Syndrome Review 1: Common Trisomies and Sex Chromosome Variations

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Objectives

• To understand the term aneuploidy in regard to numerical chromosome abnormalities
• To be aware of the importance of chromosome abnormalities as a cause of birth defects
• To be familiar with the common autosomal trisomy syndromes and their clinical features
• To be familiar with variations in sex chromosome number and their corresponding syndromes
• To understand possible mechanisms of numerical aneuploidy
Definitions

- **Aneuploidy**
  - Numerical abnormality of chromosomes
    - Any chromosome number not an exact multiple of the haploid number of 23
    - Normal number in humans is 46 (23 pairs) except for mature egg and sperm
    - Extra *(trisomy)* or absence of *(monosomy)* chromosome
- **Autosomes**
  - Chromosome pairs 1-22
- **Sex chromosomes or gonosomes**
  - The 23rd pair of chromosomes
  - X and Y chromosome
- **Constitutional** chromosome abnormalities are congenital, in contrast to acquired chromosome abnormalities associated with cancer or aging process
- **Mosaicism**
  - A combination of two or more cell lines, (e.g. One cell line with normal chromosome makeup and one with an extra chromosome)
Causes of Birth Defects among Live-born Infants

- Chromosome
- Single Gene
- Multifactorial
- Environmental
- Twinning
- Unknown

The Incidence of Chromosome Abnormalities
Is High in Spontaneously Aborted Pregnancies,
Stillbirths and Perinatal Deaths

- All recognized pregnancies ~5 %
- Spontaneously aborted pregnancies
  - All 1 st trimester ~40 %
  - All second trimester ~15 %
- Stillbirths and perinatal deaths 7-10 %
- All liveborn children 0.5–0.7 %

The earlier the loss, the higher the incidence of a chromosome abnormality.
The type and proportions of aneuploidies found in SABs are different from those found among liveborns.

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Jacobs et al., Advances in Genet 1995;33:101-133
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Down Syndrome

• Phenotype first described by Dr. John Langdon Down in 1866
• The first chromosomal abnormality described in humans
• The most common chromosome aneuploidy seen in live-born infants
• 1 in 700 births
- Upslanting eyes and epicanthal folds
- Brushfield spots
- Dysplastic ear
- Excess nuchal skin
- Single transverse palmar crease and clinodactyly of 5th finger
- Sandal gap of toes 1-2
Congenital Malformations and Medical Complications Associated with Down Syndrome

- Cardiac 40%
  - AV canal/endocardial cushion defect, VSD, PDA, ASD

- GI 12%
  - Duodenal atresia, TE fistula, omphalocele, pyloric stenosis, annular pancreas, Hirschsprung disease, imperforate anus
Congenital Malformations and other Medical Complications Associated with Down Syndrome

- **Thyroid**
  - 1% per year risk of hypothyroidism
- **Orthopedic**
  - Hip dysplasia, cervical spine instability
- **Hearing**
  - Conductive loss most common
- **Vision**
  - Strabismus, myopia, nystagmus
- **Hematologic**
  - Leukemoid reaction and polycythemia in newborn period 18%
  - Leukemia 1% lifetime risk
Average life expectancy 56 years in 1991 in US, 60 years in Australia in 2002

Major cause of early mortality is CHD

Risk of infections and pneumonia

Increased risk of Alzheimer disease

Bittles and Glasson, Dev Med Child Neurol 2004
95% of Patients With Down Syndrome Have 3 SEPARATE CHROMOSOME 21s “Trisomy 21”
3-4% of Patients have Down Syndrome Secondary to AN UNBALANCED ROBERTSONIAN TRANSLOCATION

Phenotype is indistinguishable from that associated with NDJ form of Down sx.
Trisomy 18

- First described by Dr. J.H. Edwards in 1960
- Prevalence of 1/5000 - 1/7000
- Excess of affected females
- 85% from maternal meiotic nondisjunction
- Mean life expectancy 4 days
- From 1-5% live more than 1 year
Microcephaly, short palpebral fissures, short upturned nose, micrognathia

Clenched hands, overlapping fingers, camptodactyly

Talipes valgus
Trisomy 18

- Growth deficiency
- VSD, ASD, TOGV, TOF, coarctation, pulmonic stenosis
- Hydronephrosis, Wilms tumor, polycystic kidneys, ectopic kidney
- Thyroid and adrenal hypoplasia
- Meckels diverticulum, hernias, omphalocele
Trisomy 13

- First described by Dr. K. Patau in 1960
- 1/12,000 births
- Mean life expectancy 130 days
- 86% die during the first year
Microcephaly, scalp defects, clefts, microphthalmia, polydactyly, cardiac defects, renal anomalies.
Trisomy 13

- 75% trisomy 13 from with separate extra chromosome
- 20% translocations
- 5% of the translocations inherited from parent
- 5% cases mosaic
Two year old female with trisomy 13, congenital sacral teratoma

Postaxial polydactyly and polysyndactyly
Trisomy 8

- Most cases have mosaicism
- Large ears, deep plantar furrows
- Spina bifida, renal and ureteral anomalies, CHD
- Increased risk of hematologic malignancy
Trisomy 9

- Most cases mosaic
- Craniofacial anomalies
- Skeletal anomalies
- Abnormal external genitalia
- Cardiac anomalies in at least 60%
- Renal malformations in 40%
Sex Chromosomes

- One of the factors that determines gender
  - Females have two X chromosomes
  - Males have one X and one Y chromosome
Sex Chromosome Variations

- Turner syndrome
- Triple X or Trisomy X syndrome
- Klinefelter syndrome
- XYY syndrome
Turner Syndrome

- 1 in 4,500 female births
- 50% 45,X
- The remainder variants with other X chromosome abnormalities (isochromosome, ring, mosaicism)
Turner Syndrome

- Lymphedema, Cystic hygroma
- Short 4th metacarpals
- Nuchal fold thickness
- Webbed neck, nipples widely spaced, carrying angle/cubitus valgus

Lymphedema
Turner Syndrome

Cardiac Abnormalities
- Bicuspid aortic valve
- Aortic dissection
- Coarctation of aorta

Renal Abnormalities
- Horseshoe kidney
- Unilateral renal agenesis

Short Stature
- Avg = 4’7”

Delayed Puberty
- 2\textsuperscript{nd} sex char

Infertility

Hearing Impairment

Learning Disabilities
- Spatial perception
Trisomy X or Triple X Syndrome
47,XXX

- Incidence 1 in 1000 female births
- Above average stature
- Normal phenotype
- Most have learning disabilities
- Behavior problems common
- Many never diagnosed
Klinefelter Syndrome
47,XXY

• 1:1000 male births
• Tall stature
• Gynecomastia
• Hypogonadism
• Infertility
• Learning disabilities
• Problems with socialization
• Many never diagnosed
47, XYY

• 1/1000 newborn males
• Tall stature
• Most phenotypically normal
• Normal IQ but 50% have learning disabilities
• Many never diagnosed
A High Degree of Lethality Exists Even Among Aneuploidies Compatible With Survival to Birth

<table>
<thead>
<tr>
<th>Aneuploidy</th>
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<td>+18</td>
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<tr>
<td>XYY</td>
<td>100</td>
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<td>45,X</td>
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Two groups (autosomes/sex chromosomes); in utero death common.
• The rate of Down syndrome and other trisomies increases with maternal age
• There is also an increase in younger women
• What is the mechanism for this?
• What factors influence this?

Hunt and Hassold, 2010
Nondisjunction During Meiosis I versus Meiosis II

- **Mono and Trisomies**
- Since meiotic NDJ occurs prior to zygote formation → all cells affected
Two hundred clearly analyzable second meiotic (MU) metaphase oocytes from 116 patients were examined for evidence of first meiotic (MI) division errors.

- 67% of oocytes were nI (23,X)
- None had an extra whole chromosome
- The only abnormality found had single chromatids replacing whole chromosomes
Premature Separation of Sister Chromatids at Meiosis I
(separated sister chromatids can then randomly segregate in multiple ways → Mono- & Trisomies)

• “So far, all such studies have focused on the human oocyte. These analyses have been hampered by the fact that the desired object of study — the fully mature, recently ovulated egg — is virtually impossible to obtain. As a result, only limited information is as yet available, and most of it is based on studies of those ‘spare’ oocytes that remain unfertilized after attempted in vitro fertilization”

• “In subsequent molecular cytogenetic studies of spare oocytes, true non-disjunction as well as PSSC errors have been observed and some investigators have suggested that PSSC is largely an artifact of cell culture”
Premature Separation of Sister Chromatids at Meiosis I

Meiosis II

Premature Centromere Division

Normal
Sister Chromatids Segregate Together

Normal
Normal
Trisomy
Monosomy
Human oocytes from 25 patients aged 29-50 years were harvested 43-45 hr after HCG

169 first polar bodies were biopsied from them by micromanipulation

Whole genome amplification (WGA)

WGA products from biopsied polar bodies and control (male) DNA were labeled with Cy3 and Cy5 fluorophores

aCGH using a commercial service (“24sure” BlueGnome, Cambridge, UK)
Summary of aCGH experiments plotted against number of observed chromosomal abnormalities.

Single chromatid errors were 11.5 times more common than whole chromosome errors (92.0% vs 8.0%)
Conclusions

• “Our observations are consistent with previous studies on metaphase preparations of human oocytes and mouse model systems, supporting the hypothesis that precocious separation of sister chromatids is the predominant mechanism leading to aneuploidy in humans. The more often cited non-disjunction model, on the other hand, appears a relatively minor player.”

What influences non-disjunction or premature sister chromatid separation?

- Age
- Recombination events
Figure 2. Chromosome-specific shifts in normalized means (and standard errors) of the number of maternal crossovers for mothers under and over 30 years of age. Position of centromere is shown for each chromosome (dotted line). Significance of the shift at the 5% (*) and 1% (**) levels is assessed by permutations.

doi:10.1371/journal.pgen.1002251.g002
What influences non-disjunction or premature sister chromatid separation leading to aneuploidy?

- Age
- Recombination events at chiasmata
- Cohesins
- Genetic factors
  - meiotic/spindle assembly checkpoints, centrosome formation/duplication, chromatid cohesion, and chromatin organization
- Environment
  - Bisphenol A (BPA exposure)?
  - Diet?
What influences non-disjunction or premature sister chromatid separation leading to aneuploidy?

• Epigenetic factors
  – heritable alterations in gene expression or phenotype that are caused by mechanisms other than changes in the underlying DNA sequence (e.g., methylation changes, histone alterations, microRNA expression)
Acknowledgements

• Art Aylsworth, MD
• Kathy Kaiser-Rogers, PhD