DNA: The Substance of Heredity

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August 24, 2021

Heredity: offspring resemble their parents

> Had any thinker in the middle of the 19th century undertaken, as a piece of abstract and theoretical analysis, the task of constructing a particulate theory of inheritance, he would have been led, on the basis of a few simple assumptions, to produce a system identical to the modern scheme of Mendelian or factorial inheritance.
>
> R.A. Fisher (1930)

What might Darwin or Mendel have guessed about the substance of heredity?

What Darwin should have known

The substance of heredity

1. Must affect our bodies, for otherwise it could not make children resemble their parents.
2. Must be transmitted from mother to child, because children resemble their mothers.
3. It must be transmitted from father to child, because children also resemble their fathers.

But if each child got all of Mom's hereditary material and also all of Dad's, the amount would double each generation. Therefore,

4. Each parent must transmit only half its hereditary material to each child.

But which half? If all offspring got same half from each parent, all siblings would be like identical twins—which they aren't. Therefore

5. Each offspring gets a random half of each parents hereditary material.

This makes siblings as similar as parents and offspring.

Recapitulation: the substance of heredity

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3. It must be transmitted from father to child, because children also resemble their fathers.
4. Each parent must transmit only half its hereditary material to each child.
5. Each offspring gets a random half of each parents hereditary material.

DNA: paired strings of *nucleotides*

```
                Read--->
5' G-G-G-G-C-A-C-A-G-G-T-T-G-T-G-A-G-G-G-T-G-C-C-A 3'
   | | | | | | | | | | | | | | | | | | | | | | | |
3' C-C-C-C-G-T-G-T-C-C-A-A-C-A-C-T-C-C-C-A-C-G-G-T 5'
                <---Read
```

Nucleotides: *adenine* (A), *guanine* (G), *cytosine* (C) and *thymine* (T).

Pairing: A with T; C with G.

Replication: strands unzip; complementary strand is built on each original strand.

Diploids and haploids

- Each of us has 23 pairs of chromosomes—46 in all.
- Because we have 2 copies of each chromosome, we are *diploid* humans.
- In each pair, one came from Mom, one from Dad.
- Gametes (sperm and ova) contain only 1 copy of each chromosome—23 in all.
- Our gametes are *haploid* humans.
- In most fungi and algae, the diploid stage is a single cell, but haploids are multicellular.

Random assortment

To make a gamete, you choose 1 chromosome at random from each pair.

Each gamete contains a mixture of DNA you got from Mom and from Dad.

Recombination: we'll get to that in a later lecture.

How DNA affects you

- Bodies are largely built of *proteins*.
- Proteins are chains of *amino acids*.
- DNA tells your body how to build proteins from amino acids.


```
1                                                   g
atg.tcg.ttt.act.ttg.acc.aac.aag.aac.gtg.att.ttc.gtt.gcc.ggt.ctg.gga.ggc.att.ggt
Met.Ser.Phe.Thr.Leu.Thr.Asn.Lys.Asn.Val.Ile.Phe.Val.Ala.Gly.Leu.Gly.Gly.Ile.Gly
61
ctg.gac.acc.agc.aag.gag.ctg.ctc.aag.cgc.gat.ctg.aag.aac.ctg.gtg.atc.ctc.gac.cgc
Leu.Asp.Thr.Ser.Lys.Glu.Leu.Leu.Lys.Arg.Asp.Leu.Lys.Asn.Leu.Val.Ile.Leu.Asp.Arg
121
att.gag.aac.ccg.gct.gcc.att.gcc.gag.ctg.aag.gca.atc.aat.cca.aag.gtg.acc.gtc.acc
Ile.Glu.Asn.Pro.Ala.Ala.Ile.Ala.Glu.Leu.Lys.Ala.Ile.Asn.Pro.Lys.Val.Thr.Val.Thr
181                                                 t
ttc.tac.ccc.tat.gat.gtg.acc.gtg.ccc.att.gcc.gag.acc.acc.aag.ctg.ctg.aag.acc.atc
Phe.Tyr.Pro.Tyr.Asp.Val.Thr.Val.Pro.Ile.Ala.Glu.Thr.Thr.Lys.Leu.Leu.Lys.Thr.Ile
241
ttc.gcc.cag.ctg.aag.acc.gtc.gat.gtc.ctg.atc.aac.gga.gct.ggt.atc.ctg.gac.gat.cac
Phe.Ala.Gln.Leu.Lys.Thr.Val.Asp.Val.Leu.Ile.Asn.Gly.Ala.Gly.Ile.Leu.Asp.Asp.His
301
cag.atc.gag.cgc.acc.att.gcc.gtc.aac.tac.act.ggc.ctg.gtc.aac.acc.acg.acg.gcc.att
Gln.Ile.Glu.Arg.Thr.Ile.Ala.Val.Asn.Tyr.Thr.Gly.Leu.Val.Asn.Thr.Thr.Thr.Ala.Ile
361                 t   a
ctg.gac.ttc.tgg.gac.aag.cgc.aag.ggc.ggt.ccc.ggt.ggt.atc.atc.tgc.aac.att.gga.tcc
Leu.Asp.Phe.Trp.Asp.Lys.Arg.Lys.Gly.Gly.Pro.Gly.Gly.Ile.Ile.Cys.Asn.Ile.Gly.Ser
421                 a
gtc.act.gga.ttc.aat.gcc.atc.tac.cag.gtg.ccc.gtc.tac.tcc.ggc.acc.aag.gcc.gcc.gtg
Val.Thr.Gly.Phe.Asn.Ala.Ile.Tyr.Gln.Val.Pro.Val.Tyr.Ser.Gly.Thr.Lys.Ala.Ala.Val
481                                 a       c           g           t
gtc.aac.ttc.acc.agc.tcc.ctg.gcg.aaa.ctg.gcc.ccc.att.acc.ggc.gtg.acc.gct.tac.acc
Val.Asn.Phe.Thr.Ser.Ser.Leu.Ala.Lys.Leu.Ala.Pro.Ile.Thr.Gly.Val.Thr.Ala.Tyr.Thr
541                                 c
gtg.aac.ccc.ggc.atc.acc.cgc.acc.acc.ctg.gtg.cac.aag.ttc.aac.tcc.tgg.ttg.gat.gtt
Val.Asn.Pro.Gly.Ile.Thr.Arg.Thr.Thr.Leu.Val.His.Lys.Phe.Asn.Ser.Trp.Leu.Asp.Val
601   t           c                                 c
gag.ccc.cag.gtt.gct.gag.aag.ctc.ctg.gct.cat.ccc.acc.cag.cca.tcg.ttg.gcc.tgc.gcc
Glu.Pro.Gln.Val.Ala.Glu.Lys.Leu.Leu.Ala.His.Pro.Thr.Gln.Pro.Ser.Leu.Ala.Cys.Ala
661                     a
gag.aac.ttc.gtc.aag.gct.atc.gag.ctg.aac.cag.aac.gga.gcc.atc.tgg.aaa.ctg.gac.ctg
Glu.Asn.Phe.Val.Lys.Ala.Ile.Glu.Leu.Asn.Gln.Asn.Gly.Ala.Ile.Trp.Lys.Leu.Asp.Leu
721
ggc.acc.ctg.gag.gcc.atc.cag.tgg.acc.aag.cac.tgg.gac.tcc.ggc.atc.
Gly.Thr.Leu.Glu.Ala.Ile.Gln.Trp.Thr.Lys.His.Trp.Asp.Ser.Gly.Ile.
```

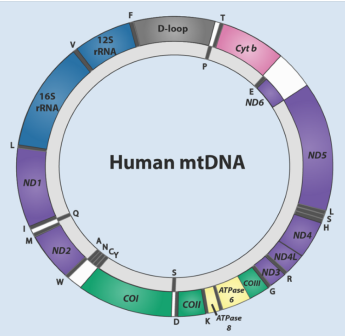
Alcohol dehydrogenase in *Drosophila melanogaster*

Each codon (above) specifies an amino acid (below).

Variant nucleotides shown above.

Variant at pos. 578 changes lysine to threonine.

Mitochondria



Origin: 1.45 billion years ago one single-celled organism engulfed another.

Involved in energy metabolism.

Own genome: 1 circular chromosome.

Haploid: inherited from mom.

Inherited as a unit: no recombination.

Evolve 10× as fast as nuclear DNA.

Recapitulation: the substance of heredity

Must affect our bodies.	Does so by making protein.
Mother → child.	DNA in ova.
Father → child.	DNA in sperm.
1/2 → offspring.	Gametes are haploid.
Random half.	Random assortment.

Origin of Human Chromosome 2

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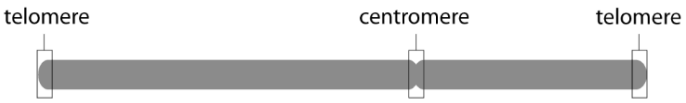
Chromosomes, centromeres, telomeres



- Centromeres organize chromosomes during cell division.
- When chromosomes replicate, the ends erode.
- Telomeres protect against this damage.

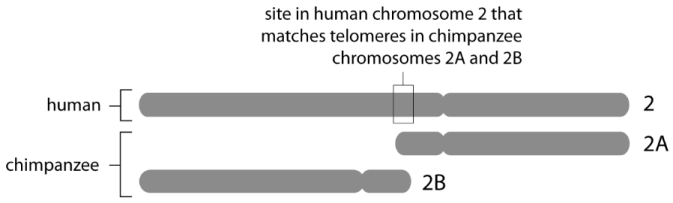
The mystery of the missing chromosome

- Humans have 23 pairs of chromosomes.
- Chimp, gorilla, and orangutan have 24 pairs.
- How did we *lose* an entire chromosome?!

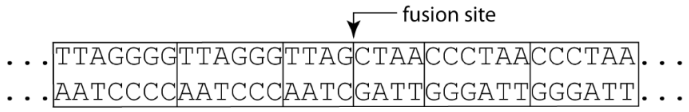
Human chromosome 2 matches *two* chimpanzee chromosomes

All other chimp/human chromosomes match one-to-one.

There are telomeric sequences in the *middle* of human chromosome 2.

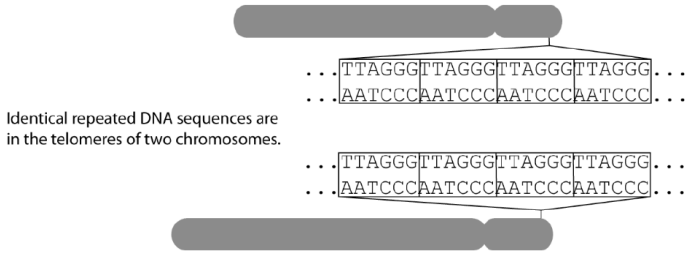


Telomeres consist of a string of repeated segments



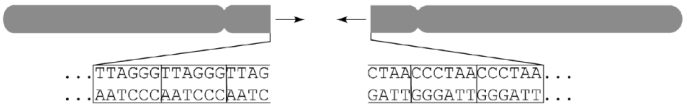
The repeats to the right of the fusion site are upside-down and backwards. How did this happen?

Begin with 2 chromosomes with similar telomeres



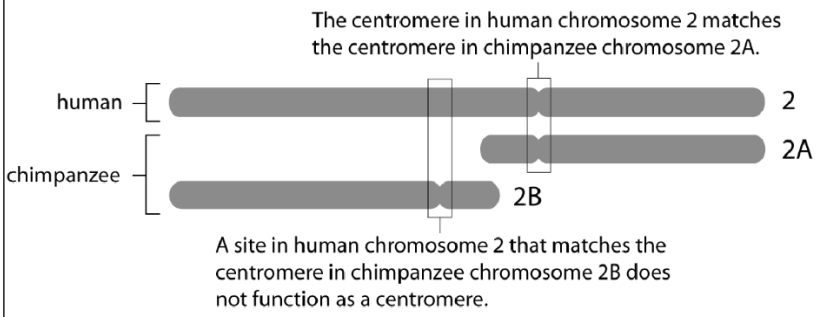
Ends get broken

Join broken ends

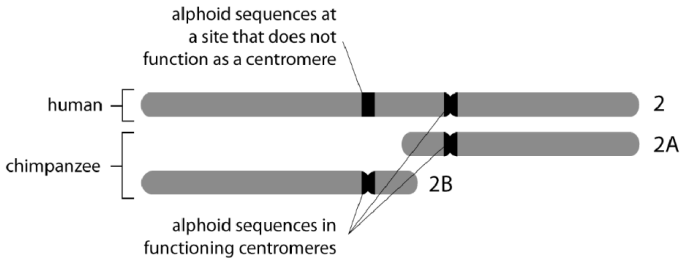


Presto: chromosome fusion

Fusion site is a molecular fossil.



Alphoid sequences: a molecular fossil



- 171 basepair "alphoid" sequence is repeated over and over in centromeres of humans and apes.
- Found in every single centromere.
- Also at site of defunct centromere in human chromosome 2.