TRISOMY 21

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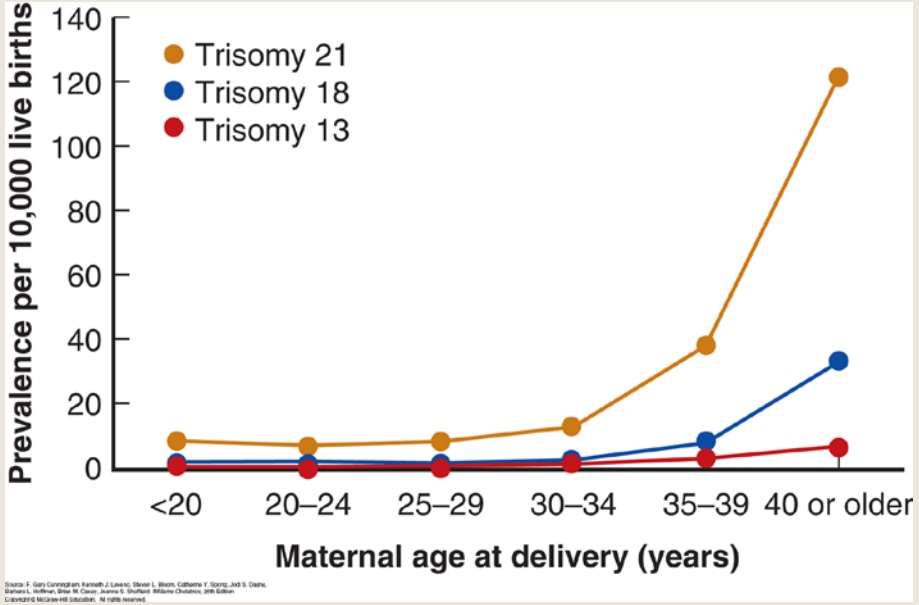
Genetics 2020

Background information

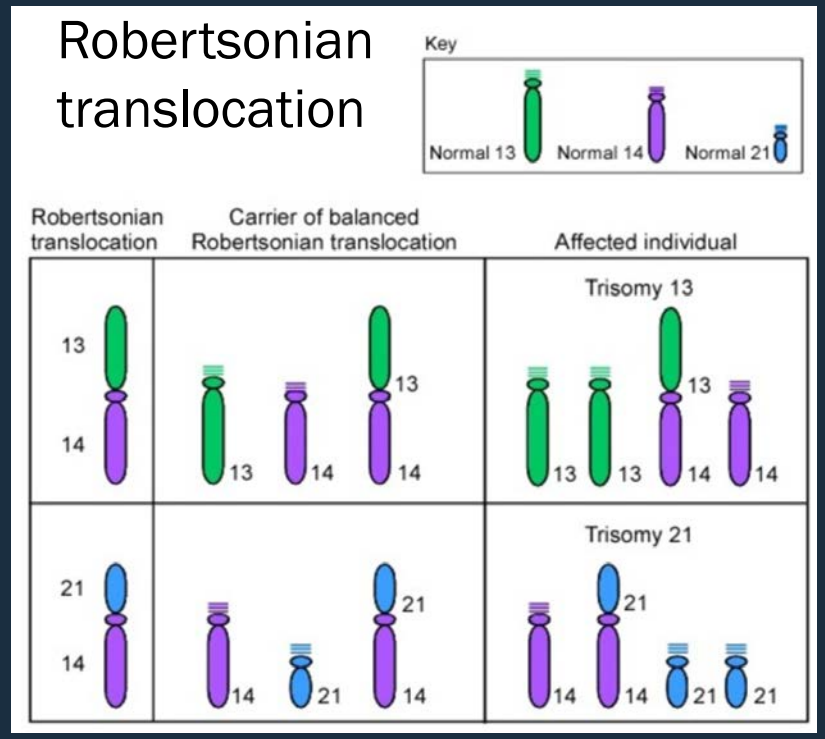
- Epidemiology
  - 1 in 800 live births
  - Most common autosomal abnormality
  - Most common cause of intellectual disability
  - Risk of autosomal trisomies increases steeply with age
- Etiology
  - Most commonly secondary to nondisjunction resulting in Trisomy (94%)
    - Can result from failure to pair up properly, premature separation, or failure of separation
  - More rarely can result from mosiacisim (2.4%)
    - 75% in Meiosis 1, 25% in Meiosis II
    - A trisomy that occurs after fertilization, so trisomy present in some cells but not all
    - Variable pheonotype
  - Also uncommonly due to unbalanced translocations (Robertsonian translocations) (3.3%)
    - 75% de novo translocations, 25% familial



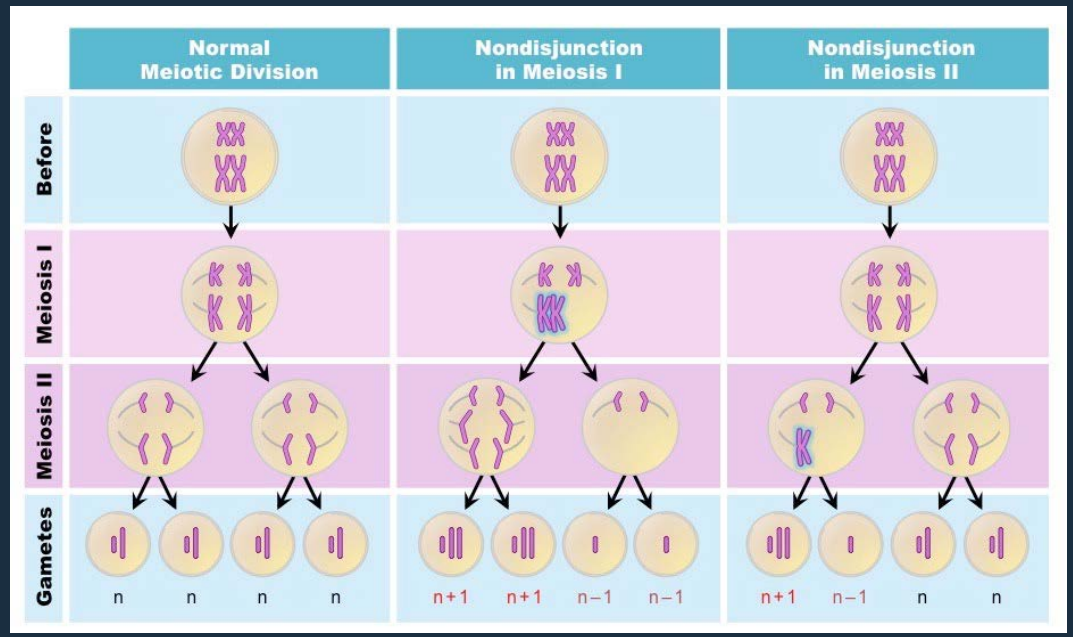
- 15-29 years - 1 case in 1500 live births
- 30-34 years - 1 case in 800 live births
- 35-39 years - 1 case in 270 live births
- 40-44 years - 1 case in 100 live births
- Older than 45 years - 1 case in 50 live births

GENETICS

Robertsonian translocation



Nondisjunction



Prenatal Testing

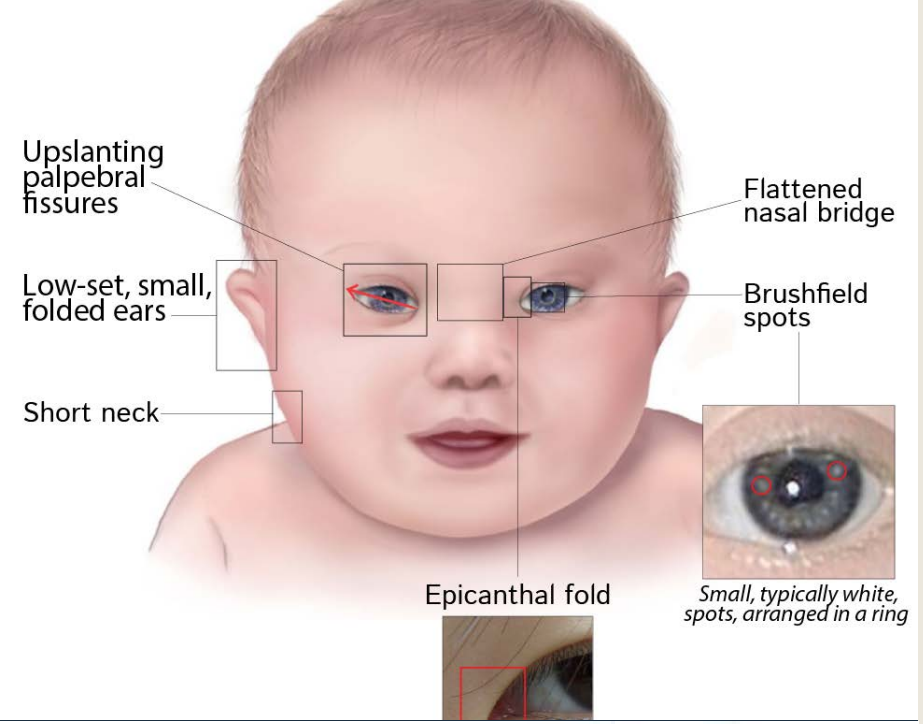
Test	Timing	Advantages	Disadvantages
1st Trimester Combined Test - PAPP - bHCG - Nuchal translucency	9-13	Early screening	Not diagnostic
Cell-free fetal DNA	>10	High sensitivity and specificity for aneuploidy	Not diagnostic
Chorionic Villis Sampling	10-13	Definitive karyotype diagnosis	Invasive, risk of miscarriage
2nd Trimester Quad Screen - MSAFP - Estriol - bHCG - Inhibin A	15-22	Screens for neural tube defects as well as aneuploidy	Not diagnostic
Amniocentesis	15-20	Definitive karyotype diagnosis	Invasive, risk of membrane rupture, fetal injury, pregnancy loss
2nd Trimester Ultrasound	18-20	Measures growth and anatomy	Cannot identify all anomalies

Interpretation of screening results

Second trimester Quad screen results

Increased risk for:	hCH	Estriol	AFP	Inhibin A
Open spina bifida	Normal	Normal	High	n/a
Anencephaly	Low	Low	High	n/a
Down syndrome	High	Low	Low	High
Edwards syndrome	Low	Low	Low	n/a

- First trimester combined screen findings suggestive of Trisomy 21
  - Increased NT
  - Increased bHCG
  - Decreased PAPP



Features

- Physical features
  - Upslanting palpebral fissures
  - Epicanthic folds
  - Flat facial profile/flat nasal bridge
  - Low-set small ears
  - Brachycephaly
  - Protruding tongue
  - Short neck with excessive skin at nape
  - Transverse palmar crease
  - Space between the first and second toes (sandal gap)
  - Hyperflexibility of joints
  - Hypotonia
  - Wide spaced nipples
- Developmental and behavioral features
  - *Mild to moderate intellectual disability*
  - *Delayed motor and speech milestones*
  - *Often, intact language comprehension with delayed production*
  - *Concomitant Autism (7%)*

Associated Health Problems

- Cardiovascular
  - *A little under one half of individuals have associated CHD*
    - Complete atrioventricular septal defect (CAVSD) – 37 percent
    - Ventricular septal defect (VSD) – 31 percent
    - ASD – 15 percent
    - Partial atrioventricular septal defect (PAVSD) – 6 percent
    - Tetralogy of Fallot (TOF) – 5 percent
    - PDA – 4 percent
- Gastrointestinal
  - *Duodenal atresia (2.5%)*
  - *Celiac disease (5-16x increased risk than general population)*
  - *Less commonly, but more common than general population: TEF, Hirschsprung*

Associated Health Problems

Growth

- *Short stature (important to reference Ds specific growth chart)*
- *Increased rate of obesity*

Vision and hearing

- *5% develop cataracts*
- *Increased rate of strabismus, nystagmus and refractive errors*
- *38-78% with hearing impairment (often secondary to recurrent otitis media)*

Endocrine

- *35% with hyperthyroidism by age 25*
- *Increased risk of Type 1 Diabetes*

Hematologic

- *65% of newborns with polycythemia*
- *1-1.5% lifetime risk of Leukemia*

Pulmonary

- *Increased risk of OSA*
- *Increased risk of pulmonary hypertension in the neonatal period*

MSK

- *Atlantoaxial instability leading to risk of cervical subluxation and spinal cord compression*
- Hip dislocation

Health Supervision

- Postnatal diagnosis
  - *Karyotyping and FISH*
    - The full karyotype is necessary as otherwise would not be able to pick up translocations
- Every neonate needs an echocardiogram
- Regular hearing screens and eye exams
- Sleep study by age 4 to monitor for OSA
- Thyroid studies: starting at 6-12 mo and then annually
- CBC (or at least Hgb) for leukemia monitoring: annually
- Any signs of atlantoaxial instability (myelopathy, neck pain, fatigue): spinal films

References

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