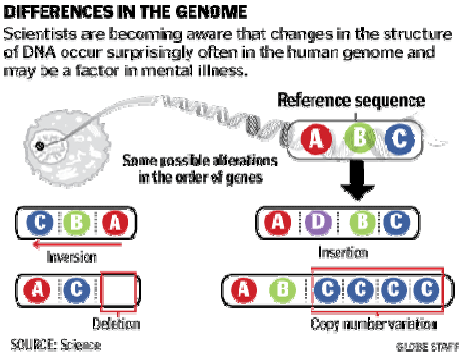
Genetics sheds light on mental illnesses

By Carey Goldberg
Globe Staff / October 14, 2008



Ploidy and Chromosomal Mutations.
1) occur as errors exerting major effects on the recipients **creating metabolic imbalance** or disruptions of "normal" ratio of gene products.
2) changes have occurred during the evolution of species.
3) used to create and modify new crops

Causes:
1) Euploid changes (change in a full set of chromosomes; 3N, 4N, 5N….)
a) diploid gamete if one of the meiotic divisions fails

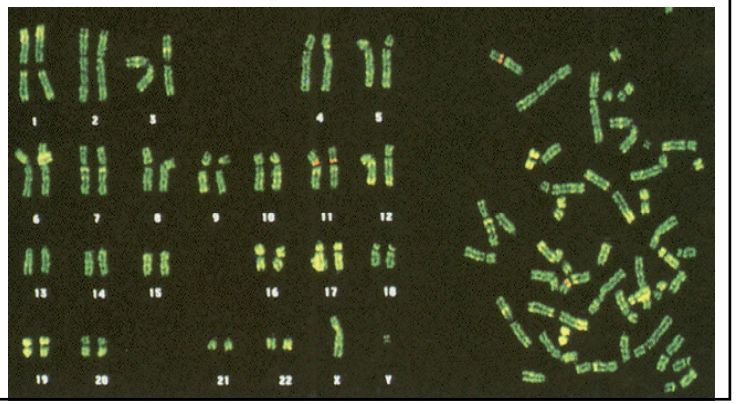
b) somatic doubling if mitotic division fails.

2) Aneuploid changes (addition or loss of single chromosomes; 2N+1, 2N-1)

a) Non-disjunction of one to many chromosomes

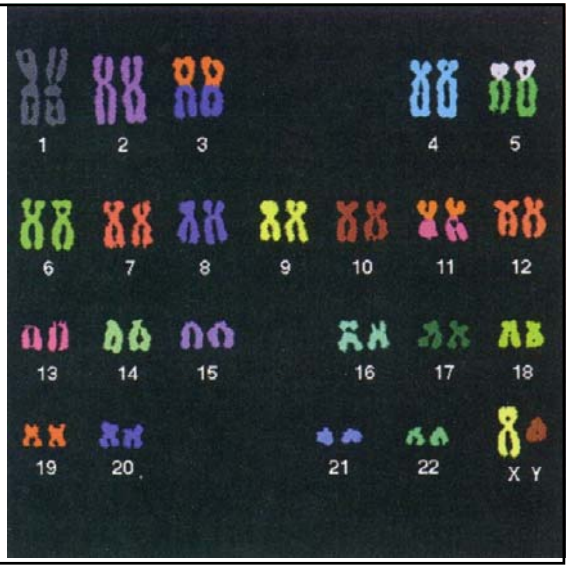
3) Chromosome rearrangements
a) Deletions and Duplications
b) Inversions
c) Translocations

You are familiar with karyotypes; Staining chromosomes to see different regions: **heterochromatic** (tightly wound) and **euchromatic** (loosely wound) regions. This and other techniques can be used to examine genome changes do to mutations, or during evolutionary processes.

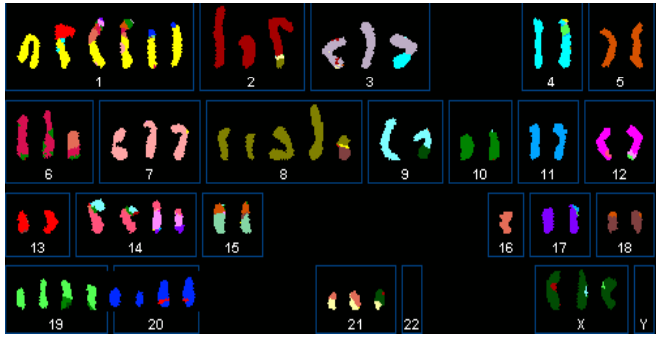


Chromosome Painting:

DNA markers that map to various chromosomes are labeled with a dye and hybridized to chromosomes.



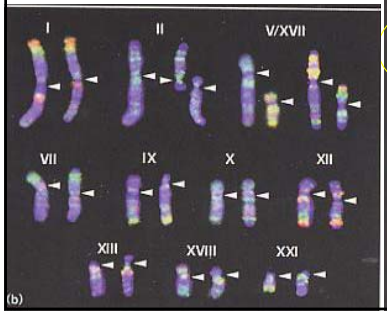
How would you like to be this person??

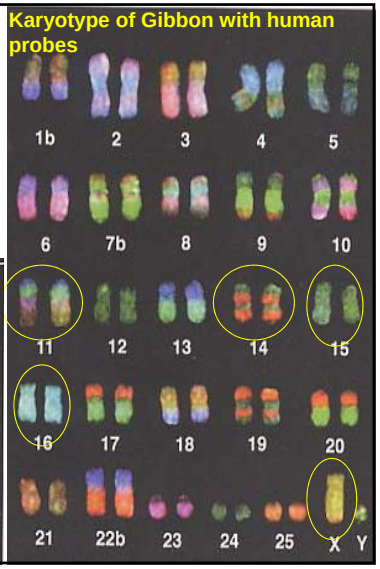


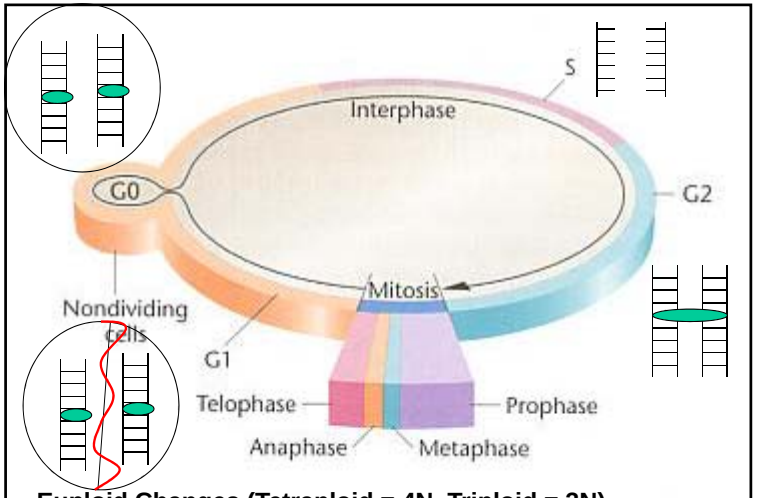
What is going on here????

Chromosome changes during speciation

Chromosome Rearrangements







Euploid Changes (Tetraploid = 4N, Triploid = 3N)

Somatic cell does not divide during mitosis or meiosis.

Do you know of any examples of Euploid changes?

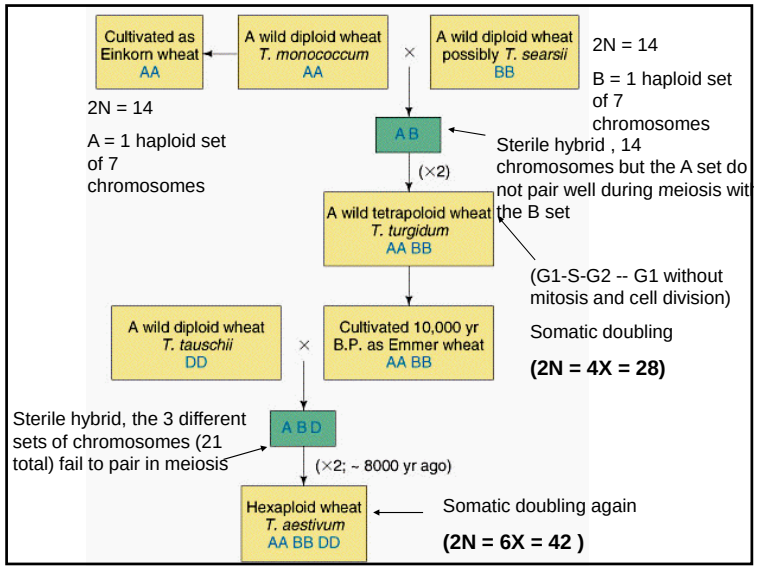
In which species do we see this occurring often?

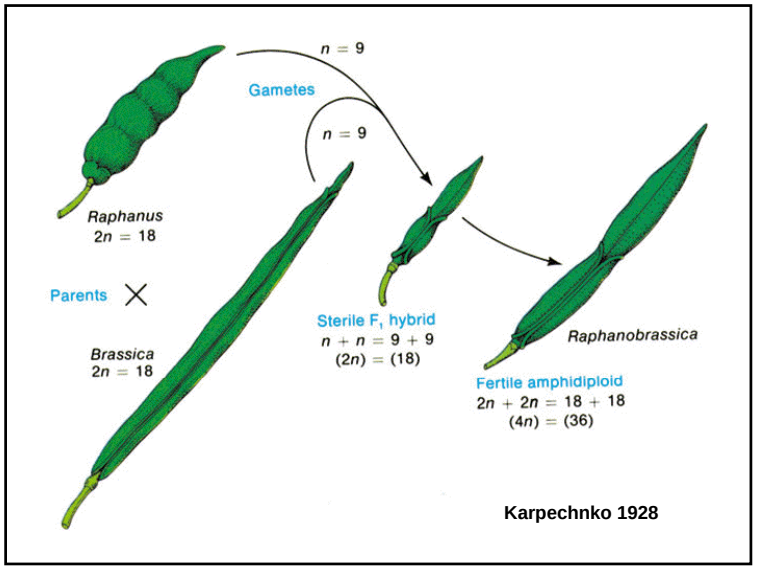
Plants

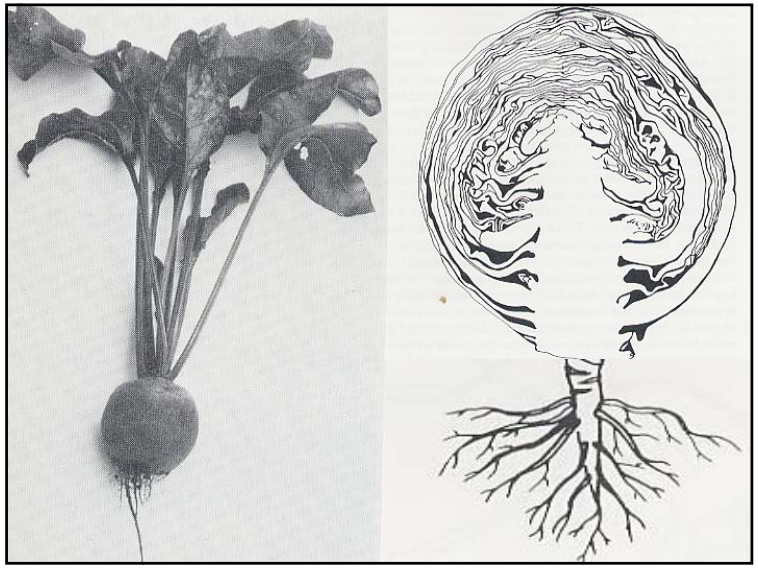
Some fish and amphibians

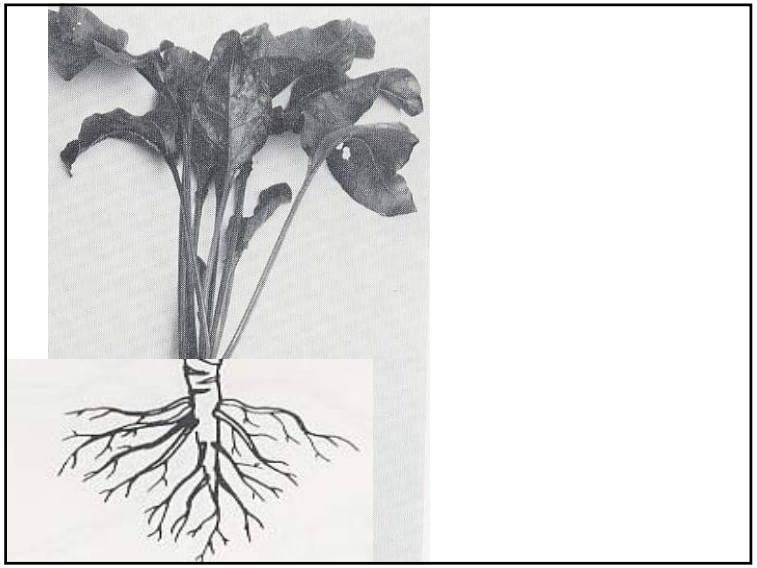
Rarely in mammals

Any explanations??


Cultivated as Einkorn wheat AA
A wild diploid wheat T. monococcum AA
×
A wild diploid wheat possibly T. searsii BB
2N = 14
B = 1 haploid set of 7 chromosomes
2N = 14
A = 1 haploid set of 7 chromosomes
A B
Sterile hybrid , 14 chromosomes but the A set do not pair well during meiosis with the B set
(×2)
A wild tetrapoloid wheat T. turgidum AA BB
(G1-S-G2 -- G1 without mitosis and cell division)
Somatic doubling
(2N = 4X = 28)
A wild diploid wheat T. tauschii DD
×
Cultivated 10,000 yr B.P. as Emmer wheat AA BB
Sterile hybrid, the 3 different sets of chromosomes (21 total) fail to pair in meiosis
A B D
(×2; ~ 8000 yr ago)
Hexaploid wheat T. aestivum AA BB DD
Somatic doubling again
(2N = 6X = 42)


n = 9
Gametes
n = 9
Raphanus
2n = 18
Parents
×
Brassica
2n = 18
Sterile F1 hybrid
n + n = 9 + 9
(2n) = (18)
Raphanobrassica
Fertile amphidiploid
2n + 2n = 18 + 18
(4n) = (36)
Karpechnko 1928





Other Important Agricultural Examples (that worked)

Triticale (X = 7; 2N = 6X = 42)
= **wheat** (tetraploid 4X) high yield and protein
+ **rye** (diploid 2X) high lysine and cold + drought tolerance

Cotton (X = 13; 2N = 4X = 52)

Why are polyploids important in agriculture?

Polyploids are generally bigger (larger fruit).

The previous examples of Eupolyploids all had even sets of chromosome and function as diploids.

What happens if instead of tetraploids (4 sets) or hexaploids (6 sets) you find a triploid (3 sets) or pentaploid (5 sets)?

Banana (3N), Watermelon (3N).

Why are triploids important in agriculture?

Banana = Triploid (3X = 33). **No seeds!!! Why???**

Diploid Banana

2N = 22

Musa x paradisiaca (Musaceae) cultivated (3N) banana is a complex hybrid derived from two diploid Asian species, **M. acuminata** and **M. balbisiana**

In Banana (3N = 33), the N = 11 different chromosomes try to find homologs during meiosis, but there are 3 not 2 of each.

When chromosome separate in anaphase I, sometimes 1 and sometimes 2 go to any given pole.

The result? Gametes can have between 11 and 22 chromosomes!!

These gametes are unbalanced, with unusual chromosomes numbers and genes will not be expressed in a proportional way.

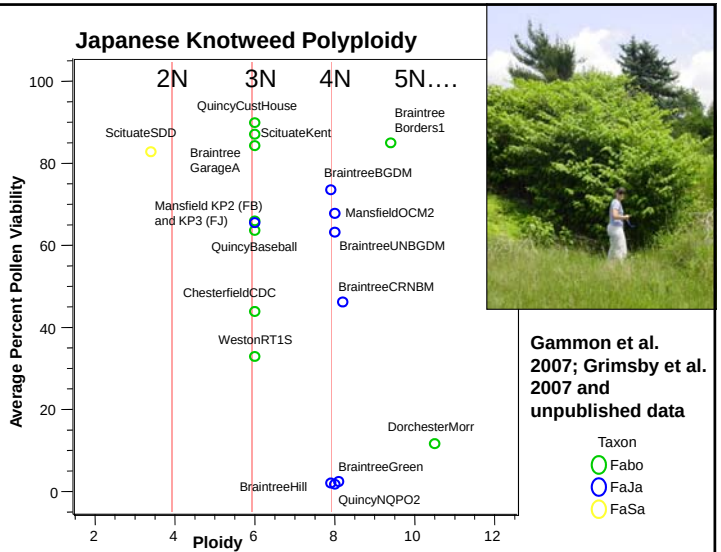
What are your chances of finding a fertile seed?

What is the probability of a banana producing a balanced gamete with N = 11?

2^{11} = 1/2048

What is the probability of having 2 such gametes fuse to make a 2N = 22 fertile diploid seed?

1/2048 x 1/2048 = 1/4,194,304



Gammon et al. 2007; Grimsby et al. 2007 and unpublished data

Many other crops are artificially produced polyploids and probably nearly all plants are naturally occurring recent or ancient polyploids

Why is it so common in plants?

Indeterminant growth and perennial.

Developmentally stable

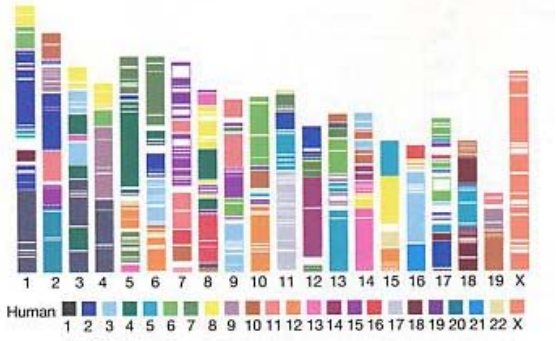
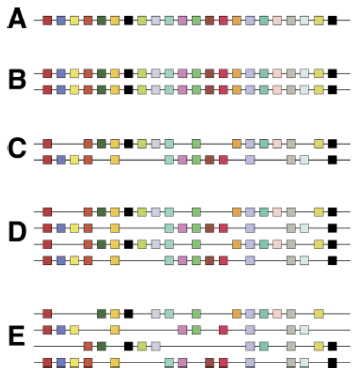


Figure 3 Segments and blocks >300 kb in size with conserved synteny in human are superimposed on the mouse genome. Each colour corresponds to a particular human chromosome. The 342 segments are separated from each other by thin, white lines within the 217 blocks of consistent colour.

Human sequences matched to the 20 chromosomes of mouse

(Mouse genome is 14% smaller; 2.5 vs 2.9 Gb, same no. genes)



Tunicates

Puffer Fish

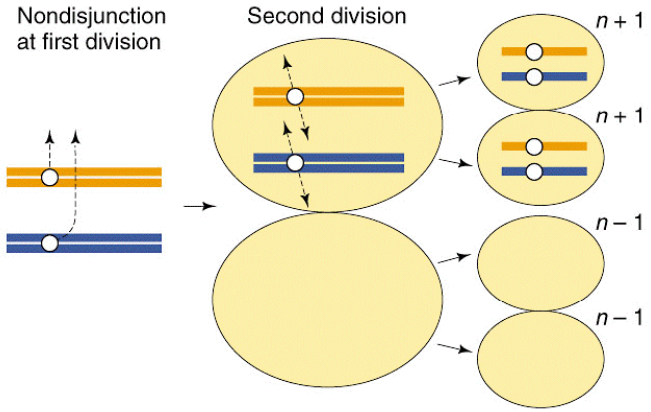
Mammals

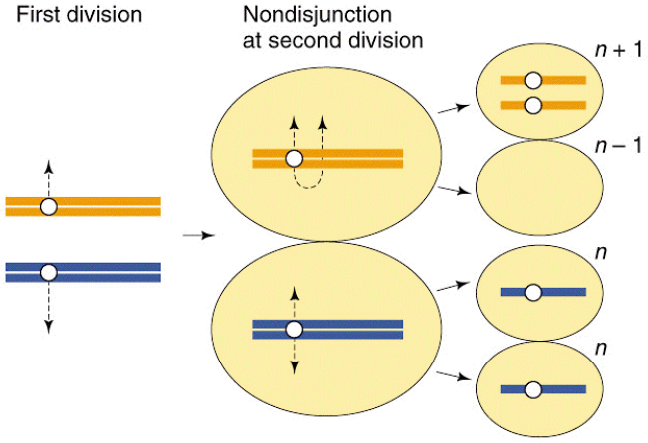
Dehal and Boore 2005

Have Euploid changes occurred in vertebrates?

Evidence now suggests the answer is YES, but the signal is hard to see because of genome streamlining and loss of duplicated copies.

Aneuploidy: How does it occur?

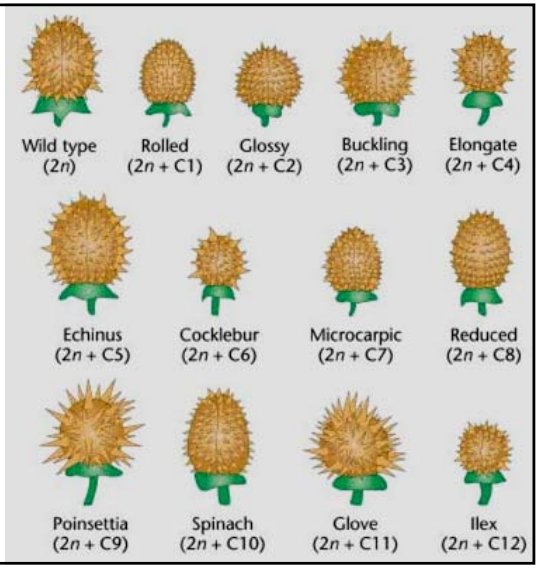




Aneuploid changes: Trisomic (2N+1), Monosomic (2N-1)

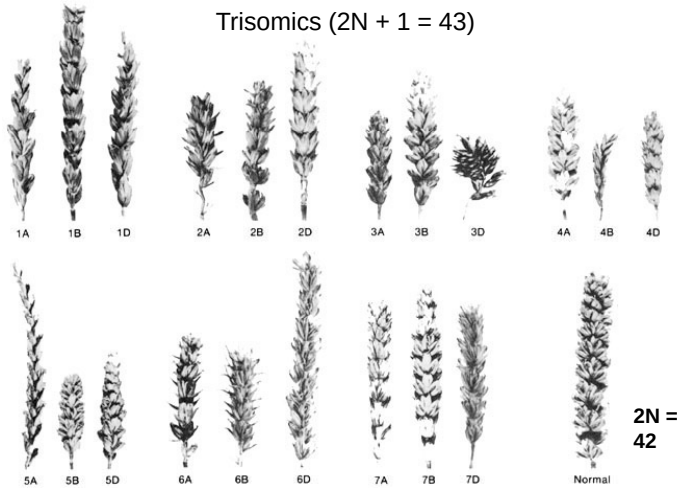
Aneuploidy and the phenotypic effects

Datura (Jimson weed)



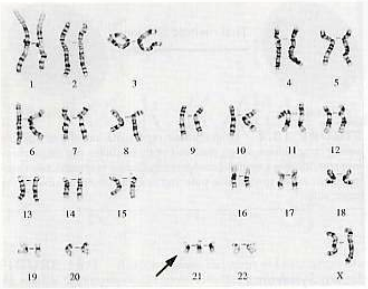
Bread Wheat (6X = 2N = 42)

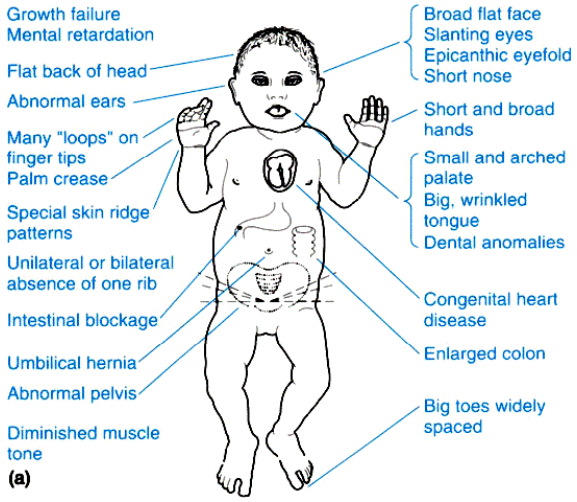
Trisomics (2N + 1 = 43)

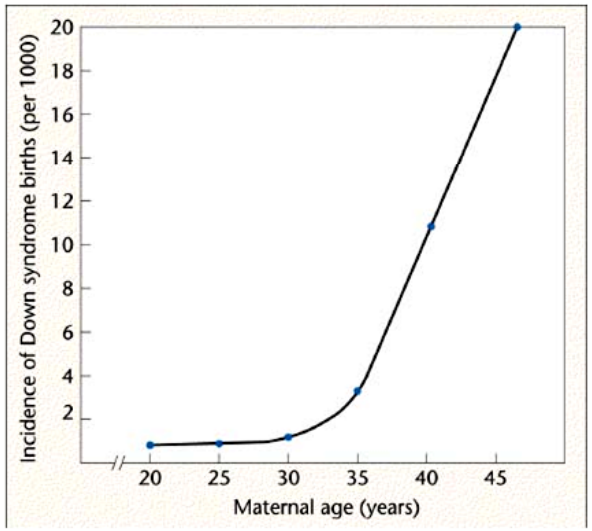


2N = 42

2N (+21) = 47 Down Syndrome







Why don't we see other trisomics in humans?

What about monosomics?

Why do we see so many aneuploids involving sex chromosomes?

Patau

Edwards

	100,000 Pregnancies	
	15,000 spontaneous abortions 7,500 chromosomally abnormal	85,000 live births 550 chromosomally abnormal
Trisomy		
1	0	0
2	159	0
3	53	0
4	95	0
5	0	0
6–12	561	0
13	128	17
14	275	0
15	318	0
16	1229	0
17	10	0
18	223	13
19–20	52	0
21	350	113
22	424	0
Sex chromosomes		
XYY	4	46
XXY	4	44
XO	1350	8
XXX	21	44
Translocations		
Balanced	14	164
Unbalanced	225	52
Polyploid		
Triploid	1275	0
Tetraploid	450	0
Other (mosaics, etc.)	280	49
Total	7500	550

Males have one Y, females have none (essentially nullisomic for Y).

Why don't females need a Y? How can XYY be balanced? Few genes on the Y chromosome explains why females don't need this chromosome and why trisomy XYY is more or less unaffected (0.01%).

Duplication of few genes on the Y creates little physiological imbalance.

We (males) have a bigger problem. How can males survive with only one X (monosomic for X)?**.**

Since even small deletions and duplications are often lethal, why do we see variable numbers of X chromosomes 164 mbp carrying about 1000 (992-1465) genes in mammals?

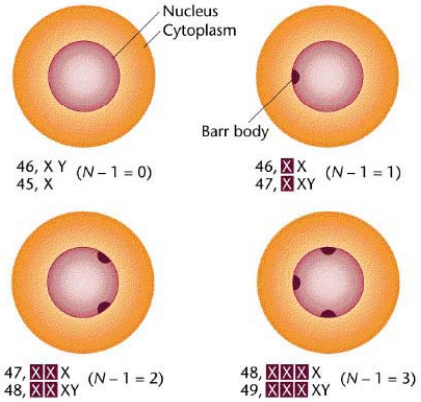
Why do individuals with Turner syndrome (XO) survive?

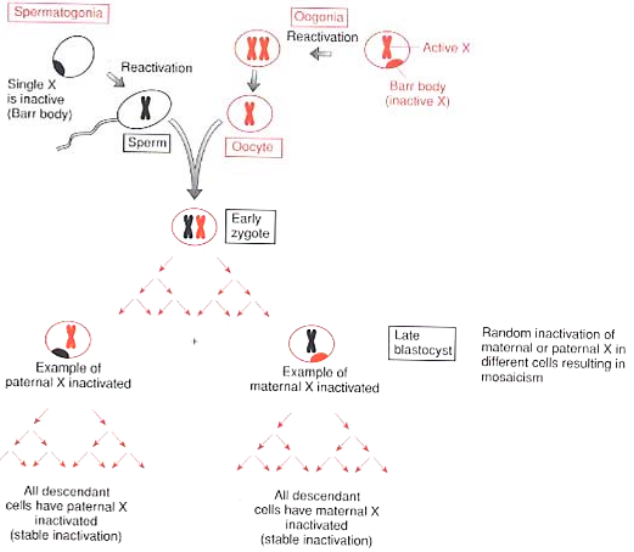
Why are females trisomic for XXX more of less normal?

Is there some form of **DOSAGE COMPENSATION** system?

Barr and Bertram 1949

Mary Lyon 1961 and Theory of X inactivation



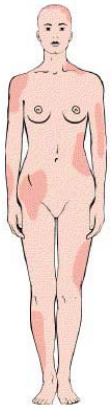


What is the phenotypic effect of this X inactivation?

Females are mosaics!!!

Timing of X inactivation and the presence of additional pigmentation genes (white patches) give different patterns.

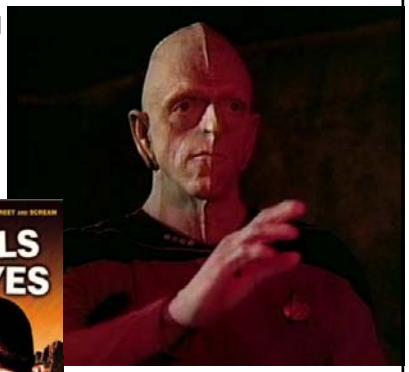
How about human females?



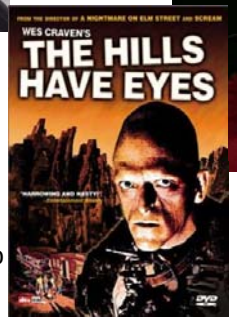
Anhidrotic ectodermal dysplasia (lack of sweat glands)

Male phenotype is more severe, sparse hair, poor or missing teeth and no sweat glands.

Actor Michael Berryman



Captain Rixx – Star Trek TNG



Pluto

What do you think happens for other genes on the X that we have discussed such as color blind, or hemophilia??

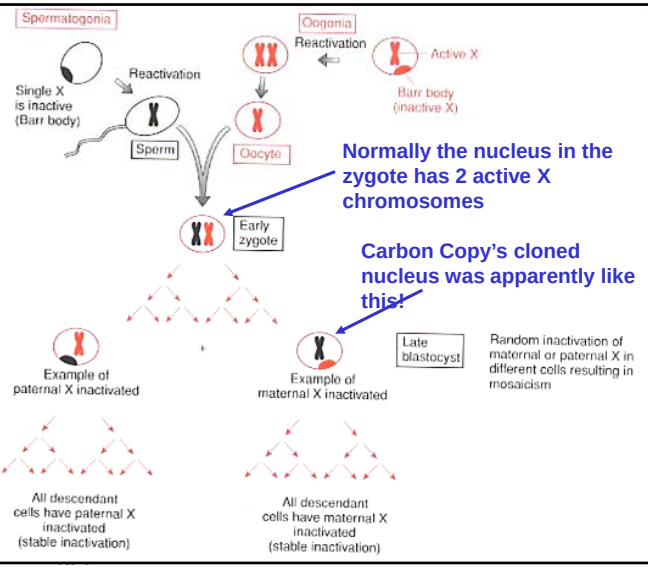
Heterozygous females (for Hemophilia or color blindness for example) will be mosaic for these as well.

Some patches of cells that eventually give rise to the bone marrow will not be able to make the clotting factor…but others will and that will be sufficient to avoid the disease.

Some patches in the eyes may carry the active X with the color blind allele but others will carry the normal allele to allow color detection.

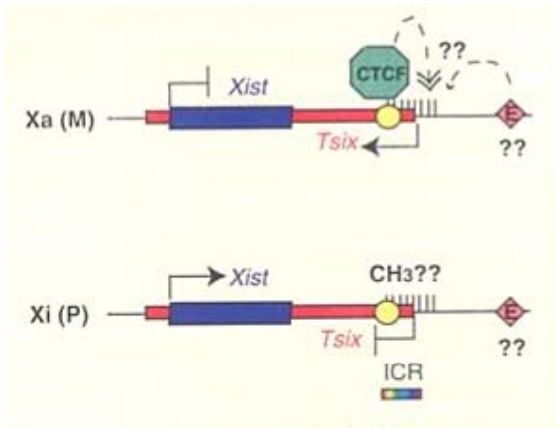
Rainbow and CarbonCopy:

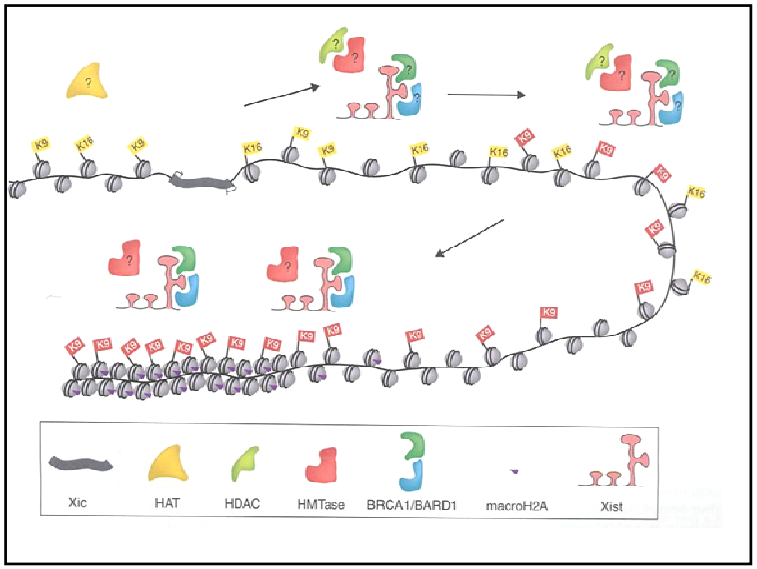
CarbonCopy does not appear to be calico!!!! Why??



What is the molecular basis of the Dosage Compensation system in mammals?

1) An entire X chromosome in females is inactivated
2) A gene **X**-**i**nactivation **s**pecific **t**ranscript (XIST) is expressed on one (random) of the two Xs in females.
3) The **RNA transcript** of this gene "coats" its own X and affects condensation of the chromosome; it becomes heterochromatic.





Trisomics occur and survive to adulthood in humans.

A) Never

B) Yes but 3N = 69 is unbalanced and causes major developmental problems

C) Yes but only for 2N = 47(+21)

D) Yes but only for 2N = 47 (+X)

E) Yes but none of the above is correct.

Trisomics occur and survive to adulthood in humans.

A) Never

B) Yes but 3N = 69 is unbalanced and causes major developmental problems

C) Yes but Down syndrome is the only example

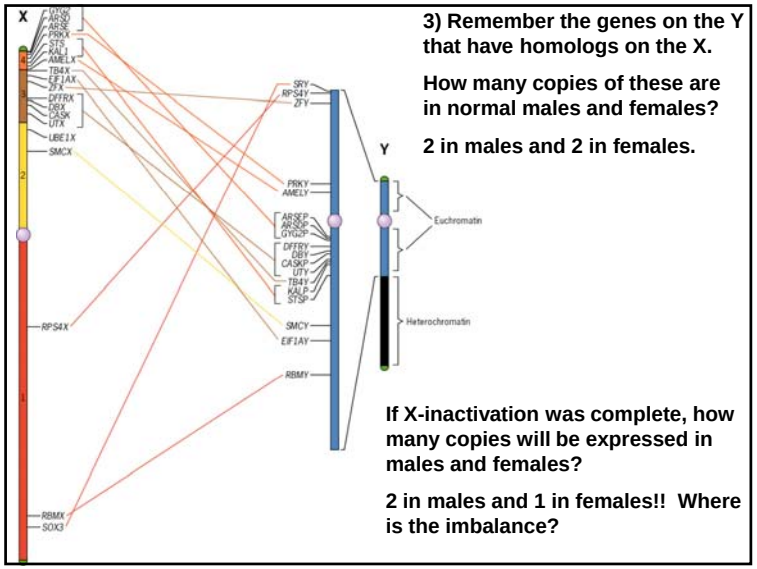
D) Yes but only for 2N = 47 (+X)

E) Yes but none of the above is correct.

If this Dosage Compensation system works well, why do we see loss of fertility and phenotypic effects on XO and XXY individuals?

1) Odd chromosome numbers may disrupt meioses and contribute to loss of fertility.

2) During early embryogenesis, before X-inactivation, how would gene expression in XX, XO and XXY individuals differ?



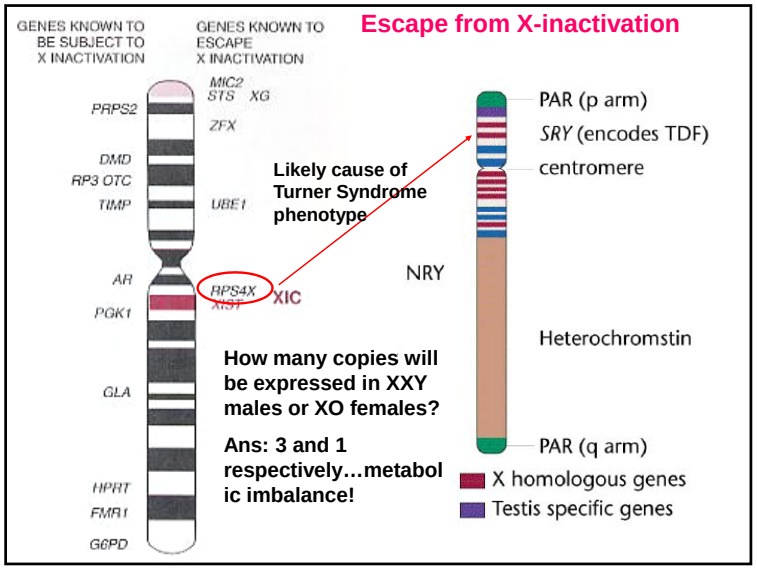
3) Remember the genes on the Y that have homologs on the X.

How many copies of these are in normal males and females?

2 in males and 2 in females.

If X-inactivation was complete, how many copies will be expressed in males and females?

2 in males and 1 in females!! Where is the imbalance?



SUMMARY:

Gain or loss of a chromosome alters the dosage and physiological expression of interacting genes. This has a severe impact in mammals and particularly for autosomes.

For sex chromosomes, the impact is less because of dosage compensation system in mammals, but still present.

Phenotype can vary remarkably for individuals with these aneuploidies from “normal” to large impacts because of the genetic variation among individuals and environmental effects.

Case in point:

XYY phenotype…. Are these people criminals?

Assuming the numbers in the Walzer and Gerald 1974 study were correct, let’s ask where most XYY males are found.

XYY individuals were found in about 2% of the prison population.

The current prison population in US is about 2 million.

Extrapolating, there would be about 40,000 XYY prisoners.

XYY individuals form about 0.1% of the general population.

The current general population in US is about 300 million

Extrapolating, there should be about 300,000 XYY people.

Most of these people (260,000) are NOT in prison!

What about dosage compensation in other species with sex chromosomes? Drosophila!!

Drosophila	X *sis a,b,c,* (*sisterless*) A *dpn* (*deadpan*)		*Sxl* *Sex lethal*		*tra* *transformer*		Sex
XX	Counting	→	X:A = 1	→	ON	→ ON →	Female
XY	Counting	→	X:A = 0.5	→	OFF	→ OFF →	Male

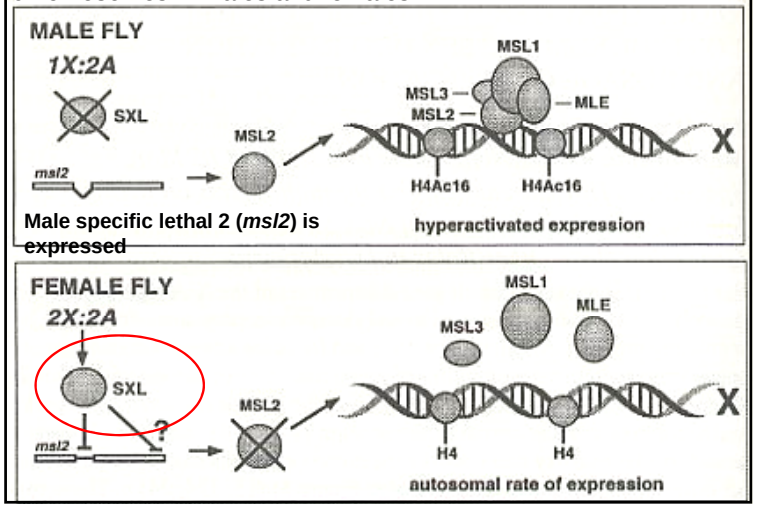
Drosophila	X *sis a,b,c,* (*sisterless*) A *dpn* (*deadpan*)		*Sxl* *Sex lethal*		*tra* *transformer*		Sex
XX	Counting	→	X:A = 1	→	ON	→ ON →	Female
XY	Counting	→	X:A = 0.5	→	OFF	→ OFF →	Male

msl 1,2,3, mle, roX
Male specific lethal, Maleless

OFF

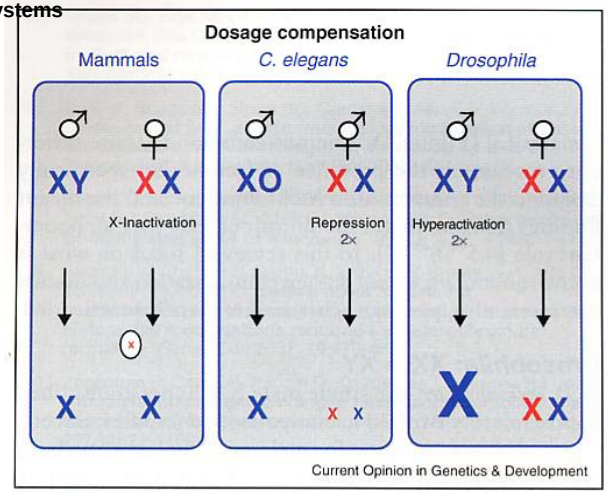
ON (X expression increased)

Step 3: Dosage compensation for the different number of sex chromosomes in males and females.

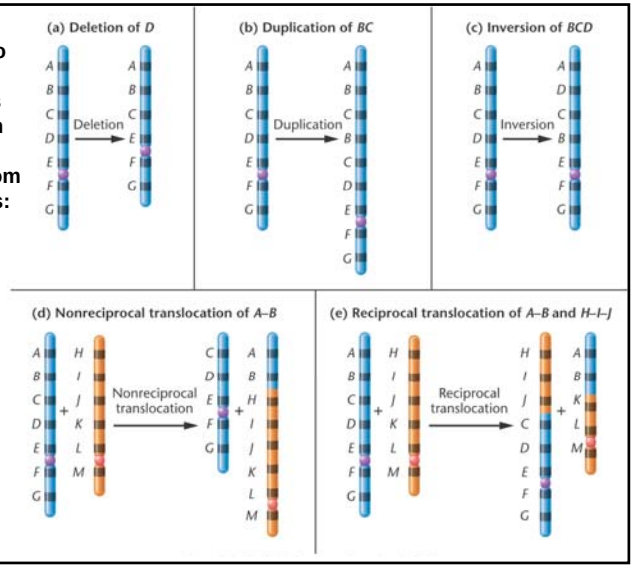


Male specific lethal 2 (*msl2*) is expressed

Dosage Compensation has apparently evolved many different times, possibly whenever there is chromosomal sex determination systems



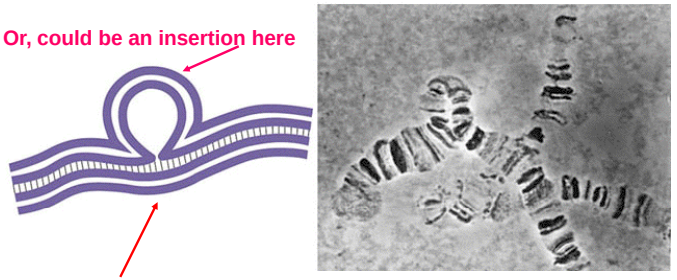
Chromosome mutations other than whole chromosome changes:



Deletions affect pairing of homologs

(a) Meiotic chromosome

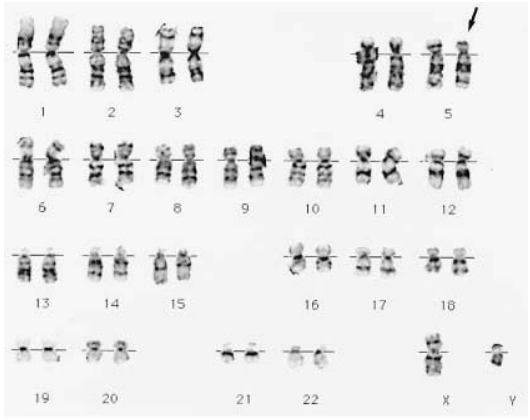
(b) Polytene chromosome



Or, could be an insertion here

Deletion is here

Cri-du-chat

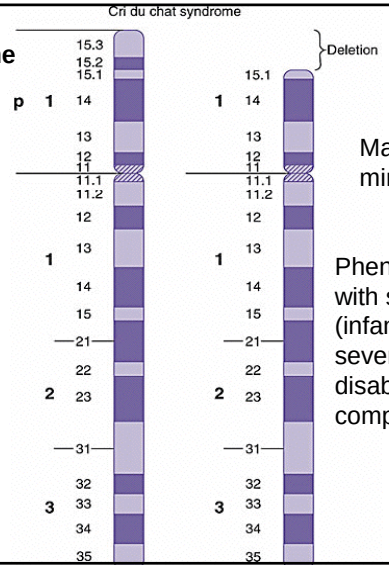


(b)

Credit: Courtesy University of Utah Cytogenetics Laboratory.

Karyotype of infant with *cri-du-chat* syndrome, 46, XY (5p-).

Chromosome 5



Major affect of a minor deletion!!

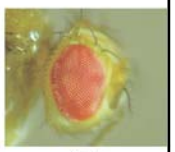
Phenotype varies with size of deletion (infant death to severe learning disabilities and heart complications).

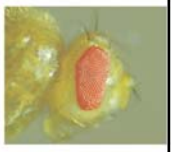
Duplications

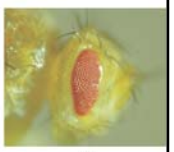
Bar Eyed in Drosophila

(a) Genotypes and Phenotypes

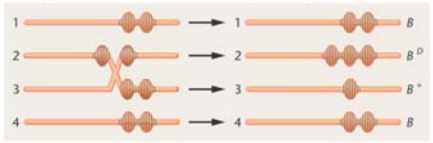
Genotype	Facet Number	Phenotype	= 16A segments
B^+/B^+	779		
B/B^+	358		
B/B	68		
B^D/B^+	45		


B^+/B^+

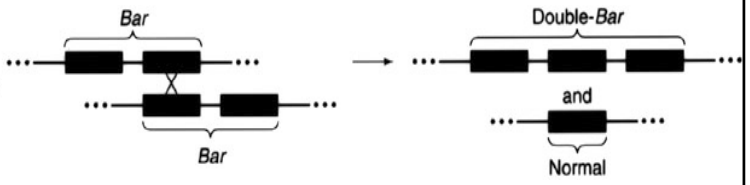

B/B^+


B/B

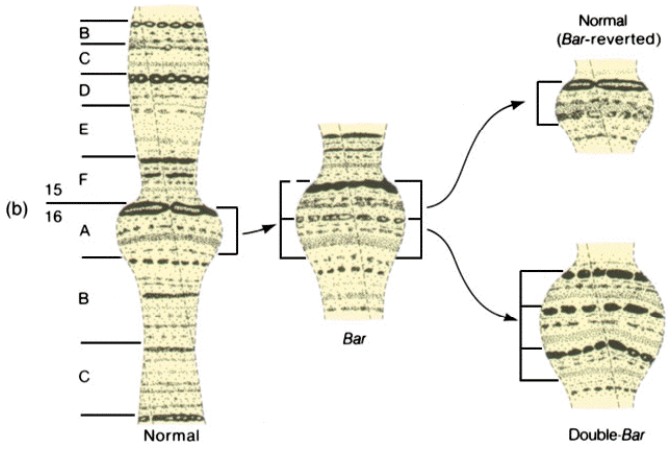
(b) Origin of B^D allele as a result of unequal crossing over



How are duplications and deletions created?



Unequal crossing over produces deletions and duplications!



Most deletions appear deleterious. The bigger the deletion the bigger the effect.

What about duplications? rRNA genes for example!!

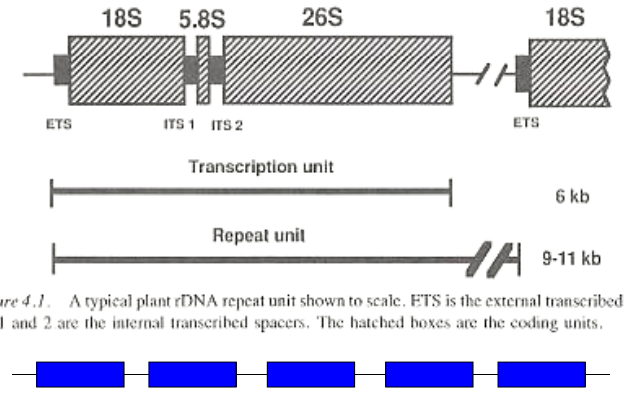
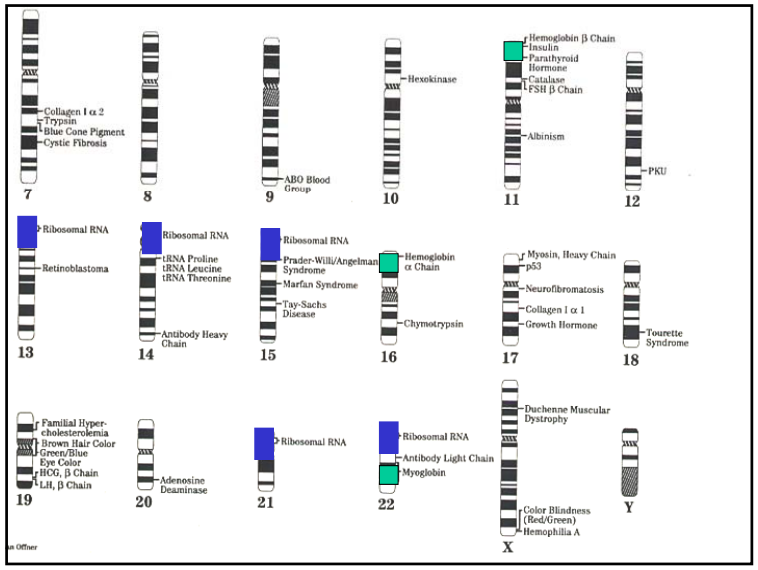


Figure 4.1. A typical plant rDNA repeat unit shown to scale. ETS is the external transcribed spacer, ITS1 and 2 are the internal transcribed spacers. The hatched boxes are the coding units.



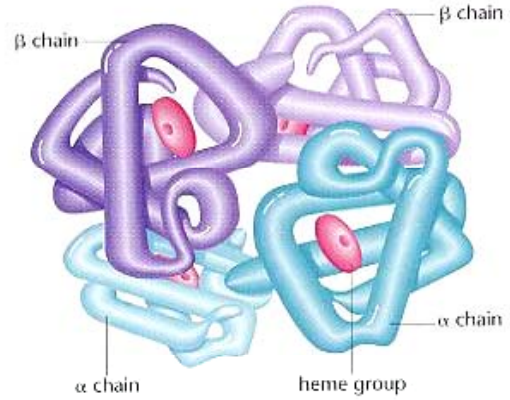
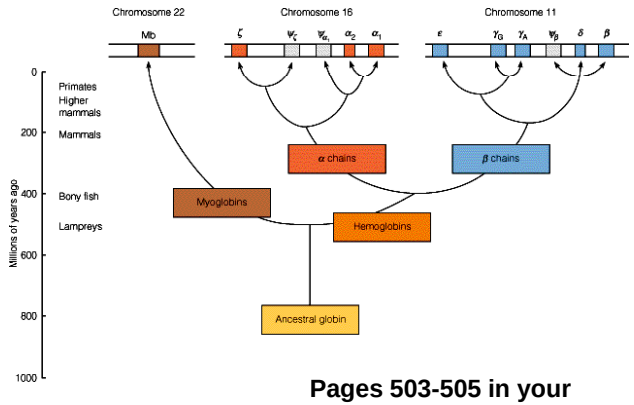
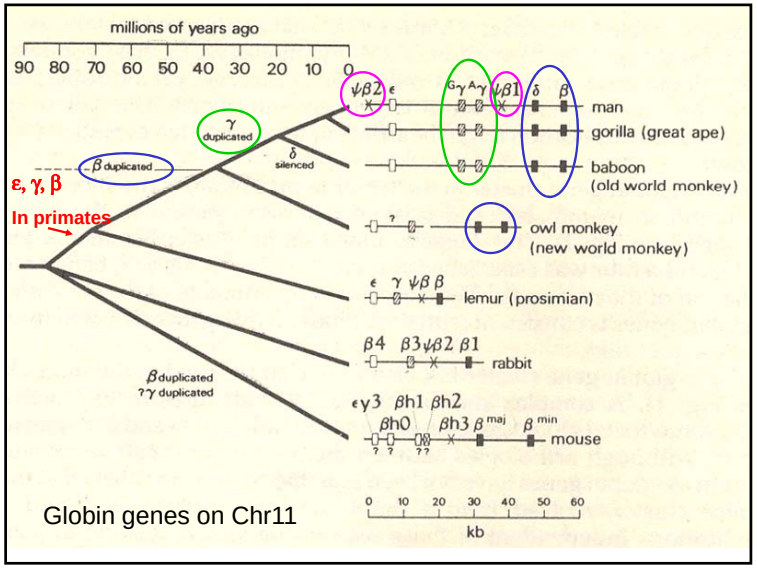


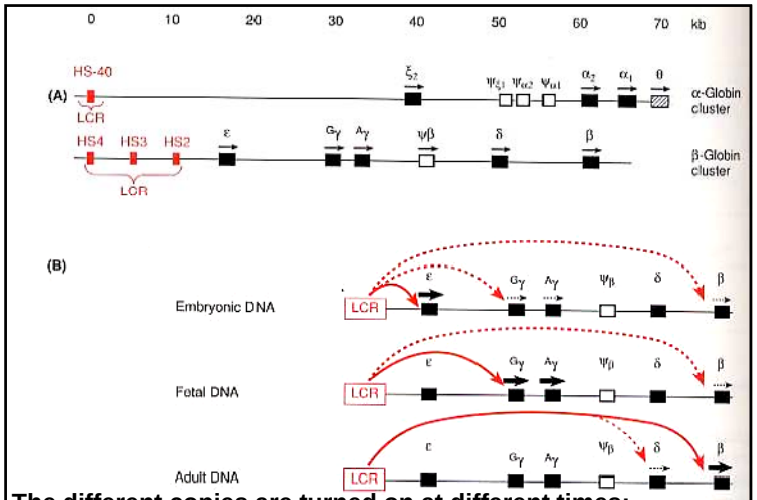
FIGURE 14.20 Schematic drawing illustrating the quaternary level of protein structure as seen in hemoglobin. Four chains (2 α and 2 β) interact with four heme groups to form the functional molecule.



Pages 503-505 in your book

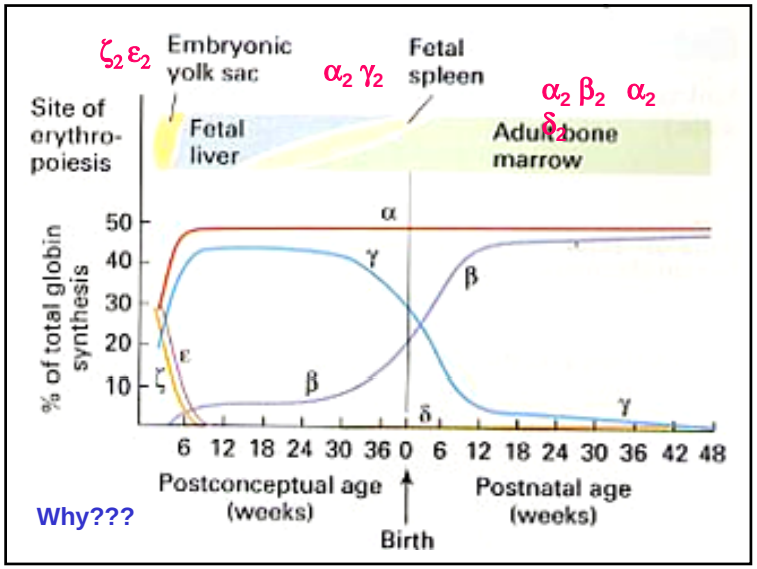


Globin genes on Chr11



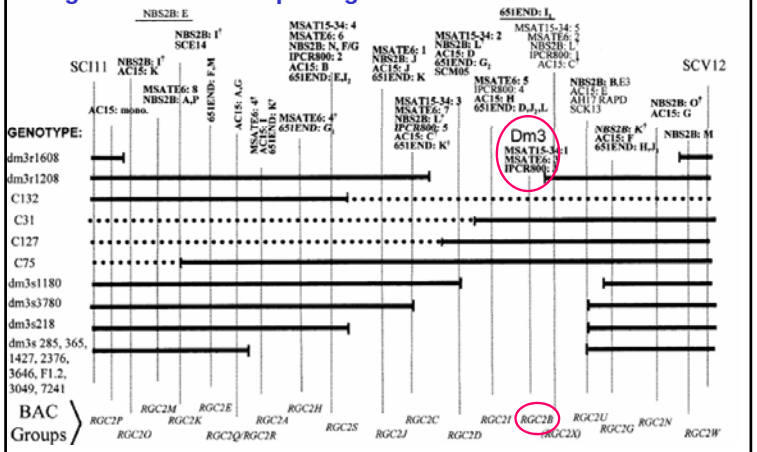
The different copies are turned on at different times;

α cluster on chromosome 16, β cluster on chromosome 11.



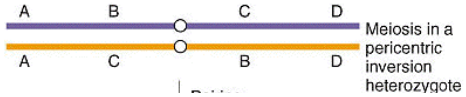
Why???

Duplicated Disease Resistance Genes in Plants; each recognizes a different pathogen.



Chin, Garcia, Ochoa, Kesseli, Lavelle & Michemore

Inversions

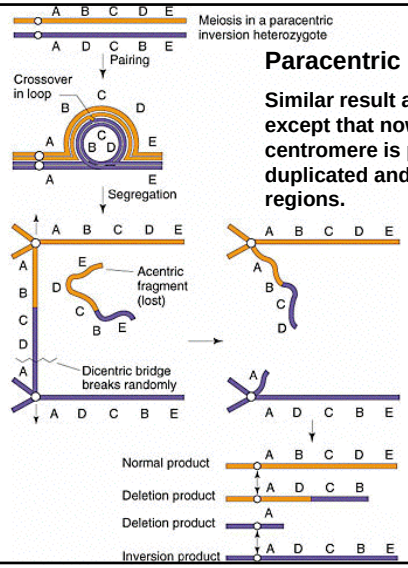


No loss or gain of genes.

What is the phenotypic effect?

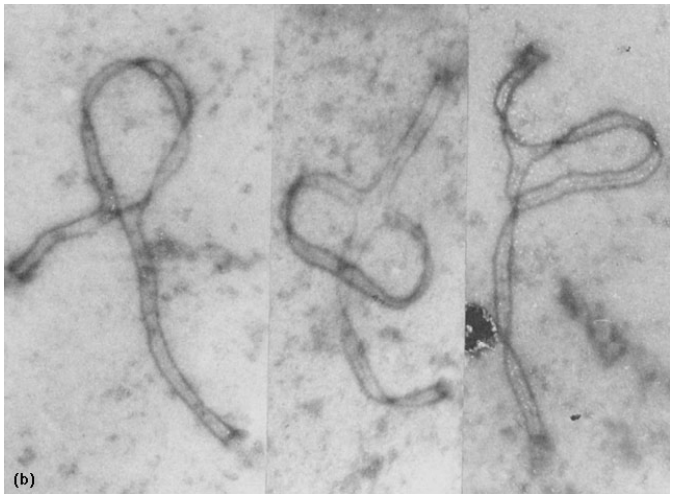
Little!!!

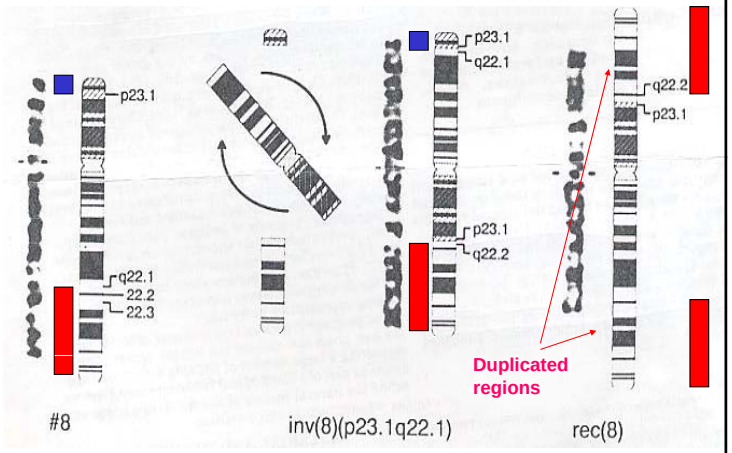
However, problems during meiosis!!



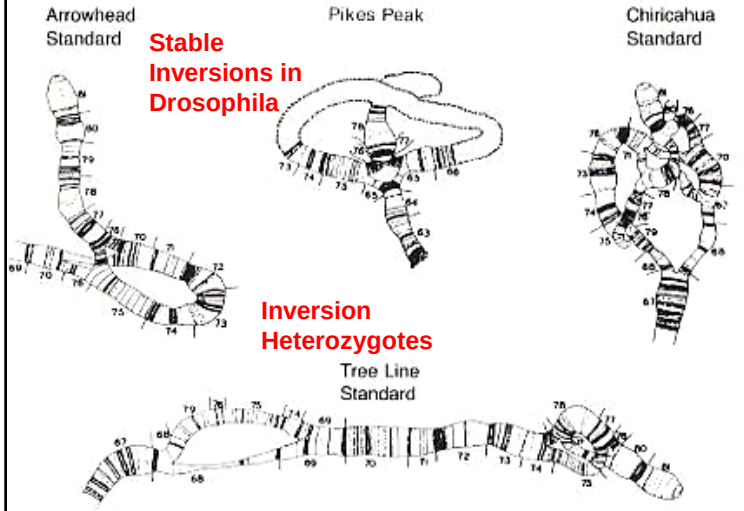
Paracentric Inversions

Similar result as with peri-, except that now the centromere is part of the duplicated and deleted regions.





Inversions in humans: Rec8, "San Luis Valley Syndrome"



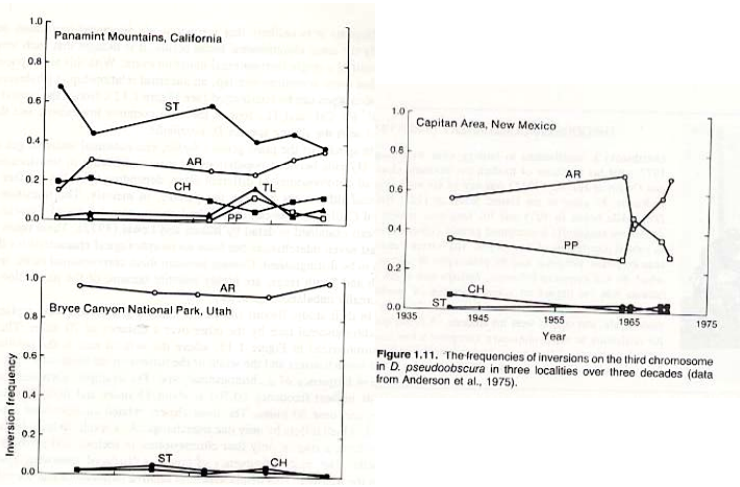
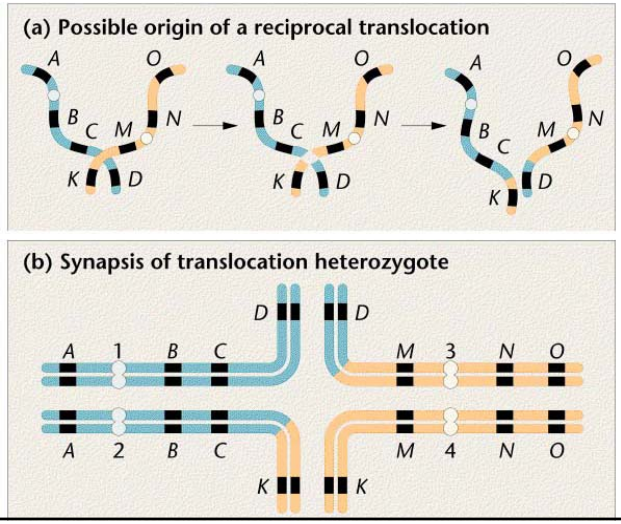
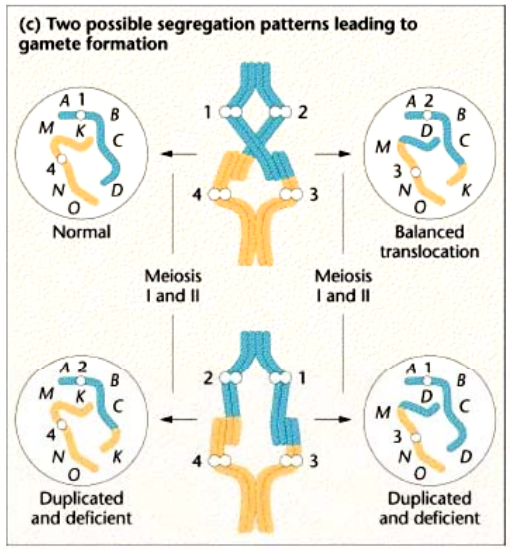


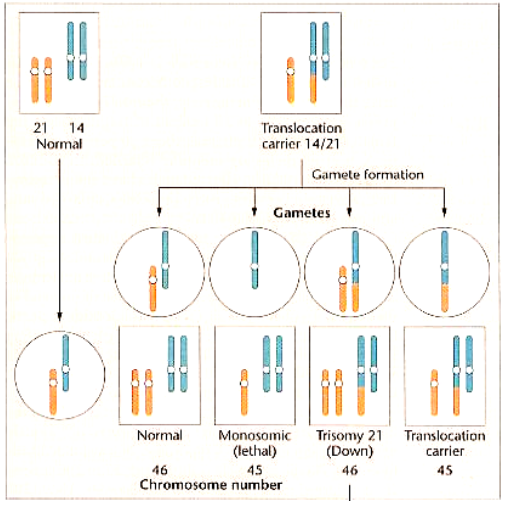
Figure 1.11. The frequencies of inversions on the third chromosome in *D. pseudoobscura* in three localities over three decades (data from Anderson et al., 1975).

Translocations:



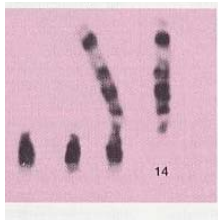


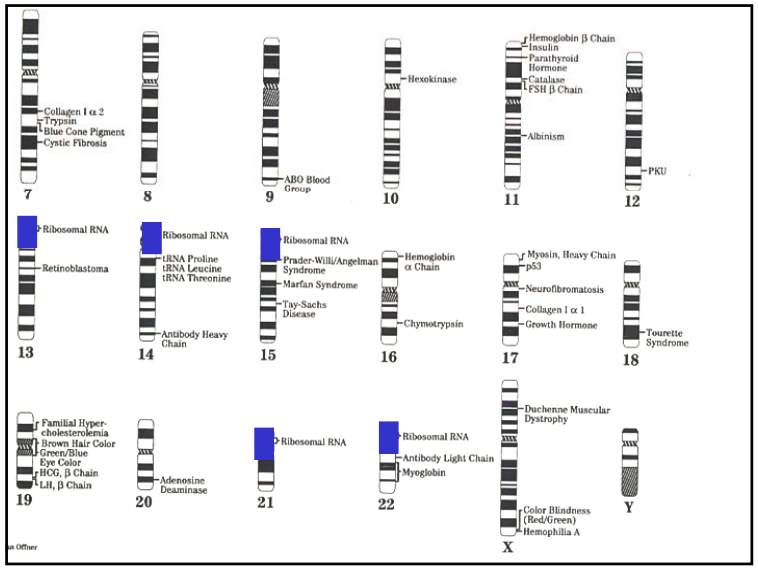
As with inversions, translocations can cause problems during meiosis and yield gametes with duplications and deletions! The next generation may suffer.



Case of Familial (Inherited) Downs

Why do you think there are translocations between Chr14 and Chr21??





One chromosome fusion "translocation" distinguishes human from other primates (chromosome 2 in humans is two different chromosomes in otl

There are 9 pericentric inversions that distinguish us from other primates.

Since recombination is "blocked" in inverted regions, the regions begin to diverge independently (2.2 x faster between humans and chimps) and likely important in speciation.

Assuming that the same small chromosomal fragment is altered for each of the following chromosome mutations below, rank them from largest to smallest impact on the phenotype of their carrier.

A) deletion < duplication < translocation < inversion

B) duplication < deletion < inversion < translocation

C) translocation < duplication < inversion < deletion

D) inversion < translocation < duplication < deletion

E) translocation < deletion < inversion < duplication

Which of these mutations creates the most problems during meiosis?

A) deletions; B) duplications; C) inversions; D) translocations