

Thinking and motor skills in people with the fragile X premutation

There is a growing interest in the relationship between inherited disorders and dementia. Our health care systems need to find the best ways to care for the unique needs of people who would otherwise feel isolated and poorly understood. In this article, **Julian Trollor** and **Rachael Birch** provide an update on findings from an Australian study into fragile X-associated tremor ataxia syndrome (FXTAS), one of the most common inherited causes of dementia and movement disorder in mid-life

The Fragile X Mental Retardation 1 (*FMRI*) gene is present in all of us, but is expanded in length in some people. The length of expansion of the gene determines its effect on health. If the gene expansion is small, it functions well and has no obvious effects on health. If the gene is considerably expanded, it results in fragile X syndrome, the most common inherited cause of intellectual disability (Verkerk *et al* 1991). Individuals who have only a moderate expansion in their gene (known as a 'premutation') are referred to as carriers. Premutation expansions of the *FMRI* gene are relatively common, being found in approximately 1 in 209 females and 1 in 430 males in the general population (Tassone *et al* 2012).

It was previously thought that there were no negative health effects associated with the *FMRI* premutation. However, it is now known that carriers may experience specific problems with thinking and motor skills from mid-life. This may include problems with balance, coordination, memory and thinking skills. These changes can be profound and in a significant proportion of carriers will result in a progressive dementia and movement disorder called fragile X-associated tremor ataxia syndrome (FXTAS) (Hagerman *et al* 2001). At present, the understanding of this syndrome, including why some people develop cognitive and motor symptoms when others do not, is in its infancy.

Our study

Our team recently undertook a project with an overarching aim to establish a cohort of adult male carriers of the *FMRI* premutation and determine the effect of the gene on their health. Twenty five male carriers of the *FMRI* premutation (ages 26-80, seven with FXTAS) and 25 male 'controls' with normal *FMRI* expansions (ages 26-77) were recruited into the study. Carriers were recruited by mail-out through clinical genetic and genetic counselling services, and by

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advertisements through the Fragile X Association of Australia. Control participants were recruited from the general community. Comprehensive assessments included measures of cognitive function, psychiatric symptoms, motor function, general physical health, brain imaging and *FMRI* genetic measures.

The results

The results of our study suggested that carriers with FXTAS tended to perform worse on cognitive tasks measuring executive function (eg planning, reasoning, problem solving) and thinking speed compared to controls. However, scores on tests of language function, verbal memory, spatial abilities, and attention were similar in carriers with FXTAS and controls. Carriers with and without FXTAS were also more likely to experience at least one mood or anxiety disorder in their lifetime.

These findings were consistent with previous studies examining cognitive and psychiatric features in carriers with FXTAS (See Birch & Cornish *et al* 2014 for a review). Cognitive and psychiatric features reported by carriers in our study were not associated with *FMRI* gene length. Further research is needed to better understand the factors that may contribute to increased risk of cognitive and psychiatric symptoms in carriers of the *FMRI* premutation.

The results from brain imaging techniques showed that compared to controls, carriers with FXTAS had

smaller volumes in brain regions important for motor control. This included the cerebellum (located at the back of the skull) and a group of structures located deep within the brain called the basal ganglia. An important finding from the study was that larger *FMRI* gene expansions in carriers were associated with smaller cerebellar volume (Birch & Hocking *et al* 2015). Smaller cerebellar volume in carriers was also associated with increased body sway, which may indicate greater risk for falls. These findings raise the possibility that *FMRI*-related changes in cerebellar volume may provide a 'marker' of risk for the development of balance problems in carrier males, but this needs to be investigated in future longitudinal studies.

Conclusion

Taken together, the results of our study suggest that male carriers of the *FMRI* premutation may be at risk of developing specific cognitive signs and psychiatric symptoms, including problems with executive function, thinking speed, and symptoms of depression and anxiety.

The findings also suggest that the length of *FMRI* gene expansion and cerebellar volume are particularly important for balance control. Further funding is now being sought to continue recruitment of participants into the study and to repeat the same tests with these individuals. This will allow us to examine whether changes in thinking skills and balance over time are associated with specific biological or lifestyle factors. This information could then be used to develop much-needed information resources to better support fragile X families and to educate health professionals about the identification and management of FXTAS. ■

Study investigators

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First online test to

Are you worried about developing dementia? You are not alone. Many people who have cared for a loved one diagnosed with dementia, or are part of the growing workforce of carers and health professionals, wonder about their own risk for dementia and Alzheimer's disease – the most common cause of dementia among older adults. Australian researchers have developed a free, online tool which allows people to assess their risk of developing Alzheimer's disease after the age of 60.

Sarang Kim and Kaarin Anstey explain

Currently there is no cure or effective treatment for dementia. Available pharmacological treatments may delay the progress of the disease – but so far the effects of dementia cannot be reversed. Prevention is therefore one of the key objectives of current dementia research, and increased attention has been paid to identifying risk and protective factors for the disease (see box below).

It is also essential that people understand and address their risk profile for dementia as early as possible before the progression of this unrecoverable neurodegenerative disease. It has been estimated that an achievable 10% to 25% reduction in seven key risk factors (diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity and physical inactivity) could prevent between 1.1 to three million Alzheimer's disease cases internationally each year (Barnes & Yaffe 2011).

As public health campaigns raise awareness of dementia, people in the community are also very interested to learn about their personal risk

for developing dementia.

How can we reliably measure risk for dementia? Until now there has been no method of assessing future risk of Alzheimer's disease that did not involve undergoing medical tests. Yet most of the dementia risk connected with factors we know we can do something about (see box below) can be estimated without invasive and expensive medical tests – by answering questions about lifestyle and life risk.

Professor Kaarin Anstey, Associate Professor Nicolas Cherbuin and Dr Pushpani Herath, supported by funding from the Dementia Collaborative Research Centre: Early Diagnosis and Prevention, have developed such a test, which can be done from the comfort of home via the internet. It's called the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI).

Risk and protective factors

The ANU-ADRI is a highly accessible tool that is freely available to the general public and assesses an individual's exposure to the following 11 risk and four protective

Risk and protective factors for Alzheimer's disease

A comprehensive review of international research literature has identified risk and protective factors for Alzheimer's disease. The risk factors included in the ANU-ADRI are based on strong evidence. There are other risk factors for which evidence is still being obtained and it is likely that these will be added to the ANU-ADRI in the future.

The identified protective and risk factors for Alzheimer's disease include:

Protective factors

- Light to moderate alcohol consumption
- High physical activity
- Cognitive activity
- High fish intake

Risk factors

- Increasing age
- Female gender
- Low education
- Overweight and obese Body Mass Index (BMI) in mid-life
- Diabetes
- Depression
- High serum cholesterol in mid-life
- Traumatic brain injury
- Current smoking
- Low social engagement
- Pesticide exposure

Source: ANU Alzheimer's Disease Risk Index (ANU-ADRI) website <http://anuadri.anu.edu.au/alzheimer-s-disease-facts-figures/risk-factors.html>