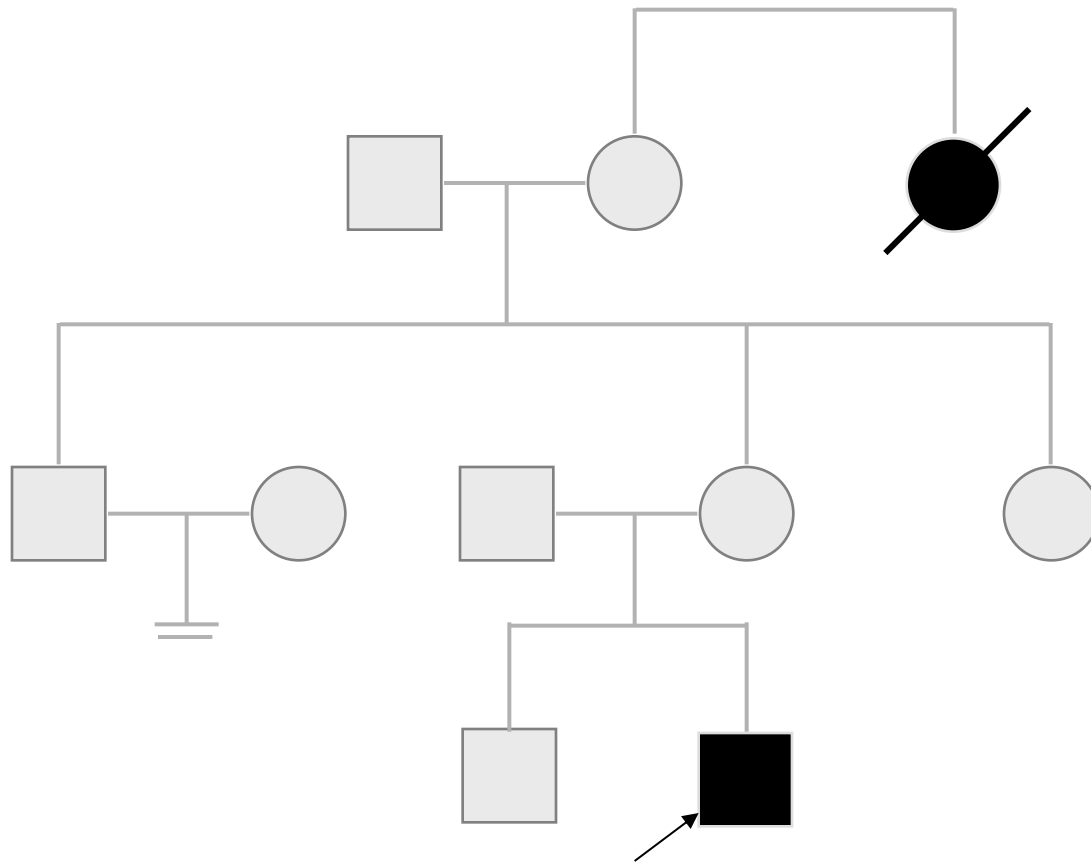
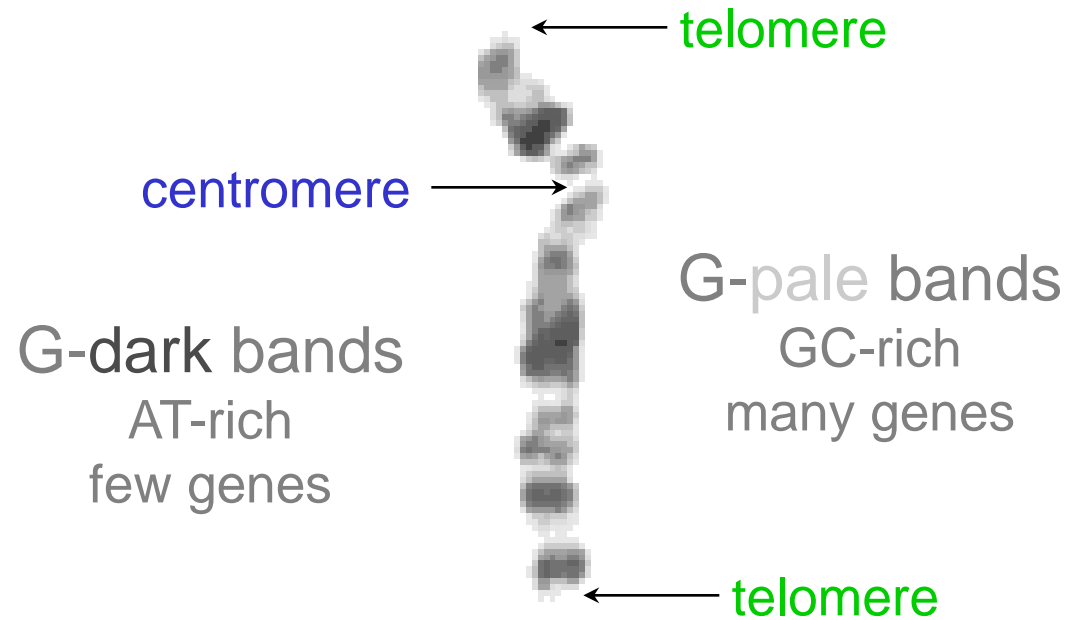


Case 1B



46,XY,-14,+t(14;21)

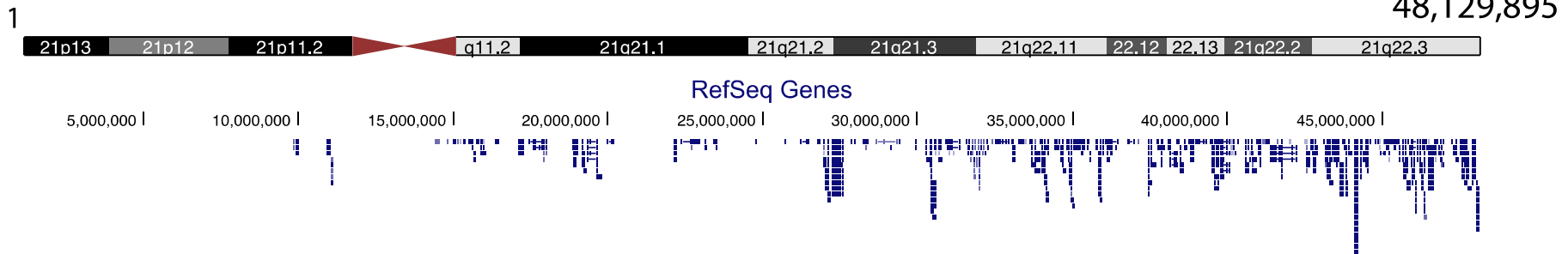
G-banded Chromosome



genome.ucsc.edu

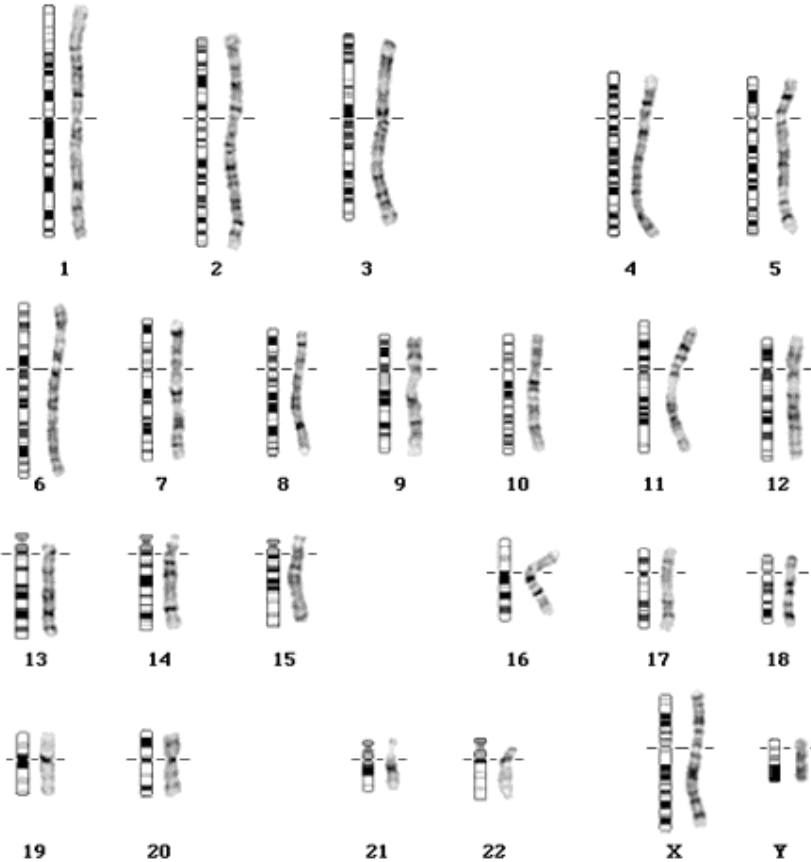
chr21 (p13-q22.3)

chr21:1-48,129,895



Conventional (light microscopy)

ideograms

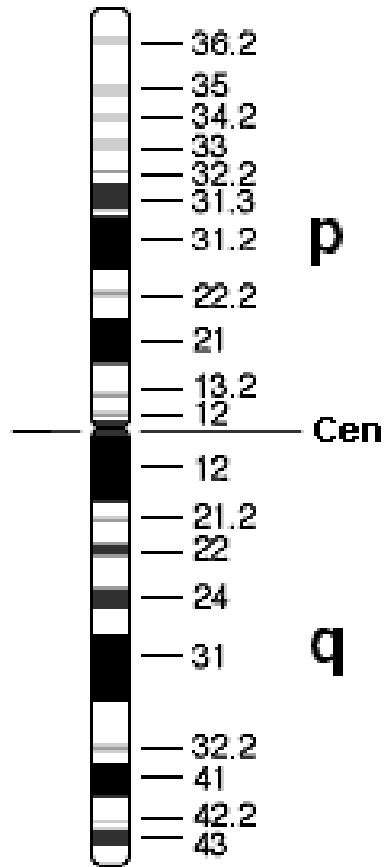


ideograms

p = short arm
q = long arm

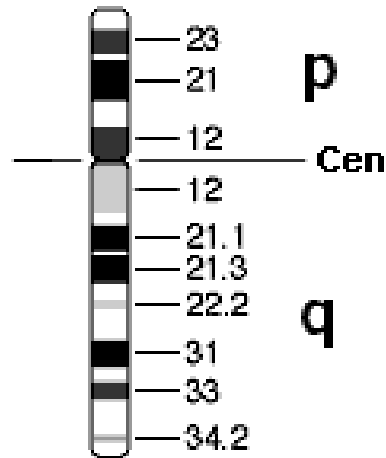
numbering from
centromere -> telomere

Chromosome 1



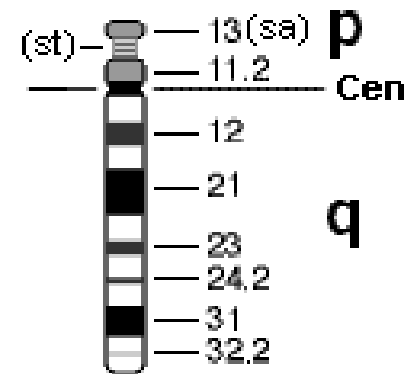
metacentric

Chromosome 9

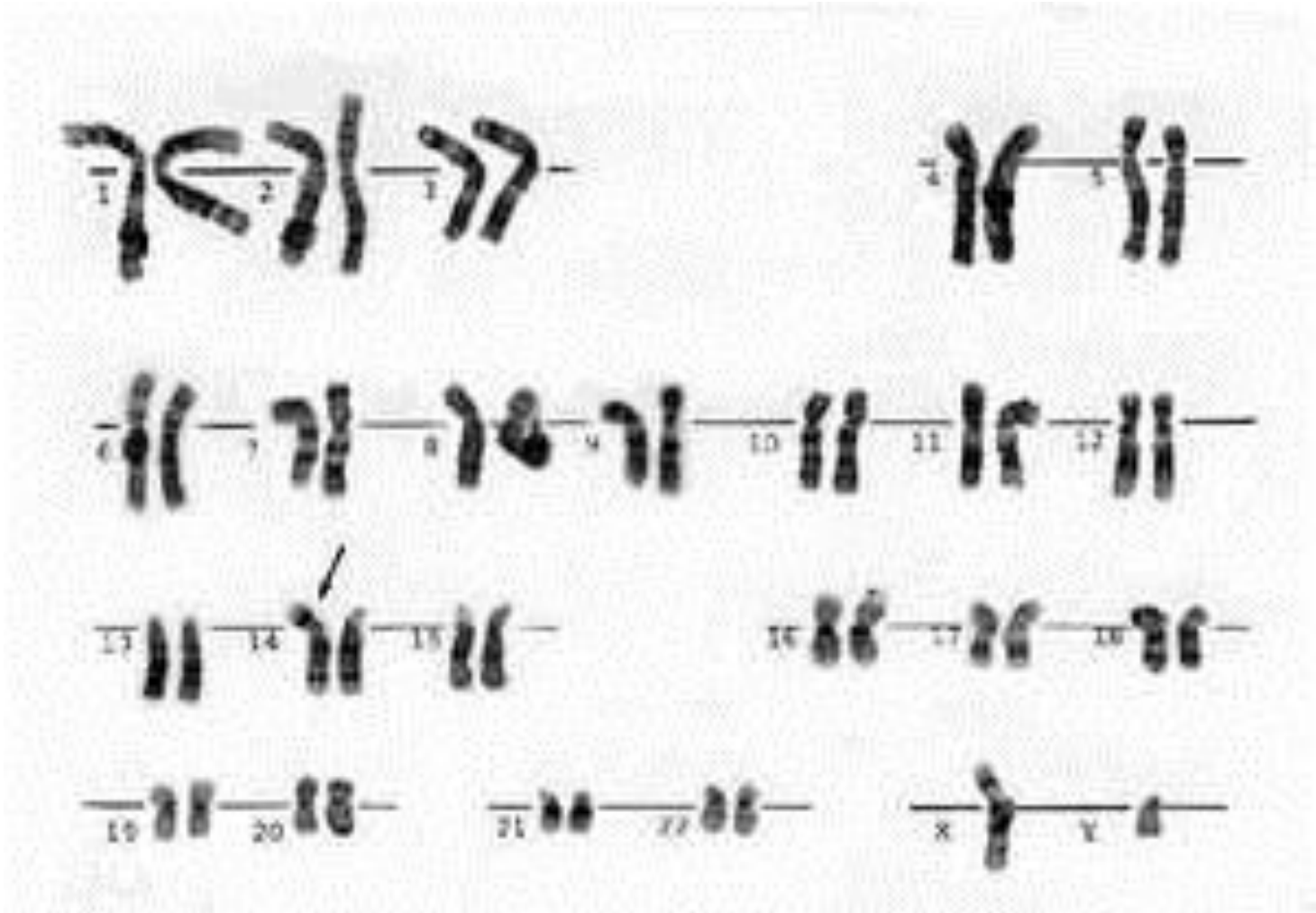


submetacentric

Chromosome 14

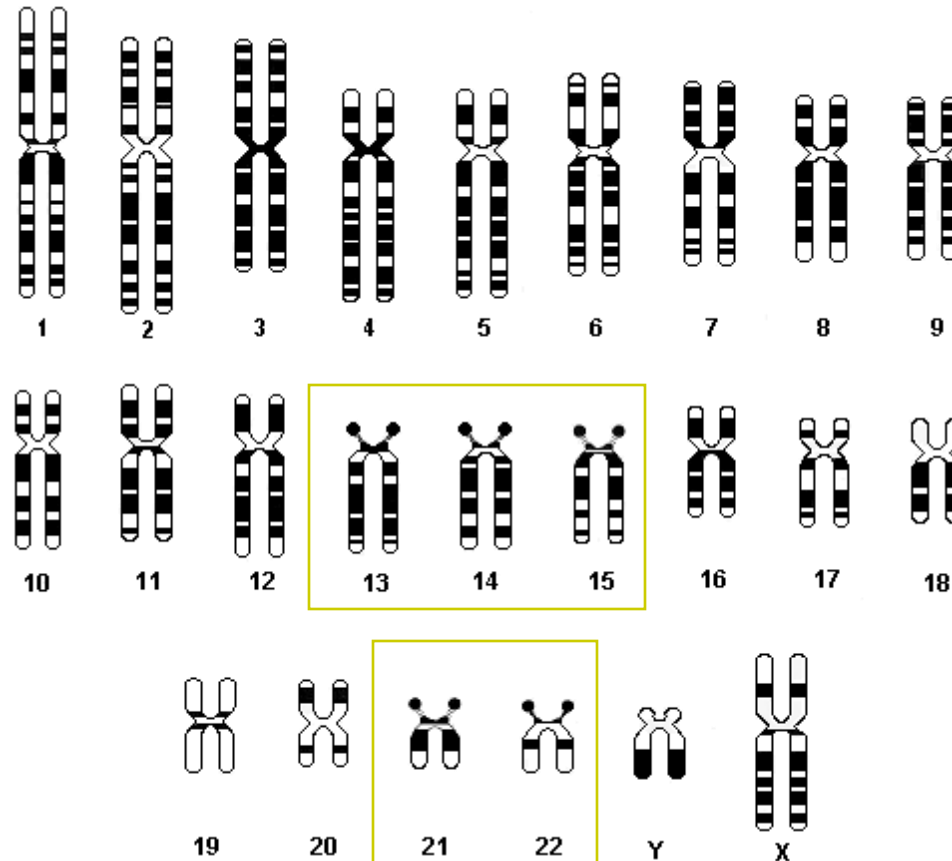


acrocentric



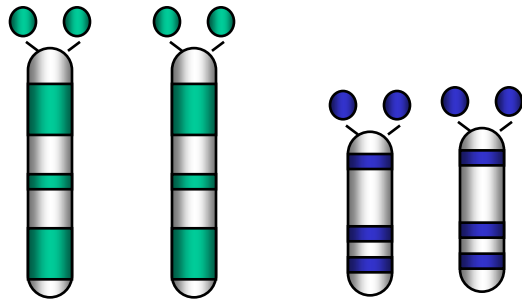
David FitzPatrick
Chromosomes II Jan 2014

Acrocentric Chromosomes



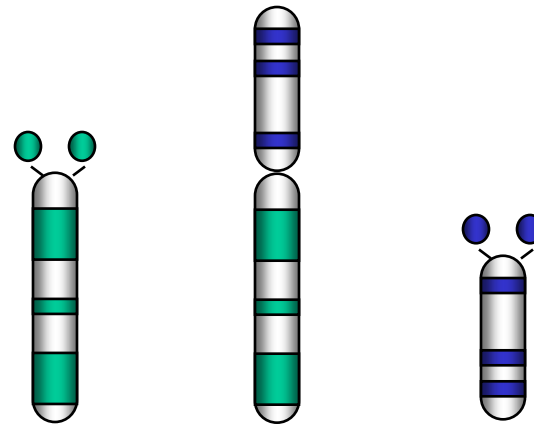
Robertsonian Translocation

normal



46

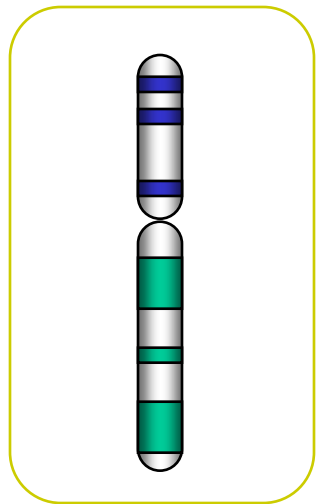
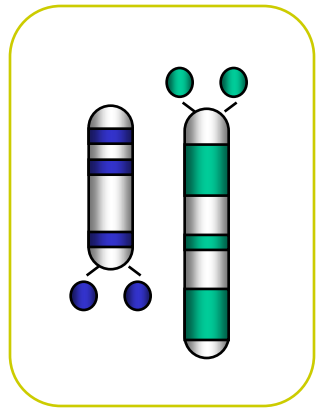
robersonian balanced translocation



45

balanced

normal



balanced

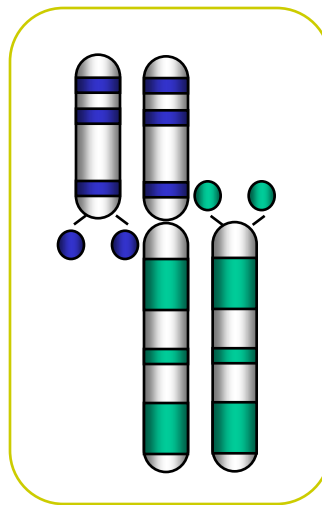


unbalanced

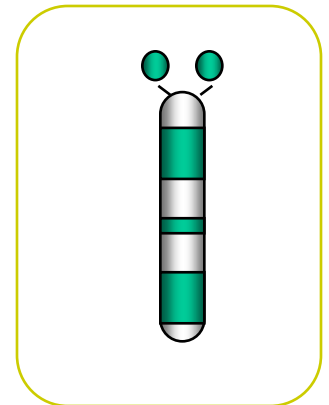
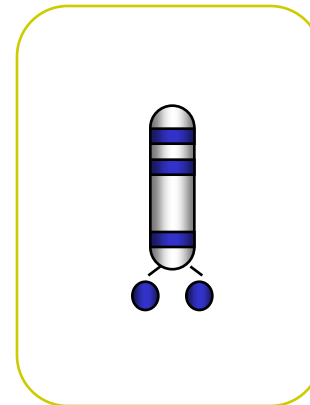
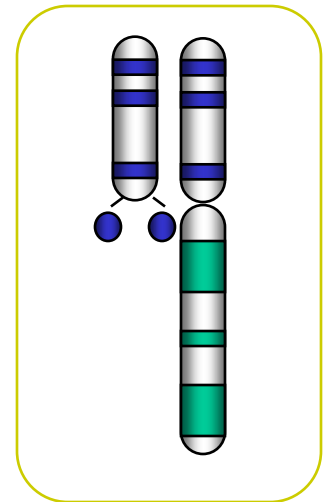
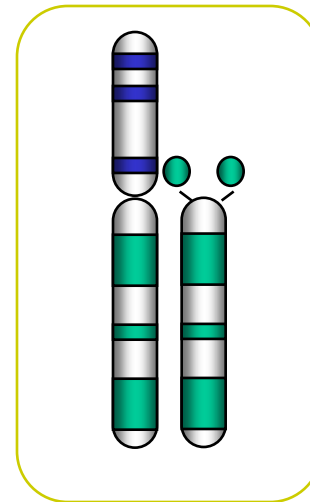
MI

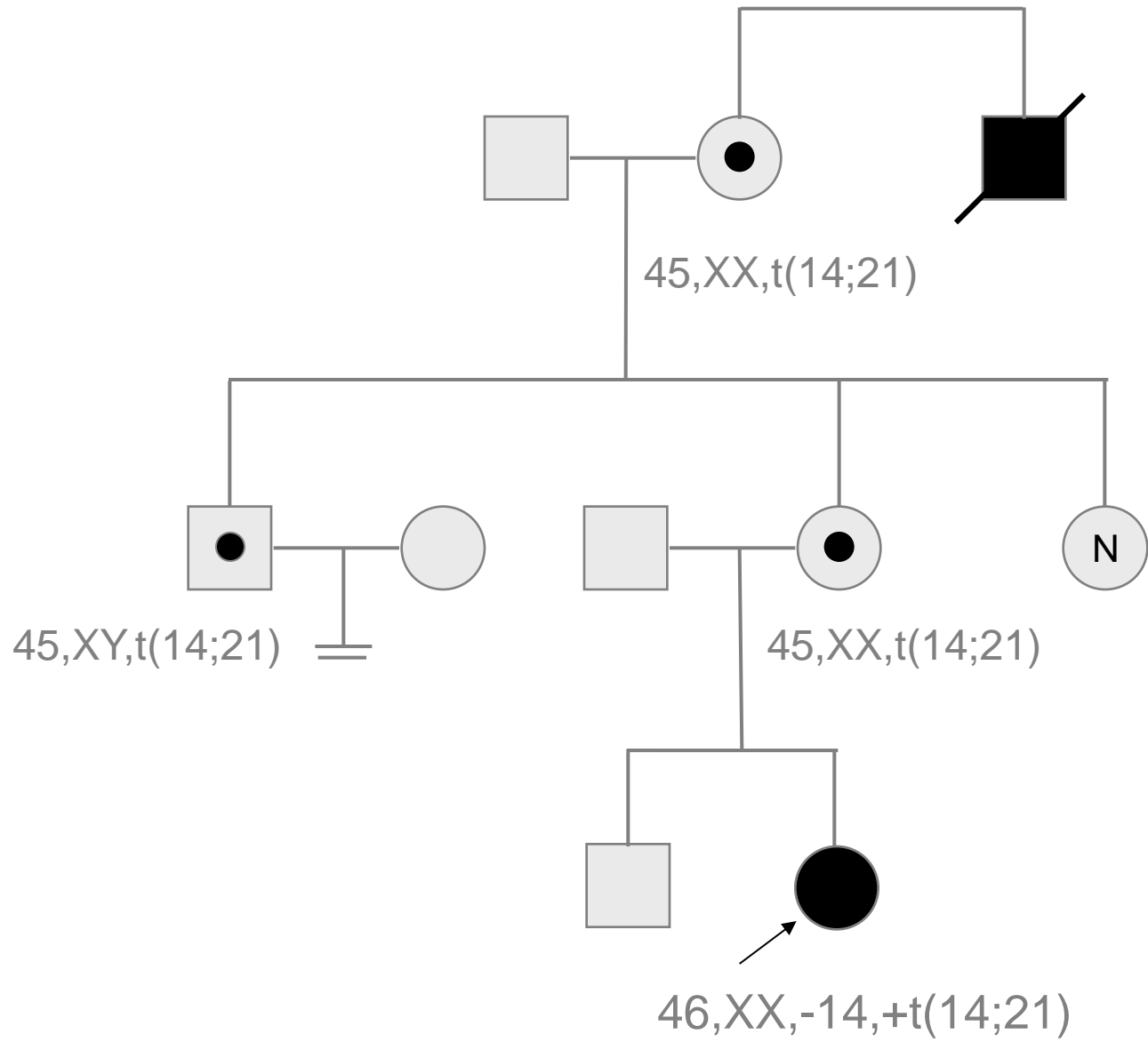


parent cell

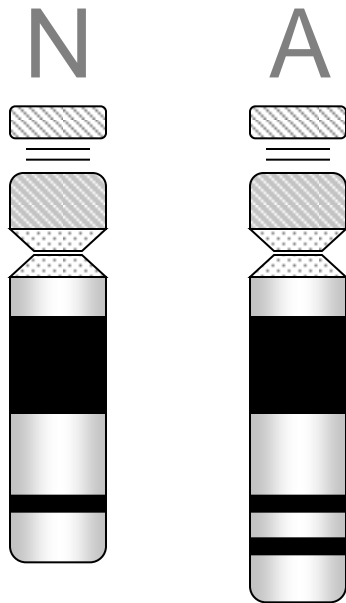


MI



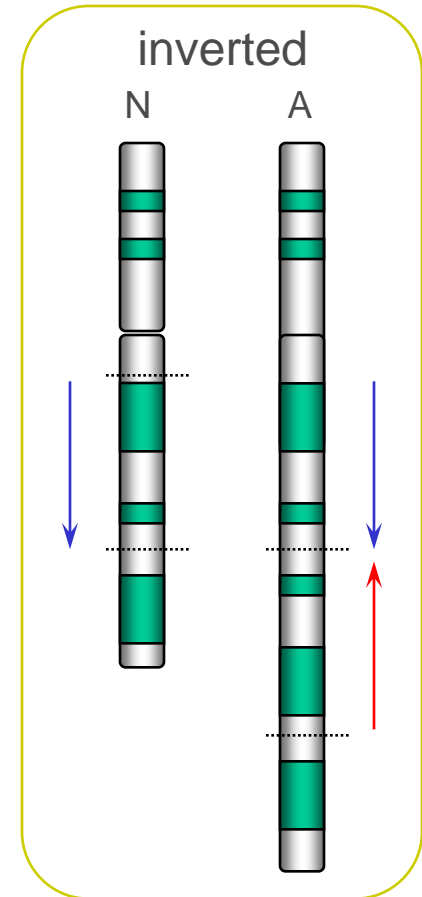
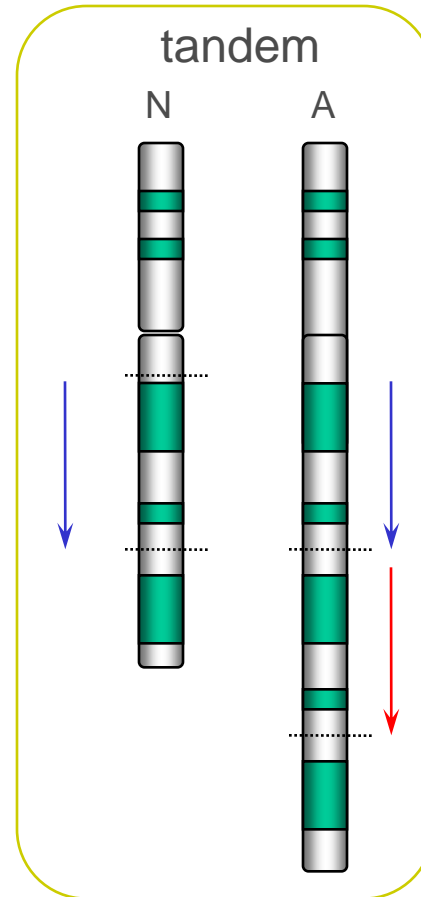


Structural Chromosome Abnormalities



46,XY,dup(21)(q22.2)

Down Syndrome Critical Region



duplications

structural chromosome abnormalities

David FitzPatrick
Chromosomes II Jan 2014

Structural Chromosome Abnormalities

- **balanced**
 - translocations (robertsonian & reciprocal)
 - inversions
 - fragile sites
- **unbalanced** (aka aneuploid - *not* euploid)
 - deletions
 - duplications
 - translocations (robertsonian & reciprocal)
 - ring chromosomes

categorising structural chromosomal anomalies

- structural change
- meiotic mechanism
 - non-homologous end-joining
 - mostly unique
 - may be cytogenetically visible or cryptic
 - non-allelic homologous recombination
 - recurrent
 - common
 - basis of most normal copy number variation

non-homologous end joining

This is the maternal chromosome 21 that replicates to form a sister chromatid which is joined at the centromere
This is the paternal chromosome 21 that replicates to form a sister chromatid which is joined at the centromere
This is the maternal chromosome 21 that replicates to form a sister chromatid which is joined at the centromere
This is the paternal chromosome 21 that replicates to form a sister chromatid which is joined at the centromere

double-stranded DNA breaks

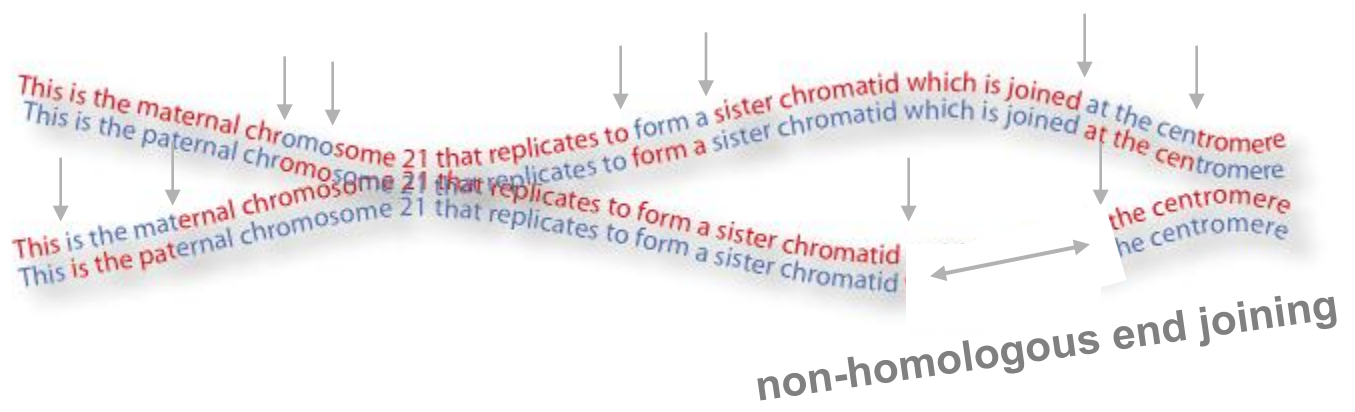
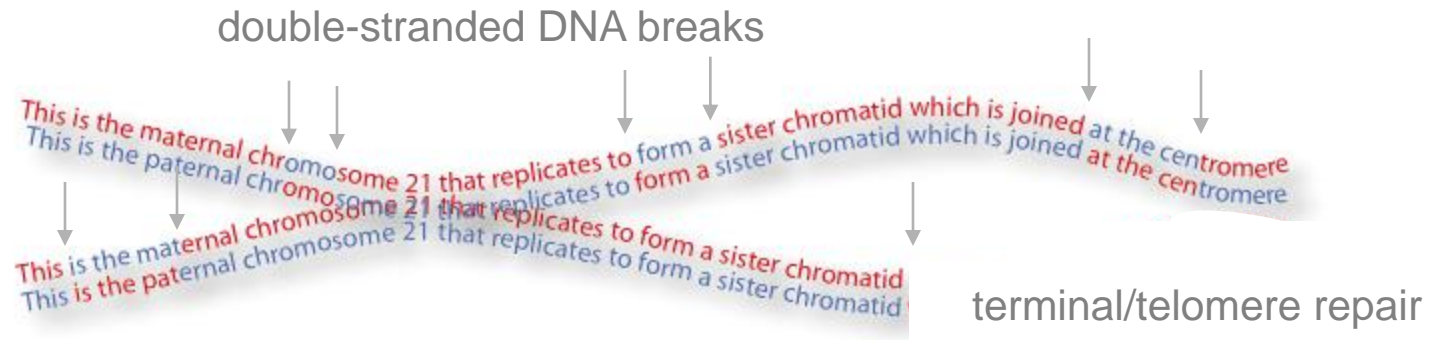
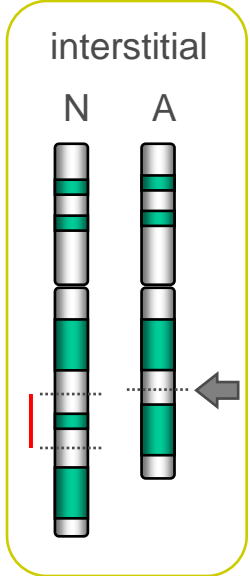
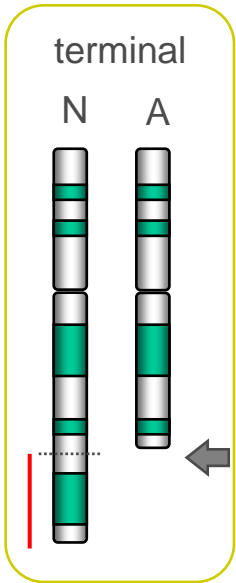
This is the maternal chromosome 21 that replicates to form a sister chromatid which is joined at the centromere
This is the paternal chromosome 21 that replicates to form a sister chromatid which is joined at the centromere
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homologous recombination

Structural Chromosome Abnormalities

- **balanced**
 - translocations (robertsonian & reciprocal)
 - inversions
 - fragile sites
- **unbalanced** (aka aneuploid)
 - deletions
 - duplications
 - translocations (robertsonian & reciprocal)
 - inversions
 - ring chromosomes

deletions





1



2



3



4



5



6



7



8



9



10



11



12



13



14



15



16



17



18



19



20



21



22



X



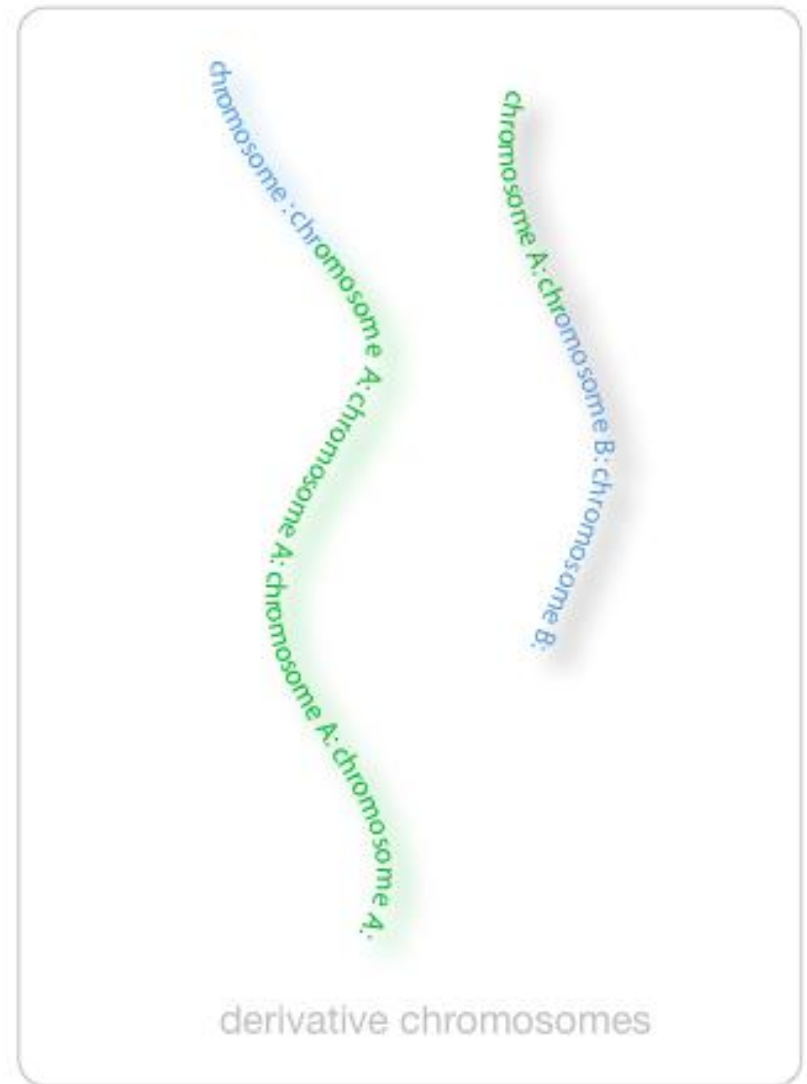
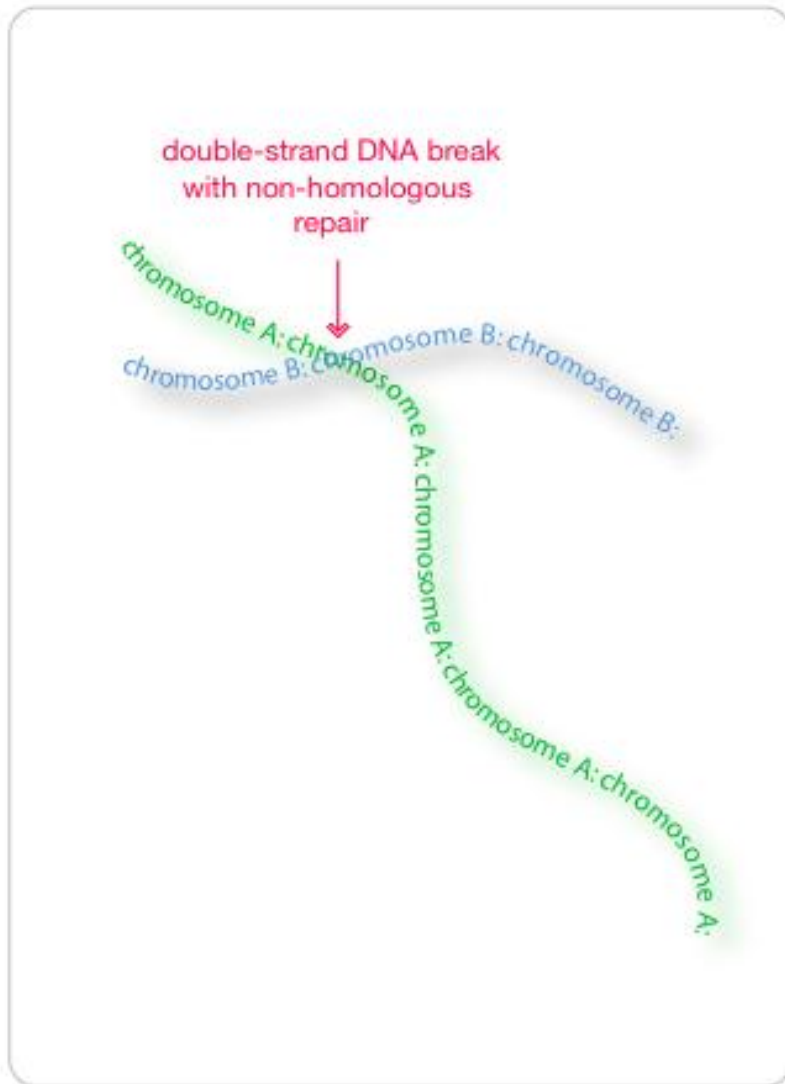
Y

NHEJ Contiguous Gene Syndromes

recognised *via* phenotype as a result of *haploinsufficiency* for one or more high-penetrant genes

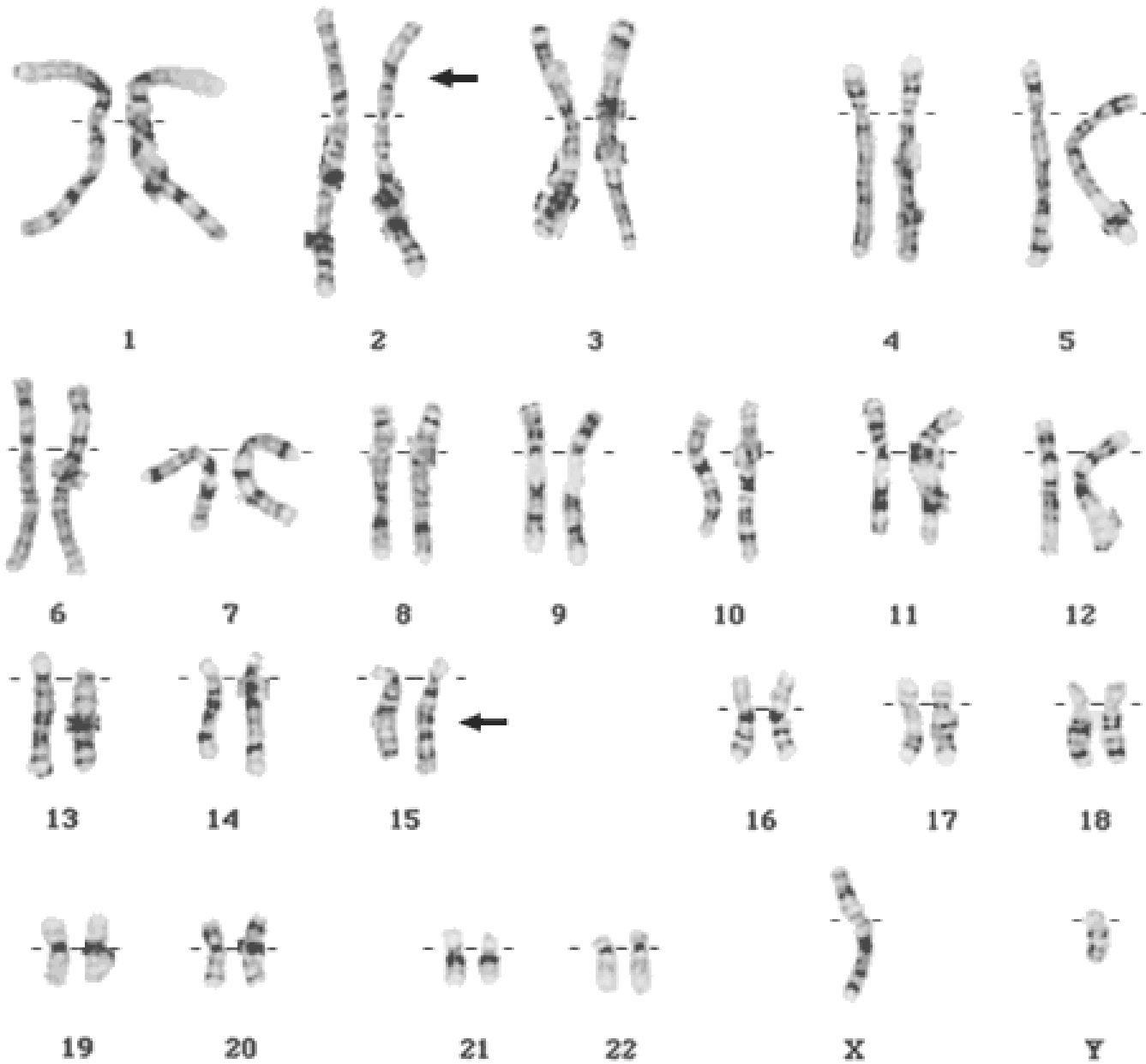
Miller-Dieker Syndrome	17p11.3	Rare	Distinctive facial appearance, lissencephaly, severe learning disability, heart defects, growth retardation and seizures. Major genes seems to be LIS1 and 14-3-3
Cri du Chat Syndrome	5p15	Rare	microcephaly, micrognathia, epicanthic folds, and high-pitched cry. Major gene/genes are unknown
Retinoblastoma	13q14	Rare	Retinoblastoma, learning disability. Major gene is RB1
Rubinstein-Taybi Syndrome	16p13.3	Rare	Distinctive facial appearance, short stature, broad thumbs. CREB deletions account for <10% of cases
Wolf-Hirschhorn Syndrome	4p16.3	Rare	distinctive facial appearance, seizures, short stature, cleft lip, coloboma. Major gene seems to be WHSC1
WAGR Syndrome	11p13	Rare	Aniridia, Wilms tumour, male genital tract malformations, learning disability. Major genes are PAX6 , WT1

non-homologous end-joining



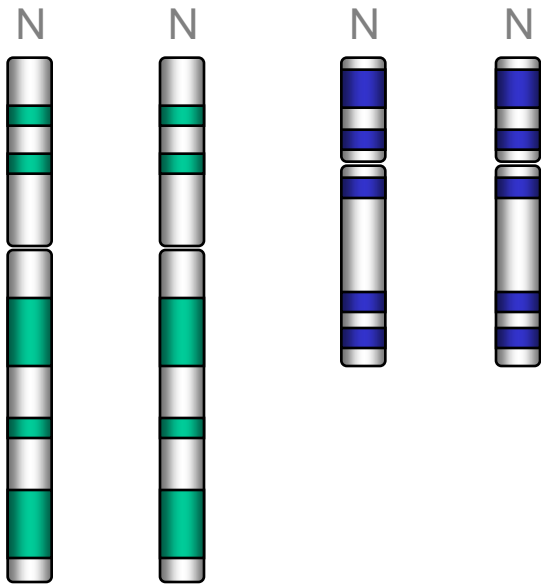
Structural Chromosome Abnormalities

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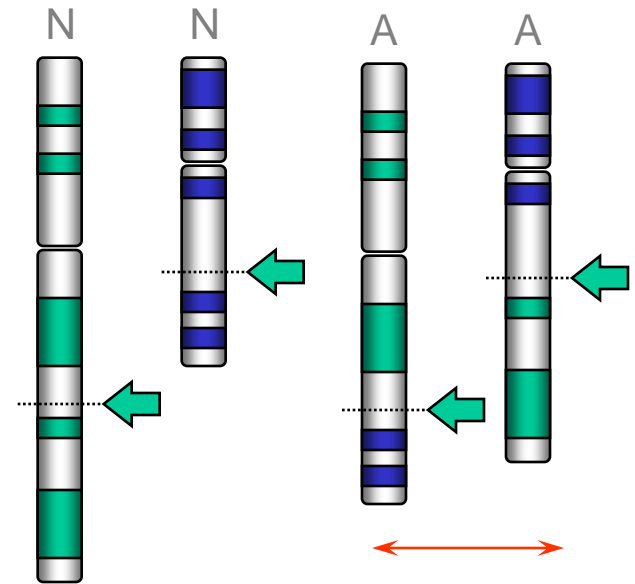


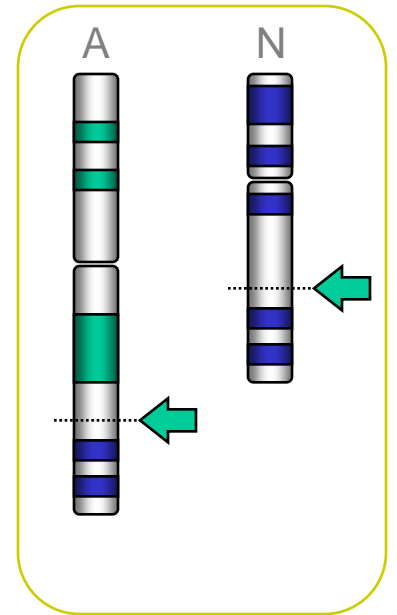
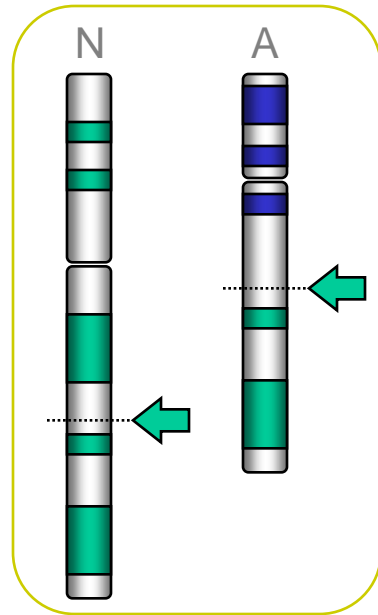
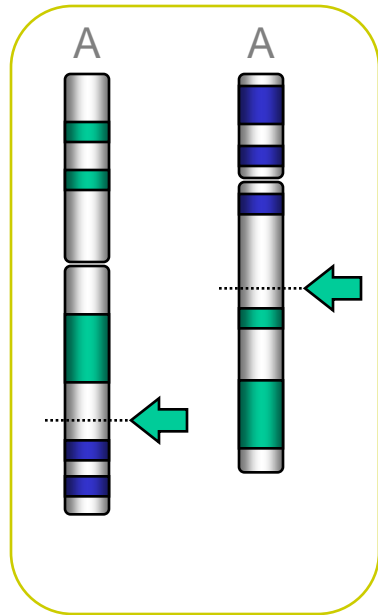
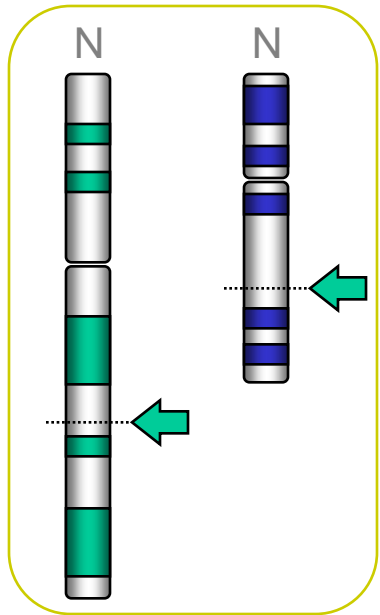
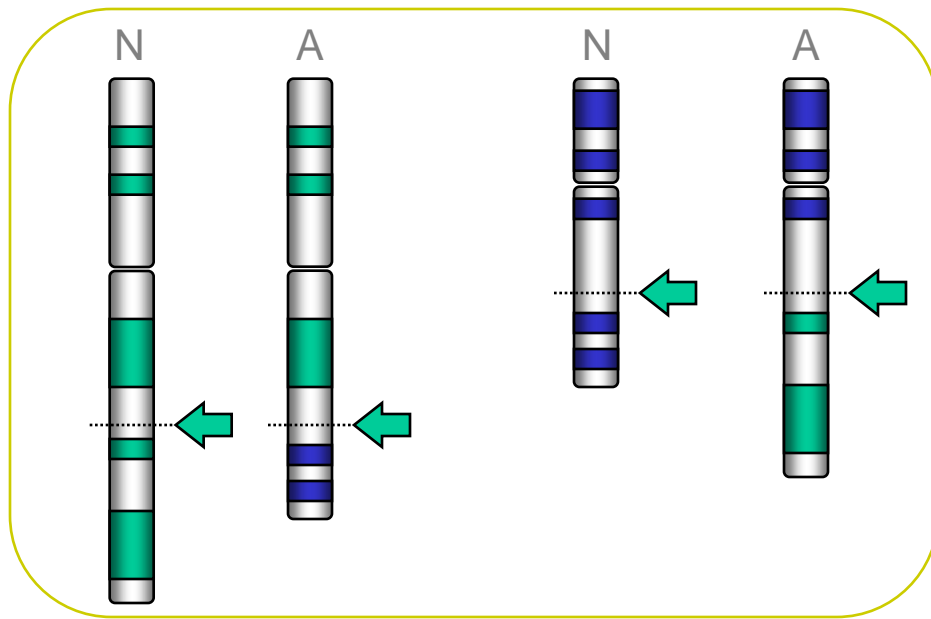
Reciprocal Balanced Translocations

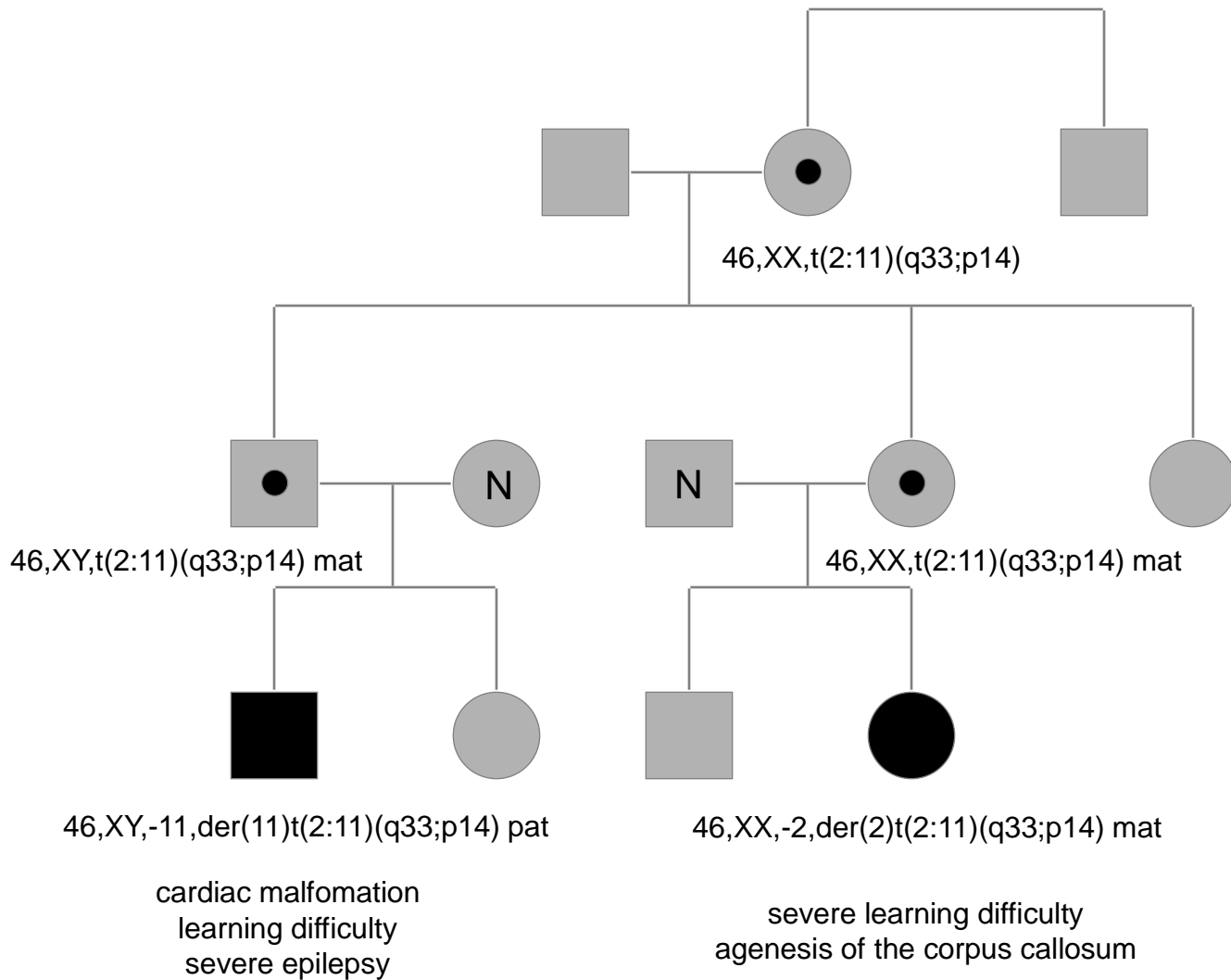
normal



reciprocal balanced translocation







non-allelic homologous recombination

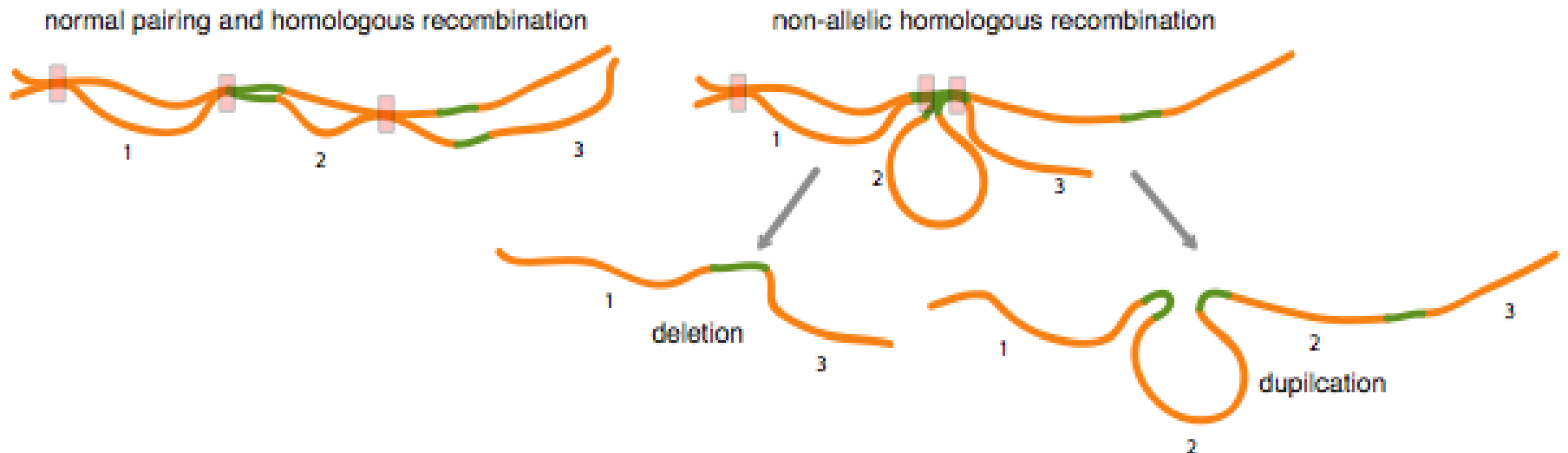
microdeletion syndromes

Di George/ velocardiofacial syndrome	22q11.2	1 in 4,000	Cardiac outflow tract defects, distinctive facial appearance, thymic hypoplasia, cleft palate and hypocalcaemia. Major gene seems to be TBX1 (cardiac defects and cleft palate)
Prader Willi Syndrome	15q11-q13	1:15,000	Distinctive facial appearance, hyperphagia, small hands and feet, distinct behavioural phenotype. Imprinted region, deletions on paternal allele in 70% cases
Angelman Syndrome	15q11-q13	1:15,000	Distinctive facial appearance, absent speech, EEG abnormality, characteristic gait. Imprinted region, deletions on maternal allele in UBE3A
Williams Syndrome	7q11.23	1:10,000	Distinctive facial appearance, supravalvular aortic stenosis, learning disability and infantile hypercalcaemia. Major gene for supravalvular aortic stenosis is Elastin
Smith-Magenis Syndrome	17p11.2	1 in 25,000	Distinctive facial appearance and behavioural phenotype, self-injury and REM sleep abnormalities. Major gene seems to be RAI1

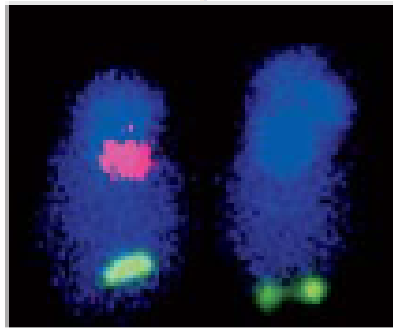
non-allelic homologous recombination

mechanism underlying recurrent deletions and duplication: non-allelic homologous recombination

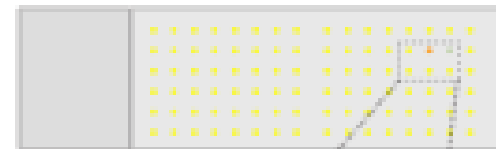
this is segment 1 of a normal chromosome :this is a repeat: this is segment 2 of a normal chromosome :this is a repeat: and segment 3



Fluorescent in situ hybridisation (FISH)

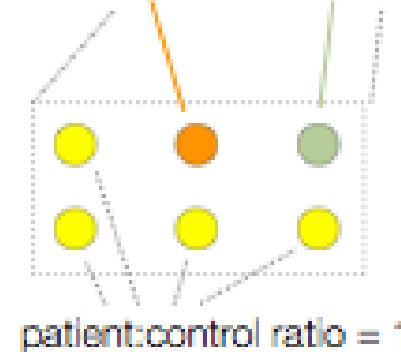


Apply DNA mix to glass slide with high-density array of different DNA probes with known location in the human genome

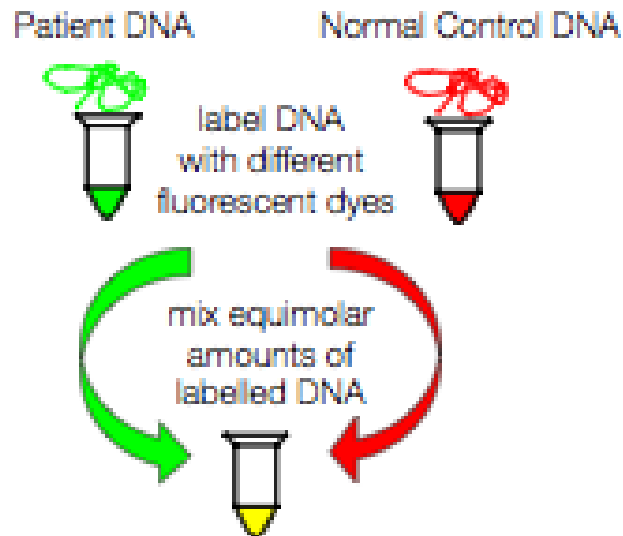


patient:control ratio = 0.5:1
i.e. deletion in Patient DNA

patient:control ratio = 1.5:1
i.e. duplication in Patient DNA

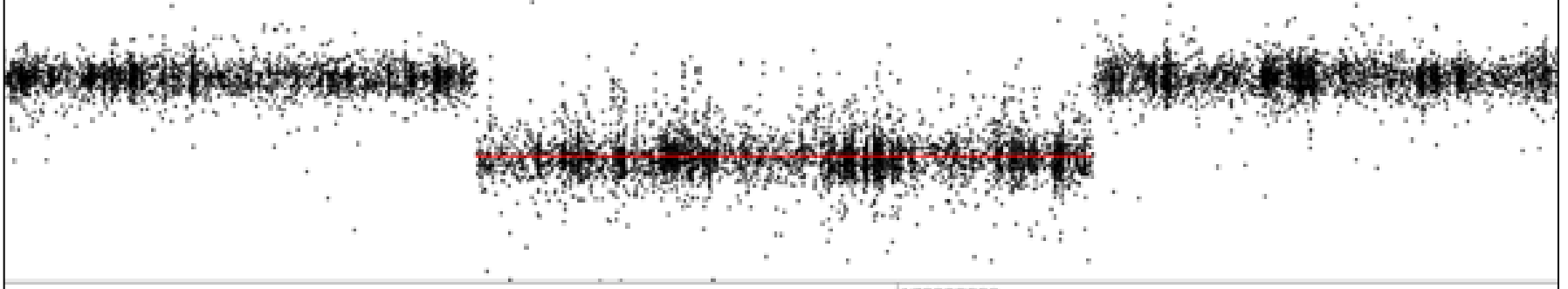


Comparative Genomic hybridisation (aCGH)



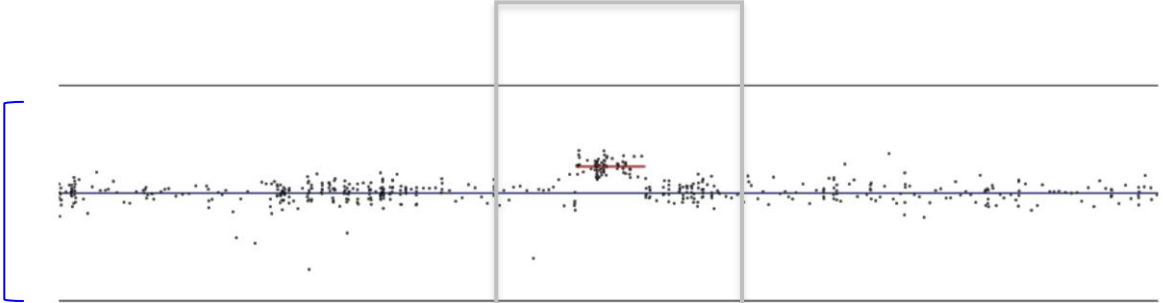
aCGH Deletion

CHILD (array-CGH)



CNV Discovery

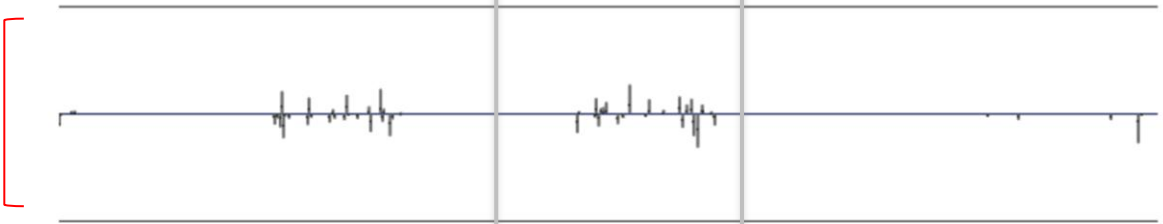
aCGH: child



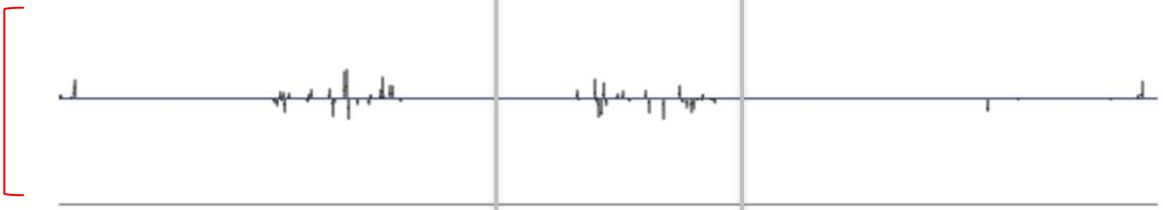
Exome: child



Exome: mother



Exome: father



genome-wide microarray analysis

- learning disability
 - 15-25% of moderate/severe learning disability is due to sub-microscopic structural chromosome anomalies
- normal populations
 - many loci in the genome show polymorphic copy number variation (CNV)
 - CNV may predispose to common adult disorders

Structural Chromosome Abnormalities

- Summary
 - meiotic recombination = double-stranded DNA breaks with rejoining: the process has an error rate.
 - errors in homologous pairing leads to recurrent changes in copy number of specific genomic regions
 - structurally abnormal chromosomes cannot pair properly during meiosis: this increases the rate of abnormal chromosome segregation