Why Identifying 22q11.2 MicroDeletion Syndrome is Important?

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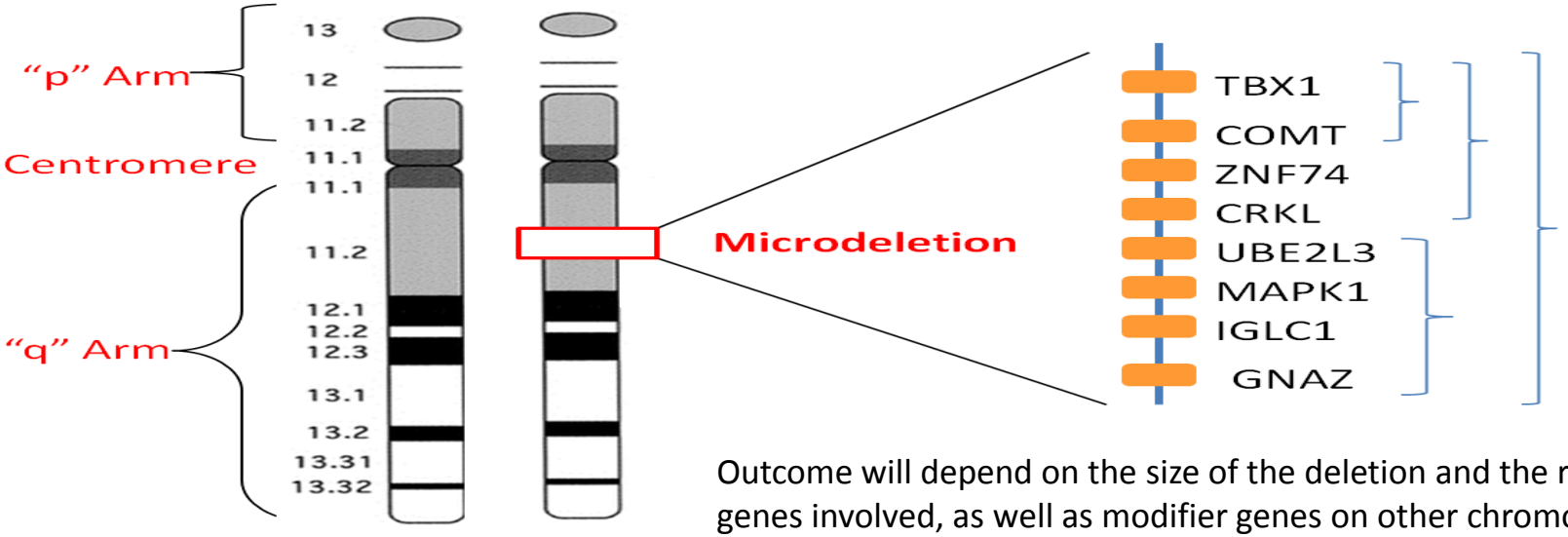
  - ✓ *Wide variability hampers early diagnosis*
- **Early Intervention Matters**

What is a Microdeletion?

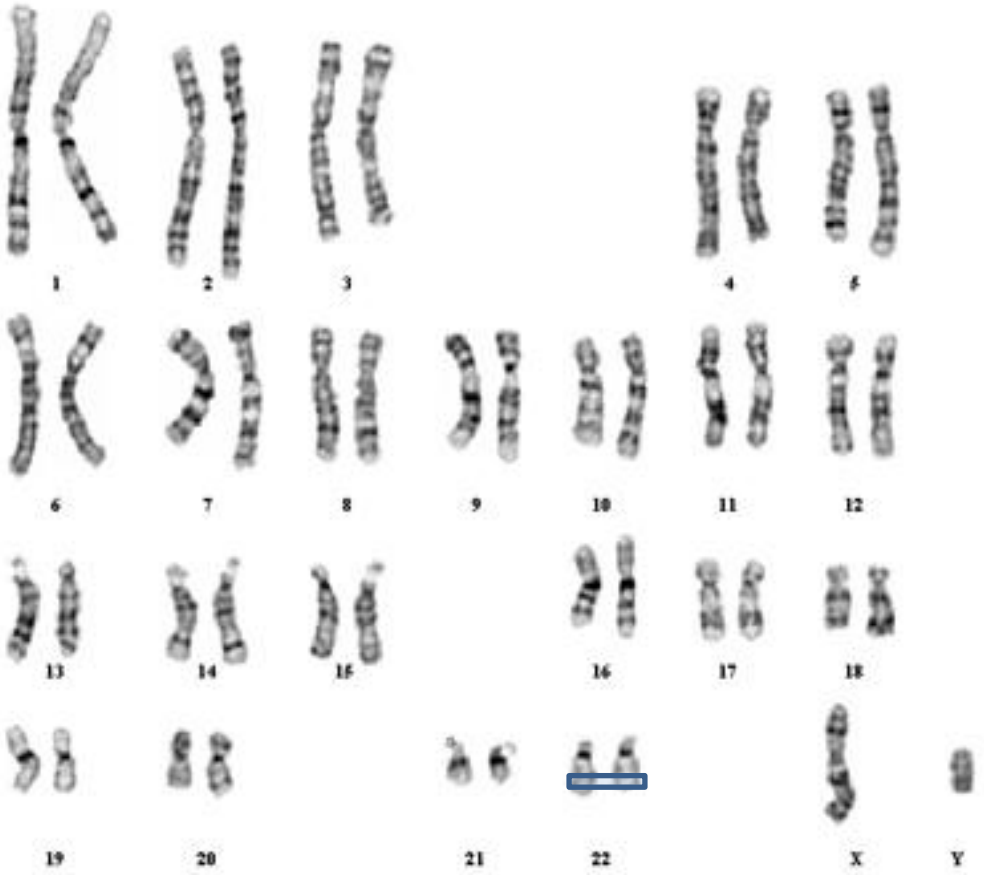
- 1MB (megabase) = 1 million base pairs
- Microdeletions are 100kb to several MB
- Karyotype can usually only visually detect ≥7-10 MB



Outcome will depend on the size of the deletion and the resultant genes involved, as well as modifier genes on other chromosomes

Overview of the 22q11.2DS

Karyotyping



22q11.2 Deletion Syndrome[1,2]

- Population incidence ~1 in 2000, though NEJM suggests higher
- Several other names: DiGeorge, Velo-Cardio-Facial Syndrome (VCFS)
- Often unrecognized at birth
- Common features
  - Congenital heart defect (75%)
  - Immune deficiencies (75%)
  - Palatal abnormalities (70%)
  - Schizophrenia in young adulthood (25%)
  - Hypocalcemia (77%)
  - Developmental delay and learning disabilities (70-90%)

[1]International 22q11.2 Foundation – Handbook
[2]www.genereviews.org

Medical Genetics Matters

Deletion Disorder	Frequency	Most common deletion	% cases with common large del	Additional comments
22q11.2	1/2,000	3Mb	87	**Various smaller dels**

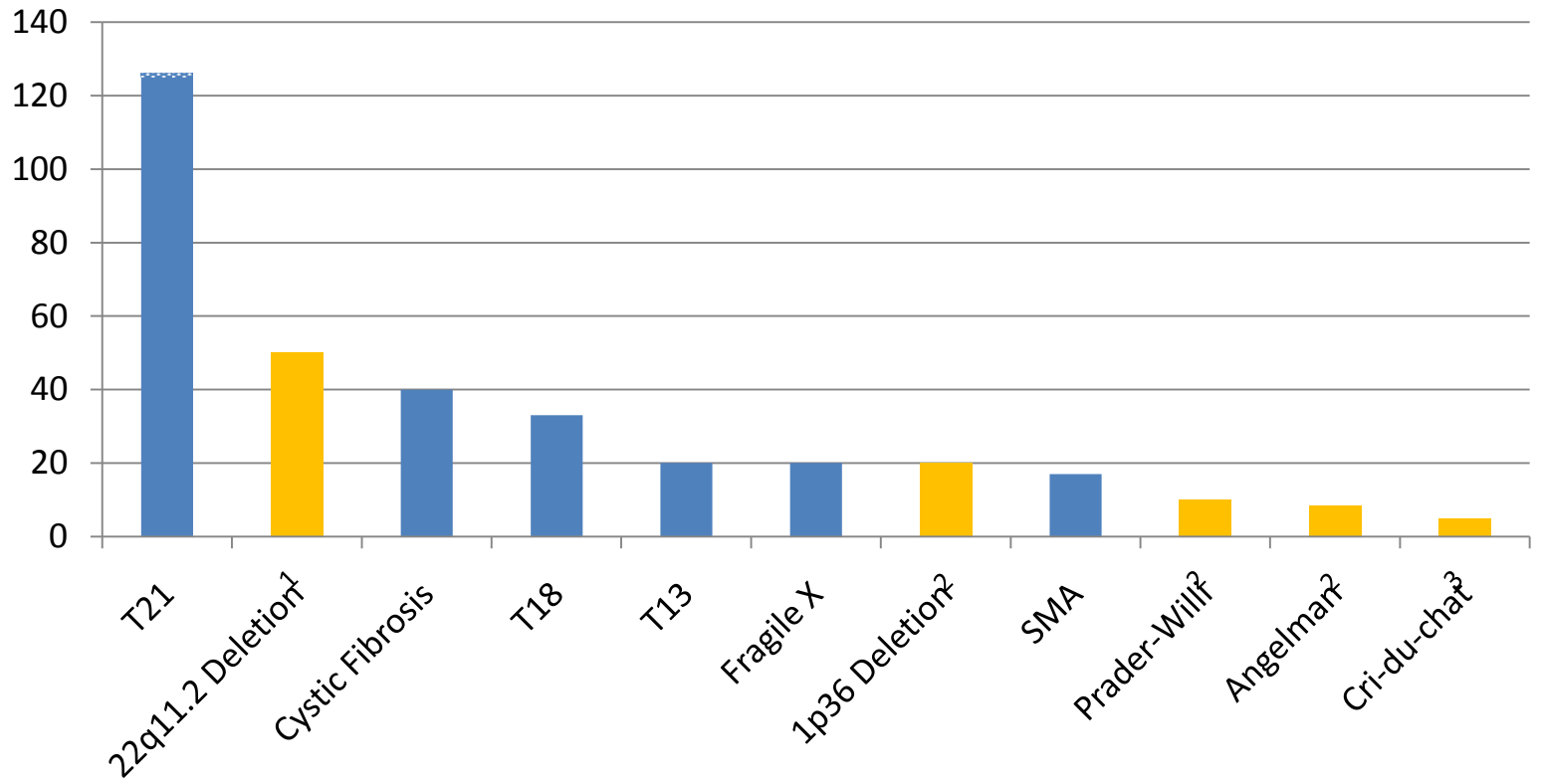
22q deletion/DiGeorge

- Involving haploinsufficiency of aprocimately 30 – 40 genes
- Resulting in a multisystem disorder
- May have ultrasound findings (heart defects)
- 93% have no family history

Why 22q11.2DS is Important to the OB Community?

High Incidence Conditions

Incidence out of 100,000 Live Births



[1]Nussbaum et al. 2007. Thompson and Thompson Genetics in Medicine (7th edn). Oxford Saunders: Philadelphia

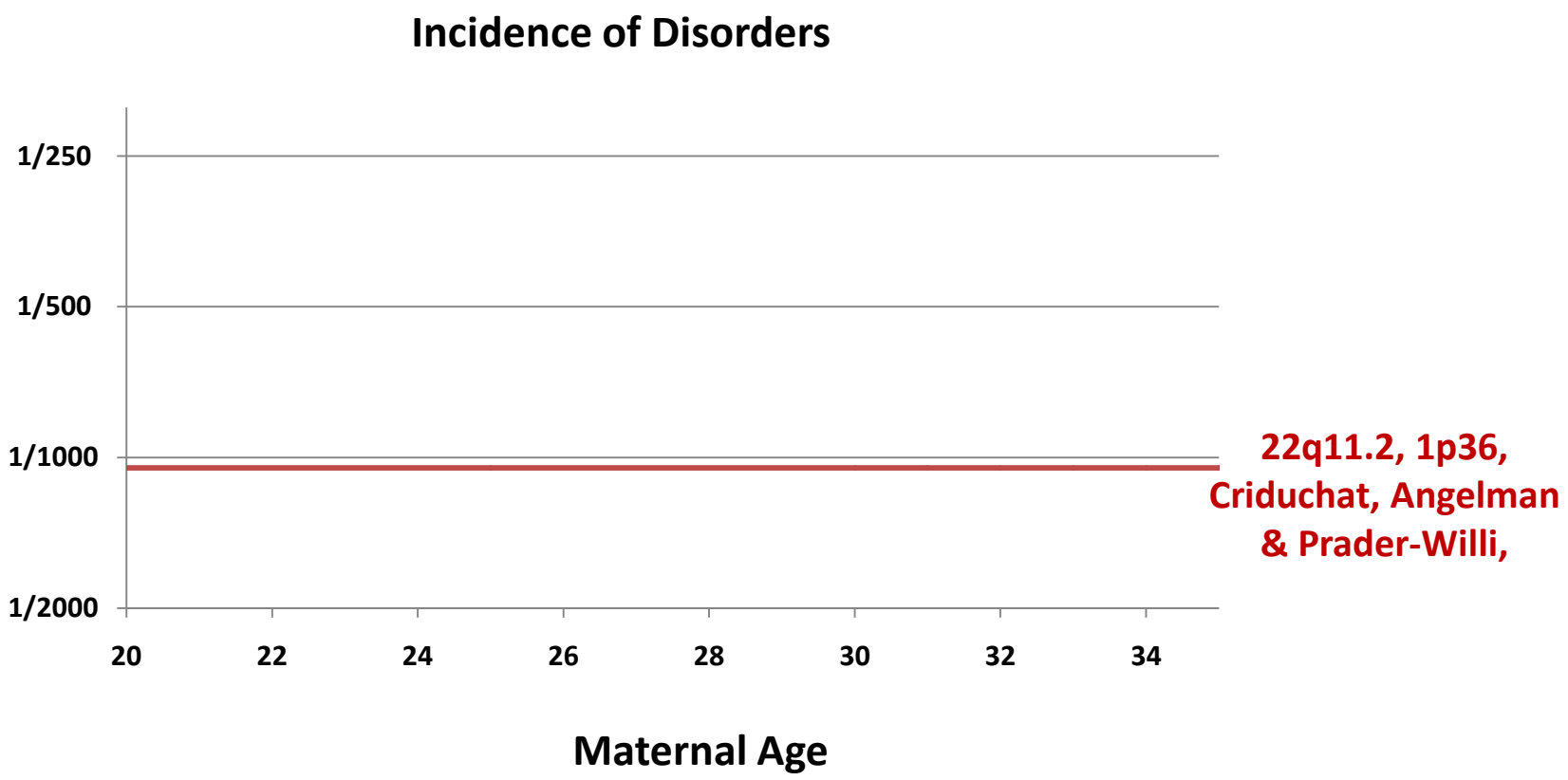
[2]http://www.genetests.org.

[3]http://ncbi.nlm.nih.gov

22q11.2 is the most common microdeletion syndrome

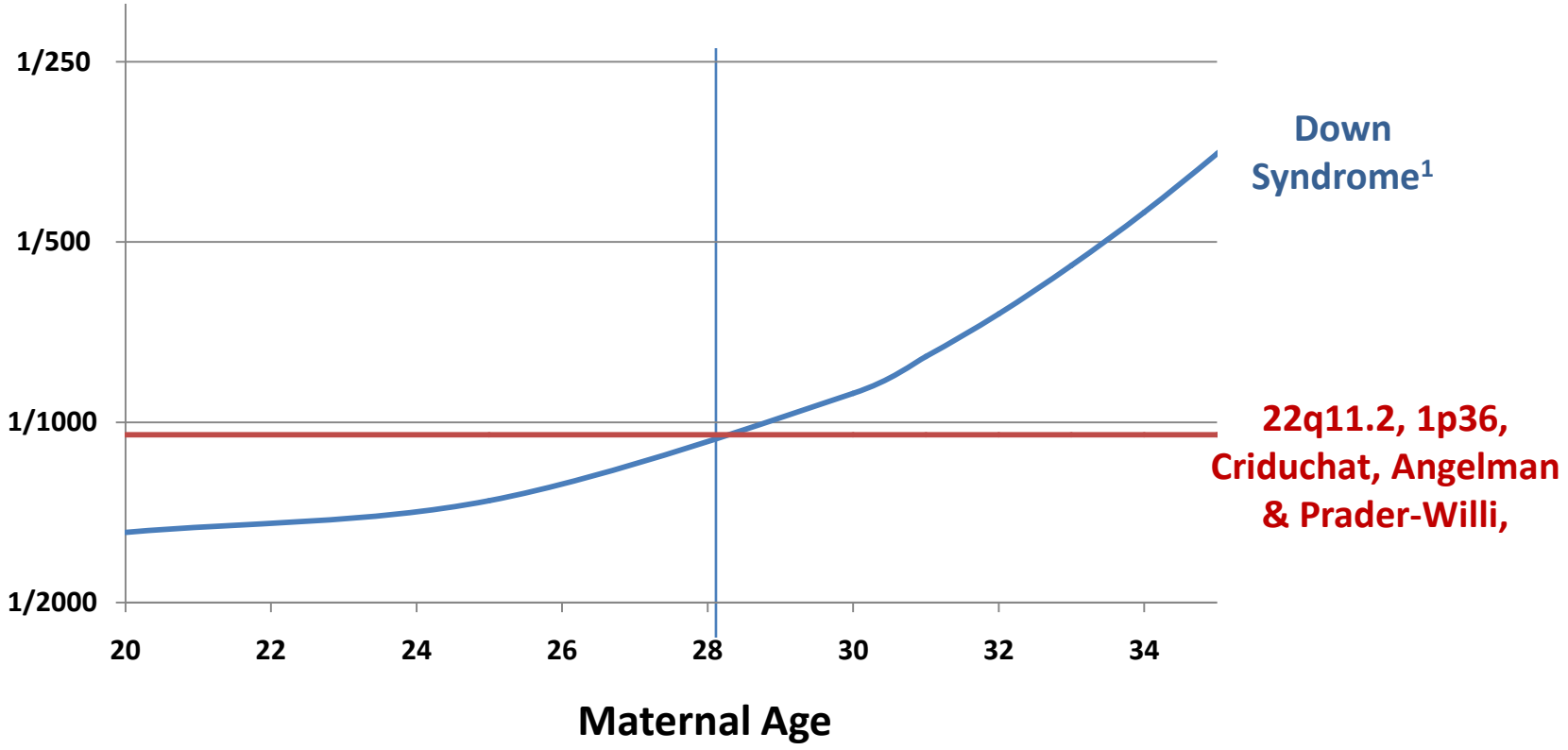
- With an estimated prevalence of ≈ 1/2000 – 1/4000 live births.
- Actual occurrence may be higher in light of the variable expressivity.

More Common Than Down Syndrome in Younger Women



[1]Combined prevalence using higher end of published ranges from Gross et al. Prenatal Diagnosis 2011; 39, 259-266; and www.genetests.org.
Total prevalence may range from 1/1071 - 1/2206.

More Common Than Down Syndrome in Younger Women



[1]Snijders, et al. Ultrasound Obstet Gynecol 1999;13:167–170.
[2]Combined prevalence using higher end of published ranges from Gross et al. Prenatal Diagnosis 2011; 39, 259-266; and www.genetests.org. Total prevalence may range from 1/1071 - 1/2206.

The 2nd most common cause of congenital heart disease after Down sydrome

- **Identified in**
  - 52% of patients with IAA type B
  - 35% with truncus arteriosus
  - 16% with tetralogy of fallot

** Goldmuntz 1993; Bassett 2011*

The 2nd most common case of major developmental disabilities after Down syndrome

- Accounting for ≈ 2.4% of infividual with such delay

** Rauch 2006; Goldmuntz 1993; Bassett 2011*

The most common cause of syndromic palatal anomalies

- Including:
- Overt cleft palate
- Cleft lip/palate
- SMCP/bifid uvula/velopharygeal dysfunction

** McDonald MCGim 1997, 1999; Solot 2000; Bassett 2011*

Early Screening & Diagnosis of 22q11.2DS

Screening for 22q11.2 DS

Different Context – No Longer High Risk Only

- Previously – high risk referrals only
  - focus on cardiac anomalies (75% in 22q11.2 deletion syndroe)
- What are other anomalies to consider on ultrasound in low risk setting?
  - Renal Abnormalities - Both Unilateral and Bilateral
  - Neurological Defects
  - Limb and Skeletal Defects
  - Craniofacial
  - Gastrointestinal Anomalies
  - Nuchal translucency
  - Polyhydramnios

Peer Review - NIPT for Microdeletions (AJOG; 12/2014)

RESEARCH ajog.org

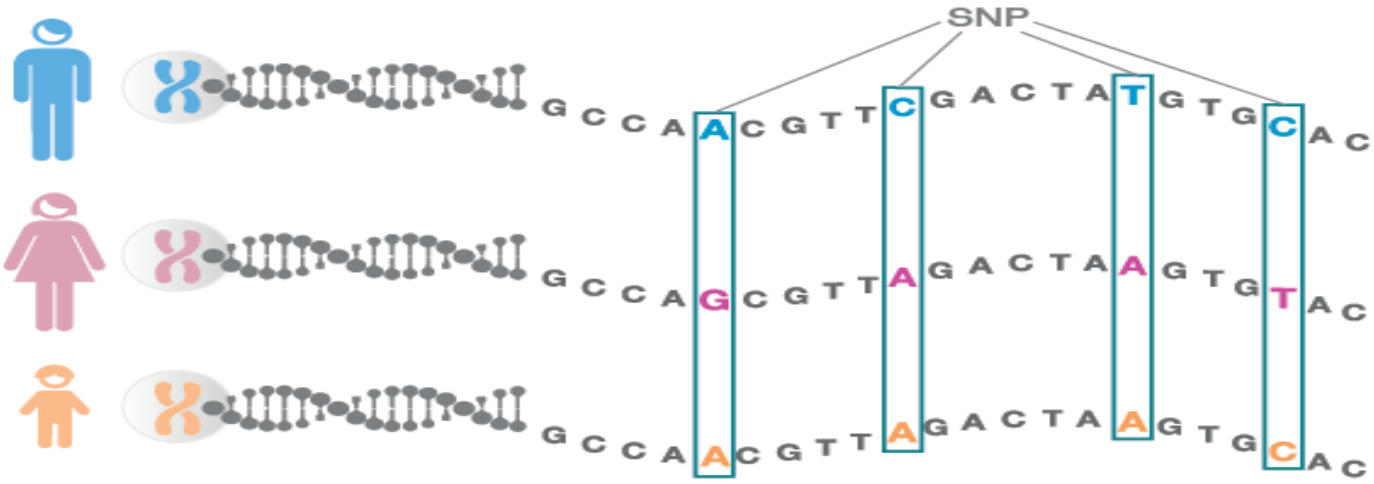
OBSTETRICS

Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes

Ronald J. Wapner, MD; Joshua E. Babiarz, PhD; Brynn Levy, MSc (Med), PhD; Melissa Stosic, MS; Bernhard Zimmermann, PhD; Styrmir Sigurjonsson, PhD; Nicholas Wayham, BS; Allison Ryan, PhD; Milena Banjevic, PhD; Phil Lacroute, PhD; Jing Hu, PhD; Megan P. Hall, PhD; Zachary Demko, PhD; Asim Siddiqui, PhD; Matthew Rabinowitz, PhD; Susan J. Gross, MD; Matthew Hill, PhD; Peter Benn, DSc

NIPT: Screening for 22q11.2 DS

- NIPT method using SNPs



- A DNA sequence variation occurring when a single base pair (nucleotide) - A, T, C, or G – is changed.
- These are **normal** genetic changes that occur in every person

Screening for 22q11.2 DS - NIPT

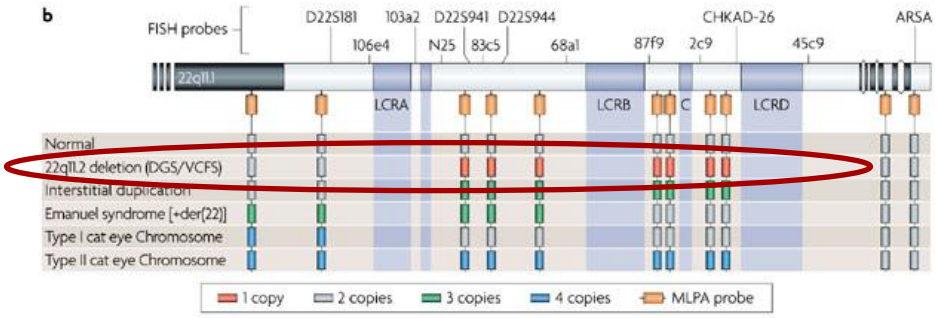
Syndrome	Incidence	Sensitivity [1]	Specificity [1]	Location (Size of Region) # SNPs	Lifespan	Mental Effects	Heart Defects	Other features
22q11.2 Deletion/ DiGeorge	1 in 2,000 [2]	95.7% (45/47) (85.5-99.5%) [5]	>99% (419/422) (97.9-99.9%) [5]	22q11.2 (2.9 MB) 672 SNPs	Reduced	Mild to moderate intellectual disorder & schizophrenia	Yes	Palate and feeding Immune problems, low calcium, seizures
Prader-Willi	1 in 10,000 [3]	93.8% (15/16) (69.8-99.8) [5]	>99% (453/453) (99.2-100%) [5]	15q11-q13 Paternal (5.9 MB) 1,152 SNPs	Reduced	Mild to severe intellectual disorder & behavioral problems	No	Hypotonia in babies, insatiable appetite
Angelman	1 in 12,000 [3]	95.5% (21/22) (77.2-99.9%) [5]	>99% (447/447) (99.2-100%) [5]	15q11-q13 Maternal (5.9 MB) 1,152 SNPs	Normal	Severe intellectual disorder	No	"Happy" affect, ataxia, microcephaly, no speech, seizures
Cri-du-chat	1 in 20,000 [4]	>99% (24/24) (85.8-100%) [5]	>99% (444/445) (98.8-99.9%) [5]	5p15.2 (20 MB) 1,152 SNPs	Infancy to adult	Moderate to severe intellectual disorder & behavioral problems	No	Cat like cry, growth problems, wide set eyes
1p36 Deletion	1 in 5,000 [3]	>99% (1/1) (2.5-100%) [5]	>99% (468/468) (99.2-100%) [5]	1p36 (10 MB) 1,152 SNPs	Normal in most	Severe intellectual disorder & behavioral problems	Yes	Limited/no language, hearing loss, abnormal ears, seizures

[1]Performance specifications reflect presence or absence of the complete targeted region
[2] Wapner et al. Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes. Am J Obstet Gynecol 2015; 212:xxxx; [3]Nussbaum et al 2007. Thompson and Thompson Genetics in Medicine (7th edn). Oxford Saunders: Philadelphia; [4] http://www.ncbi.nlm.nih.gov/books/NBK1330/; [5] http://www.ncbi.nlm.nih.gov/books/NBK1144/ ; [6]http://omim.org/entry/123450; [7]http://www.ncbi.nlm.nih.gov/books/NBK1191/ [8]Calculated based on the test performance including pregnancy samples, [9]Calculated based on the test performance including artificial plasma samples; [10]95% confidence interval

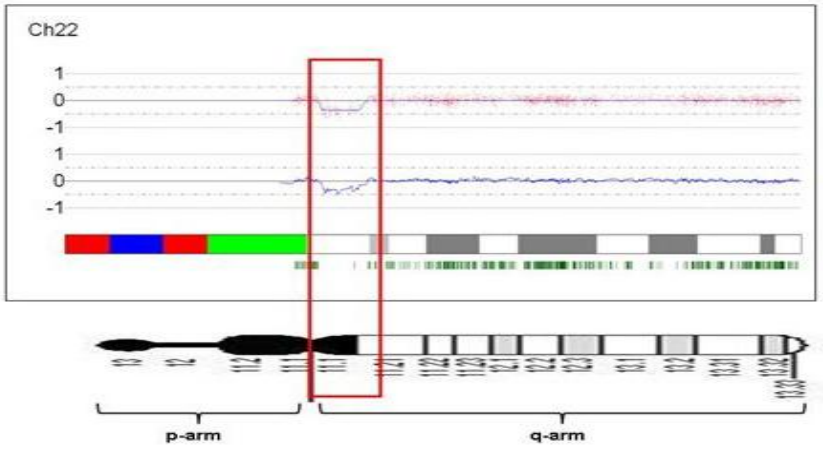
Total incidence: approximately 1 in 1,000

Confirm Deletion - Current Detection Methods Still Include FISH

- MLPA and microarrays are preferred



- MLPA



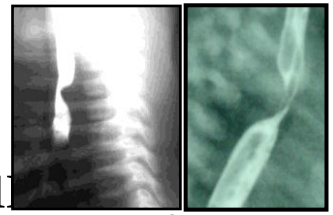
- Microarray

Early Diagnosis of 22q11.2DS can Dramatically Decrease Morbidity and Likely Mortality

- As 3/4 of children with 22q11.2DS have congenital heart disease
  - Many associated lesions require neonatal surgery
  - Ductal dependent lesions may not be identified using postnatal pulse oximetry monitoring
  - Late diagnosis increases morbidity and mortality
  - Early diagnosis of congenital heart disease markedly reduces overall healthcare costs

Early Intervention Matters

- Prepare to deliver at a tertiary care facility
- No live viral vaccines until immune system has matu
- Calcium monitoring to avoid seizures and cognitive impairment
- Palatal exam to pre-anticipate difficulties with feeding and speech



vascular ring

FOR THE FIRST TIME, PRENATAL SCREENING CAN AFFECT LONG TERM OUTCOME FOR THE BABY

In Summary

- 22q11.2DS is common
  - 2nd most common cause of CHD
  - More common cause of TOF than Down syndrome
  - Most common cause of syndromic palatal anomalies
  - 2nd most common cause of developmental differences
- 22q11.2DS has significant morbidity
  - Multi-organ system involvement
  - Immune, Endocrine and Gastrointestinal problems
  - Variable cognitive deficits and psychiatric illness
- 22q11.2DS is not related to advanced maternal age
  - Affected offspring - equally likely born to young mothers as with AMA
- Wide variability hampers early diagnosis
  - Delaying interventions and leading to poorer prognoses

Summary (cont.)

- **Prenatal Dx offers both medical and emotional preparedness**
- **Concurrently reducing costs related to late/missed diagnoses**

Thank you for your attention!

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