Spindle asymmetry drives non-Mendelian chromosome segregation

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Mendelian inheritance (1866)

- Law of Segregation
- Law of Independent Assortment
- Law of Dominance

Gregor Mende (1822 - 1884)
wikipedia
Law of segregation (分離定律)

- Every individual organism contains two alleles (等位基因) for each trait
- Alleles segregate during meiosis each gamete contains only one of the alleles
Law of Independent Assortment (獨立分配定律)

- The separation and combination of genetic elements that control different traits do not interfere with each other.
Law of Dominance (顯性法則)

- Recessive alleles will always be masked by dominant alleles.
Theory of Evolution

“Survival of the fittest”

Charles Darwin, On the Origin of Species (1859)?
Theory of Evolution

“Survival of the fittest”

Herbert Spencer, Principles of Biology (1864)

“Survival of the successful reproducers”

- Evolution is change in the heritable characteristics of biological populations over successive generations.
- In evolution, fitness simply means reproductive success and reflects how well an organism is adapted to its environment.
- All life on Earth shares a common ancestor.
The selfish gene (The Immortal Gene)

- Richard Dawkins, 1966
- Gene centered view of Evolution
  - Evolution occurs through the differential survival of competing genes, increasing the allele frequency of those alleles whose phenotypic trait effects successfully promote their own propagation.
Numbers of genes

(M. Lynch, The Origins of Genome Architecture)
<table>
<thead>
<tr>
<th>Organism</th>
<th># of protein coding genes</th>
<th># of genes by prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>9</td>
<td>10 viruses</td>
</tr>
<tr>
<td>Influenze A virus</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Bacteriophage</td>
<td>66</td>
<td>49</td>
</tr>
<tr>
<td>Buchnera sp.</td>
<td>610</td>
<td>640 prokaryotes</td>
</tr>
<tr>
<td>T. maritima</td>
<td>1900</td>
<td>1900</td>
</tr>
<tr>
<td>E. coli</td>
<td>4300</td>
<td>4600</td>
</tr>
<tr>
<td>S. cerevisiae</td>
<td>6600</td>
<td>12000 eukaryotes</td>
</tr>
<tr>
<td>C. elegens</td>
<td>20000</td>
<td>100000</td>
</tr>
<tr>
<td>D. melanogaster</td>
<td>14000</td>
<td>140000</td>
</tr>
<tr>
<td>M. musculus</td>
<td>20000</td>
<td>28000000</td>
</tr>
<tr>
<td>H. sapiens</td>
<td>21000</td>
<td>32000000</td>
</tr>
</tbody>
</table>
Chromosome theory (1902)

“Chromosomes are the carriers of genetic material (genes).”

1. Chromatid
2. Centromere
3. Short (p) arm
4. Long (q) arm

Walter Sutton (left)
Theodor Boveri (right)
Chromosome structure
Junk DNAs (1)

- Susumu Ohno (大野乾)
- Noncoding region of the genome.
- Any DNA sequence that does not play a **functional role** in development, physiology, or some other organism-level capacity

L: https://www.nap.edu/read/10470/chapter/14
R: http://www.imm.ox.ac.uk/_asset/image/junkdna.jpeg
Junk DNAs (2)

- ENCODE Project
- Goal:
  - Mapping and characterizing the functionality of the entire human genome.

“The data enabled us to assign biochemical functions for 80% of the genome, in particular outside of the well studied protein-coding regions.”

The ENCODE Project Consortium 2012, *Nature*
Junk DNAs (3)

“… We examine several lines of evidence that support the notion that a substantial percentage of the DNA in many eukaryotic genomes lacks an organism-level function and that the junk DNA concept remains viable post-ENCODE.”

Alexander F. Palazzo, T. Ryan Gregory

2014, PLOS Genetic
Genome structure (1)

Genome: The genetic material of an organism.

Genome structure (2)

Main components of human genome

- Protein coding genes: 1.5%
- Introns: 26.1%
- SINEs: 13.1%
- LINES: 20.1%
- LTR: 8.0%
- DNA transposons: 3.0%
- Simple sequence repeats: 3.0%
- Segmental duplication: 5.0%
- Heterochromatin: 8.0%
- Others: 12.1%

Genome structure (1)

Genome: The genetic material of an organism.

Tandem repeats (TRs, Simple sequence repeat)

- Microsatellites (1-10nt)
- Minisatellites (> 10nt)
- Repeat 5 - 50 times
- 50,000-100,000 dinucleotide microsatellites in human genome
Tandem repeats (TRs)

- **Mutation rate**
  - $10^{-2} - 10^{-6}$ / sexual generation
  - points mutation ($10^{-10} - 10^{-11}$ / sexual generation)
  - $(10^{-6}) \times (2 \times 3 \times 10^9) = 6 \times 10^3$ mutations per gen.

- **Telomeres**
  - TTAGGG 2,500 times in human
  - 11 kilobases at birth $\rightarrow$ 4 kilobases in old age

- **Huntington’s disease**
  - Expansion of CAG in gene coding region of Huntingtin protein
Genome structure (1)

Genome: The genetic material of an organism.

Transposable Elements (TE, transposons) (1)

- Barbara McClintock (1902 - 1992)
- First discovered in Maize (1948)
- 1983 Nobel Prize
- A DNA sequence that can change its position within a genome.
Transposable Elements (TE, transposons) (2)

- **Retrotransposons**
  - copy and paste
  - LTRs, LINEs, SINEs
  - Retroviruses

- **DNA transposons**
  - cut-and-paste
  - Transposase

Horizontal Transmission of TEs (1)

- Mariner-like element

Active elements

Proliferation (Increase in copy number)

Spread in population

Stochastic loss

Mutational inactivation

Further HT
Horizontal Transmission of TEs (2)

Transfer of carbohydrate active enzymes from marine bacteria to Japanese gut microbita

Hehemann, *Nature*, 2010

“The consumption of food with associated environmental bacteria is the most likely mechanism that promoted this CAZyme update into the human gut microbe.”

Hehemann

Figure 3 | Phylogenetic analysis of GH16 galactanases reveals

(Hehemann, *Nature*, 2010)
Crossing over
Unequal crossing over
Chromosome translocation

Karyotype of Normal Cell

Karyotype of Cancer Cell

L: https://www.yourgenome.org/facts/what-is-a-chromosome-disorde
R: Janssen et al, Science 30 Sep, 2011
The structure of a eukaryotic protein-coding gene

UTR: UnTranslated Regions
ORF: Open Reading Frame
Which is bigger, mRNA or the protein it codes for?
Which is bigger, mRNA or the protein it codes for?

mRNA
(myoglobin, 1078 bases)

protein
(myoglobin, 153 aa)

5' cap
5' UTR
coding sequence (465 bases)
3' UTR
3' polyA tail

5 nm
Cell division

- mitosis
- meiosis

Sister chromosome and homologous chromosome

Mitosis

https://en.wikipedia.org/wiki/Cell_cycle

Meiosis

https://upload.wikimedia.org/wikipedia/commons/thumb/9/96/Meiosis_Overview_new.svg/1280px-Meiosis_Overview_new.svg.png
Meiosis

Gametogenesis

- spermatogenesis
- oogenesis

Centromere and Kinetochore

Spindle fibers

https://en.wikipedia.org/wiki/Microtubule
Microtubule and tubulin

https://en.wikipedia.org/wiki/Microtubule
Assembly and Disassembly

GTP-tubulin

+ end
β

- end
α

https://www.mcb.ucdavis.edu/faculty-labs/al-bassam/research.html

Akhmanova and Steinmetz, 2008
Tyrosine and alpha-tubulin

TTL: tubulin-tyrosine ligase

http://cancerres.aacrjournals.org/content/71/4/1219
Cortical side and egg side
Preferential inheritance during female meiosis

A parasitic DNA sequence in centromeric repeats exploits the asymmetry inherent in female meiosis to bias their chances of transmission to the next generation.

Strong centromeres with more parasitic DNA repeats detach from tyrosinated (Y) microtubules and flip toward the oocyte interior.

1 GTP-RAN from chromosomes activates cortical GTP-CDC42
2 GTP-CDC42 promotes local tyrosination (Y) of tubulin microtubules
3 Chromosome flipping of stronger centromere to oocyte side of spindle

Chromosomes on the cortical side of the oocyte are eliminated in the first polar body during meiosis I.
Chromosomes on the cortical side of the oocyte are eliminated in the first polar body during meiosis I.

After meiosis II, one of the chromatids with more parasitic DNA repeats is preferentially inherited.
Strong centromere and week centromere

[Diagram showing a cross between CF-1 strain (Stronger centromere) and CHPO strain (Weaker centromere), resulting in CHPO x CF-1 cross, and meiotic bivalents.]
Chromosome Flipping -I
Chromosome Flipping -II

<table>
<thead>
<tr>
<th></th>
<th>Early Meta I</th>
<th>Late Meta I</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAN^{69L}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC42^{17N}</td>
<td></td>
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</tr>
</tbody>
</table>

Stronger centromeres orienting toward the egg pole (%)

A

CENP-B H2B

0 min

20 min

40 min
Spindle asymmetry
Conclusion

● Microtubule tyrosination promotes unstable interactions between selfish centromeres and the cortical side of the spindle.
● Spindle asymmetry drives non-Mendelian chromosome segregation
● Selfish centromeres have bigger chance to face toward egg side, and pass their genetic information into next generation.
Take home message

- Selfish meiotic drivers exploit the asymmetry inherent in female meiosis to bias their transmission.
Video link

https://www.youtube.com/watch?v=uNRBZ6ARQp4