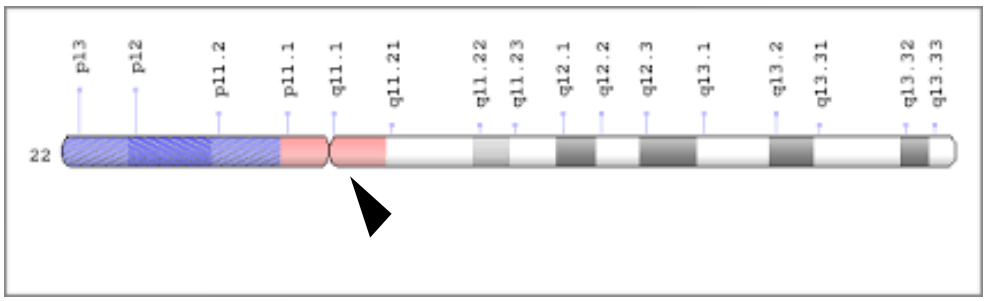
22Q11.2 DELETION INFORMATION

22q11.2 Deletion Syndrome

The chromosome disorder known as "22q11.2 deletion syndrome" has an unusual history. In 1965 Dr. Angelo DiGeorge[1] observed several children with absent thymi and immune defects. They noticed that similar immune defects were reported in a chicken with ablation (basically the removal) of the thymic system.



Later this condition became known as DiGeorge syndrome. In the 1970s a complex of congenital heart defects and facial dysmorphism became known as Cayler cardiofacial syndrome. Some patients who also had velo-pharyngeal insufficiency were reported as velocardiofacial syndrome. In the early 1980s it was shown that several patients with unbalanced translocations leading to the loss of the proximal part of 22q revealed the DiGeorge syndrome phenotype. It was a clear indication that this condition was caused by a deletion of this segment of 22q. It was confirmed in the late 1980s-early 1990s when the diagnosis of this condition became possible using FISH probes for this specific region. And it was shown that DiGeorge syndrome, Cayler cardiofacial syndrome and velocardiofacial syndrome actually are different sides of the same condition. Molecular cytogenetics showed that in most cases a typical picture may be found in patients having a ~2.5-3 Mb deletion in 22q11.2[2-4]. To avoid problems with nomenclature we will use the term "22q11.2 deletion syndrome".

A detailed examination of the 22q11.2 region shows that most patients have a "standard" ~2.5-3 Mb deletion in the area A-D of 22q11.2. This segment includes 30-35 genes. This typical deletion is found in ~85% of patients. Other patients have deletions of shorter segments (A-B, A-C, B-D).

22q11.2 deletion syndrome is a very common disorder. It occurs in ~1:3000 newborns. It is even more common among fetuses: the most severely affected fetuses die in utero. The high incidence of this syndrome allows a detailed examination of the phenotype based upon the considerable number of patients.

The syndrome does not have pathognomonic traits (specifically characteristic or indicative of a particular disease or condition) which present in all patients. Some persons with del 22q11.2 have very mild manifestations and may remain undiagnosed.

Clinical manifestations include neuro-developmental and psychiatric problems, facial dysmorphism, abnormalities of the heart, palate, endocrine system, problems with hearing etc.

A comparison of patients with del 22q11.2 and persons with normal karyotypes shows that the mean IQ in patients with this deletion is lower than in the “normal” group by approximately 15-20 points. However in each individual case developmental delay is usually relatively mild. Some patients reveal only learning disabilities, especially in math. Children with this deletion have a high risk to develop autism and attention deficit hyperactivity disorder. Schizophrenia and schizo-affective disorders are common among teenagers and adults with this condition.

Most patients have facial dysmorphism: an elongated relatively narrow face, narrow palpebral fissures, epicanthus, abnormalities of the ears (low-set ears, an abnormal helix or protuberant ears), or the nose (tubular nose with bulbous tip). In most cases however these dysmorphic features are mild and may be unnoticed by parents.

The most important internal abnormalities are heart defects observed in almost 2/3 of all patients. These defects may be very serious and include tetralogy of Fallot, defects of ventricular septum, anomalies of the aortic arch or even interrupted aortic arch. Correction of these defects may require surgery. Congenital heart defects are the main cause of death of children with del 22q11.2 syndrome. The vital prognosis for children without heart defects (or with successfully corrected heart defects) is relatively favorable.

Defects of the palate are an important component of the syndrome. Overt cleft palate occurs rarely (~5%). 20% of patients have a submucous cleft palate, even more (> 50%) reveal velopharyngeal dysfunction (a condition causing a leakage of air into nasal passages when speaking). As a result these patients have hypernasal speech.

Immunodeficiencies are very common, they may be found in ~ ¾ of all patients. The primary effect of thymic hypoplasia is a restriction of T-cell production. A significant number of the patients have such abnormalities, including a low number of regulatory T-lymphocytes. It explains the poor response to vaccination in such children. Multiple allergies and frequent “common” infections are clinical manifestations of these defects. Although autoimmune disorders occur more frequently in these patients than in the general population this is still relatively rare.

Hypocalcemia caused by hypoparathyroidism is another frequent manifestation of 22q11.2 deletion. It may be seen in half of patients, both with and without heart abnormalities. Another endocrinopathy is thyroid disease. Both hypo- and hyperthyroidism occur in patients more frequently than in the general population.

A significant number of patients with del 22q11.2 have abnormalities of the urinary system. The most common defect in this group is hydronephrosis. Unilateral renal agenesis and dysplastic kidney are also repeatedly reported in such patients. ~5% of boys have hypospadias. Defects of the uterus and vagina are highly uncommon.

Chronic infections frequently affect the ear, nose, throat and respiratory system. Chronic otitis may result in hearing loss, although sensori-neural hearing loss was also repeatedly reported among such patients.

Musculoskeletal defects are uncommon, but scoliosis may be found in a large number of affected patients.

It should be noted however that because the syndrome is so frequent there are many thousands of reported patients. And if we have thousands of patients numerous defects of different organs may be found only by chance (even if these defects are unrelated to the deletion itself).

Adults with del 22q11.2 basically have normal fertility. Of course, they have a 50% chance of transferring the deleted chromosome to their children.

Because this syndrome affects multiple systems patients should be under the supervision and treatment of a multi-disciplinary team that includes geneticists, pediatricians (for children), allergologists, otolaryngologists, speech and language pathologists, cardiologists, plastic surgeons, gastroenterologists, neurologists and neuro-psychiatrists. Sometimes patients may also need treatment from urologists, pulmonologists and other specialists.

Diagnosis of the condition usually requires array comparative genomic hybridization (or multiple ligation probe amplification). These tests may show the exact size of the lost segment and the position of the breakpoints. More simple FISH testing may show the presence or absence of the deletion but is unable to provide further details.

REFERENCES

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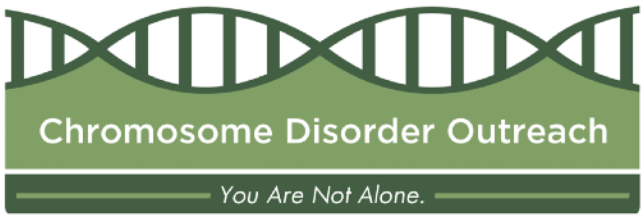

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