Syndrome Review 1: Common Trisomies and Sex Chromosome Variations

Cynthia M. Powell, M.D.
Associate Professor of Pediatrics and Genetics
The University of North Carolina at Chapel Hill

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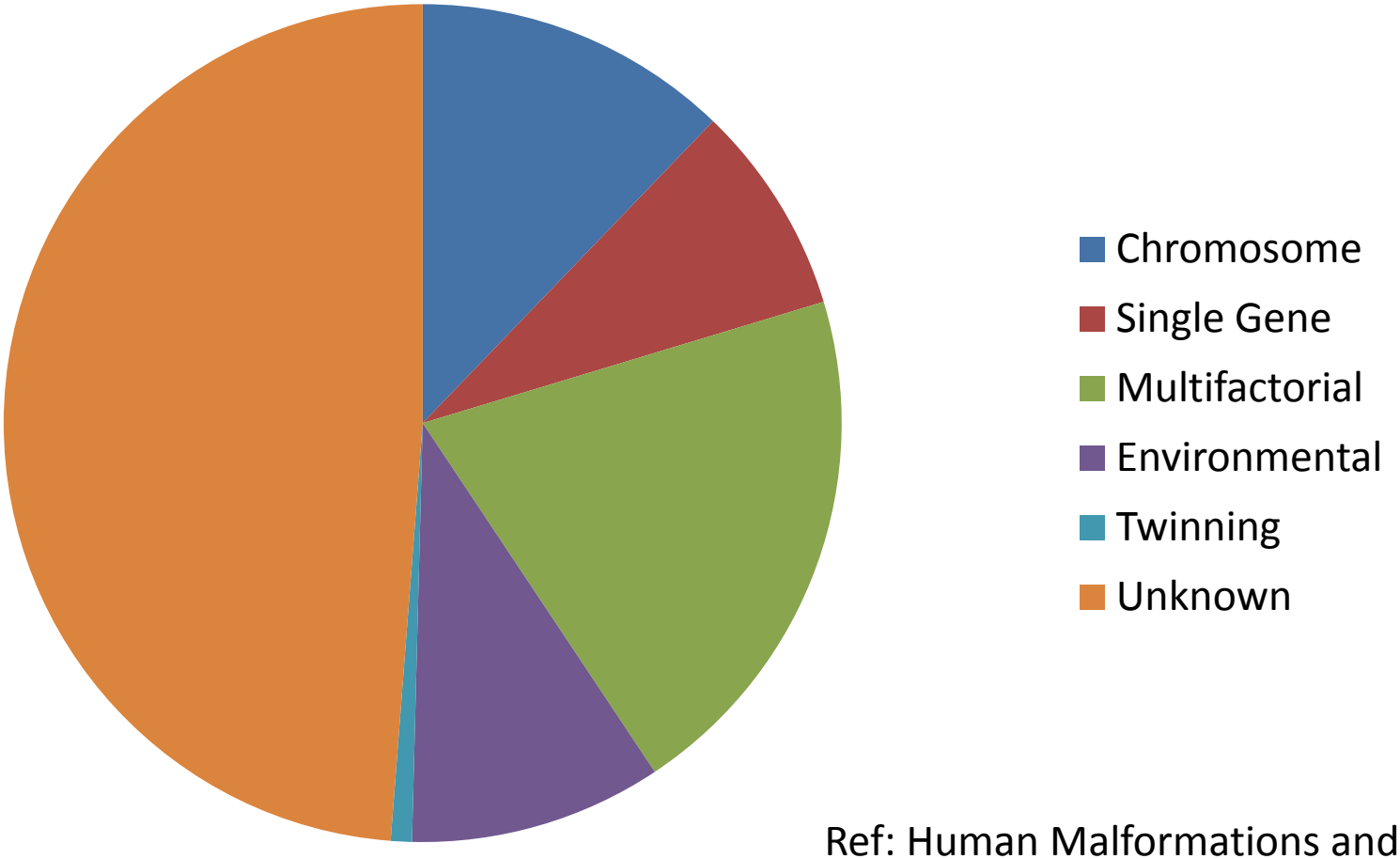
Objectives

- 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



Ref: Human Malformations and Related Anomalies, 2nd edition, 2005, Stevenson and Hall ed.

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

All recognized pregnancies	~5 %
Spontaneously aborted pregnancies	
All 1st 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

Chromosome	Spontaneous Abortions	Stillbirths	Livebirths
1	Rare	—	—
2	1.1	—	—
3	0.3	—	—
4	0.8	—	—
5	0.1	—	—
6	0.3	—	—
7	0.9	—	—
8	0.8	—	—
9	0.7	0.1	—
10	0.5	—	—
11	0.1	—	—
12	0.2	—	—
13	1.1	0.3	0.005
14	1.0	—	—
15	1.7	—	—
16	7.5	—	—
17	0.1	—	—
18	1.1	1.2	0.01
19	Rare	—	—
20	0.6	—	—
21	2.3	1.1	0.13
22	2.7	0.1	—
XXY	0.2	0.4	0.05
XXX	0.1	0.3	0.05
XYY	—	—	0.05
XO	8.6	0.25	<0.01
Total	**32.8**	**3.75**	**0.3**

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

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6	0.3	—	—
7	0.9	—	—
8	0.8	—	—
9	0.7	0.1	—
10	0.5	—	—
11	0.1	—	—
12	0.2	—	—
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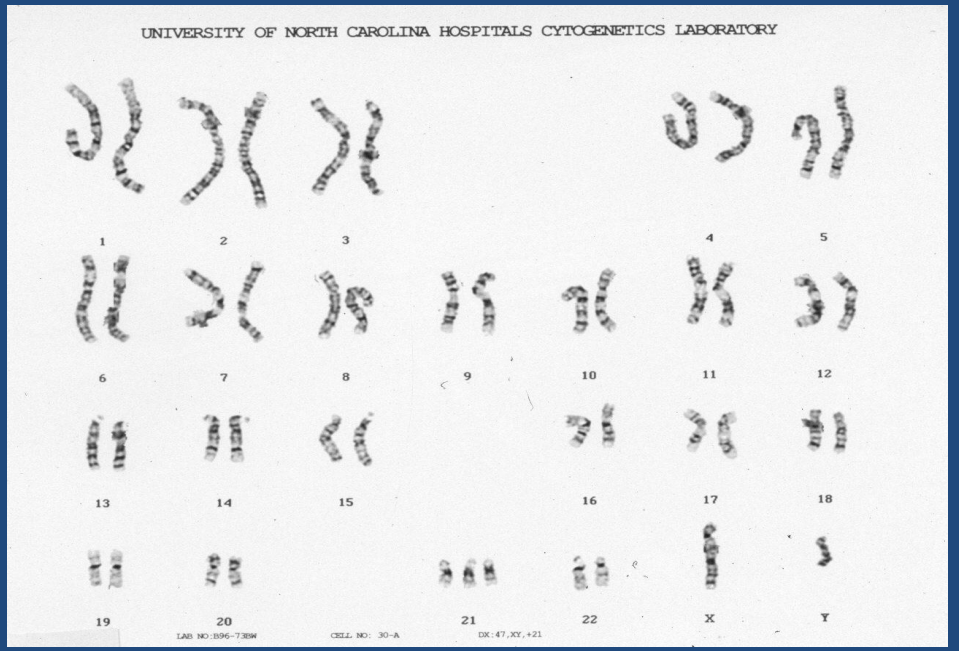
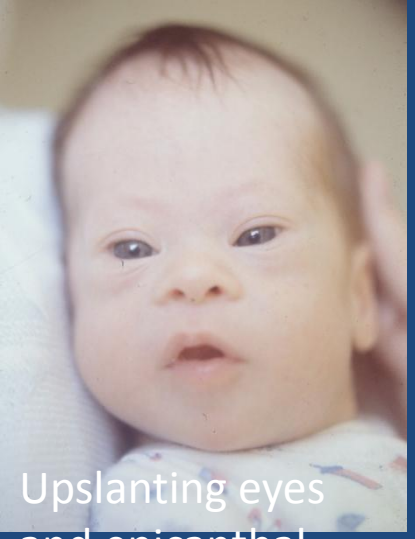
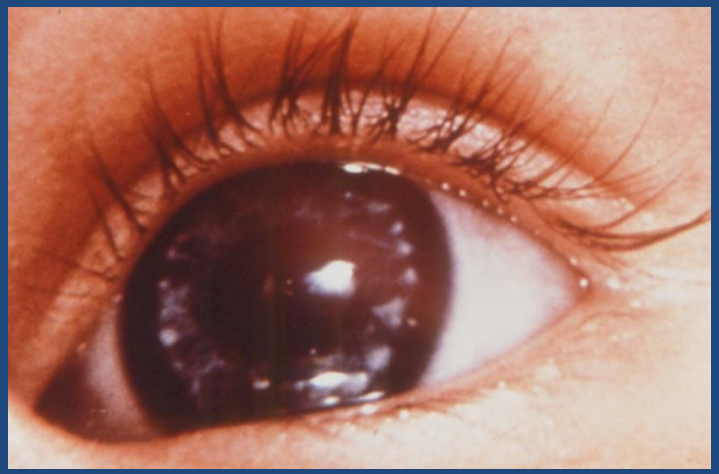
Down Syndrome

- 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

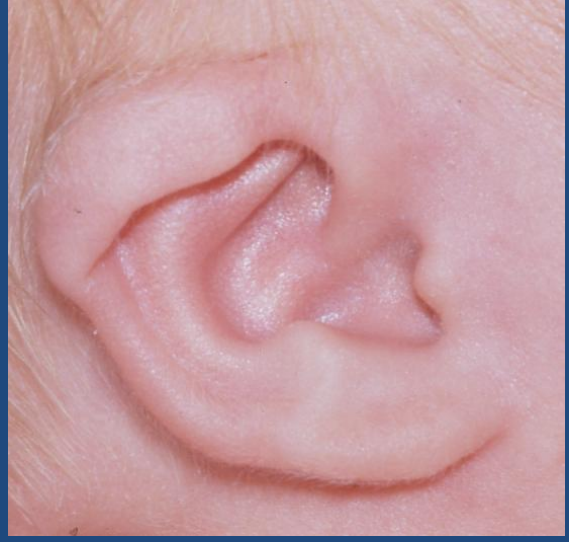




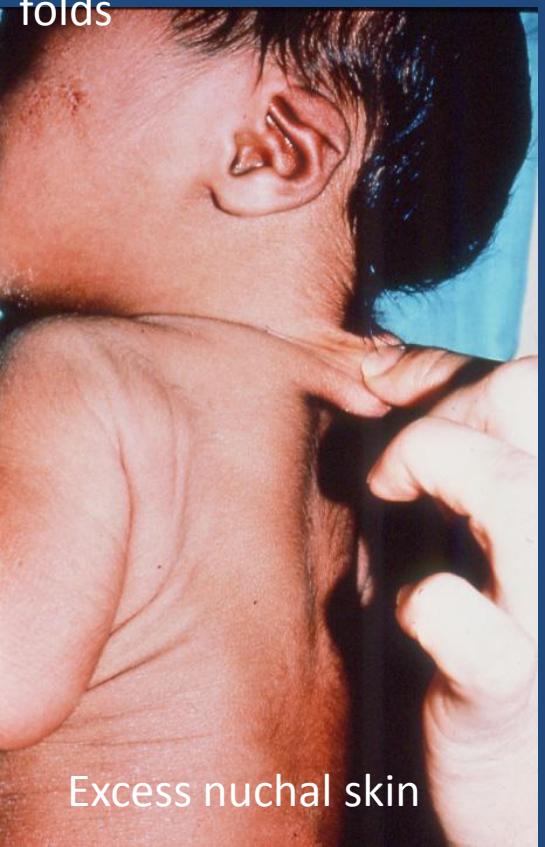
Upslanting eyes and epicanthal folds



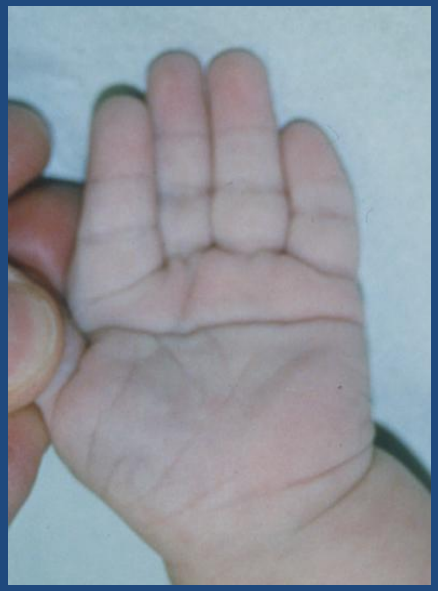
Brushfield spots



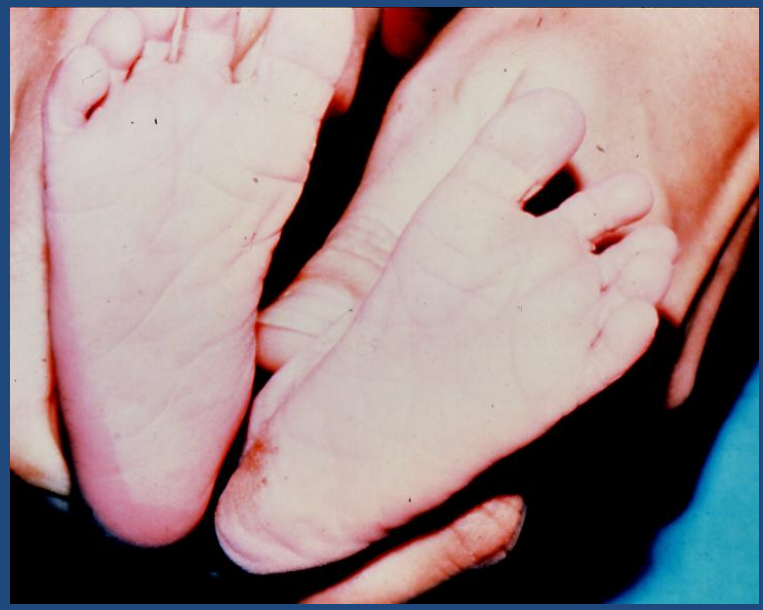
Dysplastic ear



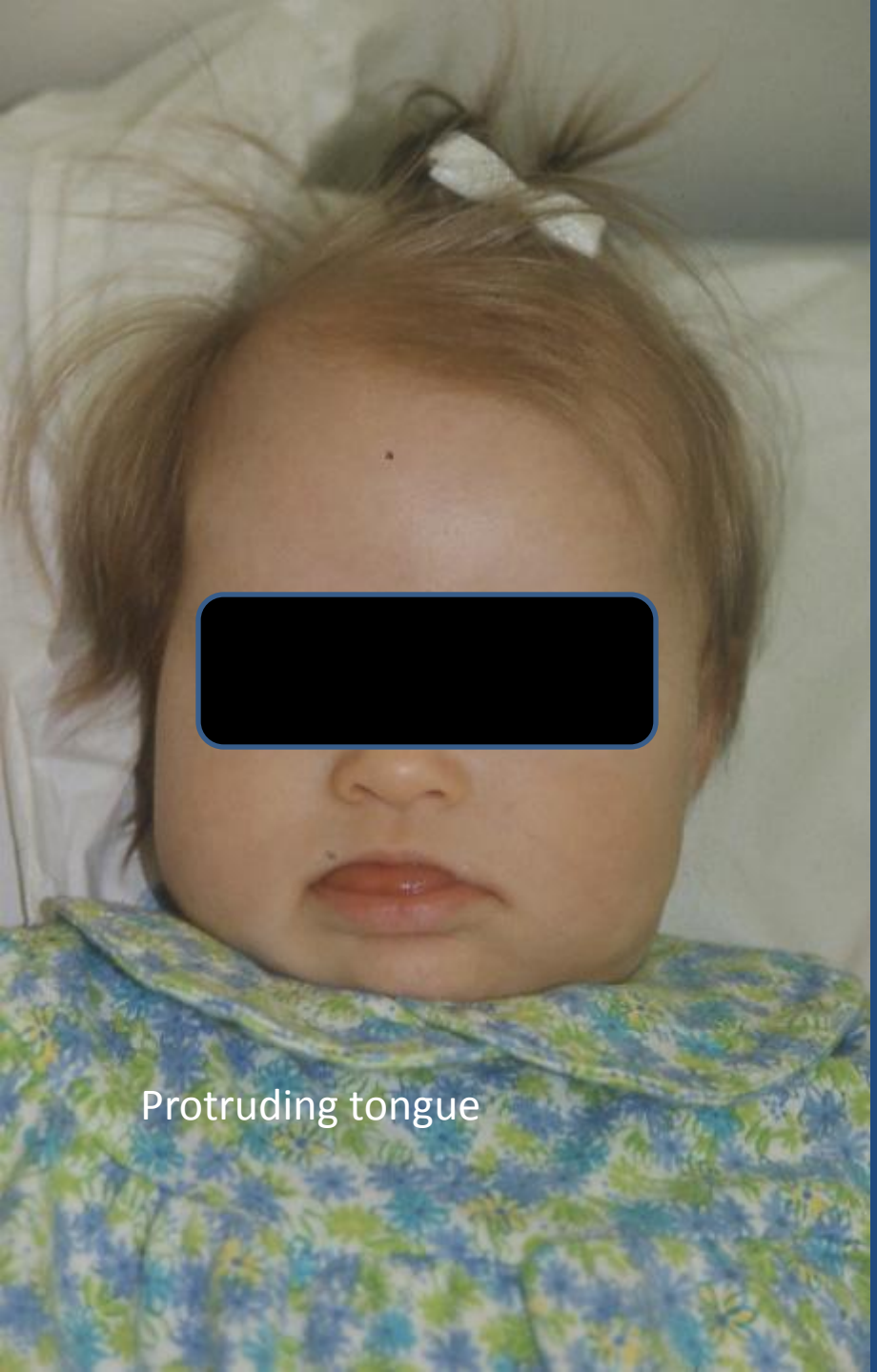
Excess nuchal skin

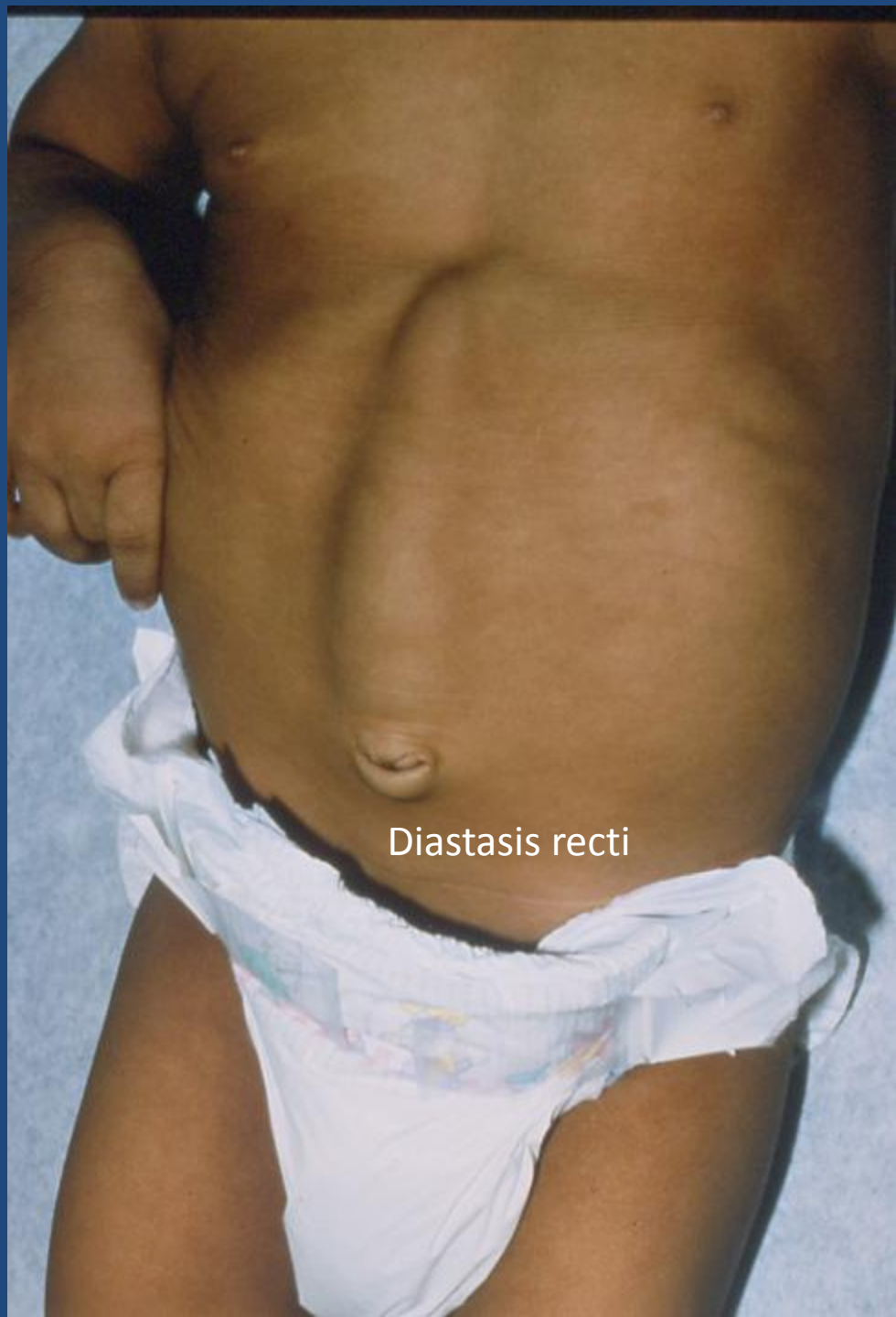


Single transverse palmar crease and clinodactyly of 5th finger



Sandal gap of toes 1-2


Protruding tongue


Diastasis recti

Congenital Malformations and Medical Complications Associated with Down Syndrome

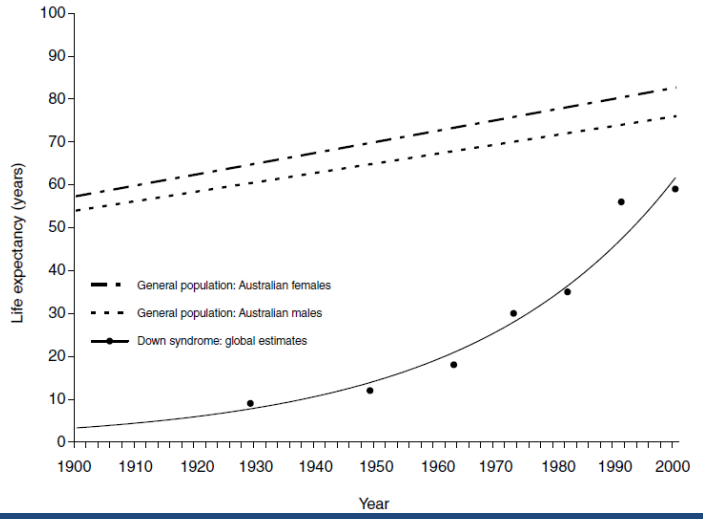
- Cardiac 40%
  - AV canal/endocardial cushion defect, VSD, PDA, ASD
- GI 12%
  - Duodenal atresia, TE fistula, omphalocele, pyloric stenosis, annular pancreas, Hirschsprung disease, imperforate anus

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

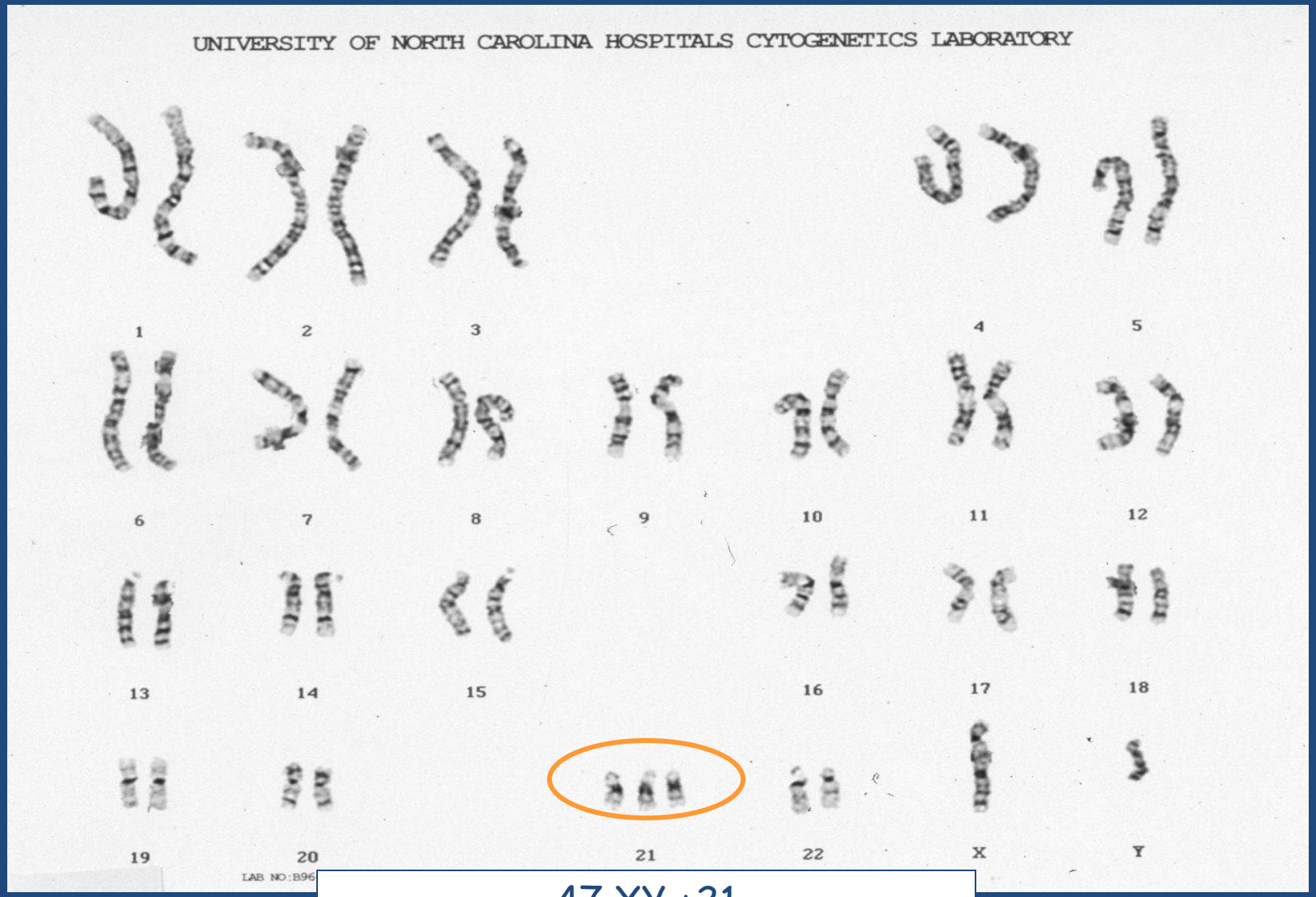
- Average life expectancy 56 years in 1991 in US, 60 years in Australia in 2002
- Major cause of early mortality is CHD
- Risk of infections and pneumonia
- Increased risk of Alzheimer disease

Figure 1: *Global trends in life expectancy estimates for people with Down syndrome compared with those for the general Australian population, 1900–2000. Sources: Australian data, Australian Bureau of Statistics;[77,78] Down syndrome data drawn from various developed countries, see Table I.*



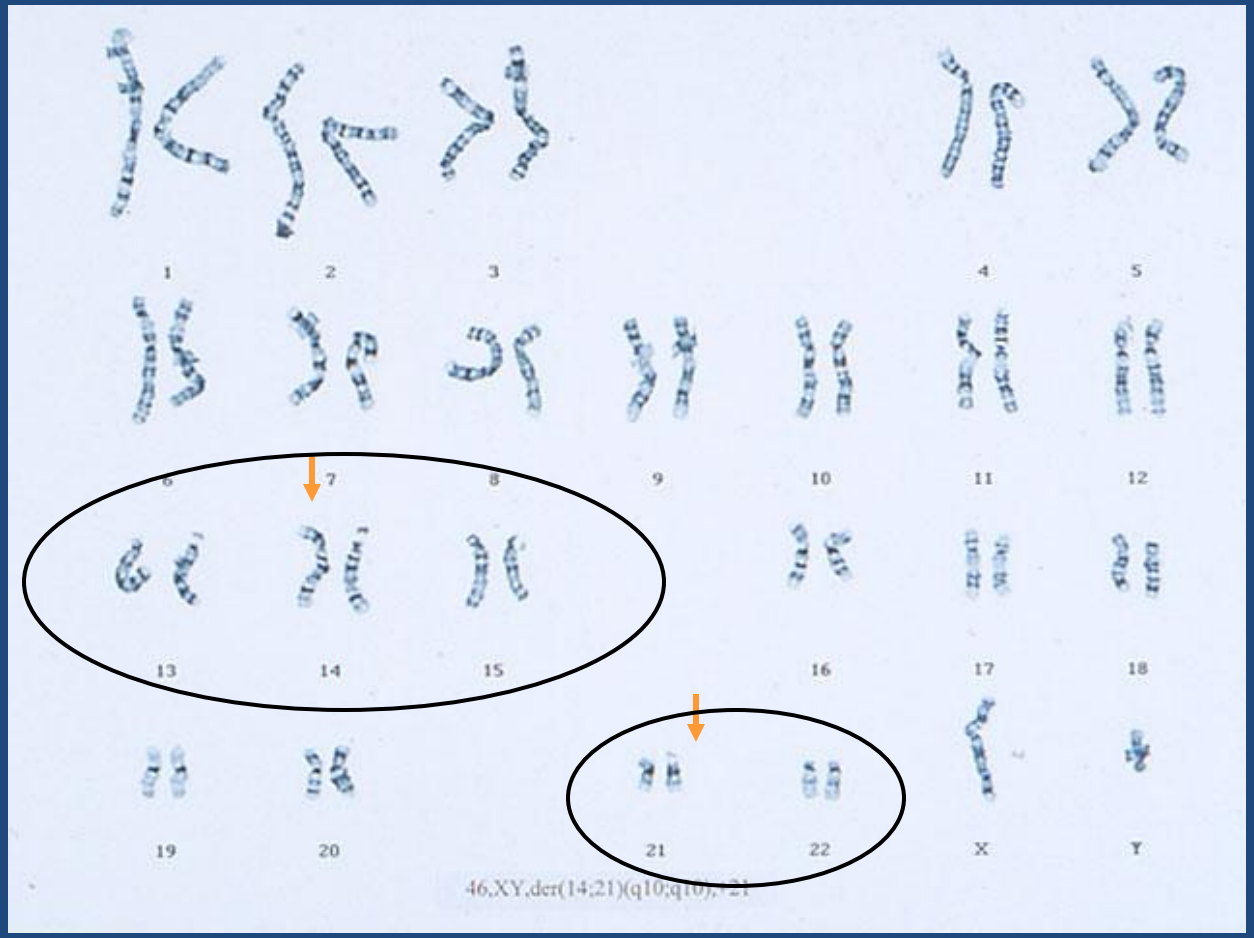
Bittles and Glasson, Dev Med Child Neurol 2004

95% of Patients With Down Syndrome Have 3 SEPARATE CHROMOSOME 21s "Trisomy 21"



47,XY,+21

3-4% of Patients have Down Syndrome Secondary to AN UNBALANCED ROBERTSONIAN TRANSLOCATION

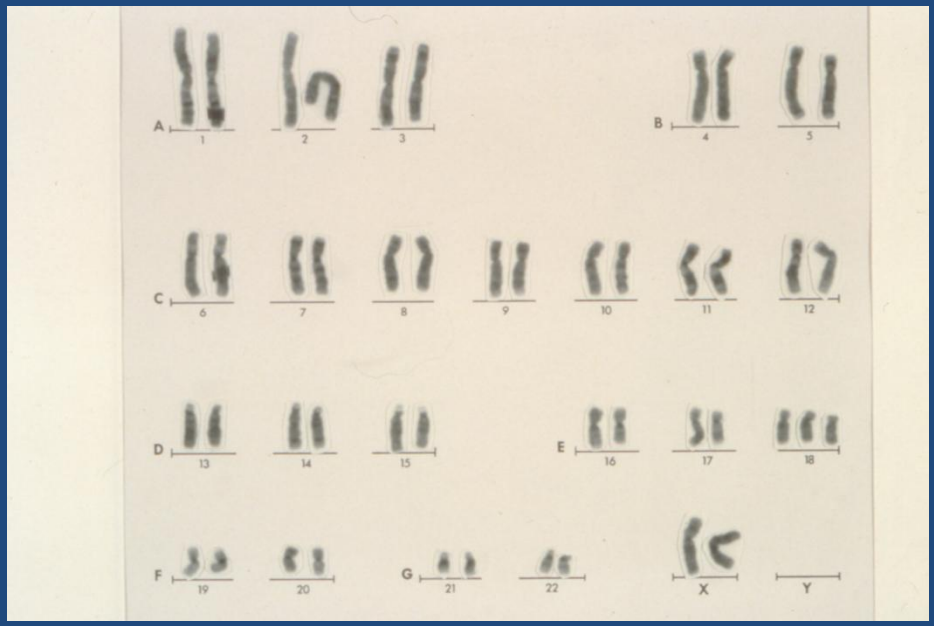


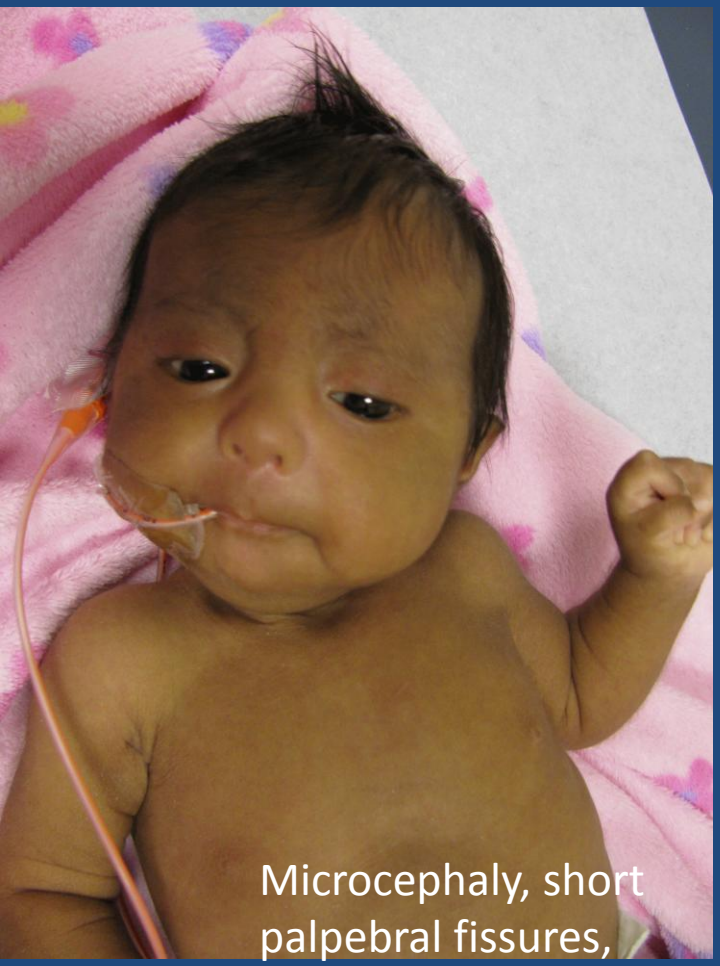
46,XY,der(14;21)(q10;q10),+21

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

Trisomy 18

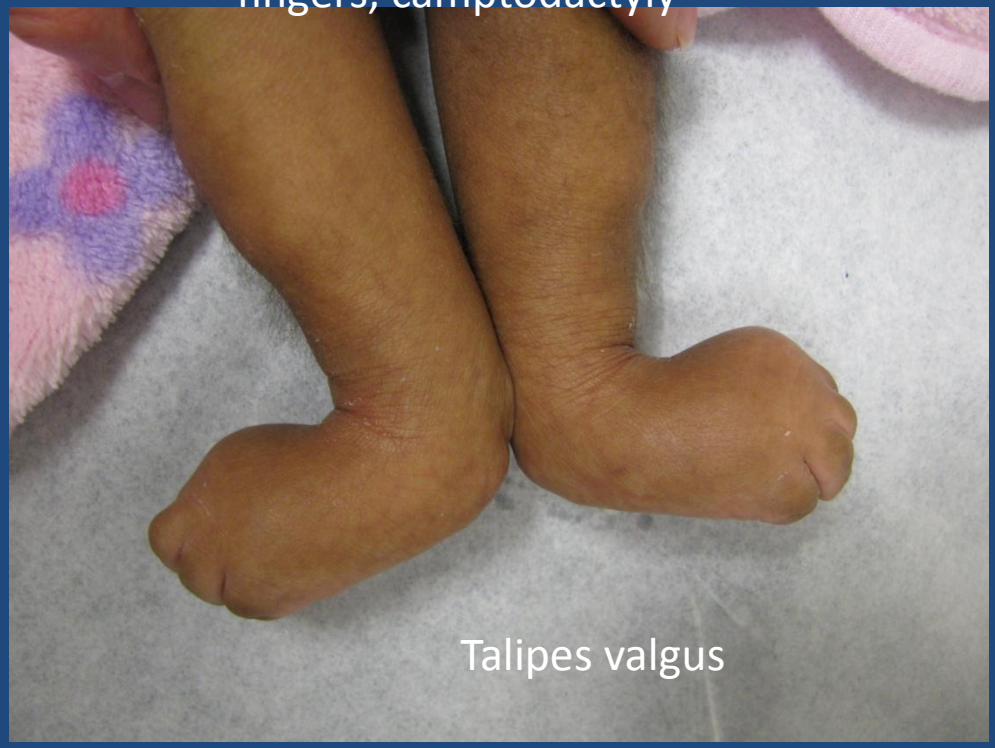
- First described by Dr. J.H. Edwards in 1960
- Prevalence of 1/5000 - 1/7000
- Excess of affected females
- 85% from maternal meiotic nondisjunction
- Mean life expectancy 4 days
- From 1-5% live more than 1 year





Microcephaly, short palpebral fissures, short upturned nose, micrognathia

Clenched hands, overlapping fingers, camptodactyly

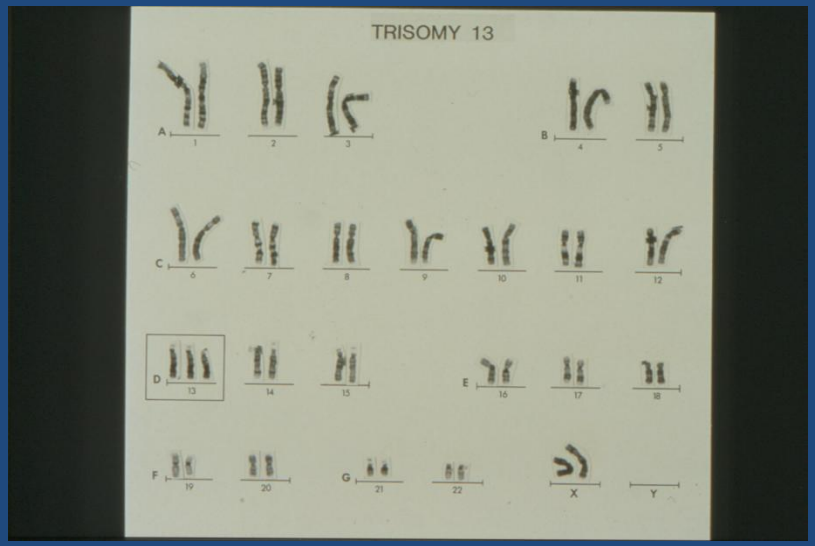


Talipes valgus

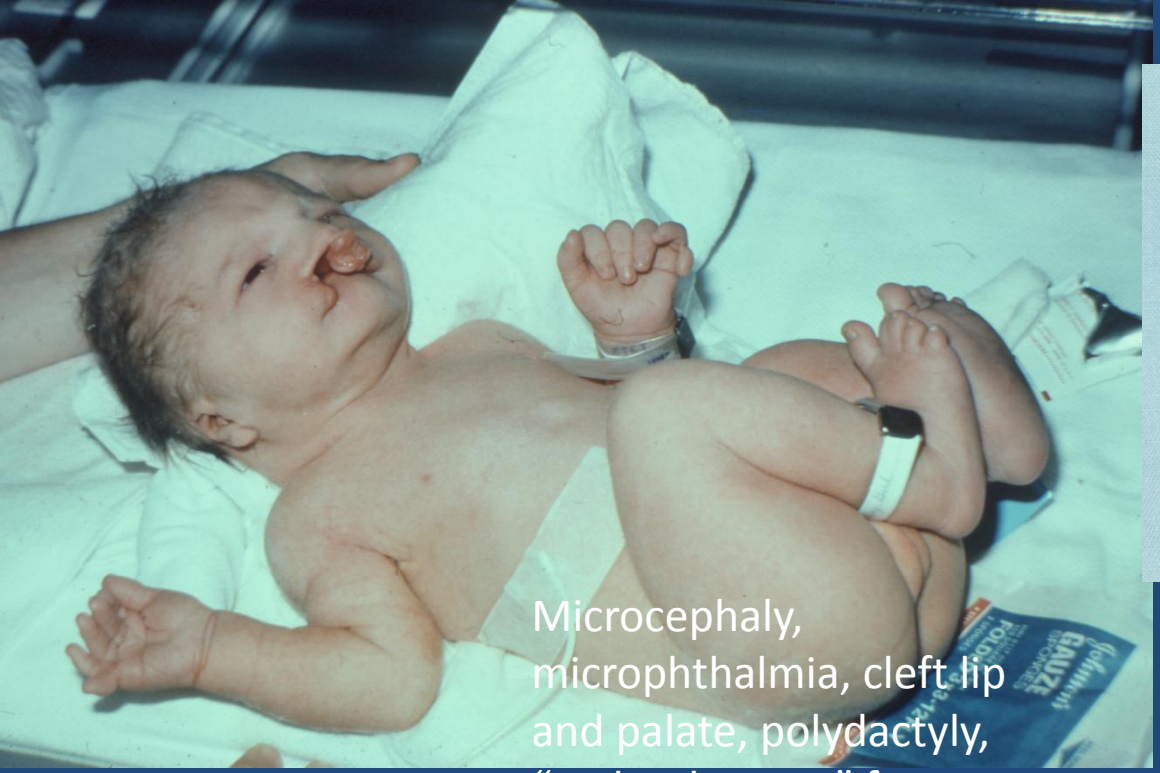
Trisomy 18

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

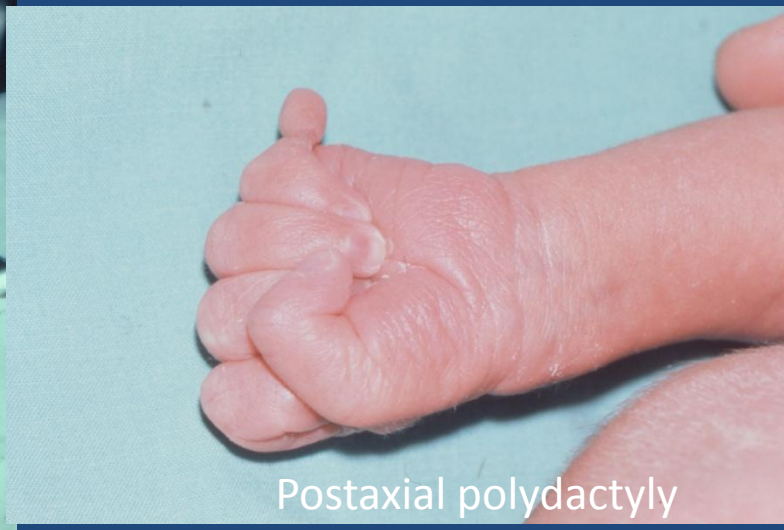
Trisomy 13



- First described by Dr. K. Patau in 1960
- 1/12,000 births
- Mean life expectancy 130 days
- 86% die during the first year



Microcephaly, microphthalmia, cleft lip and palate, polydactyly, “rocker-bottom” feet

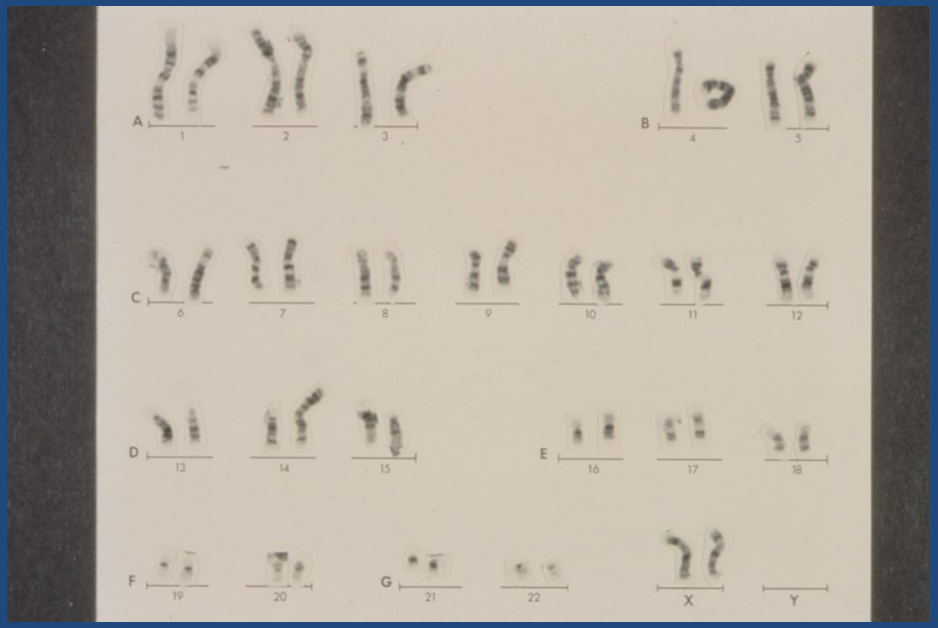


Postaxial polydactyly

Microcephaly, scalp defects, clefts, microphthalmia, polydactyly, cardiac defects, renal anomalies

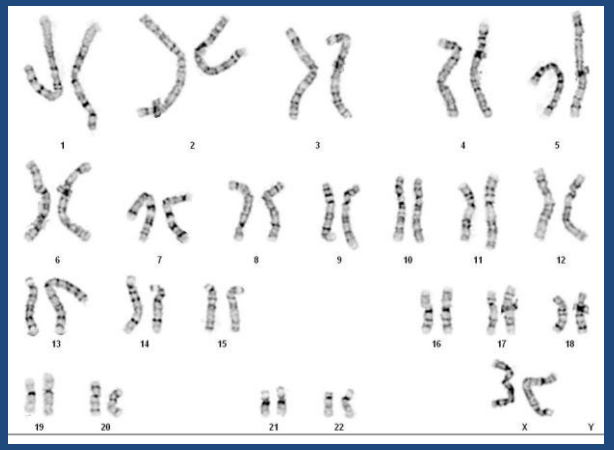
Aplasia cutis congenita or scalp defects

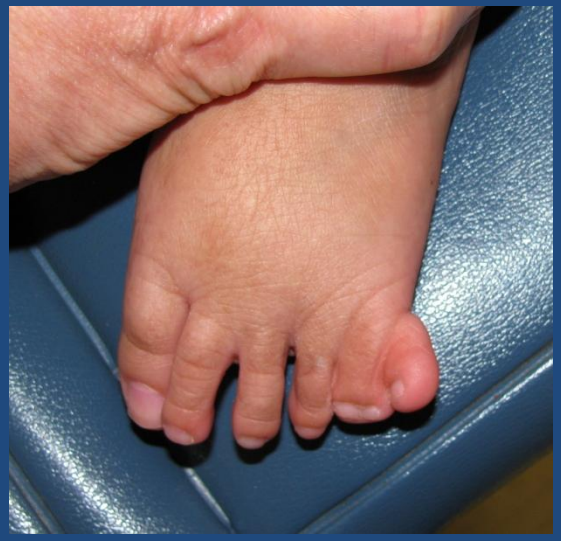
Trisomy 13



- 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

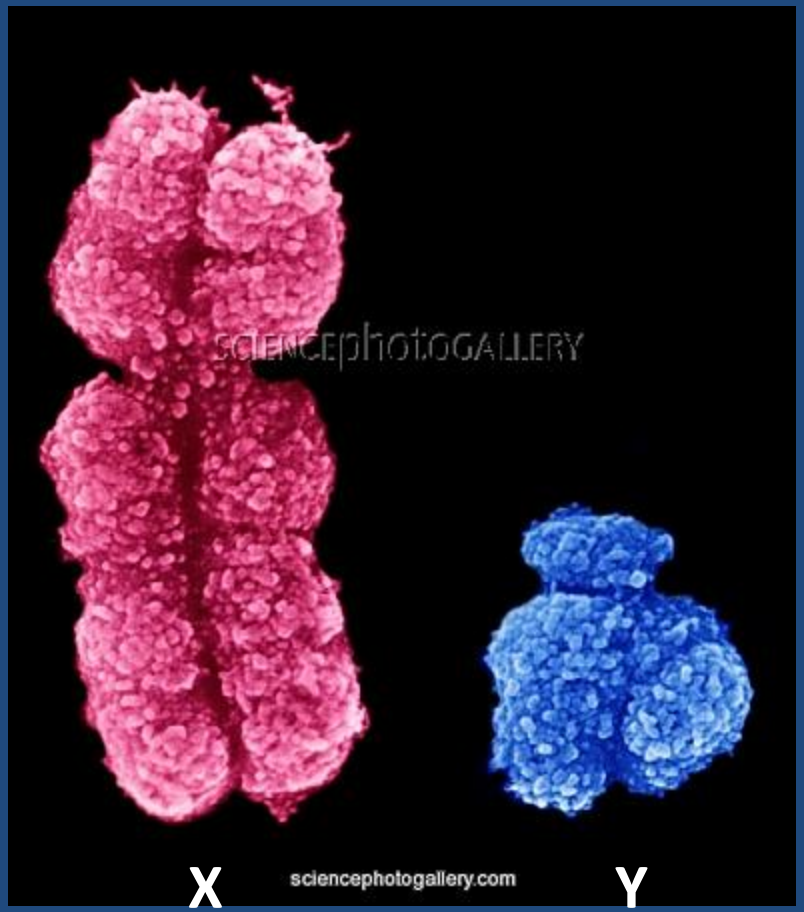
Trisomy 8

- 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



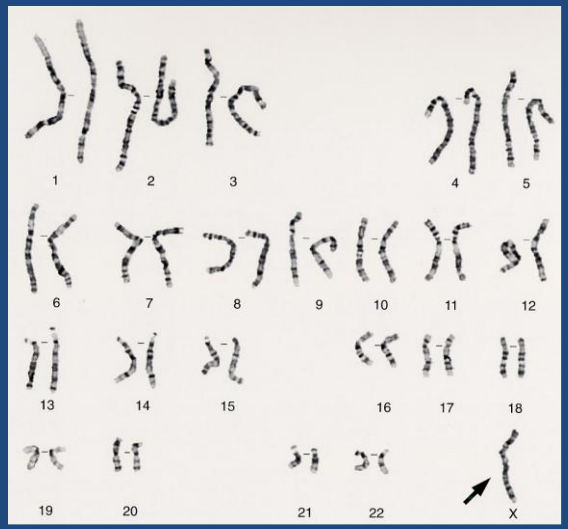
- One of the factors that determines gender
  - Females have two X chromosomes
  - Males have one X and one Y chromosome

Sex Chromosome Variations

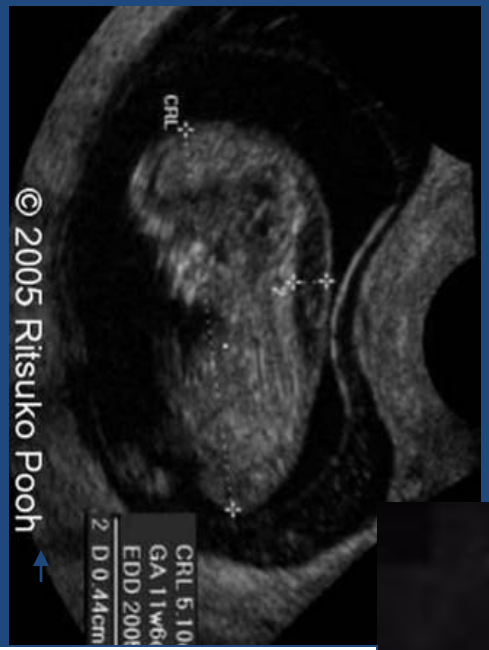
- Turner syndrome
- Triple X or Trisomy X syndrome
- Klinefelter syndrome
- XYY syndrome

Turner Syndrome

- 1 in 4-5000 female births
- 50% 45,X
- The remainder variants with other X chromosome abnormalities (isochromosome, ring, mosaicism)

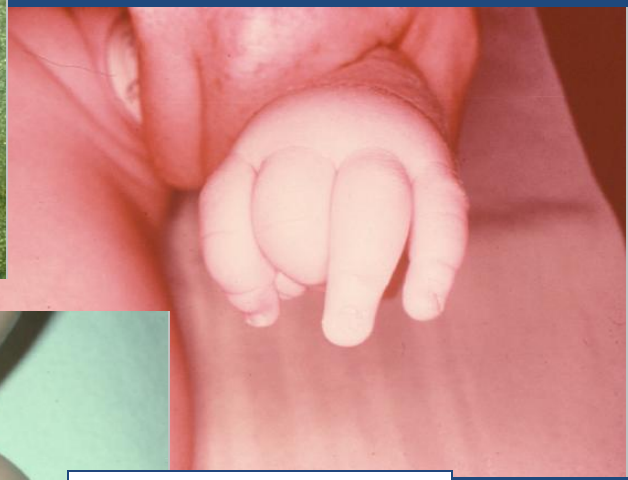


Turner Syndrome

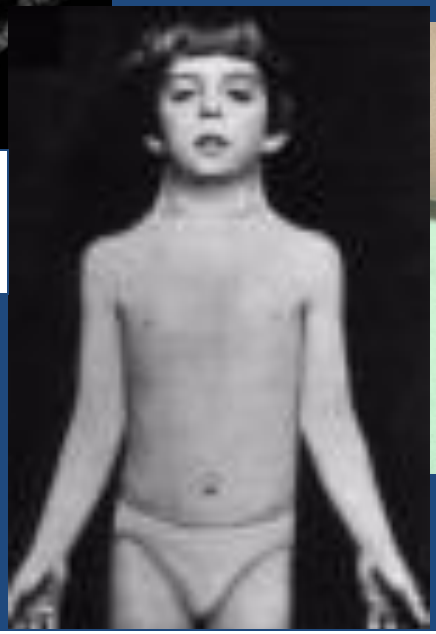


↑ Nuchal fold thickness

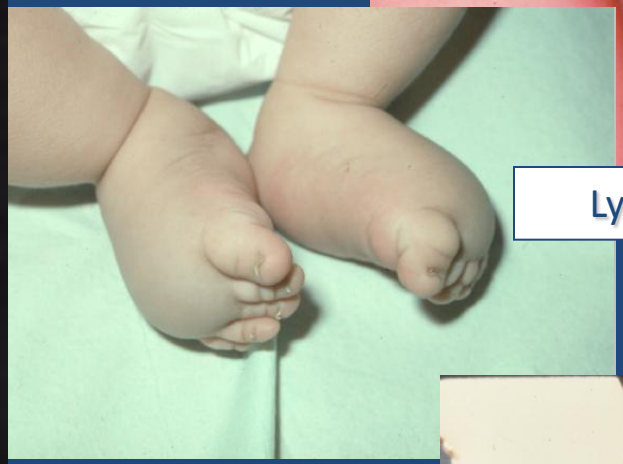
Lymphedema, Cystic hygroma

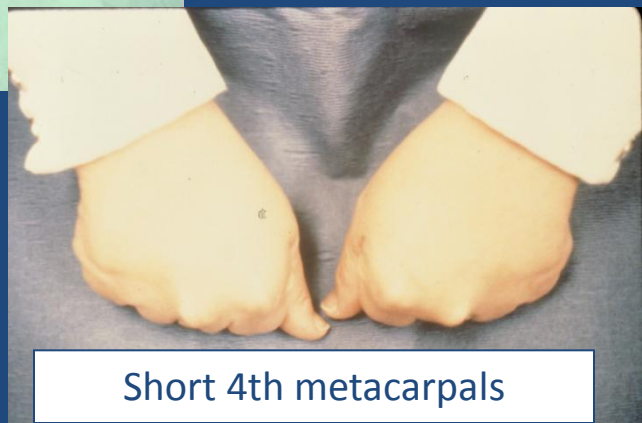


Lymphedema



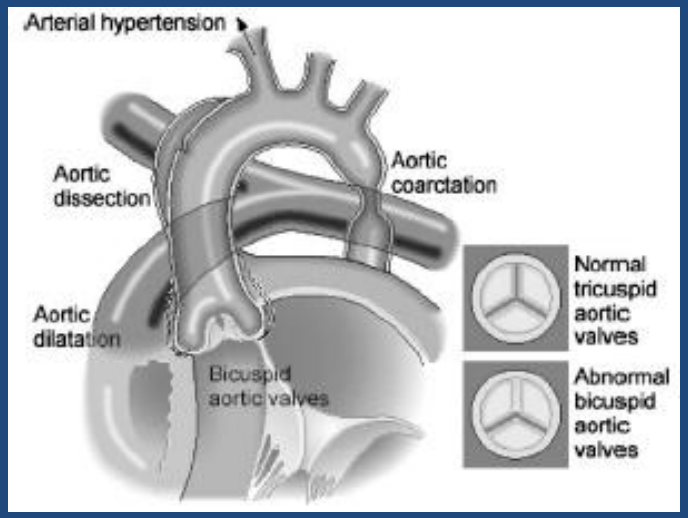
Webbed neck, nipples widely spaced, carrying angle/cubitus valgus





Short 4th metacarpals

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

- 2nd 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

Aneuploidy	Liveborn (%)
+13	3
+18	5
+21	22
XXY	55
XXX	70-94
XYY	100
45,X	0.3

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?

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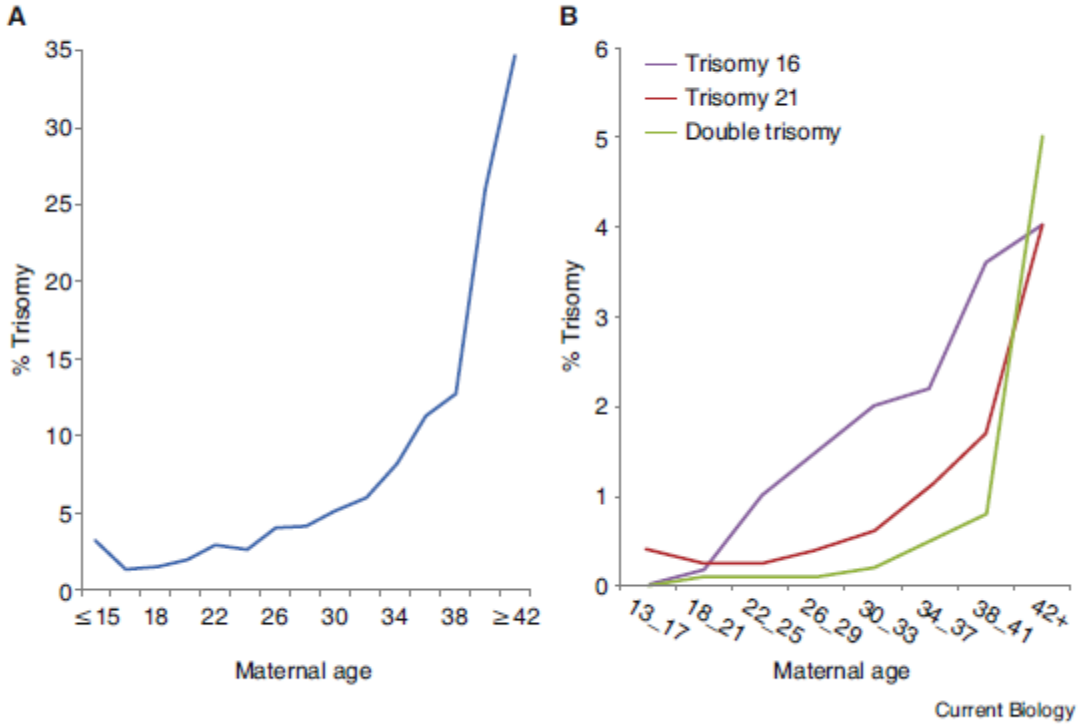
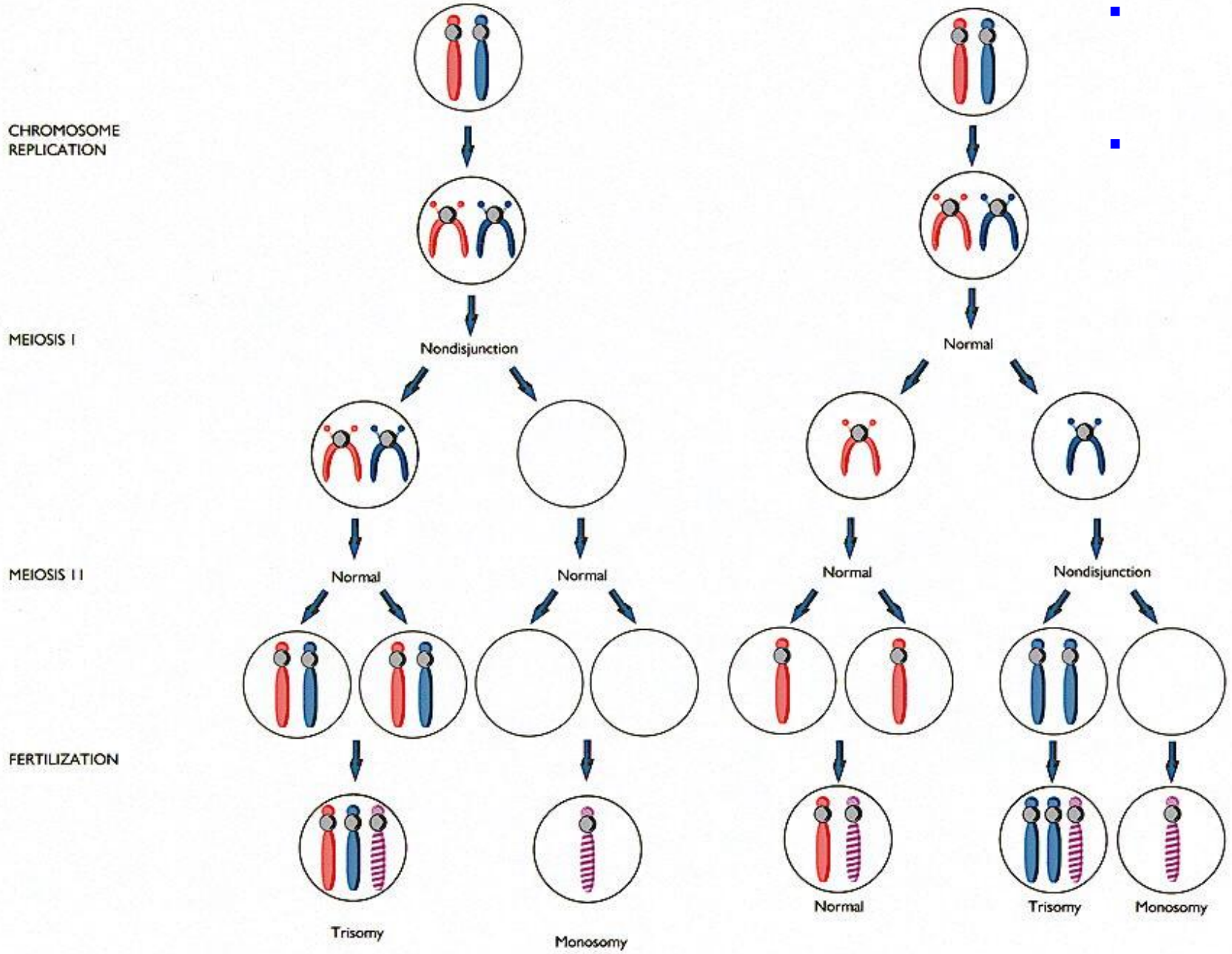


Figure 1. Maternal age affects the incidence of trisomy in clinically recognized pregnancy.

Hunt and Hassold, 2010

Nondisjunction During Meiosis I versus Meiosis II

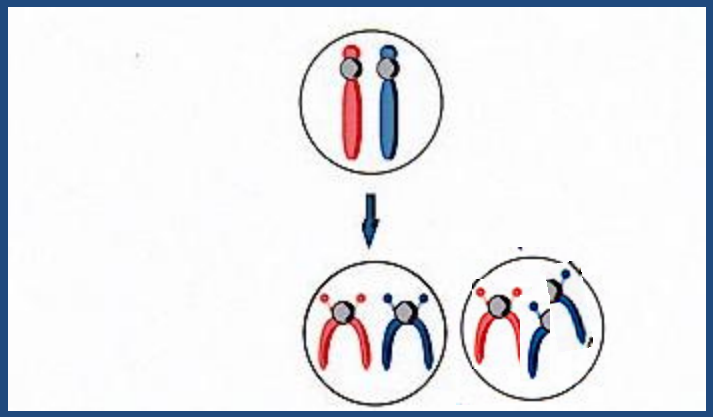


Roslyn R. Angell Am J Hum Genet. 1997;61(1):23-32

- 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 nl (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)



Premature Centromere Division

Normal

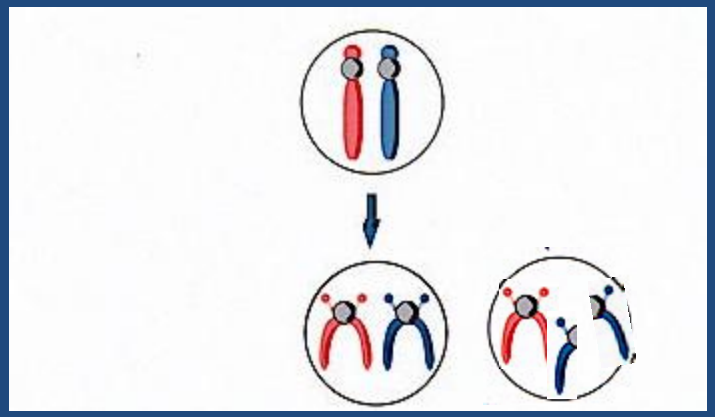
Sister Chromatids Segregate Together

Normal

Normal

Trisomy

Monosomy



Premature Centromere Division

Normal

Anaphase Lag

Normal

Normal

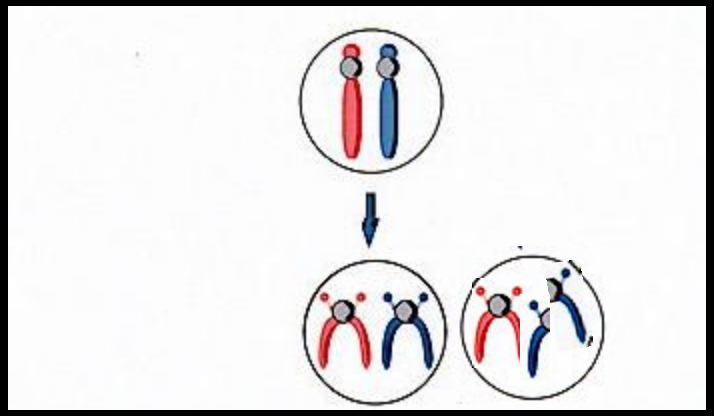
Normal

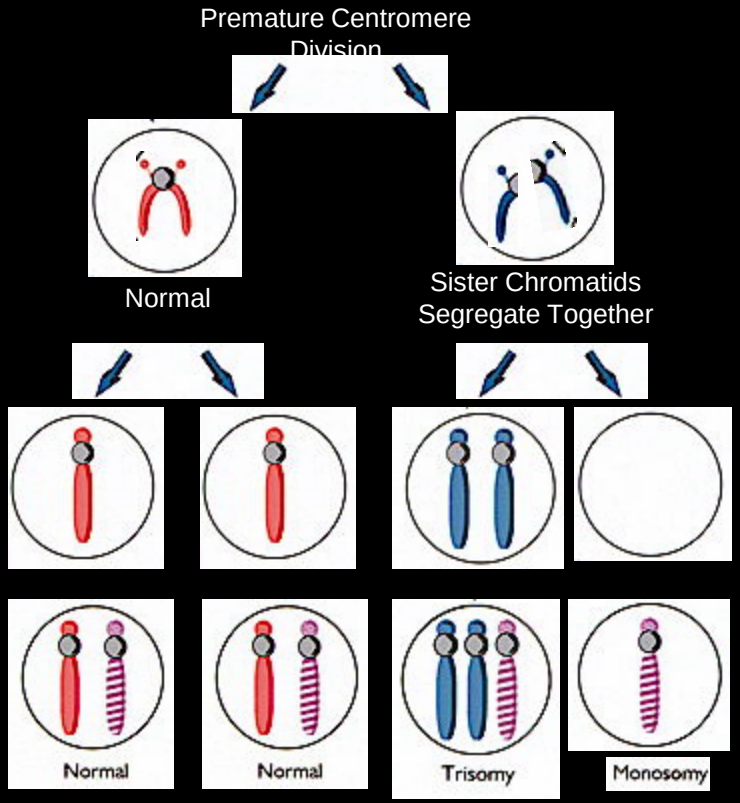
Monosomy

Critiques of Angell's studies: Hassold T, Hunt P. "To err (meiotically) is human: the genesis of human aneuploidy." Nat Rev Genet. 2001;2(4):280-91

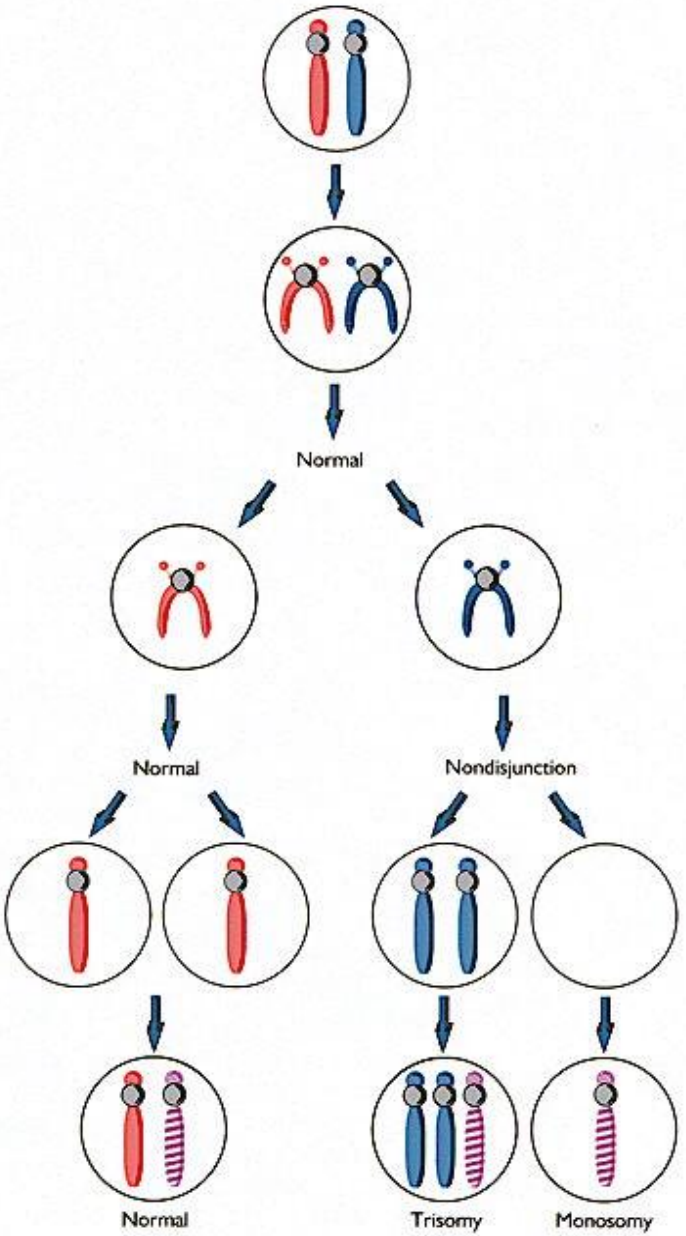
- "So far, all such studies have focused on the human oocyte. These analyses have been hampered by the fact that the desired object of study — the fully mature, recently ovulated egg — is virtually impossible to obtain. As a result, only limited information is as yet available, and most of it is based 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





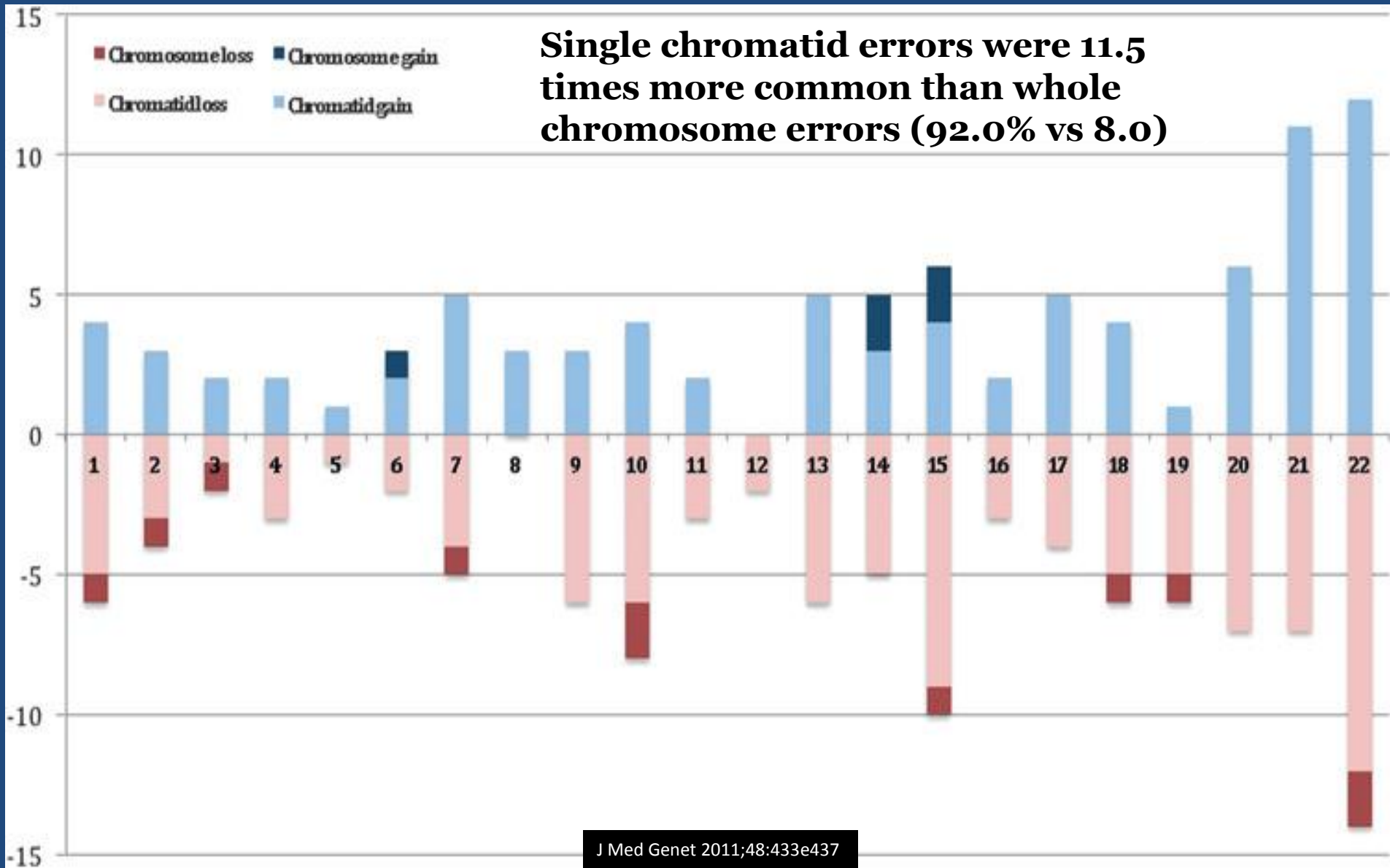
Meiosis II



Gabriel AS, et al. J Med Genet. 2011;48(7):433-7.

- 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)

J Med Genet 2011;48:433e437

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."

Gabriel AS, et al. J Med Genet. 2011;48(7):433-7

What influences non-disjunction or premature sister chromatid separation?

- Age
- Recombination events

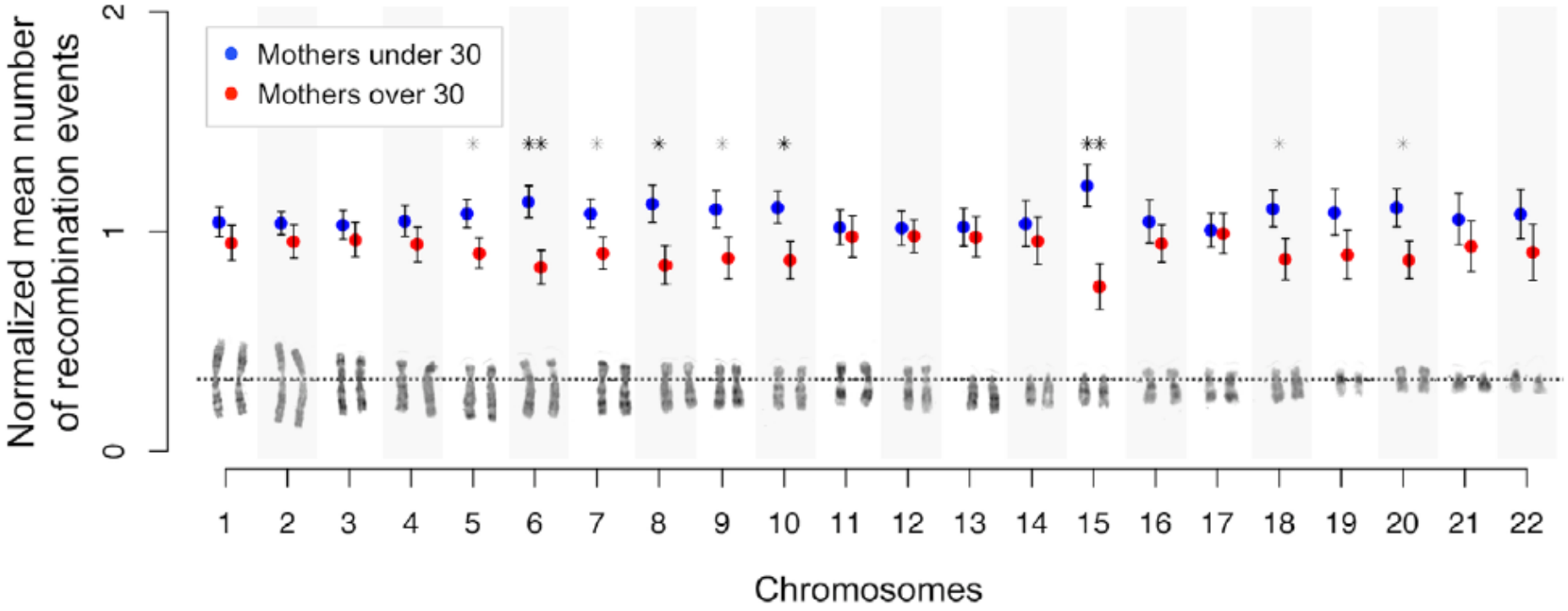


Figure 2. Chromosome-specific shifts in normalized means (and standard errors) of the number of maternal crossovers for mothers under and over 30 years of age. Position of centromere is shown for each chromosome (dotted line). Significance of the shift at the 5% (*) and 1% (**) levels is assessed by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

doi:10.1371/journal.pgen.1002251.g002

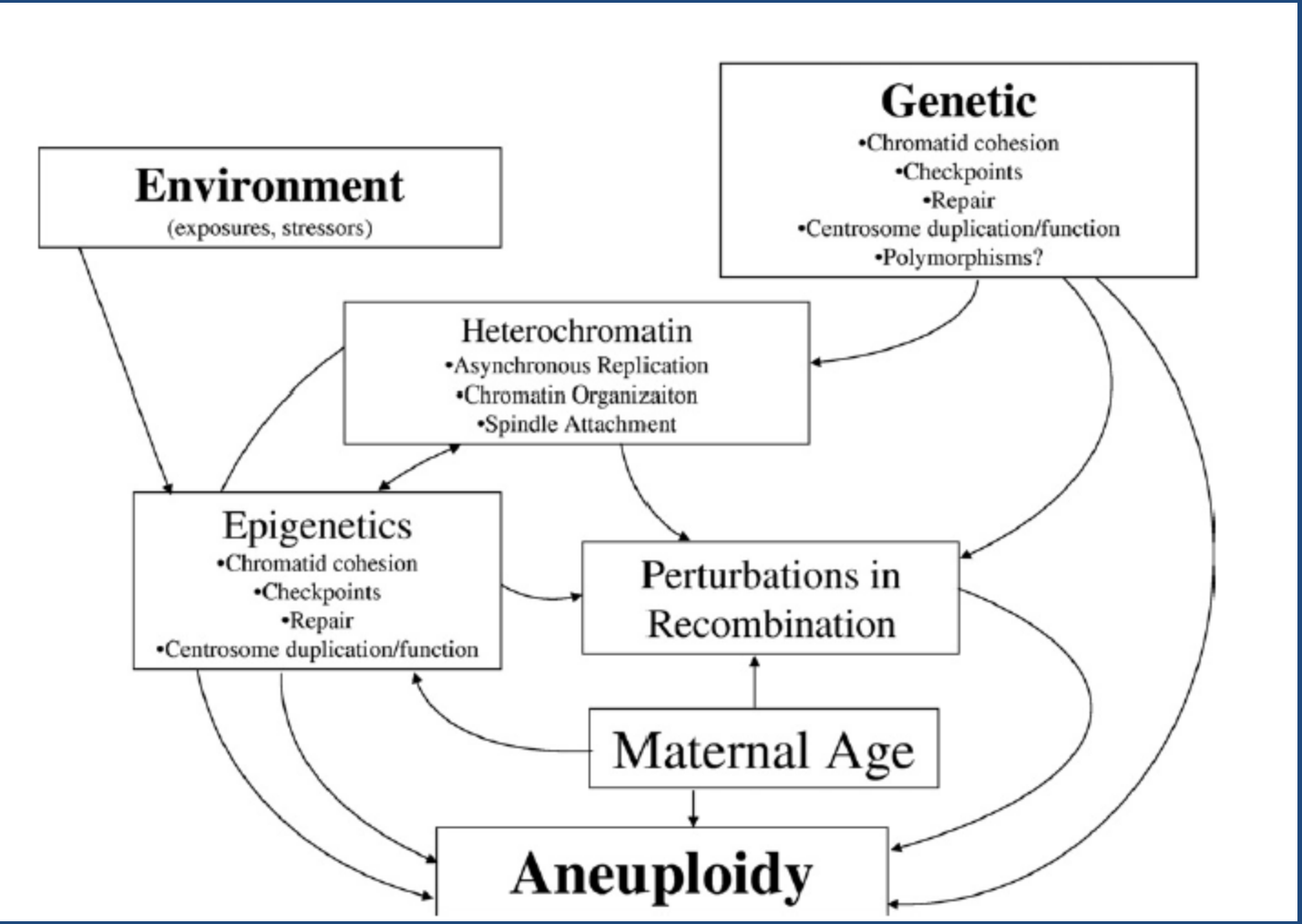
Hussin et al. PLoS Genetics, September 2011

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 (eg, methylation changes, histone alterations, microRNA expression)



Colleen Jackson-Cook, Clin Lab Med 31 (2011) 481–511.

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