Overview of Medial Characteristics of 22q11DS/VCFS

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Definition

- Interstitial microdeletion of chromosome 22 at band q11.2
- Range of medical and neurodevelopmental abnormalities
- Incidence: 1 in 2000 live births
  - Second only to Down syndrome among autosomal chromosomal conditions
- Prevalence: 1 in 6000 in population
- Most common microdeletion in humans

Nomenclature

- Various terms in use
- Imply that there are several distinct disorders associated with 22q11.2 deletion
- "Geneticists are more likely to share their toothbrushes than their terminology"
  - Michael Cohen, MD

Nomenclature

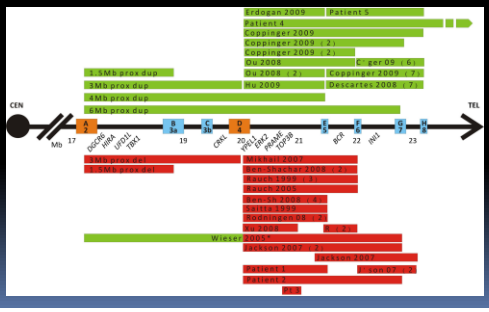
- DiGeorge Syndrome (1968)
  - Developmental field defect of the 3rd and 4th pharyngeal pouches
  - Conotruncal heart abnormality
  - Aplasia/hypoplasia of thymus and parathyroid glands
  - Orofacial Clefting
- Velocardiofacial Syndrome (Shprintzen Syndrome) (1978)
  - Velopharyngeal Incompetence (VPI)
  - Congenital heart disease
  - Dysmorphic features
  - Cognitive deficits

Nomenclature

- Cayler cardiofacial syndrome (1969)
- Conotruncal face anomaly syndrome (1976)
- Sedlakova syndrome
  - All of above found to have 22q11.2 deletion (1992)
- Others:
  - Opitz BBB syndrome
  - VATER, CHARGE
  - 10q13 deletion
  - Maternal diabetes syndrome
- Distal deletion in 22q11.2 region- overlapping clinical features

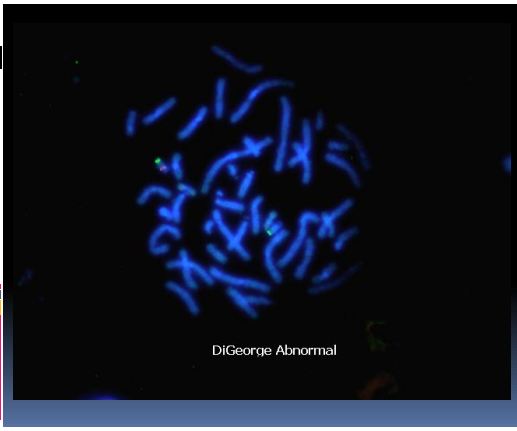
- CATCH22
  - Acronym
  - Not desirable- negative connotation
- Which term should be used?

22q11.2 interval- proximal and distal regions (Tan et al, 2011)



Testing

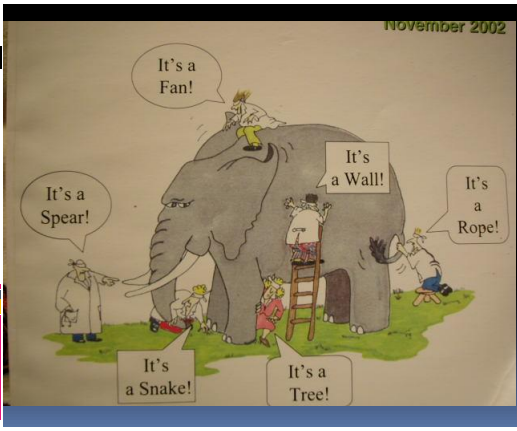
- 90% will have the common 3Mb deletion
- 7% nested 1.5 Mb deletion
- Fluorescence in situ hybridization (FISH)
- Direct DNA testing
- Chromosomal microarray
- <1% will have a chromosomal rearrangement of the 22q11.2 region



Clinical Diagnosis

Initial diagnosis dependent on

1) Age
2) Manifestations
   - Change with age
   - Variable, even within a family
3) Type of specialist



Important Manifestations-Prenatal/Antenatal

- Affected parent/sibling*
- Conotruncal heart defects
  - Interrupted aortic arch* (50%)
  - Tetralogy of Fallot* (20%)
  - Truncus arteriosus* (35%)
- Renal agenesis
  - Oligohydramnios/Polyhydramnios
- Thymic hypoplasia*
- Club feet, polydactyly

*** offer test even if isolated finding**

Infancy

- Conotruncal heart defects*
- Hypocalcemia/hypoparathyroidism*
- Absent/hypoplastic thymus*
- T-cell deficiency*
- Nasal regurgitation with feeding difficulty*
- Facial features*
- Renal abnormalities
- Polydactyly
- Imperforate anus

Additional signs in school years

- Hypernasal Speech*
- Facial features*
- Cognitive difficulties
- ADHD, difficulties with social skills, anxiety

Signs emerging in Adulthood

- Child with 22q11.2 deletion*

Psychoses/Bipolar disorder/Depression

+

Conotruncal heartdefects/facial dysmorphisms

Other medical problems

Cardiac Features (~70%)

- Conotruncal and outflow tract anomalies
  - + Tetralogy of Fallot 20%
  - + Interrupted aortic arch 15%
  - + Ventricular septal defect 13%
  - + Truncus arteriosus 7%
  - + Vascular ring 5%
  - + Atrial septal defect
  - + Right aortic arch
- Ebstein's anomaly and transposition of great arteries are infrequent anomalies

Cardiac findings that warrant consideration of 22q11DS

- ~50% of neonates with interrupted aortic arch (type B)
- ~15-20% of cases of Tetralogy of Fallot (esp with pulmonary atresia)

Palatal Abnormalities~70%

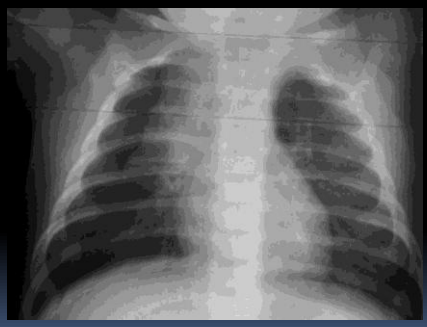
- Velopharyngeal incompetence 30%
- Submucosal cleft palate/bifid uvula 20%
- Overt cleft palate 10%
- Cleft lip/palate 2%

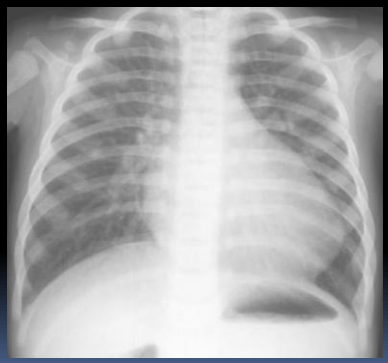
Hypoparathyroidism (17-60%)

- Hypocalcemia most common and serious in neonatal period
  - 70% of neonates with hypoparathyroidism believed to have 22q11.2 deletion
- Can have spontaneous resolution with age
- Recurrence with infections, puberty
- Occasionally onset may be in adulthood

Immune Deficiency ~60%

- Thymus supports maturation of T-cells
- Thymic hypoplasia results in impaired maturation of T-cells
- Less common
  - T-cell functional defects
  - Antibody deficiency
- Spontaneous improvement in first few years of life
- Can wax and wane in later years





Feeding difficulties ~30%

- Severe dysphagia in infancy
- Independent of cardiac defects and palatal abnormalities
- Dysmotility in pharyngoesophageal area (derived from 3rd and 4th pharyngeal pouches)
- Nasogastric tube/ G-tube feeds

Others

- Skeletal abnormalities
- Autoimmune disorders
- Grave's disease, juvenile rheumatoid arthritis, vitiligo, thrombocytopenia
- Hearing loss
- Conductive and sensorineural
- Gastrointestinal and Genitourinary findings
- Increased rates of hospitalization