Velo Cardio Facial Syndrome: Recognition and Therapy for a Common Microdeletion Syndrome

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Objectives
1. Define genetic/genomic basis.  
2. Discuss historical context.  
3. Review clinical presentation.  
4. Outline medical management.  
5. Identify resources for families and professionals.

What is Velo Cardio Facial Syndrome?
- Microdeletion of chromosome 22q11.2  
- Associated with congenital anomalies, endocrine and immunologic abnormalities, cognitive disabilities and psychological disturbances.  
- Highly variable phenotype.
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...and Widely Variable Nomenclature

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History: What’s in a Name?
- DiGeorge syndrome
- Cayler cardiofacial syndrome
- Takao syndrome
- Shprintzen syndrome
- Velo-Cardio-Facial syndrome
- Sedlac'kova’ syndrome
- Conotruncal anomalies face syndrome

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History
This syndrome was described
(based on clinical features)
long before the genetic basis was discovered.
History: What’s in a Name?

Angelo DiGeorge, M.D.
Pediatric Endocrinologist

Robert Shprintzen, Ph.D.
Speech Pathologist

• 1965: Dr. DiGeorge describes children with low calcium, seizures, infections, and heart defects.
• 1976: Dr. Kinouchi reports a typical facial appearance seen in patients with heart problems and calls it conotruncal anomaly facial syndrome (CTAF).
• 1978: Dr. Shprintzen describes a condition running in families. Patients have cleft palate or velopharyngeal incompetence, heart defects, learning disabilities, and a characteristic facial appearance. He calls it velocardiofacial syndrome.
• 1981/1982: Some patients with DiGeorge syndrome noted to have a rearrangement of chromosome 22 that caused them to be missing a very small piece of chromosomal material on the long arm (q11.2).
• 1990: Some parents of DiGeorge patients noted to have features of VCFS.
• 1992: DGS and VCFS found to lie due to deletion 22q11.2.
• 1994: Diagnostic test (FISH) becomes available in clinical laboratories.
• 2004-present: Better diagnostic test (Chromosomal DNA “Chip” or Microarray) is widely used.

A single genomic abnormality explains many syndromes

22q11.2DS
DiGeorge syndrome
Shprintzen syndrome
Velo-Cardio-Facial syndrome
Conotruncal anomalies face syndrome
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Genetics 101

Chromosomes
Ps and Qs
Bands
Genes

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GENEtics is NOT a 4-letter word

~20,000 genes
packaged on 23 pairs of chromosomes
**Slide 13**

**Ideogram**

**Karyotype & FISH**

Microdeletion is NOT visible on G-banded chromosome analysis.

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**Laboratory Diagnosis**

**Karyotype vs FISH vs Microarray**

Chromosomal microarray (aCGH) is greatly improving the rate of diagnoses.

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**Deletion 22q11.2**

- DiGeorge
- Velocardiofacial

- Presenting in infancy
- Childhood/adulthood
- Severe heart defects
- Minor heart defects
- Severe infections
- Weak palate; cleft palate
- Seizures
- Long face and fingers
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**Deletion 22q11.2**

- Fetal Demise
- Severe Neonatal
- Early Childhood
- School Years
- Teens
- Adult

IUFD—CHD/Seizures—Feeding/DD—Behavior—Psych—Incidental

**CATASROPHIC to ASYMPTOMATIC**

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**Deletion 22q11.2**

- Fetal Demise
- Severe Neonatal
- Early Childhood
- School Years
- Teens
- Adult

**Incidence of ~1 in 2000**

Diagnosis is dependent on:
- Experience and Awareness of Providers
- Severity of Phenotype

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**Objectives Redefined**

1. Recognize 22qDS in your patients.
2. Confirm diagnosis by laboratory testing.
3. Discuss recurrence risk for family members.
4. Provide recommendations for medical intervention and surveillance.
5. Provide information regarding support/advocacy groups.
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Case Presentation

- 10 month old girl
- History of atrial septal defect
- Developmental delay
  - Hypotonia
  - Poor feeding
  - Delayed milestones
- Observation in clinic
  - Nasopharyngeal reflux


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What type of Genetic Test would you recommend?

- Chromosome analysis
  - NO
- FISH for 22q
  - NO
- Chromosome microarray


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Intrauterine Fetal Demise

24yo prima gravida; 26yo father
No maternal illnesses or exposures
Normal ultrasounds
Normal maternal serum screens
Lack of fetal movement at 28 weeks
Consent for autopsy
Absent thymus
Hypoplastic parathyroid glands
Tetralogy of Fallot

Three Years Later

- SGA male BTA 27yo G2P1-2
- Interrupted aortic arch
- Hypocalcemic seizures
- Severe immunodeficiency
- Overwhelming sepsis

Diagnostic Approach

- Chromosomal microarray deletion 22q11.2
- Should we stop there?
- Family history
- Parental studies
- Mother with deletion 22q

Recurrence Risk

- 95% deletions—“de novo”
- 5% are inherited from a parent.
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**Recurrence Risk**

For someone who HAS the deletion

Recurrence risk is 50%

Always test the parents

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**Case Presentation**

17yo girl

ADHD dx in childhood

Learning disabilities identified in H.S.

Dx recently with ODD

Physical examination

CMA revealed 22q11.2 deletion

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**Indications for Genetic Evaluation**

1. Establish diagnosis
2. Anticipatory guidance
3. Medical management
4. Developmental intervention
5. Behavioral intervention
6. Psychological management
7. Recurrence risk
**Clinical Features of Deletion 22q11.2**

Over 180—Involving many organs and systems:
- Brain
- Heart
- Immune system
- Calcium regulation
- Palate
- Gastrointestinal track
- Growth
- Vision
- Hearing loss
- Learning
- Anxiety
- Kidneys
- Feeding difficulties
- Speech delay
- Swallowing problems
- Infections
- Seizures
- Low muscle tone
- Gastroesophageal reflux
- Submucous cleft
- Hypernasal speech
- Vascular anomalies
- Autism
- Over 180—Involving many organs and systems

**Diagnosis of Deletion 22q11.2**

1 in 2,000

- Birth: 30%
- By age 5 years: 70%
- By age 18 years: 95%

Some people with deletion 22q11.2 are diagnosed following birth of affected child.

**Clinical Features of Deletion 22q11.2**

Facial features can be very subtle.
Clinical Features of Deletion 22q11.2

- No feature occurs in ALL patients.
- NO patient has all features.
- Extremely variable.
- Current laboratory techniques allow earlier diagnosis.
- Early diagnosis leads to better clinical and educational outcome.

22q11.2DS: Congenital Anomalies

<table>
<thead>
<tr>
<th>Area</th>
<th>Diagnostic Tests</th>
<th>Follow Up</th>
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<tbody>
<tr>
<td>Brain</td>
<td>EEG; MRI</td>
<td>Neurologist</td>
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<td><strong>Ear</strong></td>
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**Developmental and Behavioral Problems**

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<th>Follow Up</th>
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<td>Developmental Delay (70-90%)</td>
<td>Early Childhood Intervention</td>
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<td>Speech delay (70-80%)</td>
<td>Occupational/Physical Therapy</td>
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<tr>
<td>Articulation difficulty</td>
<td>IQ; Speech therapy</td>
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<tr>
<td>Learning disability (70-90%)</td>
<td>Augmentative communication</td>
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<td>Attention deficit</td>
<td>Developmental specialist</td>
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<tr>
<td>Autistic spectrum disorder</td>
<td>Psychiatric</td>
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<td>Schizophrenia, Bipolar</td>
<td>Psychiatric</td>
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<tr>
<td>Depression, Anxiety disorder</td>
<td>Psychiatric</td>
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**International Consortium on Brain and Behavior in 22q11.2 Deletion syndrome (2014)**

- ADHD—most frequent in children: 37% (M>F)
- Disruptive disorders—(ODD/Conduct): 7-14% (M>F)
- Anxiety disorders—in children and adolescents (F>M)
- Panic disorder—increased with age
- Mood disorders—increased with age (F>M)
- Autism Spectrum—(M>F)
- Psychotic disorders—in adults ≥25 years

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**Living With a Child at Risk for Psychotic Illness: The Experience of Parents Coping With 22q11 Deletion Syndrome: An Exploratory Study**

- Survey of 41 caretakers of individuals with deletion 22q11.2.
- Information about the association between deletion 22q11.2 and psychiatric disease was omitted at diagnosis most of the time and rarely addressed by medical specialists.
- Families frequently received their information only from non-medical sources, principally the internet.
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Which problems are cause for parental concern?


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22q11.2 DS Resources

- Your local geneticist.
- Internet:
  - GeneReviews www.genetests.org
  - Genetic Home Reference
  - 22q and You (CHOP)
  - VCFS Texas
  - PubMed, Amazon, Google

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References:

9. 22q and You Website: Children's Hospital of Philadelphia. http://www.chop.edu/consumer/jsp/division/service.jsp?id=74652
10. Also see 22q and You Newsletter AND Faces of Sunshine—A Handbook for Parents and Professionals