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FRAGILE X SYNDROME: LESSONS LEARNED FROM THE MOST TRANSLATED NEURODEVELOPMENTAL DISORDER IN CLINICAL TRIALS

Phan Q. Duy[1]*,
Dejan B. Budimirovic[2]

[1] *Department of Biology Johns Hopkins University Baltimore, MD 21218*

[2] *Clinical Research Center, Clinical Trials Unit & Fragile X Clinic, Kennedy Krieger Institute, Johns Hopkins Medical Institutions Baltimore, MD 21205*

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Abstract

Fragile X syndrome (FXS) is the leading genetic cause of autism spectrum disorder (ASD) and inherited intellectual disability (ID) worldwide. Preclinical successes in understanding the biology of FXS have led to numerous translational attempts in human clinical trials of therapeutics that target the excitatory/inhibitory neural signaling imbalances thought to underlie FXS. Despite the preclinical success story, the negative results of the human clinical trials have been deemed to be at least in part disappointing by the field. In this commentary, we contend that such negative studies results in clinical trials may actually propel the FXS field forward by serving as important lessons for designing and implementing improved future clinical trials such that can objectively assess the full range of responses to new therapeutics.

Keywords

• Autism spectrum disorder • Clinical trial • Fragile X syndrome• Translational research

Fragile X Syndrome (FXS)is the most translated among all neurodevelopmental disorders in human clinical trials. FXS is a global neurodevelopmental disorder that is caused by the epigenetic silencing of the *fragile X mental retardation 1* (*FMR1*) gene and absence of its encoded protein, fragile X mental retardation protein (FMRP). Found in up to 1:2500 males, FXS is a global neurodevelopmental disorder of the most common monogenetic cause of inherited intellectual disability (ID) and autism spectrum disorder (ASD). The clinical complexity arises from that FMRP, an RNA-binding protein, targets approximately 4% of the transcribed mRNAs in the brain [1], and 842 of the identified targets to date converge on the same cellular pathways as idiopathic ASD [2,3]. Since FMRP acts as a translational 'brake,' its absence in FXS causes *up-regulation* of metabotropic glutamate receptor 5 (mGluR5) [4] and *down-regulation* of GABA signaling [5], leading to an excitatory/inhibitory imbalance. Correcting these imbalances with mGluR5 antagonists or GABA receptor agonists rescues the pathological hallmarks of synaptic function and social behavior in the mouse model of FXS (the *FMR1* knock-out) [6,7,8]. These preclinical breakthroughs have generated much interest by the field to translate into humans with FXS, and possibly ASD. Indeed, a January 2016 search of the US Food and Drug Administration (FDA) and National Institute of Health (NIH) www.clinicaltrials.gov website and the scientific literature revealed 22 double-blind, placebo-controlled clinical trials in humans with FXS, mostly from 2008 to 2015 [9]. Reflecting the key preclinical findings, the vast majority of the clinical trial studies targeted the aforementioned excitatory/inhibitory imbalances (14/22, 64%) [9].

Since FXS is a genetic diagnosis and ASD is purely behaviorally defined, FXS is the most-studied genetic model for ASD. Present research is focused on identifying shared pathways and common therapeutic targets between FXS and ASD, neither of which currently has any effective treatments. New understanding into the biology of FMRP has led FXS to become the most translated neurodevelopmental disorder in human clinical trials. Yet over the last few years, these trials failed to meet the primary efficacy endpoints, including the well-powered 2016 study by Berry-Kravis and colleagues that studied the mGluR5 antagonist mavoglurant [10]. Moreover, recent attempts to translate preclinical success stories into human FXS were largely considered to be disappointing by the field [11]. Nevertheless, such "negative" results in the clinical trials actually provide us with valuable lessons for designing future treatment studies in FXS, ASD, and other neurodevelopmental disorders. For instance, post hoc analysis of mavoglurant and arbaclofen clinical trial studies revealed statistically significant therapeutic benefits when patients are stratified based on molecular properties of the *FMR1* gene and baseline severity of social withdrawal [12,13]. These data suggest that shortcomings in the design of clinical trial and the outcome measures used failed to capture areas of positive response to the newly developed therapeutics.

Clinical trials of new treatments are inherently difficult to design and implement, but FXS and other neurodevelopmental disorders such as ASD pose a unique challenge, including the lack of previous clinical trial studies that establish standard precedents for future treatment studies. Therefore, recent FXS clinical trials can guide us in determining major areas that require continued study for future

* *E-mail: dphan7@jhu.edu*

improvements on how to conduct treatment studies. For example, we need to recognize that although FXS is genetically homogeneous, phenotypic variability exists among individuals with FXS, such as differences in severity levels of neurobehavioral manifestations and ASD diagnosis [14]. It may be possible this phenotypic heterogeneity leads to differential responses to therapeutics, and therefore future treatment studies need to identify patient stratification paradigms that may reveal a sub-population of FXS individuals that exert optimal therapeutic response.

More importantly, differential therapeutic response among FXS individuals is due to a widespread lack of studies that support the reliability, validity, and sensitivity to treatment changes of the mostly parent-based outcome measures to assess responses to treatments. For example, the Aberrant Behavior Checklist-Community Edition (ABC-C) and Fragile X version (ABC-CFX) are two outcome measures that have been widely applied as key primary efficacy endpoints of targeted therapeutics in trials involving individuals with ID (including FXS) or ASD [15,16]. While the ABC-C has generally good psychometric properties and a successful track record for documenting improvements in some problem behaviors, several limitations of the ABC-C (e.g., test-retest reliability) can affect its sensitivity to changes, and therefore, its ability to detect response to treatment. In addition, as other measures developed for ID or ASD, ABC-C's relevance to the FXS behavioral phenotype characterized by prominent anxiety-like behaviors was also questioned. Importantly, significant dependence on parental report of ABC-C contributes to the placebo effect, compelling the need to validate and apply existing tools toward developing new clinician-based measures.

As a whole, we argue that despite the perceived setbacks, "negative" results in recent FXS clinical trials present valuable opportunities to reflect on future clinical trial design and implementation. There is a significant need for more translational and clinical research to improve psychometric properties and sensitivity to treatment change(s) of existing and to develop new paradigms to quantify learning. Refined methodologies in the way treatment studies are conducted will enable us to more definitively and objectively determine and assess the full range of response to new therapeutics.

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