REVIEW

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Different faces of autism: Patients with mutations in *PTEN* and *FMR1* genes

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Autism spectrum disorder (ASD) is among the most common neurodevelopmental conditions in humans. While public awareness of the challenges faced by individuals with autism is steadily increasing, the underlying causes of abnormalities observed in ASD remains incompletely understood. The autism spectrum is notably broad, with symptoms that can manifest in various forms and degrees of severity. Core features of ASD, such as communication difficulties, impaired social interactions, and restricted patterns of behavior, interests, and activities, are often accompanied by other co-occurring conditions, such as anxiety. ASD affects individuals regardless of gender, race, or ethnicity. Although we are currently unable to pinpoint a single definitive cause of autism, it is clear that genetics play a crucial role in its development. The first genes associated with an increased risk for ASD were discovered in rare monogenic disorders, such as fragile X syndrome (FXS), caused by mutations in the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene, and macrocephaly, linked to mutations in the phosphatase and tensin homolog (*PTEN*) gene. This review aims to summarize the current knowledge of ASD in patients with mutations in the *FMR1* and *PTEN* genes.

Key words: *PTEN*, *FMR1*, autism, ASD

INTRODUCTION

What are autism spectrum disorders?

Autism spectrum disorder (ASD) constitutes one of the most prevalent neurodevelopmental conditions in humans, with growing recognition of the challenges faced by affected individuals. The autism spectrum demonstrates a wide range of clinical manifestations, characterized by variability in symptoms and their severity. Central features of ASD include impairments in three core domains: communication deficits (verbal and non-verbal), difficulties in social interaction, and restricted, repetitive patterns of behavior, interests, and activities (Bailey et al., 2008). Sensory hypersensitivities are also frequently observed (Sharma et al., 2018; Hirota & King, 2023; Patil & Kaple, 2023; Trayvick et al., 2024). These symptoms typically emerge before the age of four, which is the most common period for diagnosis (Qin et al., 2024).

The clinical manifestations of ASD vary from mild to severe forms, significantly influencing the quality of life and daily functioning of individuals. ASD is often comorbid with other medical and psychological conditions (Al-Beltagi, 2021; Khachadourian et al., 2023). For instance, motor impairments are reported in up to 79% of individuals with ASD, gastrointestinal disturbances in up to 70%, and depression in 12–70% (Lai et al., 2014). Allergies and autoimmune diseases affect up to 38%, while 50–80% experience sleep disorders (Lai et al., 2014). Additionally, intellectual disabilities are present in 45% of cases, anxiety disorders in 42–56%, attention deficit hyperactivity disorder (ADHD) in 28–44%, and seizures in up to 30% (Lai et al., 2014). Despite the lack of specific neuroanatomical hallmarks for ASD that could serve as diagnostic criteria, approximately 10% of cases are associated with macrocephaly, often accompanied by structural abnormalities in the brain (Sparks et al., 2002; Courchesne et al., 2003; Schumann et al., 2010).

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ASD affects individuals across all genders, ethnicities, and racial groups. The prevalence varies geographically. Which may be explained by distinct diagnostic criteria or general standards of ASD management in different countries. Globally ASD is estimated to affect approximately 1% of the population, however, in the United States, recent epidemiological studies report a prevalence of 2–3% (Baxter et al., 2015; Maenner et al., 2021). According to the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/autism/index.html), this corresponds to an ASD diagnosis in approximately 1 in 36 children and 1 in 45 adults. Notably, males are diagnosed with ASD approximately four times more frequently than females (Lord et al., 2006; Lai et al., 2017).

What causes autism?

At present, a definitive cause of autism remains unknown. It is hypothesized that the range of causes may reflect the heterogeneity of clinical manifestations (Lewandowska-Pietruszka et. al., 2023; Rajabi, et al., 2024; Khaliulin, et al., 2024; Cano et. al., 2024). Twin studies strongly support a significant genetic component in ASD pathogenesis. Cooccurrence rates for ASD in monozygotic twins approach 90%, compared to approximately 30% in dizygotic twins (Rosenberg et al., 2009). Furthermore, younger siblings of individuals with ASD demonstrate a 20% likelihood of receiving an ASD diagnosis (Ozonoff et al., 2024).

It is estimated that up to 30% of ASD cases can be linked to changes in gene expression (Genovese & Butler, 2023). According to the SFARI database (https://gene.sfari.org/), mutations in over a thousand genes may be associated with various forms of ASD. The first genes linked to ASD risk were identified in rare monogenic disorders, such as Fragile X Syndrome (FXS; caused by mutations in the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene), tuberous sclerosis, neurofibromatosis type 1, and macrocephaly – caused by mutations in the phosphatase and tensin homolog (*PTEN*) gene (Betancur, 2011; Muhle et al., 2018). Among the genetic causes of autism, FXS is the most common inherited monogenic disorder, accounting for an estimated 1% to 6% of all ASD cases (CDC, https://www.cdc.gov/autism/index.html). Similarly, mutations in the *PTEN* gene, which regulates the mammalian target of rapamycin (mTOR) kinase pathway, represent a significant risk factor (Varga et al., 2009; Busch et al., 2019). In subsequent sections of this review, we summarize the current understanding of autism in patients with mutations in the *FMR1* and *PTEN* genes.

The *FMR1* gene and autism

Fragile X Syndrome is one of the most common hereditary causes of intellectual disability and ASD. Its clinical presentation includes macroorchidism, learning difficulties, cognitive and behavioral impairments (including social deficits), and seizures. FXS is inherited as an X-linked, dominant single-gene. The primary cause of FXS is an excessive number of CGG trinucleotide repeats located in the 5 untranslated region of the *FMR1* gene. When the CGG repeat count exceeds 200, the *FMR1* gene is silenced through methylation, resulting in a deficiency of the protein FMRP (Fragile X Mental Retardation Protein) (Ranjan et al., 2023; Hunter et al., 2024; Stone et al., 2024). FMRP is an RNA-binding protein essential for the proper expression of the numerous other proteins, including those involved in synaptic plasticity such as neuroligins and, neurorexins, postsynaptic density protein 95 (PSD-95), SHANK3, Arc, and others (Mercaldo et al., 2009; Hagerman et al., 2011; Telias, 2019). It is suggested that FMRP-driven synaptic alterations contribute to the complex pathogenesis of ASD in FXS patients (Hagerman et al., 2011). Among different synaptic pathways dysregulated upon *FMR1* mutation, the mTOR signaling seems to play a particular significance in development of ASD. Interestingly, cumulating scientific data indicates alteration of mTOR signaling as a common central mechanism linking *FMR1* and *PTEN* dysfunctions with ASD development (Thomas et al., 2023).

ASD affects 50%-70% of individuals with FXS (Kidd et al., 2020), with a higher prevalence in males compared to females. This sex-based disparity is partially explained by the location of the *FMR1* gene on the X chromosome. Approximately one-third to one-half of females with the mutation retain normal intellectual function, a phenomenon partly attributable to X-chromosome inactivation. In females, one X chromosome is randomly silenced in each cell, leading to cellular mosaicism. Thus, a proportion of active X chromosomes may carry a functional copy of *FMR1*. In males, who possess only one X chromosome, a mutation affects all cells carrying the gene (Abrams et al., 1994; Bartholomay et al., 2019). Studies of individuals with FXS reveal that around 50% of males and 20% of females meet diagnostic criteria for autism (Clifford et al., 2007; Bailey et al., 2008).

Although FXS is the most common single-gene cause of autism, FXS and ASD are distinct conditions. Comparisons between individuals with FXS alone and those with FXS and ASD highlight key differences: intellectual disability is more prevalent in FXS than in FXS with ASD; motor coordination deficits are more

pronounced in FXS than in FXS with ASD; interest in social integration is generally greater in FXS than in FXS with ASD; adaptive skills are superior in individuals with FXS compared to those with FXS and ASD; language abilities are better developed in FXS than in FXS with ASD; seizure rates are lower in FXS than in FXS with ASD (Kaufmann et al., 2017; National Fragile X Foundation (https://fragilex.org/)).

Does autism linked to FXS have unique characteristics? Few studies described by Niu and coworkers (2017) have directly compared individuals with FXS and ASD to those with idiopathic ASD. One such study observed less severe social deficits in individuals with FXS and ASD compared to those with idiopathic ASD. Conversely, other research using ASD diagnostic tools has reported more significant social impairments, higher levels of anxiety, and less severe repetitive behaviors in individuals with FXS and ASD without ASD (Boyle & Kaufmann, 2010; Talisa et al., 2014).

The *FMR1* premutation and autism

Patients who have 55–200 CGG repeats in the *FMR1* gene are said to have a *FMR1* premutation. The *FMR1* premutation is a relatively recently identified condition linked to various disorders. Subset of children with the *FMR1* premutation experience developmental challenges, such as ADHD, social anxiety, shyness (Farzin et al., 2006; Clifford et al., 2007). Additionally, the premutation is linked to adult-onset conditions including Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), Fragile X-associated Primary Ovarian Insufficiency (FXPOI), and more recently, neurodevelopmental disorders associated with FXS, anxiety and depression (Johnson et al., 2020; Tassanakijpanich et al., 2021). In contrast to *FMR1* mutation, the *FMR1* premutation leads to elevated levels of *FMR1* mRNA. This excess mRNA causes a toxic gain-of-function effect, disrupting neuronal processes -potentially leading to ASD development (Hagerman et al., 2011).

The premutation is relatively prevalent in the general population, occurring more frequently in females than in males (Dombrowski et al., 2002; Song et al., 2003; Fernandez-Carvajal et al., 2009). While most carriers of the *FMR1* premutation allele do not meet diagnostic criteria for ASD, studies have identified a small proportion of premutation carriers in ASD cohorts (Baker et al., 2019; Gassman-Pines et al., 2020). Other data suggest that ASD prevalence is higher among premutation carriers compared to the general population (Farzin et al., 2006; Clifford et al., 2007; Zucker & Hinton, 2024). For example, Farzin et al. (2006) assessed ASD prevalence in 14 males with the premutation and clinical symptoms, compared to 13 males with the premutation but no clinical symptoms, and 16 males without the premutation. The prevalence of ASD was 79% in symptomatic premutation carriers, 8% in asymptomatic carriers, and 0% in non-carriers. Additionally, recent studies on genetic risk factors documented a higher prevalence of autism-related traits among mothers with the premutation compared to control mothers without it (Losh et al., 2012; Maltman et al., 2021; White et al., 2021). These findings suggest a connection between the *FMR1* premutation and ASD, raising important questions about the mechanisms driving the development of ASD in premutation carriers.

The *PTEN* gene and autism

The *PTEN* gene, located on chromosome 10 (10q23.3) in humans, was first described by Li and colleagues (Li et al., 1997). *PTEN* is classified as a tumor suppressor gene, which means that it regulates numerous cellular processes that, when disrupted, can lead to tumorigenesis (Song et al., 2012). Functionally, *PTEN* serves as a key antagonist of the phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PKB/AKT) signaling pathway, governing various cellular physiological processes, including differentiation and apoptosis (Hopkins et al., 2014; Kreis et al., 2014). *PTEN* is also known to play an important role in brain development (Veleva-Rotse & Barnes, 2014).

While heterozygous mutations in *PTEN* are predominantly associated with cancer in conditions such as Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Lhermitte-Duclos disease (Blumenthal & Dennis, 2008), these mutations have also been identified in individuals with ASD (Butler et al., 2005). *PTEN* mutations linked to ASD primarily function through a dominant-negative mechanism with catalytically active, but structurally unstable gene product (Rademacher & Eickholt, 2019). *PTEN* mutations have been implicated in disruption of key processes such as neuronal migration and cortical lamination, contribute to neuronal hypertrophy, and impaired synapse formation. Such changes disturb intrinsic neuronal properties, leading to altered neuronal excitability, synaptic plasticity, and compromised connectivity (Rademacher & Eickholt, 2019). *PTEN* mutations also affect glial cell function, disrupting differentiation and myelination processes. Together, these neural and glial abnormalities impair the brain's capacity for efficient information processing and result in broad neurocognitive ASD deficits (Rademacher & Eickholt, 2019). *PTEN* is an important element

of mTOR signaling pathway. Loss of *PTEN* function is responsible for mTOR hyperactivation so as loss of *FMR1* function. This, as already mentioned, opens the perspective that altered mTOR signaling is a common mechanism linking *PTEN* and *FMR1* dysfunctions with ASD development (Thomas et al., 2023).

The link between *PTEN* and ASD was first observed in 2005 (Butler et al., 2005) when *PTEN* sequencing revealed mutations in individuals with ASD and macrocephaly. This link was subsequently confirmed in later studies (Buxbaum et al., 2007; Herman et al., 2007; McBride et al., 2010; Klein et al., 2013). Macrocephaly is the most prominent clinical feature associated with *PTEN* mutations and is frequently accompanied by structural abnormalities in the brain (Reardon et al., 2001; Butler et al., 2005; Schaefer & Mendelsohn, 2013; Frazier et al., 2015). *PTEN* mutations have also been associated with seizure disorders.

Is there a distinct phenotype of ASD associated with *PTEN* mutations (ASD-*PTEN*)? The first study comparing patients with ASD-*PTEN* to a robust control group -patients with idiopathic ASD and macrocephaly was published in 2015 (Frazier et al., 2015). This study revealed a significantly higher frequency of missense mutations in the *PTEN* gene in ASD-*PTEN* patients. Frazier and others (2015) report a markedly larger head size correlated with significantly increased brain volume was a defining feature of ASD-*PTEN*. Additionally, the authors found that ASD-*PTEN* patients exhibited severe white matter deficits, as detected by magnetic resonance imaging (MRI), as well as lower intelligence quotients (IQ), slower information processing speeds, and more profound working memory deficits relative to the control group. Social and communication impairments were also more pronounced in the ASD-*PTEN* group than in the control group (individuals with idiopathic ASD and macrocephaly). Further data on the specificity of ASD phenotype in patients with *PTEN* mutations were published in 2019 (Busch et al., 2019). This study corroborated earlier findings of greater impairments in working memory, slower sensory information processing, and lower overall intelligence in ASD-*PTEN* patients compared to control individuals with idiopathic ASD and macrocephaly. Additional differences documented in this study included deeper attention deficits, more severe motor impairments, and reduced sensory processing capabilities in ASD-*PTEN* patients relative to the control group (individuals with idiopathic ASD and macrocephaly). However, no significant differences were observed in the extent of impaired social integration between these two groups (Busch et al., 2019).

CONCLUSIONS

A review of the literature on ASD in patients with mutations in the *FMR1* and *PTEN* genes indicates that these mutations can lead to the development of typical ASD-related impairments, which are often exacerbated in severity. Mutations in the *PTEN* gene are predominantly associated with structural brain abnormalities, including extreme macrocephaly and changes in white matter integrity, as well as profound deficits in sensory processing and working memory. In contrast, the specific characteristics of ASD in individuals with *FMR1* mutations are more difficult to define. Notably, ASD has also been identified in patients with *FMR1* premutations, a relatively recent discovery that expands the spectrum of clinical features associated with *FMR1* premutation carriers.

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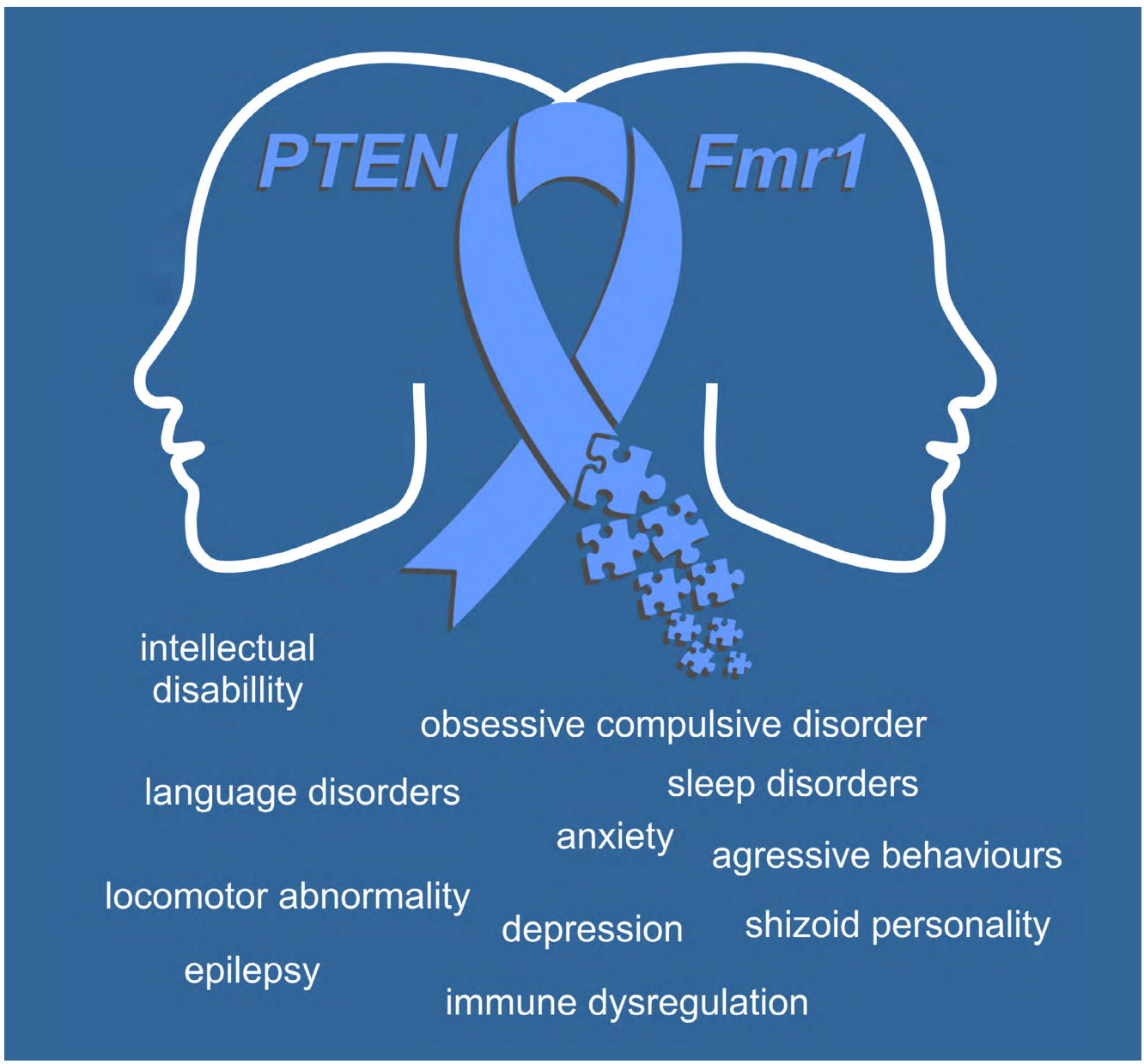
SUPPLEMENTARY MATERIALS



Graphical abstract