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Rare Genetic Syndromes and Autism Education and Practice

Written by Joe McCleery, PhD

Since Autism was first identified by Leo Kanner in 1943 (1), extensive research has been conducted and shown that autism is caused by a complex set of genetic and environmental factors (2). For example, the results of studies comparing co-occurrence of autism in identical twins, who share nearly 100% of their genes, compared with non-identical twins, who share approximately 50% of their genes, suggest that genetics account for approximately 45% to 65% of the variability in causing autism spectrum disorders (2,3).

In regards to specific genetic factors, evidence to date suggests that the genetic contribution to causing autism is primarily due to normal variation in a relatively large number of normal genes (i.e., "Common Variation" see 2,4,5). For environmental factors, examples that evidence suggests may increase risk for autism include the mother taking the epilepsy medication valproic acid during pregnancy (6), birth complications (7), and heavy traffic-related air pollution (8), among others. However, for the vast majority of both the genetic and environmental risk factors that have been identified to date, each individual factor contributes only a very small amount to the individual developing autism. In addition, a large number of the genetic and environmental factors that contribute to causing autism have yet to be identified (see 2,4). Finally, it is generally assumed that a large number of genetic and environmental factors interact with one another to cause autism (see also 9,10,11).

Genetic Syndromes with Characteristics of Autism

In addition to the complex genetic contributions to causing "regular" autism, there are also genetically-mediated syndromes in which a diagnosis of autism is especially common. These include Fragile X Syndrome, Rett Syndrome, Dup15q Syndrome, Tuberous Sclerosis Complex, Cornelia de Lange Syndrome, and even Down Syndrome, among others. For some of these conditions, rates of autism have been estimated to be over 50%, compared with the approximately 1% rate of Autism Spectrum Disorders in the general population (Table 1). Each of these genetic syndromes has its own unique genetic cause that brings with it a set of physical and/or behavioral characteristics that occur whether or not autism is also present (Table 1). The co-occurrence of the genetic syndrome and autism often leads to a number of additional complications and challenges for both the individual and the clinician/educator.

Although the majority of the genetic syndromes associated with autism are individually rare, collectively these syndromes are relatively common. For example, it has been estimated that the genetic mutation that causes Fragile X Syndrome may be present in approximately 2% to 8% of autism cases (12) and that the genetic duplication that causes Dup15q Syndrome is present in approximately 1% to 3% of autism cases (13). Furthermore,

many of the genetic syndromes in which autism is common are associated with moderate to severe intellectual disability (Table 1). This means that many of these genetic syndromes will be much more common in the sub-group of individuals with autism who are experiencing moderate to severe intellectual / learning disabilities. As a result, many of these children will be placed in autism specialist or mixed disability classrooms, often without recognition of the fact that the child has a unique genetic syndrome.

The Value of Identifying Genetic Syndromes

The first characteristics that many will notice about individuals with a number of these genetic syndromes are differences in their outward physical appearance. For example, individuals with Fragile X Syndrome have longer faces and larger ears than others. Individuals with Tuberous Sclerosis Complex exhibit characteristic rash patterns on their skin. And, individuals with Cornelia de Lange Syndrome present with a number of characteristic facial features and are also sometimes missing portions of limbs (Table 1). In fact, a number of these genetic conditions are commonly diagnosed in the medical community based solely on the presence and nature of apparent physical and behavioral features. Alternatively, for some of these conditions, such as Dup15q syndrome, there are no physical features that are consistently present.

There are compelling clinical/educational and community support related factors that warrant consideration of whether or not an individual may have one of these genetic syndromes. Among the most compelling reasons to consider and identify the presence of a genetic syndrome are characteristic behavioral patterns and developmental trajectories (Table 1). For example, individuals with Rett Syndrome engage in "hand wringing" at the midline that becomes increasingly persistent and increasingly resistant to behavioral modification over time. Therefore, clinical/educational intervention plans may ultimately need to be focused on working around this difficulty as the child ages. For another example, individuals with Tuberous Sclerosis Complex often experience pain from tubers/tumors in their internal organs that are unobservable. This pain is highly likely to contribute to causing and exacerbating challenging behaviors. This information is critical for both assessing and treating the sources of challenging behaviors, which are common in this population. Other examples include particular deficits in play skills in individuals with Tuberous Sclerosis Complex, hyperactivity in individuals with Dup15q Syndrome, social impulsivity and emotional reactivity in individuals with Klinefelter Syndrome, body heat intolerance in individuals with Phelan McDermid Syndrome, and insatiable appetite in individuals with Prader Willi Syndrome.

In addition to improved understanding of the intervention and other needs of the individual, identification of a genetic syndrome can also provide invaluable informational and social support for the family. For example, there are informational and family/peer support organizations for the majority of known genetic syndromes (see below). Many of these organizations are well-established and professionally run, provide pathways to

clinically-relevant information and supports, and hold annual conferences. Several such organizations also directly or indirectly support international communication and cooperation among families and/or clinicians serving the population.

Implications for Clinical/Educational Practice

As described above, there are a number of genetic syndromes in which a diagnosis of an autism spectrum disorder is especially common. While these syndromes are individually rare, collectively they make up a notable percentage of individuals who are receiving services based upon a diagnosis of an autism spectrum or related disorder. Furthermore, individuals with some of these syndromes are significantly more likely to be represented in the sub-group of individuals with autism and other special needs who are experiencing moderate to severe intellectual disabilities.

Although individuals with genetic syndromes are often placed in schools/classrooms and clinics that provide autism specialist services, the autism symptoms and behavioral patterns and needs of these individuals often differ from individuals with "regular" autism in important ways. Individuals with genetic syndromes also often experience additional physical and/or behavioral challenges that are related to their genetic condition. In many cases, being aware that the individual has a particular genetic syndrome will be very valuable information for both clinicians and educators. Alongside the value for direct support for the individual, the identification of a genetic syndrome can also lead to life-changing informational and peer support for family members.

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Table 1. Characteristics of several genetically-mediated syndromes related to Autism Spectrum Disorders.

Genetic Syndrome	Estimated Prevalence	Autism Spectrum Diagnosis	Intellectual Disability	Physical Characteristics	Behavioral Characteristics
Fragile X Syndrome	1 in 4,000 males;1 in 8,000 females	Estimated 20% – 50% ASD in males; 1% – 3% ASD in females. ASD diagnosis more common in those with moderate to severe intellectual disability. Estimated 2% to 8% of boys with autism have Fragile X Syndrome.	Mild to profound (females experience only mild intellectual disability in approximatel y 75% of cases)	Long face, large protruding ears, low muscle tone. Pale skin is also common.	Pervasive shyness, reduced eye contact (but warm up somewhat over time), reduced social reciprocity. Autism and social withdrawal symptoms may increase with age. Hyperactivity and impulsivity are

					common.
Rett Syndrome	1 in 10,000 to 1 in 22,000 (almost exclusively females)	Autism-like behaviors are present in most; however, the social symptoms of autism are often only temporary in this population. Approximately 18% of children with Rett Syndrome are diagnosed with autism before they are properly identified as having Rett Syndrome.	Nearly all will have intellectual disability (commonly severe) that is associated with progressive stages of motor and cognitive deterioration.	Slowed head growth, slowed physical growth, scoliosis, and irregular heartbeat are common. Lifespan may be shortened to 40 to 50 years of age.	Regression of motor and cognitive skills after a period of approximately 6 to 18 months of relatively normal early development, loss of muscle tone, difficulty feeding, jerkiness in limb movements, hand "wringing" at the midline, loss of purposeful use of hands, loss of speech. Seizures, loss of ability to walk, anxiety, sleep problems, and breathing difficulties are also common. Interest in socialization often increases with age following the initial periods of regression.
Dup15q Syndrome	1 in 4,000	Estimated 85% ASD. ASD is equally common in boys and girls with Dup15q Syndrome. Estimated approximately 1% to 3% of ASD cases have 15q duplications.	Most individuals experience early developmental and language delays. Intellectual and adaptive functioning difficulties persist in many	Physical characteristics are common but non-specific. Flat nasal bridge ("button" nose), full cheeks, long philtrum, skin folds at corner of eyes, deep set eyes, low-set and/or posteriorly rotated ears, physical growth delays, and low muscle tone are common.	Most individuals experience early developmental and language delays. Intellectual and adaptive functioning difficulties persist in many individuals. Gross and fine motor delays are common. Seizure disorders and abnormal EEG are common. Hyperactivity and

			individuals.		sleep problems are common.
Tuberous Sclerosis Complex	1 in 6,000 to 1 in 11,400	35% – 45% ASD. ASD is more common in individuals with intellectual disability.	45% intellectual disability (30% profound intellectual disability)	Benign tumors/tubers throughout organs, including the brain in many cases. Epilepsy. Permanent skin rashes, skin tumors, and/or skin patches. Retinal lesions are common.	Aggression, self-injury, pain and discomfort (from growths), headaches, photophobia. Global deficit in play skills is common, even in the absence of autism.
Cornelia de Lange Syndrome	1 in 10,000 to 1 in 40,000	Estimated 32% – 67% ASD	Mild to severe intellectual disability.	Short stature, below average weight, and small head size are common. Short upturned nose, thin downturned lips, low-set ears, long eyelashes, thin eyebrows that meet in the middle. Upper limb abnormalities, including missing fingers, hands, or forearms, are common. Gastroesophageal reflux is very common.	Self-injury, compulsive behaviors, anxiety, obsessive-compulsive tendencies, attention deficits, hyperactivity, and impulsivity are common.
Cri du Chat Syndrome	1 in 50,000	Estimated 40% ASD	Severe to profound intellectual disability	Small head size, low birth weight, low muscle tone, widely set eyes, low set ears, small jaw, rounded face. Increased risk for heart defects.	Frequent high-pitched cry. Verbal behavior is typically more affected than nonverbal behavior. Expressive language is typically more affected than receptive language. Hyperactivity, impulsivity, self-injurious behavior, aggressive behavior, stereotyped behavior, unusual attachment to

					objects, and sensory sensitivities are common.
Angelman Syndrome	1 in 12,000 to 1 in 20,000	Estimated 40% to 80% ASD. ASD associated with profound intellectual disability.	Severe to profound intellectual disability.	Unusually fair skin and light-colored hair are common. Curvature of the spine is common. Adults often have distinctive facial features.	Typically have a happy, excitable demeanor, with frequent smiling, laughter, and hand flapping. Most experience reduced mobility, impaired communication skills, and seizures. Absence, or near absence, of speech is common.Hyperactivity, impulsivity, a short attention span, and sleep difficulties are common. Fascination with water is common. Even when diagnosed with ASD, as a group individuals with Angelman Syndrome are not as impaired on social smiling, directing facial expressions to others, shared enjoyment in interaction, response to their name being called, or unusual interests and repetitive behavior as other individuals with ASD.
Down Syndrome	1 in 1,000	Estimated 6% – 39% ASD. ASD is more common in those with a greater degree of intellectual disability.	Approximately 80% experience moderate to profound intellectual disability.	Flattened face, flattened nose bridge, almond-shaped eyes, short neck, small ears, protruding tongue, short stature. Most individuals have low muscle tone. Approximately 50% have heart defects. Gastroesophagel reflux is common. Increased risk of hearing and vision	Delays in motor development are common. Attention difficulties, obsessive/compulsive behavior, stubbornness, and tantrums are common. Difficulties in emotion perception and theory of mind are

				problems. Increased risk for sleep apnea. Increased risk of Alzheimer's Disease.	common.
CHARGE Syndrome	1 in 8,500 to 1 in 12,000	Estimated 15% – 50% ASD.	Approximately 70% experience mild to severe intellectual disability.	Most have abnormalities in the structure of one or both eyes. Most have heart malformations. Many have upper airway abnormalities, with narrow or blocked nasal passages common. Cranial nerve abnormalities, facial paralysis, and hearing loss are common. Retarded growth and development, genital abnormalities, and ear abnormalities are common. Square-shaped face, prominent forehead, prominent nasal bridge, flat midface, and facial asymmetry are common. Hand and limb anomalies are common.	Pervasive communication and language difficulties are common. Swallowing problems, facial paralysis, and diminished sense of smell are common.
Prader-Willi Syndrome	1 in 10,000 to 1 in 25,000	Estimated 20% to 25% ASD	Borderline to moderate intellectual disability	Prominent nasal bridge, strabismus (eyes not properly aligned), small hands and feet with tapering of fingers, excess fat, high and narrow forehead, downturned mouth, thin upper lip, almond-shaped eyes, low muscle tone, short stature is common.	Insatiable appetite (and obesity), compulsive behaviors (especially skin picking), anxiety. Low activity levels are common.
Klinefelter Syndrome	1 in 50,000 males(Note: a variant of the syndrome that is not associated with autism or other learning difficulties occurs in 1 in 500 to 1 in 1,000	Estimated 11% ASD	Intellectual functioning is commonly in the normal or below average range. However, most individuals require some level of special education or	Shortage of testosterone, delayed or incomplete puberty, breast enlargement, reduced facial and body hair, infertility, and genital abnormalities.	Shyness, social withdrawal, social anxiety, difficulties in peer relationships, social impulsivity, and communication difficulties are common. Decreased ability to identify emotions in faces and voices, and increased levels of emotional stress and reactivity are common.

	males)		other support.		Increased arousal in response to emotional stimuli and avoidance of looking to the eyes during emotionally charged events.
Phelan McDermid Syndrome	Unknown, but extremely rare. Equal ly common in females and males.	Possibly as high as 84% ASD	Moderate to profound intellectual disability in 85% of individuals	Large fleshy hands, bulbous nose, long eyelashes, ear anomalies, and thin flaky toenails are common.	Absent to severely delayed speech. Overheating is common due to decreased perspiration. Increased tolerance for pain and low muscle tone are common. Ear and respiratory infections are common. Gastroesophegal problems are common. Frequent mouthing and chewing of objects is common. Sleep disorders and seizure activity are common. Toilet training is commonly particularly difficult.

Further Information and Support:

Fragile X Syndrome: http://www.fragilex.org

Rett Syndrome: https://www.rettsyndrome.org

Dup15q Syndrome: http://www.dup15q.org

Tuberous Sclerosis Complex: http://www.tsalliance.org

Cornelia de Lange Syndrome: http://www.cdlsusa.org

Cri du Chat Syndrome: http://www.criduchat.org

Angleman Syndrome: http://www.angelman.org

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Prader-Willi Syndrome: http://www.pwsausa.org

Klinefelter Syndrome: http://www.klinefelter.org.uk

Phelan McDermid Syndrome: http://22q13.org/j15

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