



## Genomics in general practice

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Marie, a 25-year-old woman comes to see her GP for her routine pap smear in a country town in rural South Australia. In discussion with the GP she mentions that two of her aunts, her dad's sisters, had breast cancer at the ages of 39 and 41 years respectively. She has heard about 'the breast cancer gene' from the experience of the famous actor Angelina Jolie and she wonders if it is possible that she also has it. She is otherwise fit and healthy, hasn't had any breast symptoms and asks the GP if she should be having some further tests to see if she has an increased risk of breast cancer. The GP explains that her family history does put her in a higher risk category for breast cancer. Given her history, the GP suggests referral to a familial cancer clinic to further explore her risk of breast cancer.

In recent decades, there has been an extraordinary technological revolution underway in which the very building blocks of life, our genetic codes, are increasingly well understood and even manipulated by rapidly advancing scientific techniques. Meanwhile, the humble local general practitioner (GP) is still the backbone of most health systems around the world, a trusted source of advice and health care in the community, and is likely to play a growing role in communicating the significance of new genetic technologies. Increasingly, GPs will be asked to order and interpret genetic tests for their patients (Blashki et al., 2014).

There are lots of good reasons that GPs can play a role in integrating what has been termed genomic medicine at a

community level. GPs often know patients well and their extended families well, and are usually the main point of patient care over many years. They are also, of course, scientifically trained, and a great deal of their work is dedicated to preventing all sorts of diseases.

At the same time, clearly GPs are not genetic specialists and it's fair to say that the ethical and technical issues involved with genetic testing in many instances may be beyond the expertise of GPs. It could also be argued that the busy general practice setting may not be the best place to try to sort out highly complex genetic issues. For example, some genetic testing, even more than regular pathology testing, may require a detailed informed consent process with the patient. The stakes are high in terms of the potential to cause patient distress, to identify issues that may have implications for the broader family; genetic testing may also introduce insurance issues that need to be considered prior to embarking on testing.

In this chapter, we seek to outline some of the genetic issues that are already part of daily discussions in GP consultations, and we explore some of the emerging genetic issues that are likely to become pertinent in the coming years. We provide an overview of the common diseases and clinical scenarios that may prompt genetic testing in a general practice setting, or may result in your GP referring you to a specialist genetic service. We also look at the increasing range of pre-conception testing that is available. Finally, we examine some of the genetic testing that is being made available directly to the public and look at the pros and cons of this approach.

## **Genetics and disease prevention**

GPs spend a lot of their time trying to detect and prevent early problems such as cancers and cardiovascular diseases so that

they can be dealt with before they become more serious. Much of a GP's work is spent checking people's blood pressure, helping them to stop smoking, encouraging them to exercise and eat healthily, and to have regular check-ups for things like cholesterol, blood sugar, pap smears and skin checks as well as a variety of other preventive check-ups throughout the life course. Indeed, the Royal Australian College of General Practitioners, the peak professional body for GPs in Australia, produces a wonderful resource called the *Red Book* (RACGP, 2016), which lists a systematic approach to undertaking preventive activities at each stage of life. GPs are very much in the business of preventing disease whether there is a genetic contribution or not.

As our understanding of genomic medicine improves, GPs will focus their preventive work on individuals who are at increased risk based on their genetic background. So, before considering any of the new fancy genetic tests, it's important to remember that so much can be gleaned by the GP simply discussing with you your own family history. This includes the health history of not only your parents, but also grandparents, uncles, aunts, children, nieces, nephews and grandchildren. Based on the risks identified, the GP is in a much better position to assess your risk of developing a particular condition. For example, if you have a first-degree relative who had bowel cancer under the age of 55 years, the GP knows that you have a 3 to 6 times increased risk of having bowel cancer and will recommend that you undertake early bowel screening by having a colonoscopy test with a gastroenterologist or surgeon. Similarly, if you have a strong family history of heart disease or are found to have what geneticists call 'familial hypercholesterolemia', your GP is going to be very vigilant at helping you lower your lipid levels and reducing all your cardiovascular risk factors such as managing blood pressure, encouraging you to

stop smoking, checking for and managing diabetes and encouraging regular exercise. Or, consider the case of breast cancer risk, where identification of variants in certain genes — for example, one of the *BRCA* genes — may warrant discussion about prophylactic mastectomy or salpingo-oophorectomy (removal of the ovaries and Fallopian tubes). Recently, a structured survey has been developed that can assist to identify a family's genetic risks based on their family history of certain common conditions. It is called the Family Health Questionnaire (Emery et al., 2014) and is available online in the RACGP's *Red Book*.

One common condition, familial hypercholesterolemia (FH), affects approximately one in 500 people, runs in families and results in a very high cholesterol. It leads to an excess of a 'bad' type of cholesterol called LDLs, which leads to high rates of early onset heart disease. Doctors will suspect this condition in a family where members have experienced heart disease below the age of 50 years. Sometimes a red flag for the doctor will be the presence of some classic physical signs such as fatty lesions around the eyelids called xanthelasma, or subtle rings around the irises of the eye called corneal arcus, or even a fatty build-up in the tendons called xanthomata. Often, the GP picks up the high cholesterol on a routine blood test, and a characteristic pattern for FH is that the other blood fats apart from the LDL level are normal. Variants in two genes are responsible for most of the cases of this condition, the *LDLR* gene and *APOB* gene, though there are other genes sometimes involved. Treatments include dietary advice, especially a diet high in plant sterols and stanols such as vegetable oils and nuts. The cholesterol lowering medications called statins are also very helpful to bring down levels and sometimes the doctor will suggest other lipid-lowering agents. The GP will be also be focused on reduc-

ing any other cardiovascular risks, and will talk to the patient about whether other family members should consider testing.

Another common and important gene that patients are understandably worried about is the *BRCA* gene, which is associated with breast cancer. While women in the general community have around a 12% lifetime risk of breast cancer, women with a mutation of either *BRCA1* or *BRCA2* genetic variant have a lifetime risk breast cancer of 30–60%, and the lifetime risk of ovarian cancer is in the range of 10–40%. Notwithstanding, it is worth keeping in mind that most cases of breast cancers don't involve the *BRCA* gene.

Patients of course want to know if they should be tested for variants in one of the *BRCA* genes, such as in the case of the patient Maria described at the start of this chapter. Indeed, genetic clinics in Australia saw a surge in patients wanting to be tested after the high profile story of Angelia Jolie's experience with the *BRCA1* gene. Guidelines for who should be tested are complex, and your GP will ask the patient questions to help determine their risk: the number of relatives who have had breast cancer and the age at which they were diagnosed, whether they were on the same side of the family, whether they had breast cancer in both breasts, or perhaps also had ovarian or other cancers. Other considerations will be whether a relative has an identifiable *BRCA* gene mutating already, whether perhaps a male relative has had breast cancer, and some ethnic groups are more at risk such as Ashkenazi Jews. The sensitive decision of whether to test for a *BRCA* gene mutation should be made with a specialist in familial cancer — for example, a clinical geneticist or breast specialist — and there are detailed guidelines available about who ought to consider testing (Cancer Australia, n.d.).

If the *BRCA* gene test is positive, it will be managed in conjunction with a specialist. Patients will be advised about the

inheritance of the mutation, which is 'autosomal dominant'. This means offspring have a 50% chance of having the same variant in the *BRCA* gene and being at increased risk of several cancers. The range of possible treatment options that will be discussed will include hormonal treatments to reduce oestrogen levels, additional cancer screening such as MRI scans of their breasts, through to surgical options such as prophylactic mastectomy, and bilateral salpingo-oophorectomy.

### Its complicated

While it is true that many diseases do 'run in families', there is an important caveat to this, for the many diseases that are inherited in what we call an 'autosomal recessive' pattern. This pattern of inheritance is described in more detail in the introductory chapter in this book, but the key point about autosomal recessive diseases is that people only experience the disease when they get two copies of the gene variant, one from each parent. For autosomal recessive genetic diseases, there is usually no obvious family history of the condition running through the generations.

Haemochromatosis is one example of an autosomal recessive disease, and is one of the most common genetic diseases with one in 200 Australians having a genetic predisposition. It is a disease in which the body stores too much iron and can result in damaging organs such as the liver, the heart, the pancreas and the pituitary gland. Haemochromatosis can result in symptoms that are very non-specific initially, and so in many cases the diagnosis may not be made. It usually presents with a constellation of symptoms: fatigue, weakness, diabetes, darkening of the skin, menstrual or sexual dysfunction, liver dysfunction and joint pains, especially in the fingers. Usually, your doctor will check your iron levels, particularly the body's storage of iron, with a ferritin test, which usually comes back high. It is well

worth diagnosing as much can be done to reduce the long-term complications, including donating blood regularly to reduce iron levels, avoiding iron and vitamin C supplements, and protecting the liver from other insults such as alcohol and viral infections.

In this short book chapter, we have not covered the literally thousands of illnesses that have a significant genetic component. We have focused on a few common conditions that come up in general practice. But, of course, there are many other conditions affected by genetics, such as skin diseases, diabetes, blood diseases and neurological diseases, to name a few. We now discuss how genetics has become an important part of preconception planning and outline some tests to consider.

### **Preconception testing**

Before starting a family, it is well worth a couple having a preconception consultation with the GP. There are literally thousands of recessively inherited genetic conditions and each individual carries some of these genetic variants without them having any effect on their health. However, the problem arises when both parents have the same genetic variant, which means that there is a one in four chance of their child having two copies of the faulty gene and thus developing the disease. Some of these genes are very rare, but some are relatively common such as thalassemia and cystic fibrosis, which are discussed below.

Historically, the choice about which preconception tests to offer a couple has been largely guided by their ethnic background; for example, testing for thalassemia has been suggested for people of South East Asian or southern Mediterranean background, or Tay Sachs disease for people of Ashkenazi Jewish origin. However, because these tests are becoming cheaper, there has been a shift towards what have

been termed preconception screening panels. These panels test literally hundreds of genes in one blood or cheek-brush test. What they are looking for is whether both partners in a couple have the same genetic abnormality in a particular recessively inherited condition. This allows couples to decide how they want to plan a family, what testing they might consider, and whether they might want to use one of the assisted reproductive technologies such as Preimplantation Genetic Diagnosis (PGD; see Chapter 8).

Thalassaemia is the most common inherited blood disease in the world. There are two types, alpha thalassaemia, which occurs mainly in Asia and parts of Africa, and beta thalassaemia which occurs mainly in Mediterranean populations. Many people have a single gene fault and are called carriers, and generally do not experience any problems from this. However, a disease called thalassaemia major results when two carriers have a child together and the child inherits both copies of the faulty thalassaemia gene. In this situation, the baby experiences severe problems such as anaemia (which is a low red blood cell blood count), failure to grow and, without treatment, can die. Treatment is lifelong, involving frequent blood transfusions and medicines to help reduce the extra iron that blood transfusions introduce to the body. Therefore, it is worthwhile for couples who are considering having a family, especially when one of the couple is known to be a carrier or from a higher risk ethnic background, to consider testing for thalassaemia carrier status.

### *Cystic fibrosis*

Another important autosomal recessive disease is cystic fibrosis, which occurs in one in 2,500 births in Australia. It causes serious abnormalities in the respiratory, digestive and reproductive systems. People who have cystic fibrosis often struggle with ongoing respiratory symptoms of recurrent chest infections and

gastrointestinal symptoms. Treatment involves regular chest physiotherapy, antibiotics, enzyme and dietary supplements, and regular exercise. People affected unfortunately have a reduced life expectancy usually because of the respiratory problems. One in 25 people of European descent are carriers of one faulty copy of the cystic fibrosis gene, which causes no problem for those individuals. However, if both parents have a mutation in one copy of the gene, there is a one in four chance they will have an affected child. So this is a simple test that is worth considering to see if you and/or your partner carry a faulty copy of the cystic fibrosis gene.

Tay-Sachs disease is another serious genetic disorder, which occurs particularly in Ashkenazi Jews and French-Canadians. Again, having a single gene fault for the disease (i.e. being a carrier) is very common, but the problem arises when a double dose of the gene fault is inherited, one from the mother and one from the father. The prognosis is very poor for such individuals, with serious neurological problems and sadly with death usually around the age of three or four years of age. Testing for faults in this gene among at-risk couples before starting a family is most worthwhile and is becoming more available in schools and in the community in Australia to allow couples to make informed reproductive choices.

Another genetic condition that couples might consider pre-conception is fragile X syndrome, a genetic problem affecting about one in 6,000 births, more commonly boys than girls. It causes a range of intellectual and development disabilities, behavioural and communication problems, and often the child experiences autism-like symptoms. The genetics of this condition is complex and different to the simple autosomal inherited diseases we have discussed thus far. The fragile X syndrome is caused by an alteration to *FMR1* gene on the X chromosome

(women have two X chromosomes, men have one X and one Y). The change in the gene is an enlargement of one region of the *FMR-1* gene, which is a gene that is essential for normal brain functioning. Like all genes, the *FMR1* gene code is made up of base pairs that are labelled A, C, G and T. In the *FMR1* gene there is a repeating pattern, CGG, which varies in length from one person to another. The normal range of repeats is less than 45 repeats, an intermediate range is 45–54 repeats and the premutation range is 55–200 repeats. The full mutation occurs with over 200 repeats. Women who have an X chromosome in the premutation range of CGG repeats are at risk of having a child, male or female, with the premutation (i.e. a carrier) or the full mutation (i.e. an affected child).

### Tests during pregnancy

In the previous section, we have been discussing tests that might be done before conception; we now explore some genetic tests that can be done during pregnancy. The two tests that we explain here are the Maternal Serum Screening Test (MSST) and the more recently developed Non-Invasive Prenatal Testing (NIPT), which may well replace the MSST in coming years.

#### *Maternal serum screening*

Your doctor will offer you a test called the Maternal Serum Screening Test, which involves a blood test to measure levels of various proteins. The results of the MSST are usually combined with an ultrasound ‘nuchal translucency’ test to assess the chance of having a child affected with a chromosomal abnormality including trisomy 21 or trisomy 18. It is important to realise that these tests only provide an estimate of risk. If an increased risk result occurs, parents can decide whether they want to go on to have a more invasive test such as an amniocentesis that will provide a definitive diagnosis.

### *Non-Invasive Prenatal Test*

More recently, an alternative to the MSST is being offered to parents, called a Non-Invasive Prenatal Test (NIPT), usually when a woman is about 12 weeks pregnant. It involves only a blood test and is more accurate than the MSST at detecting chromosomal abnormalities such as trisomy 21, though at this stage, it is also costlier to parents. The test identifies small fragments of the fetal DNA in the bloodstream to reconstruct a picture of the baby's genetics. It seems likely that this sort of testing is going to become more widespread and cheaper over time. One concern among doctors is that it may discourage women from having the ultrasound that they would have had with the MSST, which also provides an opportunity to pick up structural abnormalities — for example, in the spine or heart — which are not detectable just on a blood test.

### **Caveat emptor**

With all the excitement about these powerful new medical tools, there has been a rush from the health industry to offer a range of new genetic tests directly to the public. This includes personal genomics, nutrigenomics and pharmacogenetics. As with any new technologies, some caution is required to make sure that the tests are appropriate, accurate, based on scientific evidence, properly interpreted and that patients receive sufficient support to understand what they mean for their health. Below we briefly discuss two key examples, the *MTHFR* gene test and pharmacogenomics.

### *MTHFR*

Testing for faults in the *MTHFR* gene has become a very popular yet controversial test requested by patients and promoted by some alternative health practitioners in discussions about tailored nutritional advice including folic acid supplementation

(Long & Goldblatt, 2016). The acronym stands for methylenetetrahydrofolate, and it refers to gene testing for an enzyme involved with the metabolism of the vitamins folate and homocysteine. The medical profession is largely of the view that these normal variations in the gene (called polymorphisms), which are present in a high proportion of the population, are probably not significant in increasing the risk of disease. Despite early studies suggesting that common variations in *MTHFR* may increase risk of several conditions, including autism, schizophrenia, cardiovascular disease, poor pregnancy outcomes and colorectal cancer, more recent studies have not confirmed these findings. Nevertheless, some alternative health practitioners and patients have become very enthusiastic about this test; for example, to suggest increase consumption of foods or supplements rich in folic acid. But the current consensus among the medical profession is that many of the claims about this genetic test are exaggerated and to date, testing in well individuals is not supported by evidence in studies. In our opinion, it is more important that we all try to increase our consumption of vegetables rich in folic acid, such as green leafy vegetables, than spending money on the *MTHFR* genetic test or expensive vitamin supplements.

### *Pharmacogenetics*

Understanding how different individuals respond to various medications is potentially a very valuable outcome of our better understanding of genetics. There are common genetic variants that alter how our body metabolises widely used medications. These might put you at higher risk of certain side effects, or of receiving an inadequate dose of the drug. The new field of pharmacogenetics promises to assist individuals and their health providers to better understand what types and dosages of various medications are appropriate for individuals. For

some situations, pharmacogenetic testing may well be helpful — for example, in assessing the best dose of a blood-thinning medication called warfarin, or to take another example, titrating the dose of an antiepileptic drug called Carbamazepine. At this stage, the usefulness of these tests for prescribing a wider range of medicines is still being researched, but it is likely that in the future this will become a common genetic test used by doctors.

Genomics is a rapidly developing field and promises to revolutionise the way that health care is provided, including by the general practitioner. In this chapter, we have outlined some of the key issues and flagged some emerging issues too. It seems certain that general practice of the future will look very different in the coming decades as these technologies are integrated into healthcare.

## References

- Blashki, G., Metcalfe, S., & Emery, J. (2014). Genetics in general practice. *Australian Family Physician*, *43*, 428–431.
- Cancer Australia. (n.d.). Genetic testing for breast/ovarian risk 2017. Retrieved from <https://canceraustralia.gov.au/clinical-best-practice/gynaecological-cancers/familial-risk-assessment-frabc/genetic-testing>
- Emery, J.D., Reid, G., Prevost, A.T., Ravine, D., & Walter, F.M. (2014). Development and validation of a family history screening questionnaire in Australian primary care. *Annals of Family Medicine*, *12*, 241–249.
- Long, S., & Goldblatt, J. (2016). MTHFR genetic testing: Controversy and clinical implications. *Australian Family Physician*, *45*, 237–240.
- Royal Australian College of General Practitioners (RACGP). (2016). *Guidelines for Preventive Activities in General Practice*. Retrieved from <http://www.racgp.org.au/your-practice/guidelines/redbook/>