ASD AND ASSOCIATED GENETIC CONDITIONS

Autism Spectrum Disorder (ASD) and features of ASD can occur as part of some genetic conditions. Approximately 20% of children with ASD will have a diagnosable genetic syndrome. These syndromes can be due to missing or extra stretches of DNA, misspellings in genes, or biochemical abnormalities.

Some of these conditions are easy for a general pediatrician to recognize (for example, Down syndrome), while other conditions can be subtle and require specialized testing (for example, Smith-Lemli-Opitz syndrome). For this reason, the American College of Medical Genetics recommends that anyone with an ASD diagnosis receive an evaluation by a clinical geneticist. Accurate diagnosis is important because there can be other health implications for the affected child, as well as differences in the risk of having another child on the autism spectrum.

In addition to genetic causes of ASD, exposure to certain medications during pregnancy (for example, Valproic acid) can cause ASD. During your child’s visit with a clinical geneticist, they will review any medications that you may have taken during pregnancy.

Examples of genetic abnormalities that can be associated with ASD are listed below.

22q deletion syndrome

22q11.2 deletion has had several different names in the past, including: DiGeorge syndrome, Velo-cardio-facial syndrome, Conotruncal Anomaly Face syndrome, Opitz G/BBB syndrome, and Cayler cardiofacial syndrome, but doctors now know that each refers to the exact same syndrome. 22q11.2 deletion syndrome has a pattern of both behavioral and physical features. A person with this syndrome may have heart disease, cleft palate, hearing loss, kidney problems, and feeding difficulties, among other things. It is not usually inherited from a parent; rather it is
most often “de novo” (a new event). Only about 10% of children with 22q11.2
deletion syndrome have a parent who is affected. About 20% of children with 22q
deletion syndrome also have a diagnosis of ASD. This represents about a 20%
increased risk for ASD over the general population’s risk.

Angelman syndrome

Children with Angelman syndrome show delayed development, intellectual
disability, and balance problems. Most children have seizures and small head size.
This syndrome is usually diagnosed in early childhood. Children with Angelman
syndrome are usually happy and excitable, with frequent laughter and hand-
flapping. These children usually have minimal or absent speech. Children with
Angelman syndrome most likely also have a diagnosis of ASD, as many features of
the two overlap. Angelman syndrome shares a common genetic basis with some
forms of ASD.

CHARGE

CHARGE syndrome is a genetic disorder that affects many areas of the body.
Children with CHARGE syndrome usually have multiple birth defects and
differences in their physical appearance (for example, very unusually shaped ears).
People with CHARGE have eye problems, hearing loss, and developmental delay.
Children also have a secondary diagnosis of Obsessive Compulsive Disorder,
Attention Deficit Hyperactivity Disorder (ADHD), or ASD. One study shows that 27%
of children with CHARGE could be classified as autistic.

Cornelia de Lange syndrome

Cornelia de Lange syndrome is a genetic disorder that is characterized by slow
growth, intellectual disabilities, and skeletal problems with the arms and hands.
People with this syndrome often have excessive body hair, low-set ears, and small
teeth. Severe cases of Cornelia de Lange syndrome are usually not inherited from
a parent, but children who are mildly affected may have inherited it from a parent
who does not know they also have the condition. Many individuals have autistic-
like behaviors such as hypersensitivity to touch, repetitive and self injurious
behaviors, and difficulties in receptive language and expressive language.
Research shows that about 60% of people diagnosed with Cornelia de Lange
syndrome also have a diagnosis of ASD.
**Down syndrome**

Also known as Trisomy 21, Down syndrome is a genetic condition in which a person has an extra chromosome 21. This extra chromosome causes problems in the way the brain and body develop. The symptoms of Down syndrome can range from mild to severe. People with Down syndrome have a similar appearance, with a smaller head, upward slanting eyes, small mouth, and small ears. About 7% of children with Down syndrome also have a diagnosis of ASD.

**Duchenne Muscular Dystrophy**

Duchenne Muscular Dystrophy (DMD) is a genetic disorder that is characterized by weakness in the arms and legs. Diagnosis is usually made by age 5. DMD is caused by a lack of a protein called ‘dystrophin’ which normally works in the muscles. This protein is also in the brain, which researchers think may contribute to the high rate of ASD seen in patients with DMD. DMD can be inherited from the child’s mother in an X-linked recessive manner. This means that a male child only needs one changed copy of the gene to be affected, but female children need two. Since females have two copies of the X chromosome, they have one that will act as a “backup.” DMD can also be “de-novo,” meaning it is from a new mutation and not inherited.

**Fragile X**

Fragile X syndrome is a genetic condition that causes a range of developmental delay. Usually males are more severely affected than females. Children may be hyperactive or have a secondary diagnosis of ADHD.

About one-third of people with Fragile X syndrome also meet diagnostic criteria for ASD. Half of children with a Fragile X diagnosis have autistic behaviors such as avoiding eye contact, language delays, and repetitive behaviors. Within individuals on the autism spectrum, 1-3% of them have Fragile X syndrome, making it the most common syndromic form of ASD.

Changes in the FMR1 gene cause Fragile X syndrome. In order to work properly, the FMR1 gene must be a certain length, though there is a range of “normal.” The length is determined by the number of “trinucleotide repeats” in the gene. A typical person has 5-40 repeats. People who have a “pre-mutation” have 55-200 repeats. Fragile X syndrome is caused by 200 or more repeats.
People with a pre-mutation are usually within the normal range for intelligence. Some children who are evaluated for ASD fall in the pre-mutation range. People with “pre-mutation” of FMR1 also can have other symptoms such as premature ovarian failure or movement problems that develop later in adulthood (called Fragile X Associated Tremor Ataxia syndrome).

FMR1 is found on the X chromosome. Males have one copy of the X chromosome, and females have two copies. Since females have an extra copy of the X chromosome, if one is changed, the other can act as a backup; this is why males are usually more severely affected. Unaffected parents are able to pass Fragile X onto their children since the number of repeats has the ability to expand from generation to generation. Although parents may be unaffected, their child can have Fragile X syndrome.

Prader-Willi syndrome

Prader-Willi syndrome is usually diagnosed in infancy because of significant problems with feeding and very low muscle tone. After a year of age, individuals with Prader-Willi begin to eat excessively, and they can have very rapid weight gain. In addition to their feeding difficulties and low tone, children with Prader-Willi syndrome are characterized by behavioral problems such as temper outbursts, stubbornness, and compulsive behaviors. People with Prader-Willi syndrome have distinctive facial features, such as a narrow forehead, almond shaped eyes, and triangular mouth. They also tend to be short with small hands and feet. About 1% of children on the autism spectrum have Prader-Willi syndrome. Because there are several types of genetic changes that can result in Prader-Willi syndrome, genetic testing is required in order to determine the risk of having another child with Prader-Willi syndrome.

Rett syndrome

The classic form of Rett syndrome is a disorder that predominantly affects females. Girls develop normally at first, then lose their developmental milestones, developing problems walking, beginning seizures, and developing an intellectual disability. The severity and age of onset varies from child to child. Most cases are “de-novo,” meaning a new event and not inherited from a parent. Classic Rett syndrome is caused by a change in the gene MECP2.

Atypical Rett syndrome can affect males or females and is characterized by
developmental regression, very little speech, and seizures that develop early in childhood. There are several genes that are associated with “Rett-like” syndromes, and consideration of multiple genes is necessary whenever there is developmental regression or seizures.

Rett syndrome was previously considered one of the pervasive developmental disorders included with autism in the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th Edition. It is no longer included with ASD in the current DSM-5th edition. However, children with Rett syndrome can be diagnosed with both ASD and Rett syndrome. (For example, they can be diagnosed as having “ASD due to Rett syndrome.”)

**Smith-Lemli-Opitz syndrome**

Smith-Lemli-Opitz syndrome is a genetic disorder that is characterized by intellectual disability and behavioral problems. Children with this syndrome often show autistic behavior such as self-injury and sensory hyperactivity. The syndrome is autosomal recessive, meaning that a person needs two changed copies of the gene (one from each parent) to be affected. Since the parents only have one changed copy of the gene, not two, they are not affected. Children with Smith-Lemli-Opitz have some minor physical features that are easily recognized by a clinical geneticist. About 75% percent of children with Smith-Lemli-Opitz syndrome have a diagnosis of ASD.

**Smith Magenis syndrome**

Smith Magenis syndrome is a genetic disorder that is characterized by intellectual disability, delayed speech, and behavioral problems. People with the syndrome often have deep-set eyes, full cheeks, and a downward turned mouth. Many have behavioral problems including tantrums, aggression, self-injurious behavior, and impulsiveness. This syndrome is usually not inherited, and occurs “de-novo,” or as a new event. Between 50 and 75% of people with a Smith Magenis diagnosis also have a diagnosis of ASD.

**Sotos syndrome**

Sotos syndrome is a genetic disorder that is characterized by developmental delays, learning disabilities, and overgrowth during childhood. Children with Sotos are usually much heavier than their siblings at birth, and continue to be much
taller and heavier than their siblings. People with this syndrome often have behavioral problems such as ADHD, obsessions, and impulsive behaviors. It is caused by a change or deletion of a gene called NSD1, which usually helps control normal growth and development. Sotos syndrome is usually not inherited, and occurs “de-novo,” or as a new event. Sotos syndrome is not a significant cause of classic autism, however the behavioral problems that are associated with the syndrome usually cause the patient to be referred to an autism clinic. Referrals are generally for lack of awareness of social cues and difficulty with peer group relationships.

**Tuberous Sclerosis**

Tuberous Sclerosis is a genetic disorder that is characterized by tumors in the brain, kidneys, heart, etc. The syndrome affects the nervous system, resulting in seizures, developmental delay, and behavioral problems. Tuberous Sclerosis is caused by a change in one of two genes, TSC1 and TSC2. The syndrome is usually not inherited, and occurs “de-novo” (a new event). Approximately 1-2% of children with an ASD diagnosis have Tuberous Sclerosis, and about 50% of children with Tuberous Sclerosis meet the criteria for ASD at age 5. Children who have Tuberous Sclerosis and ASD are usually more cognitively impaired than those with only Tuberous Sclerosis.

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