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DiGeorge Syndrome: New Insights

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DiGeorge syndrome was first described in 1968 as a rare developmental field defect affecting structures derived from the third and fourth embryonic pharyngeal arches [1,2]. Characteristic features included distinct facial features, hypoplasia or aplasia of the thymus, hypoplasia or aplasia of the parathyroid glands, and conotruncal cardiac defects. Infants presented with hypocalcemia, immunodeficiency, and severe heart defects, which, at the time, were often incompatible with life. The syndrome was observed to be etiologically heterogeneous, occurring in the context of maternal diabetes or alcohol use and in conjunction with a variety of chromosomal abnormalities. Studies subsequently demonstrated that approximately 10% to 20% of patients with the DiGeorge phenotype had a chromosomal alteration resulting in the loss of the proximal long arm of chromosome 22. Further molecular analysis demonstrated that nearly 90% of patients with the clinical features of DiGeorge syndrome had a microdeletion of a section of chromosome 22, called a 22q11 deletion [3–5].

Two patient populations that shared common features with DiGeorge syndrome, namely, velocardiofacial (or Shprintzen's) and conotruncal anomaly face (CTAF) syndromes, had also been described. Velocardiofacial syndrome was characterized in 1978 by typical facial features, a cleft palate, learning disabilities, and specific congenital heart defects [6]. CTAF syndrome was originally described in Japan in 1976 and was defined by conotruncal cardiac defects, hypernasal speech, mild mental retardation, neonatal tetany, thymic aplasia or hypoplasia, and facial dysmorphia [7]. As of 1993, molecular investigations had identified chromosome 22q11 deletions in 80% to 90% of patients with velocardiofacial or CTAF syndrome [8–11]. Thus, three clinical

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syndromes—DiGeorge, velocardiofacial, and CTAF—were found to share a common genetic cause in most cases, namely, a chromosome 22q11 deletion. These studies defined the most common deletion syndrome currently known, namely, the 22q11 deletion syndrome, estimated to occur in approximately 1 in 4000 to 6000 live births [12].

Clinical characteristics of the 22q11 deletion syndrome

The clinical phenotype of the 22q11 deletion syndrome is highly variable among related and unrelated individuals. Most patients have a subset of the most common features. The presentation can be subtle and difficult to identify or more severe and easily recognized at birth. Approximately 6% to 10% of cases are familial; frequently, one of the parents is only recognized to carry the 22q11 deletion after a more severely affected child is diagnosed. The most common features are listed in Box 1 and are described briefly here.

Congenital heart disease

Hospital-based studies estimate that approximately 75% to 80% of patients with a 22q11 deletion have congenital heart disease [13,14]. These studies may overestimate the true frequency with which cardiac defects are seen in the deleted population, given that children and adults without significant heart disease may escape diagnosis in the current era. As noted, many parents only learn of their own deletion status on the delivery of a child with congenital heart disease who is diagnosed with a 22q11 deletion. A recent report identified two families

Box 1. Common features of the 22q11 deletion syndrome

- Congenital heart disease
- Immunodeficiency
- Hypocalcemia
- Palate anomalies
- Velopharyngeal dysfunction and other speech disorders
- Feeding disorders and growth retardation
- Otorhinolaryngologic issues
- Dysmorphic facies
- Renal anomalies
- Skeletal anomalies
- Cognitive or learning disabilities
- Behavioral or psychiatric disorders