Chromosomal Abnormalities

Part 2

Kristen Lancaster, MD, FAAP, FACMG

Clinical Geneticist

Abnormalities in Chromosome Structure

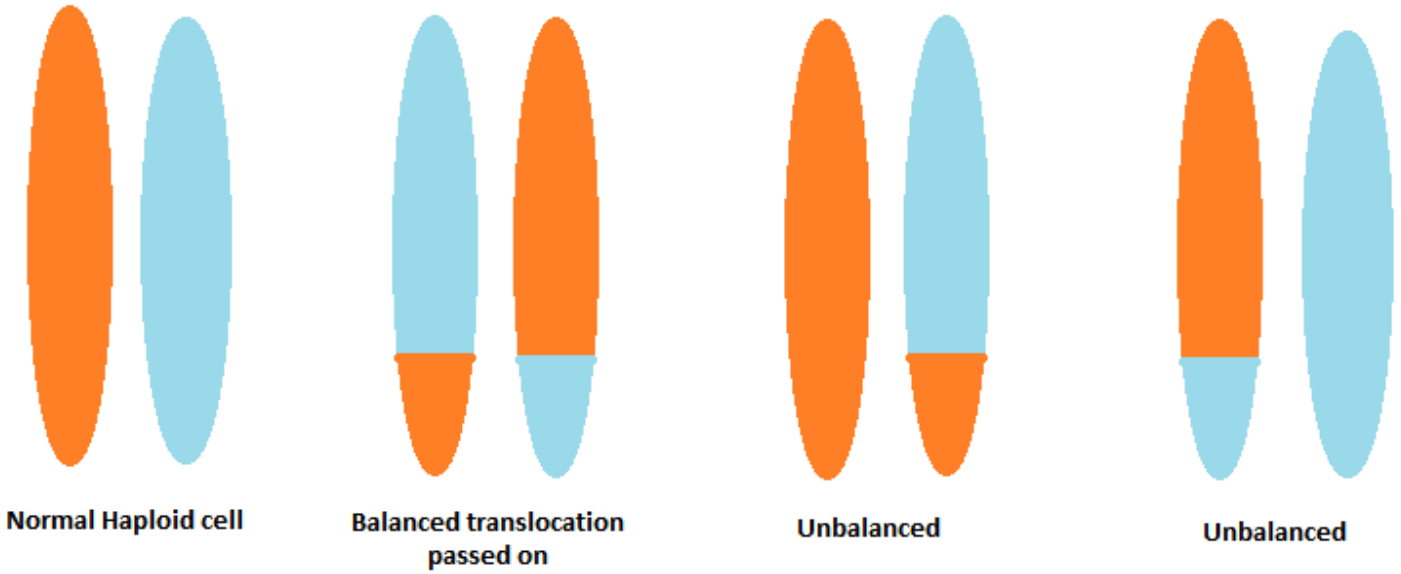
- Structural abnormalities are rearrangements in chromosomes that can originate either *de novo* (new in proband) or familial (passed through generations)
- Structural abnormalities include:
  - Translocations
  - Inversions
  - Deletions
  - Duplications
- When a structural abnormality is detected, parents should be karyotyped to determine if the abnormality is familial

Chromosomal Rearrangements

- Overall present in 1 in 375 newborns
- Result from chromosome breakage, recombination, or exchange, followed by reconstitution in an abnormal combination
- Types of rearrangements: Balanced vs. unbalanced
- Best detected on karyotype or FISH, occasionally microarray if unbalanced

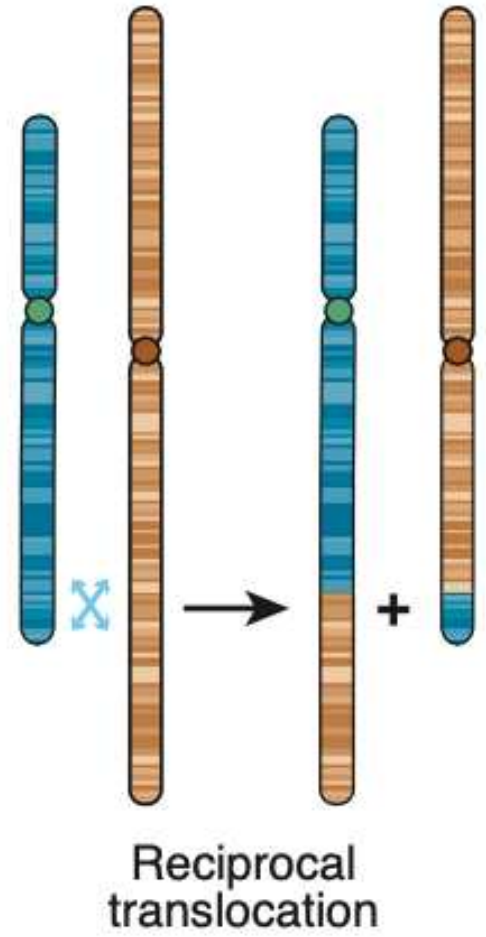
Chromosomal Rearrangements

- **Balanced:** all genetic material remains present
  - Typically **normal** phenotype
  - **Increased risk for abnormal offspring**
  - 1 in 500 people
- **Unbalanced:** either gain or loss of material
  - Typically **abnormal** phenotype
  - 1 in 1,600 live births



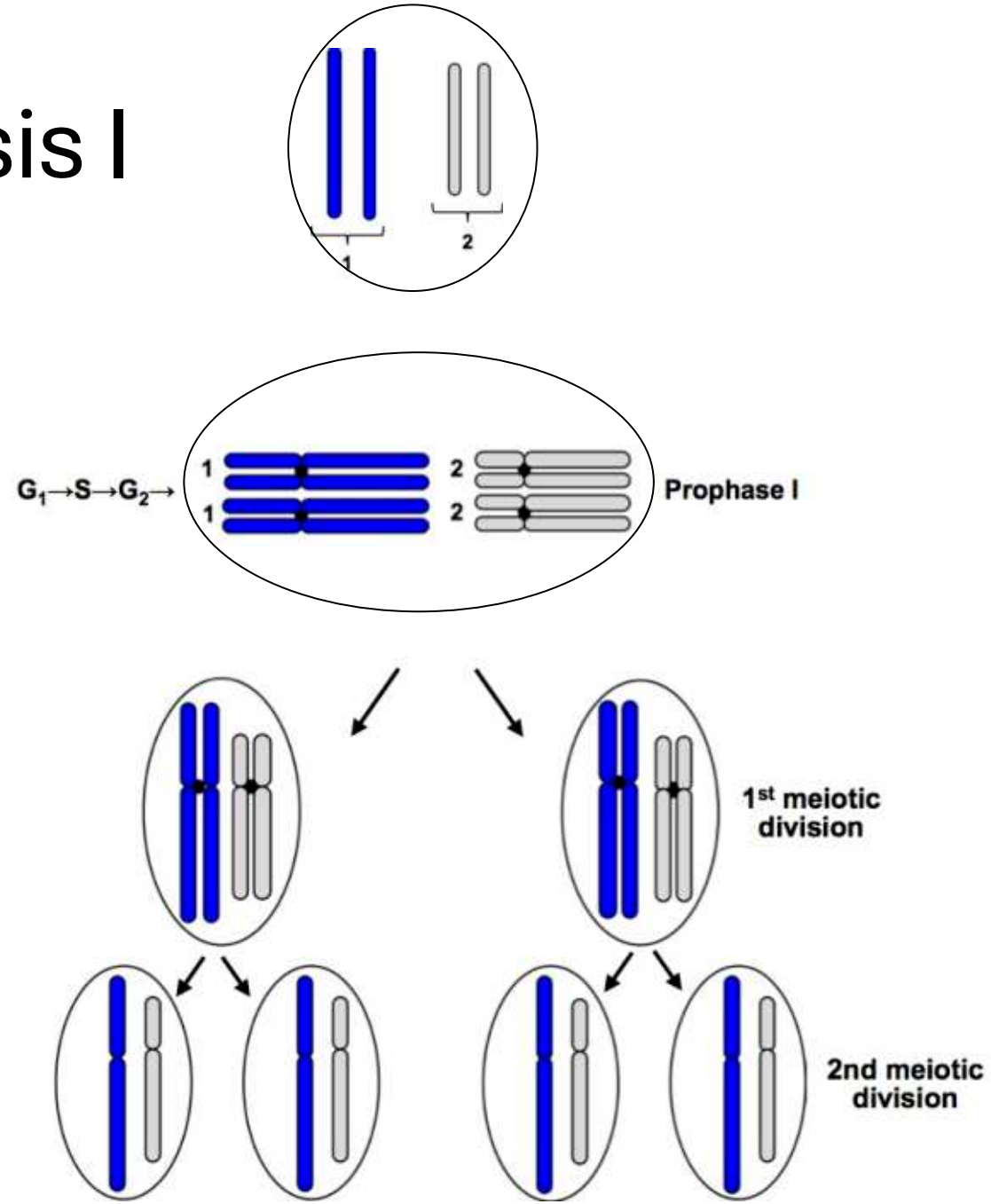
Translocations

- Involves the exchange of chromosome segments between two chromosomes
- Two main types: reciprocal and non-reciprocal
- Reciprocal:
  - Results from breakage or recombination involving nonhomologous chromosomes, with reciprocal exchange of the broken-off or recombined segments
  - Most often leads to a balanced rearrangement
  - Risk for unbalanced gametes and abnormal progeny due to malsegregation during gametogenesis



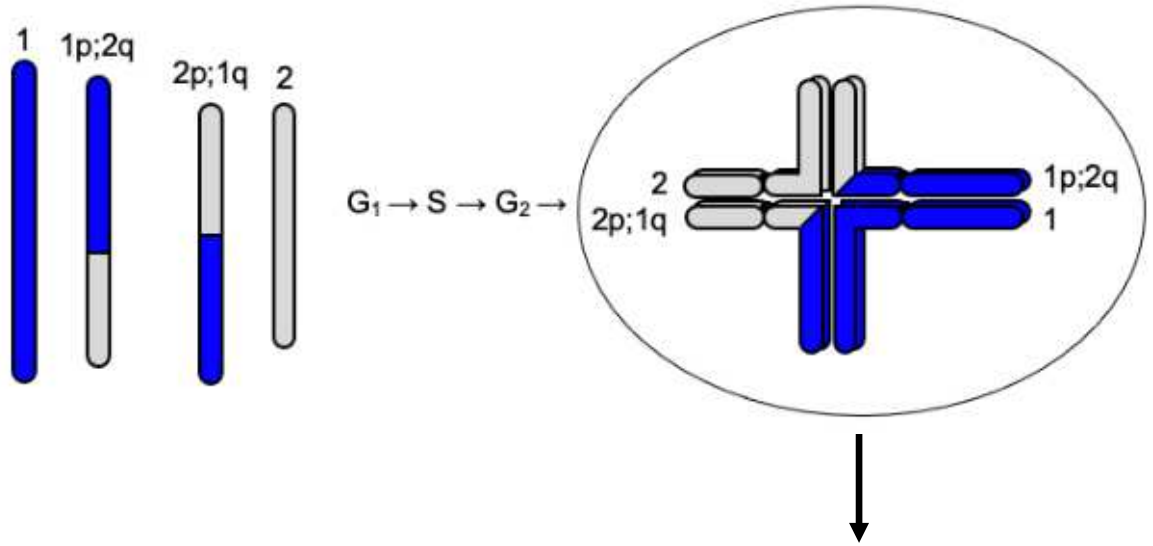
Review of normal meiosis I

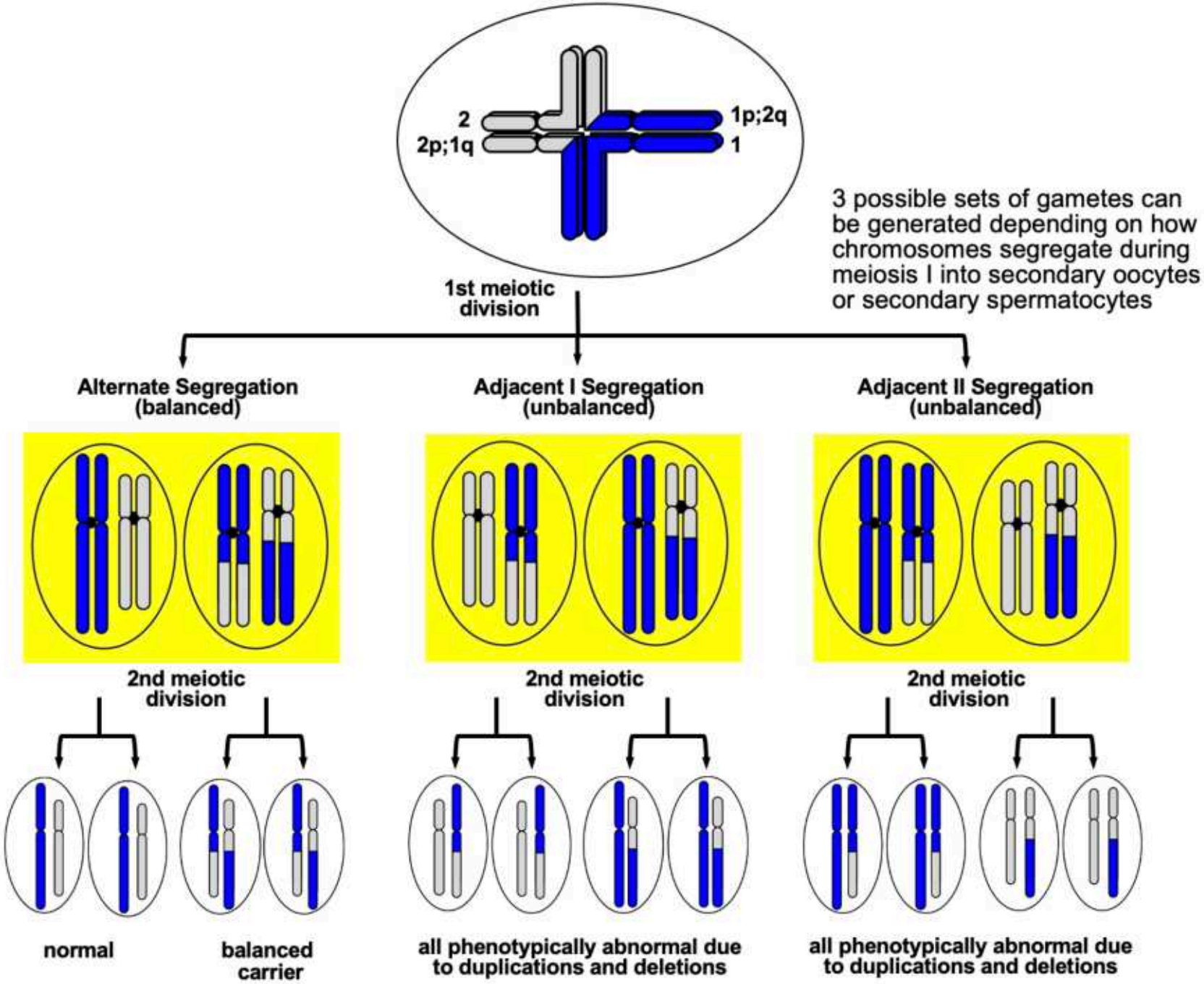
- Segregation of chromosomes
- **Tetrads** (**bivalent**) form between homologous pairs of chromosomes during prophase I
- Two pairs are shown in this schematic *(crossing over occurs, but not shown here)*



Meiosis I in balanced reciprocal translocations

- Malsegregation of chromosomes
- **Tetrads** (**quadrivalent**) form to ensure proper alignment of homologous sequences during prophase I




2
2p;1q
1p;2q
1
1st meiotic division
3 possible sets of gametes can be generated depending on how chromosomes segregate during meiosis I into secondary oocytes or secondary spermatocytes
Alternate Segregation (balanced)
Adjacent I Segregation (unbalanced)
Adjacent II Segregation (unbalanced)
2nd meiotic division
2nd meiotic division
2nd meiotic division
normal
balanced carrier
all phenotypically abnormal due to duplications and deletions
all phenotypically abnormal due to duplications and deletions

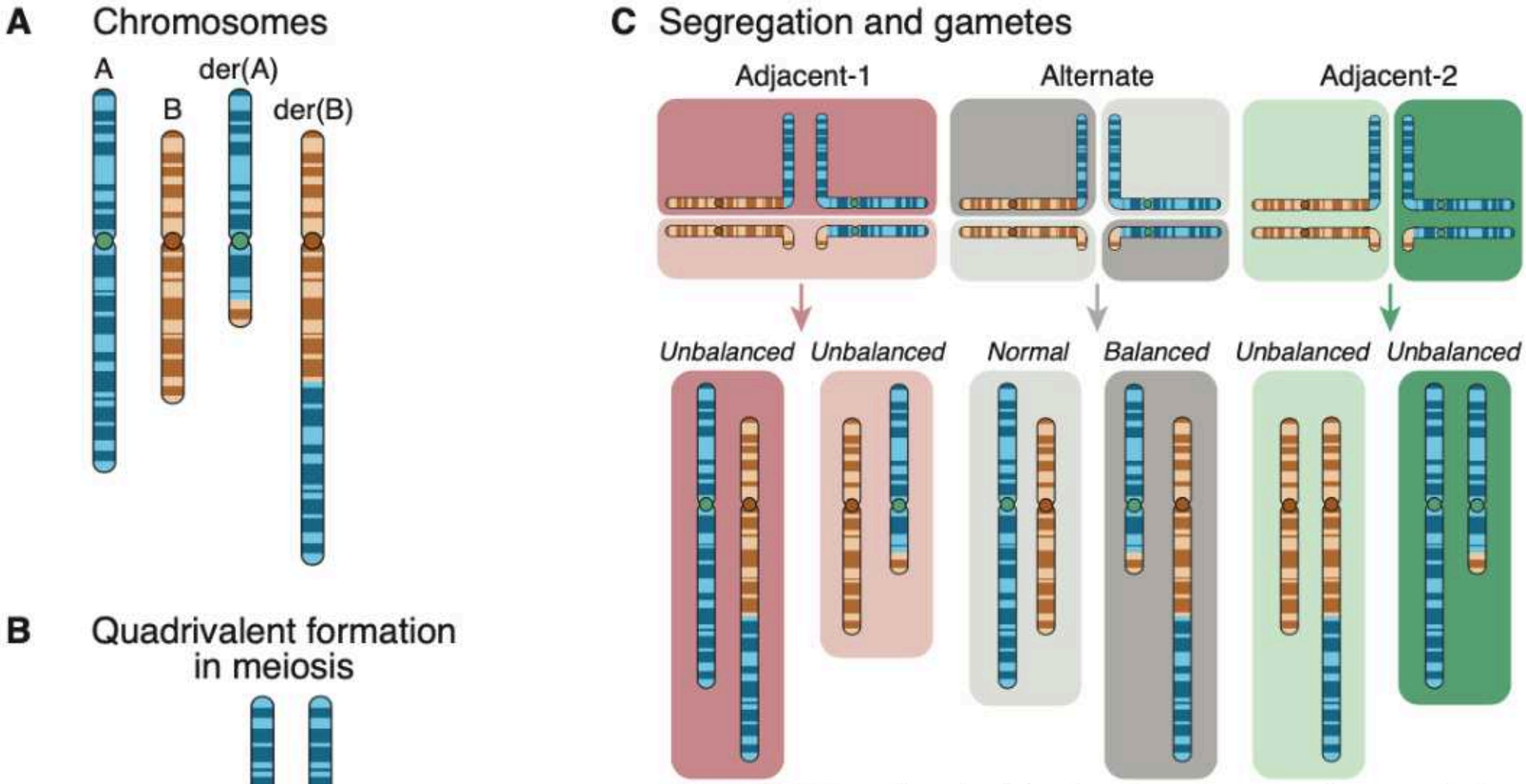
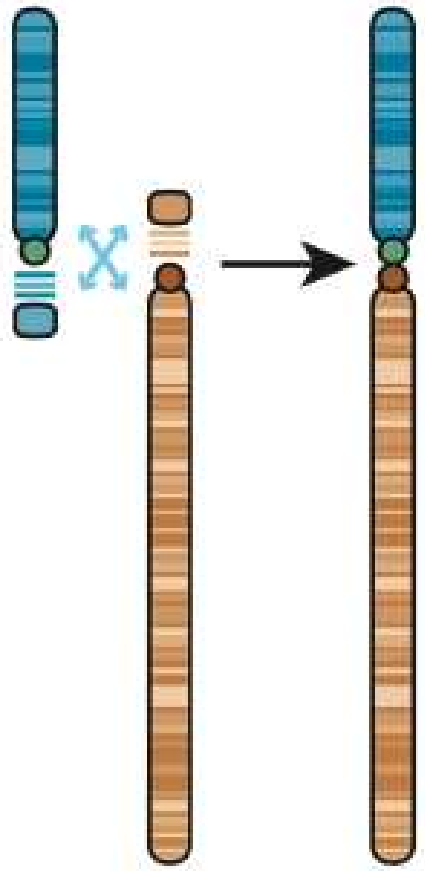


Figure 5-12 **A,** Diagram illustrating a balanced translocation between two chromosomes, involving a reciprocal exchange between the distal long arms of chromosomes A and B. **B,** Formation of a quadrivalent in meiosis is necessary to align the homologous segments of the two derivative chromosomes and their normal homologues. **C,** Patterns of segregation in a carrier of the translocation, leading to either balanced or unbalanced gametes, shown at the bottom. Adjacent-1 segregation (in *red,* top chromosomes to one gamete, bottom chromosomes to the other) leads only to unbalanced gametes. Adjacent-2 segregation (in *green,* left chromosomes to one gamete, right chromosomes to the other) also leads only to unbalanced gametes. Only alternate segregation (in *gray,* upper left/lower right chromosomes to one gamete, lower left/upper right to the other) can lead to balanced gametes.

Robertsonian Translocations

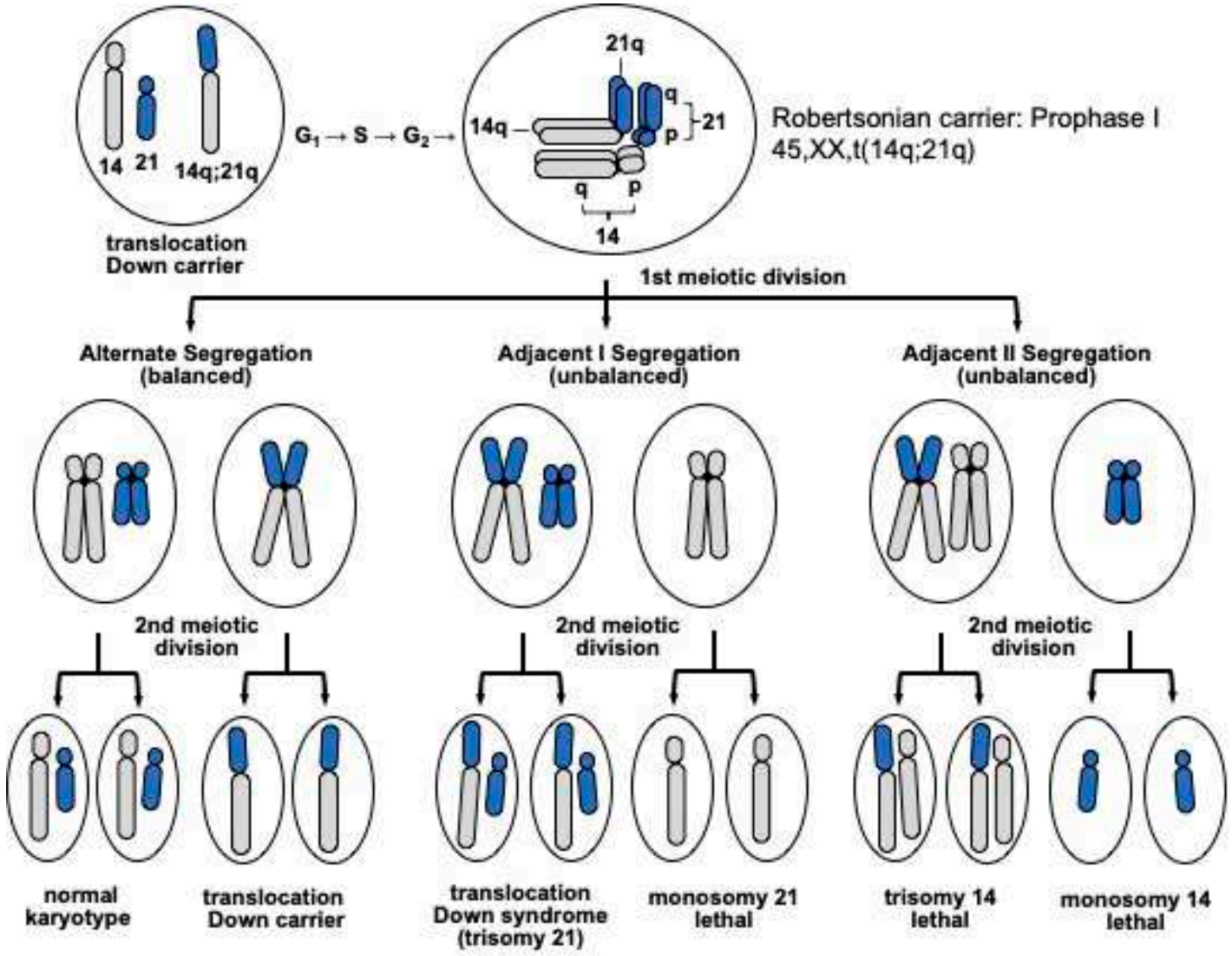
- Involve two acrocentric chromosomes (13, 14,15, 21, 22) that fuse near centromere region with loss of short arms (p)
- Results in karyotype with 45 chromosomes
- “Balanced” as loss of short arm material is not deleterious – normal phenotype
- Risk of abnormal offspring due to malsegregation of chromosomes during gametogenesis or risk for uniparental disomy
- Most common:
  - rob(13;14)(q10;q10) - 1 in 1300 people
  - rob(14;21) (q10;q10)



Robertsonian translocation

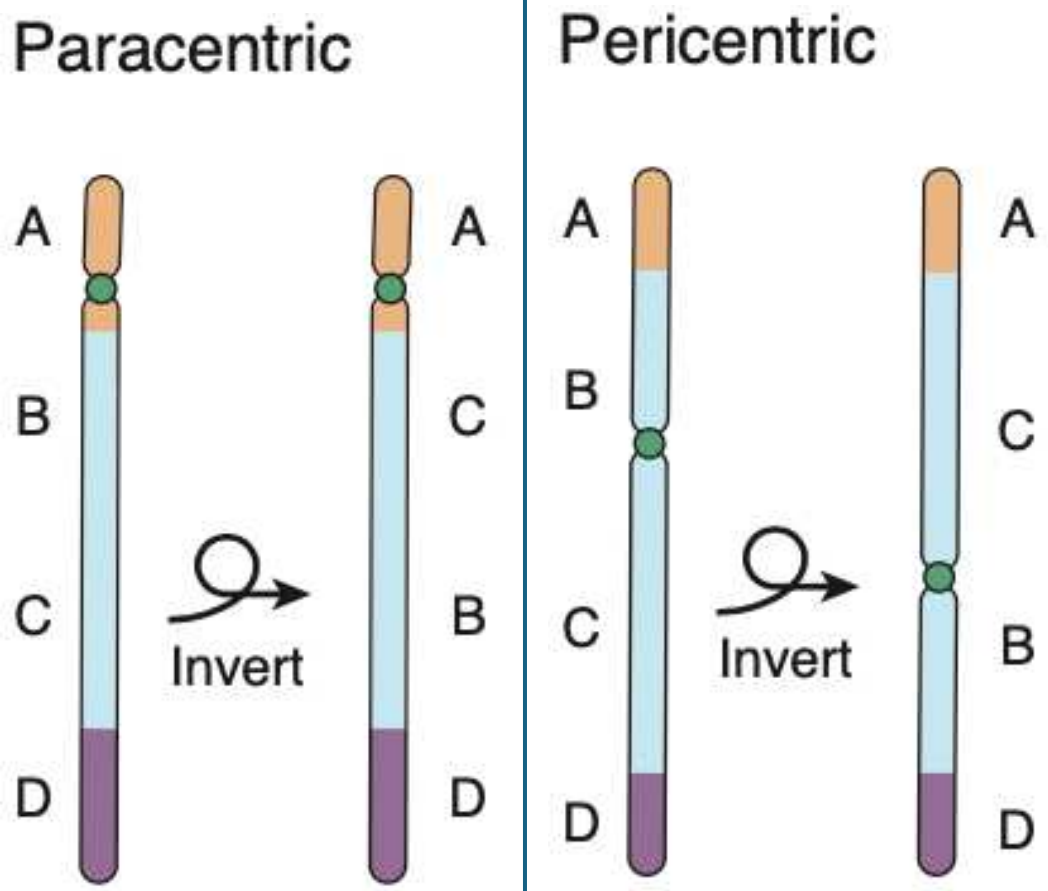
Robertsonian Translocations: Down Syndrome

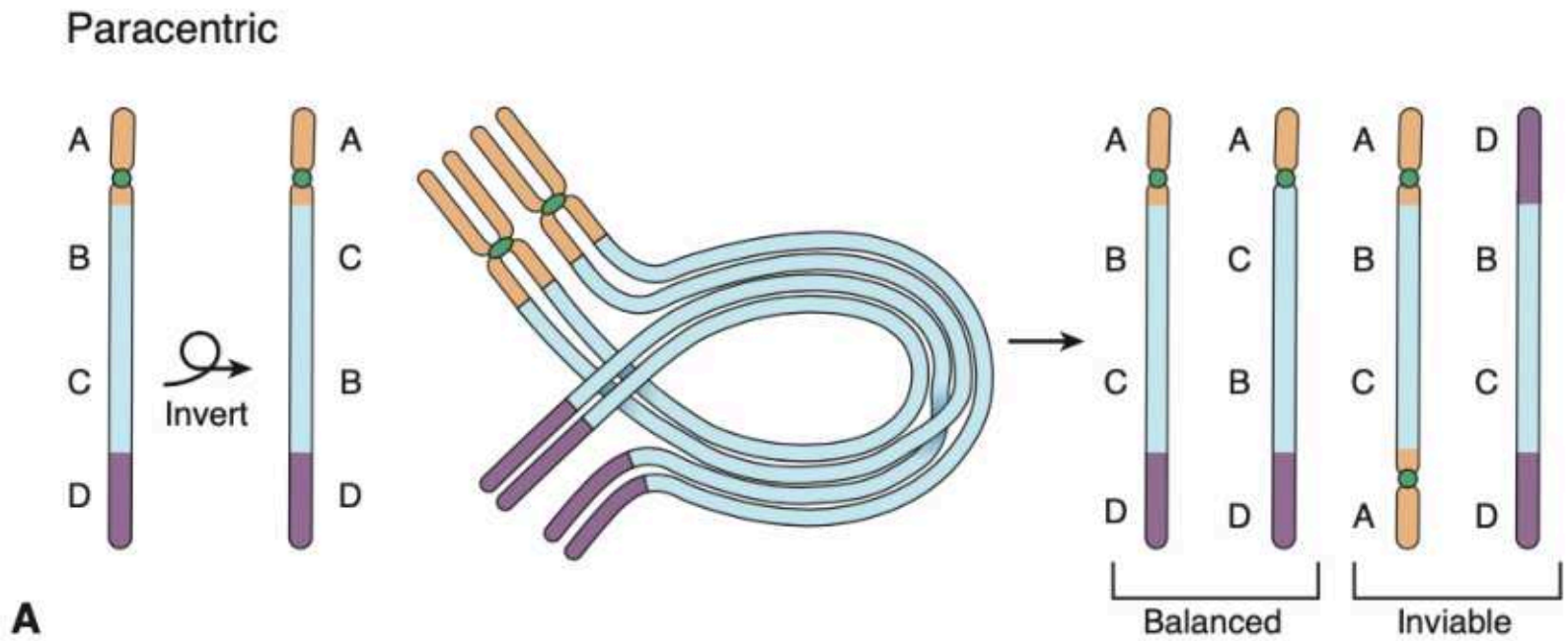
- 5% of Down syndrome patients have 46 chromosomes, one of which is a Robertsonian translocation between 21 and another acrocentric chromosome (most commonly 14 or 22)
- Carriers of Robertsonian translocations involving 21 are at risk for producing a child with translocation Down syndrome



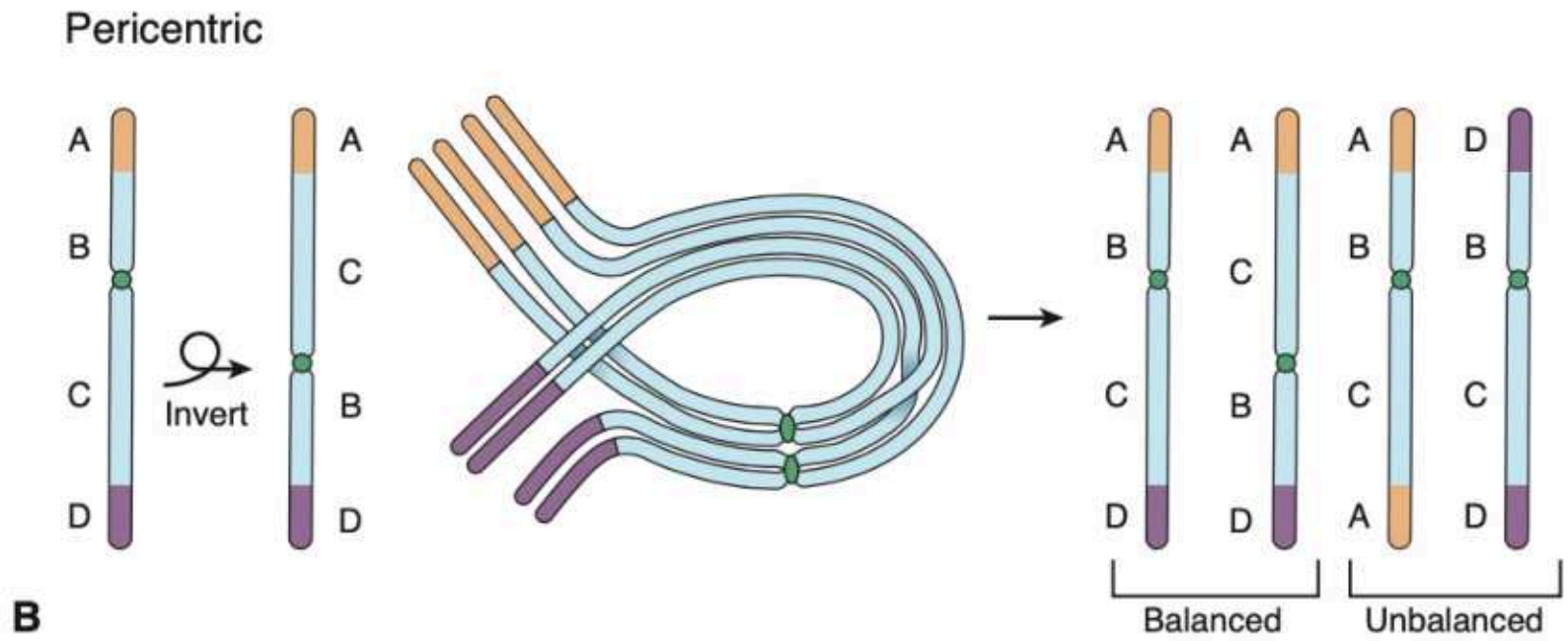
Inversions

- When a single chromosome undergoes two breaks and is reconstituted with the segment between the breaks inverted
- Types:
  - Paracentic – both breaks occur in one arm **(para = beside the centromere)**
  - Pericentric – breaks occur in each arm **(peri = around the centromere)**
- Usually normal phenotype, but risk for abnormal gametes due to loop formation for pairing of homologous segments in meiosis I





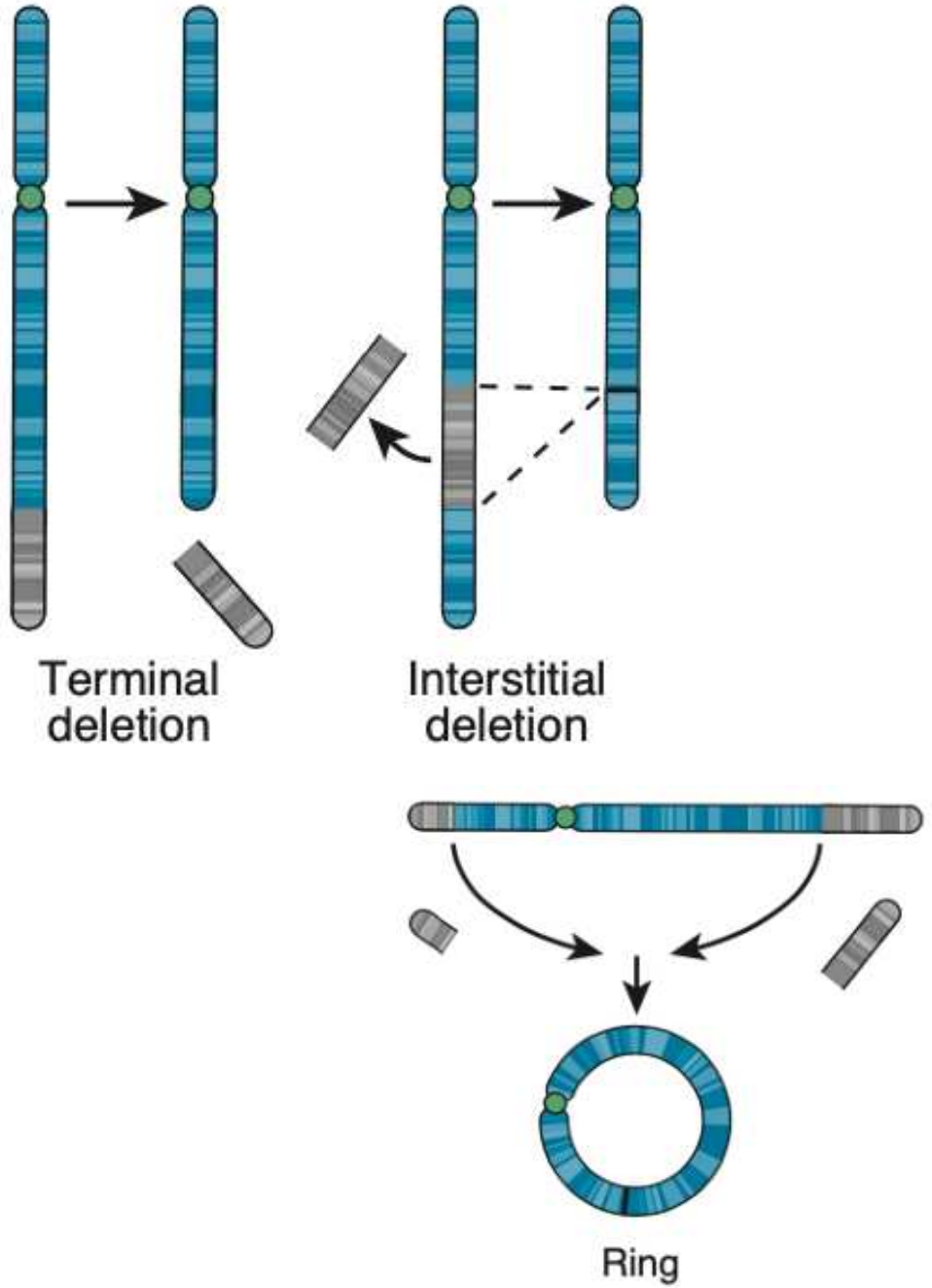
Paracentric: unbalanced recombinant chromosomes are acentric or dicentric and typically do not lead to viable offspring



Pericentric: unbalanced gametes with both duplication and deficiency of chromosome segments distal to the inversion

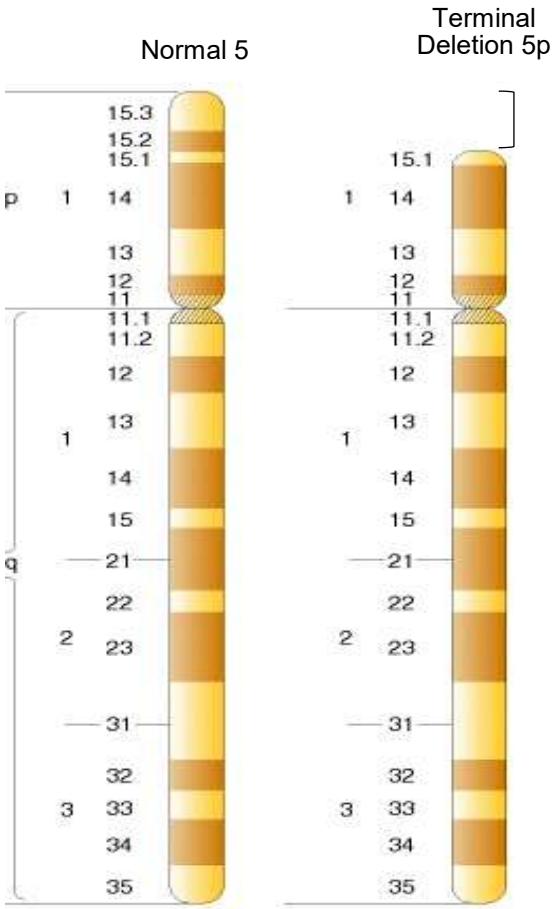
Deletions

- Involve loss of a chromosome segment, resulting in chromosome imbalance
- Monosomic or haploinsufficient
- Severity related to size and number of genes in deleted segment
- Larger, cytogenetically visible deletions detected on karyotype
- Submicroscopic deletions (microdeletions) detected on microarray



Cri du chat Syndrome

Terminal Deletion of 5p – detect on karyotype or microarray



Common Clinical Features
High-pitched cat-like cry
Microcephaly
Hypertelorism
Intellectual disability / developmental delay
Hypotonia
Round “moon” face

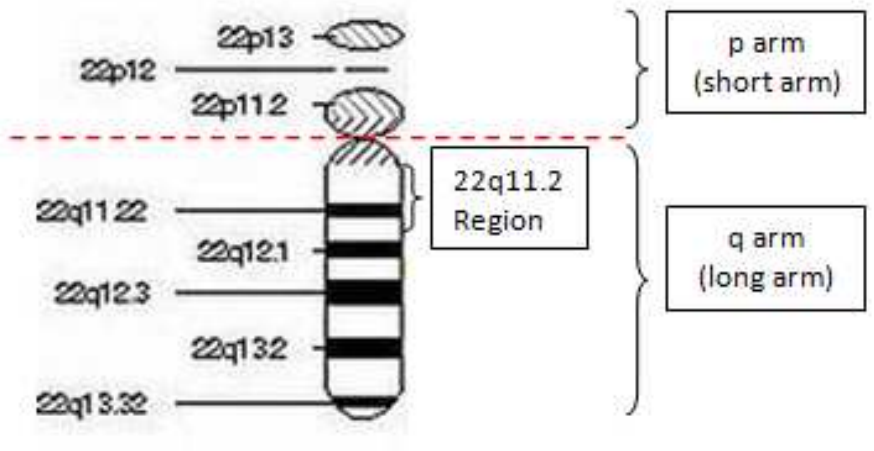
Wolf-Hirschhorn Syndrome

Terminal Deletion of 4p – detect on karyotype or microarray

Common Clinical Features
“Greek warrior helmet” (microcephaly, prominent glabella, broad nasal tip, short philtrum, hypertelorism)
Cardiac defects
Hypotonia
Seizures
Growth restriction / failure to thrive
Intellectual disability
Cleft lip and palate

DiGeorge (22q11.2 deletion) Syndrome

Interstitial microdeletion – detect on microarray

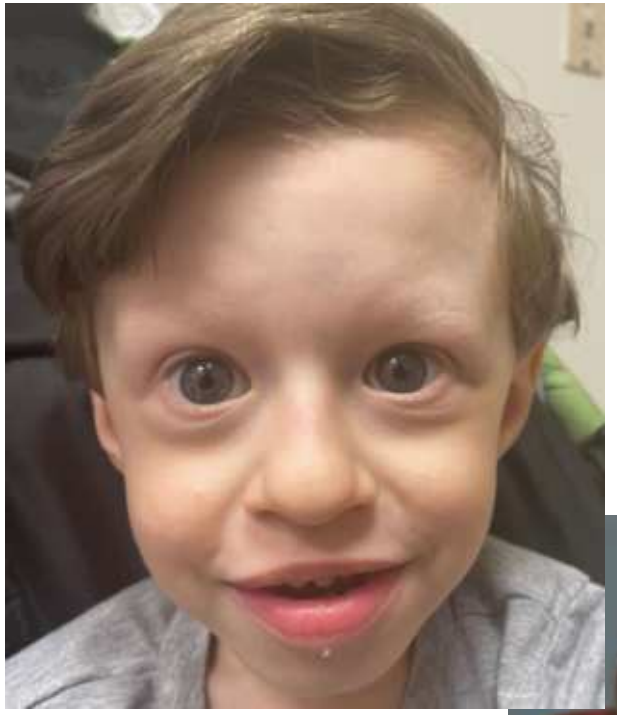


Common Clinical Features
Cardiac defects (conotruncal)
Abnormal facies (hypertelorism, bulbous tip of nose, low set ears)
Thymic hypoplasia (immunodeficiency)
Cleft palate
Hypoparathyroidism + Hypocalcemia

Williams Syndrome

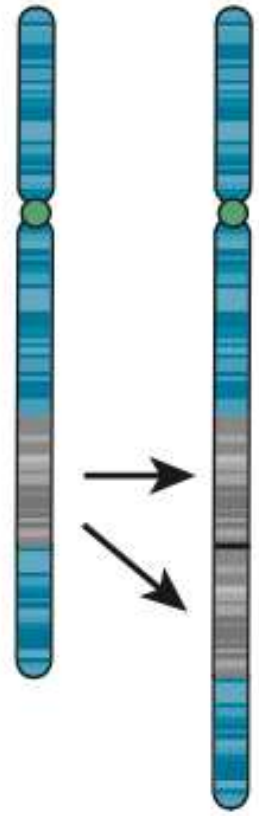
Interstitial microdeletion of 7q11.23 – detect on microarray

Common Features / Buzzwords
Outgoing (cocktail party personality)
Elfin-like facies
Cardiac defects (supravalvular aortic stenosis)
Infantile hypercalcemia
Mild to moderate intellectual disability
Stellate iris pattern



Duplications

- Duplications often occur at loci in the chromosome that contain tandem or inverted repeats.
- Duplications are generated in most cases by:
  - DNA replication errors
  - Unequal crossover during meiosis
- In general, duplications are less detrimental than deletions
- Many small duplications do not have any clinical consequences



Duplication

Questions?

- Dr. Thompson – thlaur@musc.edu
- Dr. Lancaster - lancastk@musc.edu

Come shadow us in Genetics clinic!