TMLPathology
Tasmanian Medical Laboratories
# Newsletter

INSIDE THIS ISSUE:



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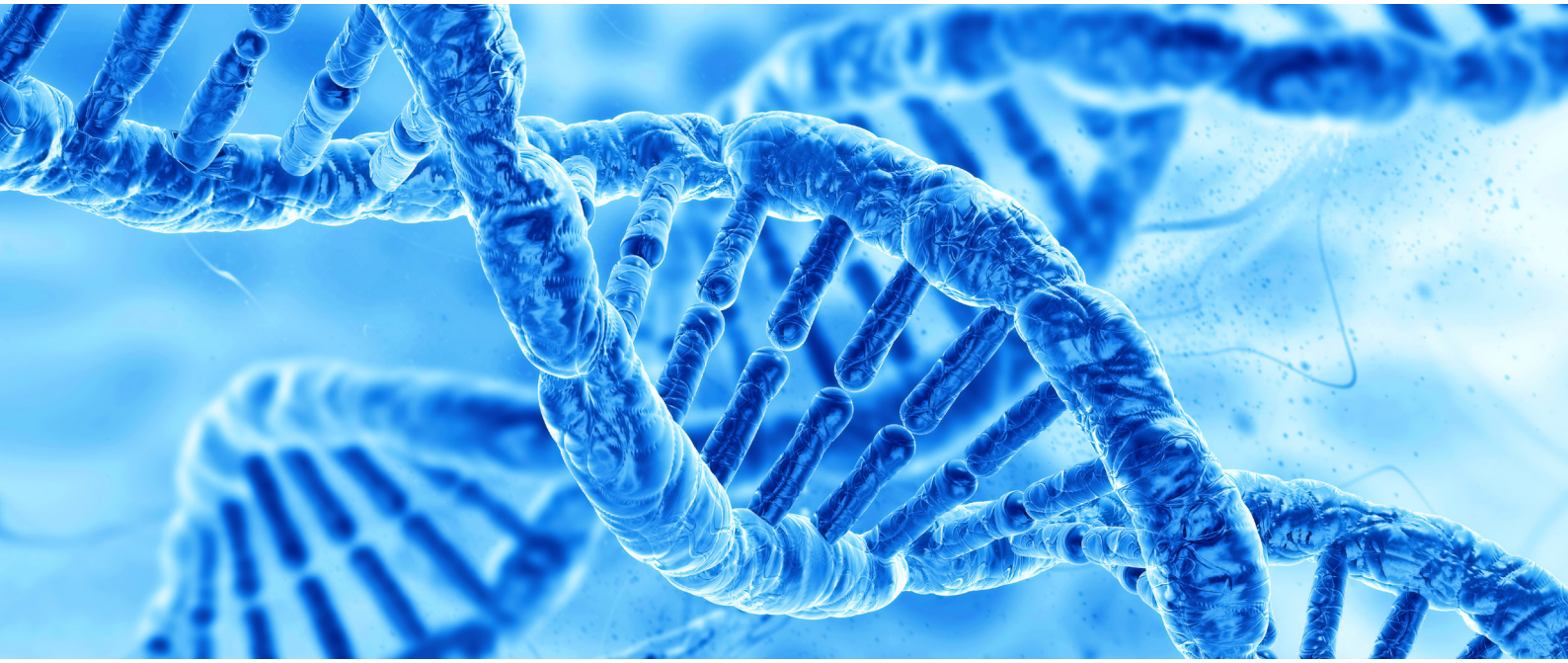

## Genomics in General Practice

### Dr Melody Caramins

Genomic medicine is the use of genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making). Genetic and genomic testing have for many years been part of mainstream diagnostic testing for specialists, but increasingly are being incorporated into everyday patient care in general practice.

The types of currently available genetic tests in human health are most usefully understood based on the affected clinical group and presentation (e.g. oncology, haematology, reproductive medicine, paediatrics), and the amount of genetic material studied and tested. Broadly speaking, genetic conditions are due to genetic variants, also known as mutations, that are either inherited, such as thalassaemia (known as germline mutations), or are acquired (known as somatic mutations). Acquired mutations often occur when there is rapid cell replication and division e.g. in cancer or during conception, leading to specific mutations in malignancies which may indicate appropriate treatments, or causing conditions such as Down syndrome in a fetus.

Genetics and genomics have a role in human health from pre-birth to death. In the diagnostic setting, this involves the detection of pathogenic genetic variation, to determine:

- Risk of future disease (e.g. carrier screening, predictive testing, PGS/D)
- Diagnose and classify current disease (e.g. oncology, adult and paediatric syndromes)
- Determine treatment (e.g. companion diagnostics, pharmacogenetics)

Therefore, the detection of pathogenic genetic variation in an affected person can have a multidimensional impact, by providing a molecular diagnosis and potentially negating further unnecessary tests, procedures and appointments; changing patient management plans; and, suggesting prognosis and/or treatment options. This impact extends to implications for other family members if testing for inherited (rather than acquired) genetic variation.

**>>> CONTINUED OVERLEAF**

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Some forms of testing may be associated with complex issues related to the potential for the identification of results with no clear significance, as well as to various ethical, legal and social issues. The probability of these issues is higher with some tests (e.g. predictive testing for Huntington disease or inherited cancer) and benefits and harms must be balanced by the provision of non-directive counselling and informed consent.

There are a number of clinical settings where genetic testing is more relevant. The following is a list of some of these settings, including tests that are more commonly encountered by GPs:

- Reproductive medicine – preconception carrier screening, non-invasive prenatal testing (NIPT), diagnosis of genetic causes for infertility or recurrent miscarriage.
- Paediatric disease: diagnosis of developmental delay – sometimes through specific mutation/gene testing (e.g. Fragile X), or through genomic tests, such as chromosome testing by microarray.
- Pharmacogenetic/pharmacogenomics tests. These have implications for treatment choice in neurology, pain management, oncology, and in the prediction of adverse drug reactions.
- Adult medicine – specific mutation/gene testing for inherited diseases of adult onset (many neurodegenerative disorders, familial cancer syndromes), or for acquired disorders in oncology and haemato-oncology. These tests are generally ordered by specialists, but GPs will be familiar with them (e.g. BCR/ABL translocation testing in chronic myeloid leukaemia (CML), predictive testing for Lynch Syndrome, and genetic testing for Huntington Disease).

Currently, very few genetic tests are funded through Medicare in Australia. Tests are accessed by patients in a variety of ways, although all Australian accredited laboratories are required to perform testing only in the context of a medical consultation – be this general or specialist medical practitioners.

GPs most often come into contact with genetic testing in the context of reproductive health, with NIPT and pre-conception carrier screening being most frequently encountered.

Carrier screening involves testing individuals or couples, ideally prior to pregnancy, to determine if they have a genetic variant that may affect their chance of having a child with a genetic condition. This testing has received increasing media coverage of late, due to announcement in February 2018 by the Minister for Health, Greg Hunt, indicating that the government intends to invest tens of millions of dollars to improving access to this testing for prospective parents. Clinical guidelines recommend testing for three of the more common conditions as a basic screen:

- Cystic Fibrosis, which has a carrier frequency in Australia ~1/25
- Fragile X Syndrome, with a carrier frequency in Australia ~1/150
- Spinal Muscular Atrophy, with a carrier frequency in Australia ~1/40

These conditions have been recommended because they are common, severe, and the tests to detect them use mature techniques which are robust, specific and sensitive. Most of the time, a family history will not be informative, due to the inheritance patterns and the rarity of these conditions individually. And yet, together, the combined collective carrier rate for these three disorders in the Australian population is 5%, or 1/20; with the combined affected pregnancy rate in Australia from these three disorders being equivalent to the population risk of Down syndrome.

Testing for carrier screening should ideally be discussed with patients and performed by GPs during the preconception period, in order to have the most time to deal with all possible testing outcomes. The recommended testing pathway is to initially test the female partner, and to only test her partner if she is found to be a carrier. If the couple are shown to be carriers for any of the conditions, then genetic counselling is recommended so that they can accurately discuss their risk, as well as get detailed information about all their reproductive options.

## TAKE HOME MESSAGES:

- Genetic and genomic testing is increasingly part of the landscape of testing in general practice, particularly in the reproductive health setting.
- GPs should discuss the option of carrier screening for common genetic disorders (SMA, Fragile X, Cystic fibrosis) as part of preconception planning with their patient;
- GPs ordering testing should ideally do this prior to pregnancy, with the female partner undergoing carrier screening first. Her partner should be tested if she is found to be a carrier of a serious genetic disorder.
- Genetic counselling is recommended to assist couples to help understand their risks after testing, and to enable them to make informed reproductive choices

## FURTHER INFORMATION

For further information, please refer to the RACGP Genomics in General Practice publication at

**www.racgp.org.au/your-practice/guidelines/genomics**

# Fragile X

Dr Melody Caramins

## WHAT IS FRAGILE X?

Fragile X syndrome is the second most common genetic cause of intellectual disability after Down syndrome. It is a syndrome characterised by a pattern of physical, behavioural and/or intellectual signs and symptoms, which together describe the features of this condition

Fragile X syndrome is caused by the expansion of three DNA letters – CCG – (this is also known as a DNA triplet), occurring near a gene called the FMR-1 gene (Fragile X Mental Retardation), which is on the X chromosome. The number of times that the 'CGG' triplet is repeated creates different lengths of the repeat sequence and contributes to different presentations. The syndrome is an example of X-linked inheritance, where the disease presents differently in men and women, as men have one copy of the gene (and one X chromosome) and women have two copies (and two X chromosomes).

The differing CGG triplet repeat lengths are categorised as follows:

- **A short repeat sequence** is seen in most people, and is considered the "normal" length. The 'CGG' triplet is repeated between 6 and 54 times; the repeat numbers are variable in different families, with the most commonly seen repeat length being about 30. A high normal repeat length (between 44-54 repeats), is also known as "the grey zone". These repeat lengths were not thought to be associated with any clinical features. More recent studies suggest this may not always be the case, although reports have been inconsistent and research in this area continues.
- **A medium repeat sequence**, known as a pre-mutation, is seen in some men and women where the 'CGG' triplet is repeated between about 55 and 200 times. People with a pre-mutation are not affected intellectually, although they are at higher risk of having neurological or reproductive sequelae, such as Fragile X Tremor/Ataxia Syndrome (FXTAS), and Premature Ovarian Insufficiency (POI). FXTAS is a progressive neurological condition which generally develops after the age of 50, with increasing risk with age. The risk of developing FXTAS in men with pre-mutations is approximately 50% by the time they reach 80. The risk of premature ovarian failure and early menopause for women who carry a pre-mutation is ~20%. In addition to this risk, pre-mutation carriers are also at risk of having children with Fragile X Syndrome, and should always be referred for genetic counselling with a qualified professional.
- **A long repeat sequence**, also called a full mutation, is where the 'CGG' triplet is repeated more than 200 times. This inactivates the FMR-1 gene, leading to Fragile X Syndrome. Males will generally be more severely affected and have the following features, which may vary in severity: Developmental delay, behavioural/emotional problems, defining physical characteristics such as large ears and a long face, and other medical conditions such as epilepsy. In females, due to the second "normal length" copy of the FMR-1 gene, features are much milder, but may include mild intellectual disability (up to 60%), as well as some emotional or behavioural disturbances.

Delayed diagnosis is common, with many individuals not being diagnosed until school age or later. It has been estimated that in 50% of families, by the time a child is diagnosed, the family has already had a second affected child.

## HOW COMMON IS FRAGILE X?

The prevalence of the Fragile X pre-mutation is more common, occurring in one in 800 males, and more often in females, with one in 150 in the general population being at risk of having a child with the full mutation. The estimated prevalence of individuals with the full mutation is about one in 3600 males and one in 4000–6000 females.

## TESTING: WHEN, HOW, AND WHAT TO DO ABOUT RESULTS

Fragile X testing should be considered/offered in the following clinical situations:

Diagnostic testing should be offered to patients who have any of the symptoms consistent with Fragile X; any individual, male or female, of any age with intellectual disability, developmental delay, or learning disability and features of FXS including anxiety, ADHD or autism spectrum disorder. Additionally, adult patients with ataxia, or women with premature ovarian insufficiency should also be tested. In all these patients, testing is funded by Medicare, and clinical details should be provided on the request form.

Cascade testing of at-risk relatives should also be offered to asymptomatic relatives who have a family member with an FMR-1 mutation. This testing is also rebated under Medicare.

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Carrier screening, the option of testing for carrier status for Fragile X has been recommended by RANZCOG for all women prior to, or early in pregnancy, in order to provide the widest range of family planning options. Knowledge of carrier status offers the full spectrum of reproductive options, including the choice of becoming pregnant naturally (with or without testing in pregnancy), adoption, or using assisted reproduction techniques including egg or embryo donation and pre-implantation genetic embryo testing.

Testing for carrier status where there is no family history of Fragile X is not funded by Medicare. Carrier screening can be undertaken for Fragile X only, or can be combined with screening for other common genetic disorders (such as cystic fibrosis and spinal muscular atrophy).

Pre-implantation or prenatal testing involves testing of the embryo or fetus of women who are carriers of a Fragile X mutation (either a pre-mutation or a full mutation). This testing is generally requested in a hospital or IVF setting by a specialist team, although GPs should be aware of these options and a discussion around them should be part of genetic counselling for women who are found to be carriers.

The pathology request should indicate 'DNA testing for Fragile X syndrome', and any relevant clinical and family history. In addition, any individual with developmental disability who has not previously been fully assessed should also be tested by 'chromosome analysis by genome-wide microarray'. This test detects other, chromosomal causes of developmental delay.

This test does not detect Fragile X syndrome, although it may detect other causes of developmental and intellectual delay when being assessed for the first time.

Fragile X is an inherited condition, likely to affect multiple family members. GPs should identify all at-risk patients in a family using genetic testing. This especially applies to females of child-bearing age, who will need to know their carrier status in order to restore reproductive confidence and choice in decisions about future pregnancies.
As indicated above, genetic counselling is strongly recommended for patients whose results indicate a longer than normal triplet repeat length.

## TAKE HOME MESSAGES

- Fragile X is the most common known inherited cause of developmental disability.
- Presenting features can include anxiety and autism spectrum disorder.
- Although males and females of all ages can be affected, in females the presenting symptoms are often attenuated by the presence of a second gene, on the other X chromosome, with a normal length CGG repeat.
- Long expansions (full mutations) of the CGG triplet repeat are associated with Fragile X syndrome, whereas shorter expansions (pre-mutations) are associated with FXTAS and POI, and a risk of having children affected with Fragile X syndrome or associated conditions.
- Ensure DNA testing for Fragile X is included in assessment of all cases of developmental disability and autism.
- Genetic counselling is recommended for all patients who are found to carry a longer than normal length triplet repeat.

CLINICAL DATA

## INFECTIOUS DISEASES REPORT: MARCH 2018

For historical clinical data please contact **enquiries@tmlpath.com.au**

| ORGANISM | MARCH | FEBRUARY | JANUARY | TOTAL |
|---|---|---|---|---|
| Bordetella pertussis | 1 | | 1 | 2 |
| Chlamydia trachomatis, not typed | 7 | 8 | 3 | 18 |
| Cytomegalovirus (CMV) | 2 | | 4 | 6 |
| Epstein-Barr virus (EBV) | 5 | | 2 | 7 |
| Hepatitis C virus | 4 | 3 | | 7 |
| Herpes simplex Type 1 | 3 | 5 | 4 | 12 |
| Herpes simplex Type 2 | 2 | | | 2 |
| Influenza A virus | 2 | | | 2 |
| Neisseria gonorrhoeae | 1 | | | 1 |
| Rhinovirus (all types) | 2 | | | 2 |
| Streptococcus Group A | 2 | | | 2 |
| Varicella Zoster virus | 3 | | | 3 |
| TOTAL | 34 | 16 | 14 | 64 |