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REVIEW ARTICLE

An Overview of Psychopathological Manifestations in DDX3X Syndrome: A Narrative Review

ABSTRACT

Typical behavioral traits play a crucial role in the recognition of neurodevelopmental features in rare disorders, such as DDX3X syndrome. DDX3X syndrome is an X-linked genetic neurodevelopmental disorder and often presents with complex symptoms in the neurological, psychiatric, cardiological, ophthalmologic, and gastrointestinal domains, as well as structural brain abnormalities and precocious puberty. This overview study aims to review the psychopathological traits that are concurrent with DDX3X mutations. Although there are nearly 300 studies recorded in academic databases related to psychiatric comorbidities in this syndrome, it has been observed that most of these reports are at the case-report level, the number of cohort studies is quite low and there is only one review. A wide range of psychopathological manifestations is presented in patients with DDX3X syndrome, which may consist of but not limited to cognitive impairments, developmental delay, intellectual disability, language difficulties/delays, autistic traits, attention deficit-hyperactivity disorder, and conduct disorders. The complexity of neurodevelopmental issues in DDX3X syndrome highlights the requirement for a broader-based psychiatric screening, particularly for autism spectrum disorders.

Keywords: Autism spectrum disorders, behavioral problems, DDX3X syndrome, developmental delay, intellectual disability, psychiatric comorbidity, neurodevelopmental issues

Although rare diseases (RD) are recognized primarily due to their low prevalence levels (1), defining their clinical phenomenology based on their genetic basis is important for early diagnosis, treatment, and prognosis. DDX3X syndrome, the second most common genetic cause of developmental delays in the pediatric population (2), is also a rare X-linked neurodevelopmental disease. DDX3X is part of the DEAD-box helicase family, located on p11.3–11.23 on the X chromosome. The demonstrated variants are located throughout the DDX3X gene; however, they tend to cluster in the helicase ATP coding domain and C-terminal coding domain (3). It has widespread expression across human tissues and, based on its function in RNA metabolism, plays a pivotal role in the regulation of gene expression, cell cycle control, viral replication, and innate immunity (4-7). Several types of sequence variants in DDX3X are reported in the literature, including missense, nonsense, frameshift, splice site, stop-loss, and in-frame deletions (8). The majority of genetic defects in DDX3X syndrome are de novo variants in the DDX3X gene, particularly in females (8,9). Only a few de novo DDX3X gene mutations have been detected in males (10). Unlike many X-linked genes, DDX3X escapes X-inactivation in females. In this regard, variance in the clinical presentation of different cases is thought to vary according to X-inactivation patterns, even in twins and siblings (11). DDX3X syndrome is the consequence of a de novo mutation within a DDX3X gene at conception, which can be inherited but not frequently (6,9-12). According to recent findings from multiple cohorts, the DDX3X gene has the highest proportion of missense variants identified among other autosomal dominant de novo monogenic rare neurodevelopmental disorders (2).

The most common psychopathological expression of DDX3X de novo variants is developmental delay in both genders (6,9,10,13). To date, a total of 848 reported cases (809 females and 39 males) exist worldwide (14). However, there is no exact epidemiological data on the real prevalence of DDX3X syndrome. The gene-based prevalence of de novo mutations was estimated in a 2022 paper by extracting data from the number of neurodevelopmental disorders cohort cases, and the prevalence of DDX3X-related neurodevelopmental

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disorders with intellectual disability was estimated at 0.0036% (2). According to another research, DDX3X gene mutations were one of the common genetic etiologies of intellectual disability, considering the 1-3% prevalence of unexplained intellectual disability in females (9). Not only intellectual disability but also neurological manifestations, motor retardation, behavioral issues, cardiac dysfunctions, ophthalmic, and gastrointestinal problems may be presented in DDX3X syndrome (9,11,13,15,16). DDX3X variants were also associated with macro-anatomical abnormalities (gross MRI findings and brain tumor) in the central nervous system (4,17). Due to the complexity of phenomenology and findings in imaging techniques, DDX3X mutations are frequently misdiagnosed as cerebral palsy or autism spectrum disorders (18,19). Therefore, compared to other diagnostic methods, careful screening of cases combined with Whole Exome Sequencing prior to a final DDX3X syndrome diagnosis is crucial.

Identifying the indicative behavioral, cognitive, affective, or physiological manifestations is helpful for clinicians to provide early diagnosis and multidisciplinary management of rare disorders (20). Knowledge of the DDX3X-related psychopathological symptom range enables early diagnosis, multidisciplinary screening, and treatment, which improves the prognosis and quality of life (3). Although nearly 300 studies are recorded in academic databases related to behavioral manifestations in this syndrome, it has been observed that most of these reports are at the case-report level, the number of cohort studies is quite low, and there is only one review (3,9,17,21). In this regard, an up-to-date review of the prevalence distribution of psychopathological features in patients with DDX3X syndrome may be useful in determining the themes for further research on the subject. The questions are:

"What are the indicative psychopathological features presented in DDX3X syndrome?"

"How is the prevalence of psychopathological features distributed among patients with DDX3X syndrome?"

Psychopathological Frame in DDX3X Syndrome

The most common behavioral issues have been reported as intellectual disability or developmental delay, speech-communication dysfunctions, autism spectrum disorders or autistic-like traits, attention deficit-hyperactivity disorder, general anxiety disorder, self-injurious behaviors, sensorial hypersensitivities, and sleep disturbances (3,8,9,11-13,19,21,22). Among these psychiatric conditions associated with DDX3X mutations, intellectual disability/developmental delay and speech/communication problems were the most commonly reported ones. The recent cohort of Tang et al. (8), the first cohort of pediatric DDX3X syndrome (n=15, 3-16 years old) in a prospective study design, provides a comprehensive characterization of neurobehavioral symptoms in contrast to previous research: high rates of intellectual disability (80%), autism spectrum disorder (60%), and attention deficit-hyperactivity disorder (53%), as well as generalized anxiety disorder (7%), were demonstrated (8). A detailed description of each psychopathological feature is presented in Table 1 and subsections as follows:

Cognitive Impairment: Intellectual Disability & Developmental Delay
Intellectual disability/developmental delay is increasingly identified and appears to be a universal characteristic among patients

Table 1. Summary of the data regarding psychopathological features of DDX3X syn.

Frequently reported psychopathological features	Approximate Ratios from Studies*
Cognitive impairments: Intellectual disability/ Developmental delay	98%
Speech problems: Communication/Speech delay Developmental apraxia of speech	70%
Autism spectrum disorders	26%
Sensory symptoms: Sensorial hypo/hypersensitivity Sensory seeking	65%
Attention deficit-hyperactivity disorder	20%
Anxiety disorders: General anxiety disorders Specific phobias	40%
Self-injurious behaviors: Hair pulling Skin picking biting hands or knees Hitting their heads Throwing themselves onto the floor	56%
Sleep disturbances: Hypo/hypersomnia Early waking Long sleep latency Difficulty maintaining sleep Midnight awakenings	70%

*References: (3,8,9,11-14,19,21,22)

with DDX3X syndrome, both in pediatric and adult samples. The average prevalence of intellectual disability (Table 1), reported in most current cohorts, was nearly 98% (3,8,9,11-13,21,22), and the majority of reported patients met the criteria for intellectual disability ranging from mild to severe (9,12,13). Additionally, up to 3% of females with unexplained intellectual disability/developmental delay were associated with DDX3X mutations (9). However, intellectual disability was not reported in some case studies or cohorts with small sample sizes (11,19). Although the case (7 years old) reported by Stefaniak et al. (19) did not exhibit intellectual disability, severe difficulties were identified in social intelligence. In the cohort of Snijders et al. (9) of 38 females with DDX3X mutations (1-33 years old), de novo mutations in DDX3X were demonstrated as the most common genetic cause of intellectual disability in females. In the cohorts of Wang et al. (13) (1-47 years old; n=28) and Dai et al. (22) (1-6 years old; n=23), the ratio of patients with developmental delay or intellectual disability was 100%. Comparatively, the vast majority of participants with DDX3X mutations exhibited intellectual disability in the studies of Lennox et al. (12) (106:107, 1-24 years old), Tang et al. (8) (13:15, 3-16 years old), and Ng-Cordell et al. (21) (13:21, 3-22 years old). In the cohort of Levy et al. (3), intelligence levels ranged from average to severe, with the vast majority of cases demonstrating a global delay across all domains of adaptive functioning (according to Vineland III: communication, socialization, and daily living skills), with -3 standard deviations below the population mean (3). A subset of missense variants, likely with a dominant-negative functional consequence, are associated with more severe clinical manifestations, such as polymicrogyria and more severe intellectual disability (8,12). Furthermore, patients with protein-truncating variants, such as nonsense, frameshift, or splice site variants, tended to have a less severe phenotype than those with missense variants (8).

Speech / Communication Problems

A global delay in developmental milestones appears to be the most common neurodevelopmental issue in DDX3X syndrome, and language difficulties were almost universal across all available cohorts, with a report of approximately a 70% ratio (Table 1) (3,8,11,19,21,22). However, Snijders et al. (9) and Wang et al. (13) did not report communication or speech delay as a feature of DDX3X syndrome. Almost half of females with DDX3X syndrome were nonverbal after 5 years of age in the cohort of Lennox et al. (12), whereas 1/3 of those were reported as nonverbal in the cohort of Tang et al. (8). Furthermore, the verbal participants in the cohort of Tang et al. (8) also presented with delays in both receptive and expressive language skills. Patients with autism spectrum disorder scored higher on all language assessments compared to those without ASD (8). Beal et al. (11) described speech or motor delays in 4 out of 6 patients, one of whom exhibited severe speech and language deficits despite having a mild to moderate intellectual disability diagnosis. Almost 91% (21,23) of the patients in the cohort of Ng-Cordell et al. (21) exhibited speech/communication abnormality, with 17% of participants presenting with severe (non-verbal), 20% with moderate (expressing only with single words), and 48% with mild symptoms (expressing with both words and phrases). In the case report of Stefaniak et al. (19), the 7-year-old female case was non-verbal and had a strong desire for social interaction. In the Chinese cohort of Dai et al. (22), almost all of the participants with DDX3X syndrome were described as minimally verbal (expressing no more than four words). In the cohort of Levy et al. (3), language milestones were achieved with significant delays, such as expressing the first word at the 31st month and phrase speech at the 48th month. The use of augmentative and alternative communication was an auspicious form of support for some patients with DDX3X syndrome, though the statistic was not given in the cohort of Levy et al. (3). Given the example of monozygotic female twins with discordant phenotypes (one with autism, aggression, and non-verbal, the other with only minimal language problems) in the same cohort, specific variants may not predict the clinical presentation of DDX3X syndrome in contrast to the known paradigm in other genetic disorders (3).

Autism Spectrum Disorders (ASD)

DDX3X syndrome has recently emerged as the most prevalent genetic cause of ASD in females (9). According to recent reports from 'ddx3x.org' covering 50 countries, up to 769 DDX3X cases (38 males and 731 females) have also presented with ASD traits (14). Most available data on DDX3X syndrome reported ASD characteristics in patients with a ratio of approximately 26% (Table 1) (3,8,12,19,21,22), whereas few data did not describe ASD characteristics as separate traits but included them along with aggression and hyperactivity in the category of conduct problems (9,11,13). The heterogeneity in reports of ASD traits in patients with DDX3X syndrome may depend on the variety of assessment techniques used in previous studies. The highest prevalence of ASD traits (63%) was reported in the study of Levy et al. (3), which used gold standard assessment techniques, including The Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-R). However, previous research using parent-proxy clinical tools for assessment of autistic traits demonstrated different prevalence of ASD-resembling characteristics, although they also reported moderately higher levels of autism traits compared to general population norms (19,21,22). A novel non-canonical splice-site variant of the DDX3X gene was recognized in recent research, which exhibited autistic-like symptoms such as stereotypic behaviors that improved with inclusive education and behavioral interventions, as well as some characteristics that did not meet the diagnostic criteria of ASD, such as spontaneous behaviors, curiosity, and good socialization ability despite being nonverbal (19). ASD-resembling symptoms appear to be prevalent psychopathological features of DDX3X syndrome that can manifest as a wide range of symptoms with varying severity (3,23,24).

Sensorial Hypo / Hypersensitivity

Sensorial hypersensitivity/hyposensitivity was considered a new criterion in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for the diagnosis of ASD but is also reported in other neurodevelopmental disorders (25,26). Sensorial symptoms, defined as behavioral reactions (hyporeactivity, hyperreactivity, or sensory seeking) associated with atypical responses or unusual interest in sensory stimuli (25), were particularly mentioned as important characteristics in DDX3X syndrome in the previous two cohorts and one case report (8,19,21). In the prospective study of Tang et al. (8), using the Short Sensory Profile and Sensory Assessment for Neurodevelopmental Disorders for assessment of sensory symptoms, definite sensorial changes were reported in all participants with DDX3X syndrome. As part of the research of Tang et al. (8), the participants with DDX3X syndrome were matched with typically developing controls (n=29), and the Z-score was calculated.

Sensory symptoms in all symptom domains and sensory modalities were more frequent in the DDX3X group (100%) compared to the control group. Findings indicated that sensory processing disorders such as sensory seeking and hyporeactivity were more frequent than hyperreactivity (8). Moreover, tactile hyporeactivity was more common than visual or auditory hyporeactivity, while visual hyperreactivity was more frequent than tactile and auditory hyperreactivity (8). In the cohort of Levy et al. (3), high levels of sensory hyporeactivity (80%) and high sensory seeking behaviors (87%) were demonstrated in the DDX3X patients.

Attention Deficit-Hyperactivity Disorder (ADHD)

ADHD was particularly mentioned in the cohorts of Lennox et al. (12) and Tang et al. (8). The ADHD ratio was identified as 15% in the cohort of Lennox et al. (12), while it was 40% in the cohort of Tang et al. (8). The disruptive and maladaptive behaviors exhibited by participants in other studies may be considered as belonging to other psychiatric or behavioral concerns (3,9,11,13,19,21,22). On the other hand, behavioral and psychotropic interventions for disruptive and maladaptive behaviors, and further assessment of these behavioral traits as ADHD diagnosis were recommended (3).

Internalizing Traits and Other Psychopathological Issues

General anxiety disorder was particularly mentioned in the two most recent cohorts (3,21), but it had not been addressed in papers before 2022 (8,9,11-13,19,22). The presentation ratio is approximately 40% for anxiety disorders in available studies (Table 1). Anxiety symptoms, including specific phobias related to sounds, animals, or objects, shyness, social withdrawal, and concerns about routines, were presented in 69% of DDX3X participants in the cohort of Ng-Cordell et al. (21). One case in the paper by Levy et al. (3) presented with separation anxiety and behavioral aggression triggered by fear of frustration. Anxiety and affective disorders require further investigation in DDX3X patients as newly described conditions in the literature.

Self-injurious behavior was mentioned only in the paper by Ng-Cordell et al. (21), where this behavioral pattern was first identified as a significant feature of DDX3X syndrome. In the cohort of Ng-Cordell et al. (21), almost 56% (13,23) of participants with DDX3X syndrome presented with self-injurious behaviors, including stress-triggered hair pulling, skin picking, biting hands or knees, hitting their heads, and throwing themselves onto the floor; the prevalence of self-injurious behaviors was higher than in the control group with autism (21). The authors of this study particularly highlighted the link between self-injurious behaviors and anxiety (21), suggesting that further research on the role of stress, anxiety, and affective traits in other frequently reported maladaptive behaviors in DDX3X syndrome is warranted. There is a need for more research on self-injurious behaviors among patients with DDX3X syndrome, particularly in the affected pediatric population, to establish appropriate management strategies.

Sleep disturbances have been recognized in some previous studies, with a prevalence of nearly 70% (3,11,19,21) (Table 1). Nearly one-third of participants in the study by Beal et al. (11) presented with sleep disturbances, while almost 56% of DDX3X patients in the study by Ng-Cordell et al. (21) presented with sleep problems such as hypo/hypersomnia, early waking, long sleep latency, and difficulty maintaining sleep. In the review by Levy et al. (3), the prevalence of sleep disturbances was summarized as high as 80% (20,25).

DISCUSSION

Early diagnosis of manifestations in different domains is crucial for the accurate management of rare disorders. DDX3X syndrome is a rare, complex genetic disorder associated with varied psychopathological phenotypes, particularly neurodevelopmental issues. However, the full spectrum of psychopathological issues in DDX3X syndrome is not well known or investigated. Therefore, more studies with diverse and larger samples are needed to broaden our understanding of this syndrome and its behavioral manifestations. Additionally, there is an important need for Whole Exome Sequencing screening in children with unexplained intellectual disability/developmental delay, developmental speech delays, and childhood apraxia of speech, as various DDX3X gene mutations are a highly plausible genetic etiology for these disorders (9,27).

The findings from this manuscript, aiming to present a narrative review of the limited literature on the psychopathological framework of DDX3X syndrome, demonstrate varied psychiatric manifestations, predominantly including neurodevelopmental issues like intellectual disability/developmental delay, speech/communication problems, autism spectrum disorders, and ADHD, as well as internalizing and behavioral traits such as general anxiety disorder, specific phobia, self-injurious behaviors, sleep disturbances, and sensory symptoms (Table 1). The wide range of externalizing and internalizing traits in pediatric patients with DDX3X syndrome also raises concerns about the high possibility of misdiagnosing early neurodevelopmental issues. Therefore, the clinical utility of exome sequencing in preventing misdiagnosis of ASD, cerebral palsy, Rett syndrome, Dandy-Walker syndrome, Toriello-Carey syndrome, or idiopathic intellectual disability is important (19,28). It should be noted that patients with DDX3X syndrome often demonstrate a strong desire to be cooperative, caring, and friendly in social situations, according to parent-proxy reports of social functioning (21), in contrast to autistic-like behaviors, self-injurious behaviors, and anxiety disorders. However, the positive social abilities of patients with DDX3X syndrome have not yet been described or explored in the literature, other than brief mentions in medical interviews with caregivers (19,21).

On the other hand, the alertness of psychiatrists regarding the association of the aforementioned developmental and behavioral traits with discordant DDX3X mutations is important to prevent overlooking the physical manifestations that accompany psychiatric problems. These include neurological issues (hypotonia, epilepsy, gait disturbance, and other movement disorders), cardiological conditions (ventricular septal defect, atrial septal defect, patent ductus arteriosus, patent foramen ovale, and long QT syndrome), gastrointestinal problems (chronic constipation, gastroesophageal reflux, and feeding issues), ophthalmological concerns (ocular and visual abnormalities such as strabismus, nystagmus, colobomas, myopia, hypermetropia, astigmatism, etc.), endocrinological disorders (precocious puberty, hypothyroidism), dermatological conditions (café-au-lait spots, eczema, congenital dermal melanocytosis, cutaneous mastocytosis, and other types of nevus), recurrent infections (recurrent otitis media, urinary tract, and upper respiratory infections), auditory problems, and scoliosis (3). Accurate and early diagnosis of each symptom domain in DDX3X syndrome can enable patients to benefit from appropriate therapy, early educational and physical rehabilitation programs, and primary care. Due to insufficient clinical data, formal diagnostic criteria for DDX3X syndrome

have not been established, nor have formal practice parameters for managing the care of patients with DDX3X syndrome (3,29).

With the help of 'Next Generation Sequencing' or 'Whole Exome Sequencing', a broader group of genes related to intellectual disability can be detected, enabling the differential diagnosis of DDX3X syndrome from other intellectual disability-related genetic disorders (3,30-32). Patients with RSRC1 gene mutations present with global intellectual disability/developmental delay, behavioral problems, and hypotonia (30), whereas ADGRL1 haploinsufficiency can lead to consistent developmental, neurological, and behavioral abnormalities (32), and variants in the RAC3 gene have been linked with structural brain abnormalities and facial dysmorphia (31). Therefore, 'Next Generation Sequencing' and 'Whole Exome Sequencing' are particularly crucial for patients who do not exhibit strictly marker features for well-known developmental disorders. Even if patients meet clinical features of such disorders as ASD, ADHD, intellectual disability, speech delay, articulation problems, general anxiety disorder, self-injurious behaviors, communication/speech delay, or sensory symptoms, psychiatric consultation and a thorough clinical investigation before a final diagnosis are essential. For patients with each specific diagnosis, a specialized educational program based on standardized adaptive and academic testing is necessary to support the individual's unique learning profile.

A developmental assessment (e.g., determination of expressive and receptive language and communication abilities, evaluation of verbal and nonverbal cognitive function, and evaluation of the achievement of fine and gross motor milestones and skills) is recommended at the time of DDX3X syndrome diagnosis. This should be followed by referrals for early intervention and special education, speech and language therapy, occupational therapy, and ABA therapy as clinically indicated. Recommendations include the possible use of pharmacological approaches, as indicated by the treating physician, behavior therapy, and caregiver training and guidance to support patient-based behavioral intervention strategies. Additionally, there is no reason to assume that individuals with DDX3X syndrome have any less risk for mood disorders; thus, mood and affect should be assessed, and developmentally appropriate engagement in pleasurable activities should be screened for and encouraged at routine pediatric visits, with referral for psychiatric assessments as indicated.

CONCLUSIONS

In this narrative review of the psychopathological features of DDX3X syndrome, the most up-to-date knowledge is presented, based on the recent increase in research on the issue over the last few years. Given the insufficiency of available data, especially regarding the small group of patients living in different locations around the world, more specific studies of these psychopathological traits are required, particularly in a wider context. This includes studies on speech and internalizing problems, as well as the correlation between anxiety and self-injurious behaviors, reflecting the increased demand for behavioral and psychotherapeutic support during childhood.

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