PRIMEVIEW

22q11.2 DELETION SYNDROME

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22q11.2 deletion syndrome (22q11.2DS) is a condition resulting from the loss of a small fragment of chromosome 22, variably affecting multiple organ systems. Clinical features include congenital anomalies and later-onset conditions, such as cardiac and palatal abnormalities; autoimmune diseases; endocrine, immune, renal and gastrointestinal problems; speech and language delays; and variable cognitive deficits and neuropsychiatric illnesses.

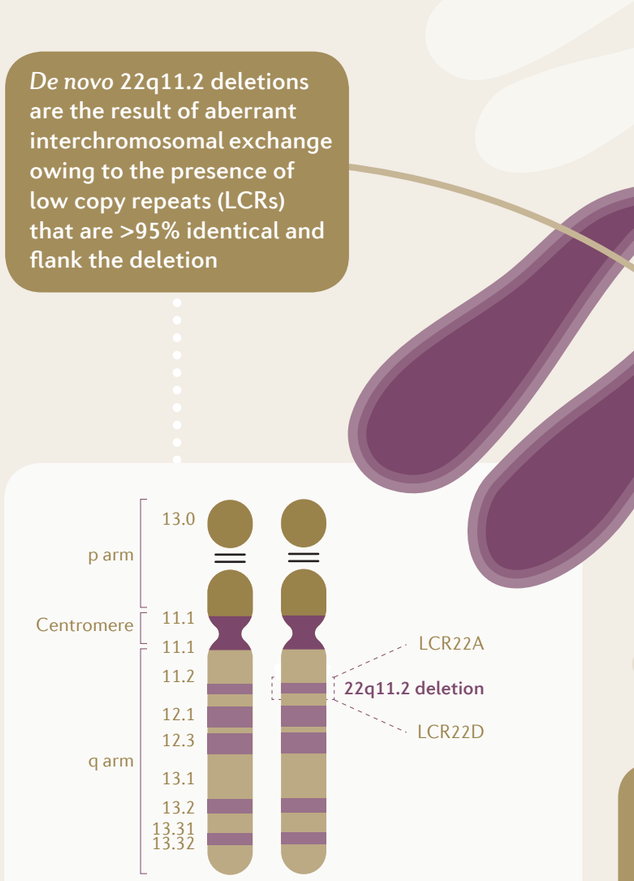
EPIDEMIOLOGY

The 22q11.2 deletion is the most frequent chromosomal microdeletion with an estimated prevalence of 1 per 1,000 fetuses. Prevalence is higher in fetuses with abnormal ultrasonographic findings (1 per 100) or in neonates with developmental disabilities (1 per ~170). 22q11.2 deletion is a common cause of congenital heart disease, syndromic palatal anomalies and developmental delay. Most patients (>90%) have a *de novo* deletion — that is, neither of their parents have the deletion. However, individuals with 22q11.2DS have a 50% chance of transmitting the deletion to their offspring. Thus, the proportion of inherited disease is expected to increase owing to increased survival and higher reproduction rates in affected individuals.

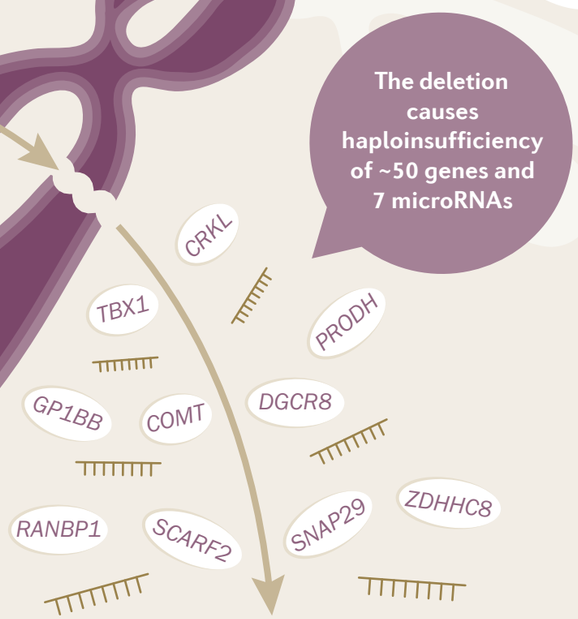
Cytogenetically visible deletions of 22q11.2 were initially identified in a subset of patients with the classic triad of DiGeorge syndrome (immunodeficiency, hypoparathyroidism and congenital heart disease) in the early 1980s. Later, submicroscopic deletions at 22q11.2 were causally identified in the majority of patients with DiGeorge, velocardiofacial and conotruncal anomaly face syndromes, among others. Now, the condition is referred to by the common factor and cytogenetic aetiology: 22q11.2DS.

MECHANISMS

De novo 22q11.2 deletions are the result of aberrant interchromosomal exchange owing to the presence of low copy repeats (LCRs) that are >95% identical and flank the deletion



Approximately 85% of the deletions involve the whole 3-Mb region between LCR22A and LCR22D; the remainder are nested, smaller deletions



Many physical attributes associated with 22q11.2DS can be ascribed to problems with morphogenesis and subsequent abnormal function of embryonic pharyngeal arch system derivatives, including the craniofacial region, the thymus, the parathyroid glands, the aortic arch and the cardiac outflow tract

OUTLOOK

The high clinical variability remains largely unexplained and might be attributed to several mechanisms, including dosage-sensitive genes, allelic variation of genes in the 22q11.2 region of the non-deleted chromosome, modifier genes outside of the deleted region and epigenetic phenomena. Another outstanding question is why the 22q11.2 region is so frequently deleted. Owing to the complexity of the LCRs in this region, the exact breakpoints remain largely unidentified; even the latest genome assembly still contains gaps in this area.

MANAGEMENT

22q11.2DS has a highly variable clinical presentation, ranging from severe life-threatening conditions to the presence of only a few, sometimes minor, symptoms. The presentation also varies with age. Some combinations of congenital heart defects, chronic infection, hypocalcaemia, palatal anomalies, and developmental and language delays are frequent in infancy and early childhood. In adolescence and adulthood, scoliosis and learning difficulties, as well as behavioural abnormalities, in many instances indicative of (emerging) psychiatric illness, predominate. As a consequence, management requires an individualized, multidisciplinary approach that takes the specific symptoms of each patient into account.

DIAGNOSIS

Lack of recognition of the condition, heterogeneous clinical presentation and often subtle characteristic facial features frequently delay diagnosis. Fluorescence *in situ* hybridization using probes that map to the LCR22A–LCR22B region is often used to detect the deletion. Nested deletions can only be identified using whole-region methodologies, such as microarray comparative genome hybridization, multiplex ligation-dependent probe amplification or digital PCR assays.

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