetics is now essential for medical practitioners regardless of their speciality, but genetic pathologists are uniquely positioned to combine a detailed understanding of the biology, familiarity with laboratory techniques and an appreciation of the clinical application of their results.

For Dr Melody Caramins, an advanced trainee in molecular genetics at the Prince of Wales Hospital in Sydney, the discipline is intellectually elegant, clinically important and a medical frontier. “It’s been a great career choice – I couldn’t imagine doing anything else,” she says.

Dr Caramins chose genetic pathology after she started training as a surgeon, and then had the chance to look at her career options from a different angle while completing a master’s degree in design.

“Surgery was exciting, but I wondered whether it would be able to maintain its interest,” she says. “My experience with art heightened my awareness of the form and function of the human body. Molecular genetics can explain that form

and function at the most fundamental level.”

Painting is based on just three primary colours, but they can provide an infinite variety of expression. Similarly, genes consist of sequences of just four bases, but this simple code also has the capacity for infinite complexity.

“Developments in genetics are explaining many things we never understood before, in every organ system,” Dr Caramins says. “Genetic pathologists are able to make a diagnosis, provide an answer to a clinical problem and contribute in a very important way to clinical decisions about how patients are treated.”

Dr Caramins is in the fourth year of her five-year training program. The first three years involved working in a genetics diagnostic laboratory at Sydney’s Royal Prince Alfred Hospital. As part of the training program, she is now completing a research project on genetic control of platelet numbers.

These small components of blood are essential in the control of bleeding. Low platelet counts, which can occur in diseases such as leukaemia, sometimes require transfusion, which is not without risk. Understanding the factors that control platelet numbers could potentially lead to new therapies.

Genetic pathology is traditionally divided into molecular genetics and cytogenetics. Molecular genetics is a very modern science. It started with the discovery of the structure of DNA and has

been facilitated by a host of new techniques to amplify or replicate DNA and define the sequence of bases that make up the human genome.

Cytogenetics involves the microscopic analysis of the 23 pairs of human chromosomes. Sophisticated manipulation of cell samples makes it possible to check for physical abnormalities such as additional or missing chromosomes, or translocation of fragments from one chromosome to another.

Cytogenetics has been the basis for prenatal screening procedures using foetal cells obtained by amniocentesis or chorionic villus sampling. Classic anomalies include Down syndrome (most commonly caused by the presence of three instead of two copies of chromosome 21), Turner syndrome (a single X chromosome in a female) or Klinefelter syndrome (two or more X chromosomes in addition to a Y chromosome in males).

Other sub-specialties include biochemical genetics, focussing on inherited disorders of metabolism such as phenylketonuria.

Professor David Ravine and Dr Graeme Suthers both started their genetics careers as paediatricians and had their interest piqued by a need to understand health and disease at their most basic levels.

Professor Ravine is the Foundation Professor of Medical Genetics at the University of Western Australia. His clinical base is within PathWest, while his



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research straddles PathWest and the Laboratory for Medical Genetics at the Western Australia Institute of Medical Research. He was impressed by the potential power of genetics in solving medical problems while completing a Bachelor of Medical Science research project as a medical undergraduate. After training as a paediatrician he worked at the Murdoch Institute and the Royal Melbourne Hospital on inherited polycystic kidney disease. From this clinical vantage point he saw the significance of genetics as a tool in all areas of medicine, not just inherited childhood diseases.

Moving to the Institute of Medical Genetics in Cardiff, he retrained in genetic pathology and, as director of the Medical Genetics Service for Wales, saw how the science could be translated into meaningful clinical practice.

“The United Kingdom has a centralised and co-ordinated health service, and is now well on the way towards implementing the opportunities for clinical practice improvement that genetics provides,” he says. “Genetics is relevant to all areas of medicine: there are interactions between genes and the environment in virtually all disease states. Genetic pathologists need a breadth and depth of knowledge about the scientific basis of genetics that extends beyond that of other specialities.

“They need to understand in detail the genetic basis of disease and be able to apply it fluently to clinical problems. They have to know about the methods of laboratory analysis and how to interpret data in a clinical context, and the managerial aspects of running a laboratory, including appropriate staffing and quality assurance.”

Genetic pathology offers opportunities for increasingly powerful synergies with other specialties within clinical and laboratory medicine. For example, anatomical pathologists are being aided by new molecular techniques to define the mutations involved in cancer tissue. Conversely, histopathology has the potential to enhance greatly genetic testing services for conditions such as hereditary colorectal cancer, hereditary breast cancer and Fragile X syndrome.

The current rapid growth of new gene-based tests, which aid diagnosis, prognosis and therapeutic choices, places laboratory medicine in the centre of clinical applications emerging from the recent expansion of knowledge about the human genome and the genetic abnormalities underpinning many human diseases. “We need a new generation of pathologists who are able to contribute to multidisciplinary clinical teams,” he says. “Clinicians are focussed on clinical problems, while genetic pathologists have the training and experience to bridge across specialties and provide helpful solutions”.

“We also need to keep up with colossal change. The technology is moving very quickly and is creating opportunities to centralise services, but this needs to be thought through carefully as it also brings a risk of undermining invaluable direct interactions between the laboratory and clinicians.”

Education of the medical profession and maintaining networks between clinicians is an essential leadership role for genetic pathologists. One example is the genetics of cardiovascular disease, a rapidly developing field. “We need to empower cardiologists, general physicians and GPs to deliver the benefits of new

genetic knowledge,” Professor Ravine says.

It’s now possible to test for a number of conditions that are dominantly inherited, including the connective tissue disorder Marfan’s syndrome and hereditary arrhythmias.

“The process of translating new genetic knowledge into clinical practice has only just begun, but it will become a huge part of medicine,” Professor Ravine says.

Identifying a genetic susceptibility to disease in an individual raises questions of ethics and privacy, but clinicians are faced with the reality of interpreting the information with patients, defining the risks, developing strategies for prevention or treatment and discussing the significance of the findings for other family members. In a condition such as Huntington’s disease, the challenges might seem overwhelming.

This disease is genetically dominant and leads to severe neurodegenerative changes, with jerky, involuntary movement and behavioural change that usually becomes apparent in middle age. Patients may have children of their own by the time of diagnosis, and the children will have a one in four chance of developing the disease themselves.

As a clinical geneticist, Dr Graeme Suthers has had to negotiate a path through such challenges. “I’d advise the children of someone with Huntington’s disease to ‘hasten slowly’,” he says. “They need to understand precisely why they are having a genetic test and consider all the possible options.”

Finding they did not have the gene would be reassuring and allow them to lead a normal life, but if they did have the gene they would be faced with the



Professor David Ravine is the Foundation Professor of Medical Genetics at the University of Western Australia

knowledge that they would almost certainly develop the disease. However, there is the prospect of substantially reducing the prevalence of the illness if people with the mutation choose not to have children.

“A genetic diagnosis of Huntington’s disease also has implications for the health-care system,” Dr Suthers says. “There is no effective treatment, but people need long-term support and follow-up. Continuity of care can be invaluable. For example, senior nurses in medical genetics units often take on the role of case managers for patients and their families, but we need the resources to be able to provide the services patients deserve.”

Dr Suthers trained as a clinical geneticist after being intrigued by a young patient with homocystinuria – an inherited deficit of amino acid metabolism – he saw as a paediatrics trainee. Following a PhD in Fragile X syndrome at the Women’s and Children’s Hospital in Adelaide, research at Oxford University and further clinical work, he also qualified as a genetic pathologist and is now director of the South Australian Familial Cancer Service.

The service assists patients with a strong inherited susceptibility to cancer to

realise that the disease might not be entirely “out of the blue” and the diagnosis might have implications for their families. “The unit of care in clinical genetics is the family rather than the individual patient,” he says. “We need to understand the biology of the disease and the role of genetic testing, and communicate this in a useful way to other family members.”

A vital point is that genetic susceptibility does not mean cancer is inevitable, and there are continuing improvements in prevention and treatment. “In familial bowel cancer, for example, colonoscopy is a superb tool for screening relatives at risk and removing polyps before they become malignant. In theory, no one should die from the disease,” he says. “The average life expectancy in families who adopt screening is increased by 15-20 years – a remarkable achievement.”

A high genetic risk of breast cancer is another area that requires extensive education and counselling of affected families. While high-risk genes such as BRCA1 account for a small proportion of all breast cancer cases, a woman with the gene might have a lifetime risk as high as 80 per cent and could consider prophylactic mastectomy.

Genetic pathologists work closely with the multidisciplinary team that advises the patient and family. If patients give consent, Dr Suthers’ unit writes to relatives to tell them about the situation and suggests they contact either their GPs or the unit. It seems only about one in three take up the offer, perhaps reflecting a continuing fear of cancer, a denial of risk or a lack of understanding about the scope for prevention.

Developments in genetics mean that the amount of raw data now available exceeds the capacity of scientists and clinicians to handle it. “We need to distinguish very carefully between data such as sequences of bases in the genetic code and information that is applicable to clinical practice,” Dr Suthers says. “Perhaps most importantly, we need wisdom to use it properly.”

He is concerned that the health system has not recognised the need to provide more resources to take advantage of the genetic revolution, including adequate numbers of doctors with appropriate skills and experience. Currently there are only four training positions funded in dedicated genetic pathology in Australasia (far short of requirements) while there are 17 laboratories that could provide training if funding was available. 🔥