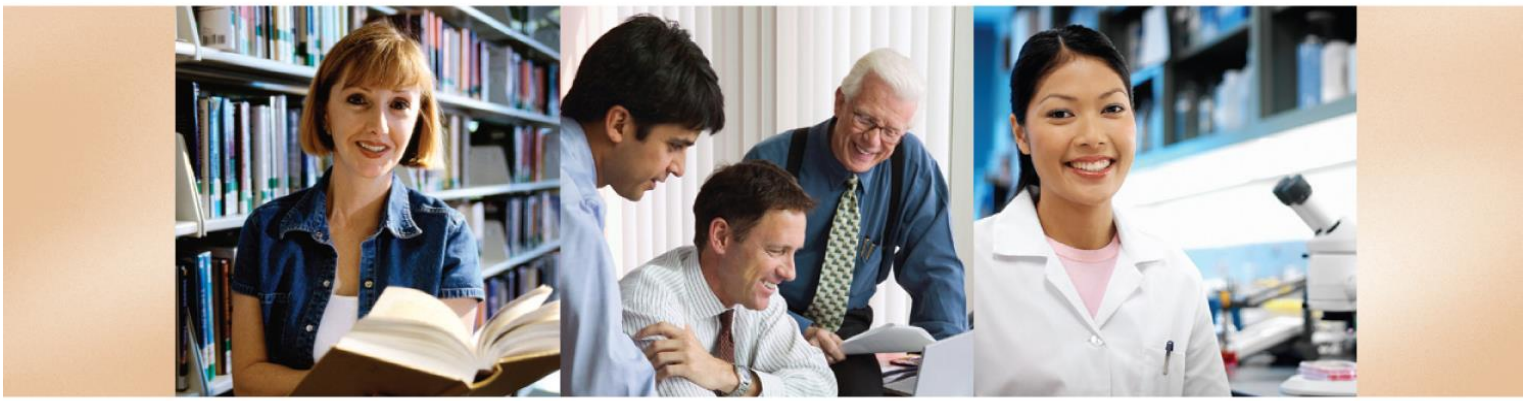
SUMMARY REPORT

Profiles and correlates of neurobehavioural features in male carriers of the *FMR1* premutation



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Translating dementia research into practice

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Profiles and correlates of neurobehavioural features in male carriers of the *FMR1* premutation

The *FMR1* 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. Individuals who have only a moderate expansion in their gene (also known as a 'premutation') are referred to as carriers. Premutation expansions of the *FMR1* gene are relatively common, being found in approximately 1 in 209 females and 1 in 430 males in the general population.

It was previously thought that there were no negative health effects associated with the *FMR1* premutation. However, it is now known that carriers may experience specific problems with cognitive and motor function in mid-to-late adulthood. Notably, some carriers may experience problems with balance, coordination, memory and thinking skills. Such changes can be profound and in a significant proportion of carriers will result in a progressive dementia and motor syndrome called fragile X-associated tremor ataxia syndrome (FXTAS). At present, the understanding of this syndrome, including why some people develop cognitive and motor symptoms when others do not, is in its infancy.

The overall aim of this project was to establish a cohort of adult male carriers of the *FMR1* premutation and to determine the effect of the gene on their health. Twenty five male carriers of the *FMR1* premutation (ages 26–80, seven with FXTAS) and 25 male "controls" with normal *FMR1* expansions (ages 26–77) were recruited into the study. Carriers were recruited by mail-out through clinical genetic and genetic counselling services, and by 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 *FMR1* genetic measures.

The results of the study suggested that carriers with FXTAS tended to perform worse on cognitive tasks measuring executive function (e.g. planning, reasoning, problem solving) and thinking speed compared to controls. However, scores on tests of language function, verbal memory, spatial abilities, and attention in carriers with FXTAS were similar to those obtained by 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 (summarised in Journal Article #1). Cognitive and psychiatric features reported by carriers in the current study were not

associated with *FMR1* 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 *FMR1* 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 *FMR1* gene expansions in carriers were associated with smaller cerebellar volume (published in Journal Article #2). 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 *FMR1*-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.

Taken together, the results of the study suggest that male carriers of the *FMR1* 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 *FMR1* 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 over time. This will allow for the examination of 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.

Journal articles published as part of this project:

1. Birch, R. C., Cornish, K. M., Hocking, D. R., Trollor, J. N. (2014). Understanding the neuropsychiatric phenotype of fragile X-associated tremor ataxia syndrome: a systematic review. *Neuropsychology Review, 24*(4): 491-513. doi: 10.1007/s11065-014-9262-9
2. Birch, R. C., Hocking, D. R., Cornish, K. M., Menant, J. C., Georgiou-Karistianis, N., Godler, D., Wen, W., Hackett, A., Rogers, C., & Trollor, J. N. (2015). Preliminary evidence of an effect of cerebellar volume on postural sway in *FMR1* premutation males. Genes, Brain and Behavior, *14*(3): 251-9. doi: 10.1111/gbb.12204
3. Birch, R. C., Hocking, D. R., & Trollor, J. N. Prevalence and predictors of subjective memory complaints in adult male carriers of the *FMR1* premutation. *The Clinical Neuropsychologist, In press.*