A plan for fragile X syndrome with wide-ranging consequences

The most common inherited cause of intellectual and developmental disability worldwide is fragile X syndrome, caused by a mutation in the *FMR1* gene on the X chromosome. To accelerate the development of effective interventions to prevent or treat fragile X syndrome and its related conditions, the USA National Institutes of Health (NIH) have launched a new report that sets out its research strategy for the next decade. The report establishes research priorities not only for this neurodevelopmental disorder, but also for a far broader set of diseases, as premutations in the *FMR1* gene can cause several additional neurological conditions that affect millions of patients.

The genetics of fragile X syndrome are complicated and intriguing. A trinucleotide repeat expansion of more than 200 CGG repeats in the promoter region of *FMR1* (repeat numbers are <55 in unaffected individuals) leads to methylation and transcriptional silencing, and to the deficiency or absence of fragile X mental retardation 1 protein (FMRP). Individuals with between 55 and 200 CGG repeats have the so-called premutation and are at risk of developing fragile X-associated tremor or ataxia syndrome (FXTAS) in middle-age or as elderly adults, or fragile X-associated primary ovarian insufficiency (FXPOI), which leads to infertility and early menopause in women. Additionally, approximately 50% of people carrying a premutation can have various neuropsychiatric disorders: anxiety and depression are the most common problems in adults, although obsessive compulsive disorder, attention deficit hyperactivity disorder, and social deficits are also prevalent.

The process to develop a new NIH Strategic Plan for Research on *FMR1*-associated conditions started in 2017, when working groups were established to review progress since the last NIH research plan (from 2009). These groups were led by researchers with expertise across basic, translational, and clinical research, and representatives from patient advocacy organisations, NIH institutes, and other federal agencies. Although the stakeholders of this report are all based in the USA, since the fragile X-associated disorders are found across people of all ethnicities and races worldwide, the NIH priorities can be used as a guide in any other country that has an investment in research in neurodevelopmental disorders.

For fragile X syndrome, the priorities include identification of mechanisms and targets for intervention, and development and refinement of animal models. With regard to possible targets for intervention, preliminary research into other conditions in which FMRP levels are purportedly reduced (such as major psychiatric disorders, specifically schizophrenia, bipolar disorder, and major depression) might also warrant further study. For FXTAS, the priorities are to describe the underlying pathogenic mechanisms and to develop easily measurable diagnostic biomarkers to distinguish it from other neurological conditions with similar symptoms, such as parkinsonism, essential tremor, ataxia, and cognitive impairment. For FXPOI, the main priority is to identify the mechanisms that lead to ovarian dysfunction. Treatment for FXPOI is not set up as a priority in this report but medications that stimulate folliculogenesis might be an important avenue to explore in the future.

The report rightly emphasises the need for more basic research on mechanisms underlying *FMR1*-associated disorders, as many gaps in knowledge remain. Importantly, the NIH plan highlights that clinical trials are needed to test promising therapeutic agents and that they should include participants with a range of backgrounds, demographic characteristics, and comorbid conditions. This is encouraging, as the previous 2009 NIH strategic plan and the subsequent funding initiatives for *FMR1*-associated conditions have not placed emphasis on clinical trials. Crucially, however, moving forward, NIH could place an even greater emphasis on research with a direct clinical impact, and commit to enough funding for these studies. For instance, the use of human engineered cells (eg, induced pluripotent stem cell [iPSC]-derived cells) and humanised mammalian models might be used to increase the biologically relevant insights gained from using model systems.

Research has already revealed that a vast number of people are potentially affected by mutations in the *FMR1* gene. The latest NIH strategic plan for research will therefore have wide-ranging consequences and draws attention to the extensive amount of work that is still needed to accelerate the development of new treatments for these complex disorders. Now, the necessary funding and resources for these research goals should also be prioritised. ■ *The Lancet Neurology*

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For more on **fragile X syndrome** see *Nat Rev Dis Primers* 2017; **3:** 17065

For more on the **premutation and neuropsychiatric disorders** see *Front Psychiatry* 2018; **9:** 564

For the **NIH draft strategic plan for research on *FMR1*-associated conditions** see https://www.nichd.nih.gov/sites/default/files/inline-files/NIHFMR1ResearchPlan2019.pdf