Meiosis - specialized cell division

1. separate homologous chromosomes

Pair

Synapse

Crossing-over

30 proteins involved

30-40 proteins involved
Homologs

mom

dad

chromosome 2

chromosome 8

Mitosis - Metaphase

microtubes
Homologs

Mitosis

- Homologs behave independantly
- Microtubtes

Mom

Chromosome 1

Dad

Chromosome 2

Mitosis - Metaphase
Homologs 

Meiosis I

- mom
- dad
- chromosome 1
- chromosome 2

Meiosis I - Metaphase I

Homologs must pair

Microtubules of spindle
Homologs

Meiosis II

Homologs must segregate and behave independently

Meiosis II - Metaphase

Microtubules of spindle

Like mitosis
4 products of meiosis

Each product is haploid ($n=23$ for humans, $n=17$ for yeast)
Vocabulary

Mitosis — produce 2 new identical daughter cells  $2n \rightarrow 2n$

Meiosis — produce 4 products that reduce the number of chromosome  $2n \rightarrow 1n$

Pairing — hold homologs by glue "synaptonemal complex"
Homologs – chromosomes with similar genes from the two parents

Recombination – exchange of material between homologs

What is the purpose of recombination?
1. Rearrange new mutations
2. Hold homologs together
Pairing of homologs

1. Search for homology
2. Stabilize interactions
3. "Stirring" the contents

SUN - KASH proteins mediate link of the nuclear envelope and telomeres to cytoplasmic motors

4. SUN is more important for short chromosomes as suN mutants slow or block pairing of short but not long chromosomes
Errors in meiosis

- in humans, a major cause of errors occur via nondisjunction.

Disjunction

Non-Disjunction

In females, most nondisjunction occurs in meiosis I and involves chromosomes that fail to recombine.
Meiosis, although essential for reproduction, is also variable and error-prone: rates of chromosome crossover vary among gametes, between the sexes, and among humans of the same sex, and chromosome mis segregation leads to abnormal chromosome
Aneuploidy in male sperm (20 donors and ~31,000 sperm)

1. Ranged from 1-5%
2. Crossovers “protected” against aneuploidy in meiosis I
3. 19/31,228 three copies of a chromosome

How might this occur?
Chiasma / chiasmata — recombination events, breaking and ligating of DNA

Centromere / kinetochore — site of microtubule attachment

Cohesin — holding sister chromatids together

Geneticist / cell biologist
PLOIDY:
- one set of homologs
  - HAPLOID
  - DIPLOID
  - HEXAPLOID
  - OCTAPLOID

Euploidy
- normal complement of chromosomes
- too few or too many chromosomes

Anteuploidy
- Trisomy
  - Trisomy 21
  - Trisomy 18
  - Trisomy 13
  - XXY
  - XYY

Monosomy
- one copy
- XO

Liveborn
Gains and losses in various cancers (Ben-David and Amin)
S. cerevisiae - budding yeast

12 Mb ~ 6000 genes
17 chromosomes

Mating-type

Tetrad
4 products
Meiosis

- N, nonfermentable carbon source
Tetrads - all four products of a single meiosis are packaged together.

First experiments used the gut of banana slugs to digest the wall

Since 1970 Sigma - Zymolyase
Maps  \( aB \times Ab \)

\[
\begin{array}{cc}
\text{parental} & \text{recombinant} \\
\text{aB} & \text{ab} \\
\text{Ab} & \text{AB}
\end{array}
\]

\[
\frac{\text{# recombinants}}{\text{Total progeny}} \times 100 = \text{map units}
\]

\[
\frac{20}{100} \times 100 = 20 \text{ map units}
\]

1 map unit = 1% recombination
Mice, Humans
Zebrafish
Drosophila
Chlamydomonases
S. cerevisiae

1 million base pairs / mu
300 kb / mu
500 kb / mo
100 kb / mo
4 kb / mu

There are hot spots and cold spots.
Telomeres, centromeres are cold spots.
MATa × MATa → Diploid a/α → meiosis
Lab strains are haploid

1. Types of Tetrads
   aB × Ab
   Parental Ditype
     aB
     aB
     A b
     aB
   Nonparental Ditype
     aB
     aB
     A b
     A B
   Tetratype
     aB
     aB
     A B
     A b
   NPD
   PD
   4 products
trp; LEU1 x TRP1; leu1

90 PD

trp LEU1

trp LEU1

TRP leu1

TRP leu1

TRP leu1

TRP leu1

1) linked or unlinked?
Linked  PD $\gg$ TT

How far apart?

\[ \frac{\text{# recombinants}}{\text{Total}} \]
\[
\frac{10 \text{TT}}{100} = 10 \text{ cM}
\]

\[
\frac{20 \text{ recomb}}{400 \text{ Total}} = 5 \text{ cM}
\]

\[
\frac{\frac{1}{2} \text{TT}}{\text{Total}} \quad \text{or} \quad \frac{\text{TT}}{2 \times \text{Total}}
\]
TRP1; CDC4 x trpl; cdc4

auxotroph
cell cycle

50 PD

50 NPD

TRP; CDC
TRP; CDC
trp; cdc
trp cdc

TRP edc4
TRP cdc4
trp CDC
trp CDC

Linked or unlinked?
PD = NPD \rightarrow \text{UNLINKED}
MATa\_j \text{ dphE1 } \times \text{ MATd phe1}

<table>
<thead>
<tr>
<th>PD</th>
<th>NPD</th>
<th>( \pi )</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>45</td>
<td>10</td>
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</tbody>
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linked or unlinked?
45:45:10

UNLINKED

How do the TT form?
Map centromeres

Tetratypes come from single crossover between a gene and its centromere

If second locus is on its centromere

then \( \frac{TT}{2 \times \text{Total}} = \text{distance of MAT to its centromere} \)
phe 1; karl × PHE1; KAR1
PD NPD TT
60 4 13% Linked or unlinked?
Linked PD ➔ NPD

How do NPD arise?
single crossover

PHEI  KARI
2 crossovers

phe1  KARI
phe1  KARI
PHE1  kar1
PHE1  Kar1
2 crossovers
2 strand or chromatid
phel1 karl
phel1 karl
PHE KAR
PHE KAR
PD
There are 2 different 3 strand doublers

2 crossovers
3 strand or chromatid
phe1 kar1
phe1 KAR1
phe1 KARI
PHE KAR1
PHE Kar

TT
There are 2 different 3-strand doublers.

2 crossovers
3 strand or chromatid

pHEL1 kar1
pHEL KAR1
PHEL KAR1
PHEL Kar

TT
Rulks

PD = NPD

PD >> NPD

Map distance between 2 genes

Map distance to centromere α- cent β- cen

unlinked

linked

\[
\frac{\frac{1}{2} TT}{\text{Total}} \times 100 = \text{cM}
\]
Mapping Equation

\[ \frac{TT + 6 \text{NPD}}{2 (TT + \text{PDT} + \text{NPD})} \times 100 = cM \]
More general mapping equation,

$$\frac{TI + 6 \times NPD}{2 \times \text{Total}} \times 100 = cM$$

assuming that doubles are

- $\frac{1}{4}$ 2 strand
- $\frac{1}{2}$ 3 strand
- $\frac{1}{4}$ 4 strand
Assignment

Derive the \( \frac{TT + 6NPD}{2 \times \text{Total}} \)

send to me by Tuesday

March 9 at 9 AM

DUTCHER@WUSTL.EDU
1) **Erythromycin** $^R \times $ Erythromycin $^S$

   $\downarrow$

   0 0 0 0

   all Ery $^R$

2) petite (small) $\times$ grande (large colonies)

   all "grande"
Both of these are examples of variants that affect mitochondrial DNA:

- petite vs. grande
- petites lack mitochondrial DNA $\rho^0$

Petite strains grow more slowly but survive with no mitochondrial DNA.

$\text{Glycerol Acetate}$

$\text{ERY}^R \rightarrow$ single nucleotide change
Aneuploidy - Int+1 disomy 13 strains

What are the consequences:

a) Chromosome loss
b) Mitochondrial drug sensitivity
c) Mutation rates
d) DNA repair

- Wild-type cells
- RAD52-GFP + plomycin
- plomycin

7/13 disomies

10/13 ↑ loss S5
8/13 ben SS
3/13 ↑ spor. mut
Why
Extra DNA
- add human chromosome
  no phenotype

Imbalance (dosage-sensitive)
- test Trisomy 2n+1
  (less imbalance)

4/5 are not sensitive to DNA damage
3/3 do not show ↑ chromosome loss
Is it the imbalance of many genes or a single gene?

Yeast deletion collection
~ 5000 genes

1536 spots

Miosis

Int 1 disome

Find disome and deletion among progeny

Score phenotype
"fitness"
small colonies/slow growth
SSDI + disome VIII
translational repressor

POL32 + disome XI
dNA polymerase / repair synthesis

EDE1 + disome IX
clathrin mediated endocytosis

COG5, 6, 7, 8 + disome XVI
cytoplasmic tethering complex - transport of vesicles to Golgi
Conclusion

Deletion of 1 gene influences fitness of disome of another chromosome

- IMBALANCE

\[ \Delta \text{edel} + \text{IX} \]

\[ \Delta \text{edel} \times \Delta \text{prk}1 \]

Doubling time \(\uparrow 2X\)

Wild-type doubling time

Dosage of one gene on the disome produced a phenotype
Aneuploidy —
- chromosome loss
- DNA repair
- transport

Different aneuploid chromosomes have different outcomes