Editorial

DOI: 10.5582/irdr.2014.01033

Translational research guided by animal studies in Fragile X Disorders

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This special issue on fragile X-associated disorders will open your eyes to the broad spectrum of clinical involvement that occurs with mutations in the *FMR1* gene. This gene creates a protein, FMRP, which is a key protein for regulating the translation of hundreds of mRNAs, particularly those involved in synapse formation and plasticity. Fragile X syndrome (FXS) results from the loss or deficiency of FMRP and it is the most common cause of inherited intellectual disability and autism or autism spectrum disorder (ASD). The review of animal models for FXS by Kazdoba-Leach *et al.* (2014) in this issue, demonstrates how these models have led the way to targeted treatments for FXS and for ASD. One of the more promising new treatments for FXS is the use of low dose sertraline in young children 2 years and older with FXS. The paper by Hansen and Hagerman (in this edition) outlines the benefits of sertraline including the enhancement of serotonin neurotransmission, neurogenesis, and BDNF levels that has the potential to improve language and development for these children. GABA agonists and mGluR5 antagonists have also been studied in FXS but the mouse model is easily rescued with many different targeted treatments, whereas the patients with FXS have only responded well to a few new treatments. There is a great need to improve the participation of minorities in the new clinical trials of targeted treatments for FXS and this is reviewed in detail by Chechi *et al.* (2014) in this issue.

Fragile X-associated disorders include both FXS and premutation disorders also. The field of premutation involvement (55 to 200 CGG repeats in the 5'end of *FMR1*) is growing rapidly as reviewed by Lozano *et al.* (2014) in this issue. RNA toxicity from elevated levels of *FMR1* mRNA leads to molecular consequences that affect neurological, endocrine, psychiatric and rheumatological health throughout the lifespan. Problems may begin in childhood, such as anxiety, ADHD and social deficits, with additional issues that complicate adult life including early ovarian insufficiency, hypothyroidism, fibromyalgia, migraines, hypertension, sleep apnea, restless legs syndrome, neuropathy and eventually for some, the fragile X-associated tremor ataxia syndrome (FXTAS). The premutation is common in the general population, approximately 1 in 130-250 women and 1 in 250 to 450 males as reviewed by Muzar *et al.* (2014) in this issue. Both FXTAS and other premutation disorders are under-diagnosed currently and it behooves physicians and other health care providers to read the enclosed papers carefully so that premutation disorders are considered in the differential diagnosis of these common medical problems. Often the diagnosis is considered when the family history includes someone with autism or intellectual disability of unknown etiology or an older relative with a Parkinsonian symptom complex or even dementia. It is easy to order a fragile X DNA test if either a premutation or a full mutation disorder is suspected. Once a diagnosis is made then a treatment plan can be made. Life style changes are important in the treatment of premutation carriers since substance abuse can exacerbate FXTAS as demonstrated in the cases of Muzar *et al.* (2014) in this issue. Other treatment options are discussed in the FXTAS review in this volume.

Once a diagnosis of a fragile X condition is made then genetic counseling is recommended and all family members who are at risk for a premutation or a full mutation should be tested. The risk for a women with the premutation to pass on a full mutation to her offspring is significantly impacted by the number of AGG anchors she has within her CGG repeats. An AGG anchor occurs approximately every 9 to 10 CGG repeats and the more anchors one has the lower the risk for expansion to a full mutation in the next generation. Yrigollin *et al.* (2014) in this issue clarifies this risk in a broad array of international populations. This work guides genetic counselors in their risk assessment for families.

This volume contains a rich array of papers that traverses molecular to animal to human studies to give a full picture of the progress in the fragile X field. Clinicians and bench scientists will all benefit from the research presented in this volume.

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(November 29, 2014)