DiGeorge Syndrome

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Definition

- DiGeorge syndrome, also known as 22q11.2 deletion syndrome, is a syndrome caused by the deletion of a small segment of chromosome 22.
- The syndrome was first described in 1968 by American physician Angelo DiGeorge. In late 1981, the underlying genetics were determined.
- Symptoms vary between somatic and cognitive.
- DiGeorge syndrome occurs in about 1 in 4,000 people.

Etiology (mainly genetic)

- DiGeorge syndrome is caused by a heterozygous deletion of part of the long arm (q) of chromosome 22, region 1, band 1, sub-band 2 (22q11.2). Approximately 80-90% of patients have a deletion of 3 Mb and 8% have a deletion of 1.5Mb. Very rarely, deletions on the short arm of chromosome 10 can be observed.
- Haploinsufficiency of the TBX1 gene (T-box transcription factor TBX1) is thought to be the cause of some of the symptoms observed. Point mutations in this gene have also been observed in individuals with DiGeorge syndrome. TBX1 is part of the T-box family of genes which have an important role in tissue and organ formation during embryonic development and it may have a role in the regulation of differentiation of post migration neural crest cells.
- About 90% of cases occur due to a new mutation during early development, while 10% are inherited from a person's parents. It is autosomal dominant.
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Etiology continued

- In mice, haploinsufficiency of the DGCR8 gene has been linked to improper regulation of the microRNA miR-338 and 22q11.2 deletion phenotypes
- Association to Parkinson’s disease: 22q11.2DS has been associated with a higher risk of early onset Parkinson's disease (PD). The neuropathology seen is similar to LRRK2-associated PD. None of the genes affected in individuals with 22q11.2DS have previously been linked to PD but there are a number that are likely candidates. These include DGCR8 which is important for biogenesis of brain microDNA, SRPT5 which encodes a protein that interacts with the PARK2 protein, COMT which is involved in regulating dopamine levels, and microRNA miR-185 which is thought to target known PD loci LRRK2

Epidemiology

- DiGeorge syndrome is estimated to affect between one in 2000 and one in 4000 live births. This estimate is based on major birth defects and may be an underestimate, because some individuals with the deletion have few symptoms and may not have been formally diagnosed.
- The number of people affected has been expected to rise because of:
    - surgical and medical advances, an increasing number of people are surviving heart defects associated with the syndrome.
    - Parents who have affected children, but who were unaware of their own genetic conditions, are now being diagnosed as genetic testing become available
    - Molecular genetics techniques such as FISH (fluorescence in situ hybridization) have limitations and have not been able to detect all 22q11.2 deletions. Newer technologies have been able to detect these atypical deletions
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Symptoms

- Somatic:
  - congenital heart problems
  - specific facial features,
  - frequent infections (usually due to a hypoplastic or absent thymus)
  - developmental delay
  - cleft palate
  - kidney problems
  - hearing loss
  - autoimmune disorders such as rheumatoid arthritis or Graves' disease.
  - hypothyroidism and hypoparathyroidism or thrombocytopenia are late symptoms
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Symptoms

- Cognitive:
  - Learning problems
  - Velopharyngeal insufficiency
  - Cognitive deficits, attention deficit disorders
  - Below borderline average IQ
  - Increased risk of schizophrenia
  - Parkinson’s disease is often a comorbidity due to similar pathophysiological genetic pathways.
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Diagnosis

- It is suspected in patients with one or more signs of the deletion. In these cases a diagnosis of 22q11.2DS is confirmed by observation of a deletion of part of the long arm (q) of chromosome 22, region 1, band 1, sub-band 2. Genetic analysis is normally performed using fluorescence ***in situ*** hybridization (FISH), which is able to detect microdeletions that standard karyotyping (e.g. G-banding) miss
- Genetic testing using BACs-on-Beads has been successful in detecting deletions consistent with 22q11.2DS during prenatal testing.
- Array-comparative genomic hybridization (array-CGH) uses a large number of probes embossed in a chip to screen the entire genome for deletions or duplications. It can be used in post and pre-natal diagnosis of 22q11.2

Diagnosis (continued)

- New Methods:
  - Multiplex ligation-dependent probe amplification assay (MLPA) and quantitative polymerase chain reaction (qPCR), both of which can detect atypical deletions in 22q11.2 that are not detected by FISH. qPCR analysis is also quicker than FISH, which can have a turn around of 3 to 14 days.
  - Some of these tests that are necessary to confirm the diagnosis, are quite expensive; this is why it is necessary to provide a rationale for picking a conformational genetic test. The clinical diagnosis must first be made, aided by the multiple symptoms visible on clinical examination. It is important to remember that there is no clinical criteria of diagnosis due to the large number of possible pathologies that usually are not all present.

Treatment

- No cure is known for DiGeorge syndrome. Certain individual features are treatable using standard treatments. The key is to identify each of the associated features and manage each using the best available treatments:
  - Immune disorders: Thymus transplantation, Antibiotic prophylaxis
  - Congenital heart abnormalities: Cardiac surgery
  - Hypoparathyrodism and hypocalcemia: lifelong Calcium and Vit D supplements.
  - Specialty clinics to provide multi-system care allow for individuals with DiGeorge syndrome to be evaluated for all of their health needs and allow for careful monitoring of the patients. Example: the 22q Deletion Clinic at SickKids Hospital in Toronto, Canada

Thank you for your attention !