

The 22q11.2 Deletion Syndrome

BACKGROUND

The 22q11.2 deletion syndrome is a chromosomal abnormality that can cause a wide range of health and developmental issues, including heart defects, breathing issues, problems with the gastrointestinal tract, immune and endocrine systems, differences in the palate, slow growth, and autism and/or developmental delays or learning disabilities in some individuals.

Children with this condition may have many or only a few of the symptoms, with varying severity. Physicians with expertise in this condition can quickly recognize the diagnosis in some patients and take steps to improve their quality of life, but in other children and adults it is not as straightforward.

HOW COMMON IS THE 22q11.2 DELETION?

The 22q11.2 deletion occurs in 1 of 4,000 live births, although this is likely a gross underestimate of the prevalence of this deletion, making it almost as common as Down syndrome. In addition, it is the most frequent cause of syndromic palatal defects and it is found in 1 of 68 children born with a heart defect. Despite this prevalence, many physicians are still not familiar with the diagnosis or its extreme variability. Because of this, a family may search for years for an explanation for the child's problems, as well as for meaningful help. Sometimes patients are in their late teens or even adulthood before the diagnosis is made.

WHAT'S IN A NAME?

Other names for the 22q11.2 deletion include DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, Opitz G/BBB syndrome, and Cayler Cardiofacial syndrome. These were all names given to a collection of findings by different sub-specialists before anyone knew about the true etiology of the various findings – the chromosome 22q11.2 deletion. For example, Angelo DiGeorge, MD, an Endocrinologist, was focusing on problems with calcium; Robert Shprintzen, PhD, a Speech Pathologist, was concentrating on palatal differences; and Dr. Kinouchi and others in Japan were looking at heart defects. In 1997, Donna McDonald-McGinn, MS, CGC likened this phenomenon to a group of near sighted veterinarians trying to describe an elephant by each examining a separate part. Each was accurate in describing his or her own area of interest but none was able to see the big picture. So too was the case of the 22q11.2 deletion prior to the availability of a laboratory test for this chromosomal deletion.

WHAT TESTS ARE USED TO IDENTIFY THE DELETION?

Today there are many tests that can identify the deletion and they are most readily performed as blood tests. They include: FISH (fluorescence *in situ* hybridization), comparative genomic hybridization (CGH), whole genome or SNP array, and multiplex ligation-probe amplification (MLPA). In general, a regular chromosome study will only identify this very small deletion about 25% of the time so one of the above more specialized tests would need to be requested in order to find the deletion.

IS THE 22q11.2 DELETION HEREDITARY?

Most times the deletion is not hereditary or “running in the family” but once it is present the person with the deletion has a 50% chance of passing it on to his or her child. It is important to know that the eggs and sperm have no memory so every pregnancy has the same 50% chance of having a child with the deletion even if there is an affected child already in the family. In addition, as the findings in people with the 22q11.2 deletion are variable it is impossible to predict how mildly or significantly affected a child will be.

When neither parent has the deletion it is said that it “just happened” in their child – that is a chance occurrence. It is nothing that the parents did or did not do that caused it to occur. It occurs on a very cellular level due to the inherent structure of the chromosome and it is nothing that anyone has any control over. This is very important as many families feel a sense of guilt over the fact that their child has a “genetic condition” but this is not anyone’s fault.

WHAT ARE THE MEDICAL NEEDS?

Unlike the early reports on children with DiGeorge syndrome, many of whom died in early infancy prior to the availability of sophisticated cardiac surgeries and antibiotics to fight infections, the mortality rate in children with the 22q11.2 deletion is very low (~ 4%) and those children who do succumb to problems associated with the deletion often pass away at a very young age (~ 4 months). However, many children and adults have numerous medical problems across their lifetime that requires specialized care. These include:

- Cardiology – where 75% of children have some type of heart defect, many of whom require surgery to correct the problem, often in the newborn period.
- Child Development – where most children (>95%) have motor milestone delays (like walking), delays in emergence of language and specific learning differences requiring special help in school; and a subset of children have autism or autistic like features and/or behavioral differences like ADHD, OCD, anxiety, perseverations, and psychosis.

It is important to note that all children benefit from Early Interventions strategies including such things as occupational therapy, physical therapy, and speech therapy/sign language in young childhood followed by specific learning style interventions as most children have relative strengths in reading and rote memorization but more difficulty with math and complex/abstract reasoning (a non-verbal learning disability).

- Cleft Palate Team – where 75% of children have differences in their palate allowing milk to come through their nose in infancy (known as nasal regurgitation) and later causing them to have hypernasal speech which makes it difficult for the child to be understood.

Here too, many children benefit from surgical interventions, usually performed by a Plastic Surgeon or an ENT as part of a Cleft Palate Team.

- Endocrinology – where ~ 50% of children have low calcium levels which usually resolve in infancy, but some children require calcium supplements for a longer period of time or during times of illness or stress such as at puberty or post operatively; in addition, some children have trouble with their thyroid (under active or over active) and some have growth hormone deficiency –all of which respond to treatment.
- ENT and Audiology – where ear infections are common (often due to the high incidence of palatal problems), as is the presence of hearing loss (both conductive and sensorineural), and problems with the child's airway due to structural differences such as a vascular ring or laryngeal web or associated with reflux. Occasionally a child will have a connection between the wind pipe and feeding pipe (tracheoesophageal fistula) or an abnormal feeding pipe (esophageal atresia).

Many children benefit from ear tube placement; some need hearing aides; whereas others require more complex care from an Otolaryngologist.

- Gastroenterology/Feeding Team – where ~ 35% of children have significant feeding and swallowing problems such as gastroesophageal reflux (GERD) and dysmotility leading to reflux and constipation; less common problems include umbilical hernia, intestinal malrotation, an absent anal opening, Hirshsprung's disease (where the child has severe constipation/blockage of the bowel), a diaphragmatic hernia where loops of bowel can be in the chest. Most common feeding problems exist in the newborn period and often resolve with medical assistance by school age.
- Hematology/Oncology – where rarely a child has had problems with bleeding due to the deletion of a gene that codes for clotting on the chromosome with the deletion and a non-

working gene on the other chromosome 22 called Bernard-Soulier syndrome and occasionally children have had problems with their blood counts due to an autoimmune problem such as Idiopathic Thrombocytopenia and Autoimmune Neutropenia; some children have rarely had a tumor, most notably in the liver (hepatoblastoma) and sometimes elsewhere such as the kidney (Wilm's tumor, Renal Cell carcinoma) or thyroid; as well as an occasional individual with Leukemia or Lymphoma. With the exception of Bernard-Soulier syndrome, these problems are likely related to the individuals' "pokey" immune system as well as other genes on other chromosomes that may predispose them to having these problems.

- Immunology/Rheumatology – where 77% of children have immunodeficiency regardless of whether or not they appear to have recurrent infections including things like recurrent infections, not mounting a normal response to vaccines, and not being able to receive live viral vaccines. Most problems resolve in infancy but some older children and adults have chronic infections. In addition, children and adults are more prone to autoimmune diseases such as Juvenile Rheumatoid arthritis, Idiopathic Thrombocytopenia, Autoimmune Neutropenia, Grave's disease, and Vitiligo.
- Neurology – where, rarely, children have seizures unrelated to their low calcium levels and/or structural brain differences/a small head. An occasional child will have spina bifida.
- Ophthalmology – where some children have eye problems such as droopy eyelids (known as ptosis); differences in the whites of their eyes (scleracornea); differences in the colored parts of their eyes (coloboma); and differences with their eye muscles. Some of these problems need surgical treatment or other interventions such as patching of the eyes and others do not.
- Orthopaedics – where ~ 50% of children have differences in the way the vertebrae of the spine are formed at the neck causing decreased room surrounding the spinal cord at the neck in a very small subset of children which often benefit from surgical correction; differences in the bones of the spine in other areas such as the chest (butterfly vertebrae); curvature of the spine (scoliosis); extra ribs, extra fingers and toes; differences in "wing bones (scapula); and occasionally premature fusion of the bones of the skull (craniosynostosis) all of which are able to be helped surgically if needed. Many children also have unexplained leg pain.
- Urology – where ~ 35% of children have differences in the way their kidneys are formed or how they work such as a single or malformed kidney and/or kidney reflux, as well as, problems with infections, potty training, and differences in the way the genito-urinary

system may be formed (hypospadias in boys where the opening of the penis is not at the tip and undescended testes and occasionally an absent uterus in girls); and hernias in the groin.

HOW SHOULD INDIVIDUALS WITH THE 22q11.2 DELETION BE FOLLOWED MEDICALLY?

Ideally, children with the 22q11.2 deletion receive coordinated care in centers comprised of multidisciplinary teams of clinicians often drawn from more than 20 specialties. Centers address each child's individual health problems, as well as issues such as speech or learning delays in order to help these children and their families lead the best life possible.

Upon initial diagnosis the standard assessment and work up for all ages generally includes:

- Cardiology
- Endocrinology
- Immunology
- Speech/Language/Developmental Assessments

As well as:

- A Renal Ultrasound (to check the kidneys)
- X-rays of the neck (in children old enough to cooperate and where the bones are well ossified – so ~ 3 to 4 years of age)
- Deletion studies in both parents when available

Thereafter, the work-up is individualized depending on the symptoms but may include any or all of the following:

- Plastic Surgery/ENT/Audiology
- Gastroenterology/Feeding Team
- Hematology
- Urology/Nephrology
- Orthopaedics
- Ophthalmology
- General Surgery
- Dentistry
- Rheumatology
- Neurology/Neurosurgery
- Psychiatry

HOW DO FAMILIES COPE?

Most children and adults with the 22q11.2 deletion do quite well both medically and as members of their families and communities at large. As with anything that is unexpected, coming to terms with the diagnosis is often difficult at first but becomes easier as more information becomes available and as families have an opportunity to meet other children and adults with the 22q11.2 deletion and/or to converse with them through diagnosis specific internet sites. In addition, attendance at family meetings/picnics; contacting support networks; and sending children to camps specifically designed for those individuals with a 22q11.2 deletion such as Dragonfly Forest (www.dragonflyforest.org) is often helpful as families realize they are not alone.