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An analysis of challenging behavior, comorbid psychopathology, and Attention-Deficit/Hyperactivity Disorder in Fragile X Syndrome☆

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ABSTRACT

The present study sought to investigate the relationship between challenging behavior, comorbid psychopathology, and Attention-Deficit/Hyperactivity Disorder (AD/HD) in Fragile X Syndrome (FRAX). Additionally, this study sought to examine how such disorders are predicted by gender, presence of autism spectrum disorder (ASD), and presence of intellectual disability (ID). A total of 47 children and adolescents with FRAX were assessed. Results revealed high levels of challenging behavior and AD/HD symptoms within the sample, with some participants exhibiting symptoms of comorbid psychopathology. Further analysis revealed that challenging behavior and comorbid psychopathology were positively correlated, with stereotypy correlating most strongly with comorbid psychopathology. In addition, ASD was found to predict challenging behavior, and gender was found to predict AD/HD symptoms. The implications of these findings are discussed.

1. Introduction

Fragile X Syndrome (FRAX) is one of the most common causes of inherited intellectual disability (ID) in males and to a lesser extent, females (Cornish, Turk, & Hagerman, 2008). FRAX is caused by the silencing of the Fragile X Mental Retardation 1 (FMR1) gene which affects the production of FMR1 mRNA and in turn disturbs Fragile X Mental Retardation Protein (FMRP) production (Hagerman, 2008). The resultant FRAX phenotype exhibited involves a varied spectrum of symptoms (Hagerman & Hagerman, 2002).

The prevalence of FRAX has been assessed in a number of population-based studies. In a screening of new-born males, Coffee et al. (2009) found that 7 of 576 males screened positive for FRAX, revealing a FRAX incidence of 1 in 5161 males. The prevalence of FRAX in females has not been calculated (Coffee et al., 2009); however two studies have been conducted examining the prevalence of the FMR1 pre-mutation in females. Crawford, Acuña, and Sherman (2001) estimated that 1 in

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every 246–461 females are carriers of the pre-mutation, whilst Rousseau, Rouillard, Morel, Khandjian, and Morgan (1995) estimated this figure to be 1 in every 259 females tested.

The expression of FRAX varies in accordance with a number of individual factors such as FMR1 mutation status, gender, presence of ID, and presence of autism spectrum disorder (ASD). This has led Hagerman and Hagerman (2002) to characterize FRAX as a 'spectrum of involvement'. Within this spectrum, the molecular status of the FMR1 mutation (full mutation, pre-mutation, FMR1 mosaicism) has a significant impact upon the presentation of FRAX, especially with regards to ID (Hagerman & Hagerman, 2002).

The FMR1 full mutation is associated with an 85% incidence of ID in males and 25% incidence of ID in females (Hagerman & Hagerman, 2002; Loesch, Huggins, & Hagerman, 2004). A number of physical features associated with the full mutation are observed, especially in males. These include large ears, long narrow faces, hyperextensible finger joints, and abnormal connective tissue structure (Hagerman & Hagerman, 2002; Hull & Hagerman, 1993). In contrast to the high incidence of ID seen in the full mutation, carriers of the FMR1 pre-mutation typically have normal to near-normal IQ (Tassone et al., 2000). Whilst those with the FMR1pre-mutation may not present with ID, a number of associated problems may be exhibited such as learning deficits, social anxiety, and social withdrawal (Hagerman & Hagerman, 2002).

FMR1 mosaicism falls somewhere between the FMR1 full mutation and FMR1 pre-mutation and describes individuals with FRAX who have both full and pre-mutation cell expansion (Nolin, Glicksman, Houck, Brown, & Dobkin, 1994). Whilst intellectual functioning in mosaic males has been found to be similar to that of full mutation males (Rousseau et al., 1994), mosaic males have been found to exhibit fewer deficits in adaptive functioning than males with the full mutation (Cohen et al., 1996). This would suggest that mosaic FRAX males may have a better prognosis than males with the full mutation.

The expression of FRAX is mediated not only by FMR1 mutation status and associated presence and severity of ID, but also by the individual factors of gender and presence of ASD. The gender of the individual with FRAX impacts significantly upon the expression of this syndrome due to the fact that FRAX is caused by a mutation on the X chromosome (Hessl et al., 2001). Females are protected from FRAX to some degree due to the presence of one unaffected X chromosome (Hessl et al., 2001). As a result, intellectual functioning in such females may not be impaired, with ID typically ranging from mild ID to no significant impairment (Bennetto & Pennington, 1996; Hagerman & Sobesky, 1989). In contrast, males are often more severely affected than females and may present with ID in the moderate to severe range (Bennetto & Pennington, 1996; Hagerman & Sobesky, 1989).

ASD is a further condition found to commonly co-occur with FRAX. Whilst only 4% of ASD cases are believed to be associated with FRAX (Belmonte & Bourgeron, 2006), it has been estimated that 35% of young males with FRAX meet the diagnostic criteria for ASD (Hall, Lightbody, Hirt, Rezvani, & Reiss, 2010). Research has investigated the impact of comorbid ASD in FRAX by comparing individuals with comorbid ASD to those with FRAX only. Such research has reported lower IQ (Hagerman et al., 1986), greater deficits in adaptive functioning (Turk & Graham, 1997), and greater deficits in socialization (Hernandez et al., 2009) in those with comorbid ASD when compared to those with FRAX only. This research suggests that presence of comorbid ASD in FRAX may result in a poorer prognosis. The above research demonstrates that the expression of FRAX is dependent upon the complex interaction of a number of individual factors. It is not surprising therefore, that the behavioral phenotype of FRAX is also highly varied. The classic behavioral phenotype has been described by Hagerman and Hagerman (2002) as involving issues with challenging behavior, comorbid psychopathology, and symptoms of Attention-Defcit/Hyperactivity Disorder (AD/HD).

Within this behavioral phenotype, challenging behavior has been found to be a common co-occurring condition. Challenging behaviors such as aggression toward others, self-injurious behavior (SIB), and stereotypy have been reported to be highly prevalent in FRAX. Bailey, Raspa, Olmsted, and Holiday (2008) estimate that 38% of males and 14% of females with the FMR1 full mutation engaged in aggressive behavior. A nationwide study conducted by Symons, Byiers, Raspa, Bishop, and Bailey (2010) found that 41% of males and 16% of females with the FMR1 full mutation engaged in SIB. This study also found that the onset of SIB occurred around the age of three years, with no gender differences found regarding the age of onset reported. Repetitive and stereotyped behavior has also been noted as posing a significant issue in FRAX. A study examining repetitive and stereotyped behavior in FRAX was conducted by Hagerman et al. (1986). This study, consisting of a sample of 50 males, found that 88% of participants engaged in repetitive and stereotyped behavior.

Psychopathology is a further condition found to co-occur with FRAX with disorders such as anxiety and depression being prevalent (Tranfaglia, 2011). The behavioral expression of anxiety in FRAX may include poor eye-contact, gaze aversion, and shyness (Tranfaglia, 2011). Moreover, anxiety may manifest itself in the form of challenging behavior such as SIB and aggression toward others in this population (Boyle & Kaufmann, 2010). A parent survey conducted by Bailey et al. (2008) reported that 70% of males and 22% of females with the FMR1 full mutation experienced anxiety. The same study found that 12% of males and 22% of females with the FMR1 full mutation exhibited symptoms of depression. An additional study conducted by Cordeiro, Ballinger, Hagerman, and Hessl (2011)) examined the incidence of anxiety disorders in a sample of 97 participants between the ages of 5 and 33 years of age. Results revealed that 86% of males and 77% of females met the criteria for an anxiety disorder, with social anxiety and specific phobias reported to be the most common disorders. Older age and comorbid ASD were associated with an increased prevalence of anxiety within the sample.

The most commonly diagnosed comorbid condition in FRAX however is AD/HD (Tranfaglia, 2011). High levels of AD/HD are typically seen in early childhood. As the individual matures, symptoms of AD/HD are found to decrease, although deficits in attention may persist (Tranfaglia, 2011). In a national parent survey, Bailey et al. (2008) found that 66% of males and 30% of females with the FMR1 full mutation exhibited significant issues with hyperactivity. The same study found that 84% of males