Consensus of the Fragile X Clinical & Research Consortium on Clinical Practices

Autism Spectrum Disorder in Fragile X Syndrome

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Abbreviations:
FXS – fragile X syndrome
ASD – autism spectrum disorder
DSM – Diagnostic and Statistical Manual of Mental Disorders
FMR1 gene – fragile X mental retardation 1 gene
FMRP – fragile X mental retardation protein
ID – intellectual disability

Introduction
Families are often confused by the relationship between fragile X syndrome (FXS) and autism. It is not uncommon for a child to initially be diagnosed with autism and later to receive an *additional* diagnosis of FXS. This document attempts to bring clarity to how the autism spectrum disorder diagnosis and FXS can overlap, and where they do not. Understanding this distinction can be particularly helpful when deciding upon the most appropriate medical, therapeutic, counseling and education interventions, and will increase the potential for both short-term and long-term improvements.

What is the definition of autism spectrum disorder?
Autism spectrum disorder (ASD) is a developmental disorder characterized by a selective impairment in social interaction. Symptoms of ASD appear in early childhood. It is a lifelong disorder, although symptoms change over time. People with ASD have differences in how they understand and react to people and social situations, which result from differences in how their brains process socially-relevant information. For a person to meet diagnostic criteria for ASD, impairment in important areas of functioning cannot be clearly attributed to limited communication skills or overall impairment in intellectual function (e.g., intellectual disability). At this time, there is no medical test, such as a blood test or brain scan that can diagnose ASD.

In the past, ASD was represented by three different diagnoses: autistic disorder; Asperger syndrome; and pervasive developmental disorder, not otherwise specified (PDD-NOS). These three diagnoses were recently combined into the one diagnosis of ASD. The term, "spectrum," in ASD means that each person can be affected in different ways, and symptoms can range from having mild to severe impacts on a person's functioning.

According to *the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychological Association, 2013),* ASD is characterized by impairments in social communication and social interaction and the presence of restricted, repetitive behaviors.

Social communication and ***social interaction*** symptoms involve:
- Deficits in socio-emotional reciprocity (e.g., having a conversation, sharing interests and emotions)
- Deficits in nonverbal communication used for social interaction (e.g., lack of or inconsistent eye contact, facial expressions, and/or gestures)
- Deficits in developing and understanding social relationships (e.g., friendships, understanding rules for social behavior).

Restricted, repetitive behaviors include:
- Stereotyped or repetitive motor movements (e.g., hand flapping), use of objects (e.g., spinning or lining up toys), and/or speech (using repetitive and/or unusual words or phrases)
- Insistence on sameness and/or ritualized patterns of behavior (e.g., extreme distress at small changes, difficulties with transitions, needing to follow the same schedule or sequence of completing activities)
- Unusual or overly intense interests (e.g., interest in an unusual object or topic, intense in a narrow area)
- Hyper- or hypo-reactivity to sensory input (e.g., negative reactions to certain textures or sounds; excessive smelling, peering at, or touching of objects)

When diagnosing ASD the clinician should state whether it is associated with a known medical, genetic or environmental factor. They should also specify whether ASD is with or without accompanying intellectual impairment and with or without accompanying language impairment.

What is known about the causes of ASD?
ASD is a complex condition with a common set of behavioral symptoms, but with varied and yet incompletely understood underlying risk factors and biological mechanisms. ASD is a lifelong neurobehavioral condition that both impacts and is impacted by a person's development. Although people with ASD share core features of social interaction and other behavioral deficits, these symptoms can vary widely in form and severity. Further complicating the picture, many individuals with ASD have co-occurring conditions, such as language disorders, intellectual disability, or mental health diagnoses (e.g., ADHD, depression).

There is a strong genetic component to ASD. For example, siblings of children with ASD have a higher risk of having ASD: almost 20% of younger siblings of a child with ASD will receive a diagnosis of ASD themselves (Ozonoff et al., 2011). This is much higher compared to the general population risk of 1-2% (CDC, 2012). About 15% of children with ASD have also been identified as having a genetic disorder, such as fragile X syndrome, tuberous sclerosis, Down syndrome or other chromosomal abnormalities, copy number variants, and single gene mutations

[Kaufmann et al., 2008]. It is expected that as genetic testing becomes more sensitive the percentage of individuals with a genetic cause of ASD will increase further, however, non-genetic factors also have been found to play a role.

What is known about the relationship between fragile X syndrome and ASD?

Fragile X syndrome (FXS) is the most common known single gene disorder associated with ASD, accounting for about 2-3% of all cases of ASD [Muhle et al., 2004; Schaefer&Mendelsohn, 2008]. FXS is caused by a expansion of a CGG repeat sequence to >200 repeats (full mutation) in the promoter region of the *FMR1* gene, which results in a loss of its encoded protein: the Fragile X Mental Retardation Protein (FMRP) [Hagerman et al., 2009].FXS can be diagnosed by a DNA blood test, unlike ASD which is a ***behaviorally***-defined diagnosis. The behavioral characteristics of FXS, although quite variable, can include many features of ASD, such as deficits in social interaction and communication (e.g., poor eye contact, problems with peer relationships, social withdrawal) (Budimirovic & Kaufmann, 2011), repetitive motor movements, need for sameness, and self-injurious behavior (e.g., hand biting) (Hagerman, 2002). Many individuals diagnosed with FXS meet criteria for a diagnosis of ASD. Direct research on FXS and ASD has suggested that 18 to 67% of males and 20% of females with FXS meet criteria for ASD [Kaufmann et al., 2004; Budimirovic et al., 2006]. Findings from the FXCRC Database through 2011 suggest that 38% overall, and 42% of males and 23% of females, with FXS, are diagnosed with ASD by a provider at their FXCRC Clinic.

Why are autistic features common in FXS?

Our current knowledge about ASD indicates that it is a developmental brain disorder, beginning shortly after birth or even earlier. It's most characteristic feature is the presence of abnormal patterns of neural "wiring" or connectivity. Because multiple genetic and environmental factors have been linked to ASD, there are probably multiple ways in which neural connectivity and other processes can be disrupted, leading to a diagnosis of ASD. It is likely that ASD is frequently present in FXS because the lack of FMRP in FXS adds to the risk of developing abnormal wiring and related brain abnormalities. In other words, a person with FXS may need fewer "other genetic or environmental ASD risk factors" to develop ASD.

There is evidence, based on gene studies and studies of proteins in neural cells, that FMRP plays a role in ASD. FMRP, which is absent or deficient in FXS, normally turns off protein synthesis (the process of proteins being made) in the neural dendrites. When certain receptors (such as GABA, AMPA, and mGluR) are activated, this releases the FMRP brake and allows proteins to be made. In this way, FMRP regulates the levels of many proteins important at brain connections. Many proteins that have similar jobs as FMRP and also interact with FMRP, have been found to be associated with ASD [De Rubeis and Bagni, 2011; Darnell et al., 2011]. In addition, many of the proteins regulated by FMRP have been found to be associated with ASD [Iossifov et al.,

2012; Ascano et al., 2012]. Thus, deficits in FMRP seem to be linked to dysfunction in brain pathways and connections that lead to behavioral symptoms of ASD.

It may be helpful to think of ASD as a "cloud" (see Figure 1), which represents a final common diagnostic category representative of abnormal patterns of brain wiring resulting from a combination of multiple diverse genetic and other etiologies. Some etiologies may be unknown or multifactorial – that is, dependent on a number of factors together.
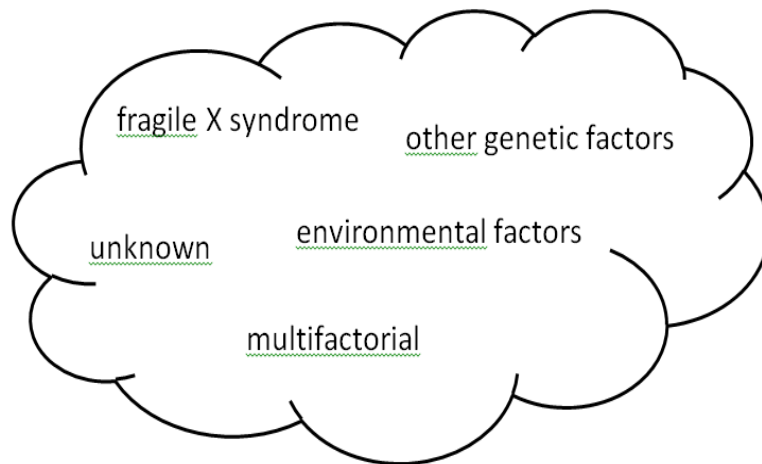

Figure 1: ASD represented by a combination of multiple diverse genetic and other etiologies

The cloud contains a common set of behavioral characteristics that are core features of ASD: social communication and interaction deficits and restricted and repetitive patterns of behaviors. Within the cloud, there are spots with specific symptom patterns. For example, individuals with ASD and high levels of insistence on sameness may represent one spot in the cloud. Similarly, individuals with FXS who meet criteria for the current definition of ASD represent a spot in the cloud where an individual may meet criteria for ASD with higher social anxiety, intellectual disabilities, hyperarousal, repetitive behaviors and other FXS-related differences (Hall et al., 2010).

However, not all individuals with FXS meet criteria for the diagnosis of ASD. FXS is not a kind of ASD but a genetic disorder with its own set of symptoms, and with several behavioral symptoms seen in ASD. The image of a cloud suggests that the borders of ASD are diffuse, and so sometimes, whether or not someone should get a diagnosis of ASD is unclear. The level of overlap between the FXS behavioral phenotype (symptoms) and ASD determines whether a person with FXS makes it into the cloud of ASD. Some individuals may have enough ASD features to be near the cloud, but not at the threshold needed for an ASD diagnosis. Those with FXS who are in the ASD cloud likely have genetic factors besides FMRP deficiency that pushed them toward meeting ASD criteria. Intellectual Disability (ID) is also a feature of FXS that is nearly uniform for males with FXS, but not for females. ID may be common in ASD but is not

necessary or sufficient for ASD, nor for FXS (see Figure 2 - the Venn diagram is used for schematic purposes showing the set relationships but is not designed to be proportional).
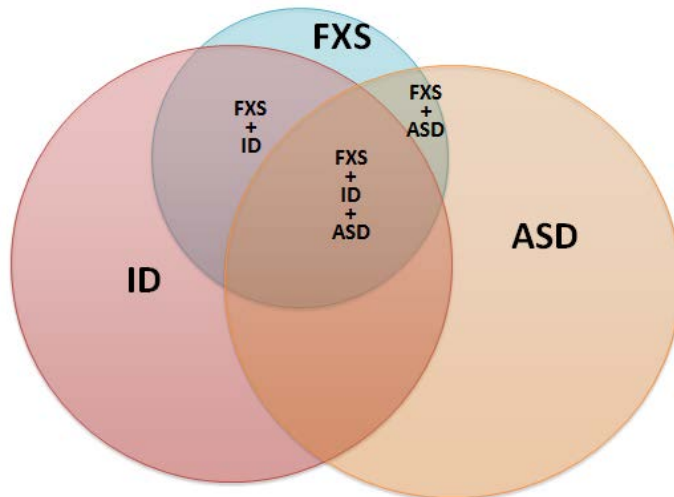
Figure 2: Venn diagram displaying set relationships between FXS, ID, and ASD (size of overlaps only approximate).

What are some similarities and differences between the behavioral phenotype of FXS and the **behavioral criteria for ASD**? Neurological and behavioral characteristics *common* to both the FXS behavioral phenotype and ASD include:

- Social interaction deficits including problems accurately reading and responding to social situations
- Communication/language deficits; in FXS involving a wide range of language and speech aspects, while ASD mainly involving non-verbal communication and language pragmatics (use of language in social situations)
- Poor eye contact
- Repetitive uses of objects and repetitive motor movements
- Intellectual disability in nearly all males and some females with FXS and a high proportion of those with ASD
- Unusual reactions to sensory input, including hyper-sensitivity (e.g., tactile defensiveness) and hypo-sensitivity (e.g., high tolerance for pain, visual fascination with moving objects or lights), the latter more common in ASD
- An area of strength in visual memory
- Seizures in a higher proportion than the general population
- Motor coordination problems (e.g., handwriting deficits, atypical walking patterns)
- Difficulties with attention, activity level, emotional behavior, and mood, often leading to additional diagnoses (e.g., ADHD, anxiety, mood disorder)
- Other problematic behaviors(e.g., aggression, noncompliance, self-injury)
- Sleep problems

While similar behavioral characteristics or symptoms may be present in individuals with ASD and individuals with FXS who meet criteria for ASD, clinicians working with individuals with FXS who meet diagnostic criteria for ASD observe distinct differences - e.g. lack of social initiative alone does not necessarily imply the absence of social awareness or social interest. For most individuals with FXS, social initiation deficits reflect intellectual disabilities and general or social anxiety. In contrast, social initiation deficits in ASD, including individuals with FXS who meet criteria for ASD, more often originate from reduced interest in and motivation for social interaction or failure to attend to social information that might promote appropriate social behavior.

A similar trend is found for eye contact. Although poor eye contact is characteristic of both FXS and ASD, the *nature* of eye contact deficits may be substantially different. Individuals with FXS typically avoid eye contact directly (Watson et al., 2008; Hall et al, 2009); looking away from people may help in coping with emotional discomfort that is driven by underlying social anxiety (Budimirovic & Kaufmann, 2011). While social anxiety might also play a role in some individuals with ASD, including those with FXS who meet criteria for ASD, other individuals with ASD make little eye contact. This is because they do not recognize social cues such as eye gaze as a source of information or interaction or are unable to respond to such cues. Brain imaging studies support this distinction [Hoeft et al., 2011; Hazlett et al., 2012].

Characteristics that have been found to **differ** between the FXS behavioral phenotype and ASD include:
- The frequency of intellectual disability is higher in FXS than ASD. Most males and about a third of females with FXS have intellectual disability, while only about 40% of individuals with ASD have intellectual disability.
- Motor coordination deficits are worse in FXS than ASD
- Individuals with ASD are more likely to show worse receptive language than expressive language, while individuals with FXS tend to show the opposite pattern.
- Interest in socializing is higher in FXS in general than ASD (although limited by anxiety and avoidance)
- Imitation skills are better in FXS than ASD when level of intellectual impairment is controlled

What are the differences between individuals with FXS who do not meet criteria for ASD and those who do meet criteria?

Outlined above were descriptions of behaviors in common and different between the FXS behavioral phenotype and ASD. Compared to individuals with FXS who do not meet criteria for ASD, characteristics of individuals with FXS who meet criteria for ASD include:
- Less developed language skills, particularly receptive skills
- Lower non-verbal cognition and IQ scores
- Lower adaptive skills

- More severe overall behavioral problems than individuals with FXS.
- Reduced interest in and motivation for social interaction or a failure to attend to social information that might promote appropriate social behavior.

Consequently, from educational and vocational viewpoints, individuals with FXS who meet criteria for ASD face similar but more severe challenges than children with FXS.

What are some recommendations for treatment of FXS who meet criteria for ASD?
Challenging behaviors seen in a higher proportion of children with FXS who meet criteria for ASD than those who don't, such as attention problems, hyperactivity and impulsivity, anxiety, and aggressive and self-injurious behaviors, can significantly impact an individual's academic and adaptive functioning, limiting their participation in the community. In addition to behavioral therapy, the mainstay of treatment, medication can sometimes be helpful to support therapeutic services (e.g., speech-language, occupational, and educational) and to allow a child to learn in the least restrictive environment. Because of the prominence of ADHD symptoms, in general, children with FXS may be more likely to respond to treatment with stimulant medication than those with ASD; however, caution should be taken as individuals with FXS in general and those with FXS who meet criteria for ASD in particular, may experience worsening symptoms of perseverative, anxious, or irritable behaviors, as is often seen in those with ASD.

For children with FXS, irrespective of whether they meet criteria for ASD, interventions that target communication and socialization skills are appropriate; however, for those who meet criteria for ASD, more intensive speech/language therapy, with emphasis on group sessions, behavioral therapy, and augmentative technology are often indicated. Young children diagnosed with FXS who meet criteria for ASD should have intensive therapeutic intervention through Early Intervention programs. Because of their relatively lower cognitive level, educational strategies for children with FXS who meet criteria for ASD may need to include as much focus on daily living skills as on academics. The crucial point for teachers, therapists, and others involved in the support of individuals with FXS irrespective of whether or not they meet criteria for ASD is to utilize existing knowledge about behavior and learning styles in an individualized manner. That approach will help to better customize these educational, behavioral and other strategies to the needs of each individual.

What are areas for further research regarding the relationship between FXS and ASD?
Further studies are needed to refine our understanding of the molecular and cellular differences and similarities between individuals with FXS who do and do not meet criteria for

ASD and other genetic types of ASD. In addition, we need further studies to understand the role of interacting genetic abnormalities and environmental factors in determining whether an individual with FXS meets criteria for ASD. Studies of educational, behavioral and non-pharmacological therapeutic interventions (e.g. Applied Behavior Analysis) are also needed to generate evidence on which to base recommendations, including the similarities and differences between recommendations for patients with FXS who meet or do not meet criteria for ASD, and idiopathic ASD. Lastly, clinical trials of both standard pharmaceutical medications and new treatments targeted to underlying brain mechanisms are needed to explore whether individuals with FXS who meet or do not meet criteria for ASD respond differently to treatment.

SUPPLEMENT

What are the key differences in criteria used to define autism in the *DSM-IV and DSM-5*?

The recent fifth edition of the *Diagnostic and Statistical Manual (DSM-5;* APA, 2013) went into effect in May 2013, and with it came significant revisions to the diagnosis of ASD. The *DSM-IV* (APA, 1994) made distinctions between autistic disorder, pervasive developmental disorder-not otherwise specified (PDD-NOS), and Asperger syndrome. One of the more significant changes to the DSM-5 was the combining of these separate, categorical diagnoses into one diagnosis: autism spectrum disorder (ASD). The DSM-5 definition of ASD identifies a smaller number of key deficits in social communication and interaction that are expected to be present in all individuals with ASD regardless of age or developmental level, but that can be shown in many different ways. In addition, DSM-5 restricted the range of language and communication impairments associated with ASD to those used for social interaction. The DSM-5 now includes "specifiers" regarding whether the individual's ASD is accompanied by intellectual impairment and/or language impairment. It also includes severity levels reflecting the level of support needed.

While controversial, the changes in DSM-5 do not represent a stark departure from current practice. In 1991, Happé and Frith proposed the term "autism spectrum disorders" based on concerns that the umbrella category of Pervasive Developmental Disorder (PDD) lacked clearly-specified deficits, and research suggested that individuals did not fit cleanly into one of three possible diagnoses. Most research to identify distinctive features of autistic disorder, Asperger syndrome, and PDD-NOS failed to find any reliable differences once IQ or language was controlled. Distinctions among these diagnoses were inconsistent over time and variable across clinicians (e.g., Frith, 2004; Howlin, 2003; Lord et al., 2011; Macintosh & Dissanayake, 2004; Ozonoff, South, & Miller, 2000; Prior et al., 1998; Snow & Lecavalier, 2011). Furthermore, the diagnoses did not necessarily predict more positive or negative child outcomes (Ozonoff et al., 2000; Szatmari et al., 2009; Szatmari, Bryson, Boyle, Streiner, &Duku, 2003) and thus were uninformative for treatment planning. Indeed, while the term was not adopted in the DSM-IV, "autism spectrum disorder" became commonly used (Williams et al., 2008).

Another significant change is the reorganization of symptoms and symptom clusters. Whereas the DSM-IV presented triad of symptoms in social interaction, communication, and restricted and repetitive patterns of behavior, the DSM-5 represents ASD symptoms across two domains: social communication and interaction and restricted, repetitive behaviors. The DSM-5 adds a new restricted, repetitive behavior symptom of unusual responses to sensory input. Other

repetitive behaviors from DSM-IV have been reorganized or consolidated in the DSM-5. For example, the stereotyped speech symptom from DSM-IV has been consolidated with repetitive motor movements and use of objects into a single symptom criterion. The DSM-IV autistic disorder criterion of a delay or complete lack of development in expressive language has been removed, because research has shown this feature is neither unique to nor universal in individuals with ASD (Hartley & Sikora, 2009; Matson & Neal, 2010). The DSM-IV criterion of limitation in or lack of development of imaginative play has been narrowed to deficits in *sharing* imaginative play with others.

In the DSM-IV, there was a more complicated algorithm necessitating a certain threshold number of qualitative impairments in social interaction, and in communication, and repetitive behaviors, with the threshold number differing between the categories. Under the DSM-5, children must meet all three social communication criteria and two of the four repetitive behavior criteria in order to receive a diagnosis. However, criteria can be met based on earlier history even if the individual is no longer showing a particular symptom or behavior. These changes were made to improve diagnostic accuracy and reduce number of individuals who are misdiagnosed with ASD.

While Asperger syndrome was incorporated into the umbrella ASD definition in DSM-5, a new diagnosis, social (pragmatic) communication disorder (SCD), was created to reassign many individuals that were previously lumped into the PDD classification in DSM-IV. Individuals with the DSM-IV label of Asperger syndrome are now captured by the specifiers of ASD "without intellectual impairment" and "without language impairment" in DSM-5 (Baron-Cohen, 2013). SCD is characterized by a persistent difficulty with verbal and nonverbal communication for *social purposes* that cannot be explained by low cognitive ability, and which leads to impairments in the ability to effectively communicate, participate socially, maintain social relationships, or otherwise perform academically or occupationally (APA, 2013). ASD must be ruled out before SCD can be diagnosed.

Finally, the DSM-IV required presence of symptoms before age 3 years. Recognizing that some children may not show clear symptoms until social expectations exceed their capacities, the DSM-5 requires that symptoms must be present early in life but no longer uses age 3 as a benchmark. The symptoms of ASD also must result in impairment in social, occupational, and/or other important areas of functioning, with the caveat that individuals may be able to reduce or mask some symptoms through intervention, compensation, or environmental supports. Although specific symptom criteria can be documented by history, ASD symptoms should remain sufficient to cause current impairment (APA, 2013).

References

American Psychiatric Association.(2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*. Arlington, VA: American Psychiatric Publishing.

Ascano, M., Jr, Mukherjee, N, Bandaru. P., Miller, J.B., Nusbaum, J.D., Corcoran, D.L., Langlois, C., Munschauer, M., Dewell, S., Hafner, M., Williams, Z., Ohler, U., Tuschl, T. (2012). FMRP targets distinct mRNA sequence elements to regulate protein expression. Nature 492:382–386.

Bagni, C., Greenough, W.T. (2005). From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome. Nat Rev Neurosci, 6, 376–387.

Baron-Cohen, S. (2013, May 30). Despite fears, DSM-5 is a step forward. [Web log post.] Retrieved from http://sfari.org/news-and-opinion/specials/2013/dsm-5-special-report/despite-fears-dsm-5-is-a-step-forward

Barton, M. L., Robins, D. L., Jashar, D., Brennan, L., & Fein, D. (2013). Sensitivity and specificity of proposed DSM-5 criteria for autism spectrum disorder in toddlers. *Journal of Autism and Developmental Disorders, 42*(5), 1184-1195.

Budimirovic, D.B., Bukelis, I., Cox, C., Gray, R.M., Tierne,y E., Kaufmann, W.E. (2006). Autism spectrum disorder in fragile X syndrome: differential contribution of adaptive socialization and social withdrawal. Am J Med Genet, 140A,1814–1826.

Budimirovic, D.B., & Kaufmann, W.E. (2011). What Can We Learn About Autism from Studying Fragile X Syndrome? *Developmental Neuroscience, 33* (5)*,* 379-394. DOI:10.1159/000330213.

Carey, B. (2012, January 19). New definitions of autism will exclude many, study suggests. *The New York Times*. Retrieved from http://www.nytimes.com

Centers for Disease Control and Prevention. (2012). Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, United States, 2008. *Morbidity and Mortality Weekly Report* (Report No.61[SS03]]). Washington, DC: Government Printing Office.

Darnell, J., Van Driesche, S.J., Zhang, C., Hung K.Y., et al. (2011). FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism. Cell, July 22, 146(2), 247–261. doi: 10.1016/j.cell.2011.06.013

De Rubeis, S., **Bagni,** C. (2011). Regulation of molecular pathways in the Fragile X Syndrome: insights into Autism Spectrum Disorders. J Neurodev Disord, September 3(3), 257–269. Published online 2011 August 13. doi: 10.1007/s11689-011-9087-2

Frazier, T. W., Youngstrom, E. A., Speer, L., Embacher, R., Law, P., Constantino, J., . . .Eng, C. (2012). Validation of proposed DSM-5 criteria for autism spectrum disorder.*Journal of the American Academy of Child and Adolescent Psychiatry, 51*(1), 28-40. doi: 10.1016/j.jaac.2011.09.021

Frith, C. (2004). Is autism a disconnection disorder? *Lancet Neurology 3*(10), 577.

Gibbs, V., Aldridge, F., Chandler, F., Witzlsperger, E., & Smith, K. (2012).An exploratory study comparing diagnostic outcomes for autism spectrum disorders under DSM-IV-TR with the proposed DSM-5 revision.*Journal of Autism and Developmental Disorders, 42*(8), 1750-1756. doi: 10.1007/s10803-012-1560-6

Grant, R, &Nozyce, M. (2013). Proposed changes to the American Psychiatric Association diagnostic criteria for autism spectrum disorder: implications for young children and their families. *Maternal and Child Health Journal 17*(4), 586-592.

Hagerman RJ: The physical and behavioral phenotype; in Hagerman RJ, Hagerman PJ (eds) (2002). Fragile X Syndrome: Diagnosis, Treatment, and Research, ed 4. Baltimore, Johns Hopkins University Press, pp 3–110.

Hagerman, R.J., Berry-Kravis, E., Kaufmann, W.E., Ono, M.Y., Tartaglia, N., Lachiewicz, A., Kronk, R., Delahunty, C., Hessl, D., Visootsak, J., Picker, J., Gane, L., Tranfaglia, M. (2009). Advances in the treatment of fragile X syndrome. Pediatrics, 123, 378–390.

Hall, S.S., Lightbody, A. A., Hirt, M., Rezvani, A., & Reiss, A.L. (2010). Autism in Fragile X Syndrome: a category mistake? Journal of the American Academy of Child and Adolescent Psychiatry, 54, 921-933.

Happé, F, &Frith, U. (1991). Debate and argument: How useful is the "PDD" label? *Journal of Child Psychology and Psychiatry and Allied Disciplines 32*(7), 1167-1168.

Hartley, S. L., &Sikora, D. M. (2009). Which DSM-IV-TR criteria best differentiate high-functioning autism spectrum disorder from ADHD and anxiety disorders in older children? *Autism*, *13*(5), 485-509.

Hatton, D.D., Sideris, J., Skinner, M., Mankowski, J., Bailey, D.B. Jr (2006). Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP. Am J Med Genet, 140A, 1804–1813.

Hazlett, H.C., Poe, M.D., Lightbody, A.A., Styner, M., MacFall, J.R., Reiss A.L., Piven J (2012). Trajectories of early brain volume development in fragile X syndrome and autism. J Am Acad Child Adolesc Psychiatry, Sep;51(9):921-33. doi: 10.1016/j.jaac.2012.07.003. Epub 2012 Aug 1.

Hoeft, F., Walter, E., Lightbody, A.A., Hazlett, H.C., Chang, C., Piven, J., Reiss, A., (2011). Neuroanatomical differences in toddler boys with fragile X syndrome and idiopathic autism. Arch Gen Psychiatry, 68, 295–305.

Howlin, P. (2003). Outcome in high-functioning adults with autism with and without early language delays: implications for the differentiation between autism and Asperger syndrome. *Journal of Autism and Developmental Disorders*, *33*(1), 3-13.

Huerta, M., Bishop, S. L., Duncan, A., Hus, V., & Lord, C. (2012). Application of DSM-5 criteria for autism spectrum disorder to three samples of children with DSM-IV diagnoses of pervasive developmental disorders. *The American Journal of Psychiatry, 169*(10), 1056-1064. doi: 10.1176/appi.ajp.2012.12020276

Iossifov, I., Ronemus, M., Levy, D., Wang, Z., Hakker, I., Rosenbaum, J., Yamrom, B., Lee, Y.H., Narzisi, G., Leotta, A., Kendall, J., Grabowska, E., Ma, B., Marks, S., Rodgers, L., Stepansky, A., Troge, J., Andrews, P., Bekritsky, M., Pradhan, K., Ghiban, E., Kramer, M., Parla, J., Demeter, R., Fulton, L.L., Fulton, R.S., Magrini, V.J., Ye, K., Darnell, J.C., Darnell, R.B., Mardis, E.R., Wilson, R.K., Schatz, M.C., McCombie, W.R., Wigler, M. (2012) *De novo* gene disruptions in children on the autistic spectrum. Neuron 74:285–299

Kaufmann, W.E., Cortell, R., Kau, A.M., Bukelis, I., Tierne.y E., Gray, R.M., Cox, C., Capone, G.T., Stanard, P. (2004). Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors. Am J Med Genet, 129A, 225–234.

Kaufmann, W.E., Capone, G., Clarke, M., & Budimirovic, D.B**.** (2008). Autism in Genetic Intellectual Disability: Insights into Idiopathic Autism. In Zimmerman, A.W. (Ed.), *Autism: Current Theories and Evidence* (81-108). Totowa, NJ: The Humana Press Inc.

King, B. H., Veenstra-Vanderweele, J., & Lord, C. (2013). DSM-5 and autism: kicking the tires and making the grade. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(5), 454-457. doi: 10.1016/j.jaac.2013.02.009

Landrigan, P.J. (2010) What causes autism? Exploring the environmental contribution. Curr Opin Pediatr, Apr 22(2), 219-25. doi: 10.1097/MOP.0b013e328336eb9a.

Loesch, D.Z., Huggins, R.M., Bui, Q.M., Taylor, A.K., Pratt. C., Epstein, J., Hagerman, R.J. (2003). Effect of fragile X status categories and FMRP deficits on cognitive profiles estimated by robust pedigree analysis. Am J Med Genet, 122A, 13–23

Lord, C., Petkova, E., Hus, V., Gan, W., Lu, F., & Martin, D. (2011). A multisite study of the clinical diagnosis of different autism spectrum disorders.*Archives of General Psychiatry, 69*, 306-313.

Macintosh, K. E., &Dissanayake, C. (2004). Annotation: The similarities and differences between autistic disorder and Asperger's disorder: a review of the empirical evidence. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 45*(3), 421-434.

Matson, J. L., & Neal, D. (2010).Differentiating communication disorders and autism in children. *Research in Autism Spectrum Disorders*, *4*(4), 626-632.

Mayes, S. D., Black, A, & Tierney, C. D. (2013). DSM-5 under-identifies PDDNOS: Diagnostic agreement between the DSM-5, DSM-IV, and Checklist for Autism Spectrum Disorder. *Research in Autism Spectrum Disorders, 7*(2), 298-306.

Mazefsky, C. A., McPartland, J. C., Gastgeb, H. Z., &Minshew, N. J. (2013). Brief report: comparability of DSM-IV and DSM-5 ASD research samples. *Journal of Autism & Developmental Disorders, 43*(5), 1236-1242.

McPartland, J. C., Reichow, B., &Volkmar, F. R. (2012).Sensitivity and specificity of proposed DSM-5 diagnostic criteria for autism spectrum disorder.*Journal of the American Academy of Child and Adolescent Psychiatry, 51*(4), 368-383.

Muhle, R., Trentacoste S.V., Rapin,I (2004). The genetics of autism. Pediatrics, 113, 472–486.

Ozonoff, S., South, M., & Miller, J. (2000). DSM-IV-defined Asperger syndrome: cognitive, behavioral and early history differentiation from high-functioning autism. *Autism, 4*, 29-46.

Ozonoff, S., Goodlin-Jones, B. L., & Solomon, M. (2005).Evidence-based assessment of autism spectrum disorders in children and adolescents.*Journal of Clinical Child and Adolescent Psychology: the official journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53, 34*(3), 523-540.

Ozonoff, S. (2012). DSM-5 and autism spectrum disorders--two decades of perspectives from the JCPP. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 53*(9), e4-e6.

Prior, M., Elsenmajer, R., Leekam, S., Wing, L., Gould, J., Ong, B., &Dowe, D. (1998). Are there subgroups within the autistic spectrum? A cluster analysis of a group of children with autistic spectrum disorders.*Journal of Child Psychology and Psychiatry and Allied Disciplines, 39*(6), 893-902.

Schaefer, G.B., Mendelsohn, N.J. (2008). Genetics evaluation for the etiologic diagnosis of autism spectrum disorders. Genet Med, 10, 4–12.

Sidorov, M.S., Auerbach, B.D., Bear, M.F. (2013) Fragile X mental retardation protein and synaptic plasticity. Mol Brain. Apr 8, 6-15. doi: 10.1186/1756-6606-6-15.

Snow, A. V., &Lecavalier, L. (2011).Comparing autism, PDD-NOS, and other developmental disabilities on parent-reported behavior problems: little evidence for ASD subtype validity.*Journal of Autism and Developmental Disorders, 41*, 302-310.

Szatmari, P., Bryson, S. E., Boyle, M. H., Streiner, D. L., &Duku, E. (2003).Predictors of outcome among high functioning children with autism and Asperger syndrome.*Journal of Child Psychology and Psychiatry and Allied Disciplines, 44*(4), 520-528.

Szatmari, P., Bryson, S., Duku, E., Vaccarella, L., Zwaigenbaum, L. , Bennett, T., & Boyle, M.H. (2009). Similar developmental trajectories in autism and Asperger syndrome: from early childhood to adolescence. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 50*(12), 1459-1467.

Taheri, A., & Perry, A. (2012).Exploring the proposed DSM-5 criteria in a clinical sample.*Journal of Autism and Developmental Disorders, 42*(9), 1810-1817.

Watson, C., Hoeft, F., Garrett, A.S., Hall, S.S., Reiss, A.L. (2008). Aberrant Brain Activation During Gaze Processing in Boys With Fragile X Syndrome. Arch Gen Psychiatry, 65(11), 1315-1323. doi:10.1001/archpsyc.65.11.1315.

Weitlauf, A. S., Gotham, K. O., Vehorn, A. C., & Warren, Z. E. (2013). Brief Report: DSM-5 "Levels of Support:" A Comment on Discrepant Conceptualizations of Severity in ASD. *Journal of Autism and Developmental Disorders*, 1-6.

Williams, K., Tuck, M., Helmer, M., Bartak, L., Mellis, C., & Peat, J. K. (2008). Diagnostic labelling of autism spectrum disorders in NSW.*Journal of Paediatrics and Child Health, 44*(3), 108-113.

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The Fragile X Clinical & Research Consortium was founded in 2006 and exists to improve the delivery of clinical services to families impacted by any fragile X-associated Disorder and to develop a research infrastructure for advancing the development and implementation of new and improved treatments. Please contact the **National Fragile X Foundation** for more information. (800-688-8765 or www.fragilex.org)