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Commentary

Analysis of Pathogenetic Pathways in Fragile X Syndrome

James William*

Department of Pediatrics, School of Medicine, University of California, Davis, Sacramento, California, USA

DESCRIPTION

The most frequent monogenic cause of autism or intellectual disability is Fragile X Syndrome (FXS), and analysis on its pathogenetic pathways has shed crucial light on this neurodevelopmental disorder. The clinical, genetic, and therapeutic response variability in FXS and to emphasise the importance of applying precision medicine-based therapies. We make a statement about how the significant genetic and phenotypic heterogeneity in FXS contributes to the challenges encountered during treatment development. We propose that the success of clinical trials can be achieved by focusing on the underlying heterogeneity in FXS by accurately stratifying patients into drug-responder subpopulations. This is because several clinical trials have shown a non-negligeable fraction of positive responders to drugs targeting core FXS symptoms. In in addition to assisting to define drug responder profiles based on particular biomarkers or phenotypic characteristics that can relate patients from different genetic backgrounds to the same candidate drug, these precision medicine-based approaches, which can first be applied to well-defined monogenic diseases like FXS, can also serve to reposition the same drug for a greater number of patients with NDD's.

Autism Spectrum Disorder (ASD), Intellectual Disability (ID), Attention Deficit Hyperactivity Disorder (ADHD), communication disorders, specific learning disorders, and motor disorders are all examples of Neurodevelopmental Disorders (NDD's), a group of common and highly heterogeneous conditions characterised by impairment in "personal, social, academic, or occupational functioning" with onset early in development. Additionally, the definition can also include some neuropsycological disorders. Comorbidity of two or more of these conditions is seen at rates that are higher than those predicted by chance, pointing to the possibility of biological mechanism clusters.

NDD's frequently also include a variety of extra-neurological clinical signs, such as hypotonia, dysmorphology, cardiologic or metabolic features, as well as gastrological risks like constipation or diarrhoea, which are particularly common in ASD and ADHD, features and conditions is frequently observed. Recent developments in genotyping and sequencing technologies have accelerated the discovery of risk and causal genes, highlighting the remarkable genetic heterogeneity among and within particular NDDs. For example, the SysID database has confirmed pathogenic mutations in more than 1,000 genes for intellectual disability alone (a systematic and manually curated catalogue of ID-associated genes).

There are different levels of phenotypic and genetic heterogeneity in syndromic neurodevelopmental problems linked to mutations in a single gene, despite the fact that they are by definition genetically more homogeneous. The fact that well-defined clinical entities can be caused by mutations in multiple genes (such as Noonan syndrome, which has been linked to mutations in 14 different genes) and that mutations in the same gene can have a wide range of symptoms (such as MECP2 mutations in Rett syndrome) further complicates matters. Additionally, different mutations can produce various pathophysiological pathways, as demonstrated most recently by mutations in SATB1, where three different types of variations were linked to various clinical effects.

A lack of FMRP (Fragile X Mental Retardation Protein, encoded by FMR1), an RNA-binding protein that controls the editing, translation, stability, and transport of several neuronal mRNAs, results in the well-known NDD disease known as Fragile X Syndrome (FXS). It was initially identified as a type of X-linked hereditary intellectual impairment in 1943. Although the FMR1 (Fragile X Mental Retardation 1) causative gene and the mutational foundation of FXS.

The entire FMR1 mutation, the typical aetiology of FXS, results in an increase of >200 CGG repeats in the FMR1 promoter region, which methylates the promoter and silences transcription of FMR1. FXS is currently the most frequently discovered monogenic cause of hereditary intellectual impairment and ASD. Nevertheless, despite being a genetically well-characterized syndrome, there is significant heterogeneity among FXS patients, and the illness continues to have a significant unmet medical need. This reinforces the need for a more thorough definition of the FXS population in order to facilitate the creation of effective treatments.

Correspondence to: Dr. James William, Department of Pediatrics, School of Medicine, University of California, Davis, Sacramento, California, USA, Email: William@james.edu

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