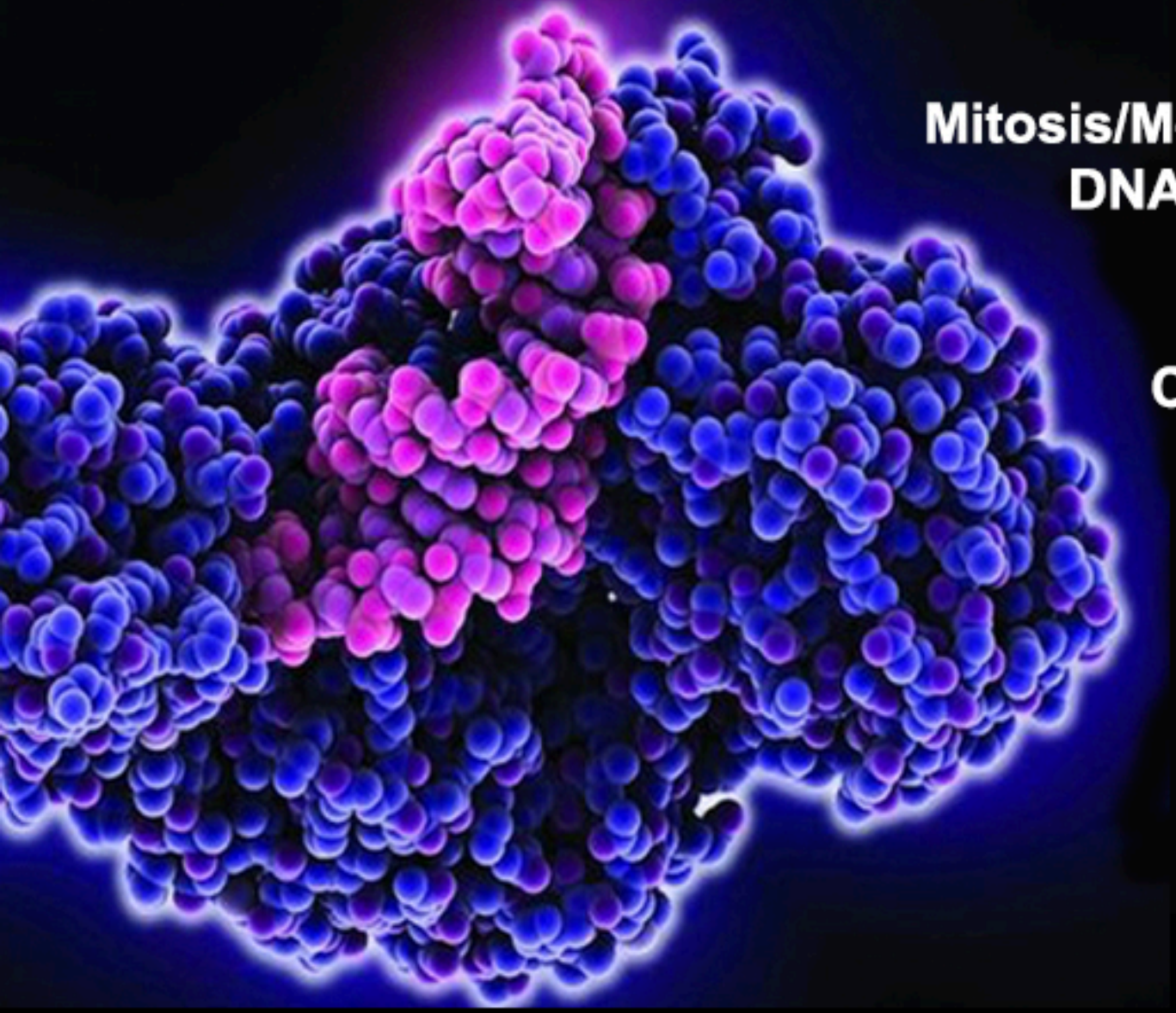
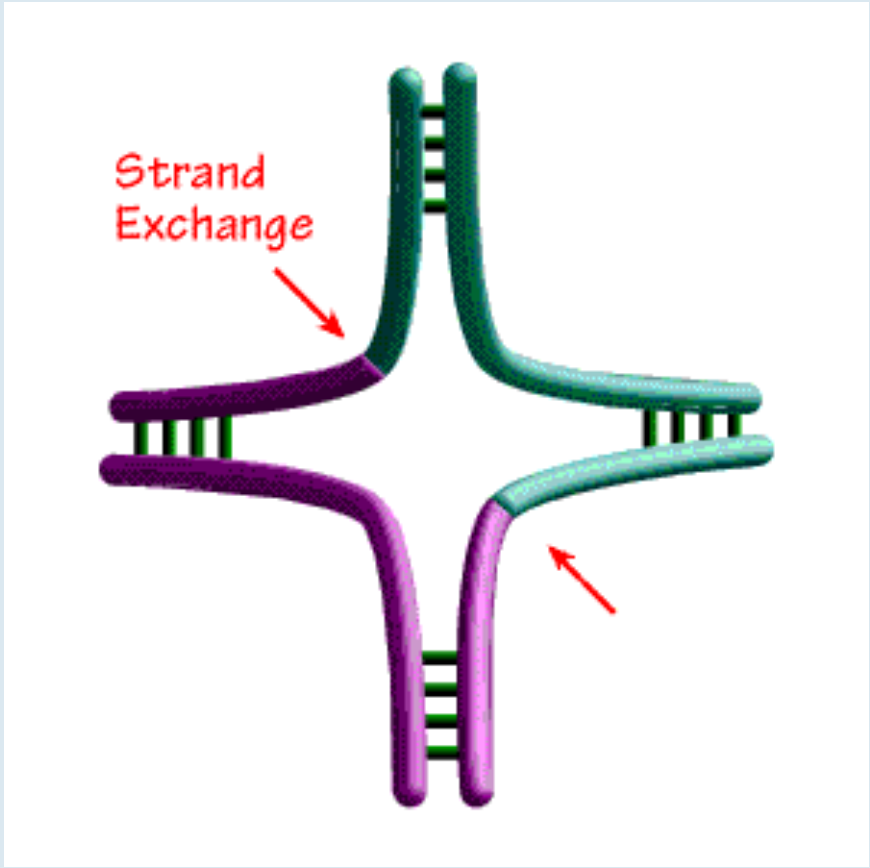
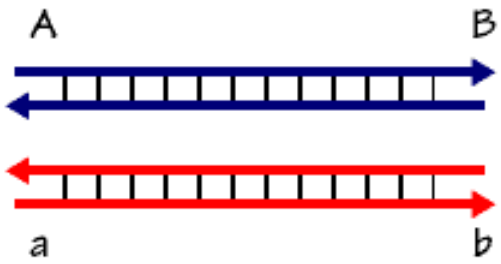
BIOL8620 Eukaryotic Genetics



Mitosis/Meiosis ,
DNA Recombination

Chapter 13 &14


Strand
Exchange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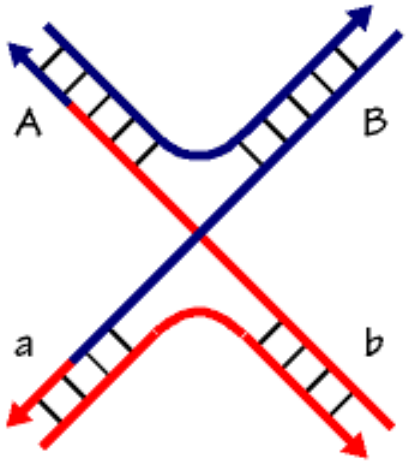
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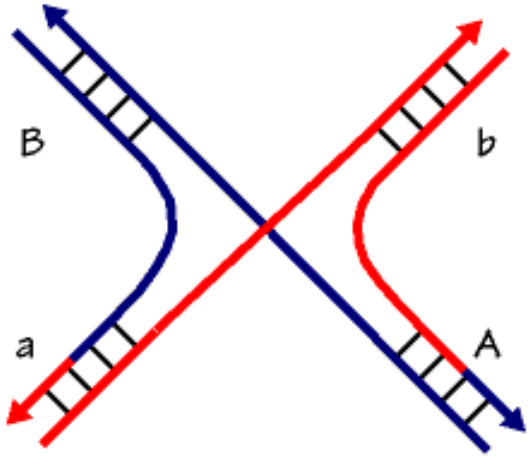
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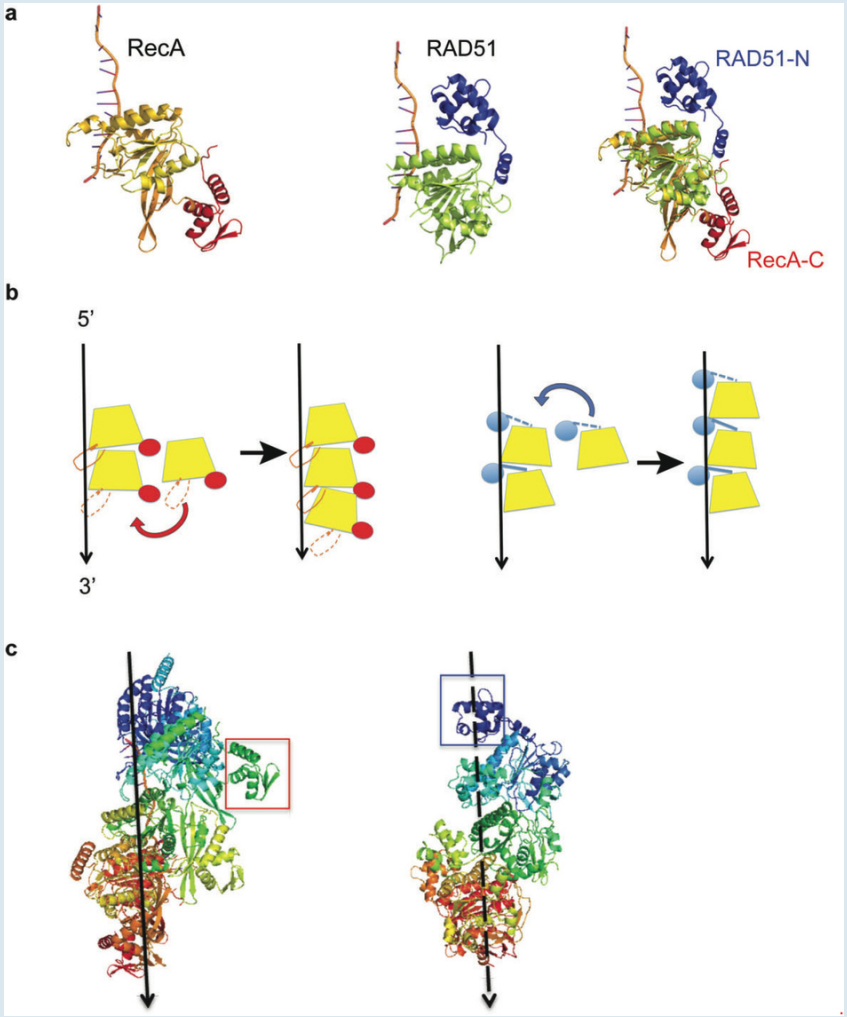
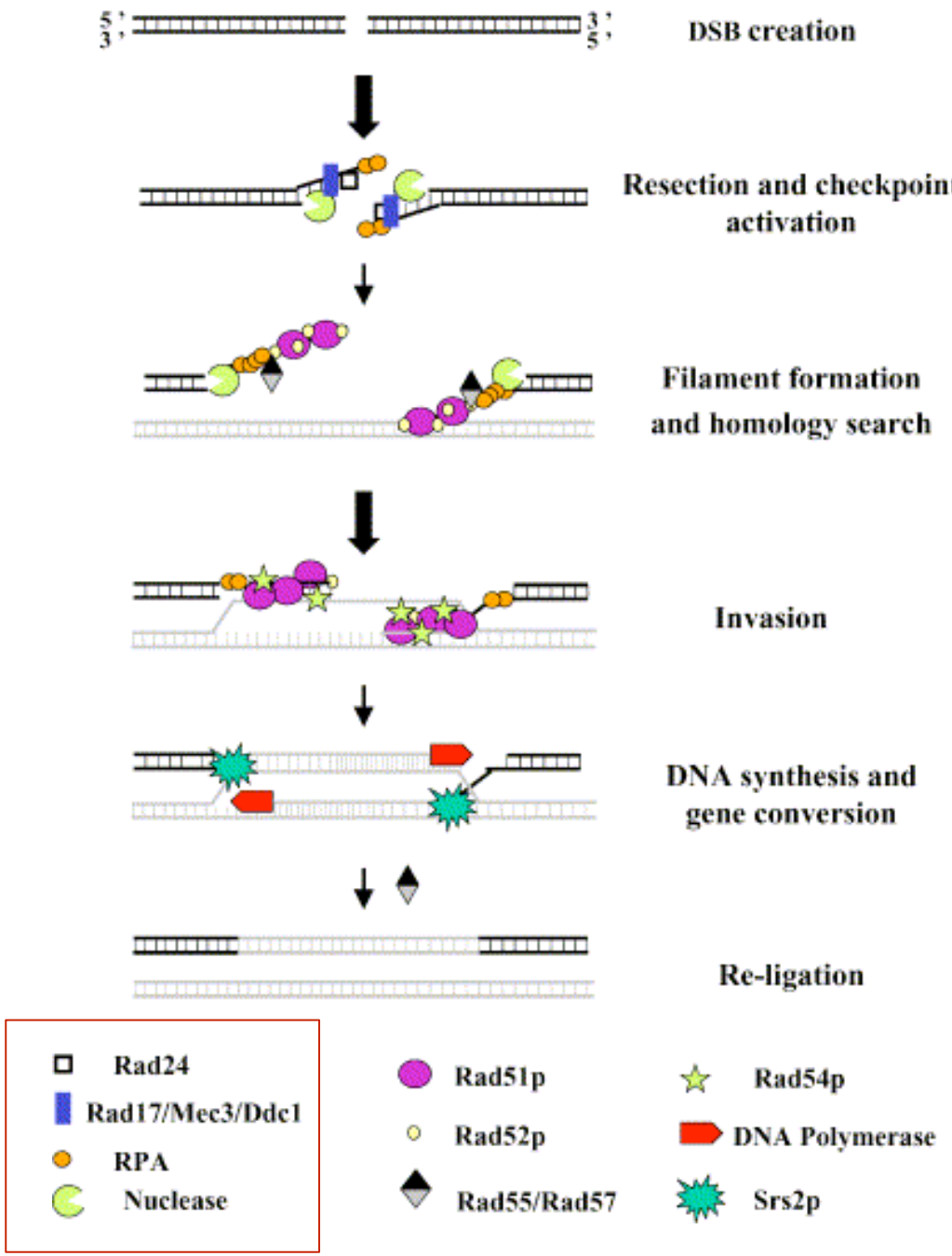


(a) In addition to the conserved ATPase core domain, RecA and RAD51 have distinct additional domains positioned on opposite sides of the ATPase core relative to ssDNA.
(b) Schematic diagram of how RecA (yellow and red) and RAD51 (yellow and blue) subunits may be added to the growing filament.
(c) RecA-ssDNA filament as observed in the crystal structure and RAD51 filament modelled onto the RecA filament. The unique domains are boxed.

Structure and mechanism of action of the BRCA2 breast cancer tumor suppressor
• **Taha Shahid, Joanna Soroka, Eric H Kong, Laurent Malivert, Michael J McIlwraith, Tillmann Pape, Stephen C West & Xiaodong Zhang**
Nature Structural & Molecular Biology **21**, 962–968 (2014)



The ssDNA created is covered by **RPA (the eukaryotic version of SSB).**

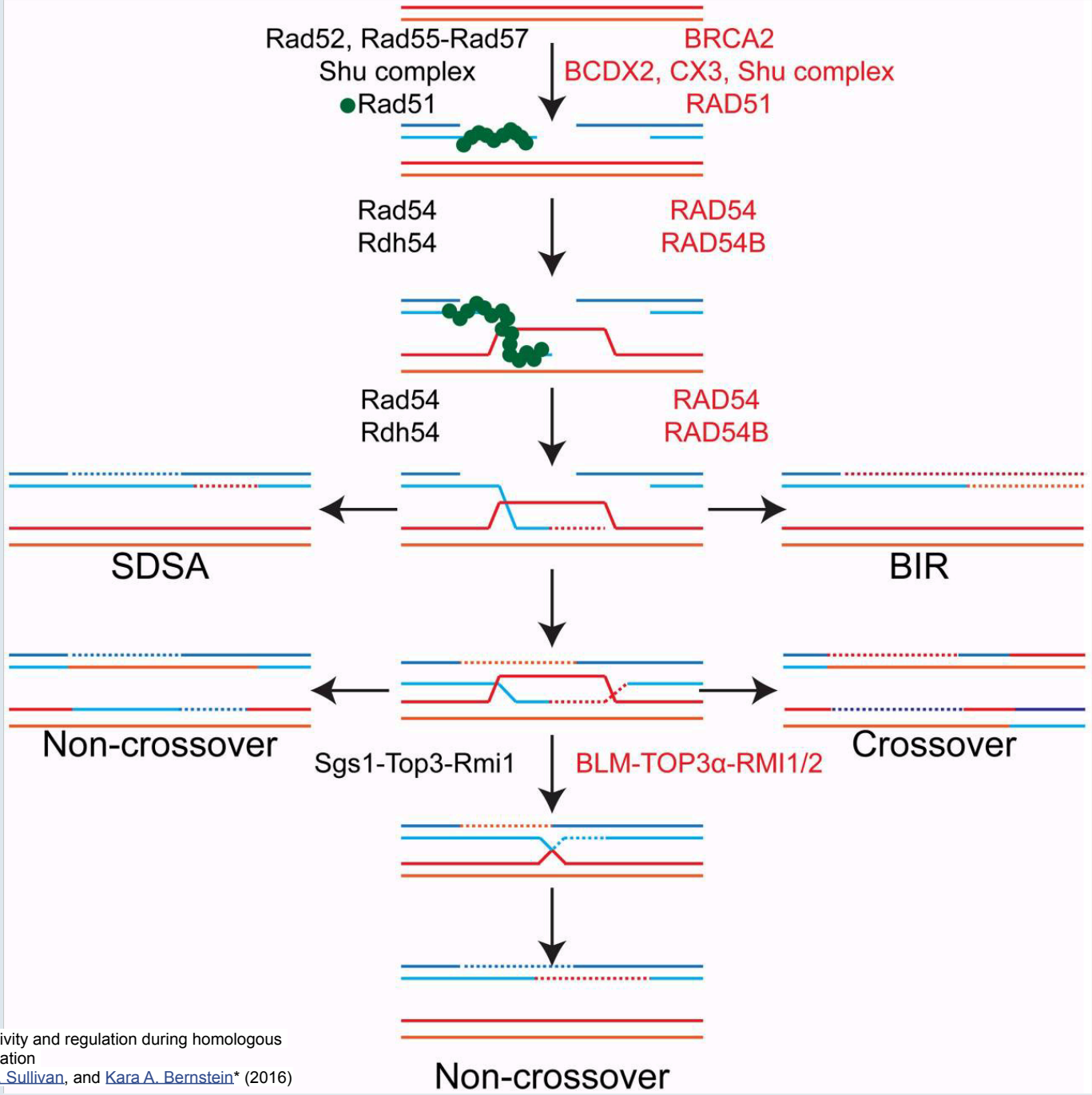
Next, the DNA is resected using a battery of proteins…

Simultaneously the **Rad51** filament is formed, displacing **RPA** from the resected DNA.

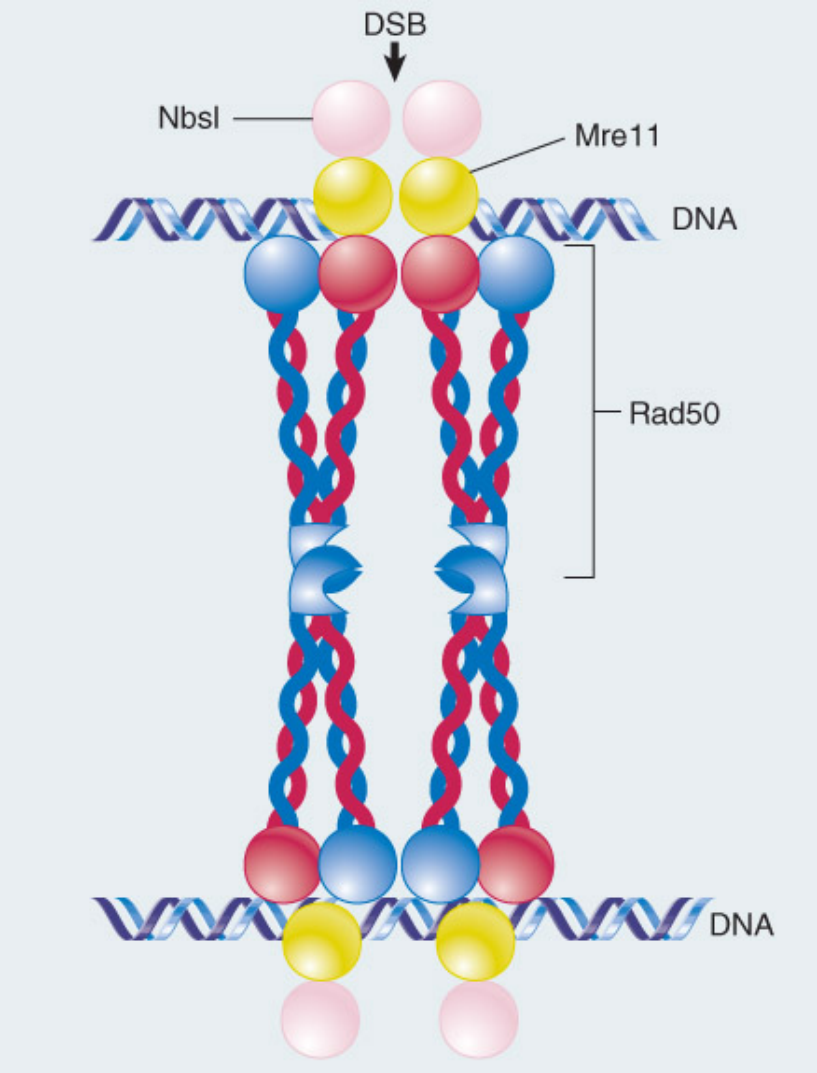
The RecA homolog **Rad51** forms a nucleoprotein filament on the single-stranded regions, assisted by **Rad52** and **Rad55/57.**

Rad54 and **Rdh54/Rad54B** are involved in homology search and strand invasion.

- The yeast *RAD* mutations were identified by radiation-sensitive phenotypes and are in genes that code for repair systems.



Novel insights into RAD51 activity and regulation during homologous recombination and DNA replication
Stephen K. Godin, Meghan R. Sullivan, and Kara A. Bernstein* (2016)



- The ***RAD52*** group of genes (which includes **Rad50)** is required for recombination repair, **and is also integral to the formation of synaptonemal complexes in yeast**

- The **MRX complex** (yeast) or **MRN complex** (mammals) is required for the resection of the dsDNA to form a single-stranded region at each DNA end.

The MRN complex, which is **required** for 5' end resection, also serves as a DNA bridge to prevent broken ends from separating.

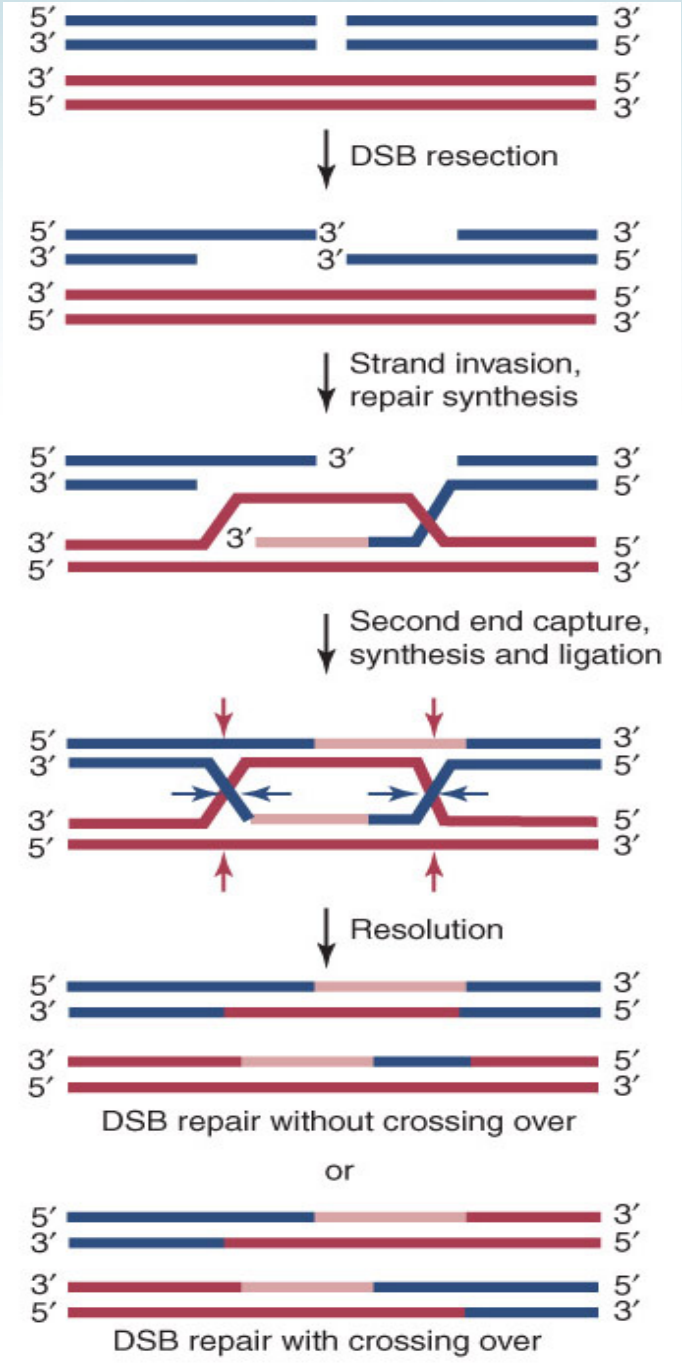
Protein Group and Function	*Saccharomyces cerevisiae*	*Schizosaccharomyces pombe*	*Homo sapiens*	*Caenorhabditis elegans*	*Drosophila melanogaster*
ssDNA Binding and Protection RPA	Rfa1, Rfa2, Rfa3	Rpa1, Rpa2, Rpa3	RPA1, RPA2, RPA3	RPA-1, RPA-2, RPA-3	RpA-70, RpA-30, RpA-8
Rad51 Filament Formation Rad52 and Brca2	Rad52	Rhp22	BRCA2, RAD52	BRC-2	Brca2
Rad51 Filament Formation Rad51 Paralogues	RAD55, RAD57	RAD55, RAD57	XRCC2, RAD51C, RAD51D, RAD51B, RAD51C, XRCC3	RFS-1, RIP-1	RAD51D, RAD51C, spn-A, spn-B
Shu Complex	Shu2, Psy3, Shu1, Csm2; Shu2/SWS1; Rad51 paralogue	Shu2, Rdl1, Rlp1	SWS1, SWSAP1	RFS-1, RIP-1, SWS-1	SWS-1
Rad51 Inhibitors	Srs2	Srs2, Fbh1	RTEL, PARI, REQL5, FBH1	RTEL-1	Unknown
Rad51 Dependent Strand Exchange SWI/SNF Translocases	Rad54, Rdh54	Rhp54, Rdh54	RAD54, RAD54B	RAD-54	RAD-54 (Okra)
Resolution of Double Holliday Junctions RecQ Helicases	Sgs1	Rqh1	BLM, WRN, RECQL4	HIM-6, WRN-1, RECQL4	Blm, WRNexo, RecQ5

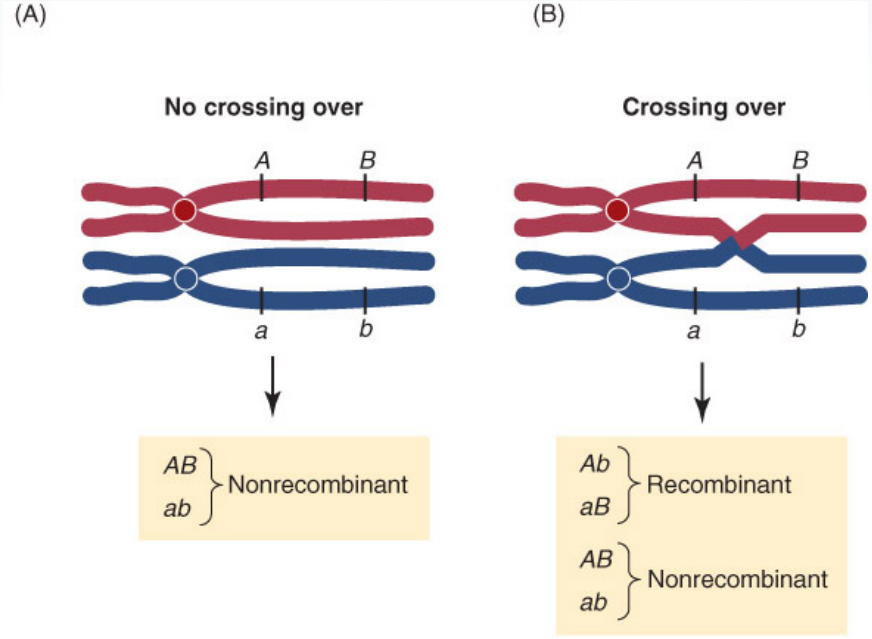
Novel insights into RAD51 activity and regulation during homologous recombination and DNA replication
Stephen K. Godin, Meghan R. Sullivan, and Kara A. Bernstein* (2016)

In both the original **Holliday** and **Meselson-Radding** models for genetic recombination, the initiation events for recombination are **single-strand nicks** that result in the generation of **heteroduplex DNA**.

However, given the finding in yeast was that transformation is stimulated **1,000-fold** when a **double-strand break** is introduced into a circular donor plasmid

.... gave rise to an additional model, the **double-strand-break DSB model**, originally formulated by **Jack Szostak, Terry Orr-Weaver, Rodney Rothstein and Franklin Stahl.**





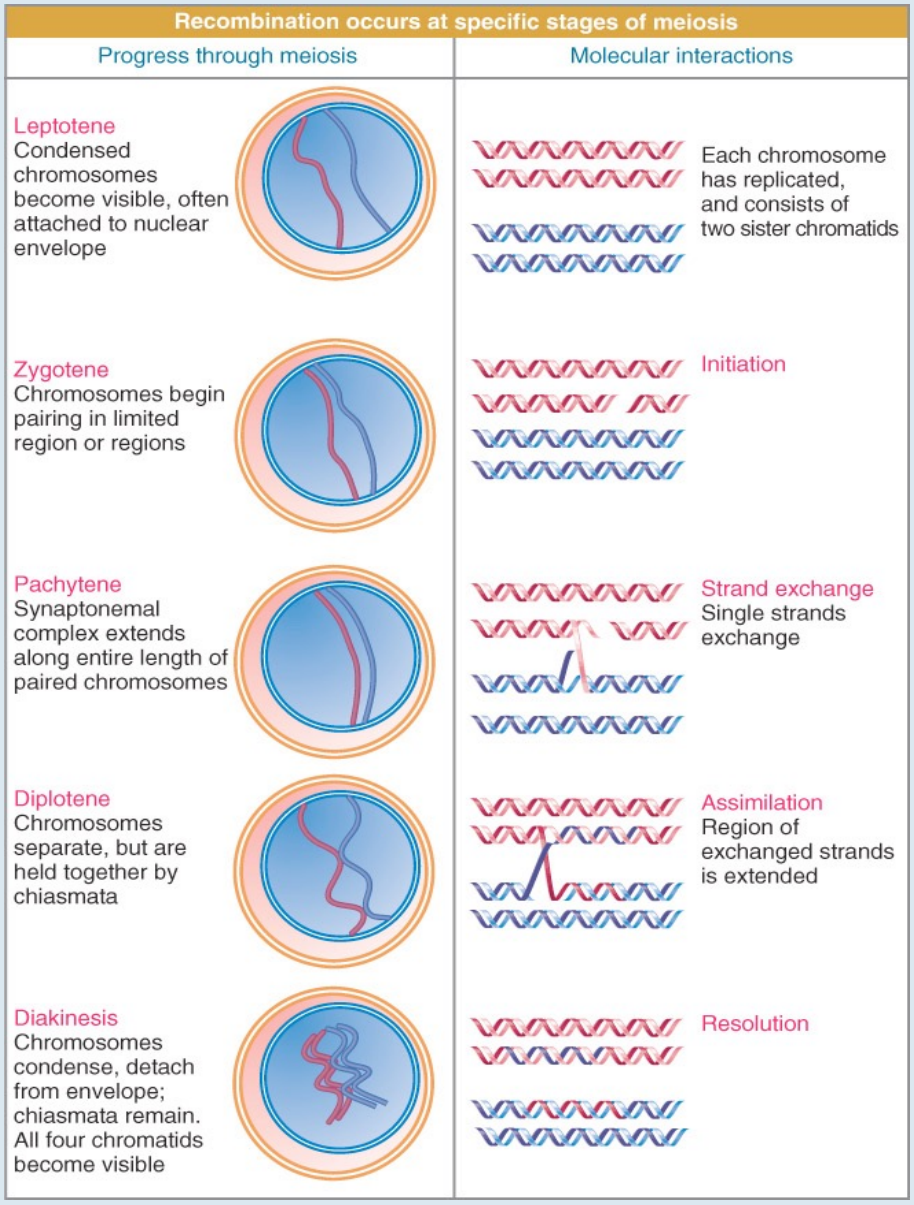
homologous recombination.

Parent * (NCO?)

Parent * (NCO?)

Recombinant

Recombinant



Homologous recombination is a reaction between two duplexes of DNA. Its critical feature is that the enzymes responsible can use any pair of homologous sequences as substrates (although some types of sequences may be favored over others). The frequency of recombination is not constant throughout the genome, but is influenced by both global and local effects.

MOLECULAR AND CELLULAR BIOLOGY, Mar. 2007, p. 1868–1880 Vol. 27, No. 5
0270-7306/07/$08.00+0 doi:10.1128/MCB.02063-06

Genome-Wide Redistribution of Meiotic Double-Strand Breaks in *Saccharomyces cerevisiae*▽†

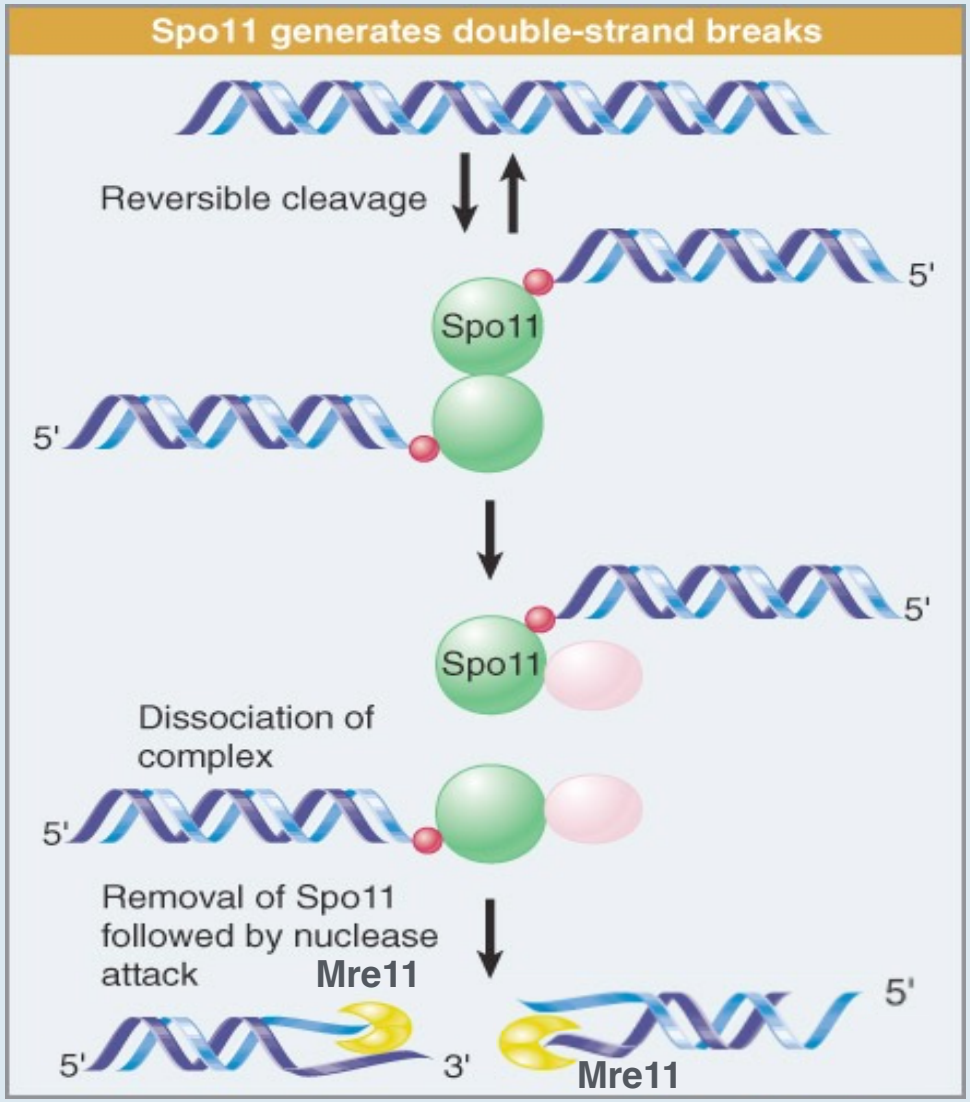
Nicolas Robine,[1,2] Norio Uematsu,[1]‡ Franck Amiot,[3] Xavier Gidrol,[3] Emmanuel Barillot,[2] Alain Nicolas,[1] and Valérie Borde[1]*

Institut Curie, Recombinaison et Instabilité Génétique, Centre de Recherche, UMR7147 CNRS-Institut Curie-Université P. et M. Curie, 26 rue d'Ulm, 75248 Paris Cedex 05, France[1]; Institut Curie, Service de Bioinformatique, 26 rue d'Ulm, 75248 Paris Cedex 05, France[2]; and Service de Génomique Fonctionnelle, CEA, 2 rue Gaston Crémieux, CP5722, 91057 Evry Cedex, France[3]

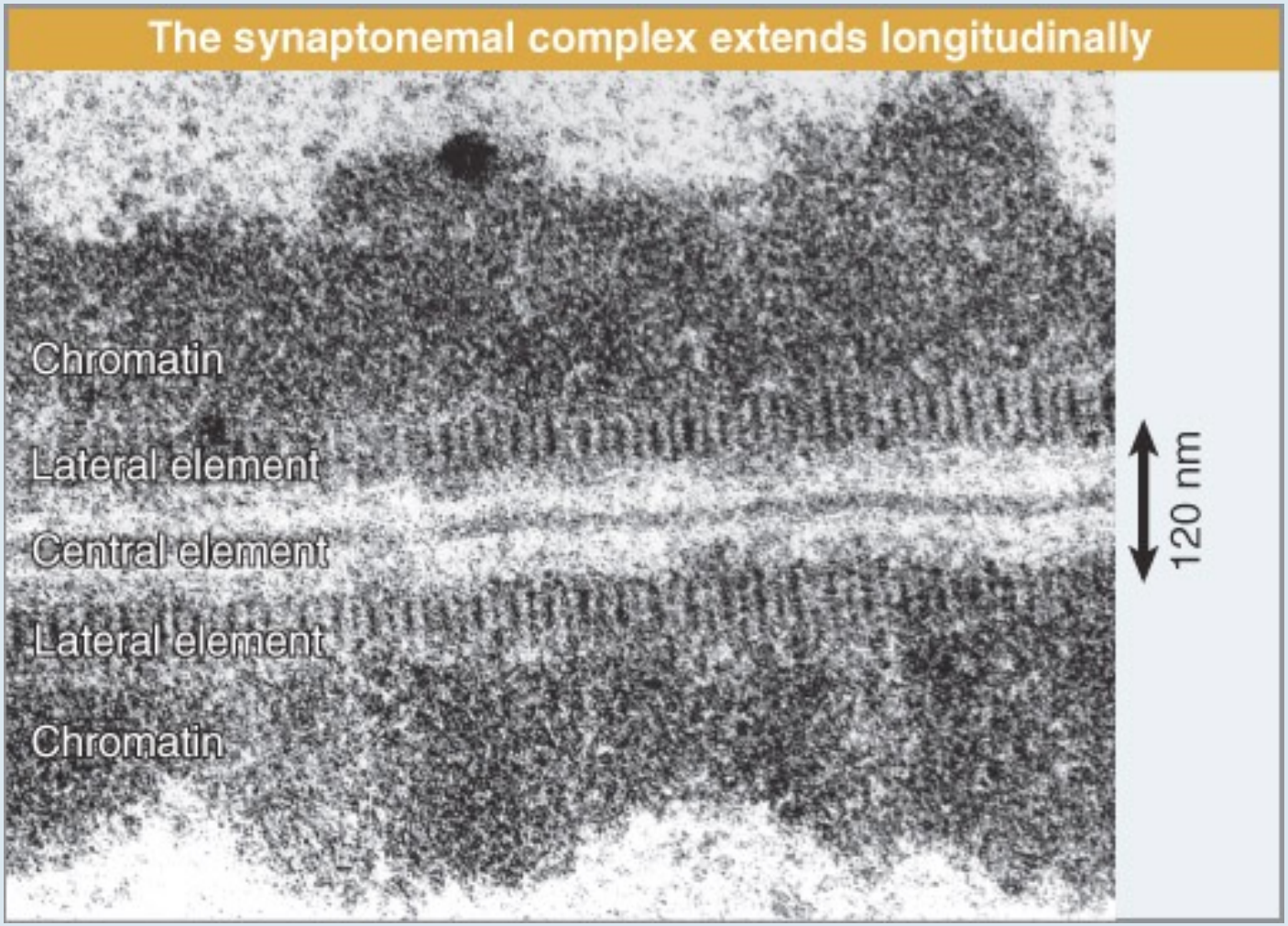
Received 3 November 2006/Returned for modification 30 November 2006/Accepted 12 December 2006

Meiotic recombination is initiated by the formation of programmed DNA double-strand breaks (DSBs) catalyzed by the Spo11 protein. DSBs are not randomly distributed along chromosomes. To better understand factors that control the distribution of DSBs in budding yeast, we have examined the genome-wide binding and cleavage properties of the Gal4 DNA binding domain (Gal4BD)-Spo11 fusion protein. We found that Gal4BD-Spo11 cleaves only a subset of its binding sites, indicating that the association of Spo11 with chromatin is not sufficient for DSB formation. In centromere-associated regions, the centromere itself prevents DSB cleavage by tethered Gal4BD-Spo11 since its displacement restores targeted DSB formation. In addition, we observed that new DSBs introduced by Gal4BD-Spo11 inhibit surrounding DSB formation over long distances (up to 60 kb), keeping constant the number of DSBs per chromosomal region. Together, these results demonstrate that the targeting of Spo11 to new chromosomal locations leads to both local stimulation and genome-wide redistribution of recombination initiation and that some chromosomal regions are inherently cold regardless of the presence of Spo11.

http://mcb.asm.org/cgi/reprint/27/5/1868



Spo11 (a **topoisomerase-like protein**) and additional **exonucleases** are used to generate double-strand breaks **during meiosis**.



Reproduced from D. von Wettstein. 1971. Proc. Natl. Acad. Sci. USA. 68: 851-855. Photo courtesy of D. von Wettstein, Washington State University

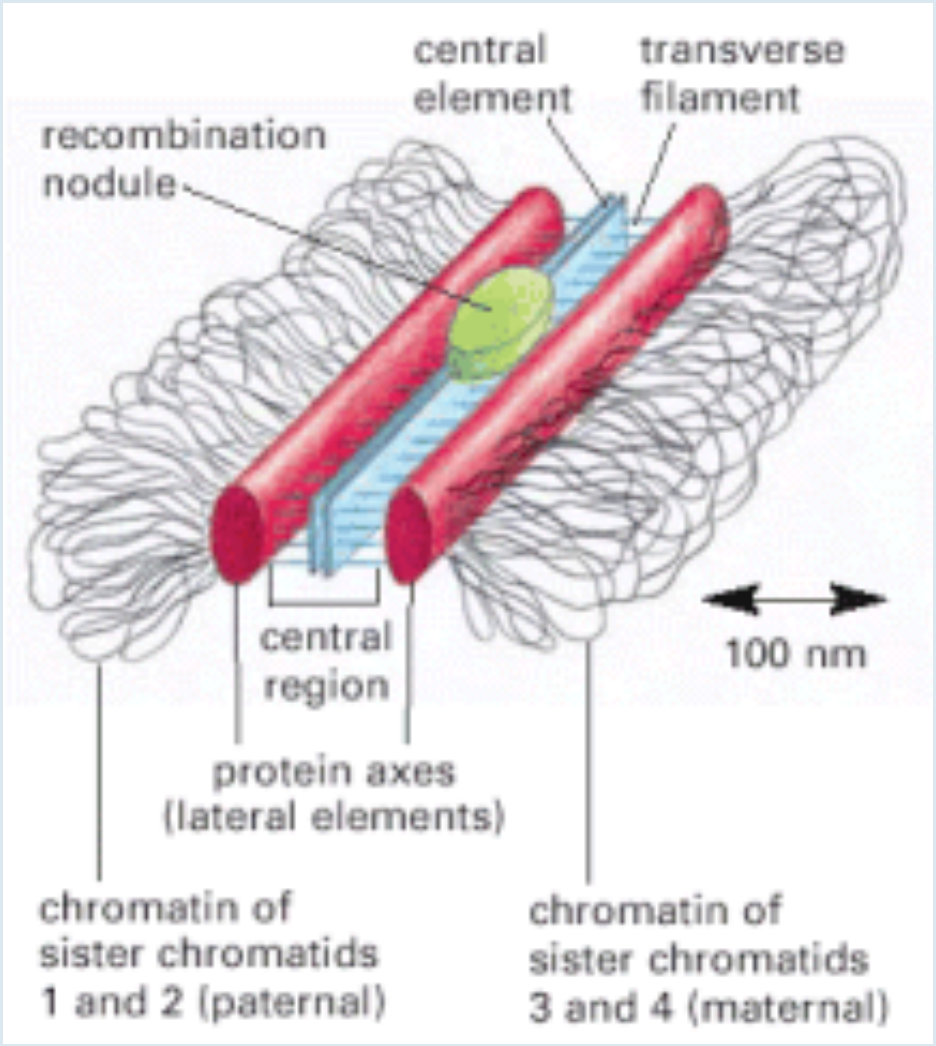
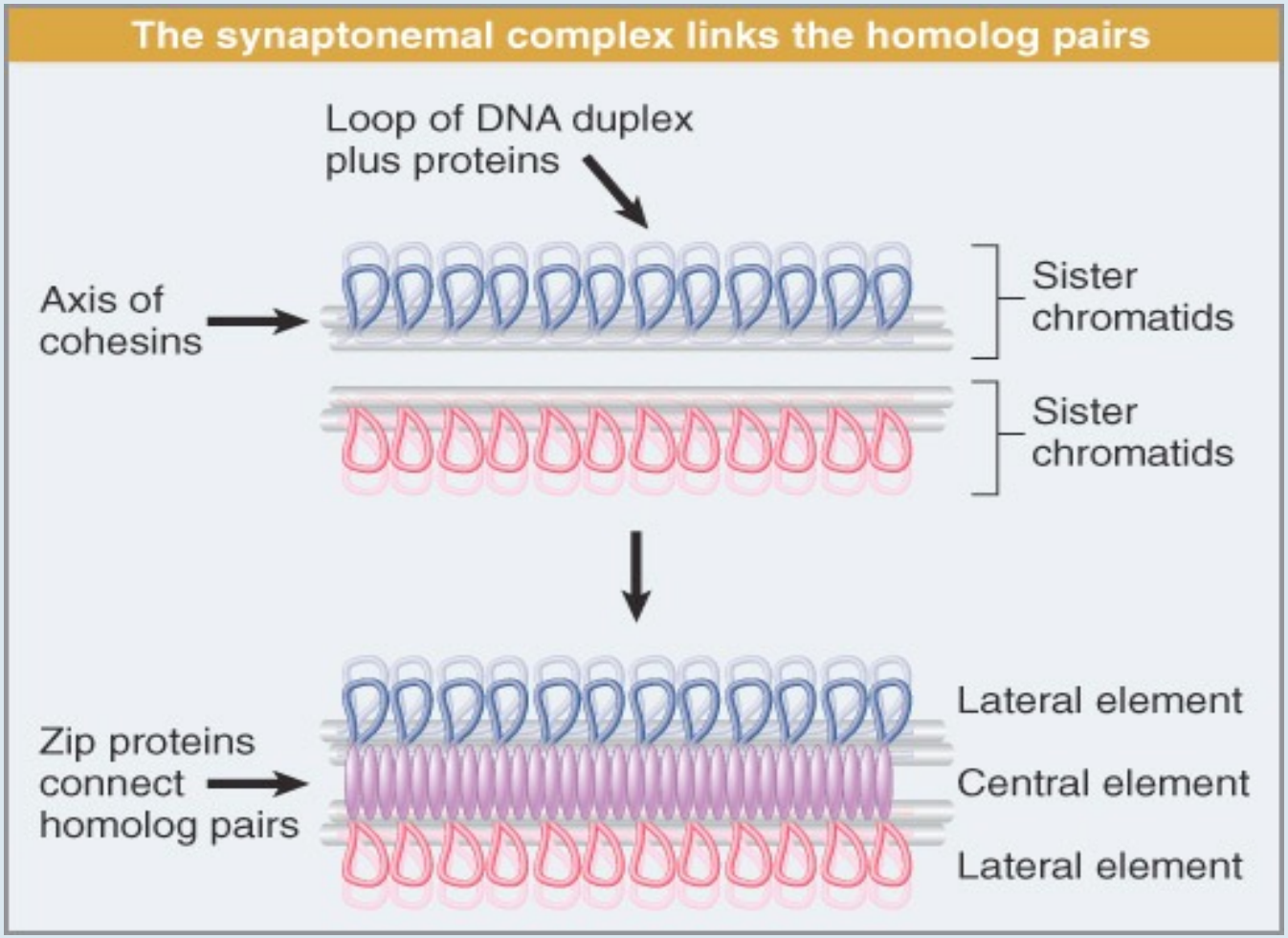


Figure 20–13. A mature synaptonemal complex. Only a short section of the long ladderlike complex is shown. A similar synaptonemal complex is present in organisms as diverse as yeasts and humans

Molecular Biology of the Cell; 4th Ed.



Synapsis begins when each chromosome (sister chromatid pair) condenses around a structure called the **axial element**, which is apparently proteinaceous. Then the axial elements of corresponding chromosomes become aligned, and the synaptonemal complex forms as a tripartite structure, in which the axial elements, now called **lateral elements**, are separated from each other by a **central element**. Figure 15.9 shows an example.

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doi: 10.1007/978-1-4939-0888-2_11

The roles of cohesins in mitosis, meiosis, and human health and disease

Amanda S. Brooker and Karen M. Berkowitz

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Summary

Go to:

Mitosis and meiosis are essential processes that occur during development. Throughout these processes, cohesion is required to keep the sister chromatids together until their separation at anaphase. Cohesion is created by multi-protein subunit complexes called cohesins. Although the subunits differ slightly in mitosis and meiosis, the canonical cohesin complex is composed of four subunits that are quite diverse. The cohesin complexes are also important for DNA repair, gene expression, development, and genome integrity. Here we provide an overview of the roles of cohesins during these different events, as well as their roles in human health and disease, including the cohesinopathies. Although the exact roles and mechanisms of these proteins are still being elucidated, this review will serve as a guide for the current knowledge of cohesins.

Keywords: cohesin, mitosis, meiosis, sister chromatid cohesion, cell cycle, chromosome segregation, aneuploidy, human health, cohesinopathies, maternal age effect

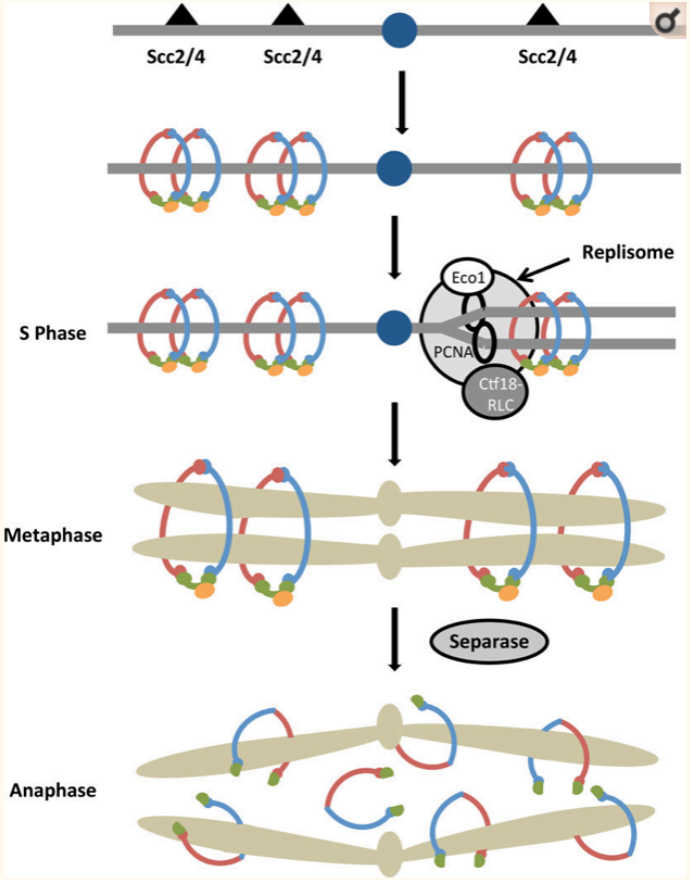

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Figure 2

Cohesion in yeast mitosis. Cohesin complexes require the Scc2/Scc4 protein complex in order to be loaded on chromosomes. Several proteins act together to establish cohesion during DNA replication. These proteins include Eco1 acetyltransferase, the CTF18-RLC complex, and the polymerase-associated protein Ctf4. Tension at centromeres is generated by the bipolar attachment of kinetochores to the mitotic spindle. Following biorientation of sister chromatids, separase is activated to cleave the Scc1 subunit resulting in removal of cohesin complexes, loss of cohesion, and separation of sister chromatids.

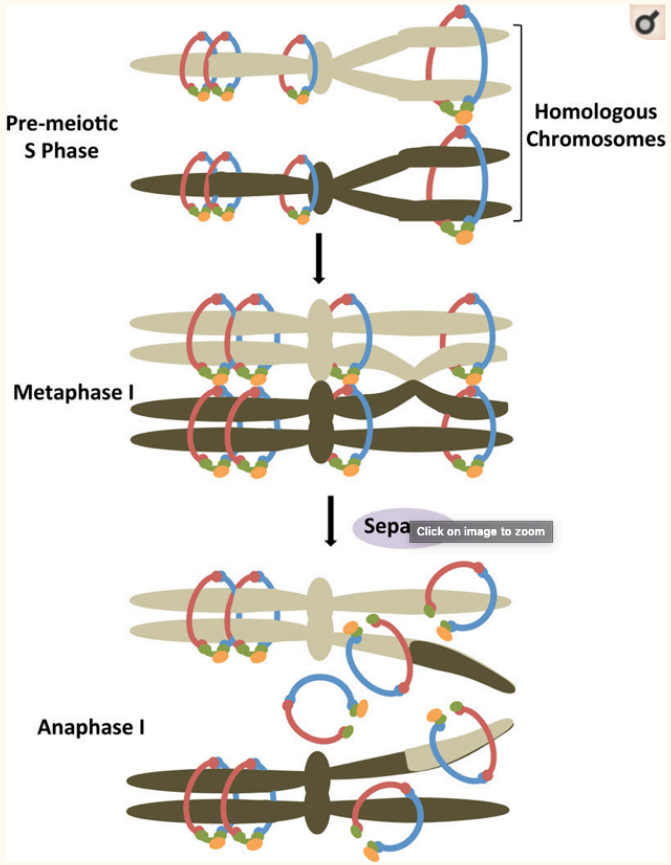

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Figure 4

Cohesion in yeast meiosis I. Rec8 replaces Scc1 of the cohesin complex in S phase. During prophase I homologous chromosomes pair and meiotic recombination leads to DNA crossovers between non-sister chromatids. In order for homologous chromosomes to segregate, kinetochores of sister chromatid pairs must each be mono-oriented to opposite poles during metaphase I. Separase cleavage of Rec8 during anaphase I, much like that during mitosis, resolves the cohesion distal to crossovers to allow segregation of homologues. In order to allow for the proper biorientation and segregation of sister chromatids during meiosis II, cohesion proximal to centromeres is preserved.

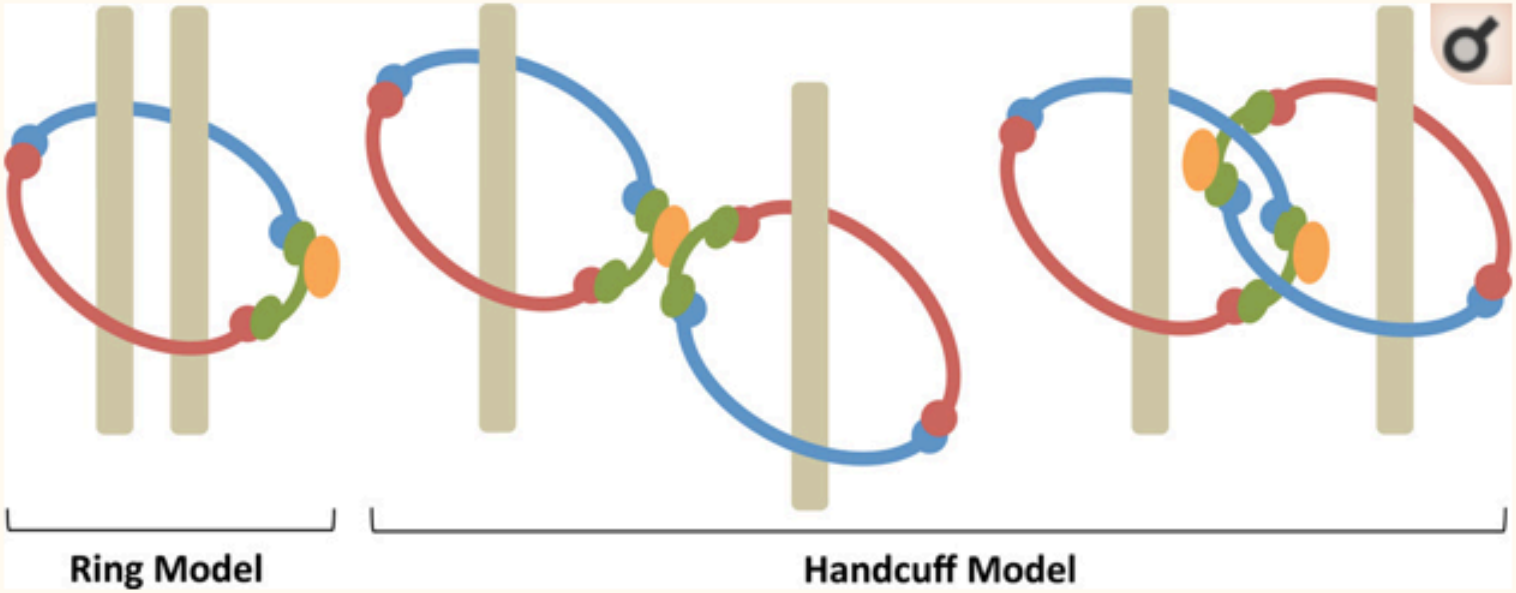


Figure 3

Models of cohesin rings. **(A)** One ring model predicts that both sister chromatids are entrapped within a single cohesin ring. **(B)** Another type of ring model, the "handcuff" model, proposes that each of two cohesin rings entraps one sister chromatid, either by binding a single Scc3 subunit or topological interconnection between rings.

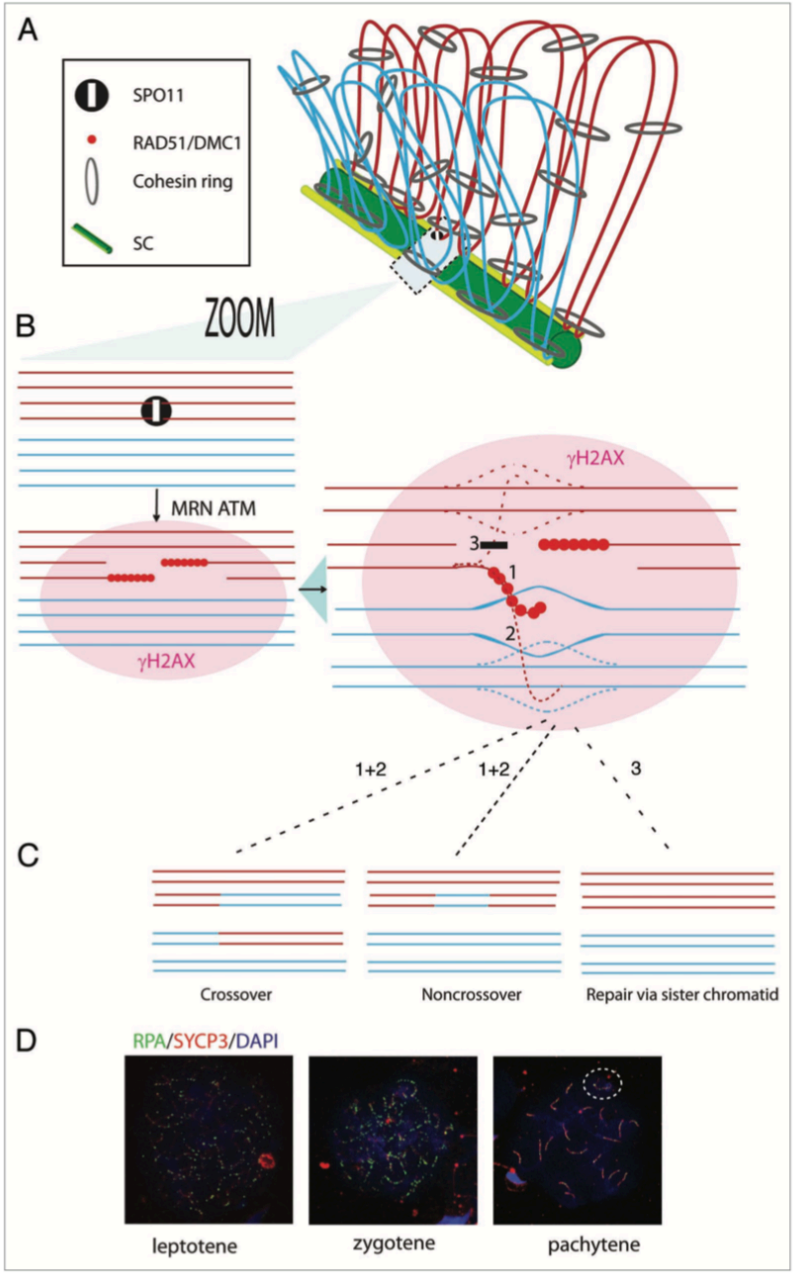


Figure 1 Homologous chromosome pairing and meiotic DSB repair.

(A) Schematic drawing of the **SYNAPTONEMAL COMPLEX** and associated chromatin in pachytene. the SC consists of lateral elements ı) (light green) that form along the bases of the protruding chromatin d loops (red and blue). The homologues are connected via the transversal and central elements of the SC (dark green). Sister chromatids are ʻia connected via cohesion rings (grey). **Cohesin is enriched at the bases of the chromatin loops. SPo11** and associated proteins mediate the ; formation of **DSBs** that are repaired in association with the (axial SC. components of the) SC.

(B) ɛ initiation of meiotic DSB repair. Upon

(B) Schematic drawing of the initiation of meiotic DSB repair. Upon ʳ the formation of a meiotic DSB, the site of the break is recognized by the MRn complex. this complex plays an essential role in the removal of SPo11, resection of the break, and the recruitment of the kinase AtM. ıg this kinase phosphorylates **histone H2AX** in the chromatin surrounding the DSB. the long ssDnA tails that have been formed during resection are most likely bound by RPA, which is subsequently replaced by D51 RAD51. this protein mediates the homology search. in theory, RAD51 laments may invade homologous DnA on the sister chromatid, or on is, one of the two chromatids of the homologous chromosome. in meiosis, interactions with the sister chromatid are somehow repressed, and ome interaction with one of the chromatids of the homologous chromosome is stimulated.

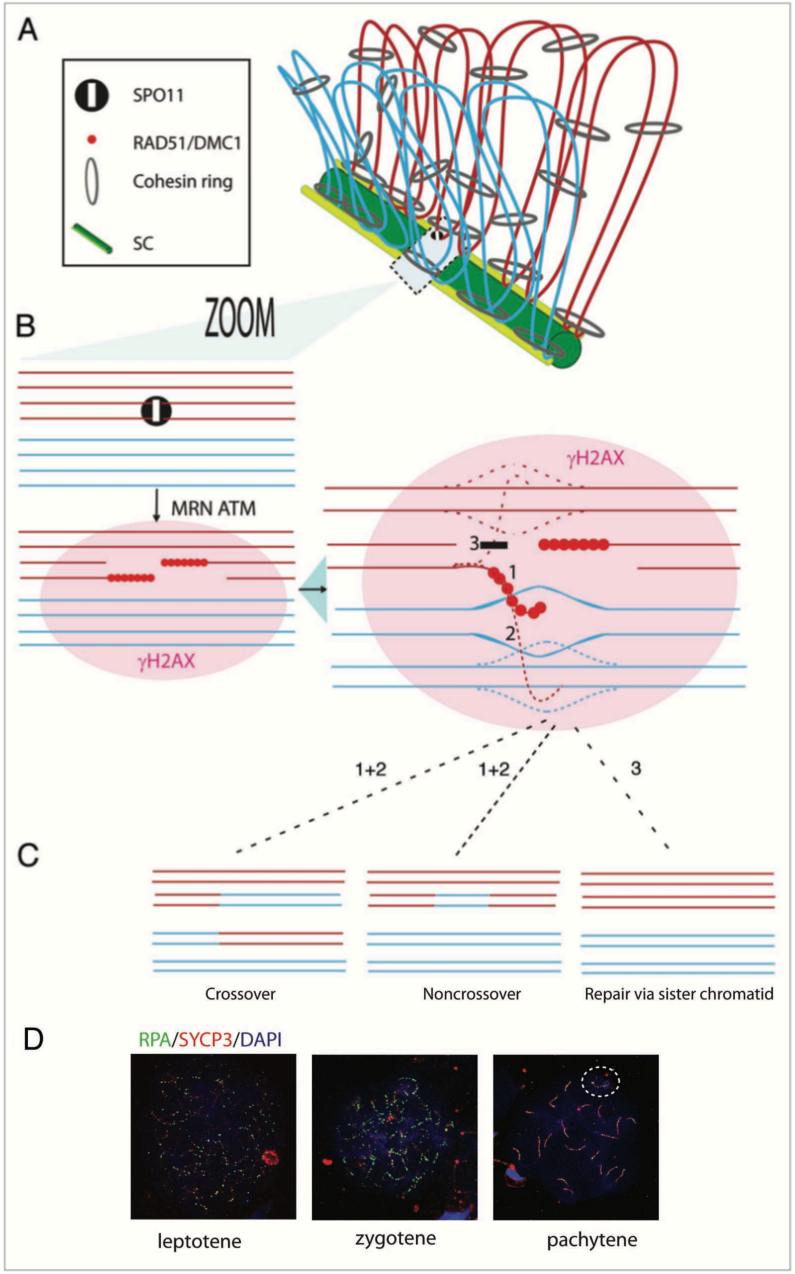
(C) mes of HR repair of meiotic DSBs. Upon strand

(C) Possible outcomes of HR repair of meiotic DSBs. Upon strand ɐpair invasion, different subpathways of homologous recombination repair using the homologous chromosome as a repair template (1 + 2) (see main text) can lead to the formation of crossovers or noncrossovers (gene conversions). if repair occurs using the sister chromatid as a template (3), the original DnA sequence is restored.

(D) (blue DAPi

(D) Localization of RPA (green), SYCP3 (red) and DnA (blue DAPi staining) in spread leptotene, zygotene and pachytene mouse ʍith the spermatocyte nuclei. nuclei were spread and immunostained with the indicated antibodies as described in ref. 81. the anti RPA antibody is described in ref. 3

Akiko Inagaki, Sam Schoenmakers & Willy M. Baarends (2010) Epigenetics, 5:4, 255-266, DOI: 10.4161/epi.5.4.11518



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(B) Schematic drawing of the initiation of meiotic DSB repair. Upon formation of a meiotic DSB, the site of the break is recognized by the **MRn complex. this complex plays an essential role in the removal of SPo11, resection of the break, and the recruitment of the kinase** [. **AtM, which is a kinase that phosphorylates histone H2AX in the** ng **chromatin surrounding the DSB.** The long ssDnA tails that have ɔn been formed during resection are most likely bound by **RPA**, which is subsequently replaced by **RAD51**. this protein mediates the homology search. in theory, **RAD51** laments may invade homologous DnA on the sister chromatid, or on one of the two chromatids of the homologous s, chromosome. in meiosis, interactions with the sister chromatid are somehow repressed, and interaction with one of the chromatids of the ɔ homologous chromosome is stimulated.

(C) Possible outcomes of HR repair of meiotic DSBs. Upon strand invasion, di erent subpathways of homologous recombination repair using the homologous chromosome as a repair template (1 + 2) (see main text) can lead to the formation of crossovers or noncrossovers (gene conver- sions). if repair occurs using the sister chromatid as a template (3), the original DnA sequence is restored.

(D) Localization of **RPA** (green), **SYCP3** (red) and **DnA** (blue DAPi staining) in spread leptotene, zygotene and pachytene mouse spermatocyte nuclei. nuclei were spread and immunostained with the indicated antibodies as described in ref. 81. the anti RPA antibody is described in ref. 3

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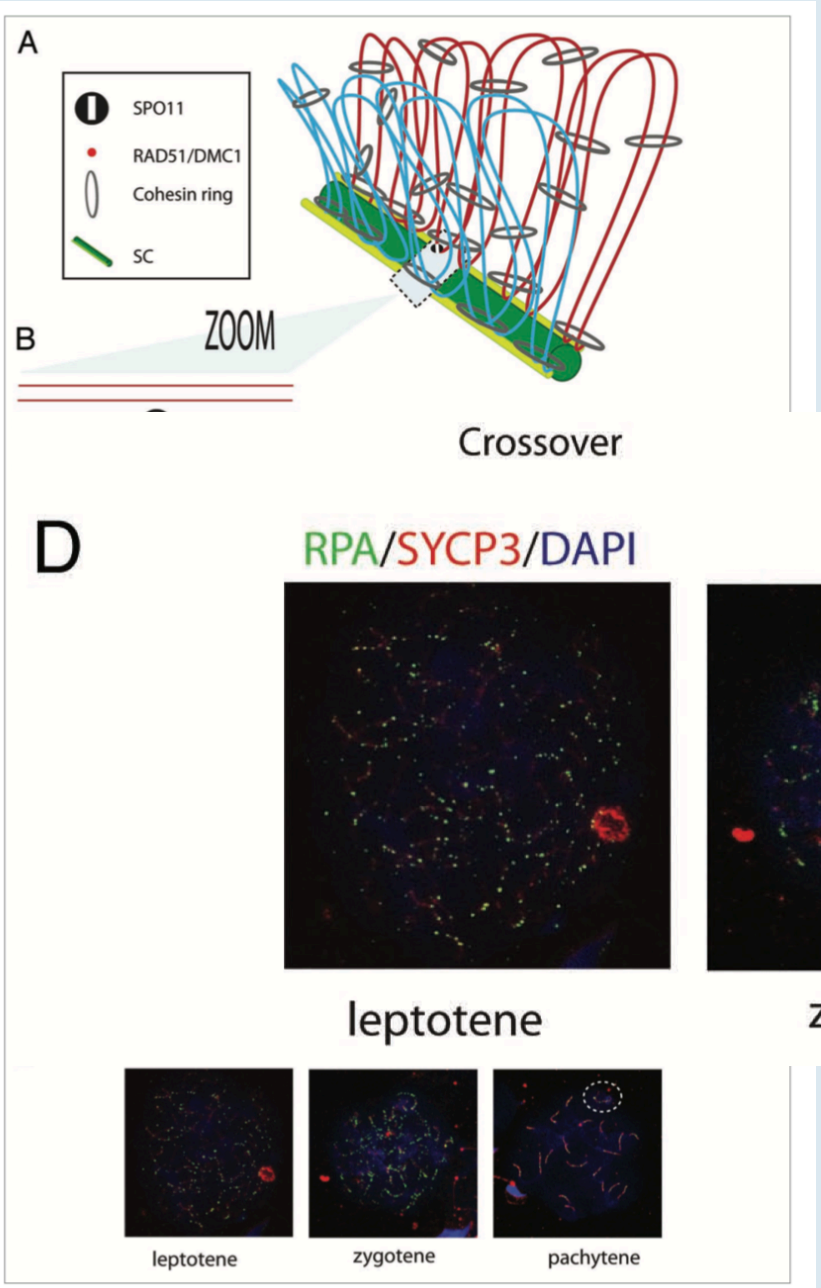

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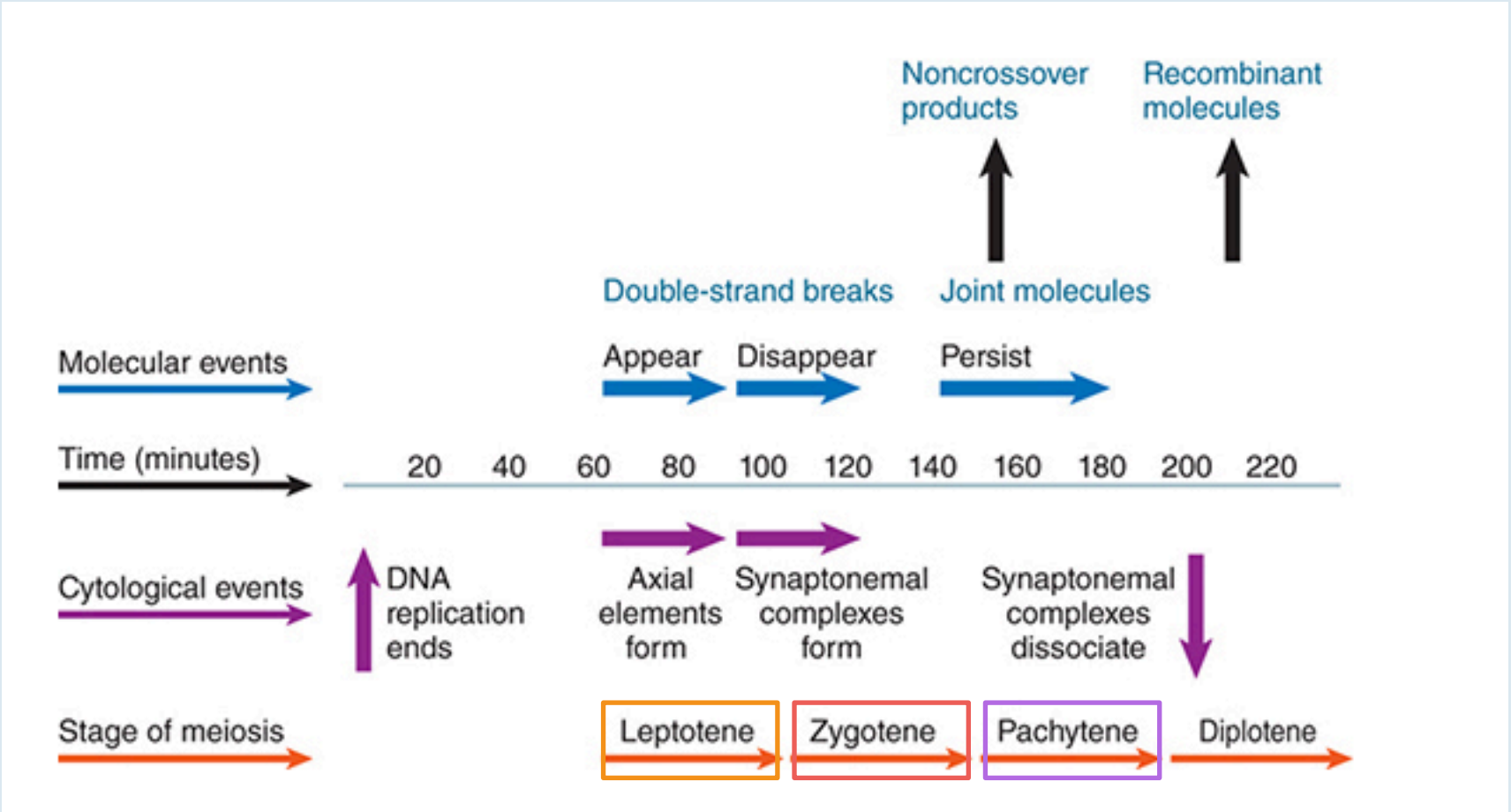
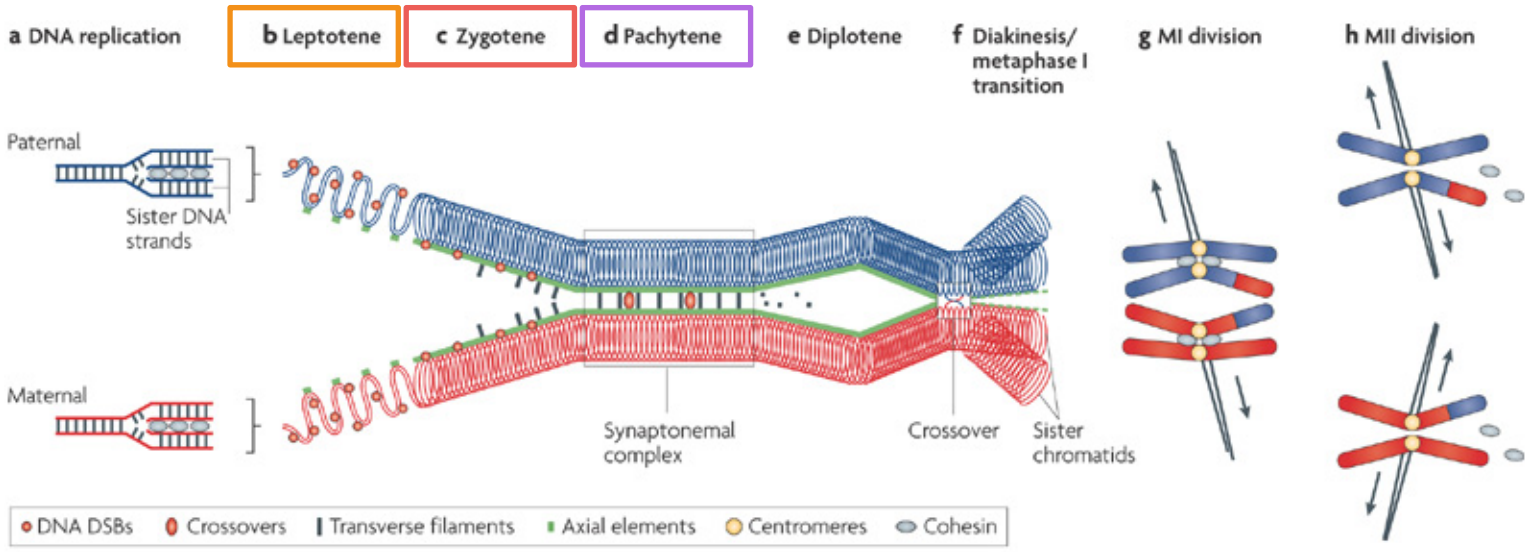
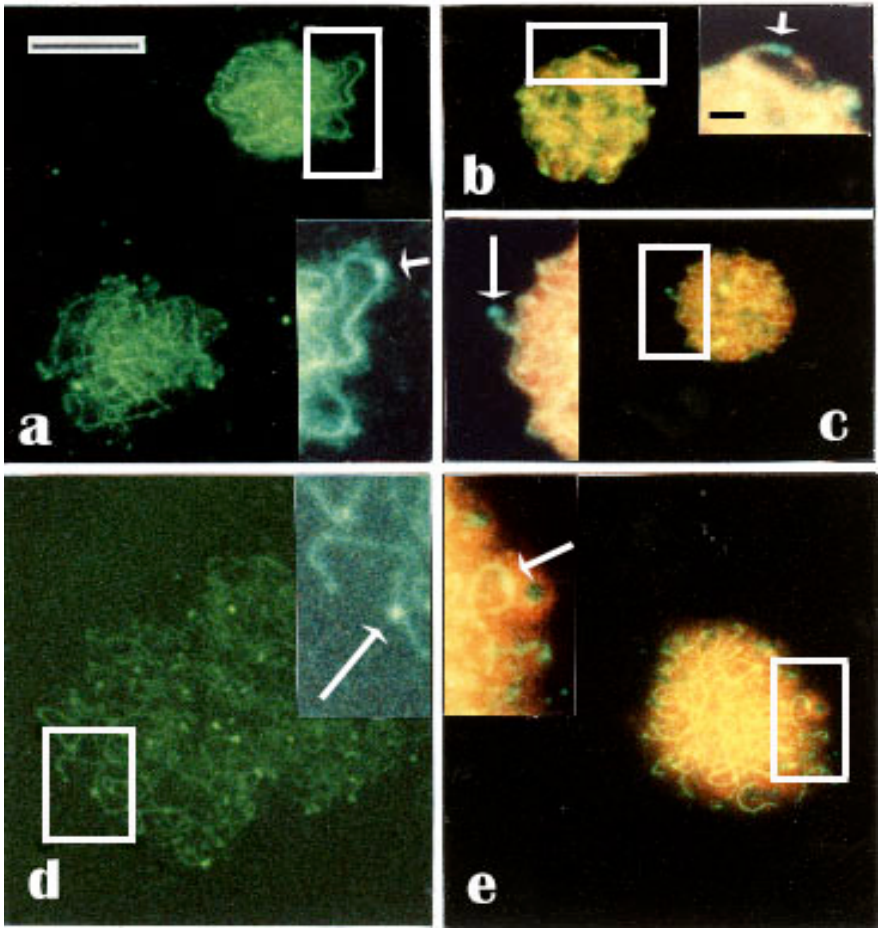


Double-strand breaks appear when axial elements form and disappear during the extension of synaptonemal complexes. Joint molecules appear and persist until DNA recombinants are detected at the end of pachytene.



a | During pre-meiotic S phase the DNA of each maternally and paternally derived chromosome is replicated to form two sister DNAs that are held together by cohesins (which remain throughout prophase).
b | During the leptotene stage hundreds of double-stranded breaks (**DSBs; red circles**) are introduced into these DNA molecules, and each pair of sister DNA strands begins to assemble a single proteinaceous axis (green).
c | By the zygotene stage the bulk of the DNA is located in the chromatin loops emanating from the chromosome axes, but the **DNA breaks have become axially located.** The axes of each pair of homologous maternal and paternal chromosomes begin synapsis via transverse filaments to form a synaptonemal complex; this synapsis is driven by single-stranded DNA tails (not shown), which are generated at the breaks and invade the DNA duplex of the homologue.
d | The beginning of the pachytene stage is marked by the completion of synapsis. The DNA breaks are repaired, with some of the breaks maturing into crossovers — a minimum of one per chromosome pair.
e | During the diplotene stage the disassembly of the synaptonemal complex means that the homologous chromosomes are now only held together by the crossovers.
f | During the transition through diakinesis to the first meiotic metaphase, the axial elements are disassembled and the cohesins that bind the sister chromatids together are removed, except at the centromeres.
g | The mode of centromere attachment at metaphase of the first meiotic division (MI) ensures that homologues separate with one homologue of each pair passing to each daughter cell.
h | At the second meiotic division (MII) the remaining cohesion between sister chromatids is lost and the mode of centromere attachment to the spindle ensures that each daughter cell receives one copy of each pair of chromatids.

Nature Reviews Genetics **10**, 207-216 (March 2009)



Indirect immunofluorescence using anti-RecA and FITC-conjugated secondary antibodies of meiotic nuclei with suggested recombination nodules. The nuclei represent early to late pachytene estimated by the presence of the SCs and the comparative size of the nuclei.
- a–c. Early to middle pachytene nuclei.
- d, e. Middle to late pachytene nuclei.
- a, d. PI omitted.
- b, c and –e. Counterstaining with PI.
- Insets: Details of the nodules (arrows) on the SCs indicate
- a, e. Ellipsoidal nodules.
- b, c and –d. Spherical nodules
- c. A terminal spherical nodule.
- b.Two spherical tandem nodules. Note, that many of the nuclei contain several nodules. Some chromosome cores with nodules (framed) are seen at higher magnification in the insets. – Bar 10 µm – In insets: –Bar 1 µm.

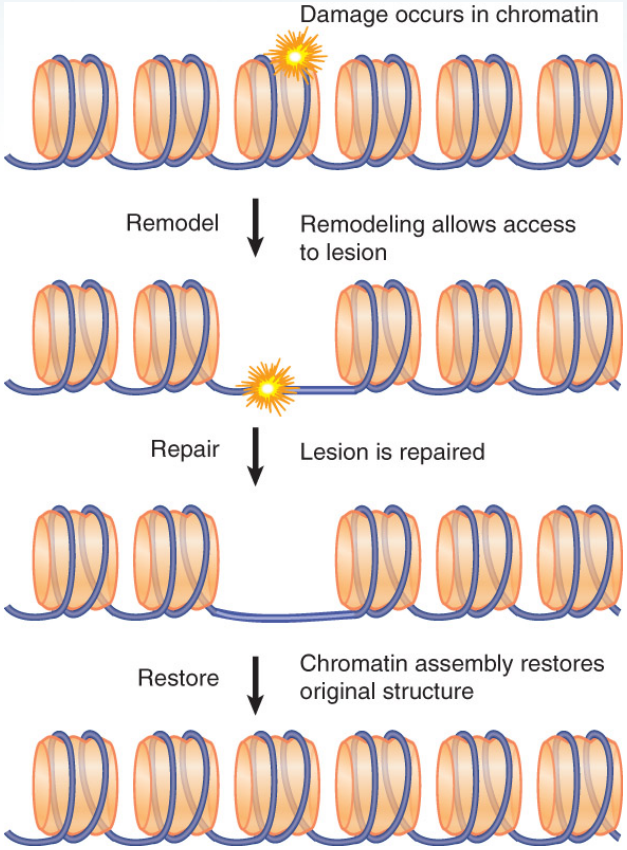
Immunological detection of RecA-related proteins in bull meiotic nuclei. http://www.csc.fi/jpr/emt/engelhar/ASCB.html

* DNA Repair in Eukaryotes Occurs in the Context of Chromatin

- Different patterns of histone modifications may distinguish stages of repair or different pathways of repair.

- Chromatin “Remodelers” and “chaperones” are required to reset chromatin structure before and after completion of repair.

* DNA Repair in Eukaryotes Occurs in the Context of Chromatin



DNA damage in chromatin requires chromatin remodeling and histone modification

- Both histone modification and chromatin remodeling are essential for repair of DNA damage in chromatin.
- H2A phosphorylation (γ**-H2AX**) is a conserved double-strand break-dependent modification that actively recruits chromatin modifying activities and facilitates assembly of repair factors.

Chromosoma (2010) 119:41–58
DOI 10.1007/s00412-009-0243-3

RESEARCH ARTICLE

Synaptonemal complex stability depends on repressive histone marks of the lateral element-associated repeat sequences

Abrahan Hernández-Hernández · Rosario Ortiz · Ernestina Ubaldo · Olga M. Echeverría Martínez · Gerardo H. Vázquez-Nin · Félix Recillas-Targa

Received: 3 March 2009 / Revised: 7 September 2009 / Accepted: 21 September 2009 / Published online: 9 October 2009

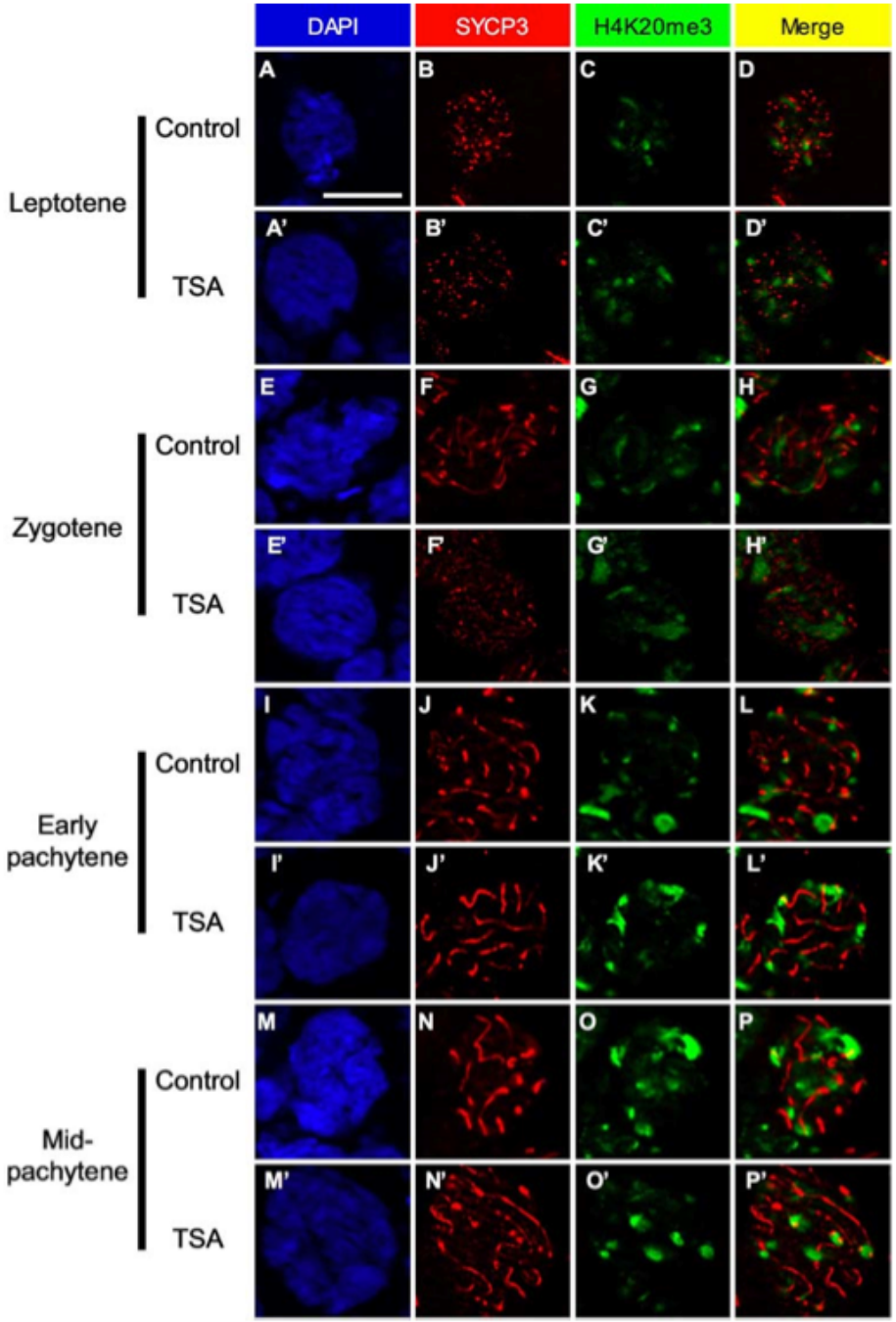


Fig. 4 Immunolocalization of histone mark H4K20me3 throughout meiotic prophase I of control and TSA-treated animals. SYCP3 immunodetection was used to indicate the SCs (*red*). Nuclei were stained with DAPI. **a**–**d** Leptotene cell from control animals. **a'**–**d'** Leptotene cell from TSA-treated animals. **e**–**h** Zygotene cell from control animals. **e'**–**h'** Zygotene cell from TSA-treated animals. **i**–**l** Early pachytene cell from control animals. **i'**–**l'** Early pachytene cell from TSA-treated animals. **m**–**p** Midpachytene cell from control animals. **m'**–**p'** Midpachytene cell from TSA-treated animals. The *bar* corresponds to 10 μm in all the optical sections

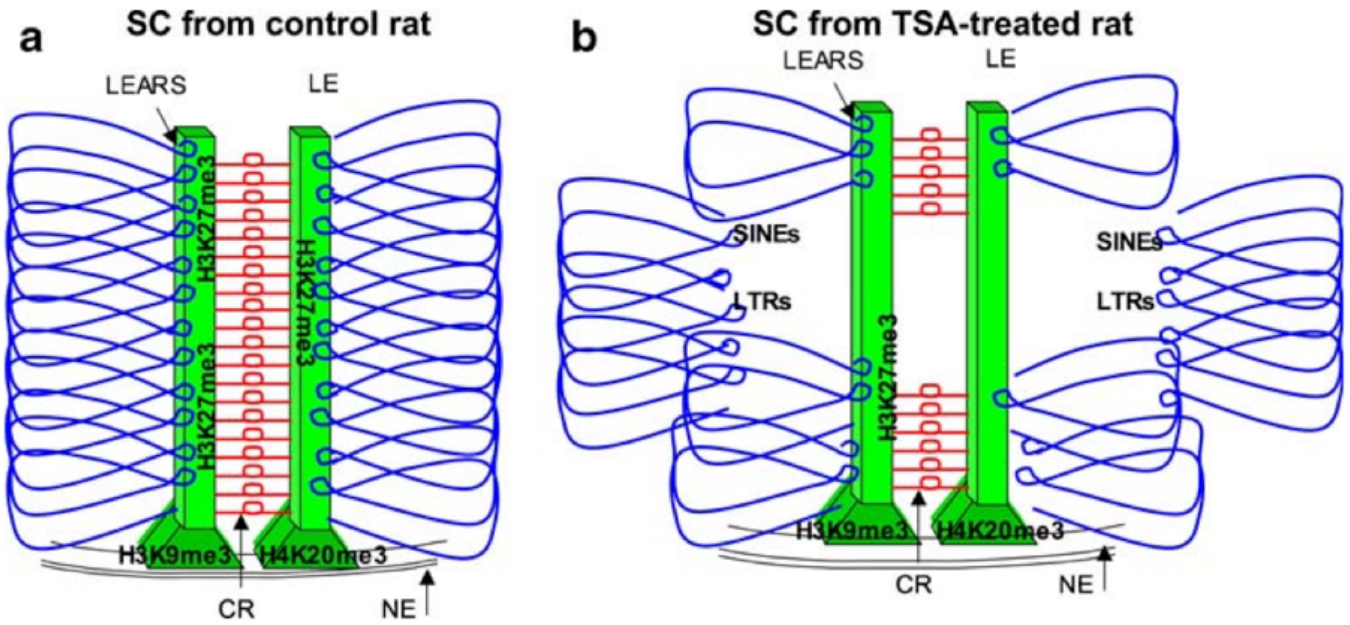
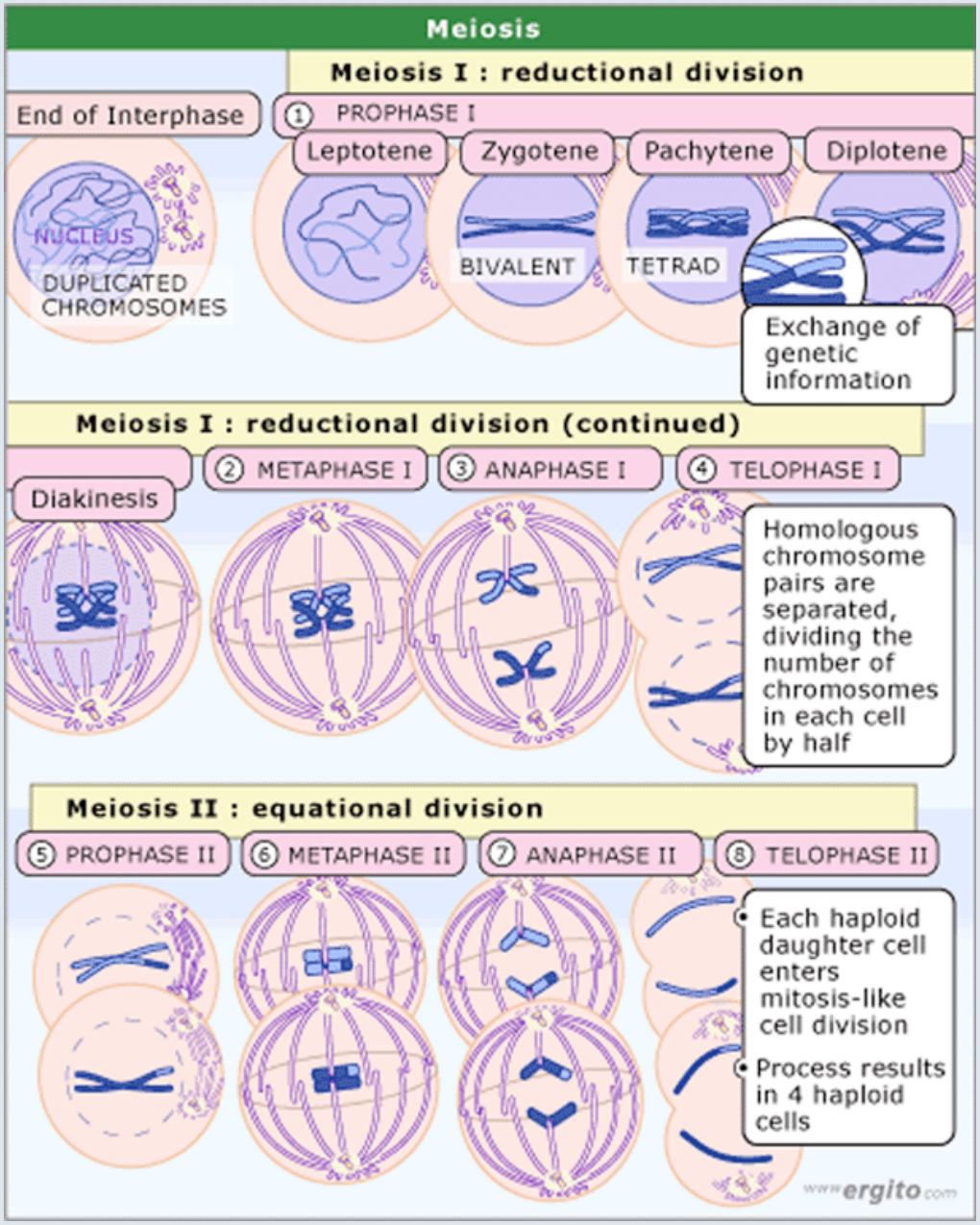


Fig. 14 Model of SC structure in control and TSA-treated rats. a SC of a control rat. The chromatin of homologous chromosomes is anchored to the lateral elements (*LE*) through lateral elements-associated repeat sequences (*LEARS*), for which chromatin structure is dictated by histone posttranslational modifications like H3K9me3, H3K27me3, and H4K20me3. **b** Upon inhibition of histone deacetylases, the presence of H3K27me3 in SINE and LTR sequences decreases dramatically, which could favor detachment of such sequences from the LEs. This is accompanied by alteration of the SC's central region (*CR*)


Meiosis
Meiosis I : reductional division
End of Interphase
1 PROPHASE I
Leptotene
Zygotene
Pachytene
Diplotene
NUCLEUS
DUPLICATED CHROMOSOMES
BIVALENT
TETRAD
Exchange of genetic information
Meiosis I : reductional division (continued)
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2 METAPHASE I
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Homologous chromosome pairs are separated, dividing the number of chromosomes in each cell by half
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8 TELOPHASE II
Each haploid daughter cell enters mitosis-like cell division
Process results in 4 haploid cells
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Chromosome tetrad showing chiasmata

Gregor Mendel's hypotheses:

1. Hereditary determinants are of a particulate nature. Each genetic trait is governed by unit factors , which "hang around" in pairs within individual organisms.

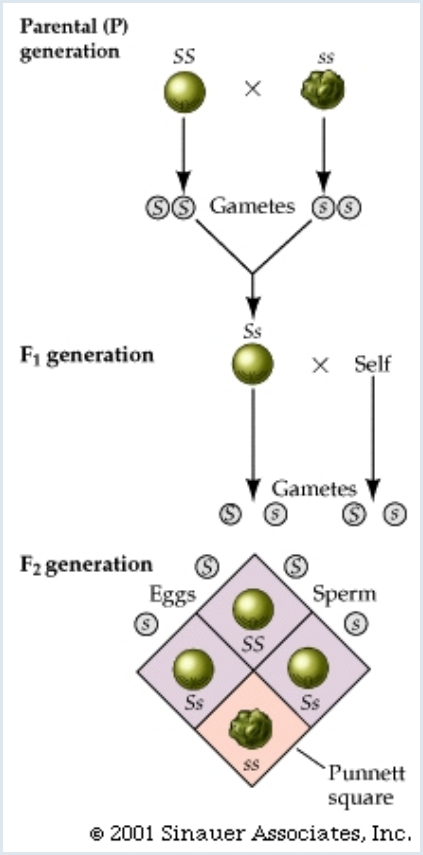
2. When two different unit factors governing the same phenotypical trait occur in the same organism, one of the factors is dominant over the other one, which is called the recessive trait.

3. During the formation of gametes the "paired" unit factors separate or segregate randomly so that each gamete receives either one or the other of the two traits, but only one .

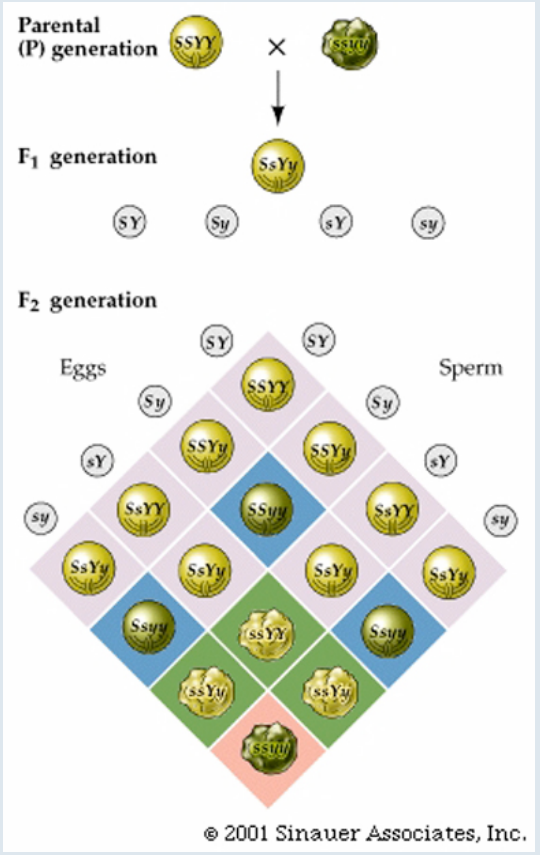
4. The union of one gamete from each parent to form a resultant zygote is random with respect to that particular characteristic.

Mendel's First Law: Two members of a gene pair segregate from each other into the gametes, whereby one half of the gametes carries one of the traits, the other half carries the other.

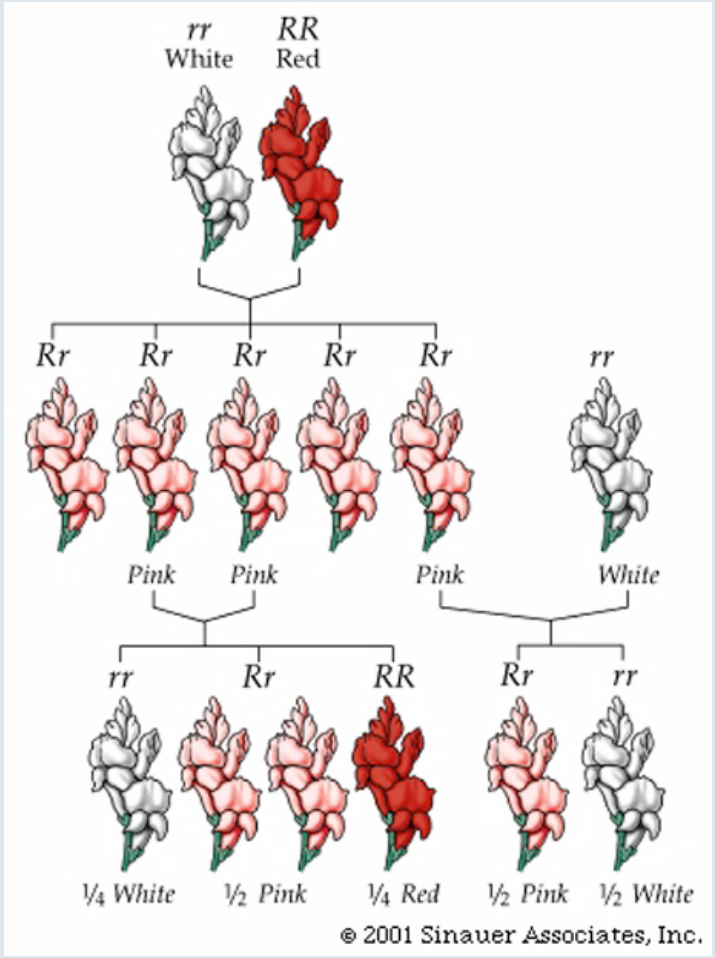
Mendel's Second Law: During gamete formation the segregation of one gene pair is independent of all other gene pairs -ONLY true if genes are on separate chromosomes OR Crossing over between paired homologous chromosomes in during meiosis.


Parental (P) generation
SS
ss
Gametes
Ss
F1 generation
Self
Gametes
F2 generation
Eggs
Sperm
SS
Ss
Ss
ss
Punnett square
© 2001 Sinauer Associates, Inc.

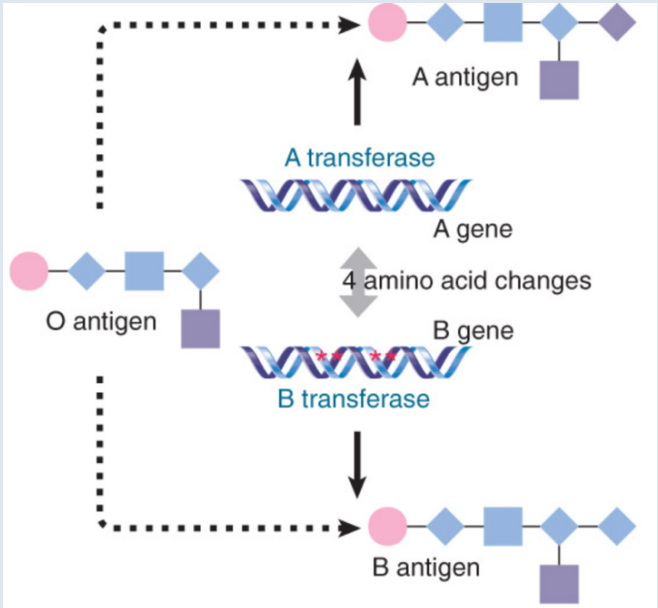
3:1


Parental (P) generation
SSYY
ssyy
F1 generation
SsYy
SY
Sy
sY
sy
F2 generation
Eggs
Sperm
© 2001 Sinauer Associates, Inc.

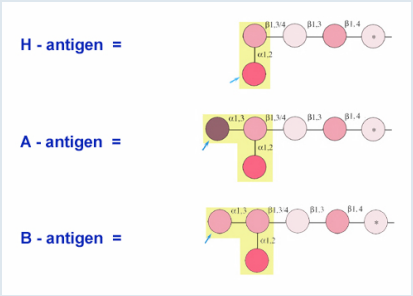
9:3:3:1



1:2:1



Phenotype	Genotype	Transferase Activity
O	OO	None
A	AO or AA	N-Ac-gal transferase
B	BO or BB	Gal transferase
AB	AB	GalN-Ac-Gal-transferase



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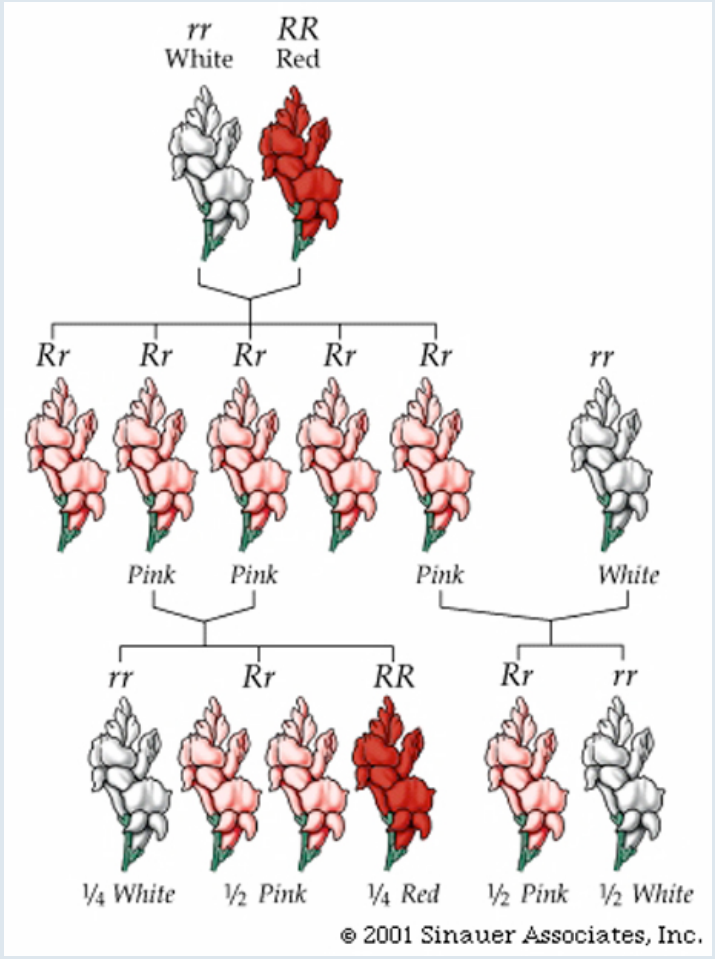
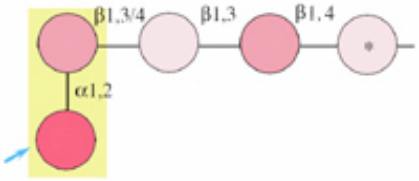


1:2:1

H - antigen =



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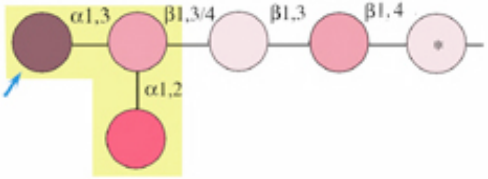

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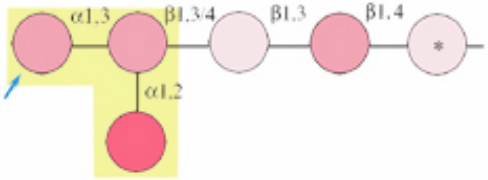

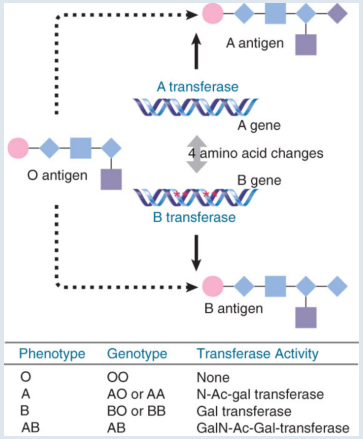

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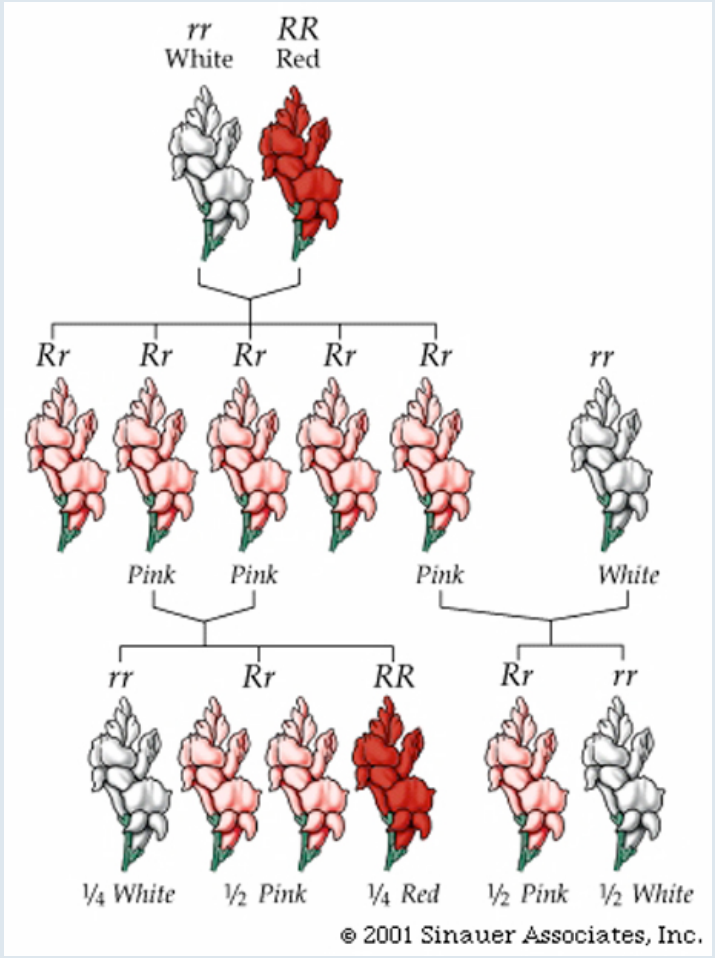
3:1 + 1:2:1 +



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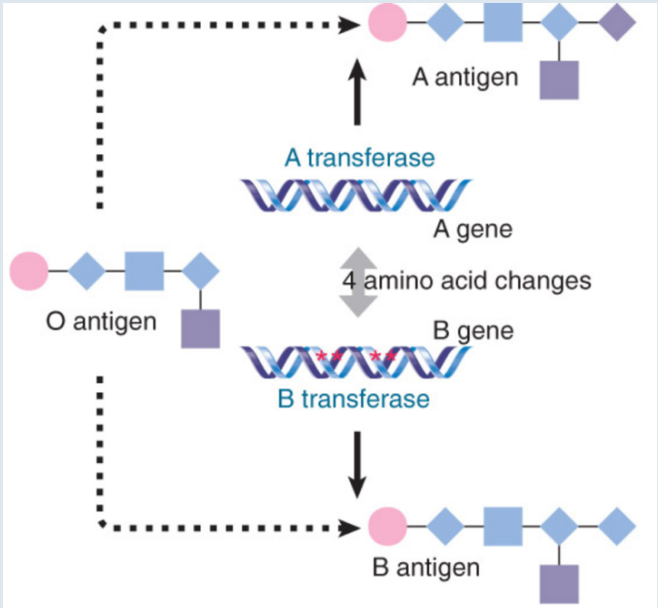

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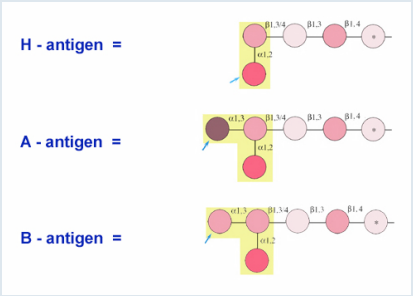
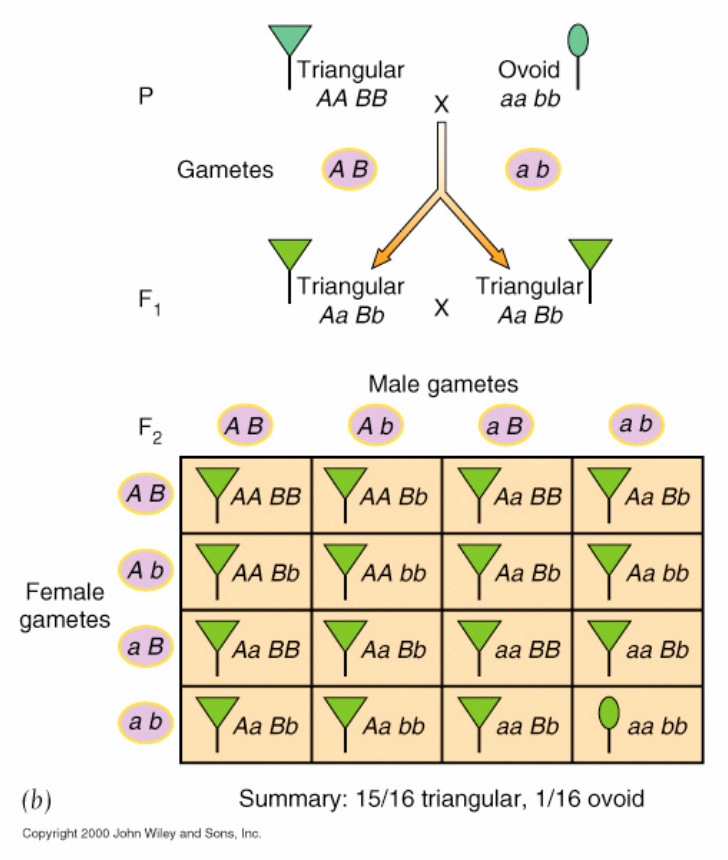


3:1 + 1:2:1 +



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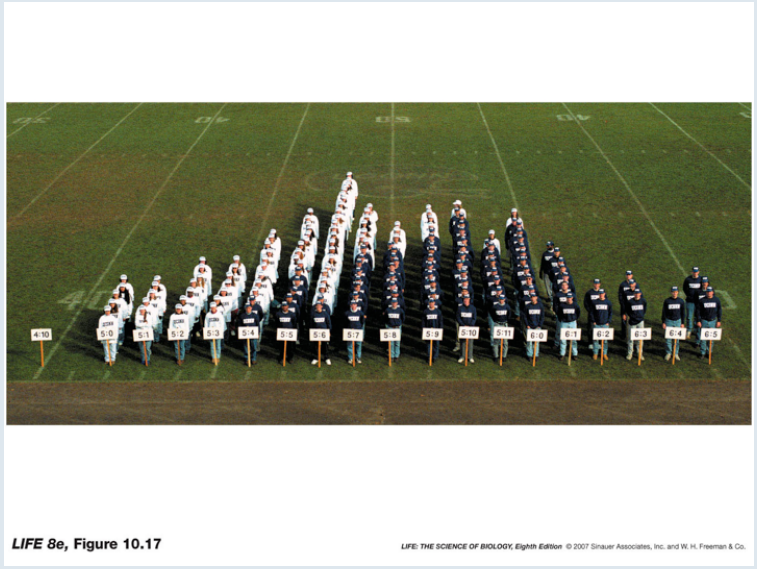
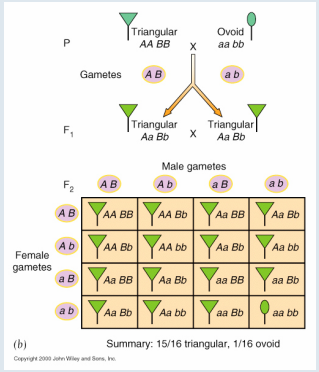


Bell Curve



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***LIFE 8e*, Figure 10.17**

Bell Curve

Number of genes linked to height revealed by study

Date: October 5, 2014

Source: Boston Children's Hospital

Summary: The largest genome-wide association study to date, involving more than 300 institutions and more than 250,000 subjects, roughly doubles the number of known gene regions influencing height to more than 400. The study provides a better glimpse at the biology of height and offers a model for investigating traits and diseases caused by many common gene changes acting together.

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RELATED TOPICS

Health & Medicine

- Genes
- Human Biology
- Personalized Medicine
- Gene Therapy
- Medical Topics
- Parkinson's Research
- Hormone Disorders
- Diseases and Conditions

FULL STORY

"We can now explain about 20 percent of the heritability of height, up from about 12 percent where we were before," says co-first author Tonu Esko, PhD, of Boston Children's Hospital, the Broad Institute and the University of Tartu (Estonia).

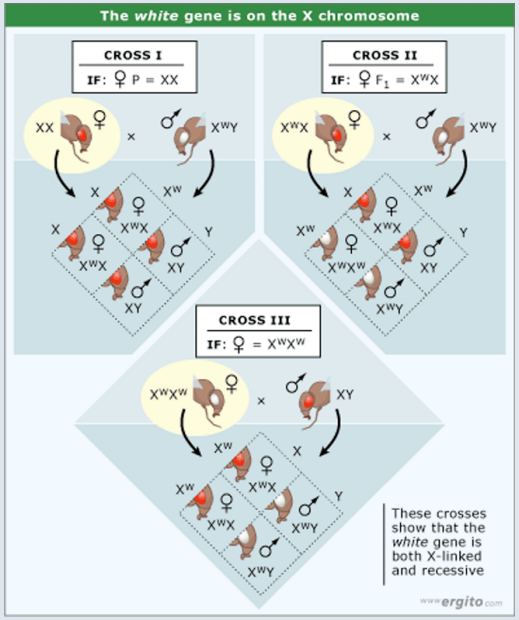
https://www.sciencedaily.com/releases/2014/10/141005134909.htm

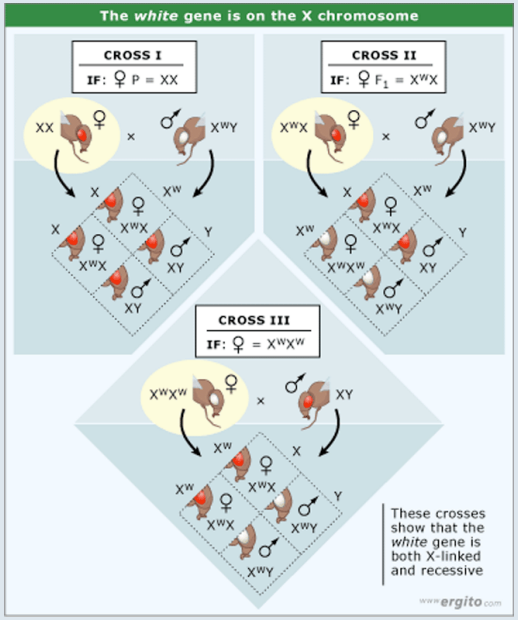
Mendel also provided the Foundation for the work of Thomas Morgan (1909)

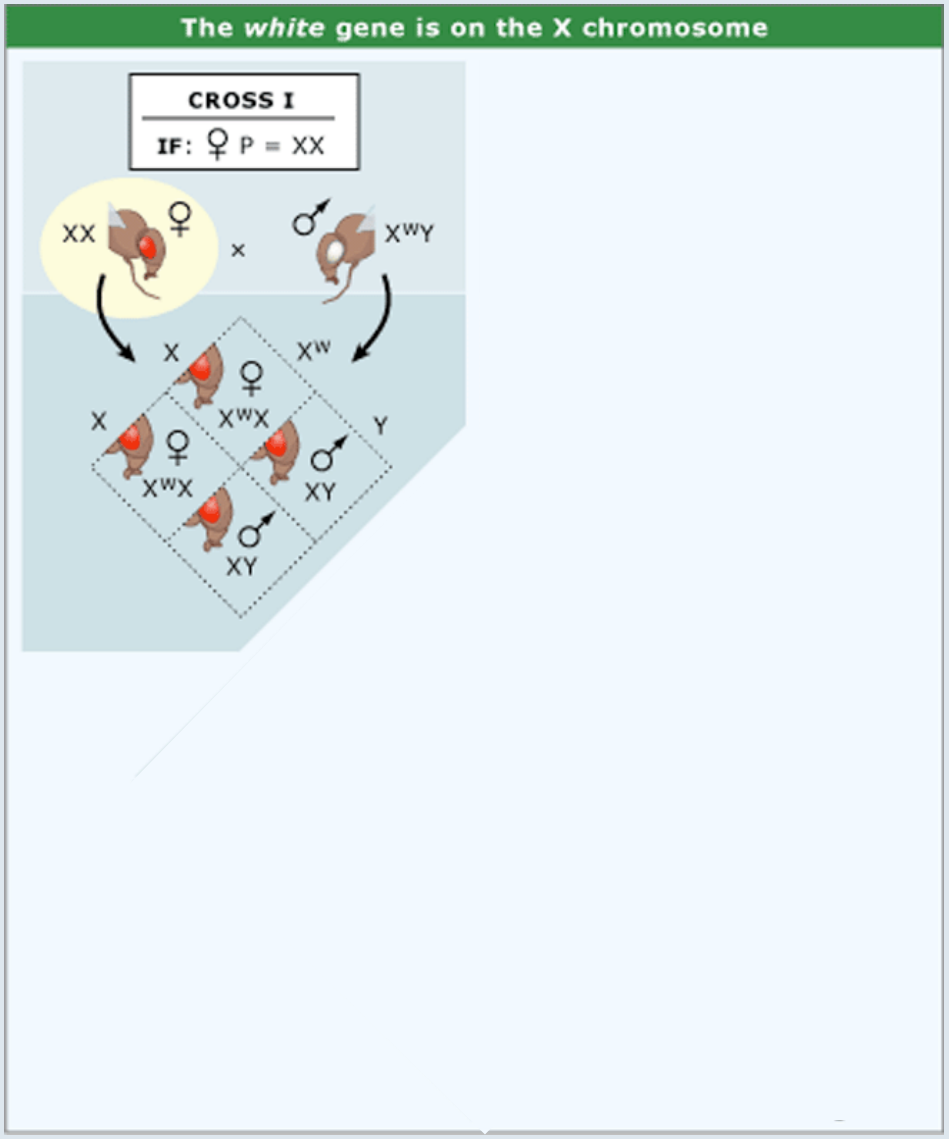
Morgan worked with a mutation, which caused a white eye instead of the red eye normally found in his stocks of *Drosophila*.

He crossed a white-eyed male fly with a normal, red-eyed female.

All the F1's were red-eyed, as might be expected if the red-eye allele were **dominant**.







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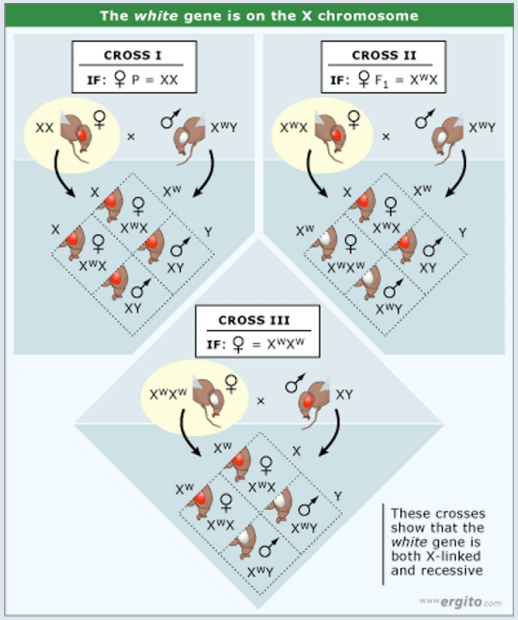

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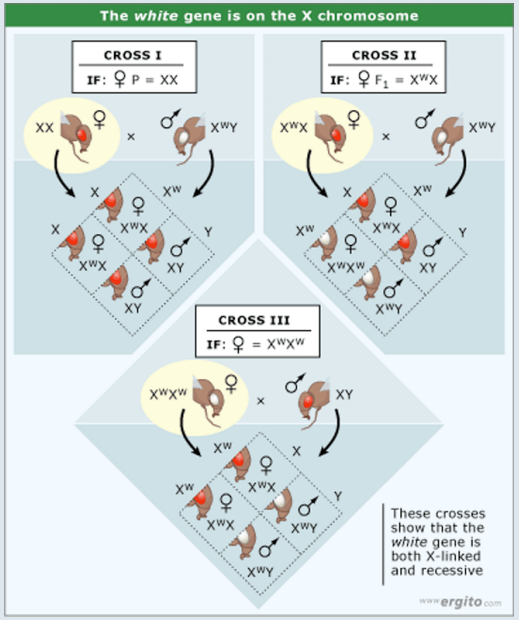
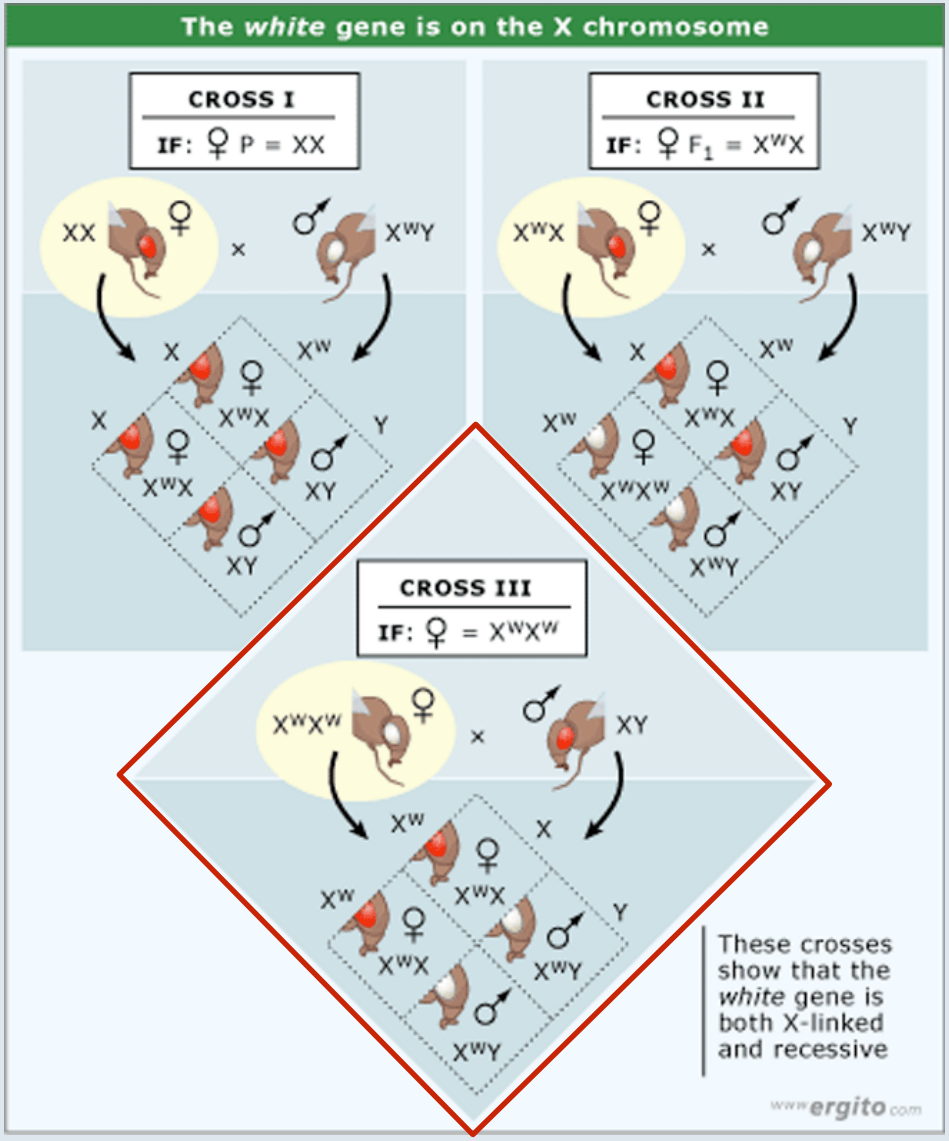




In a cross between a female with mutant white eyes and a wild-type brown body

($w\ y^+ / w\ y^+$)

and a male with wild-type red eyes and a mutant yellow body

($w^+\ y$ / Y),

the **F1** offspring are evenly divided between brown-bodied females with normal red eyes

($w\ y^+ / w^+\ y$)

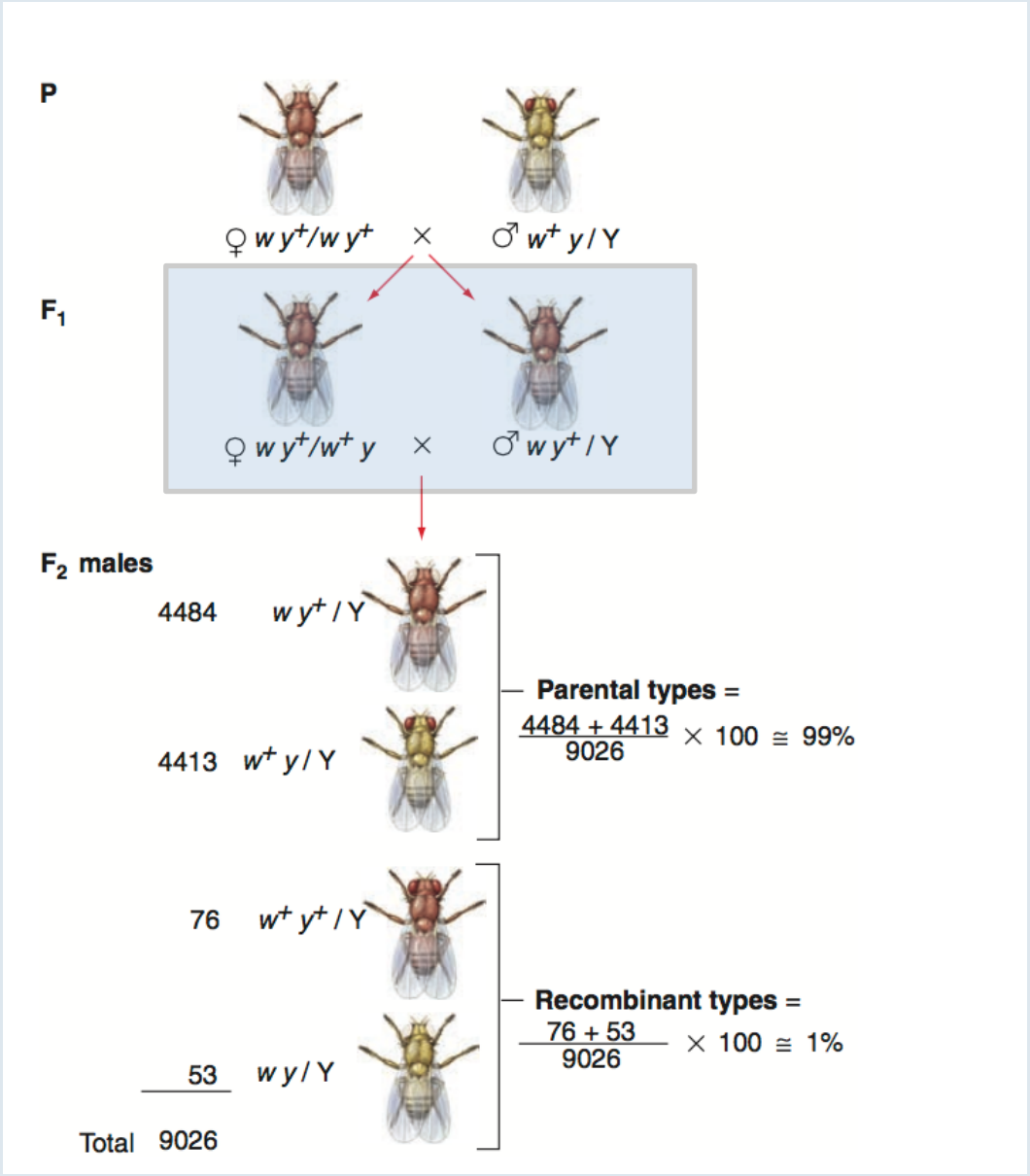
and brown- bodied males with mutant white eyes

($w\ y^+$ / Y)

Males look like their Mothers,

Females receive $w\ y^+$ from their mother and

$w^+\ y$ from their father



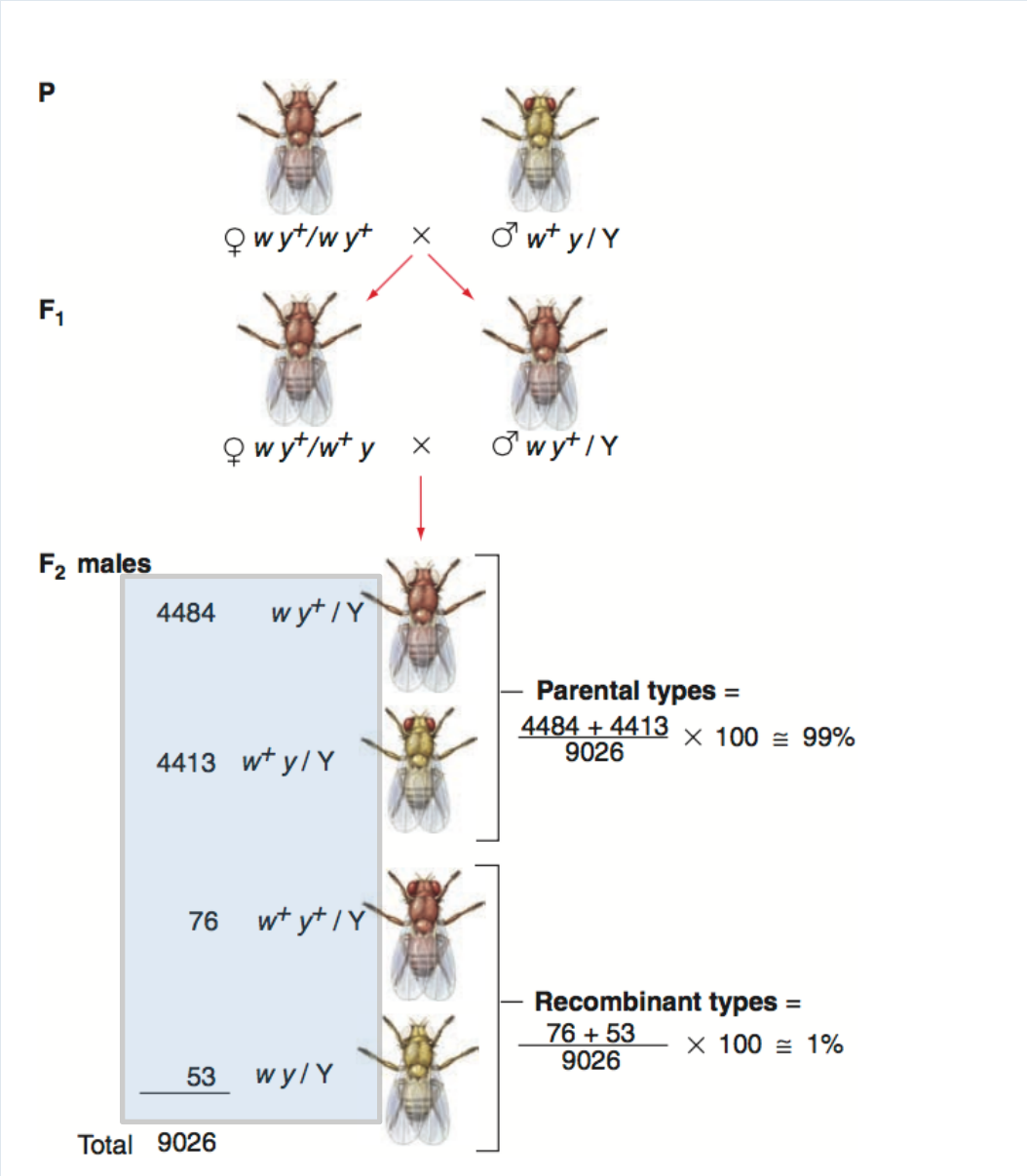
The F1 females should have made four kinds of gametes,

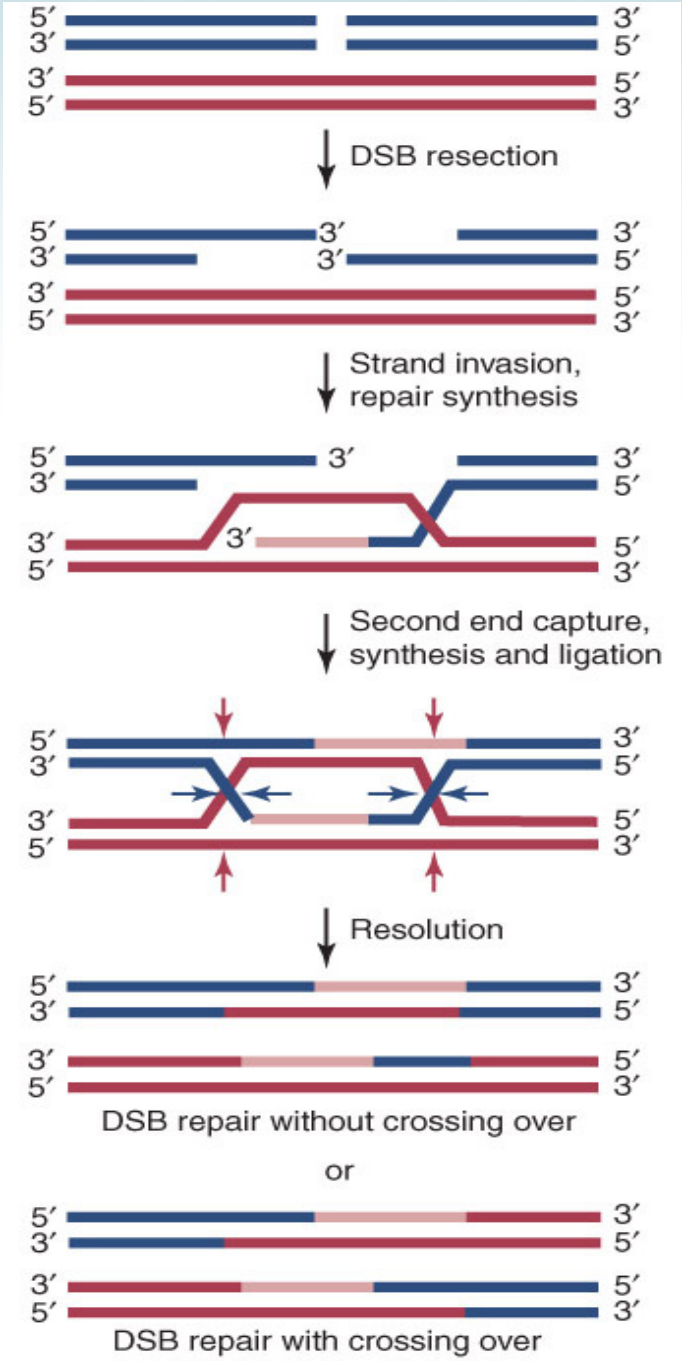
$w\ y^+$, $w^+\ y$, $w^+\ y^+$ and $w\ y$,

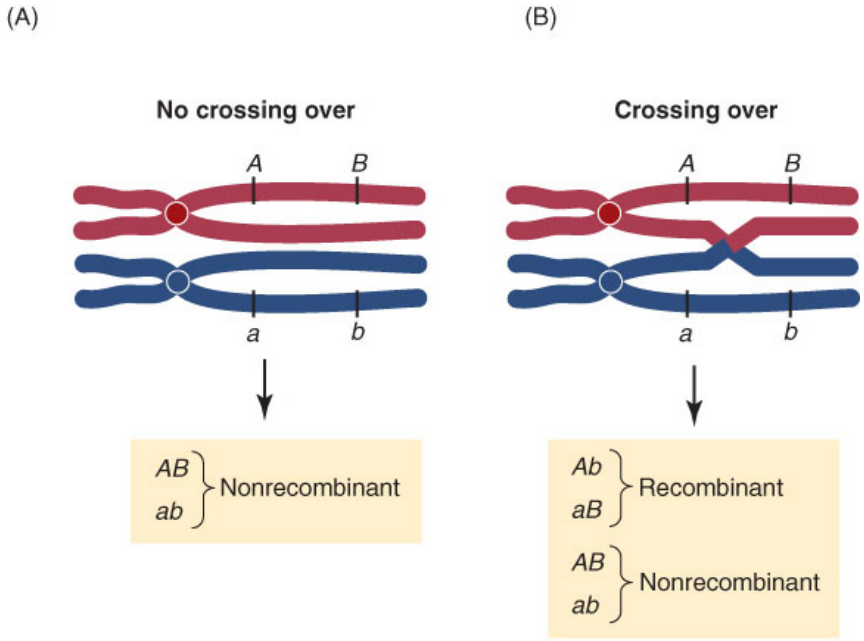
in equal amounts of

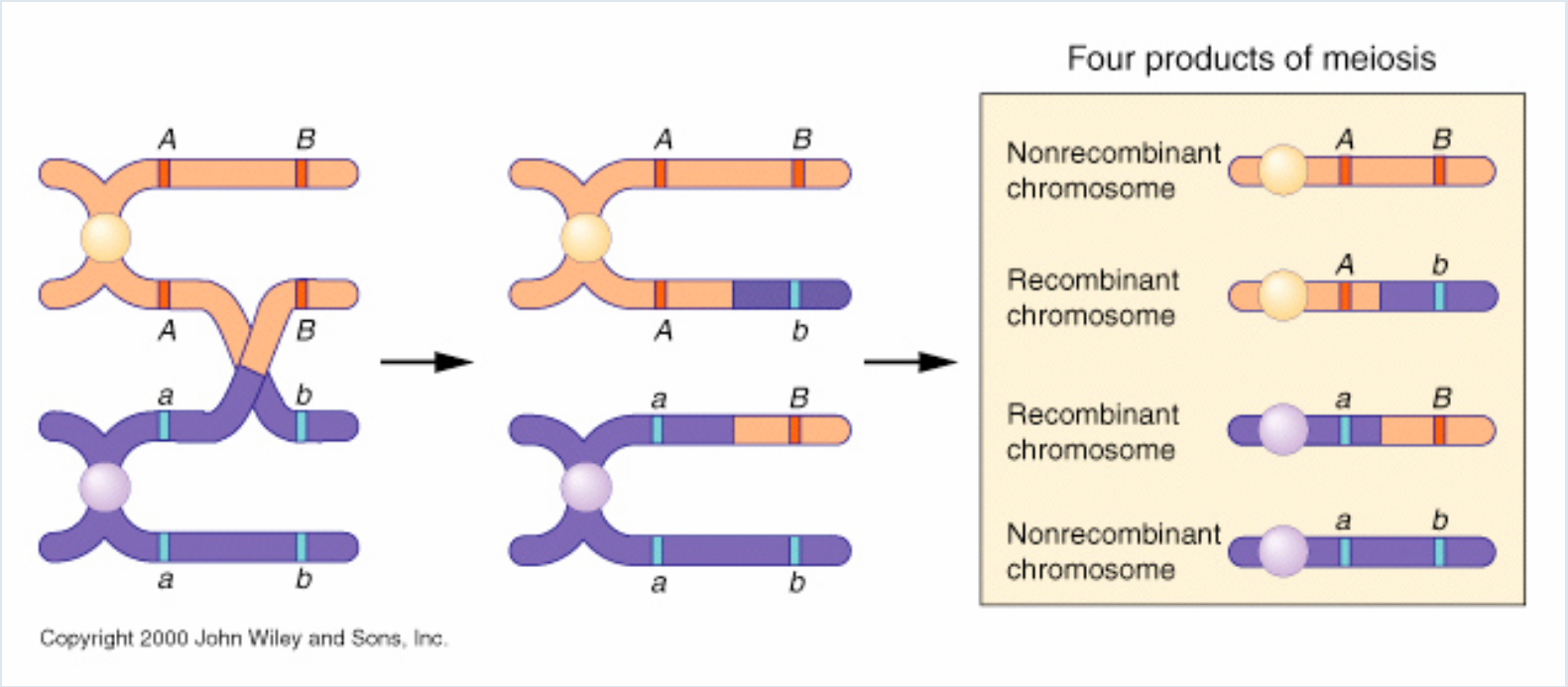
1:1:1:1…. which should have resulted in equal distribution in the F2

but DID NOT...!???









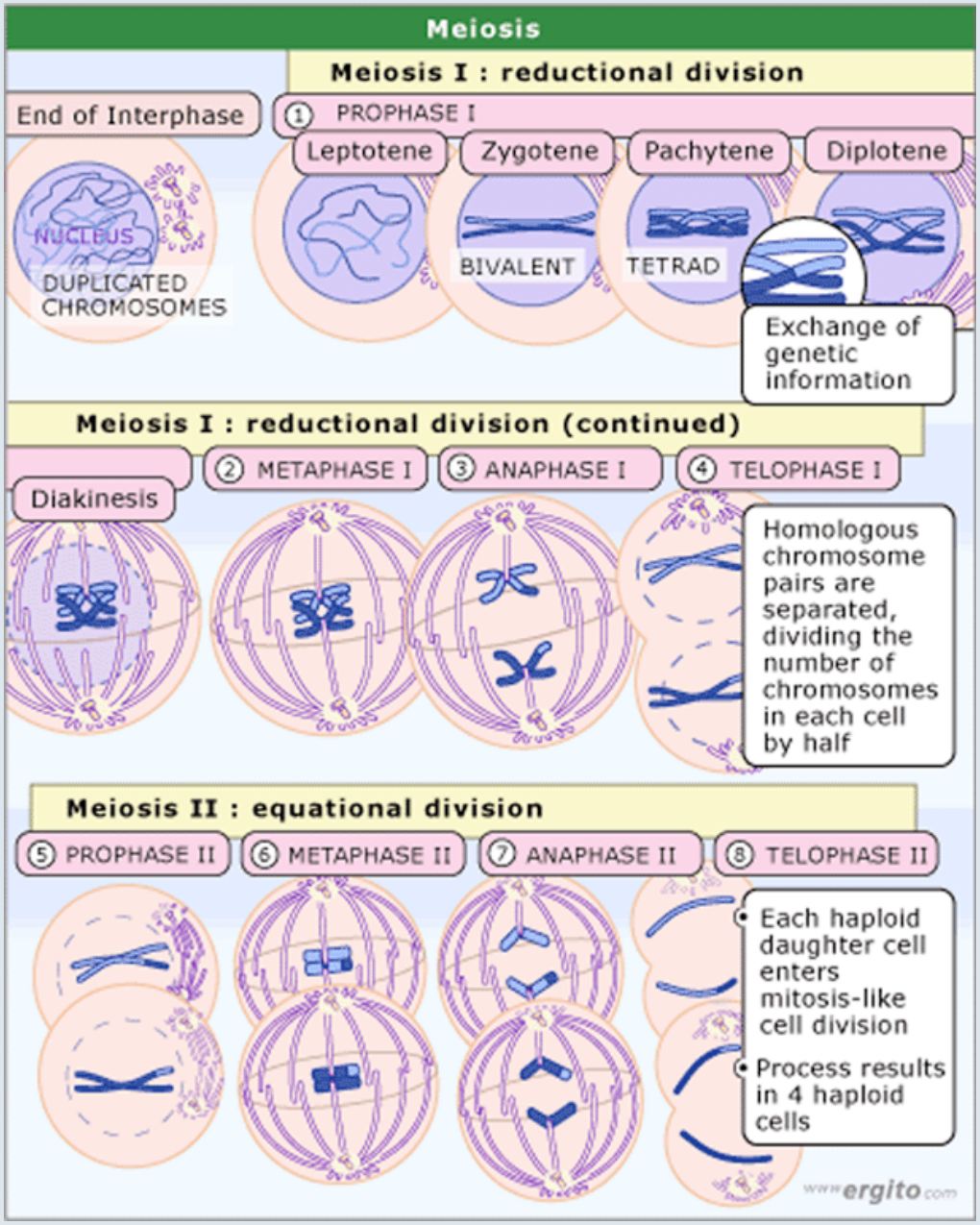
Morgan explained the anomalies by proposing that the two loci were present and "linked" on the same chromosome and also, that any variation from the parental "linkage" must have occurred through the exchange of genetic material by "crossover events"

Morgan suggested that the frequency of such cross-over events (occurring between two genes) was a **function of the genetic distance** between the two loci.

He thus defined the **unit** of genetic distance as having a:

$$\text{recombination frequency} = \frac{\text{number of recombinant progeny}}{\text{total number of progeny}} \times 100\%$$

one crossover **event/100 products of meiosis** = one map unit or 1 **centiMorgan (cM)**.


Meiosis
Meiosis I : reductional division
End of Interphase
1 PROPHASE I
Leptotene
Zygotene
Pachytene
Diplotene
NUCLEUS
DUPLICATED CHROMOSOMES
BIVALENT
TETRAD
Exchange of genetic information
Meiosis I : reductional division (continued)
Diakinesis
2 METAPHASE I
3 ANAPHASE I
4 TELOPHASE I
Homologous chromosome pairs are separated, dividing the number of chromosomes in each cell by half
Meiosis II : equational division
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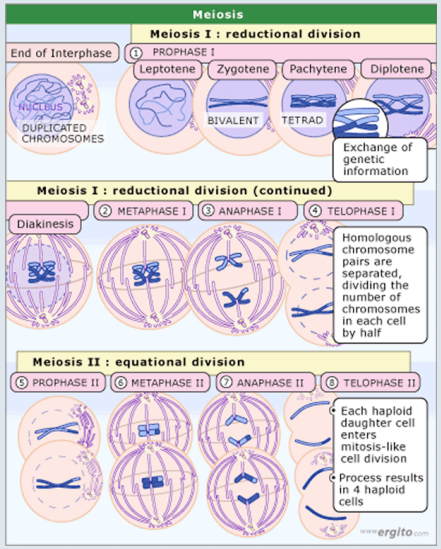
7 ANAPHASE II
8 TELOPHASE II
Each haploid daughter cell enters mitosis-like cell division
Process results in 4 haploid cells
www.ergito.com


Chromosome tetrad showing chiasmata


Meiosis
Meiosis I : reductional division
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Zygotene
Pachytene
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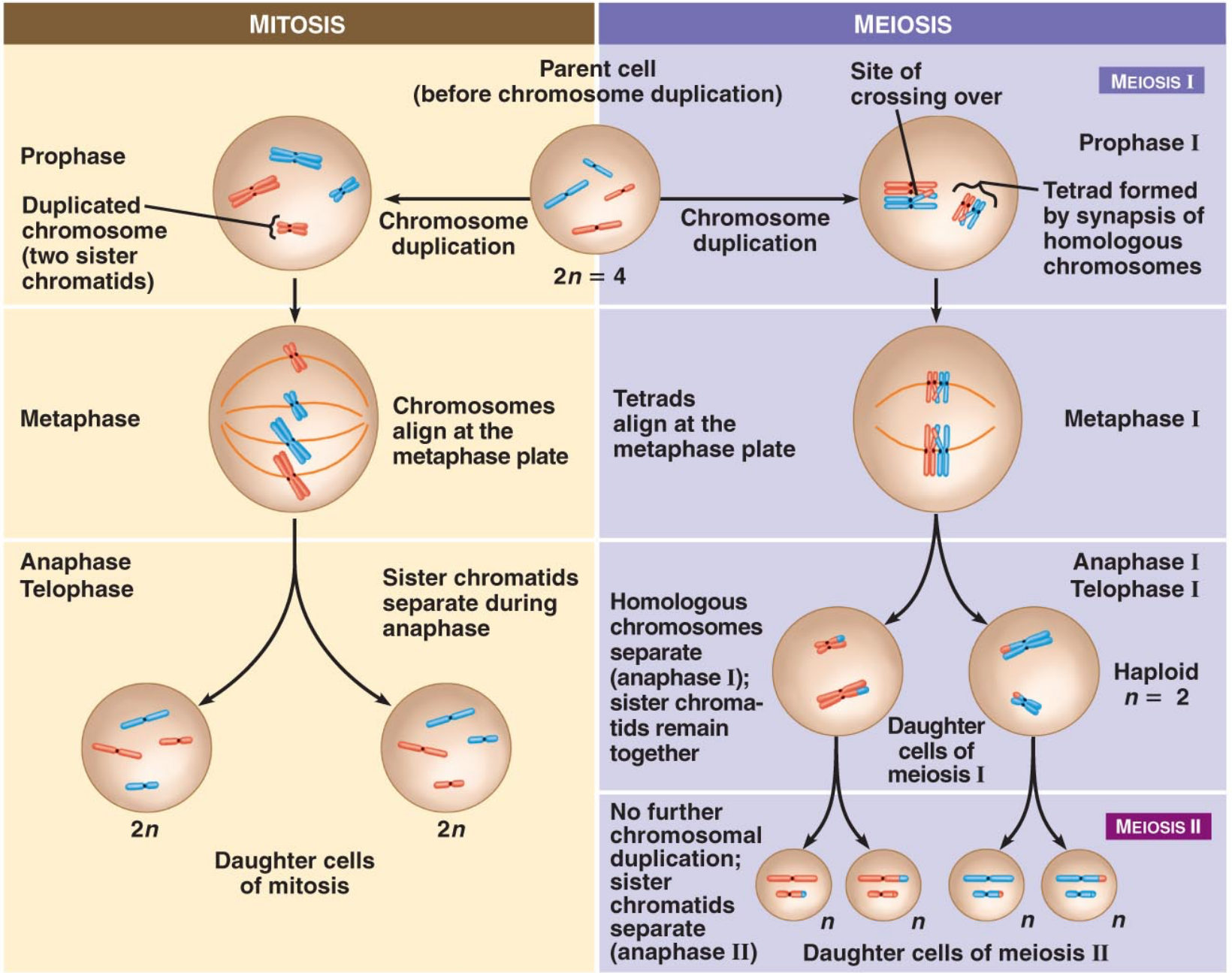
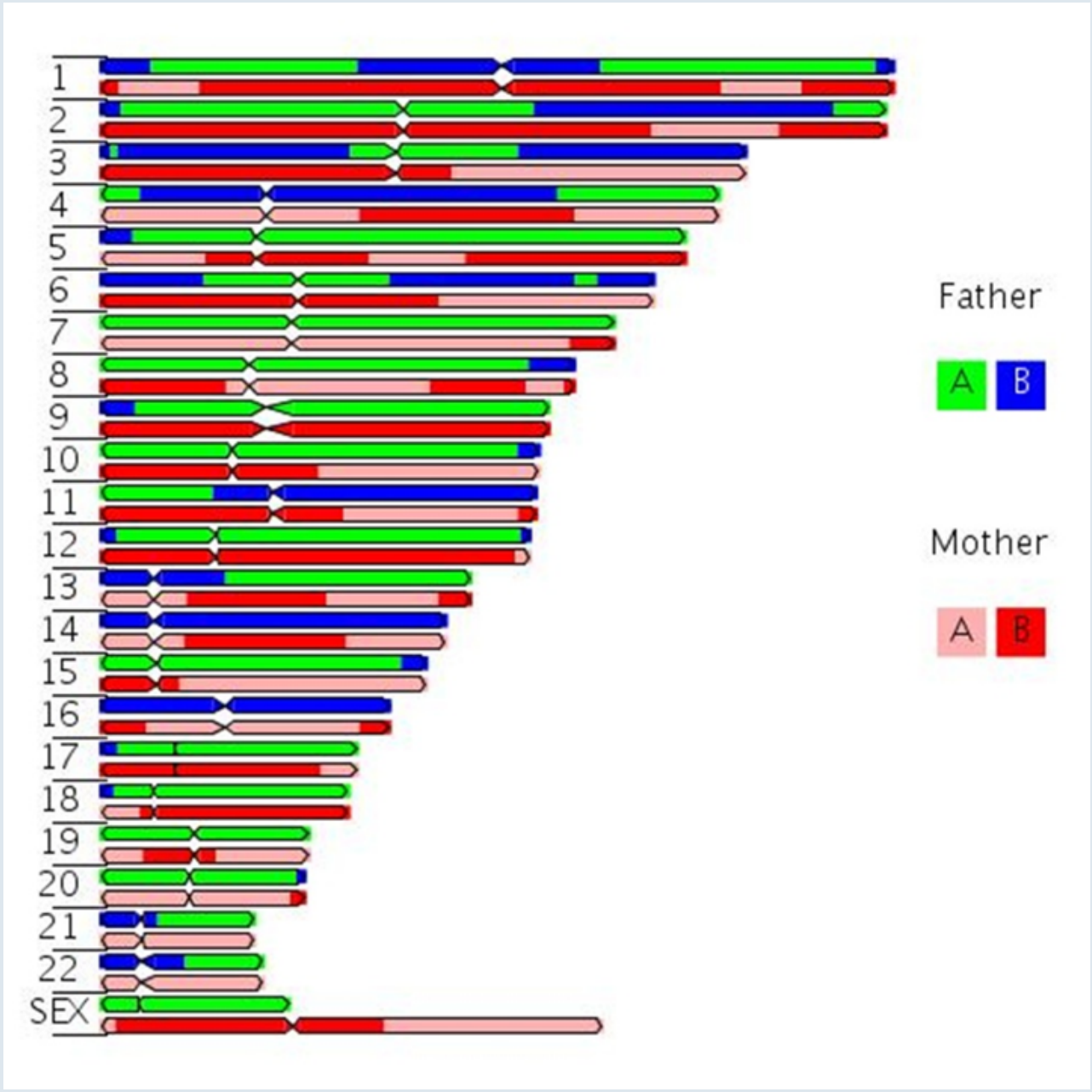
showing chiasmata

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21
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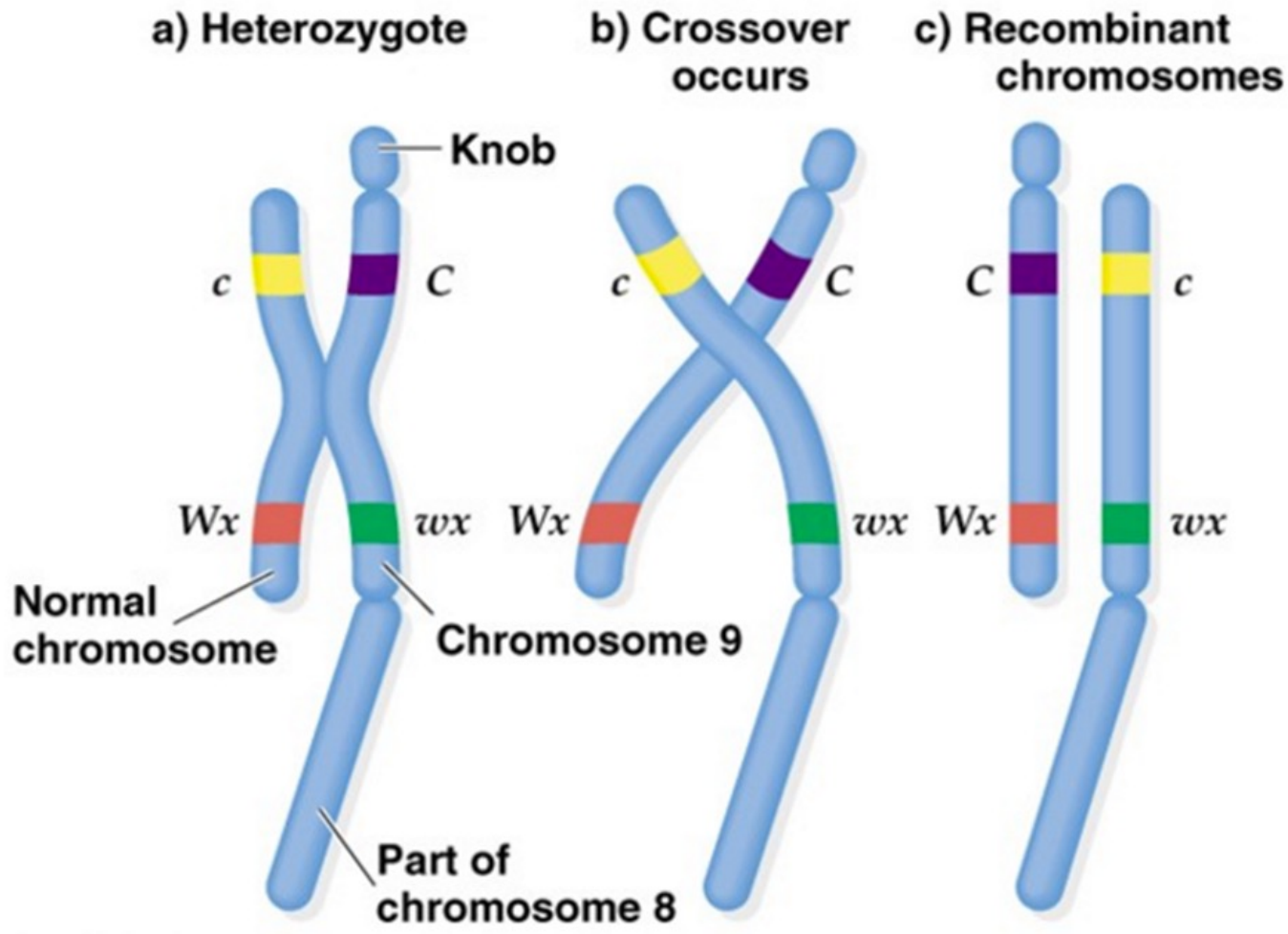
SEX
Father
A
B
Mother
A
B

Fig. 15.2 2nd edition, Creighton's and McClintock's Corn Experiment



Creighton, H. B. & McClintock, B. (1931) *Proc. Natl. Acad. Sci. USA* 17, 492–497]

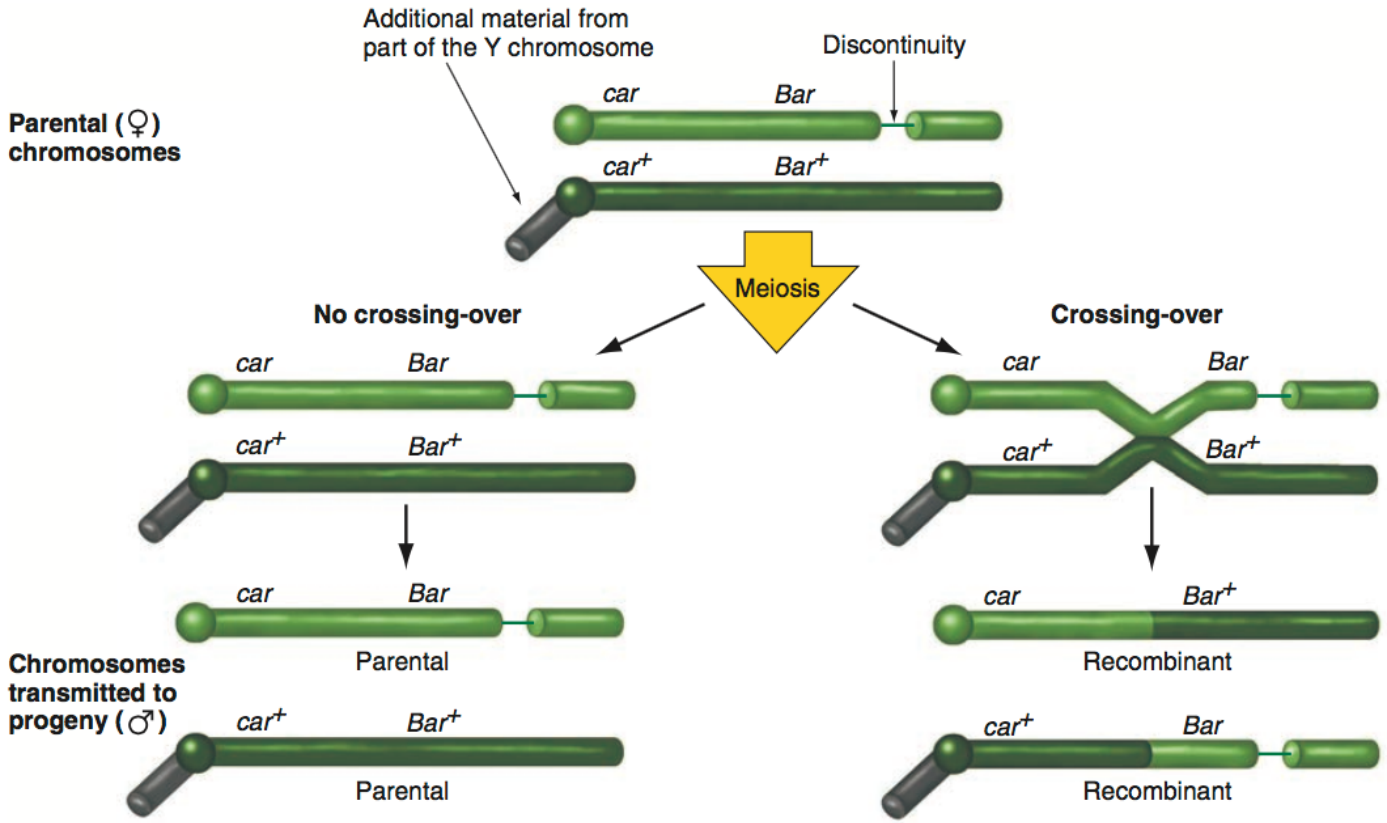


Figure 5.6 **Evidence that recombination results from reciprocal exchanges between homologous chromosomes.** Genetic recombination between the *car* and *Bar* genes on the *Drosophila* X chromosome is accompanied by the exchange of physical markers observable in the microscope. Note that this depiction of crossing-over is a simplification, as genetic recombination actually occurs after each chromosome has replicated into sister chromatids. Note also that the piece of the X chromosome to the right of the discontinuity is actually attached to an autosome.

Curt Sterns found the same phenomenon for eye colour mutants in *Drosophila*

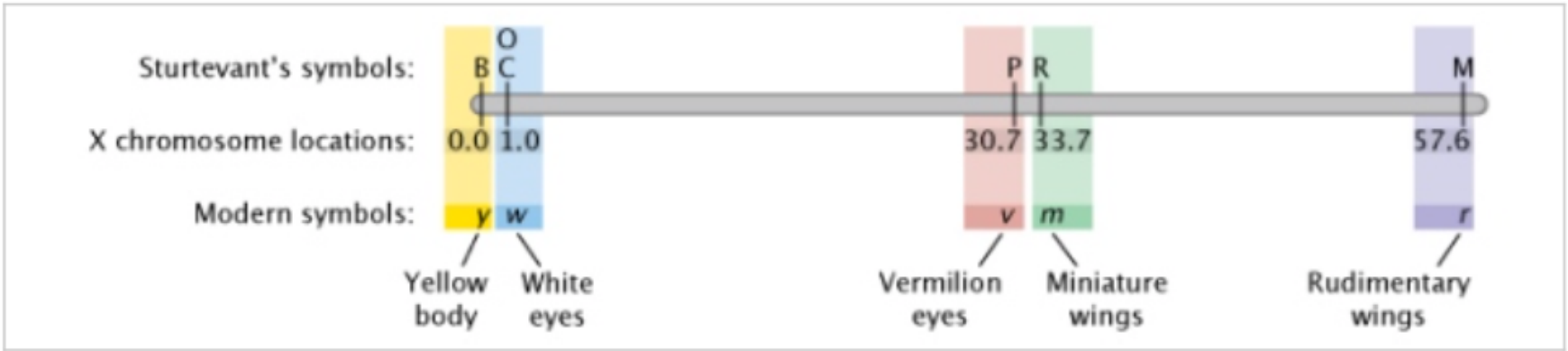
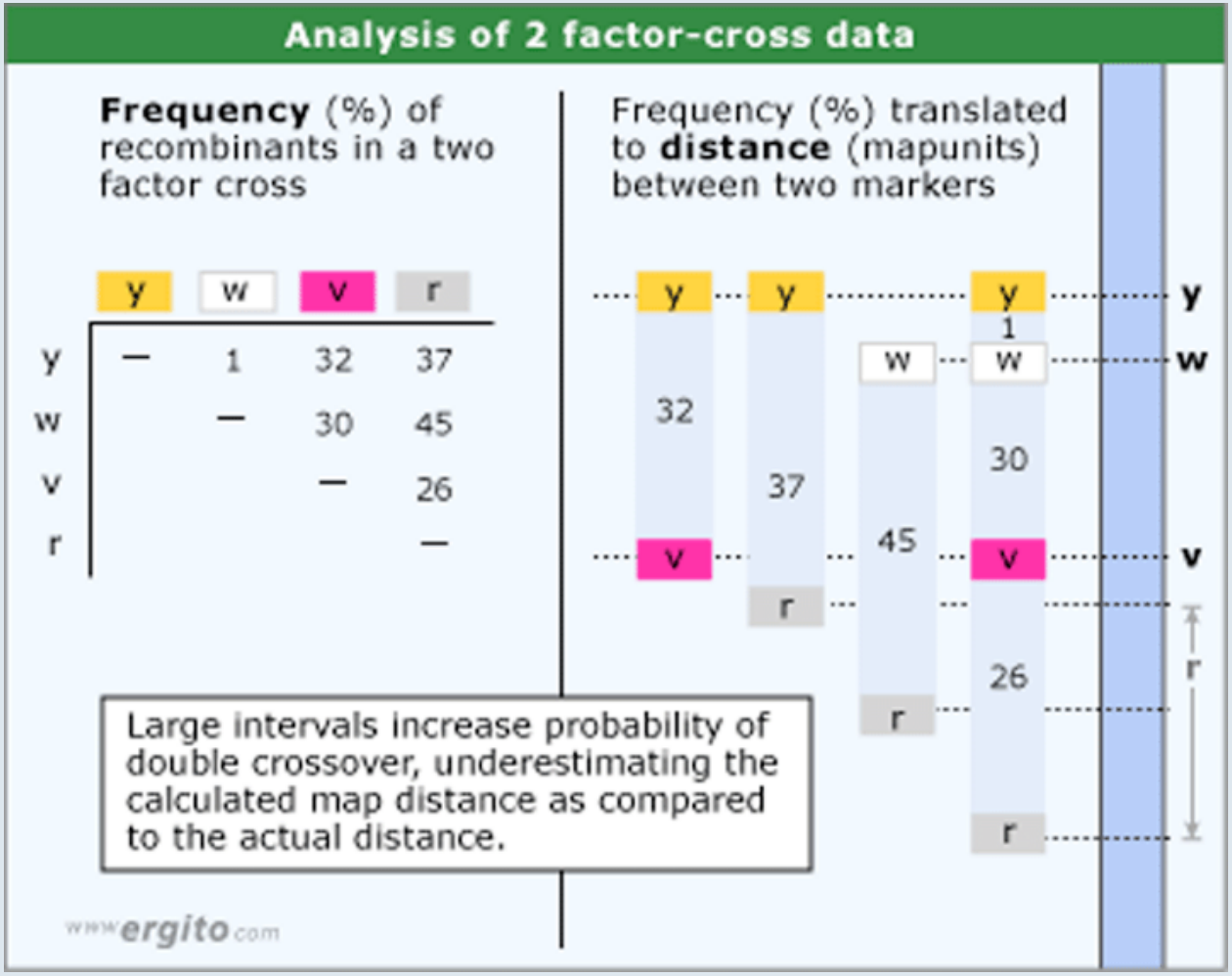


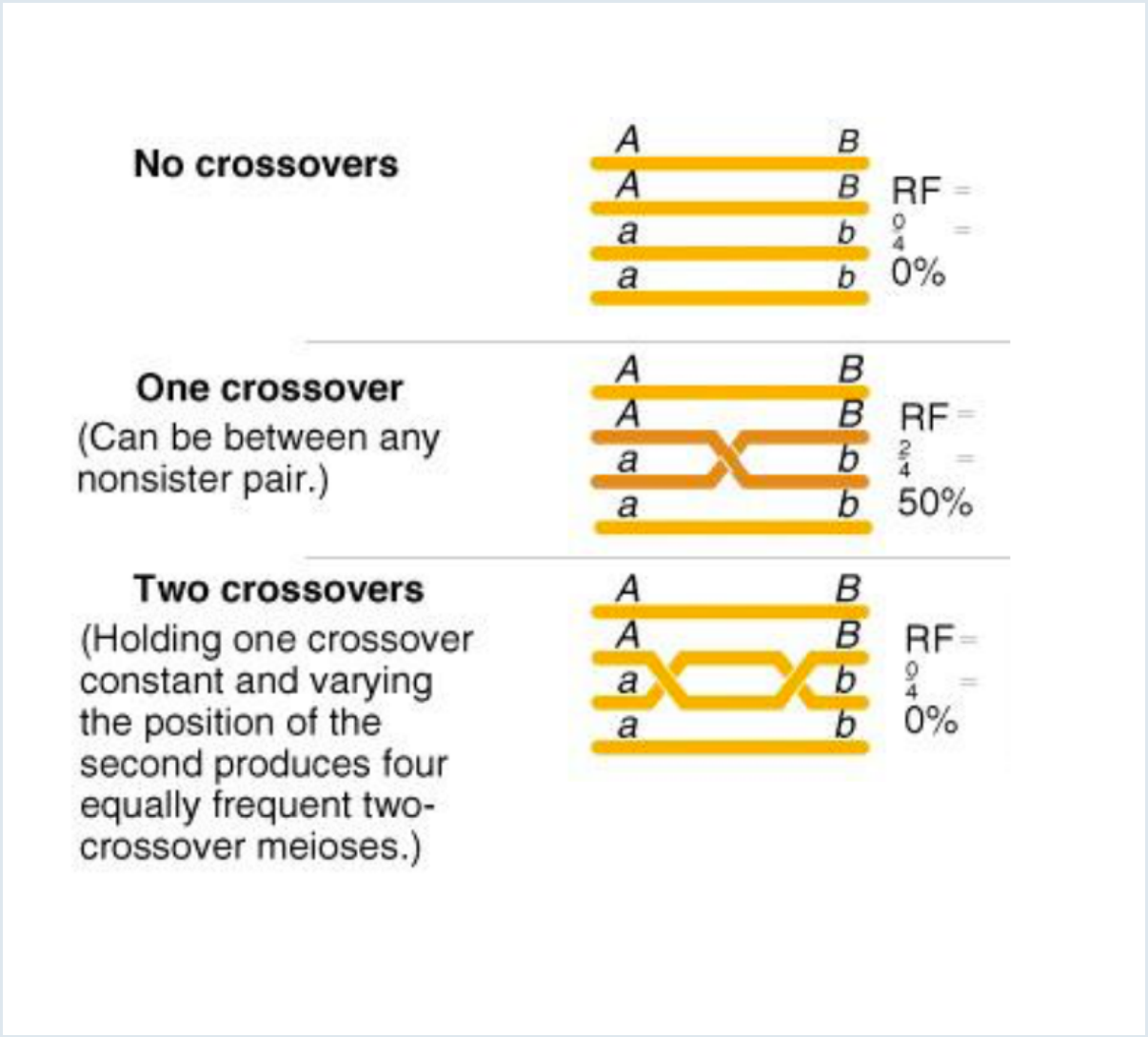
Figure 3: Sturtevant's *Drosophila* gene map.
In Sturtevant's gene map, six traits are arranged along a linear chromosome according to the relative distance of each from trait B. Traits include yellow body (B), white eyes (C, O), Vermillion eyes (P), miniature wings (R), and rudimentary wings (M).

Alfred Henry Sturtevant, a 19-year-old Columbia University undergraduate who was working with Morgan, realized that if the frequency of crossing over was related to distance, one could use this information to map out the genes on a chromosome. After all, the farther apart two genes were on a chromosome, the more likely it was that these genes would separate during recombination.

Therefore, as **Sturtevant** explained it, the "proportion of crossovers could be used as an index of the distance between any two factors" (Sturtevant, 1913). Collecting a stack of laboratory data, Sturtevant went home and spent most of the night drawing the first chromosomal linkage map for the genes located on the X chromosome of fruit flies (Weiner, 1999).



Morgan's student, **Sturtevant,** also observed at it was more accurate to add the intervening distances among multiple small recombinant intervals, rather than rely on a single cross between two fairly distant markers in order to determine accurately the map distance.



Morgan's student, **Sturtevant,** also observed that it was more accurate to add the intervening distances among multiple small recombinant intervals, rather than rely on a single cross between two fairly distant markers in order to determine accurately the map distance.

a	b	c
A	B	C

This is equivalent to the required **heterozygotic parental generation** for all three traits.

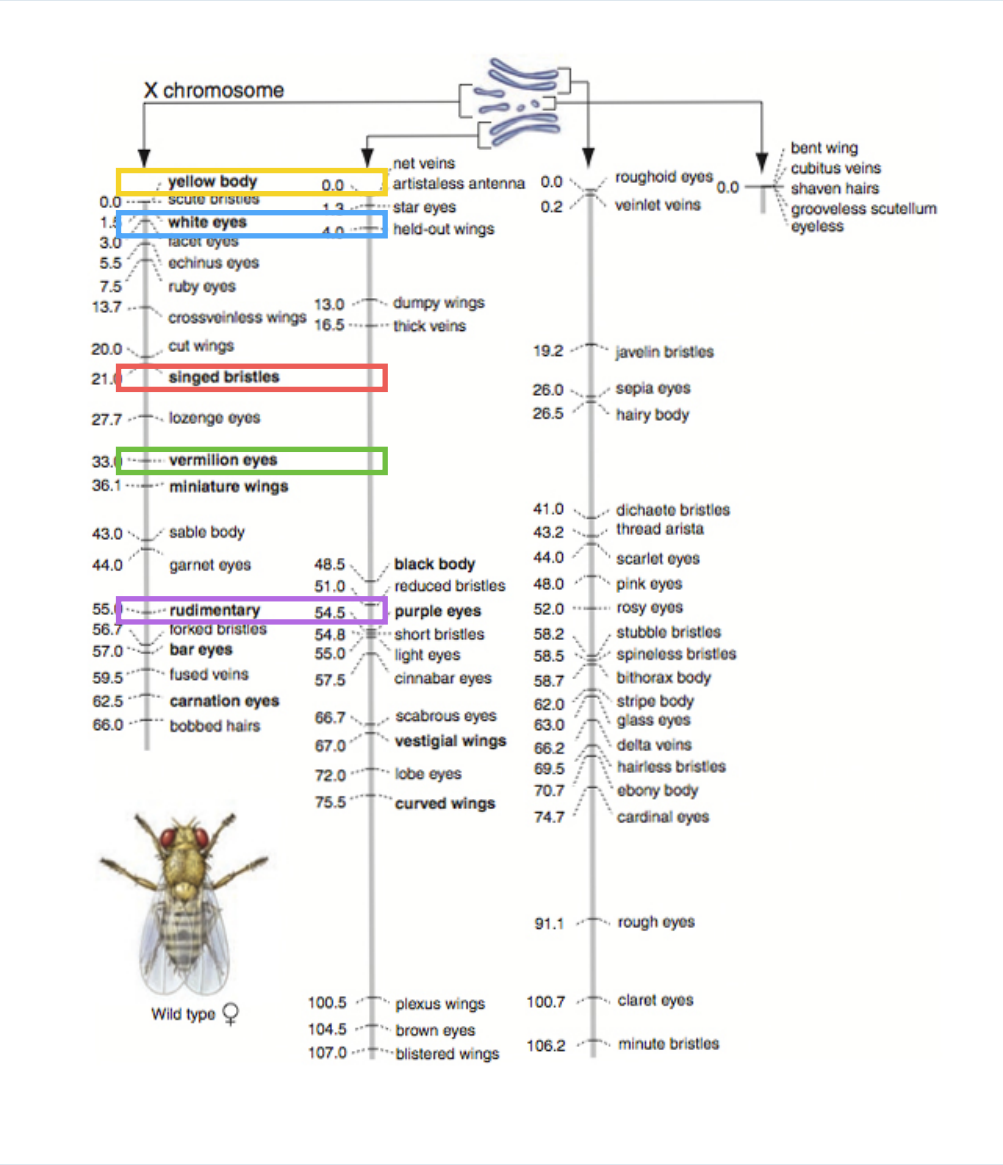
Remember that this is the simplest case where all the wild-type alleles are dominant and, at least in this case, on the same chromosome. Correspondingly, ALL the mutant alleles are iniitially on the other.

In the next generation these triple heterozygotes can be **test- crossed** with triply recessive testers (???)..... In so doing, any "crossing-over" events that have occurred in the formation of the gametes will show through against the triply recessive pairing.

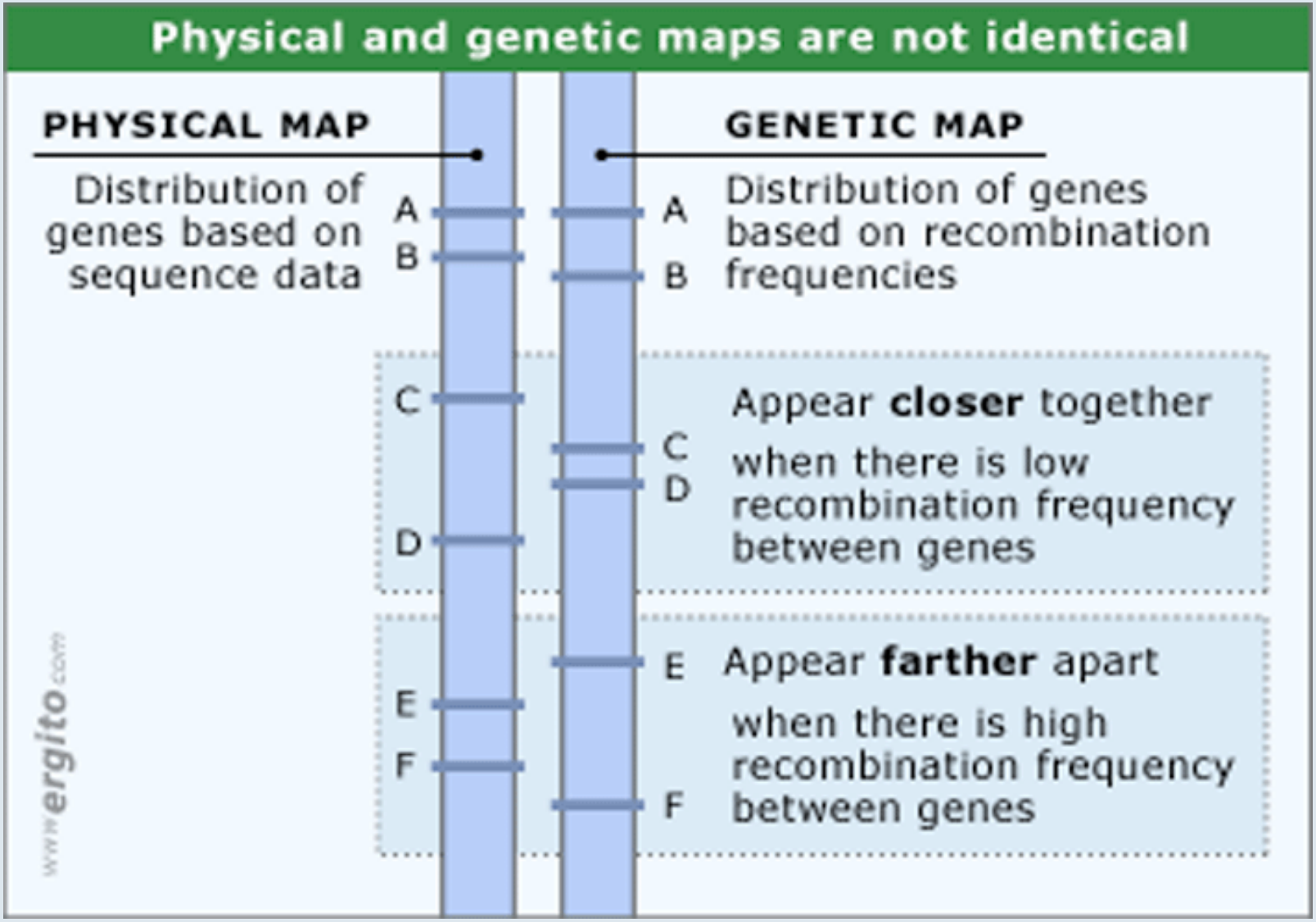
F2: listed as **gametic genotypes**...Crossover Types

a b c	= 230	= 467	= 42.1%	= NCO
A B C	= 237			
a B C	= 82	= 161	= 14.5%	= SCO
A b c	= 79			
a b C	= 200	= 395	= 35.6%	= SCO
A B c	= 195			
a B c	= 44	= 86	= 7.8%	= DCO
A b C	= 42			

Sturtevant also realized that if you had three genes that demonstrated "linkage"..... you could look at relative distances among the three to quickly organize the genes into their genetic order.



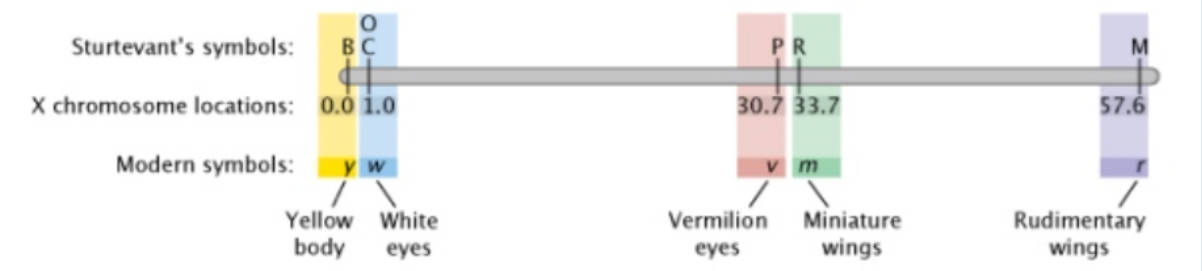
As a result **Sturtevant** was able to appreciate how genes could be mapped on a chromosome, simply by applying the rules of linkage that Morgan had presented, and assign positions or genetic loci on chromosomes as a function of their recombination frequencies -as long as the genes demonstrated linkage.



Even so, genetic maps do not always equate to physical maps.

Assorted types of gene linkage

Complete linkage refers to genes that are located so close together on any given chromosome that they are always inherited as a single "linked"unit. and can only be different iated through the use of mutants.



C gene permitted colour to show through in the eyes,
O gene, in the recessive form gave rise to eosin coloured eyes as opposed to vermillion

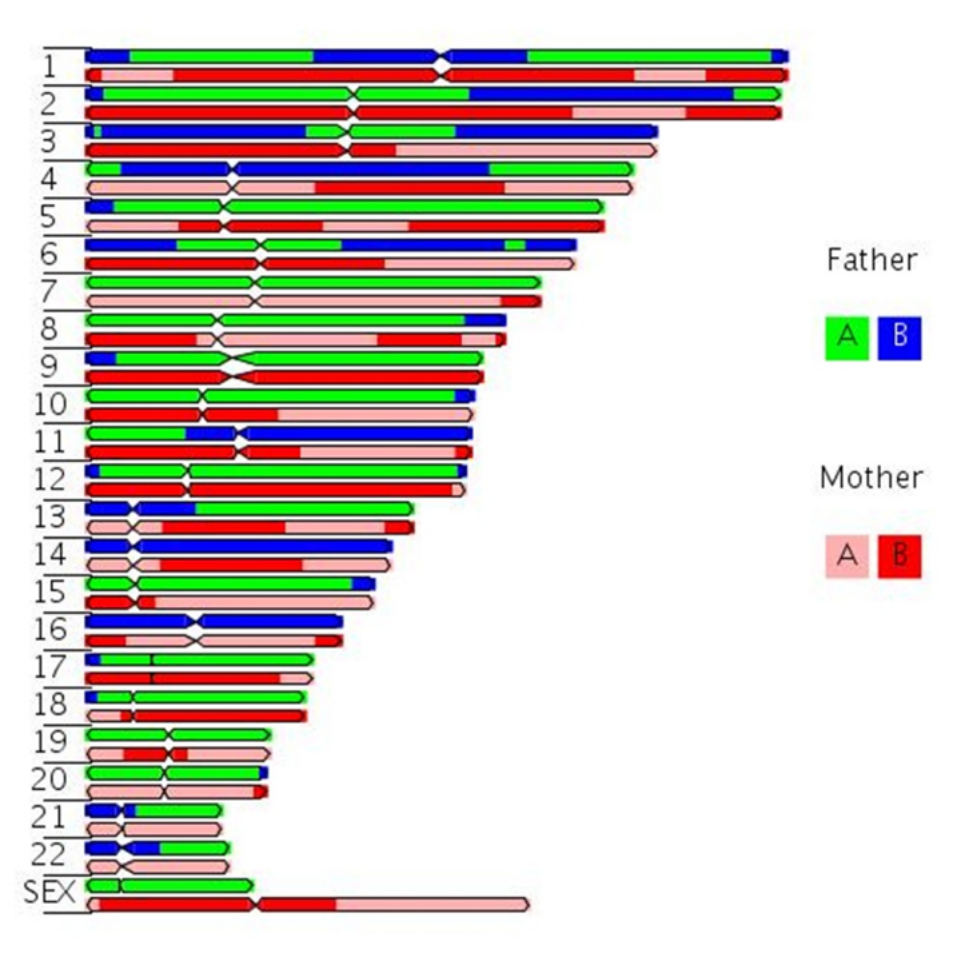
Incomplomplete linkage refers to genes that show recombinational associations between 0% and 50%

Statistical linkage refers to genes that only show statistical differences from independently assorted genes +/- 50%

Syntenic genes refers to genes that are physically located on the same chromosome, whether or not they show linkage.

What about genetic analyses in the **absence** of recombination.

Can we analyze chromosomes with a "fixed" linkage that will not change as a result of meiotic recombination (an important tool if you want to do a number of serial genetic crosses).



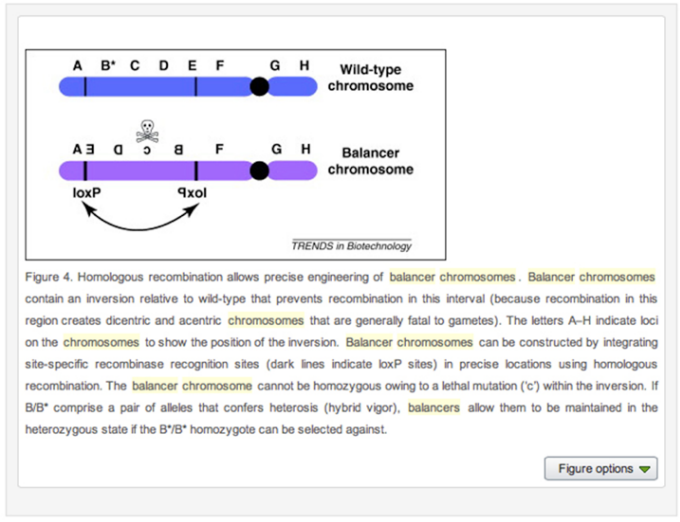


Figure 4. Homologous recombination allows precise engineering of balancer chromosomes. Balancer chromosomes contain an inversion relative to wild-type that prevents recombination in this interval (because recombination in this region creates dicentric and acentric chromosomes that are generally fatal to gametes). The letters A–H indicate loci on the chromosomes to show the position of the inversion. Balancer chromosomes can be constructed by integrating site-specific recombinase recognition sites (dark lines indicate loxP sites) in precise locations using homologous recombination. The balancer chromosome cannot be homozygous owing to a lethal mutation ('c') within the inversion. If B/B* comprise a pair of alleles that confers heterosis (hybrid vigor), balancers allow them to be maintained in the heterozygous state if the B*/B* homozygote can be selected against.

Figure options

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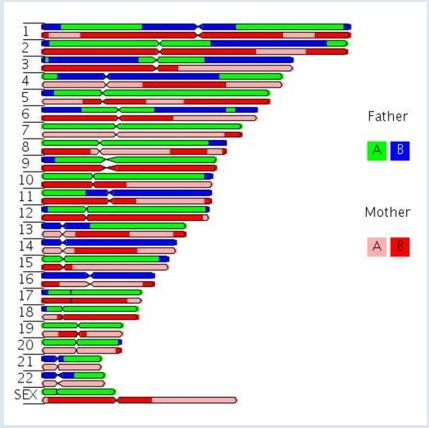

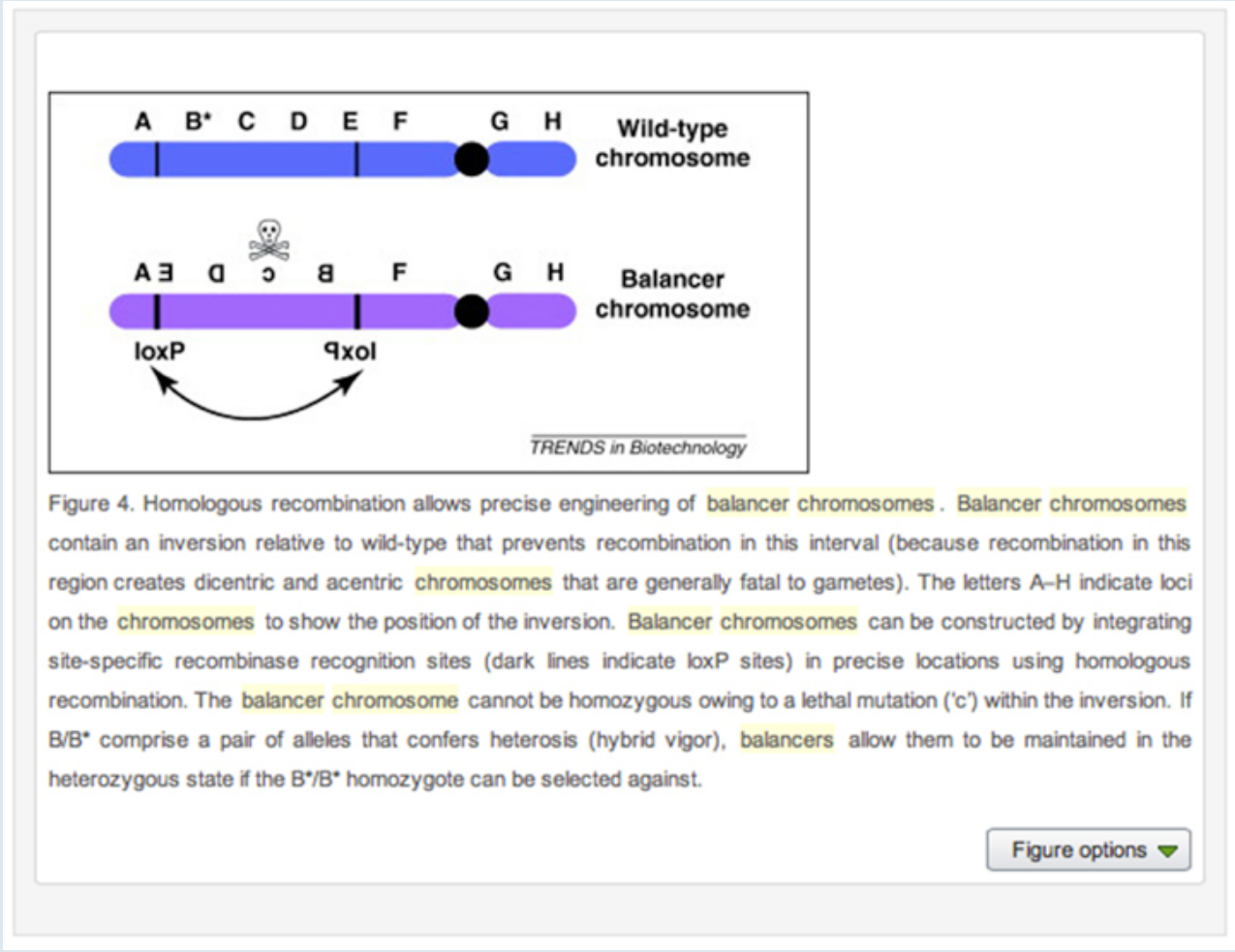

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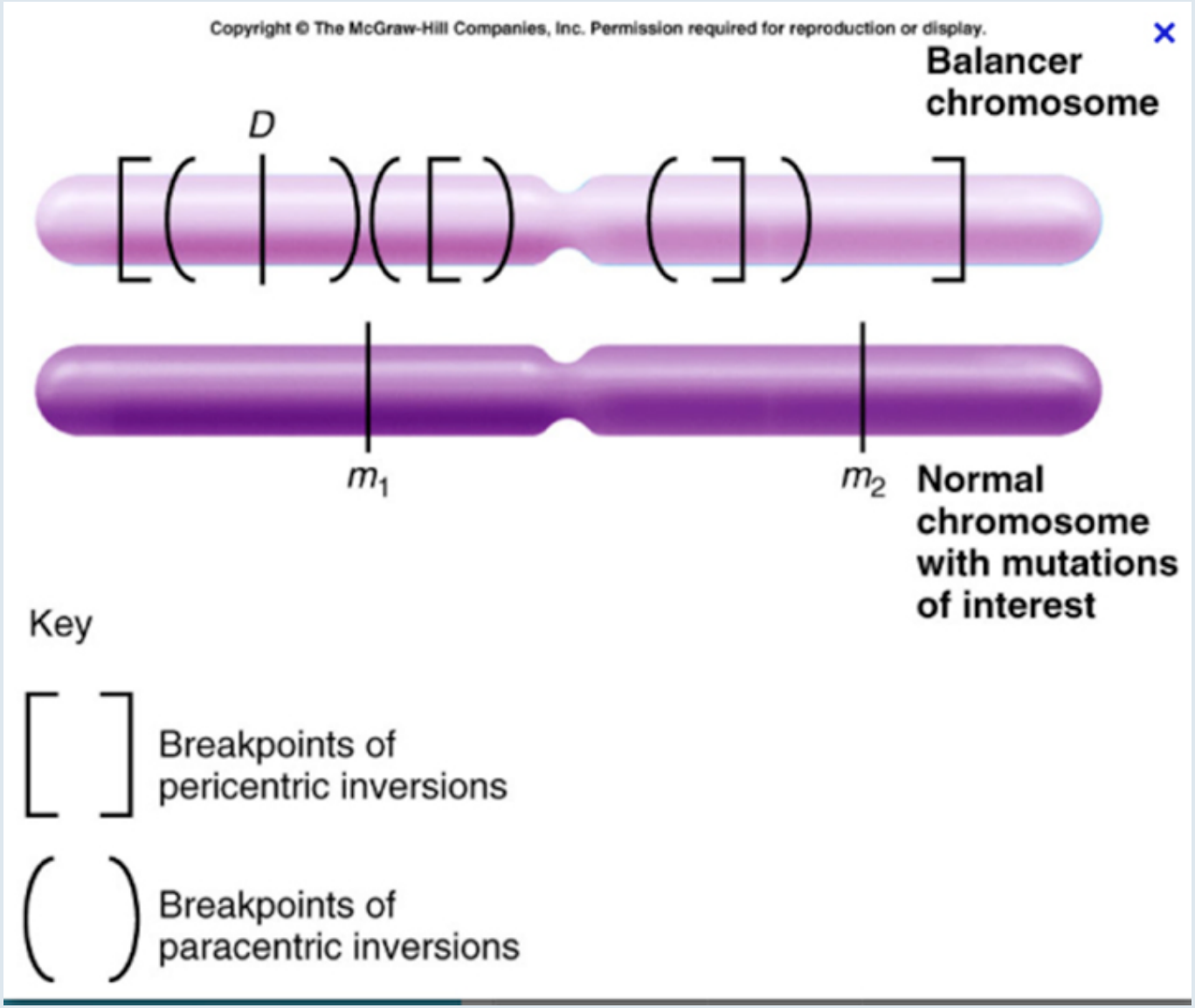
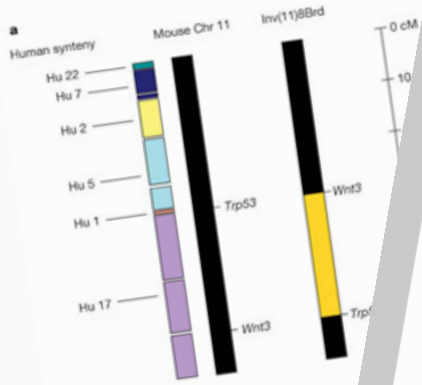
Figure options



nature International weekly journal of science

FIGURE 1. A balancer chromosome screen for the conserv... 11/human chromosome 17.

From the following article:
Functional genetic analysis of mouse chromosome 11
Benjamin T. Kile, Kathryn E. Hentges, Amander T. Clark, Hisashi Nakamura, Andrew P. Salinger, Bin Liu, Allan Bradley and Monica J. Justice
Nature 425, 81-86(4 September 2003)
doi:10.1038/nature01865



a, The distal two-thirds of mouse chromosome 11 is ... balancer contains a 24-cM inversion (34 Mb; yellow ... C57BL/6J males (black chromosomes) are mated to ... tail and ventrum) to generate first generation (F_1) ... mice carrying a balancer and *Rex* (dominant curly ... Informative F_2 animals identified by their yellow ... asterisks; test class) in the F_3 offspring. Mice ho...

▸ Figures & Tab...

G3 · Genes | Genomes | Genetics

Simplified Insertion of Transgenes Onto Balancer Chromosomes via Recombinase-Mediated Cassette Exchange

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Abstract

Balancer chromosomes are critical tools for *Drosophila* genetics. Many useful transgenes are inserted onto balancers using a random and inefficient process. Here we describe balancer chromosomes that can be directly targeted with transgenes of interest via recombinase-mediated cassette exchange (RMCE).

RMCE | targeted transgenesis | phiC31 | *Drosophila* | balancer

In *Drosophila*, balancer chromosomes bearing multiple inversions are routinely used in genetic manipulations and in the maintenance of sterile or lethal mutations as balanced heterozygotes. Balancer chromosomes typically carry dominant markers, the most common of which affect adult structures only. However, using transgenic approaches, many new markers and functions have been assigned to balancers in efforts to improve their utility. For example, transgenic insertions have been created to facilitate the identification of balanced progeny at different stages of development, including balancers that carry histological or fluorescent markers driven by embryonic enhancers (including so-called "blue" and "green" balancers) (Casso *et al.* 2000; Halfon *et al.* 2002; Le *et al.* 2006; Panzer *et al.* 1993; Rudolph *et al.* 1999). Balancers carrying transgenic insertions of GAL80, a repressor of

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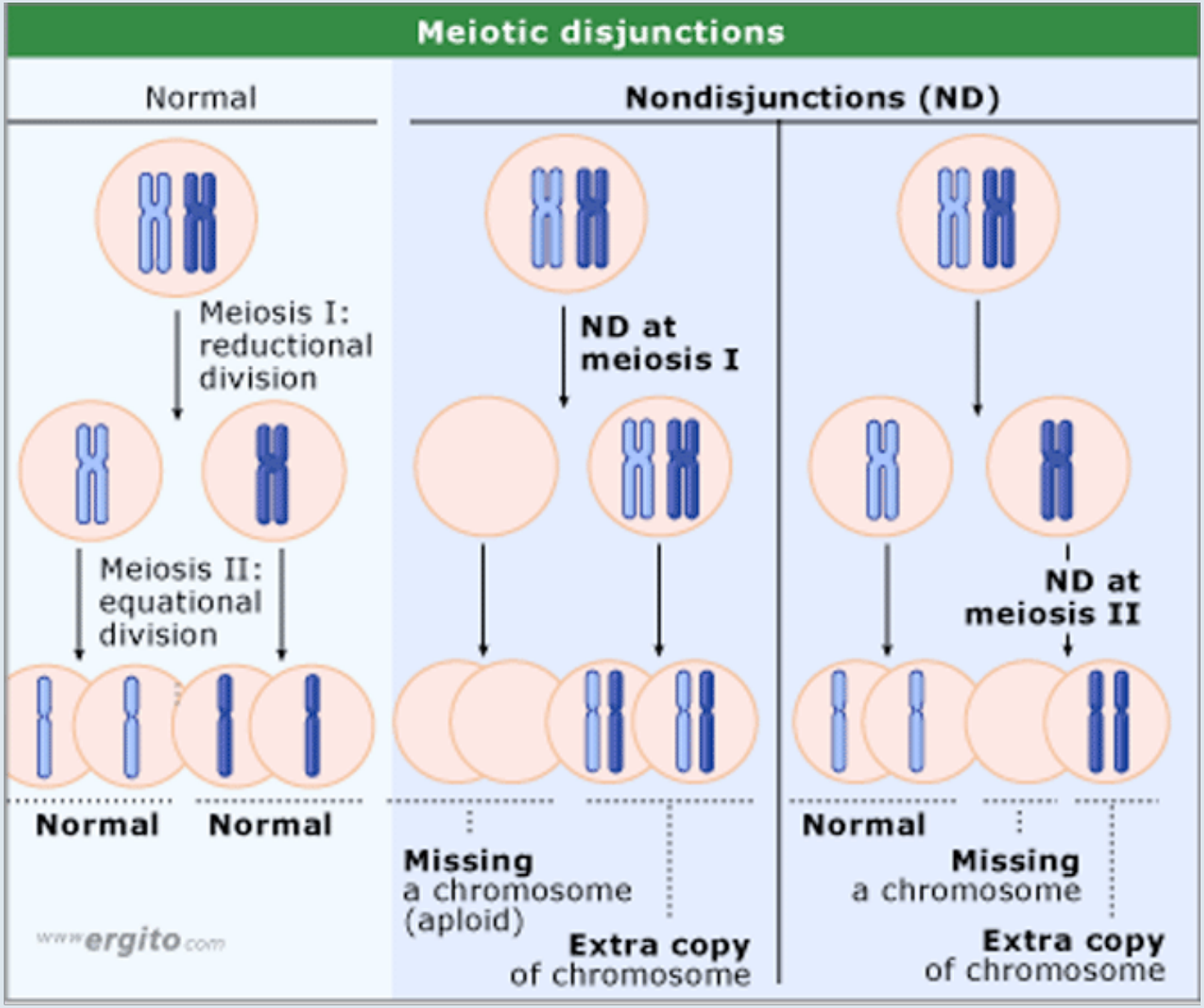
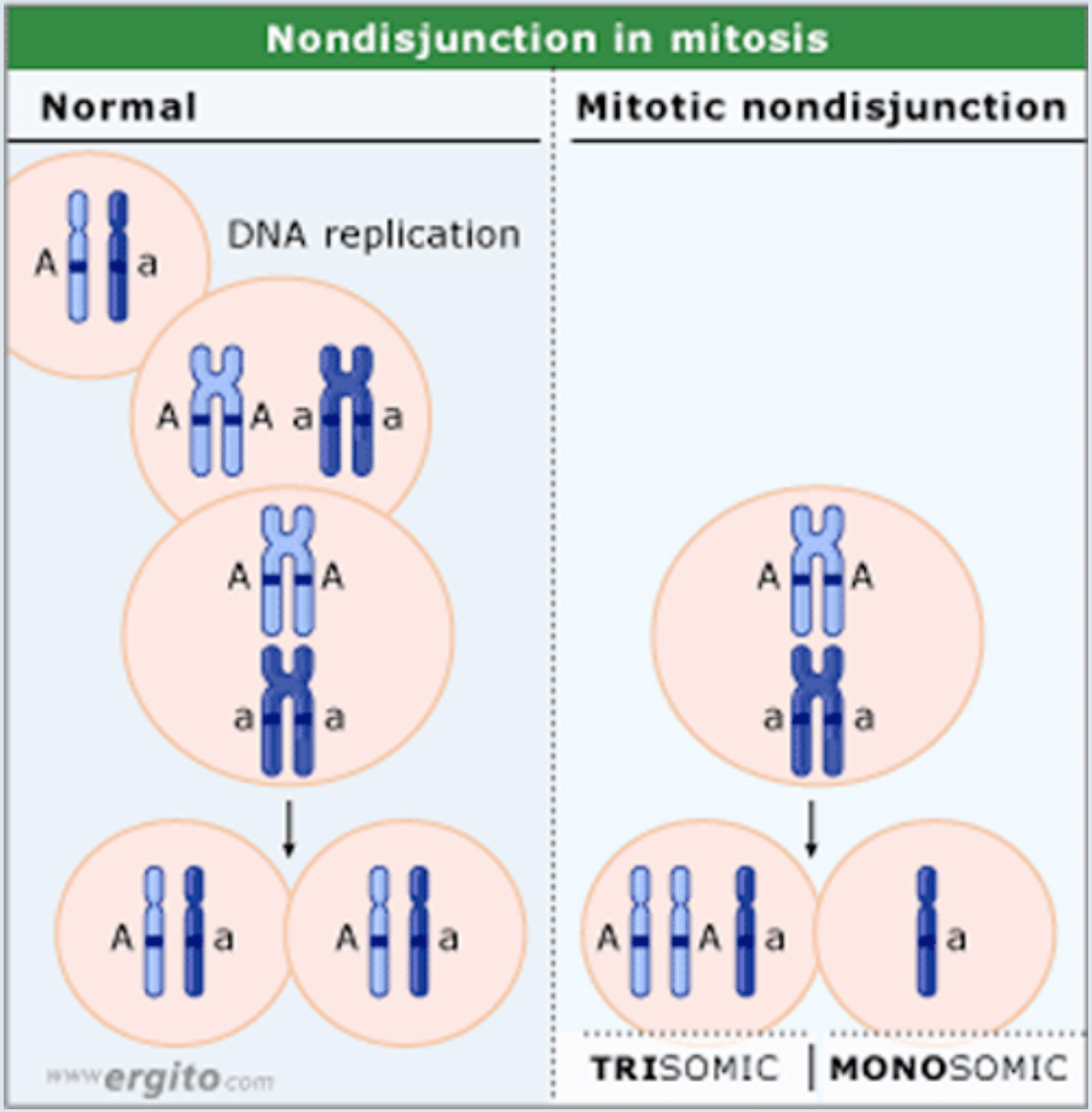


Meiotic Nondysjunction


Nondisjunction in mitosis
Normal
Mitotic nondisjunction
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A
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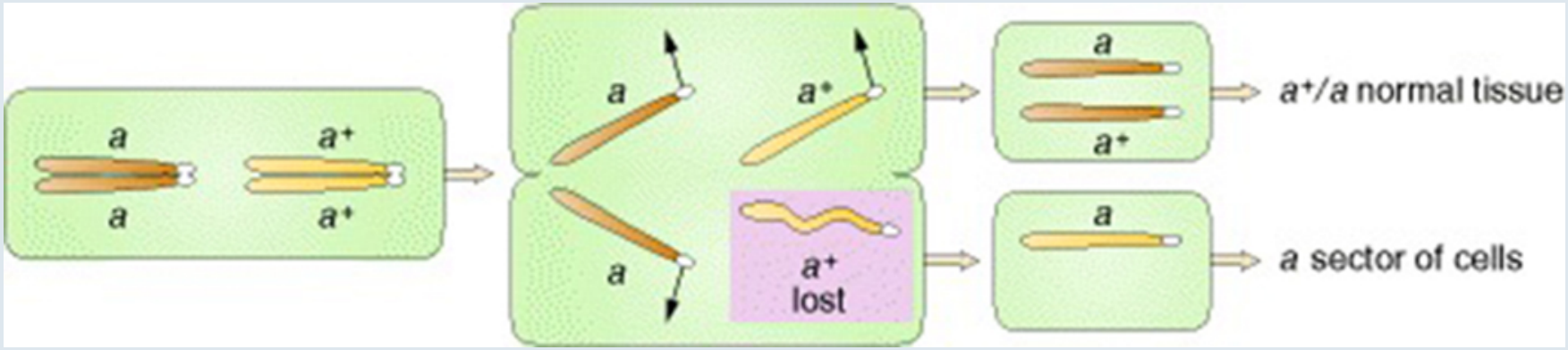
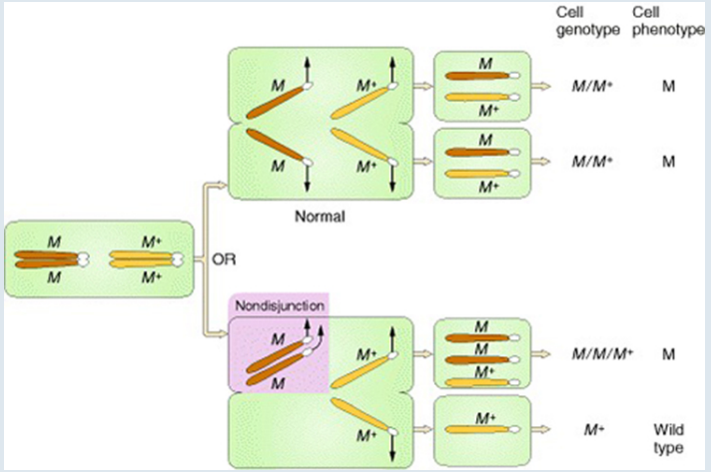
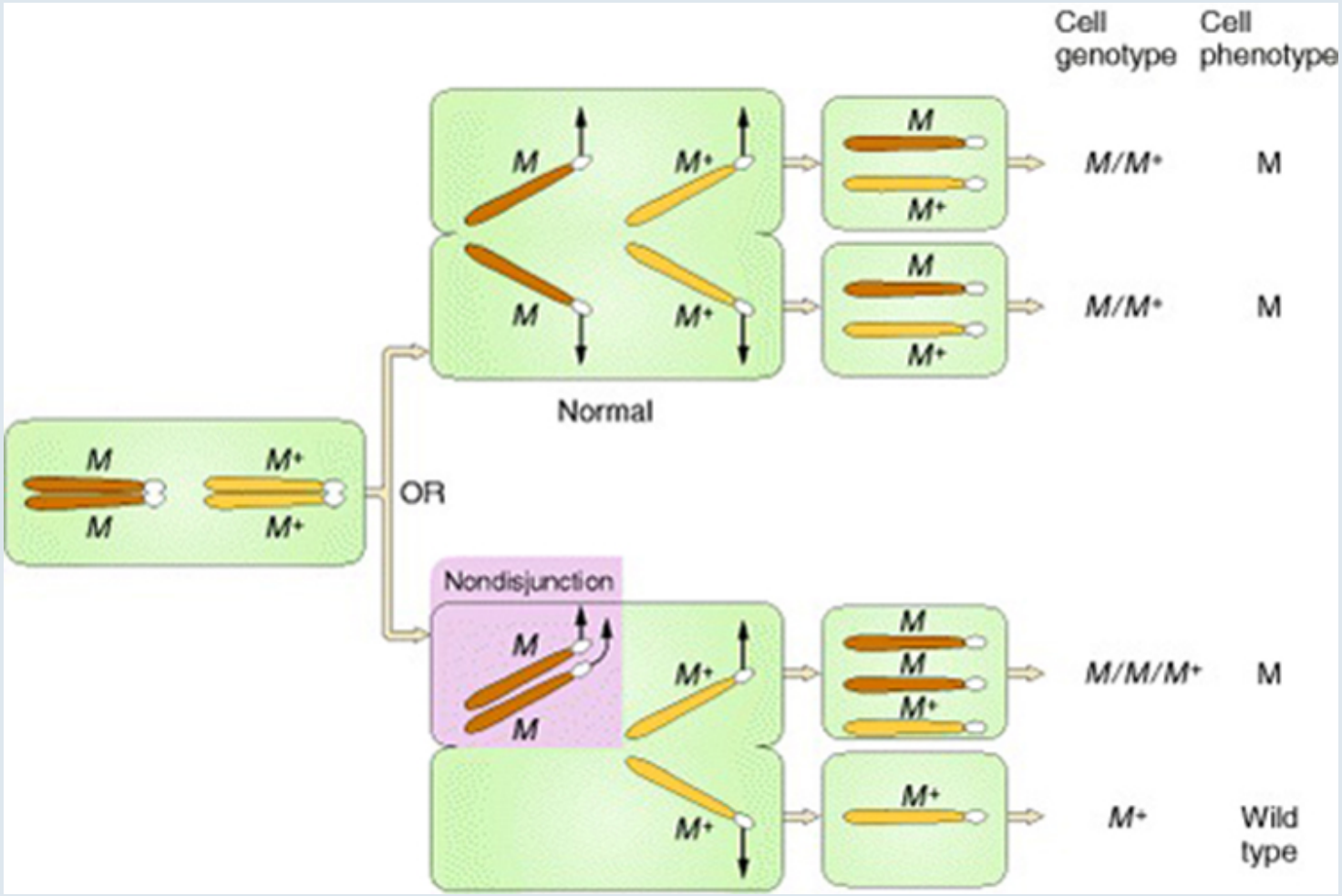


Calvin Bridges noticed that a strain of flies **MM+** (heterozygote for "bristle" configuration), sometimes expressed itself as a "local variance" of the dominant **M allele** (slender bristle) in which a region of the fly's body exhibited wild-type (**M+**) bristle characteristics.





Calvin Bridges noticed that a strain of flies **MM+** (heterozygote for "bristle" configuration), sometimes expressed itself as a "local variance" of the dominant **M allele** (slender bristle) in which a region of the fly's body exhibited wild-type (**M+**) bristle characteristics.

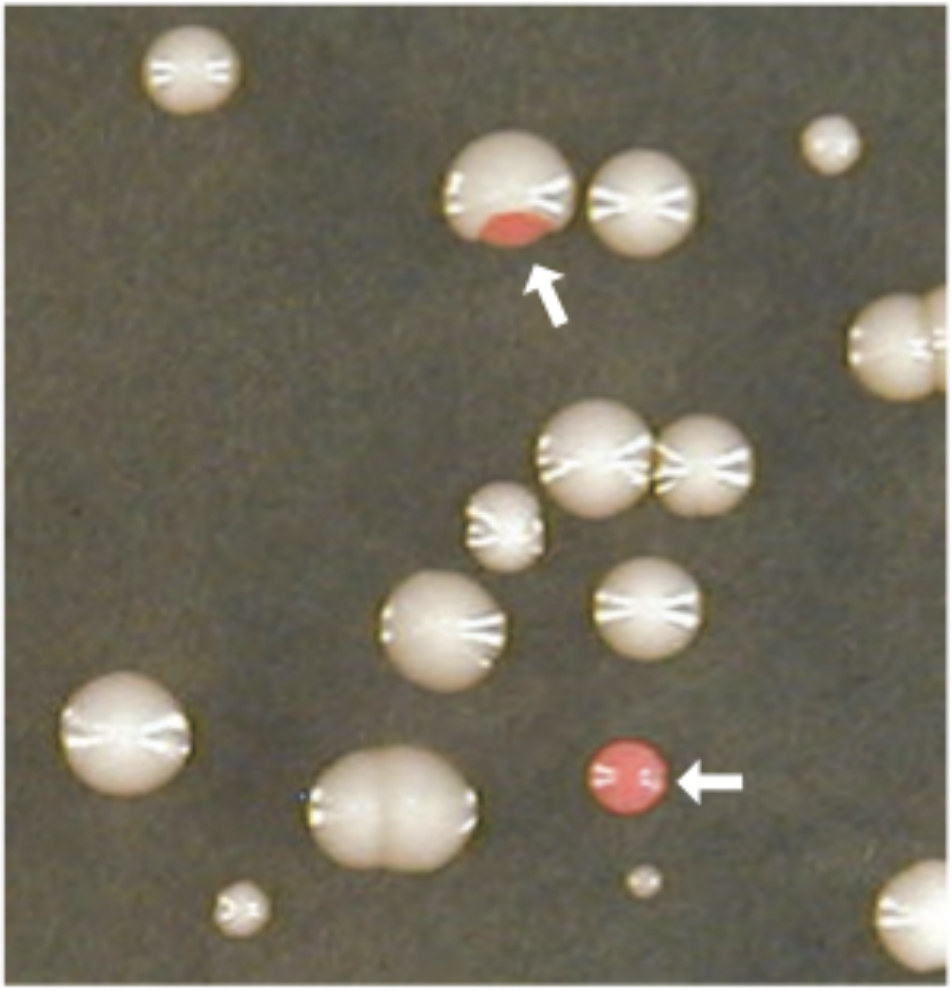
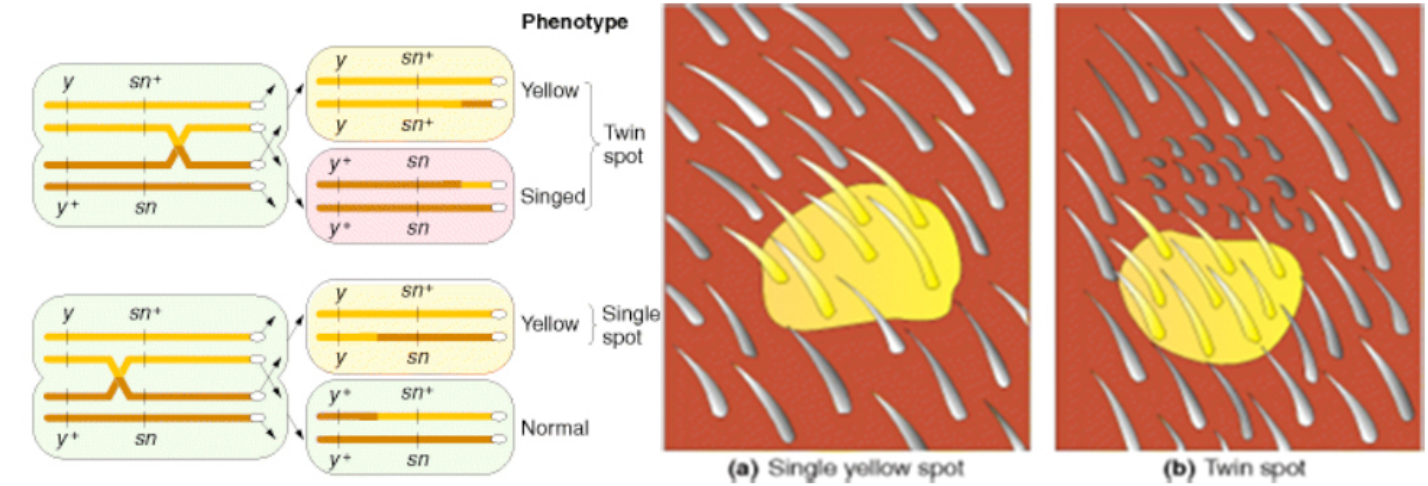


Figure 5.25 **Mitotic recombination during the growth of diploid yeast colonies can create sectors.** Arrows point to large, red *ade2 / ade2* sectors formed from *ADE2 / ade2* heterozygotes.

In 1936 **Curt Stern**s (another student of Morgan's working on *D. melanogaster*) undertook a cross of two other **sex-linked** traits y (yellow hair) and sg (singed hair).
y+ sn / y+ sn (singe-haired female) with **y sn+ /** (yellow singe-haired male)

Not too surprisingly the female progeny were mostly Wild-Type with grey bodies and normal bristles **y+ sn / y sn+**

Occasionally, however, Stern noticed that there were some "localized" **twin spots** of apparently "coupled" **yellow** and **singed hair** (**y sn)** phenotypes, which occurred as twin spots too often as to be mere coincidental juxtapositioning. He reasoned that these spots arose due to Mitotic recombinants between *sn* and the centromere



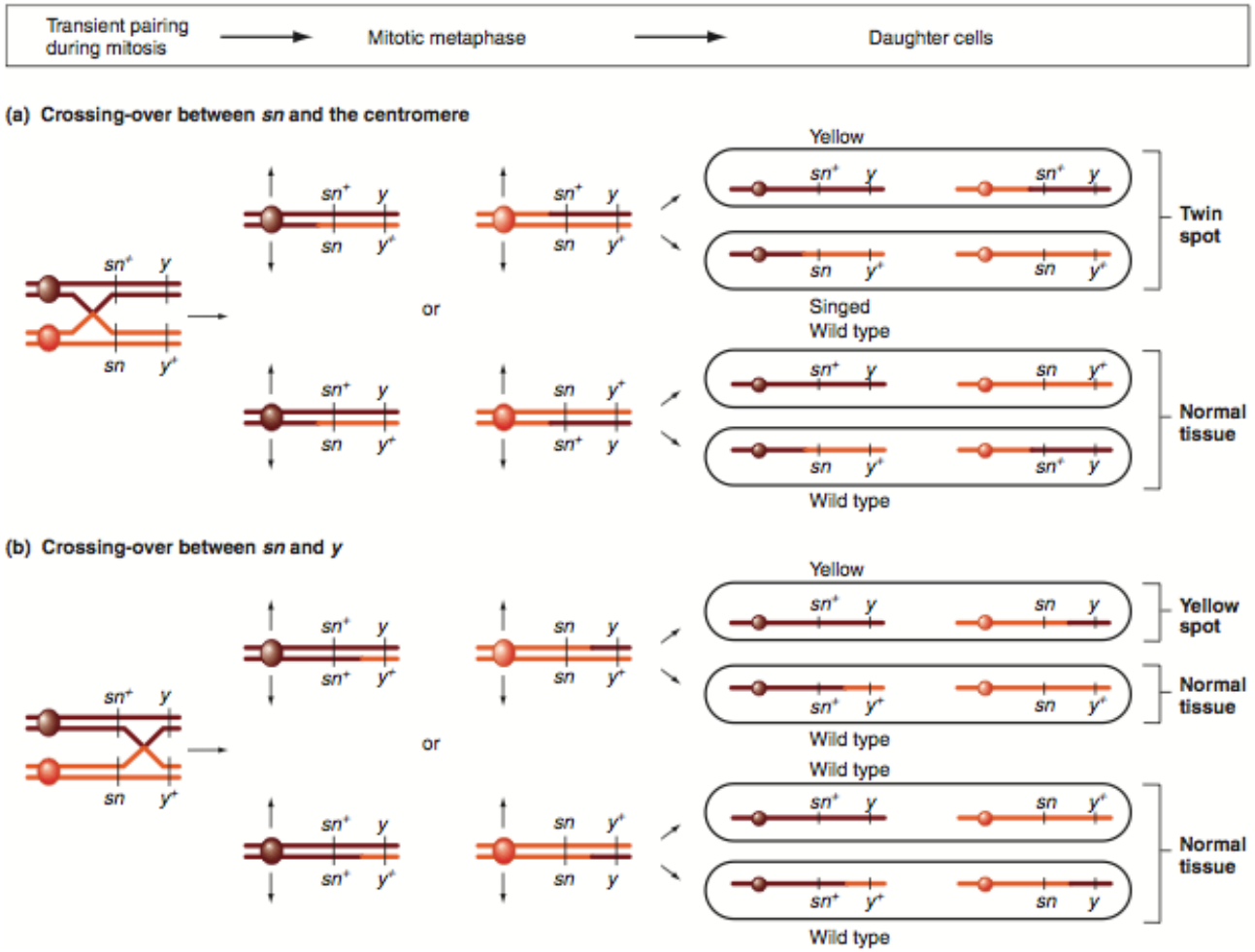
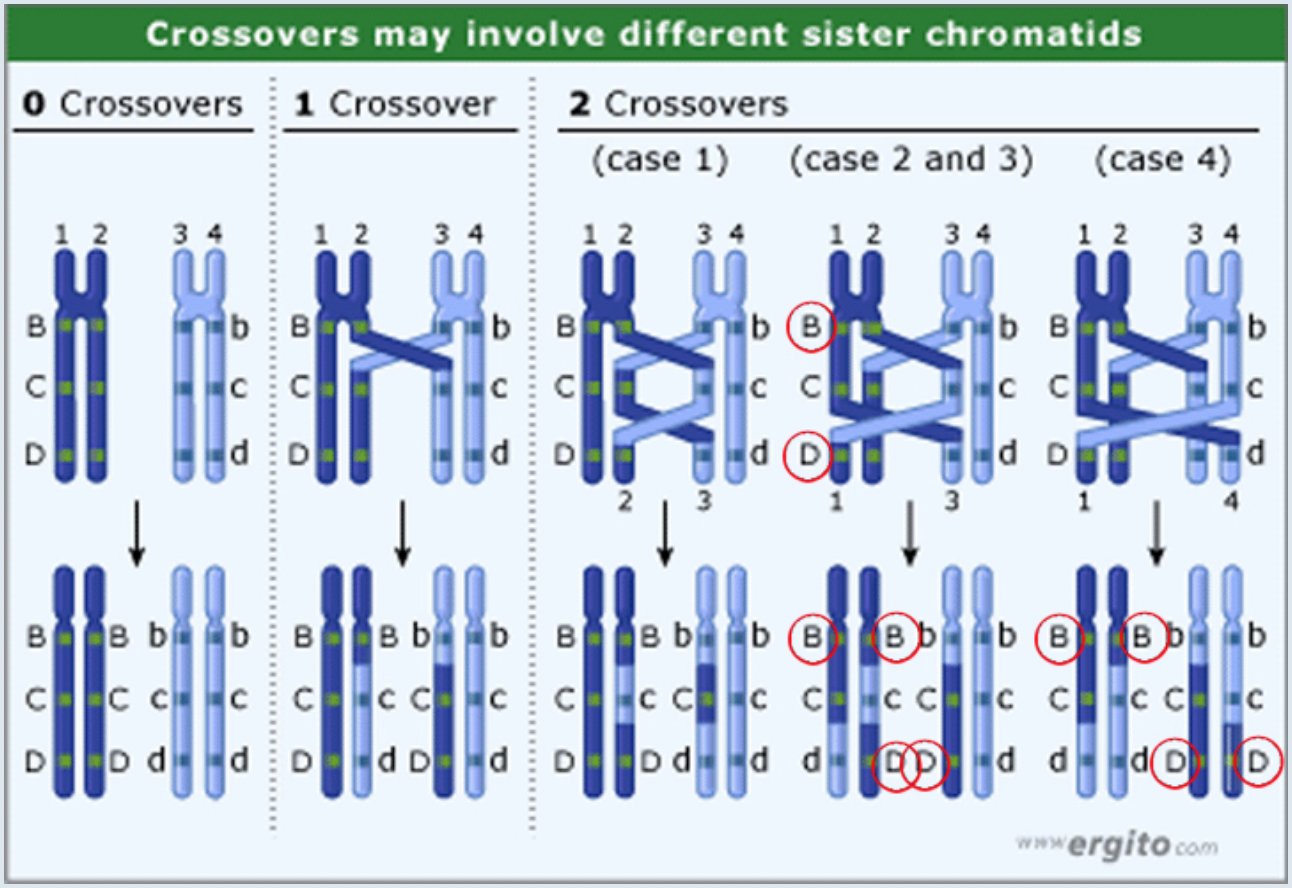


Figure 5.24 **Mitotic crossing-over.** **(a)** In a *y sn*$^+$ / *y*$^+$ *sn Drosophila* female, a mitotic crossover between the centromere and *sn* can produce two daughter cells, one homozygous for *y* and the other homozygous for *sn*, that can develop into adjacent aberrant patches (twin spots). This outcome depends on a particular distribution of chromatids at anaphase (*top*). If the chromatids are arranged in the equally likely opposite orientation, only phenotypically normal cells will result (*bottom*). **(b)** Crossovers between *sn* and *y* can generate single yellow patches. In contrast, a single mitotic crossover in these females cannot produce a single singed spot if the *sn* gene is closer to the centromere than the *y* gene. See if you can demonstrate this fact.

Meiosis



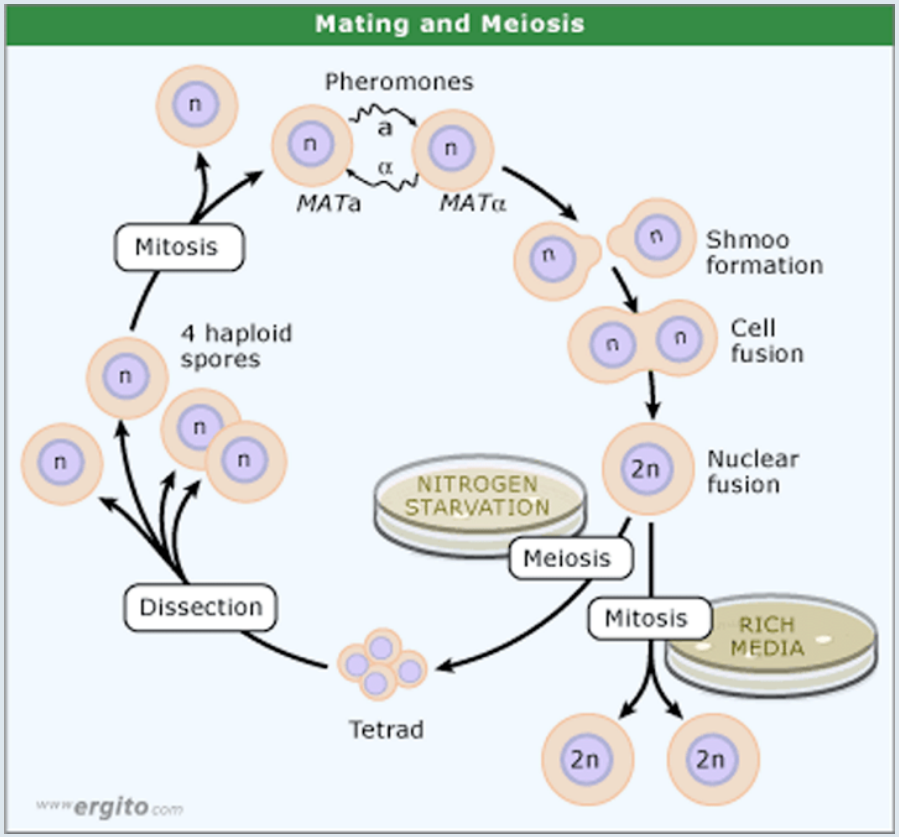
Consider a pair of homologous chromosomes prior to the MI division which contain a single crossover in the interval between markers B and D on chromatids 2 and 3, as shown in the Figure above.

The outcome of the single crossover is two chromatids carrying a recombination of the phenotypic markers associated with the B and D genes.

Now, consider that a second crossover occurs in this same interval.

Yeast and fungi.

***S. cerevisiae*:** and the potential POWER of yeast genetics -provides relatively immediate proof of all types of chiasmata and their consequences. Use of yeast and other similar fungi hav many distinct advantages ...*S. cerevisiae* can grow mitotically in a stable fashion as either a **haploid** (with one copy of each chromosome) or a **diploid** (with two copies of each chromosome). In essence, therefore, the consequences of meiosis can be "harvested" through analysis of both states, and the direct products of meoiotic events can be analyzed.



$a\ \ b \quad x \quad a^+\ \ b^+$

1	2	3
a b	a b^+	a b
a b	a b^+	a b^+
a^+ b^+	a^+ b	a^+ b
a^+ b^+	a^+ b	a^+ b^+

Parental **D**itype (PD).....**N**on-**P**arental **D**itype(NPD) .....Tetra-Type (TT)

For two **unlinked genes** on the same chromosome (where PD = NPD), a TT tetrad can arise as the result of a crossover between one of the markers and its centromere. Thus, for two **unlinked genes**, the frequency of TT tetrads will depend on the linkage of each gene to its centromere.

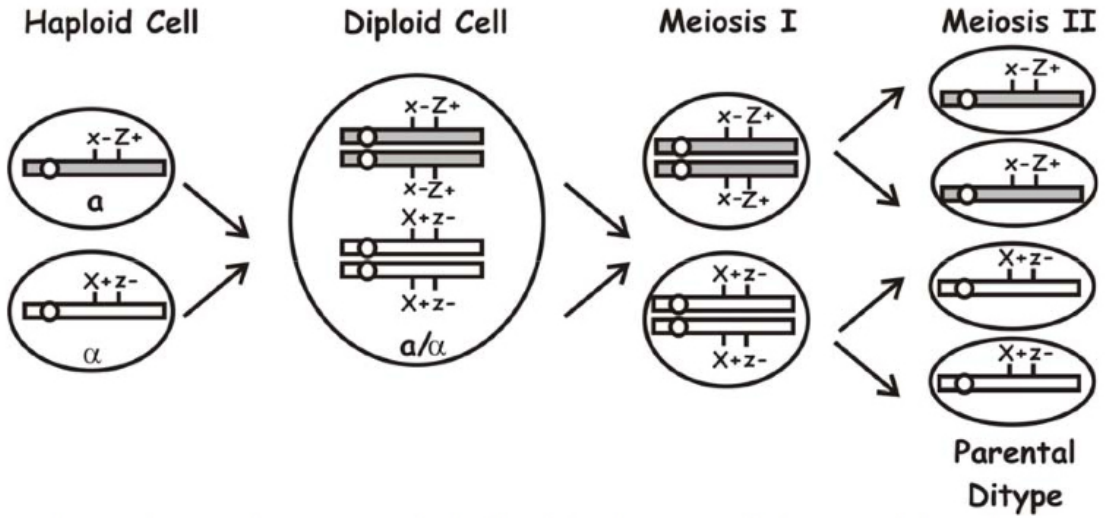
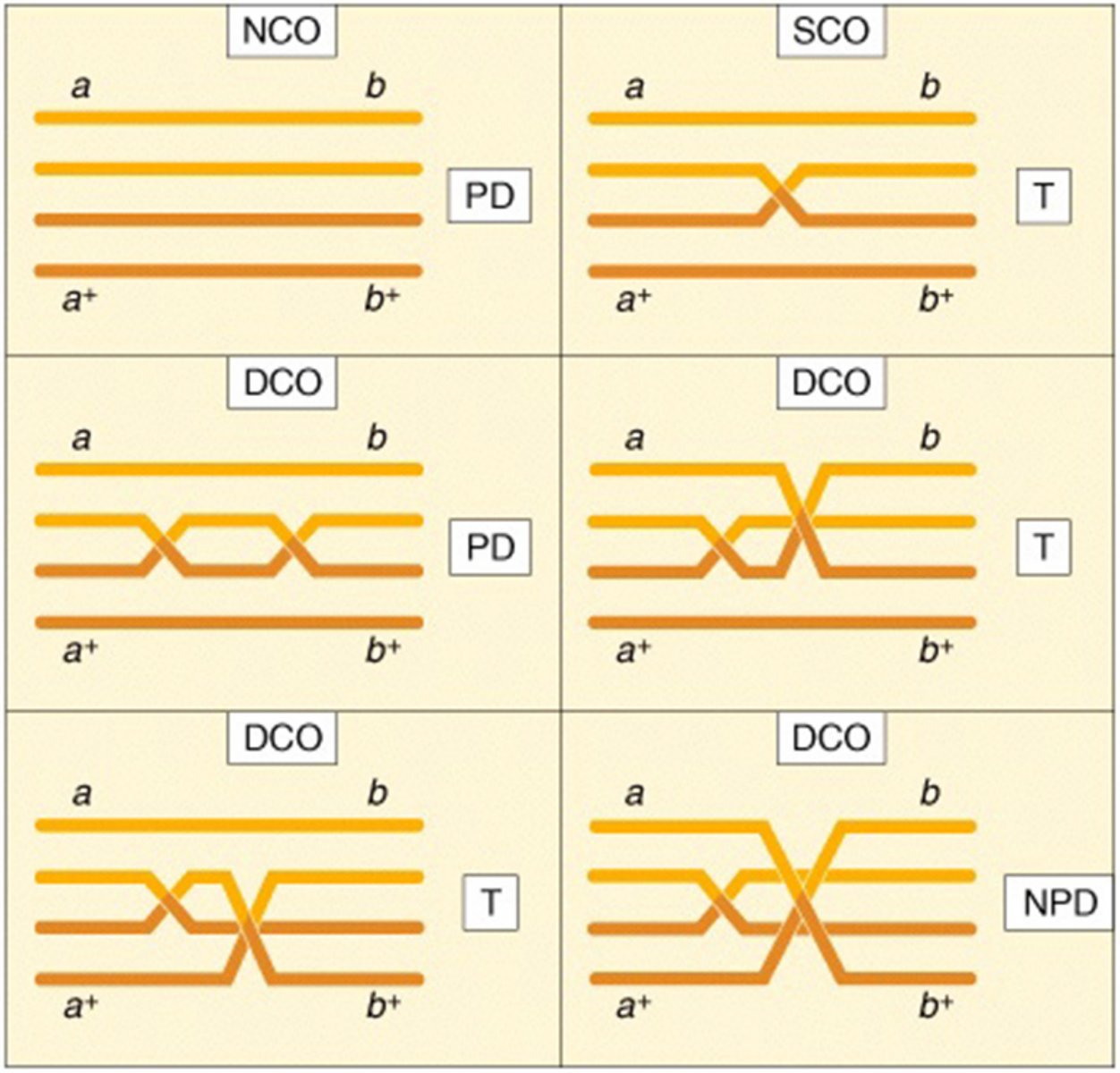


Figure 3: The production of yeast tetrads which exhibit the parental ditypes. If there had been two recombination events between X and Z involving two strands, you would see the same end result – parental ditype.

PD > NPD


NCO
a
b
a+
b+
PD
SCO
a
b
a+
b+
T
DCO
a
b
a+
b+
PD
DCO
a
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DCO
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b
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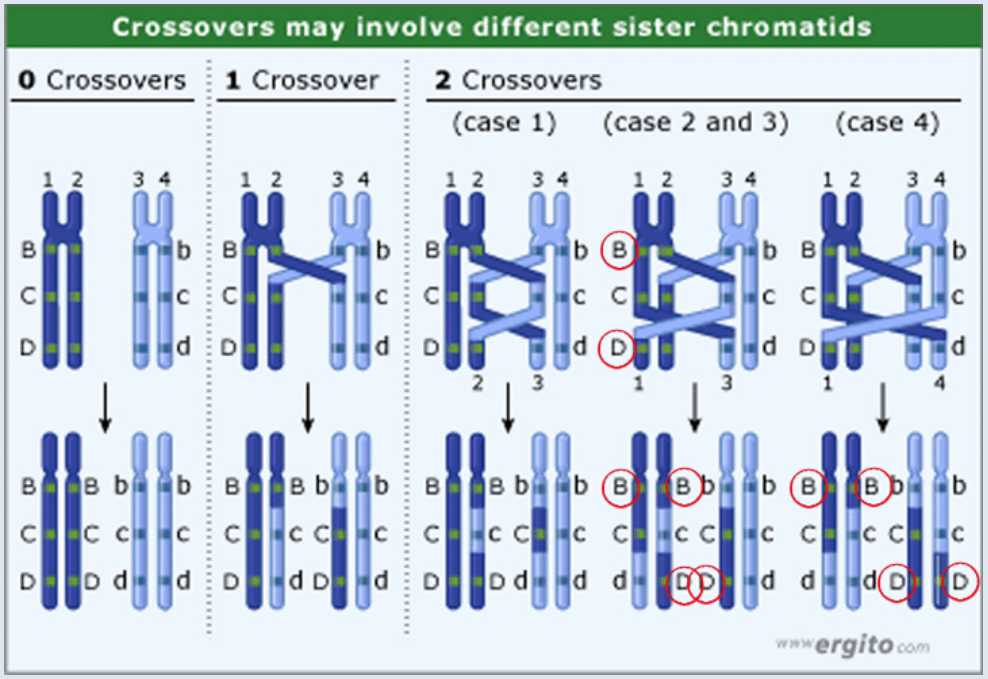
b+
NPD



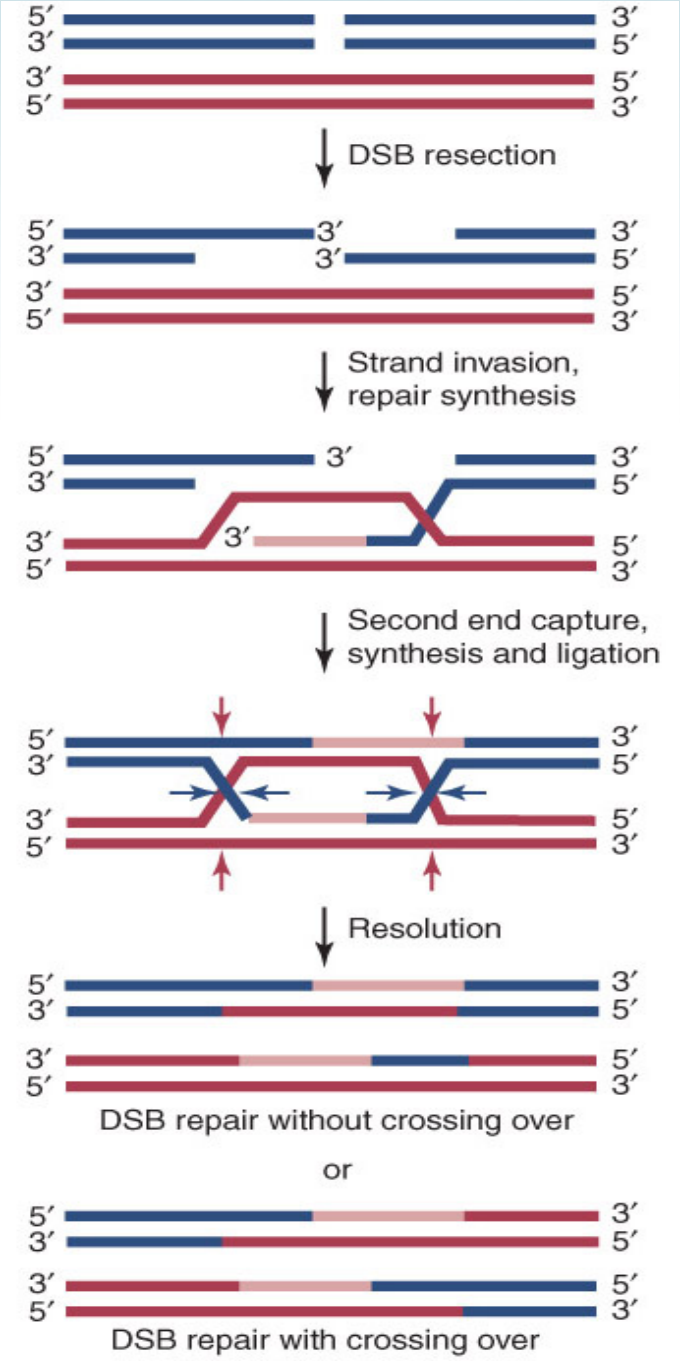
A **single crossover between linked** markers produces a **TT tetrad.**

Recombination between linked genes can actually produce **PD**, **NPD**, and **TT** tetrads.

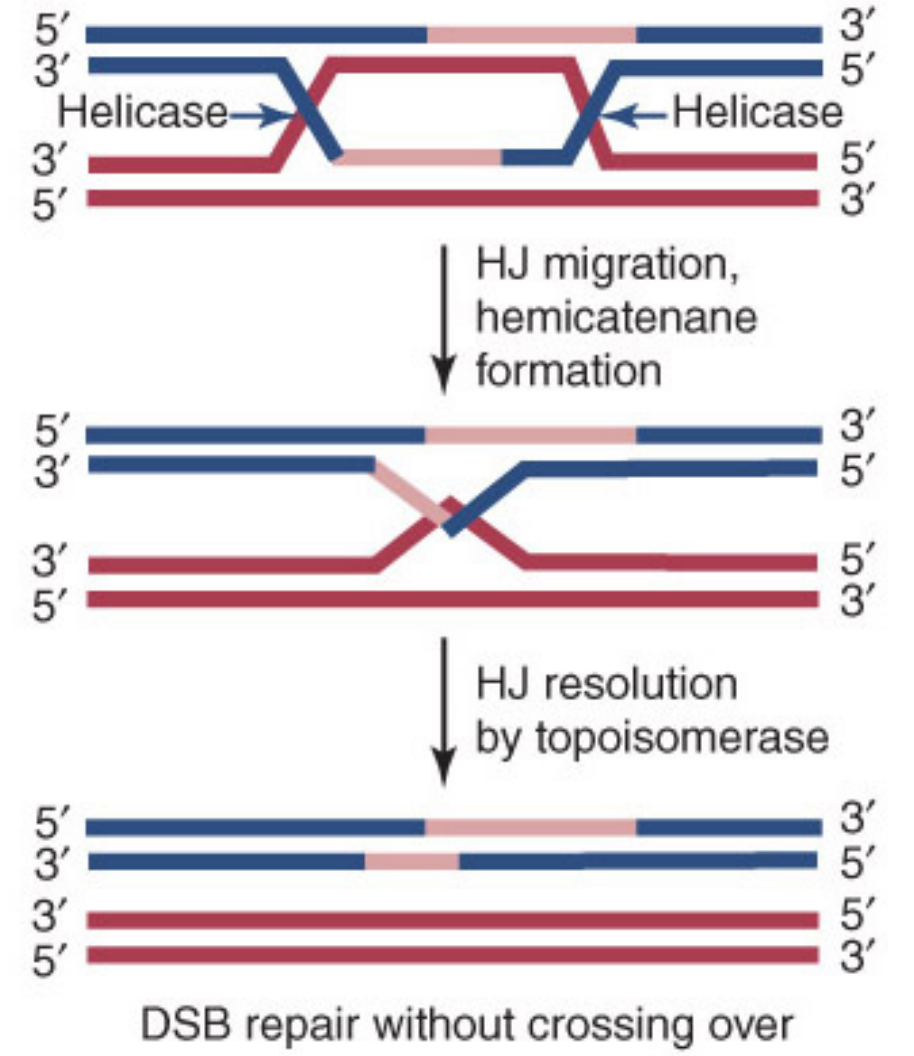
First, if there is a **single crossover** between the two markers, a **TT tetrad** is the product.

-Recall that for two unlinked genes, when PD = NPD, TT tetrads can also arise by a crossover between a gene and its centromere.

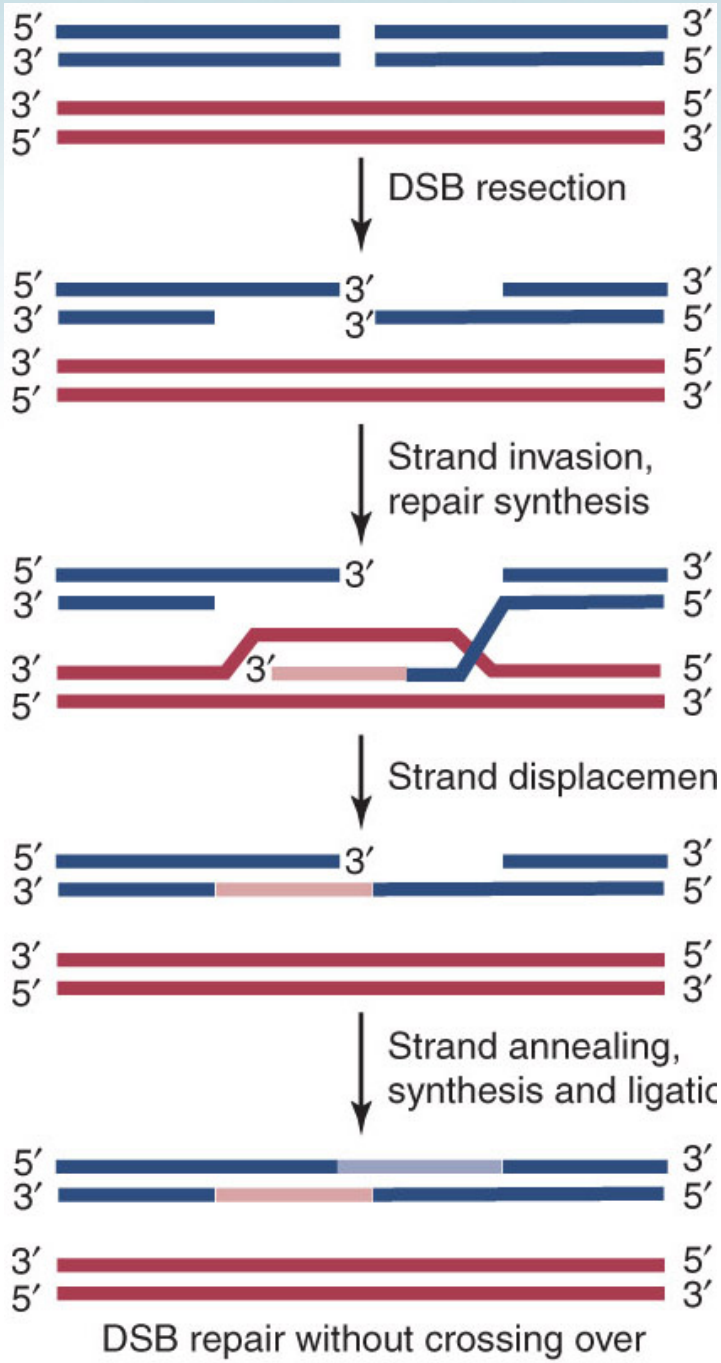
However, in the case of linkage, when PD > NPD, NPD can ONLY arise by a **double** crossover between the two genes, as shown in the multiple crossover figure.



Double-strand break-repair model of homologous recombination.

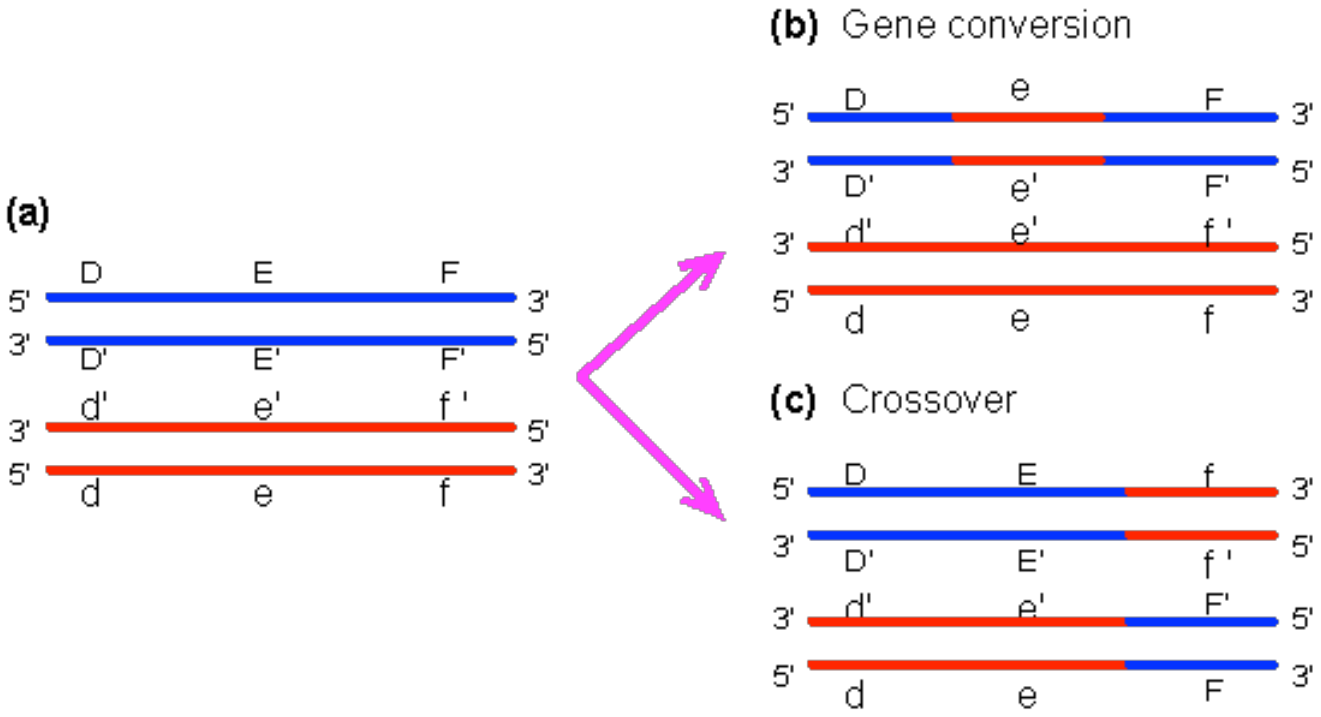


Alternatively- Double Holliday junction dissolution by the action of a DNA helicase and topoisomerase.



The Synthesis-Dependent Strand-Annealing Model

- The synthesis-dependent strand-annealing model (SDSA) is relevant for **mitotic recombination**, as it also produces **gene conversions** from double-strand breaks without having associated crossovers.



(a) Two DNA molecules. **(b)** Gene conversion - the red DNA **donates** part of its genetic information (e-e' region) to the blue DNA. **(c)** DNA crossover - the two DNAs **exchange** part of their genetic information (f-f' and F-F').

Schematic representation of DSB repair by homologous recombination and its products.

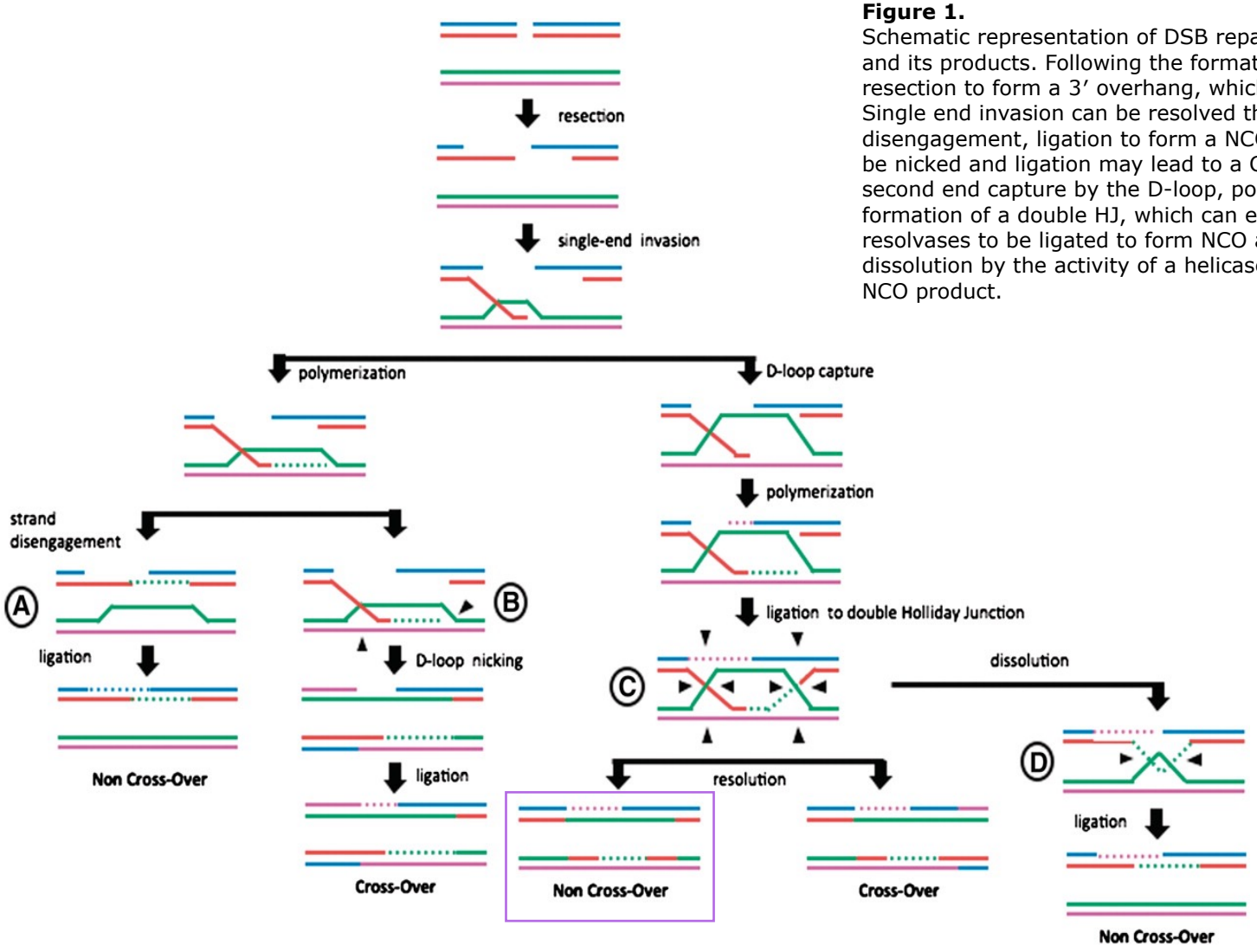


Figure 1.
Schematic representation of DSB repair by homologous recombination and its products. Following the formation of a DSB there is single-strand resection to form a 3′ overhang, which invades a homologous sequence. Single end invasion can be resolved through: (**A**) SDSA—strand disengagement, ligation to form a NCO product, or (**B**) The D-loop can be nicked and ligation may lead to a CO product. When there is also a second end capture by the D-loop, polymerization can lead to the formation of a double HJ, which can either be (**C**) resolved by HJ resolvases to be ligated to form NCO and CO products, or (**D**) undergo dissolution by the activity of a helicase and a topoisomerase to form a NCO product.

Agmon N et al. Nucl. Acids Res. 2011;nar.gkr277

Nucleic Acids Research

Research Highlight

Nature Reviews Genetics **11**, 592 (September 2010) | doi:10.1038/nrg2848

Corrected online: 19 August 2010

Mutation rate: DNA repair and indels boost errors

Mar

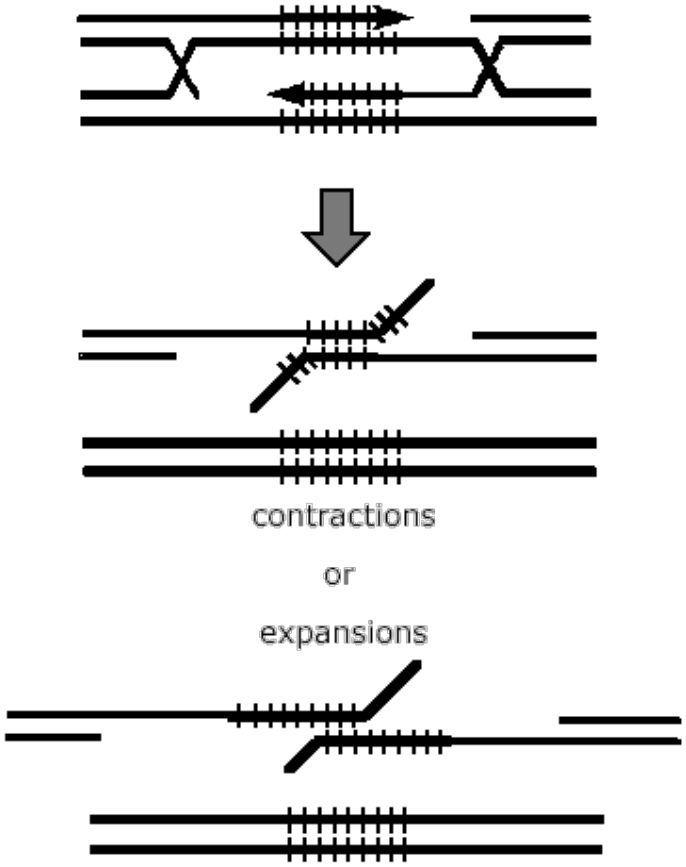
Mutation rates vary with genomic locus and cellular context, but there are many unanswered questions regarding when, where and how elevated mutation rates occur. Two papers now implicate DNA repair in increased local mutation rates, and the results may influence future studies of genetic variation and tumorigenesis.

Mitotic gene conversion is a mechanism for repairing DNA double-strand breaks (DSBs) in which a homologous sequence (donor) is used as a template for repair. Hicks and colleagues took advantage of the gene conversion that is a normal part of mating-type (*MAT*) switching in *Saccharomyces cerevisiae* to screen for errors generated by this repair process. **They inserted a gene (*URA3*) into the normal donor sequence that enabled them to chemically select cells in which mutations had arisen during gene conversion. Strikingly, they found that the mutation rate associated with gene conversion was 1,400 times higher than the rate of spontaneous mutation in the same genomic region.**

Hicks *et al*. showed that the majority of mutations were single-base-pair substitutions, but a high proportion were one-base-pair deletions and complex mutations that are probably caused by template-switching during gene conversion. Surprisingly, the normally high-fidelity DNA polymerase-δ seems to cause these template switches.

This finding suggests that gene conversion is less processive than the DNA synthesis that takes place during S phase. Furthermore, the authors suggest that some mutations required for carcinogenesis could result from gene conversion being used to repair the increased numbers of DSBs triggered by activated oncogenes.

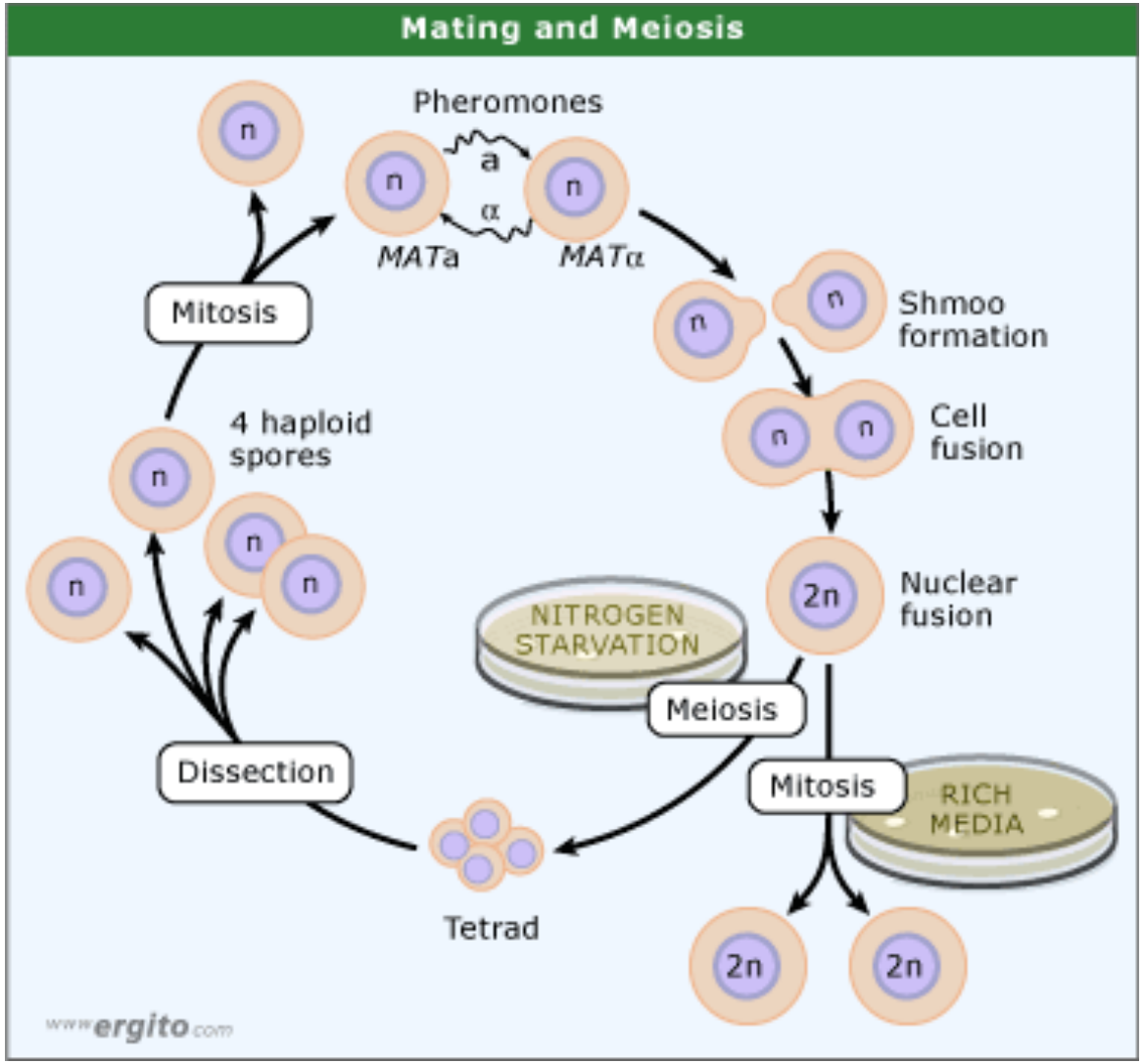
http://www.nature.com/nrg/journal/v11/n9/full/nrg2848.html



A prediction of the **Synthesis Dependent Strand Annealing (SDSA) model** is that the annealing between the two tails can lead to expansions and contraction of the tandem array.

Greater than 40% of the gene conversions were accompanied by contractions or expansions. Furthermore they were only located in the recipient copy.....i.e they are non-reciprocal.

Meiotic vs. Mitotic recombination?


Mating and Meiosis
Pheromones
a
α
n
MATa
MATα
Shmoo formation
Cell fusion
2n
Nuclear fusion
NITROGEN STARVATION
Meiosis
Mitosis
RICH MEDIA
Tetrad
Dissection
4 haploid spores
Mitosis
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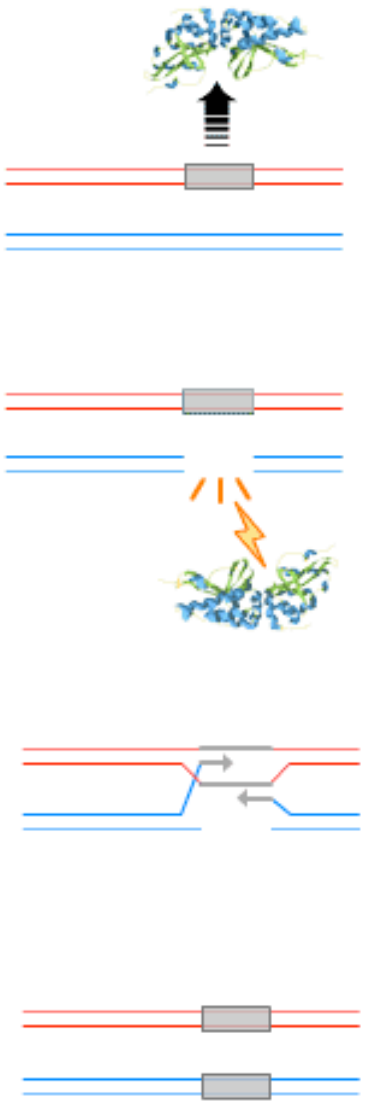
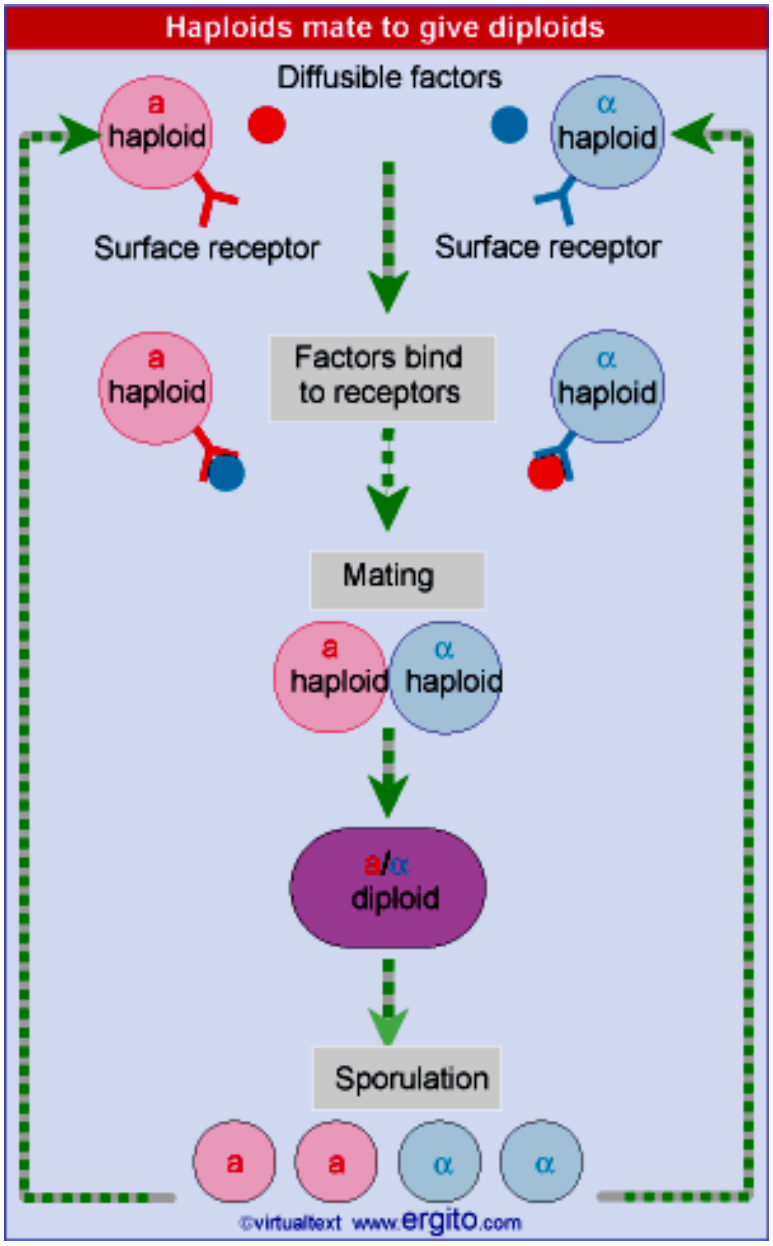
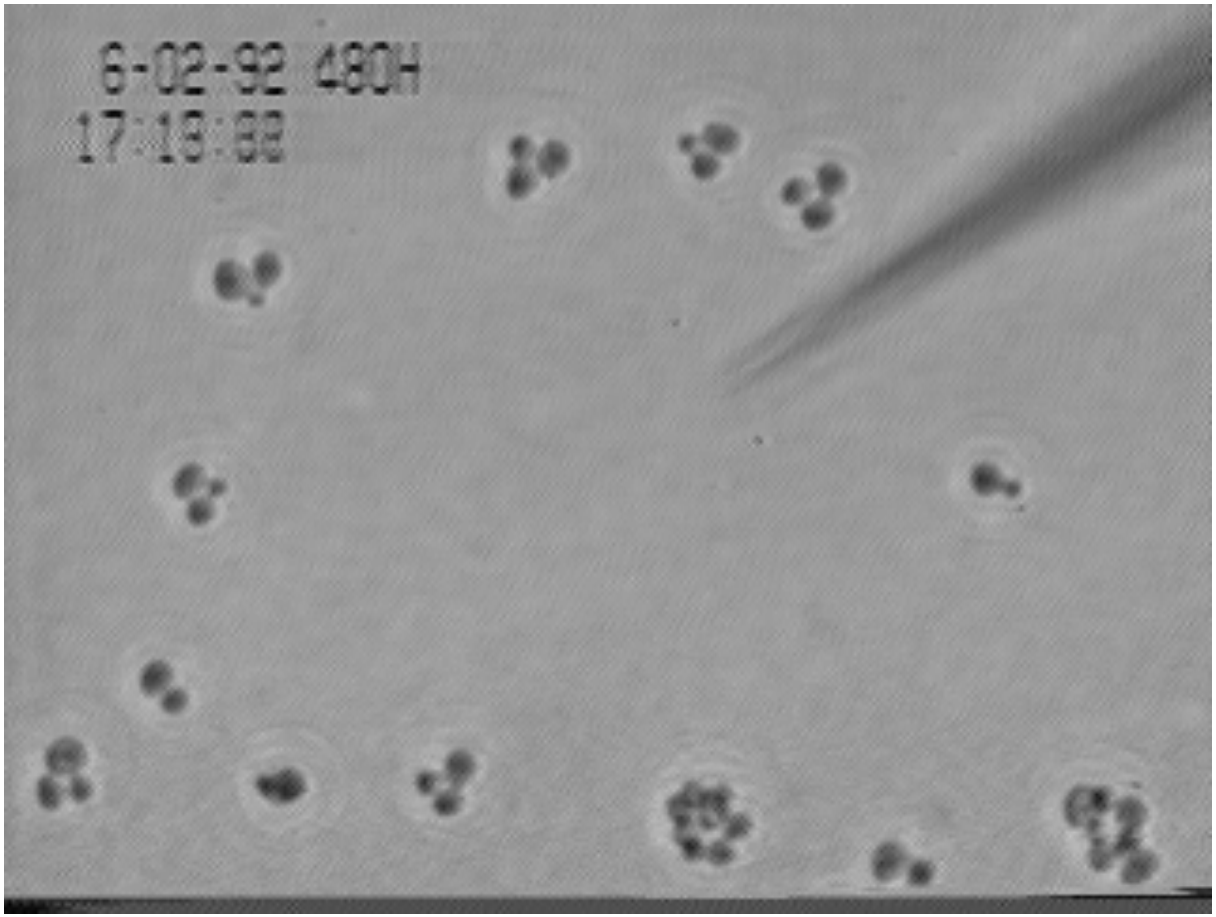
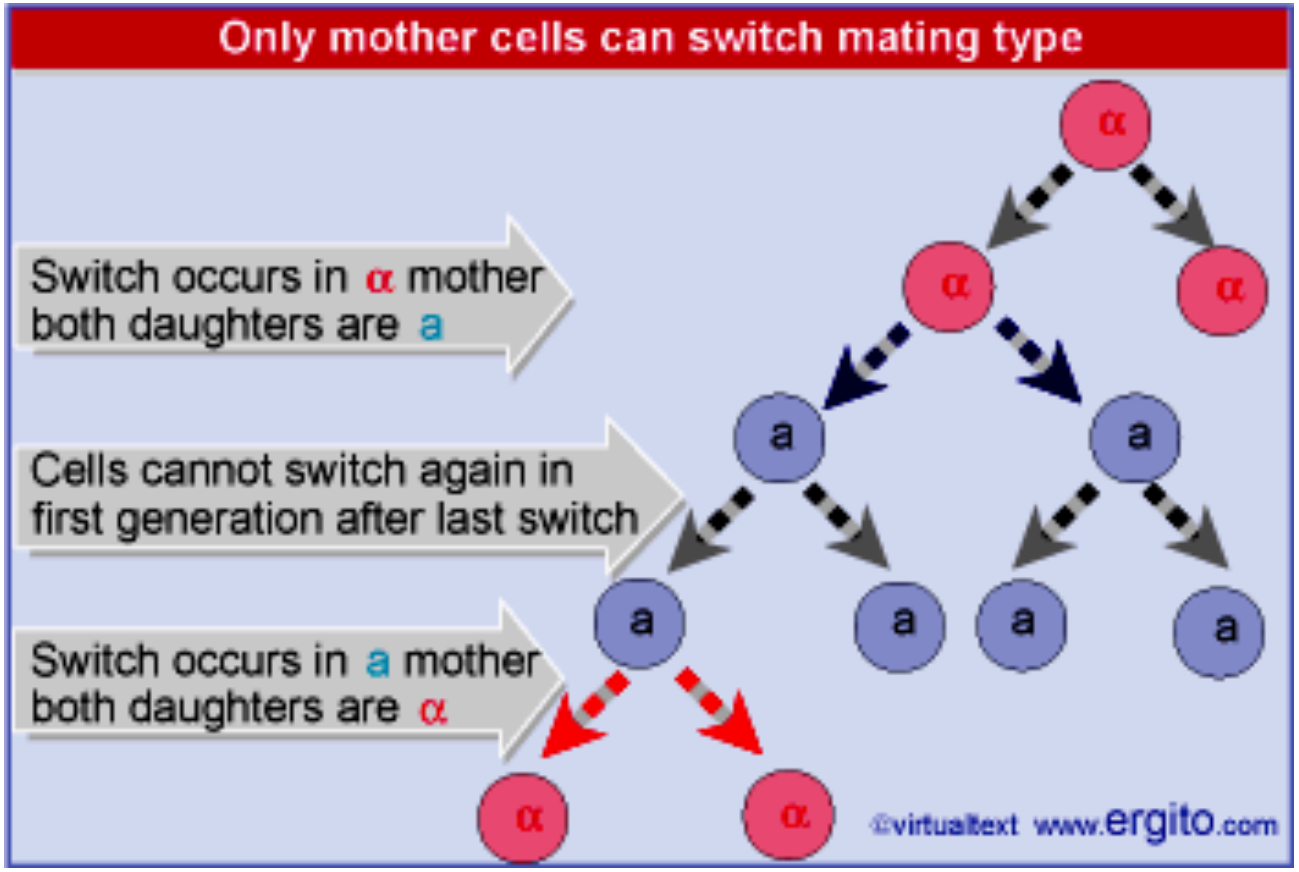


a unidirectional genetic exchange..... involves an HO (homing) endonuclease.


Haploids mate to give diploids
Diffusible factors
a haploid
α haploid
Surface receptor
Surface receptor
a haploid
Factors bind to receptors
α haploid
Mating
a haploid
α haploid
a/α diploid
Sporulation
a
a
α
α
©virtualtext www.ergito.com


6-02-92 48OH
17:18:08


Only mother cells can switch mating type
Switch occurs in α mother both daughters are a
Cells cannot switch again in first generation after last switch
Switch occurs in a mother both daughters are α
α
α
α
a
a
a
a
a
α
α
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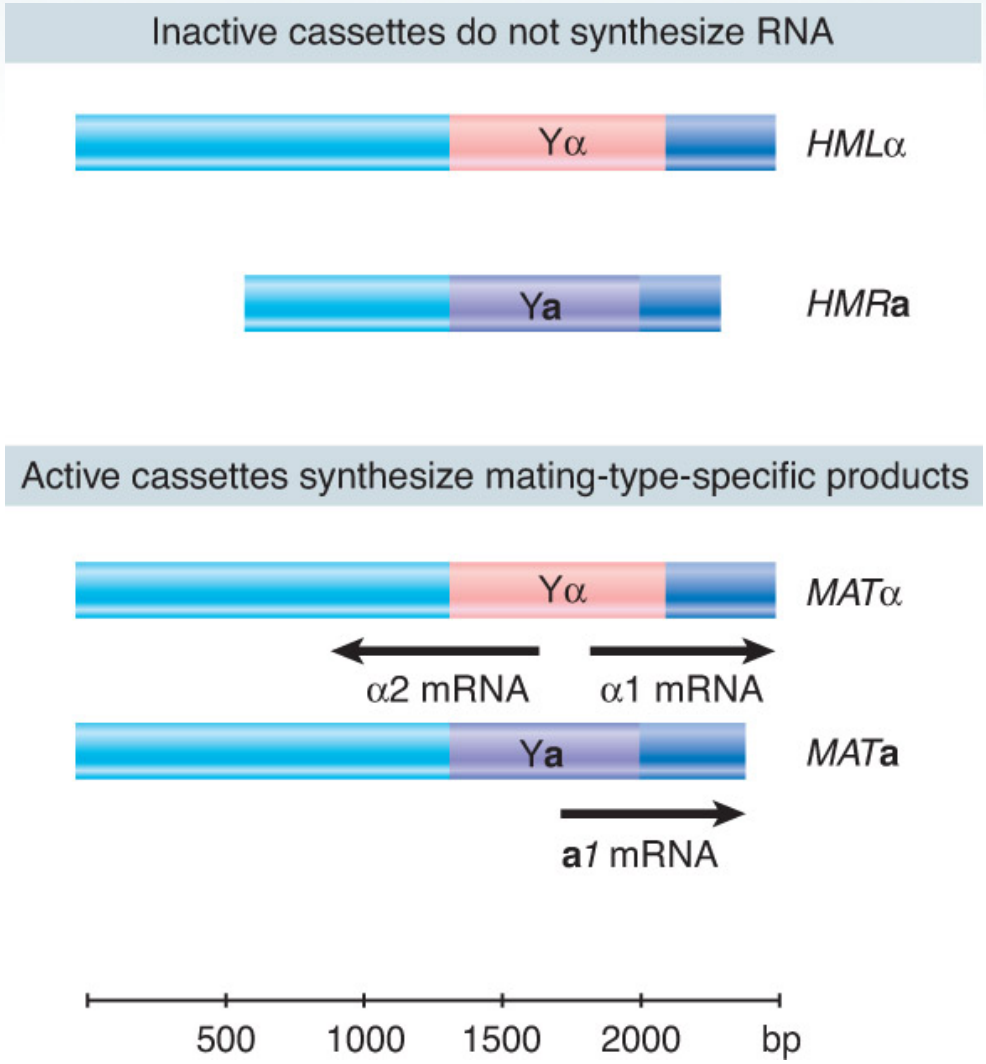
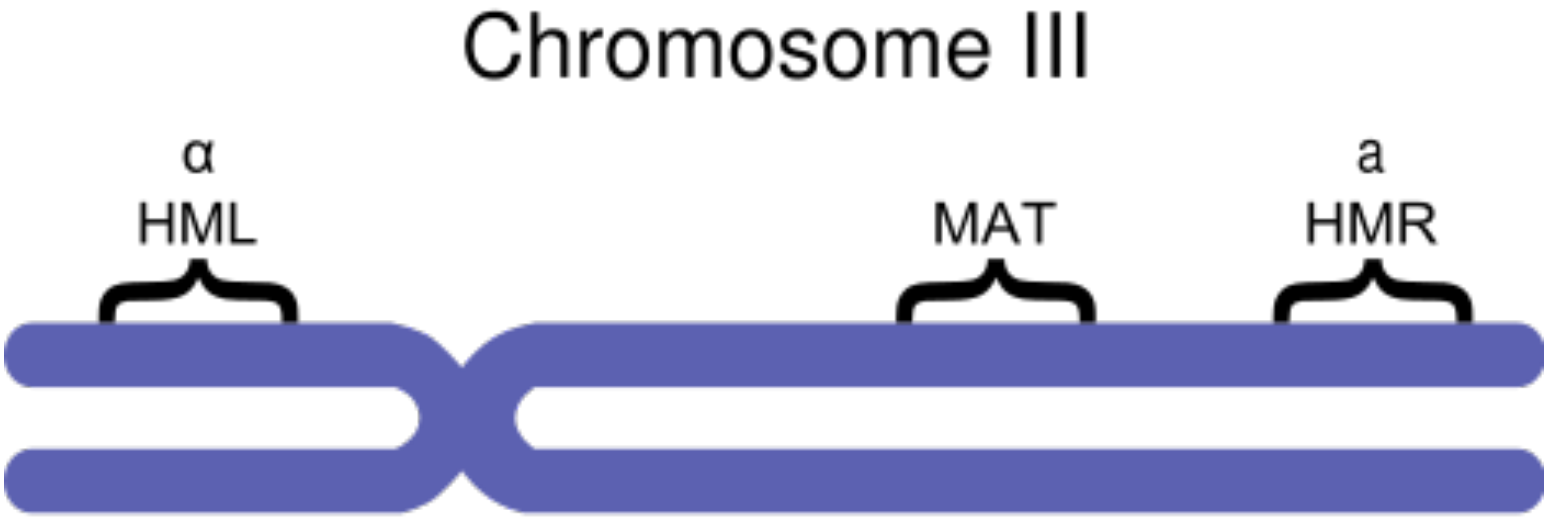
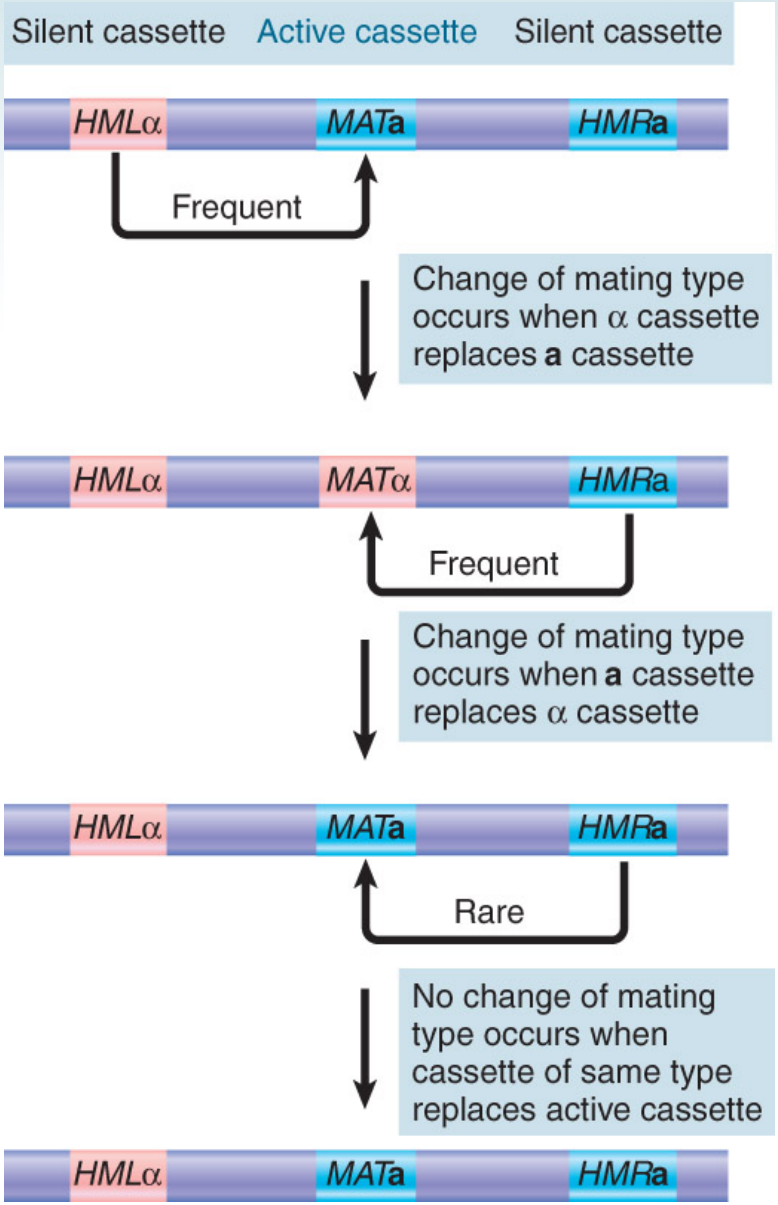
Yeast Can Switch Silent and Active Loci for Mating Type



- Switching occurs if *MAT***a** is replaced by *HMR*α or *MAT*α is replaced by *HMR***a**.

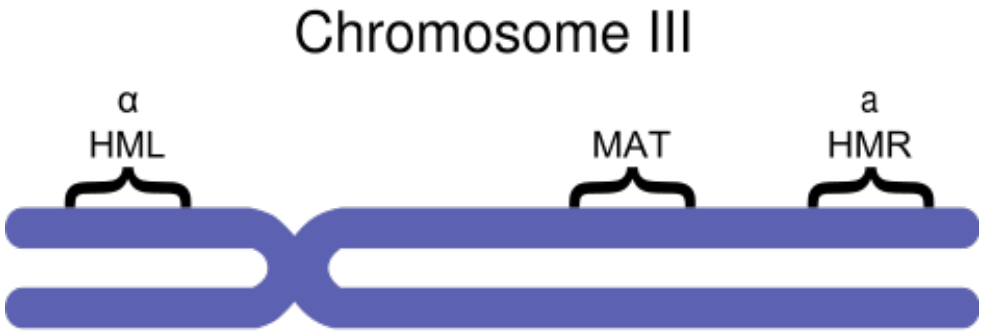
Mating type loci organization


Chromosome III
α
HML
MAT
a
HMR



- The yeast mating type locus *MAT*, a **mating type cassette**, has either the *MAT***a** or *MAT*α genotype.
- Yeast with the dominant allele *HO* switch their mating type at a frequency ~10^{-6}.
- The allele at *MAT* is called the active cassette.
- There are also two silent cassettes, *HML*α and *HMR***a**.

Cassette model for mating type



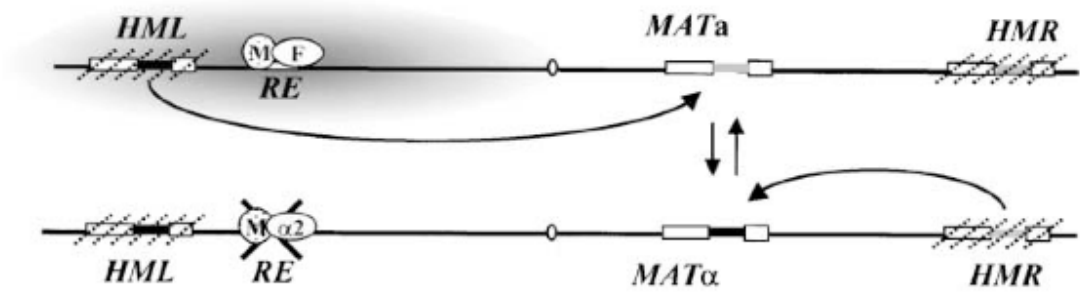
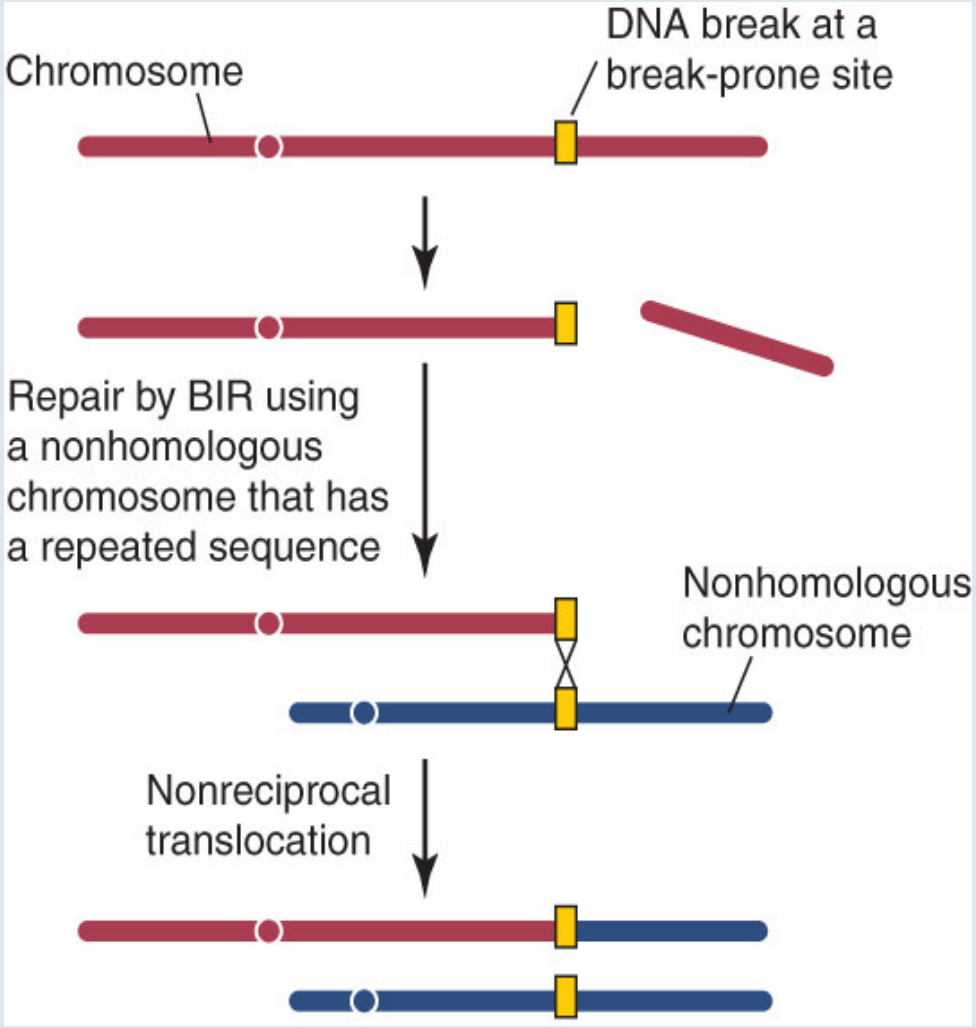
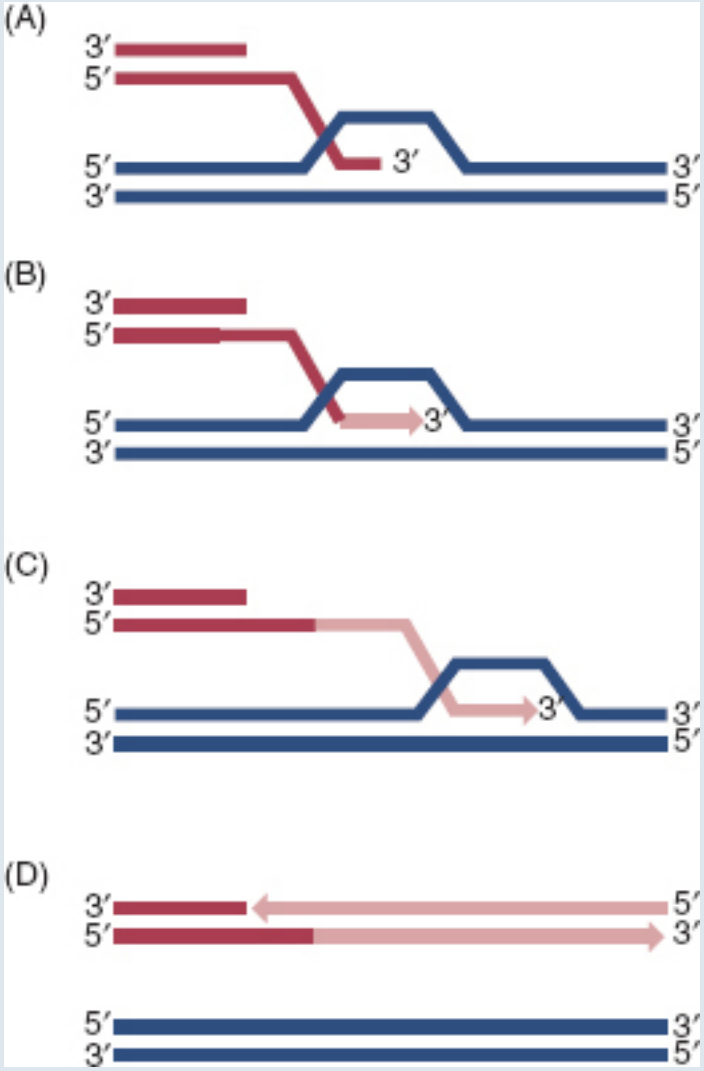


FIGURE 1.—Mating-type switching exhibits cell type-dependent donor preference. A diagram of chromosome III indicating the relative positions of the donor loci, *HML* and *HMR*, the *MAT* locus, and the recombination enhancer, *RE*, is shown. *HML* and *HMR* are transcriptionally silent, indicated by the hatched lines, while *MAT* is transcriptionally active, giving rise to the mating type of the cell. Open rectangles at the three mating loci indicate blocks of homology while the thick line indicates the allele-specific region (α allele is black, **a** allele is gray). In **a** cells (top), Mcm1 (M) and Fkh1 (F), a forkhead transcription factor, occupy *RE* and promote enhanced recombination potential (shaded area) extending over *HML*, rendering it the preferred donor during mating-type switching and resulting in conversion from *MAT***a** to *MAT*α. In α cells (bottom), α2 binds to *RE*, precluding occupation by Fkh1, to suppress enhanced recombination potential, rendering *HMR* the preferred donor through *RE*-independent mechanisms and resulting in conversion from *MAT*α to *MAT***a**.

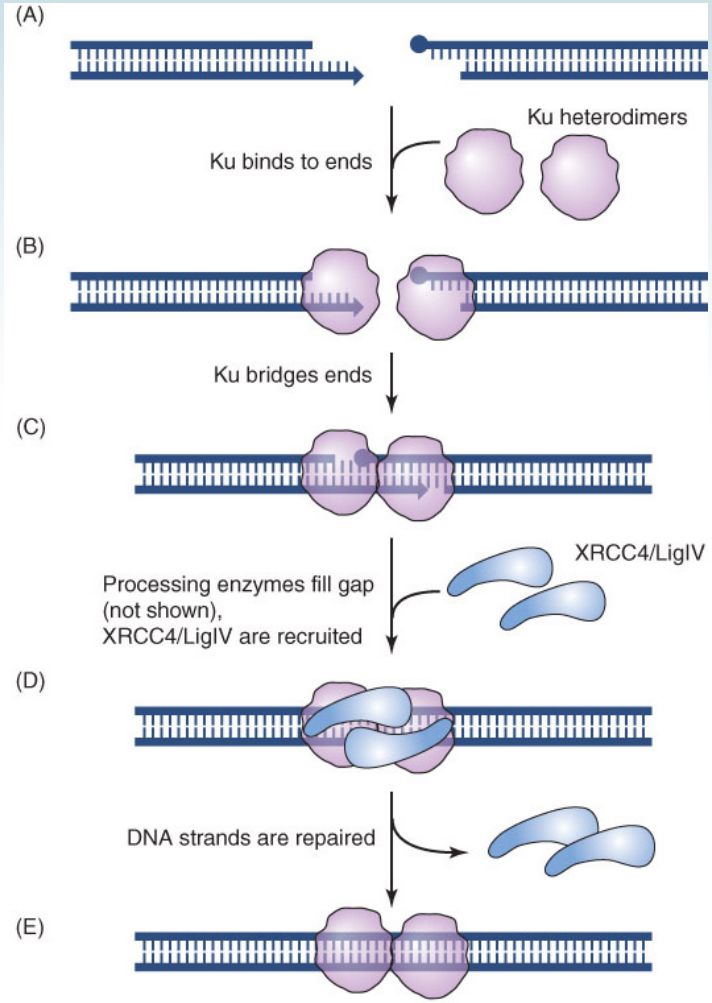
Matthew P Scott, Paul Matsudaira, Harvey Lodish, James Darnell, Lawrence Zipursky, Chris A Kaiser, Arnold Berk, Monty Krieger (2004). *Molecular Cell Biology, Fifth Edition*. WH Freeman and Col, NY



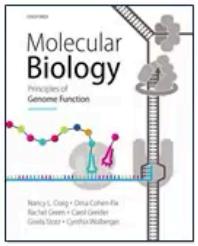
Break **I**nduced **R**ecombination (BIR) initiating translocations



Break **I**nduced **R**ecombination (BIR) initiating translocations, sometimes through regional homology with DNA potentially from other chromosomes



Break Induced Replication (BIR) promotes Non-Homologous “end-joining” involves Ku proteins… which force interactions



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Animation 12: **Non-homologous end joining**

https://www.youtube.com/watch?v=31stiofJjYw