7.03 Lecture 10
Chromosomal Abnormalities

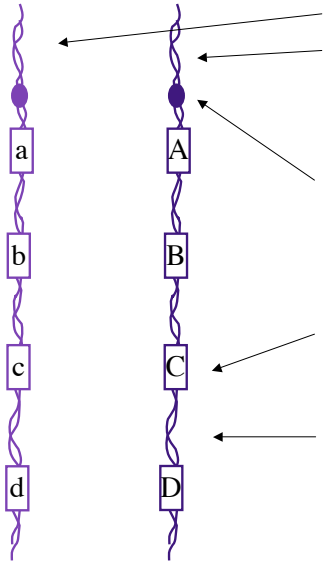
Deletions

Duplications

Inversions

Translocations

A review of chromosome structure



a chromosome (from mom)
the homologous chromosome (from dad)

The centromere (dictates chromosome segregation during mitosis and meiosis)

a gene (encodes RNA and/or protein)

non-coding DNA (does NOT encode RNAs or protein)

Looking back

Recently we have been talking about homologous recombination and how it creates new phenotypic classes of offspring that differ from their parents.

Recombination can also create large chromosomal abnormalities that can affect phenotype drastically.

Non-coding DNA is incredibly common in genomes

Less than 5% of the DNA in the human genome codes for proteins
This non-coding DNA often consists of small repeated sequences

For instance: ~5% of the human genome is a repeat of 280 bp (the Alu repeat) and there are 750,000 copies of it in the human genome (many copies on each chromosome

Recombination between repeated DNA regions is rare, but can generate deletions, duplications, inversions, and translocations.

Deletions

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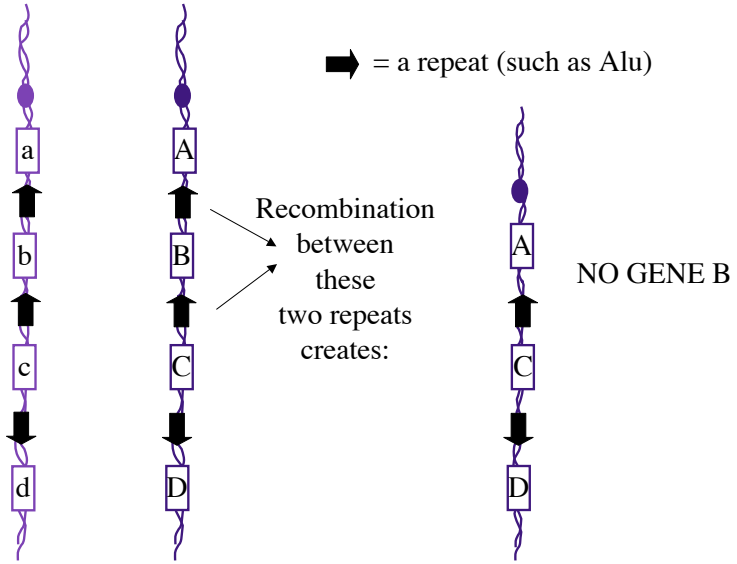
A Deletion is loss of a segment of DNA



Deletions are complete loss of function

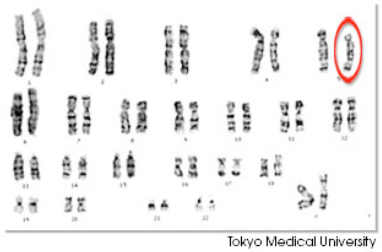
Deletions most often cause recessive phenotypes.

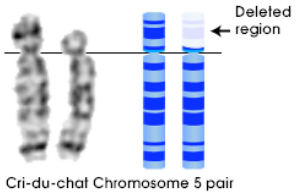
The exception to this rule are genes for which 1/2 the RNA or protein is NOT SUFFICIENT to perform the gene's function -- this is called HAPLOINSUFFICIENCY.

An example of a human disease caused by a deletion -- Cri du Chat Syndrome

Caused by a heterozygous deletion of part of chromosome #5

Symptoms: mental retardation, small head, facial abnormalities,
infant's cry sounds like the meowing of a cat





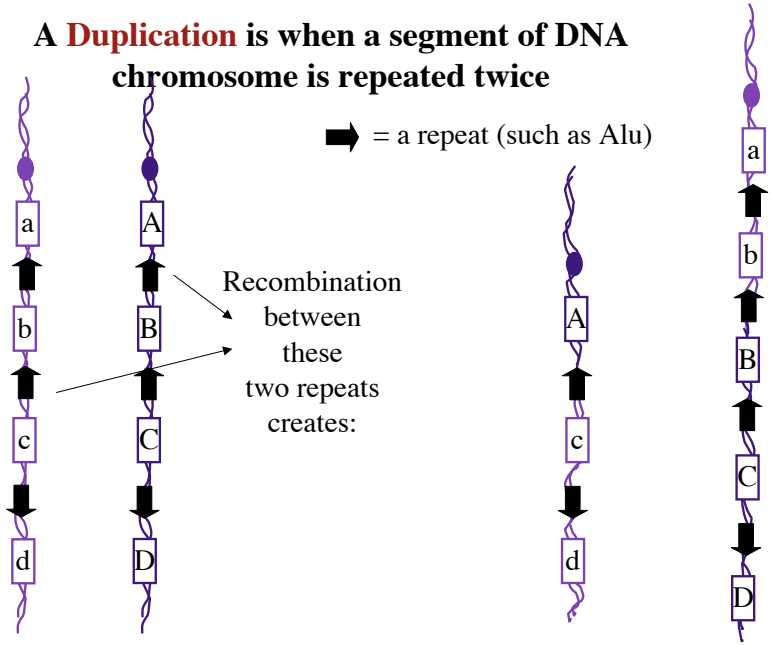
Deletions

Duplications

Inversions

Translocations

A Duplication is when a segment of DNA chromosome is repeated twice



Duplications can have a phenotype

If a duplication causes a phenotype, then it is because too much of a specific gene product is detrimental to the organism.

Thus the phenotype will be dominant, and will be visible in a heterozygote.

An example of a human disease caused by a duplication -- Charcot Marie Tooth syndrome

Often caused by the heterozygous duplication of a gene on chrom#17

This duplication increases the amount of the PMP22 myelin protein, which coats nerve cells

Symptoms: Muscle degeneration (problems with walking and grasping), tingling sensations, sensory loss, loss of reflexes

Incidence: 1/2,500-1/10,000

Is the most common form of neuropathy

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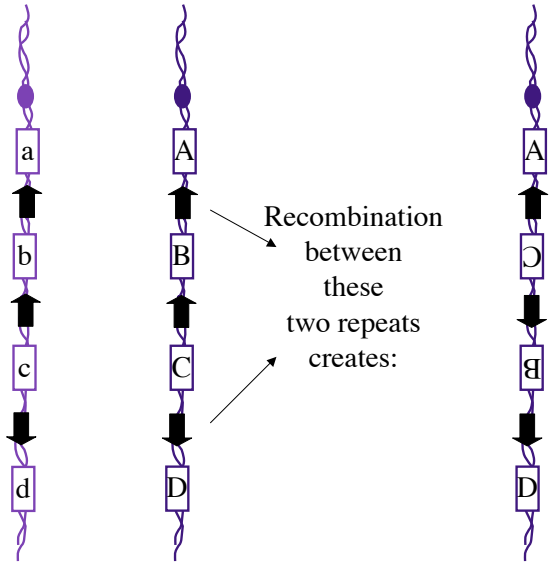
An Inversion Reverses the Order of Genes



Heterozygotes (inverted chromosome/normal) have genetic consequences

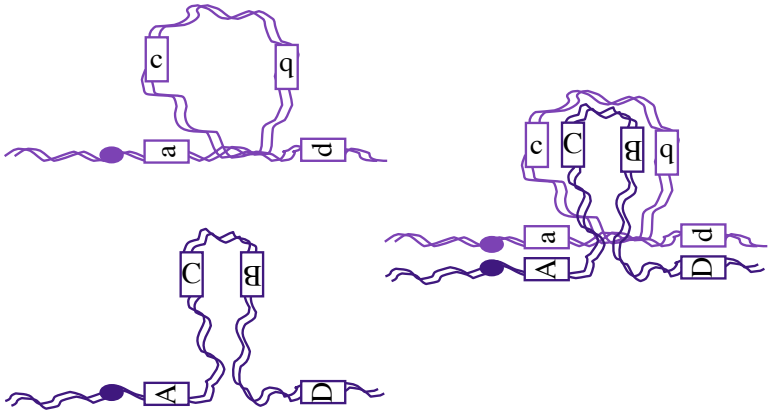
-- they suppress recombination

-- they produce inviable gametes

An inversion produces 1/2 inviable gametes if the inversion does not include the centromere

An inversion produces gametes with deletions or duplications if the inversion includes centromere

Chromosome Pairing in an Inversion heterozygote during meiosis I



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An example of a human disease caused by an inversion -- Severe Hemophilia A

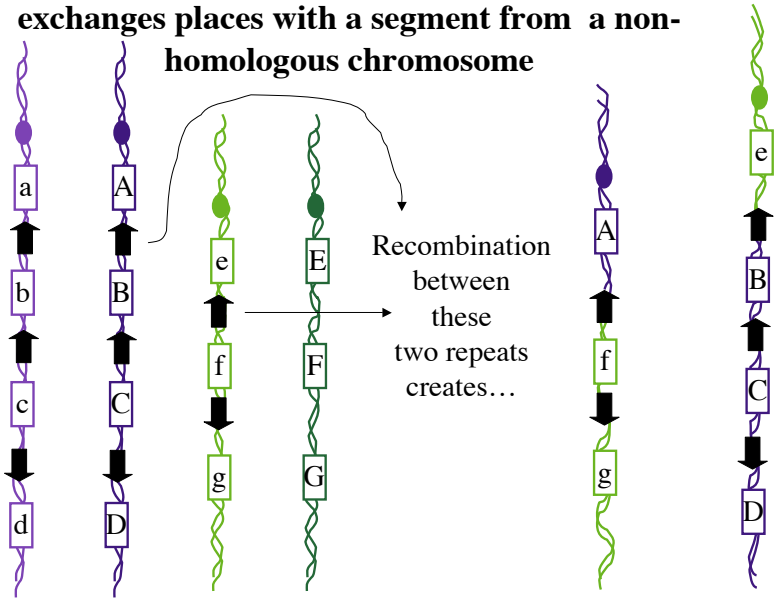
50% of the time is caused by an inversion on the X chromosome

This inversion destroys the function of a gene encoding the blood protein Factor VIII

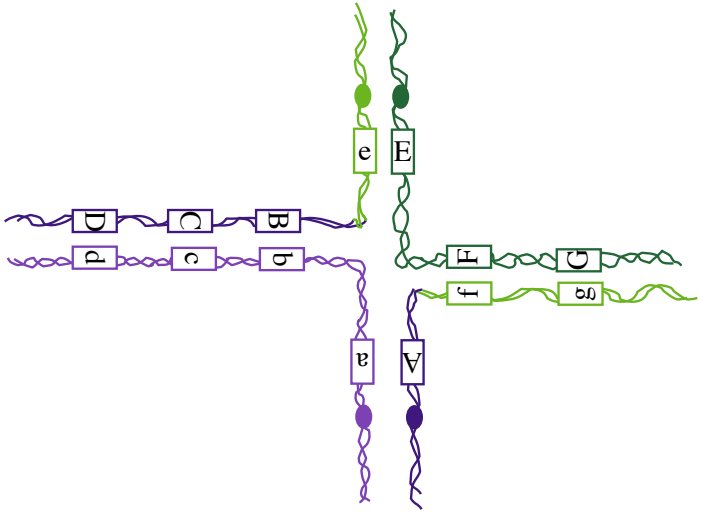
Symptoms: Bleeding and bruising

The same inversion accounts for 50% of all cases of severe hemophilia A, which affects a total of 1/10,000 **males**

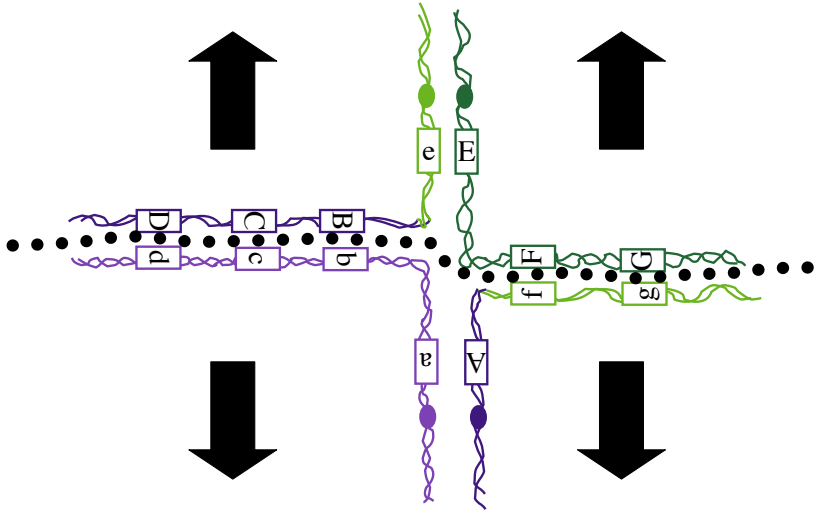
A Translocation is a segment of one chromosome exchanges places with a segment from a non-homologous chromosome



A picture of a translocation heterozygote's chromosomes pairing during meiosis I



If chromosomes segregate like this, inviable gametes will be produced



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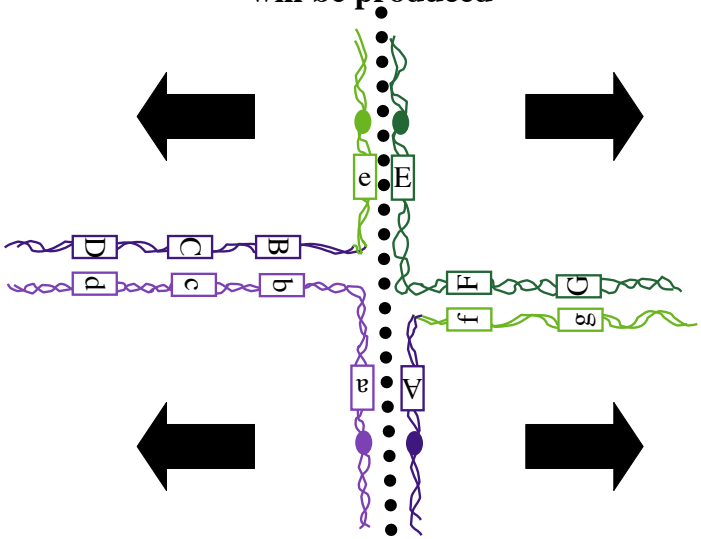
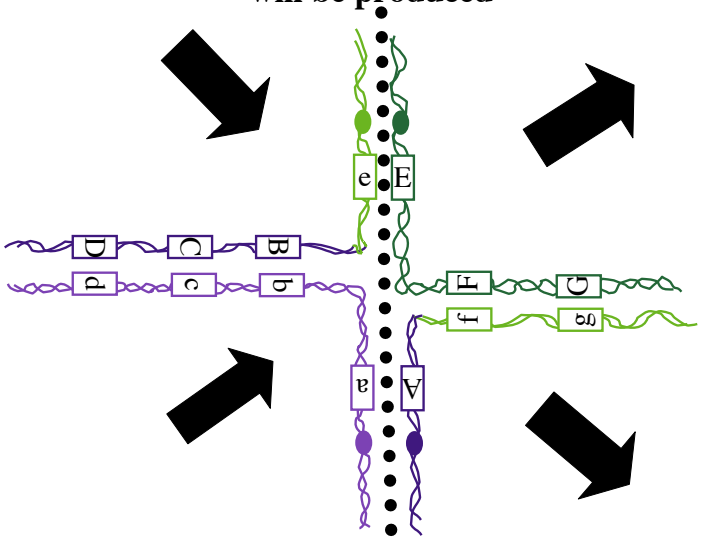


If chromosomes segregate like this, viable progeny will be produced



Translocations have genetic consequences

In a heterozygote with a normal a translocation will:
Lead to some abnormal zygotes that are inviable

In a heterozygote the translocation could:
-- cause the formation of deleterious fusion genes,
OR -- cause the disruption of a gene because of where the breakpoints that caused the translocation were located.

Looking ahead

Chromosome abnormalities can also be caused by non-homologous recombination.

Non-homologous recombination is when pieces of broken DNA join with each other, even though their ends are not homologous.

Non-homologous recombination can be induced by agents that break DNA such as X-rays and chemicals.

An example of a human disease caused by a translocation -- Chronic Myelogenous Leukemia (CML)

CML is a type of cancer that has been in the news a lot in the last five years because it is treatable by a new drug called Gleevec

Caused by a heterozygous translocation between chrom #9 and #22
(called the Philadelphia chromosome)

This translocation causes the fusion of two genes, Bcr and Abl

Incidence is 1/50,000 - 1/100,000
Accounts for 7-20% of all leukemias

We will talk a lot more about the kinds of mutations that lead to cancer at the end of the semester.