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Original article

Molecular biomarkers predictive of sertraline treatment response in young children with fragile X syndrome

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Abstract

Objectives: Several neurotransmitters involved in brain development are altered in fragile X syndrome (FXS), the most common monogenic cause of autism spectrum disorder (ASD). Serotonin plays a vital role in synaptogenesis and postnatal brain development. Deficits in serotonin synthesis and abnormal neurogenesis were shown in young children with autism, suggesting that treating within the first years of life with a selective serotonin reuptake inhibitor might be the most effective time. In this study we aimed to identify molecular biomarkers involved in the serotonergic pathway that could predict the response to sertraline treatment in young children with FXS.

Methods: Genotypes were determined for several genes involved in serotonergic pathway in 51 children with FXS, ages 24–72 months. Correlations between genotypes and deviations from baseline in primary and secondary outcome measures were modeled using linear regression models.

Results: A significant association was observed between a BDNF polymorphism and improvements for several clinical measures, including the Clinical Global Impression scale ($P = 0.008$) and the cognitive T score ($P = 0.017$) in those treated with sertraline compared to those in the placebo group. Additionally, polymorphisms in the MAOA, Cytochrome P450 2C19 and 2D6, and in the 5-HTTLPR gene showed a significant correlation with some of the secondary measures included in this study.

Conclusion: This study shows that polymorphisms of genes involved in the serotonergic pathway could play a potential role in predicting response to sertraline treatment in young children with FXS. Larger studies are warranted to confirm these initial findings.

Keywords: Fragile X syndrome; Serotonin; Sertraline; Selective serotonin reuptake inhibitor; BDNF; Cytochrome P450; Neurotransmitters; Molecular biomarkers

1. Introduction

Fragile X syndrome (FXS) is the most commonly inherited form of intellectual disability caused by methylation, subsequent to an expansion greater than 200 CGG repeats, in the 5′UTR of the FMR1 gene.

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The consequent deficit/absence of the fragile X mental retardation protein (FMRP) affects brain development and results in significant behavioral, cognitive, and emotional problems. Importantly FXS is also the most common monogenic cause of autism spectrum disorder (ASD) with approximately 60% of those with the full mutation presenting with ASD [1].

Individuals affected by FXS have phenotypic and behavioral features including macroorchidism, aggression, seizures, attention deficit hyperactivity disorder, anxiety, and deficits in sensory integration, language and attention [2].

Several neural pathways and neurotransmitters involved in the brain development are altered in FXS [3], including serotonin which plays a vital role in synaptogenesis and postnatal brain development. A study by Chugani et al. [4], revealed that children with and without ASD had differences in serotonin synthesis capacity for the first five years of life. In children without ASD serotonin synthesis capacity was 200% more than that of adults compared to 1.5 times the adult normal values in children with ASD suggesting that brain serotonin synthesis capacity during early childhood is disrupted in ASD.

Thus, introducing selective serotonin reuptake inhibitors (SSRI) within the first years of life might be effective for those with ASD [5,6]. Further, treatment with SSRIs early in postnatal development, paired with appropriate behavioral intervention may have the ability to stimulate neurogenesis and improve clinical symptoms. Indeed, to alleviate maladaptive or disruptive behaviors and social deficits that manifest as anxiety-related symptoms, SSRIs are often prescribed to patients with FXS [7,8]. According to medication usage surveys, approximately 50% of patients over five years old with FXS are prescribed an SSRI to treat in particular, anxiety, irritability, and socialization deficits [6–8]. Similarly, several studies demonstrated positive responses in anxiety, mood and irritability, with minimal adverse effects in children with ASD, with and without FXS, following low-dose sertraline treatment [9–11]. A retrospective study showed improvements in receptive and expressive language, on the Mullen Scales for Early Learning in young patients with FXS treated with sertraline compared to those not treated, suggesting that sertraline may improve language developmental trajectory in young children with FXS [8]. To further support the role of serotonin in FXS, two studies, in both humans and mouse, showed that the alteration in the GluA1-dependent long-term potentiation (LTP) and long-term depression (LTD) in patients with FXS can be partly corrected by serotonin [12,13].

Patients with FXS are often prescribed a multitude of medications to treat specific symptoms [14,15]. The neurobiological consequences resulting from the loss of FMRP, have led efforts to identify targeted treatments for FXS [16,17].

Clinical trials in FXS are usually carried out in adolescents and adult subjects, yet, none have studied the effect of targeted medications in children younger than 5 years old (Reviewed in [17]) with the exception of this recent controlled trial of sertraline in children aged 24–72 months described below on which our study is based [18]. To be more effective, targeted treatment should likely occur early within this developmental window of brain development to correct any alterations in neurotransmission, and to enhance neuroplasticity and experience-dependent change. The behavioral overlap between ASD and FXS suggests that there might be overlapping bio-molecular pathways. Thus, targeted treatments that were found effective against ASD might be effective in FXS and vice versa.

Based on this evidence a double blind, randomized, placebo-controlled 6-month clinical trial of low-dose sertraline in children ages 24–72 months old with FXS was conducted at the UC Davis MIND Institute to evaluate the efficacy and benefit with respect to early expressive language development and global clinical improvement.

Here, we further investigated the participants of this clinical trial to identify molecular biomarkers predictive of efficacy of responsiveness to sertraline treatment. Candidate genes were selected specifically on the basis of their role in serotonin metabolism, uptake and transport, including Serotonin transporter-linked polymorphic region (5-HTTLPR), Brain-Derived Neurotrophic Factor (BDNF), variable number of tandem repeat promoter of Monoamine Oxidase A (MAOA-VNTR), Cytochrome P450 2D6 (CYP2D6), and Cytochrome P450 2C19 (CYP2C19) [19]. As plasma levels of APP, MMP-9 and BDNF were found to be elevated in FXS and ASD [20–22], we also investigated if the use of sertraline would normalize the plasma levels of these biomarkers.

In this study, we aimed to identify molecular biomarkers that play an important role in the serotonergic pathway and might be predictive of clinical response to sertraline.

2. Methods

2.1. Study design

A double-blind placebo controlled clinical trial was conducted on 57 subjects aging 24–72 months at the UC Davis MIND Institute. Out of the 57 subjects enrolled in the clinical trial, five discontinued and of the remaining 52 subjects who completed the sertraline clinical trial, we received biological samples, at both baseline and follow up visit, for 51 of them. The cohort consisted of 6 females and 45 males. Details of this