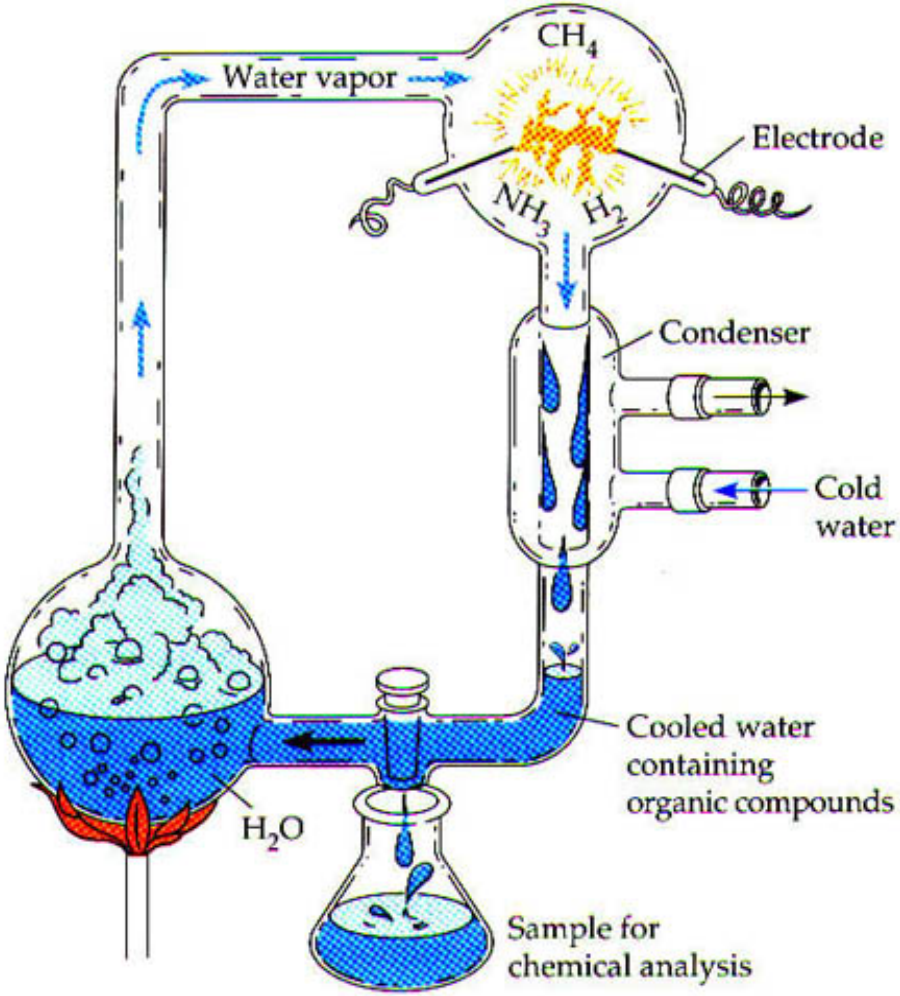
Od vzniku života po evoluci člověka

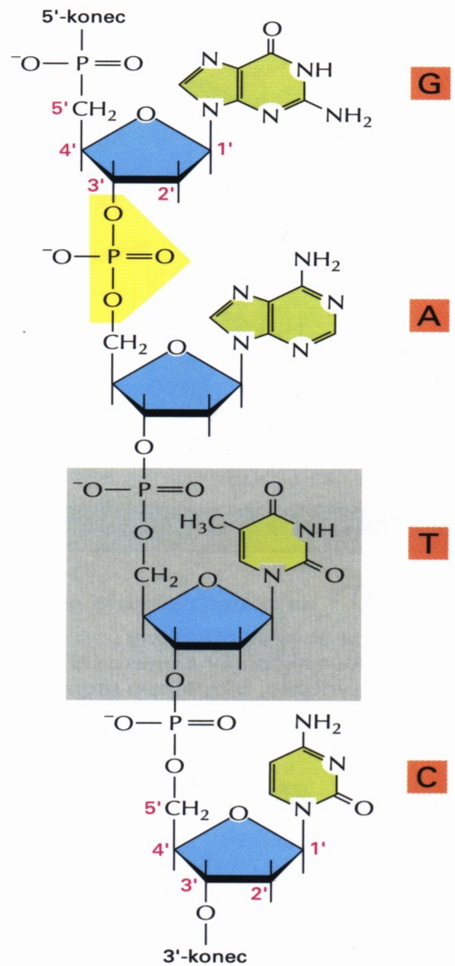
Václav Pačes

Ústav molekulární genetiky

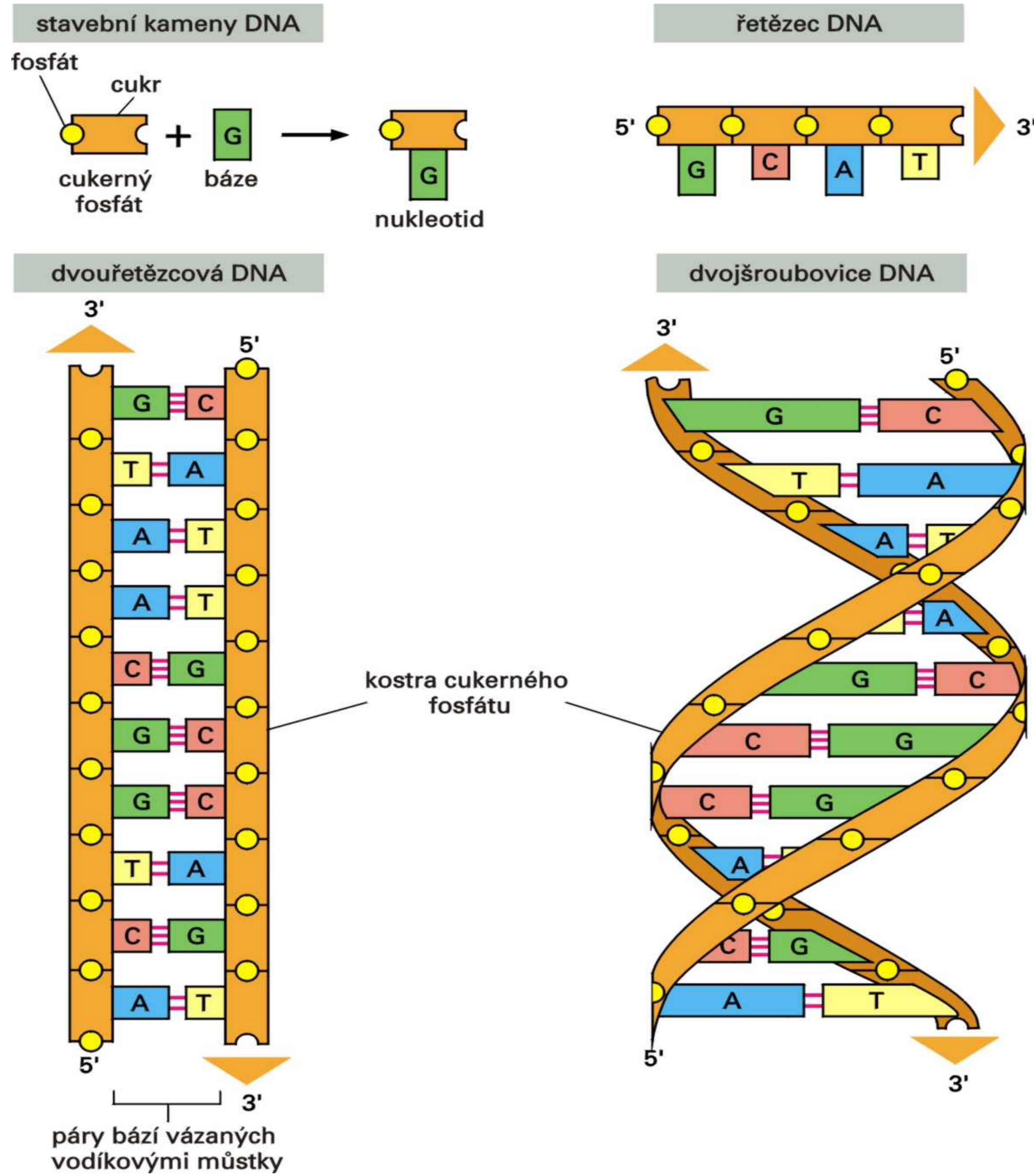
Akademie věd České republiky



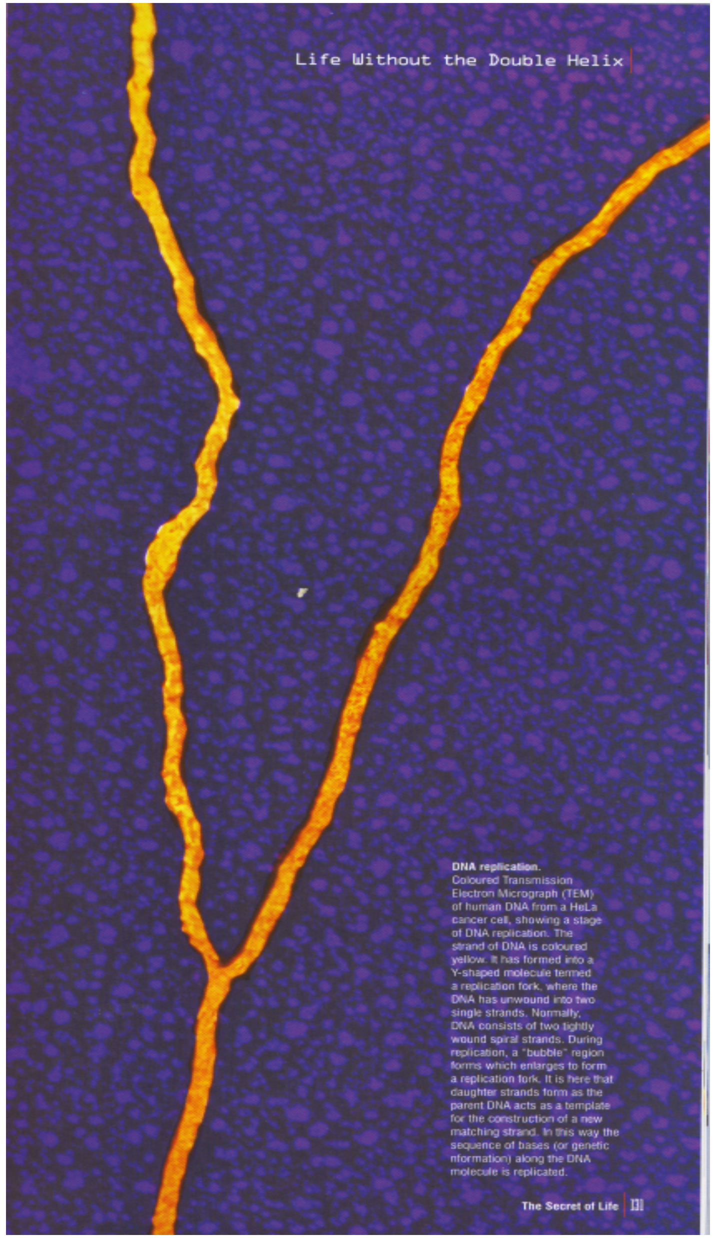
CH_4
Water vapor
Electrode
NH_3
H_2
Condenser
Cold
water
Cooled water
containing
organic compounds
H_2O
Sample for
chemical analysis



Otázka 2-7 Co se myslí „polaritou" polypeptidového řetězce a „polaritou" chemické vazby? Jak se tyto dva významy liší?



stavební kameny DNA
fosfát
cukr
cukerný fosfát
G
báze
nukleotid
řetězec DNA
5'
3'
G C A T
dvouřetězcová DNA
dvojšroubovice DNA
3'
5'
kostra cukerného fosfátu
páry bází vázaných vodíkovými můstky



DNA replication. Coloured Transmission Electron Micrograph (TEM) of human DNA from a HeLa cancer cell, showing a stage of DNA replication. The strand of DNA is coloured yellow. It has formed into a Y-shaped molecule termed a replication fork, where the DNA has unwound into two single strands. Normally, DNA consists of two tightly wound spiral strands. During replication, a "bubble" region forms which enlarges to form a replication fork. It is here that daughter strands form as the parent DNA acts as a template for the construction of a new matching strand. In this way the sequence of bases (or genetic nformation) along the DNA molecule is replicated.

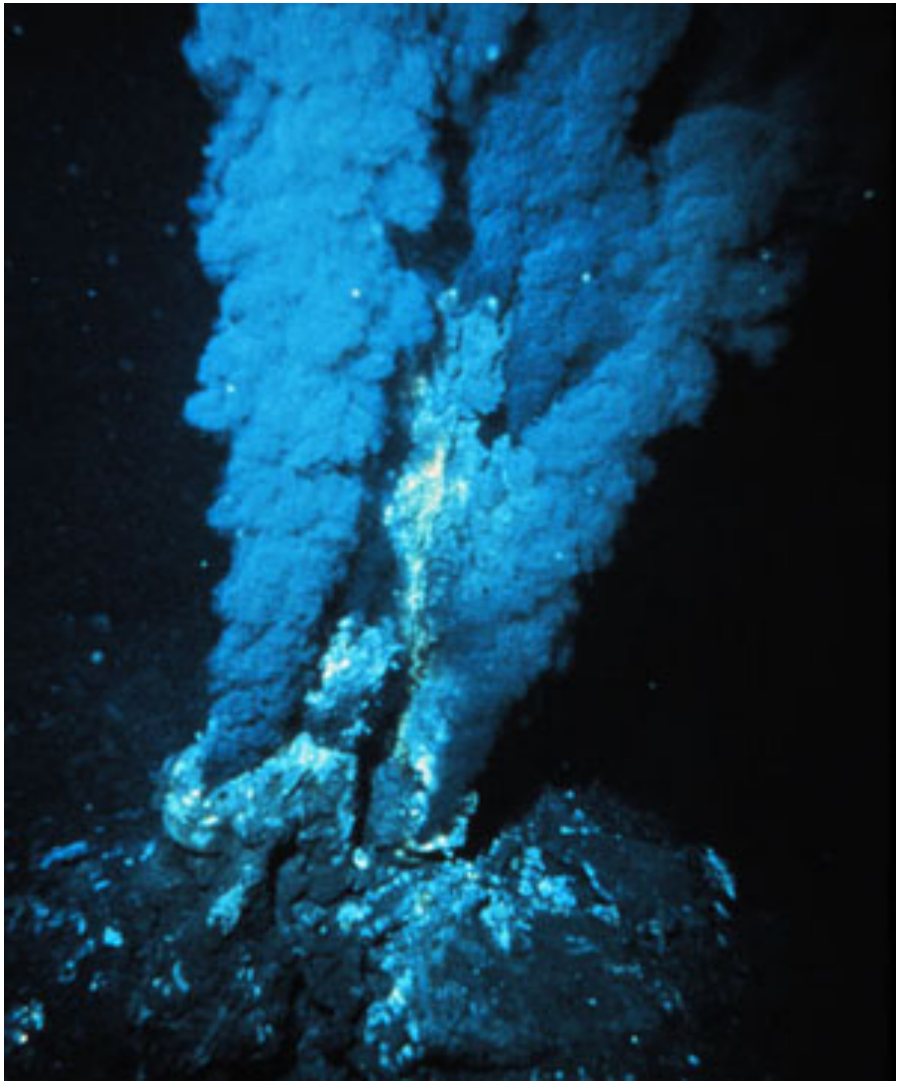
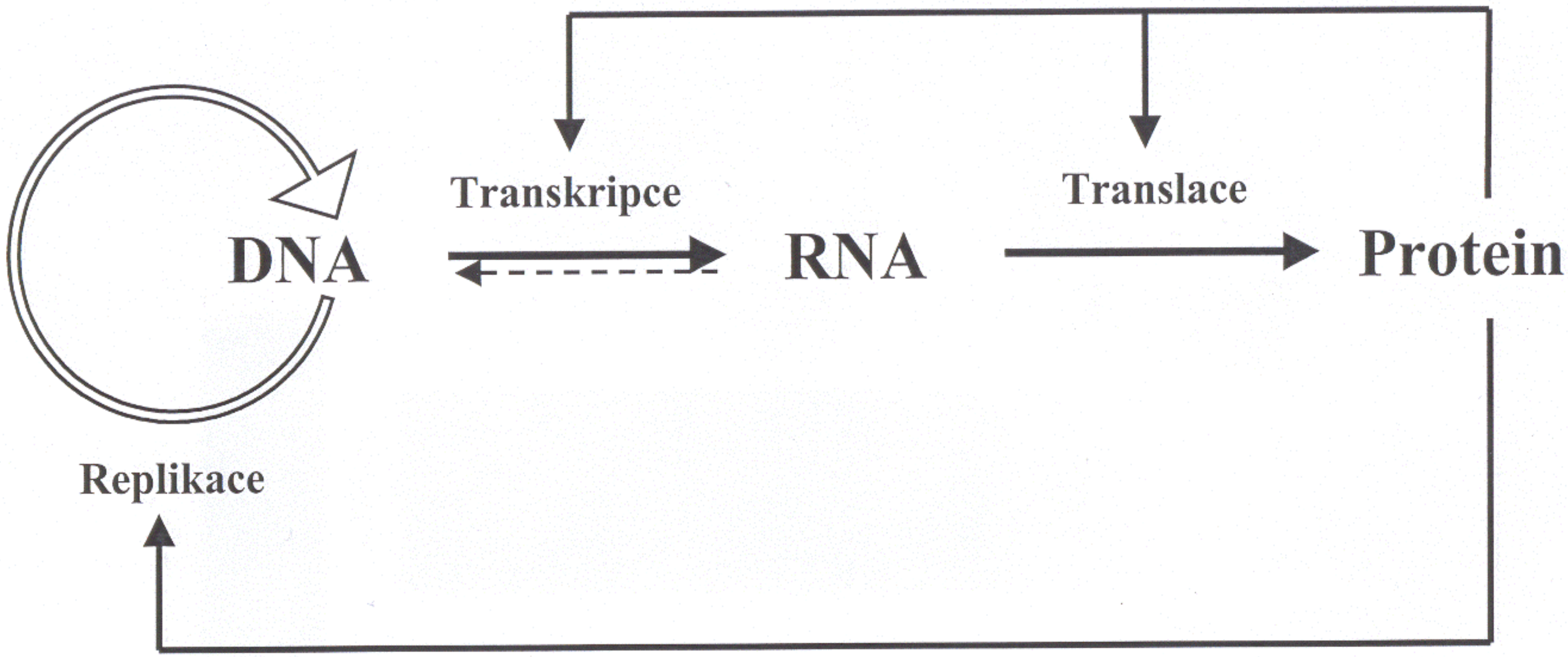
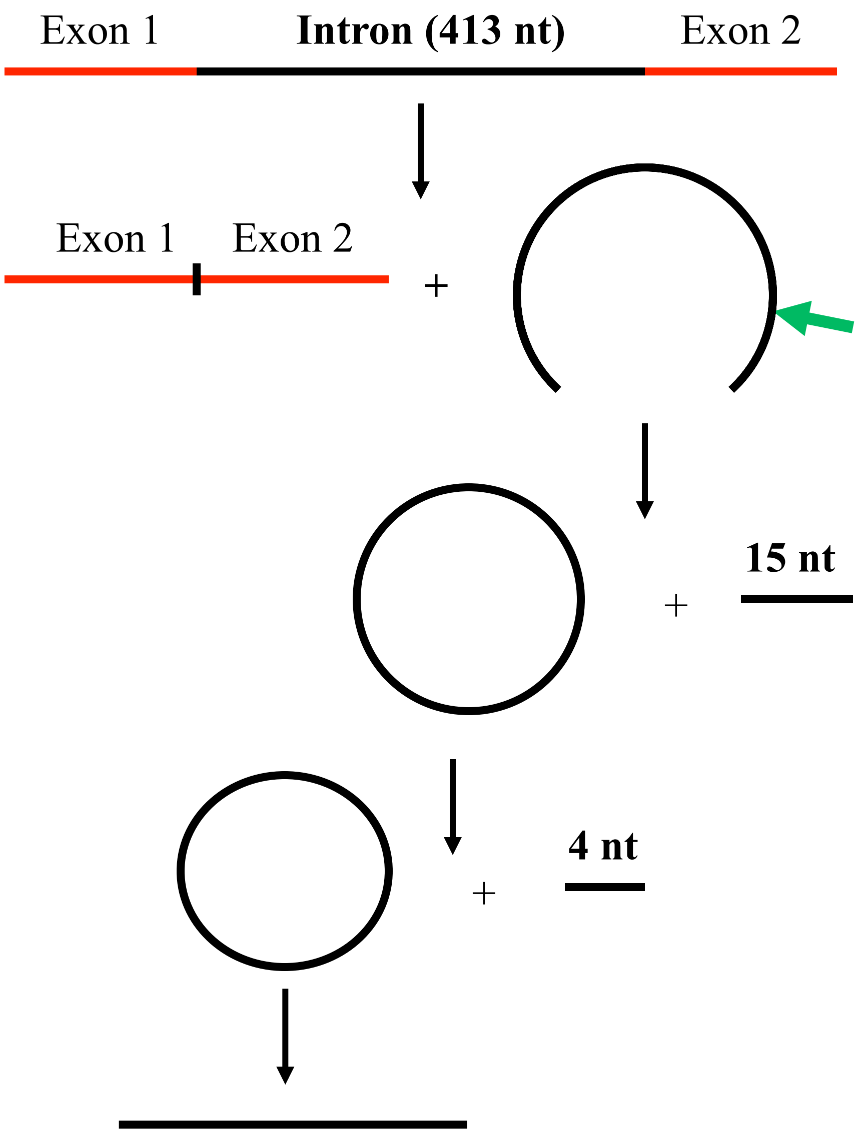


FIGURE 10-6
Electron micrograph of the DNA molecule of T-even phage released from the phage head by osmotic shock. Center: The phage ghost. Bottom right and top center: The two ends of the DNA molecule. [From A. K. Kleinschmidt, D. Lang, D. Jacherts, and R. K. Zahn, *Biochim. Biophys. Acta* **61**, 857 (1962).]

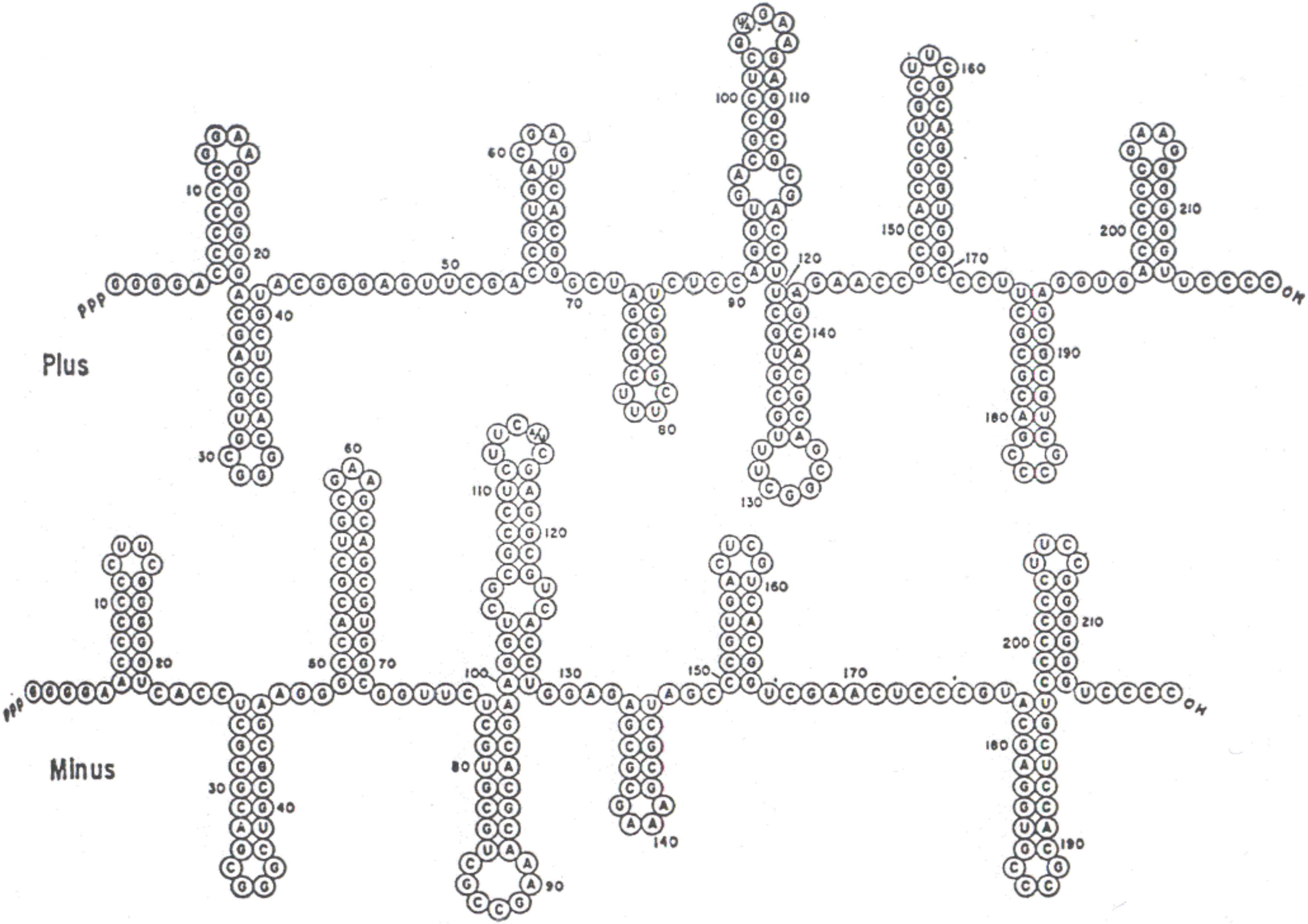
False-colour transmission electron micrograph (TEM) of the bacterium *Escherichia coli* surrounded by its DNA. The bacterium was treated with an enzyme to weaken its cell wall and then placed in water, causing its DNA to be ejected. The DNA is visible as the gold-coloured fibrous mass lying around the orange bacterial shell. The total length of DNA is 1.5 millimetres, 1000 times the length of the bacterium itself.


Transkripce
Translace
DNA
RNA
Protein
Replikace



Exon 1
Intron (413 nt)
Exon 2
Exon 1
Exon 2
+
+
15 nt
+
4 nt

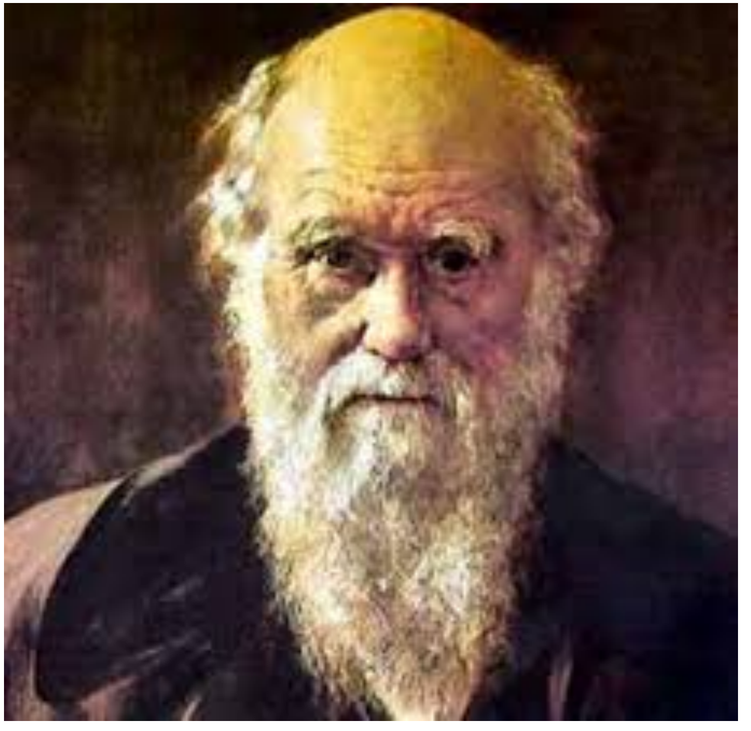
Genome of RNA-bacteriophage Qβ



Plus
Minus

Selected Genome Projects

Category	Species		Genome size (Mb)	Genes
PROKARYOTES				
Actinobacteria	*Mycobacterium tuberculosis*		4,4	4397
Chlamydia	*Chlamydia pneumoniae*		1,1	1000
Cyanobacteria	*Synechocystis species*		3,6	3215
Gram-positive bacteria	*Bacillus subtilis*		4,2	4221
	Mycoplasma genitalium		0,5	503
Oxygen-reducing bacteria	*Aquifex aeolicus*		1,5	1572
Proteobacteria	*Escherichia coli*		4,6	4397
	Haemophilus influenzae		1,8	1791
	Helicobacter pylori		1,7	1609
	Rickettsia prowazekii		1,1	834
Radioresistent bacteria	*Deinococcus radiodurans*		3,2	3000
Spirochete	*Borrelia burgdorferi*		0,9	1279
	Treptonema pallidum		1,1	1082
Archea	*methanococcus jannaschii*		1,6	1813
EUKARYOTES		Chromosomes		
Fungi	*Saccharomyces cerevisiae*	16	12	6548
Nematode	*Caenorhabditis elegans*	6	97	19000
Insect	*Drosophila melanogaster*	6	137	13500
Plants	*Arabidopsis thaliana*	5	116	25545
Fish	*Fugu rubripes*	22	400	25000
Human	*Homo sapiens*	23	3000	25000



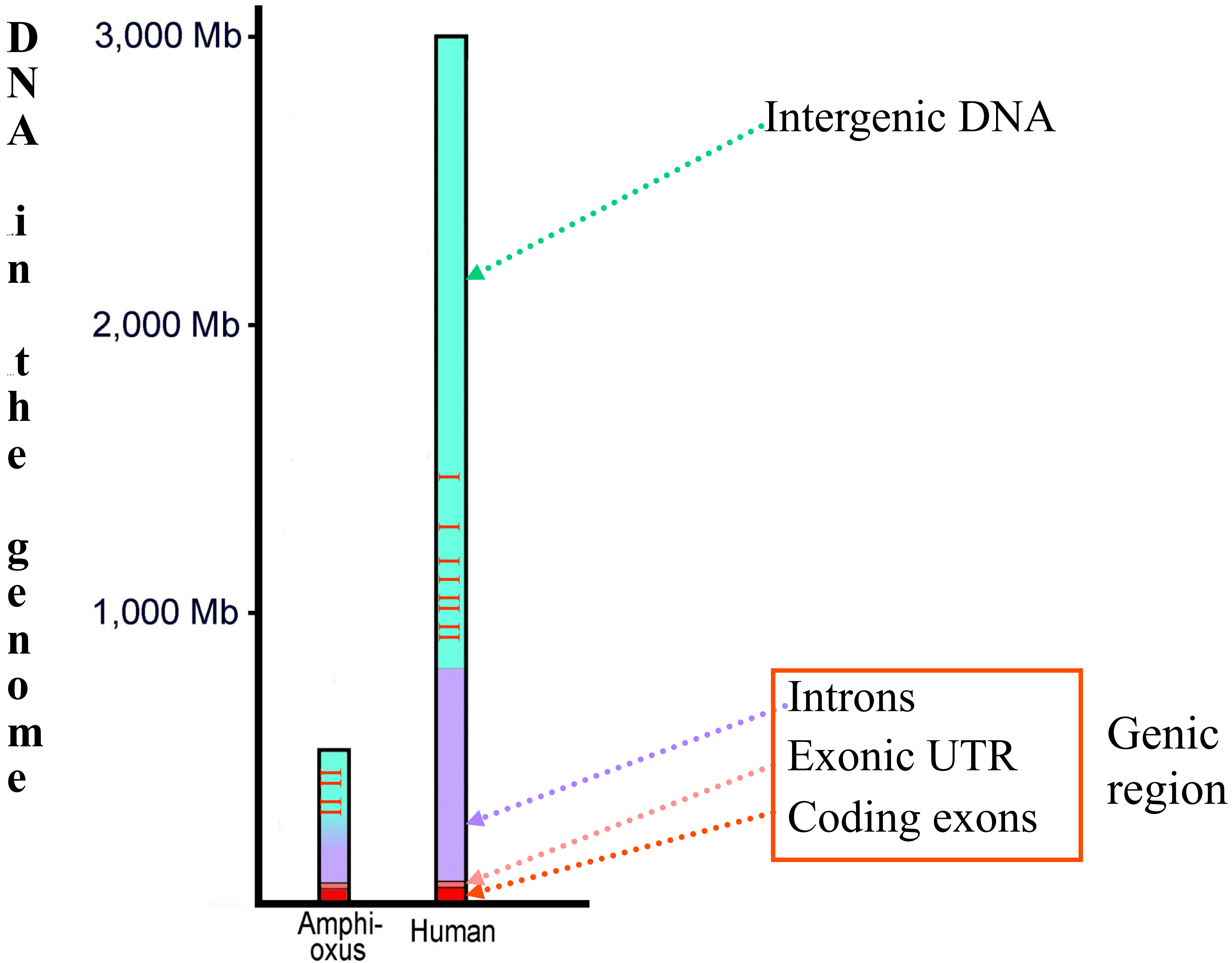
Key steps (jumps) in evolution

- How life started? (pre-biotic to biotic)
- The first cell (compartmentation)
- Multicellular organisms (cooperation)
- Tissues and organs (specialization)
- Brain (networking)
- Sexual reproduction (combination)
- Vertebrates (structure)
- Mammals (progeny)
- Humans (communication)

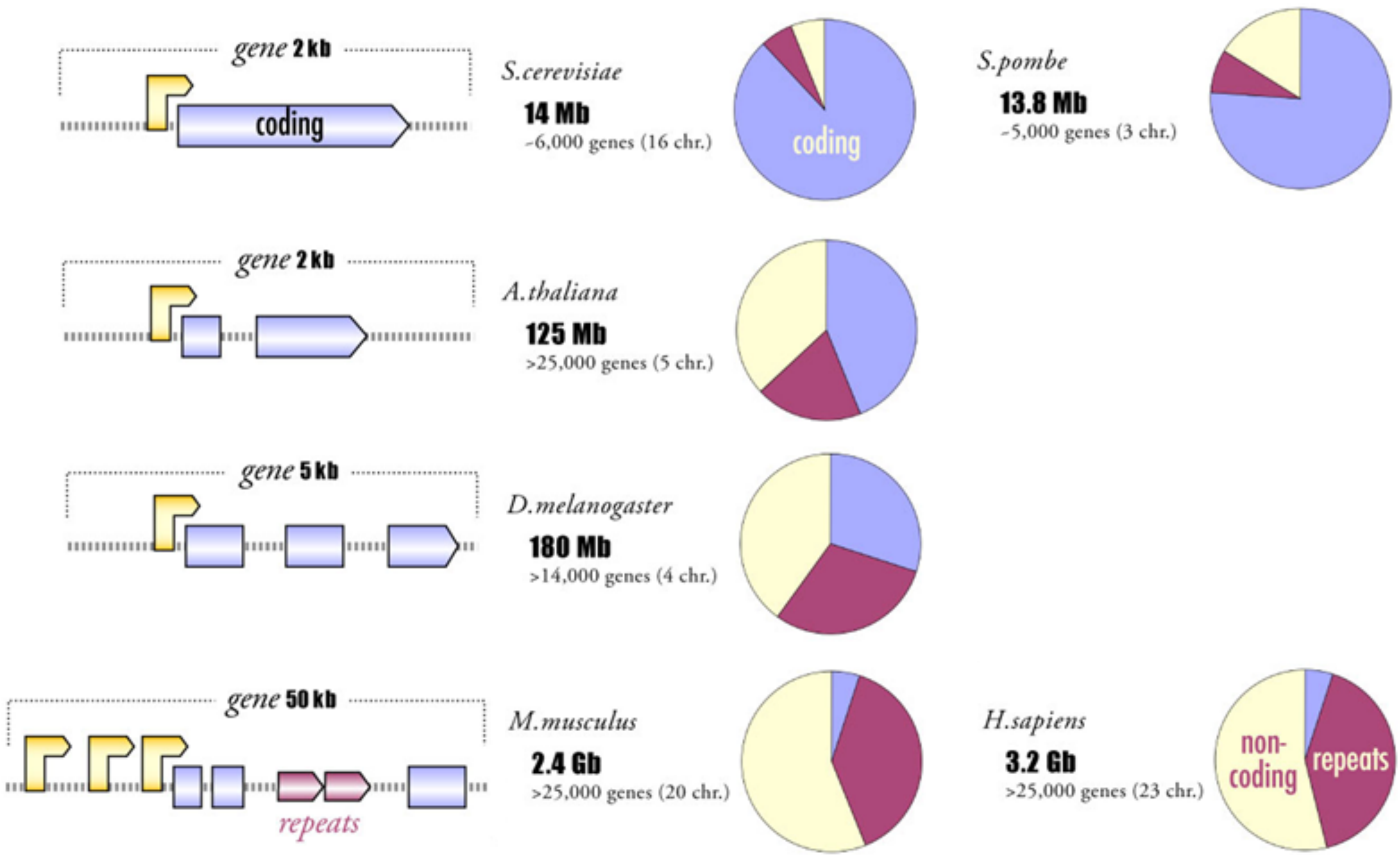
Haploid genomes:

	Chromosome # (2N)	Chromosome length (average)	DNA per cell	Megabases per genome	# of genes per genome
Amphioxus	38	3 µm	0.9 pg	520	**22,000**
Human	46	15 µm	3.5 pg	3,000	**25,000**

In spite of their much larger DNA content vertebrates have only 25% more genes than amphioxus


DNA in the genome
3,000 Mb
2,000 Mb
1,000 Mb
Amphi-oxus
Human
Intergenic DNA
Introns
Exonic UTR
Coding exons
Genic region

Genome complexity



Major events in genome evolution

- Mutations (SNP)
- Duplications
  - genome-wide duplications
  - tandem duplications - amplifications
- Rearrangements
- Horizontal transfer
- Parasitic DNA

Some Data on Human Genome

- **3.1647 Bbp**
- **Average gene is three thousand bp long**
- **The longest gene (for dystrophin) is 2.4 Mbp long**
- **Total number of genes is estimated to be 25 000**
- **Less than 2% of DNA encode proteins**
- **Over 50% of identified genes have unknown functions**
- **Over 50% of junk DNA are repetitive elements**
- **Around 20% of our genome is transcribed**

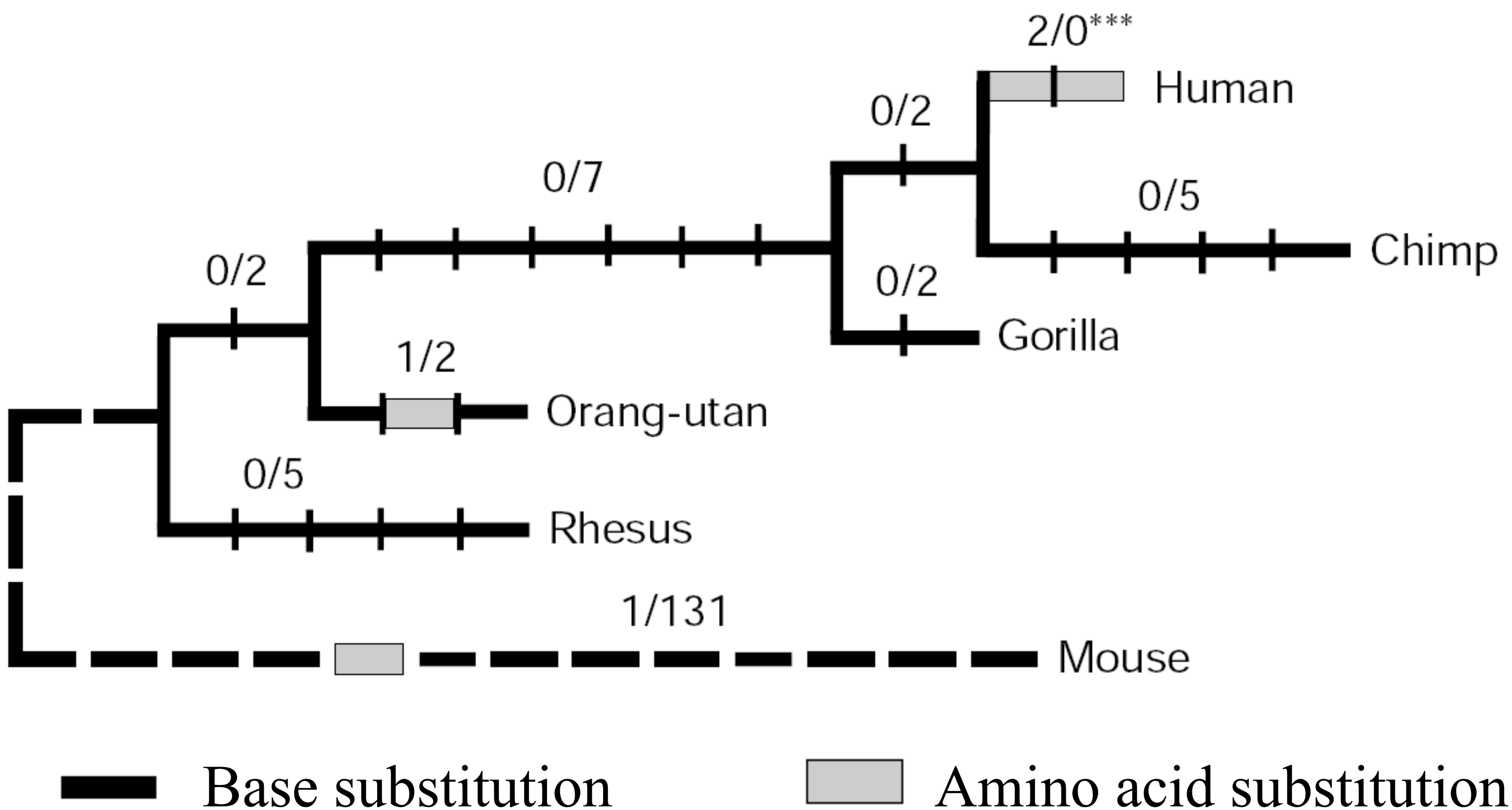
Importance of chimp genome

Medical Condition	Human	Great Apes
Definite		
HIV progression to AIDS	Common	Very rare
Influenza A symptomatology	Moderate to severe	Mild
Hepatitis B/C late complications	Moderate to severe	Mild
Malaria	Susceptible	Resistant
Menopause	Universal	Rare
Likely		
E. coli K99 gastroenteritis	Resistant	Sensitive?
Alzheimer’s disease pathology	Complete	Incomplete
Coronary atherosclerosis	Common	Uncommon
Epithelial cancers	Common	Rare
Speculative		
Menstrual blood loss	Variable	Lower amount?
Early fetal wastage	High	Low?

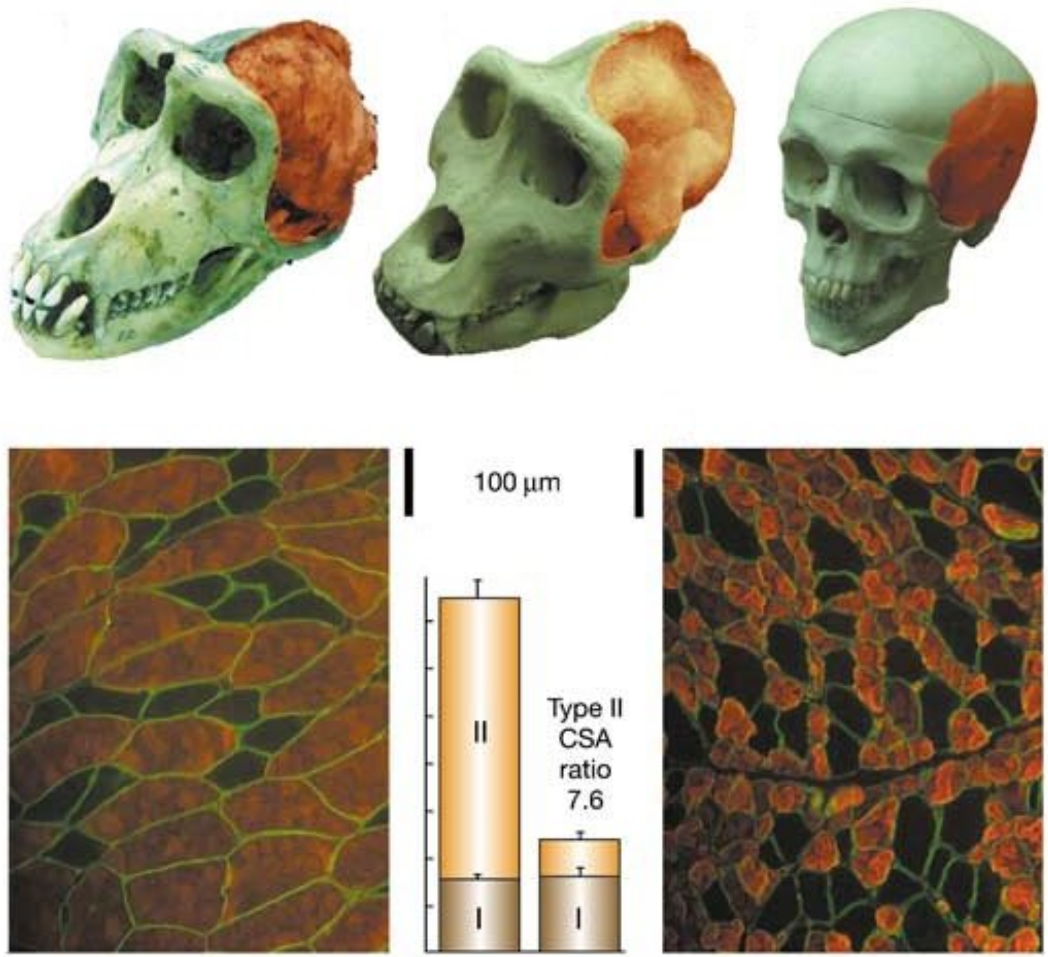

FOXP2

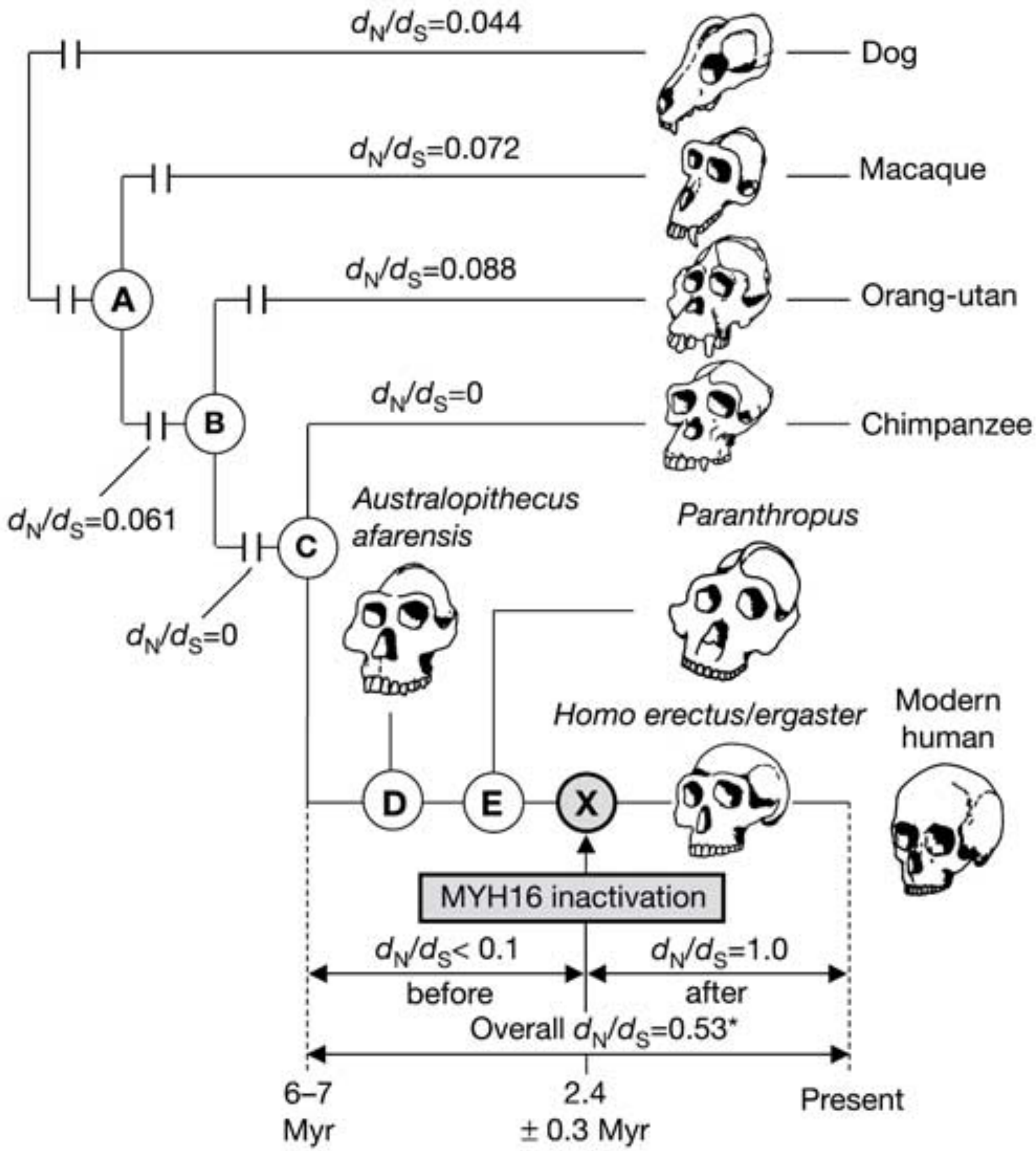
- **Mutations lead to articulation impairment (KE family).**
- **Only three aa changes between human and mouse.**
- **Two specific changes [thr -> asp (233) and asp -> ser (325)] appeared 100 000 – 200 000 years ago when *Homo sapiens* appeared.**

Evolution of FOXP2



MYH16 inactivation

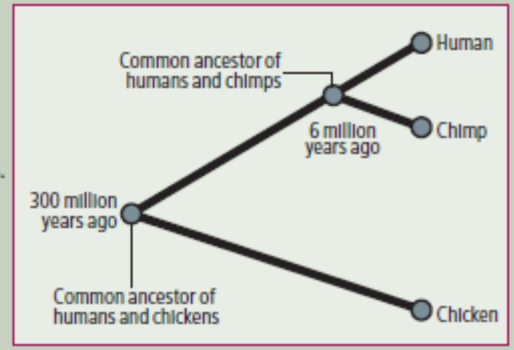




d_N/d_S=0.044
Dog
d_N/d_S=0.072
Macaque
d_N/d_S=0.088
Orang-utan
d_N/d_S=0
Chimpanzee
A
B
C
d_N/d_S=0.061
d_N/d_S=0
Australopithecus afarensis
Paranthropus
Homo erectus/ergaster
Modern human
D
E
X
MYH16 inactivation
d_N/d_S< 0.1
before
d_N/d_S=1.0
after
Overall d_N/d_S=0.53*
6–7 Myr
2.4 ± 0.3 Myr
Present

SCANNING THE GENOME

To find the parts of our genome that make us human, the author wrote a computer program that searched for the DNA sequences that have changed the most since humans and chimpanzees diverged from their last common ancestor. Topping the list was a 118-letter snippet of code known as human accelerated region 1 (HAR1). This region of the genome changed very little for most of vertebrate evolution, with chimp and chicken sequences differing by just two letters. Human and chimp HAR1s, however, differ by 18 letters, suggesting that HAR1 acquired an important new function in humans.



T	G	A	A	A	**C**	G	G	A	G	G	A	G	A	**C**	**G**	T	T	A	C
A	G	C	A	A	**C**	**G**	T	**G**	T	C	A	**G**	C	T	G	A	A	A	T
G	A	T	**G**	G	G	**C**	G	T	A	G	A	C	**G**	C	A	**C**	G	T	C
A	G	C	**G**	G	**C**	G	G	A	A	A	T	**G**	G	T	T	T	C	T	A
T	C	A	A	A	A	T	**G**	A	A	A	G	T	**G**	T	T	T	A	G	A
G	A	T	T	T	T	C	C	T	C	A	A	**G**	T	T	T	C	A		

■ Changes in human sequence relative to that of the chimp

T	G	A	A	A	T	G	G	A	G	G	A	G	A	A	A	T	T	A	C
A	G	C	A	A	T	T	T	A	T	C	A	A	C	T	G	A	A	A	T
T	A	T	A	G	G	T	G	T	A	G	A	C	A	C	A	T	G	T	C
A	G	C	A	G	T	**G**	G	A	A	A	**T**	A	G	T	T	T	C	T	A
T	C	A	A	A	A	T	T	A	A	A	G	T	A	T	T	T	A	G	A
G	A	T	T	T	T	C	C	T	C	A	A	A	T	T	T	C	A		

■ Changes in chimp sequence relative to that of the chicken

T	G	A	A	A	T	G	G	A	G	G	A	G	A	A	A	T	T	A	C
A	G	C	A	A	T	T	T	A	T	C	A	A	C	T	G	A	A	A	T
T	A	T	A	G	G	T	G	T	A	G	A	C	A	C	A	T	G	T	C
A	G	C	A	G	T	A	G	A	A	A	C	A	G	T	T	T	C	T	A
T	C	A	A	A	A	T	T	A	A	A	G	T	A	T	T	T	A	G	A
G	A	T	T	T	T	C	C	T	C	A	A	A	T	T	T	C	A		

ASPM and HAR1 involvement in brain formation

Normal brain

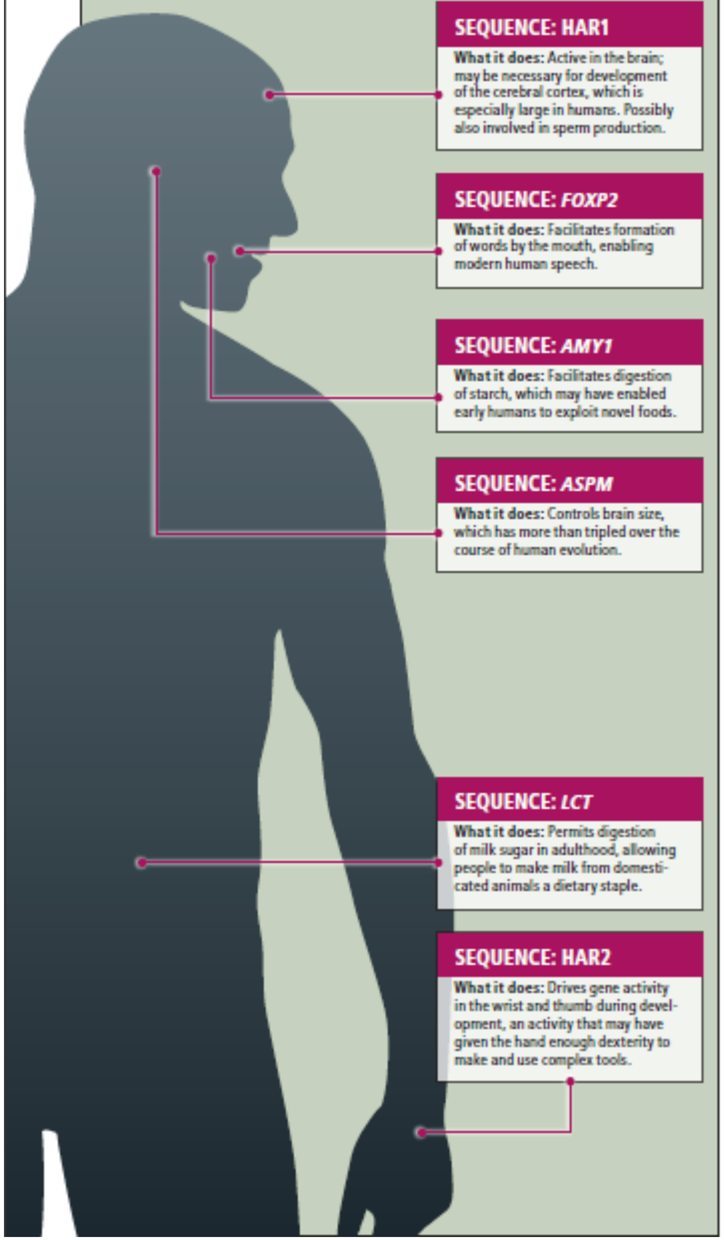
Mutated ASPM

HAR1 malfunction

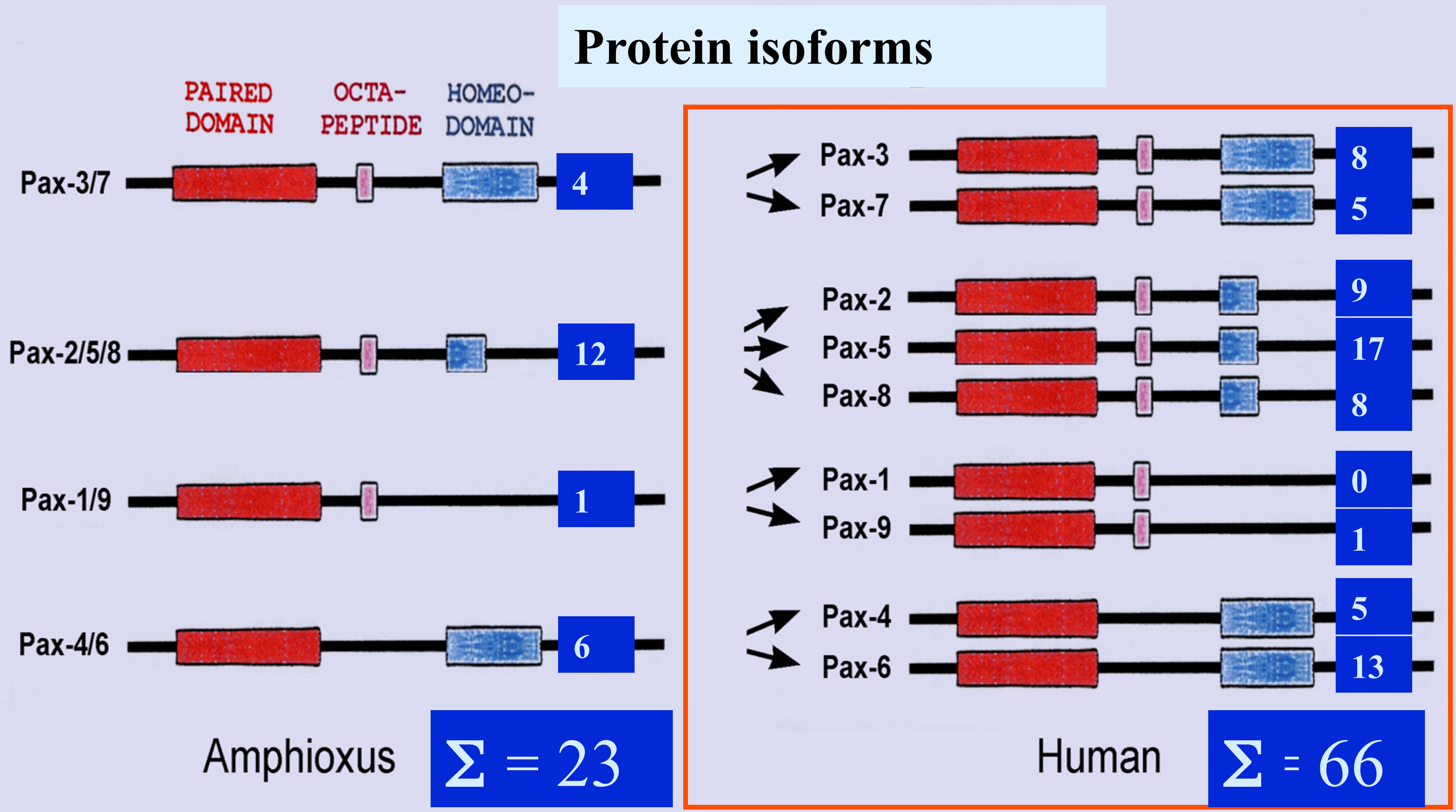
BRAIN SHAPERS: Changes to certain genome sequences can have dramatic effects on the brain. Mutation of the *ASPM* gene, for example, leads to markedly reduced brain size (*middle*) compared with a normal brain (*top*), suggesting that this gene played a key role in the evolution of large brain size in humans. Malfunctions in the neurons in which HAR1 is active during development, meanwhile, can lead to a severe disorder in which the brain's cerebral cortex fails to fold properly (*bottom*), hinting that HAR1 is essential for the formation of a healthy cortex.

DISTINCTIVE DNA

Efforts to uncover uniquely human DNA have yielded a number of sequences that are distinctive in humans as compared with chimpanzees. A partial list of these sequences—and some of their functions—follows below.



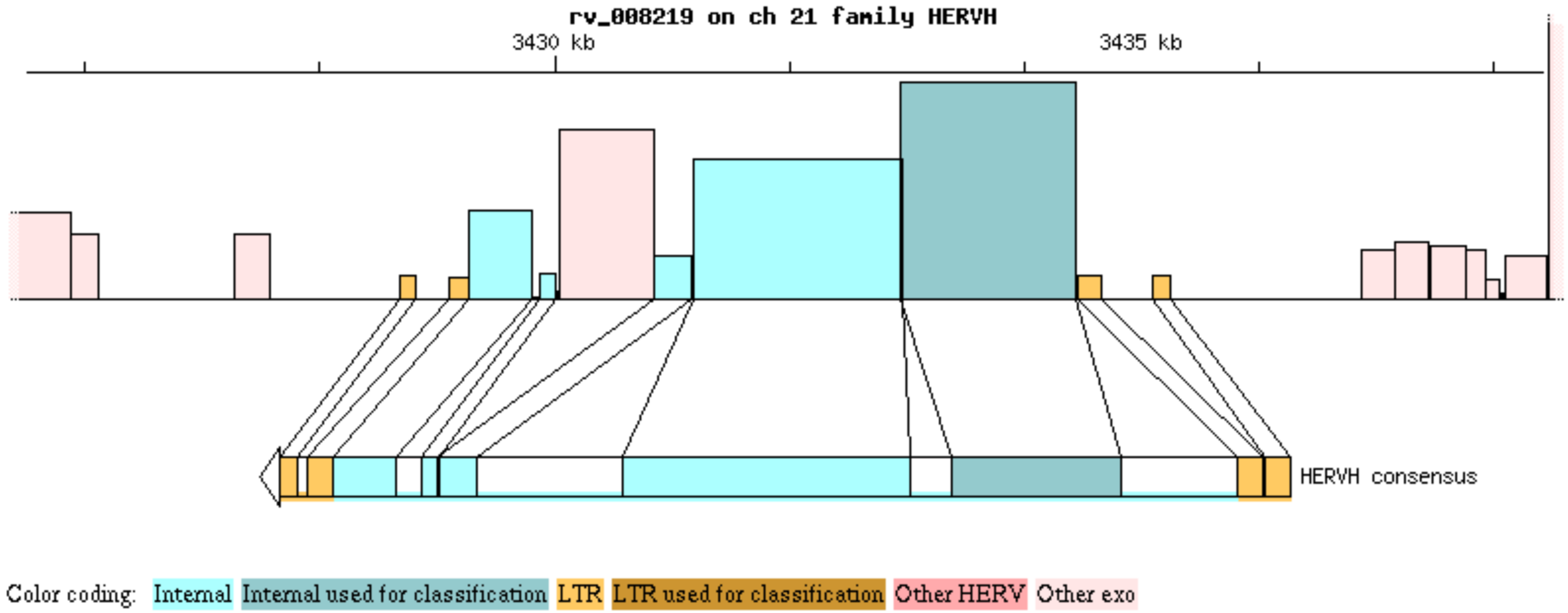
Pax genes: the vertebrate proteome is markedly larger than the amphioxus proteome:



Importance of "junk" DNA

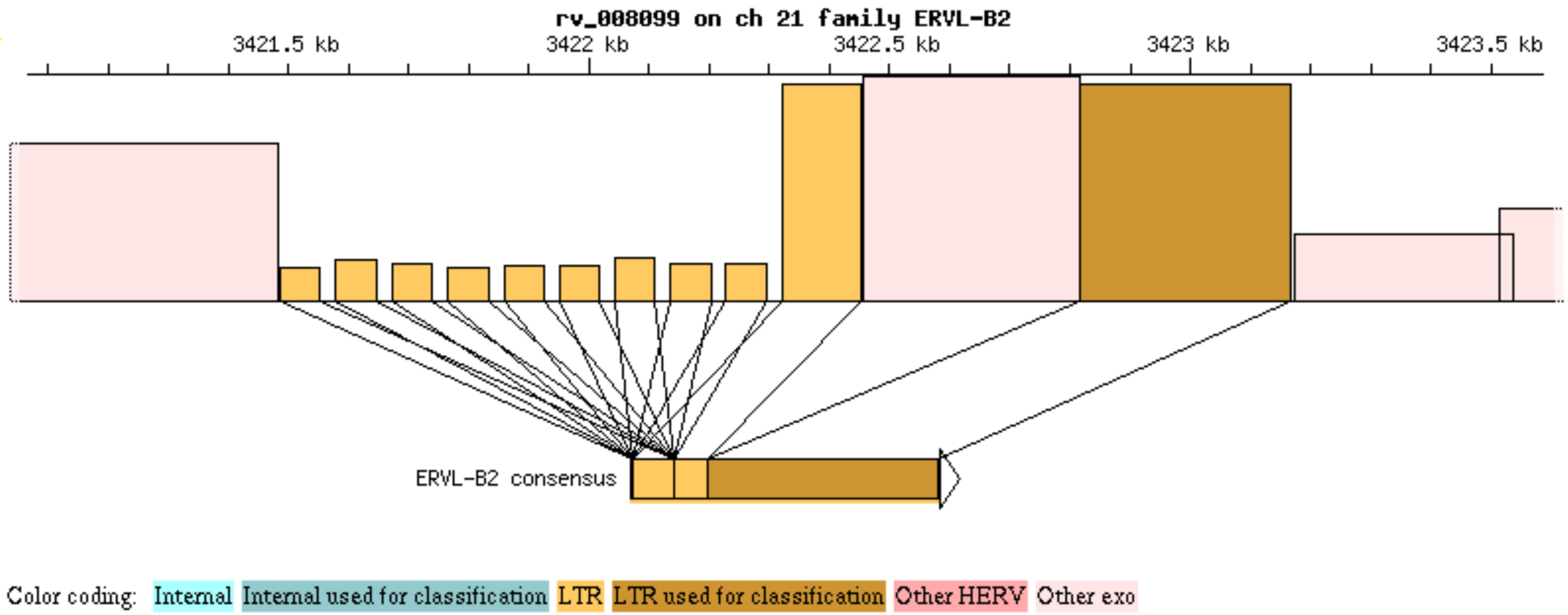
- Syncytin (adapted ancestral *env* polyprotein of HERV-W family)
- Social behavior in rodents (and possibly humans). Microsatellite instability generates diversity in brain and sociobehavioral traits
- Regulation of gene expression and promotion of genetic diversity. Retrotransposons regulate host genes in mouse oocytes and preimplantation embryos
- Antifreeze-protein gene in fish
- Source of microRNAs. Highly conserved non-coding sequences are associated with vertebrate development
- LINE-1 retrotransposition is involved in repair of broken DNA strands

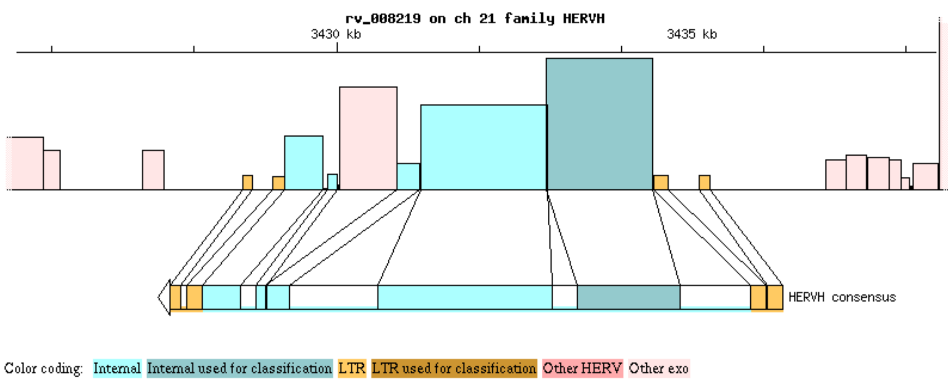
Human Endogenous Retroviruses (Example of HERV H)



HERV

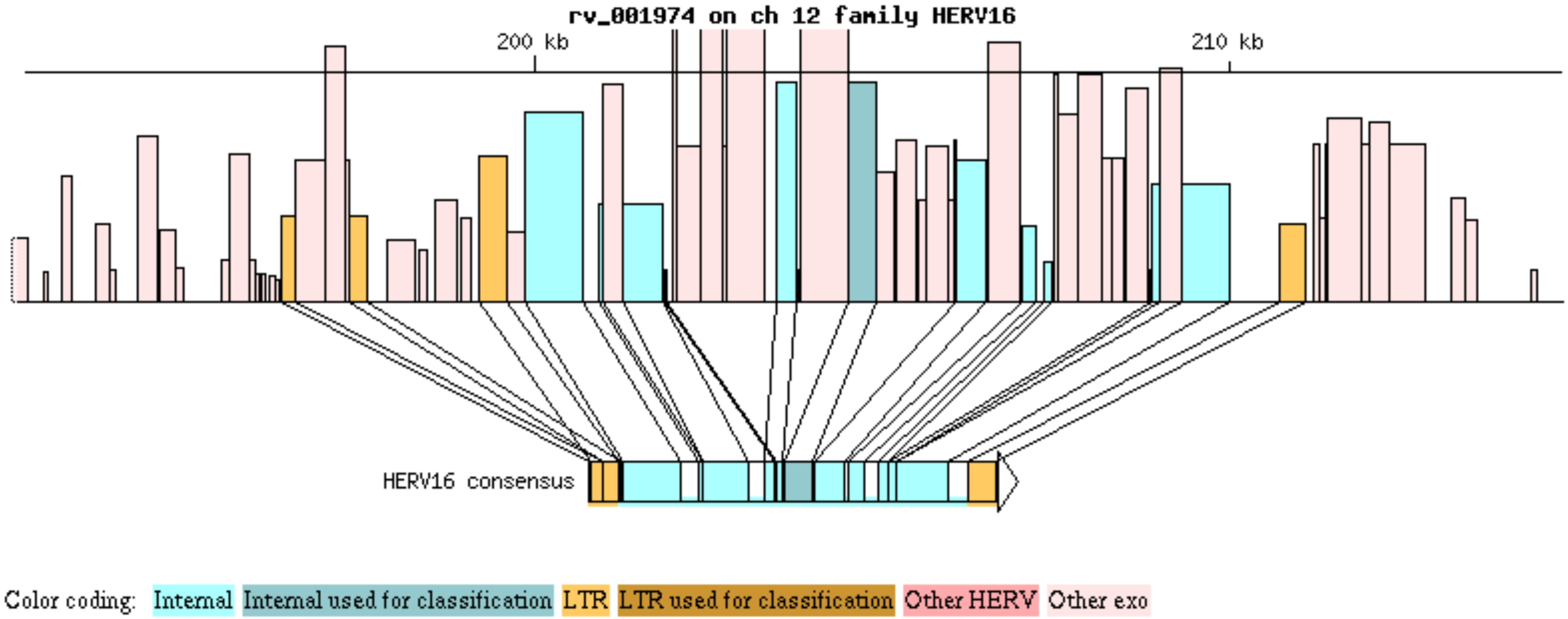
Human Endogenous Retroviruses (Example of HERV L)

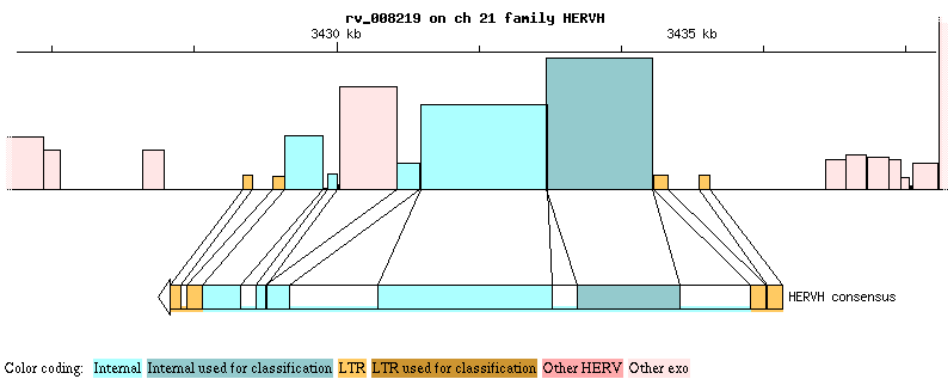


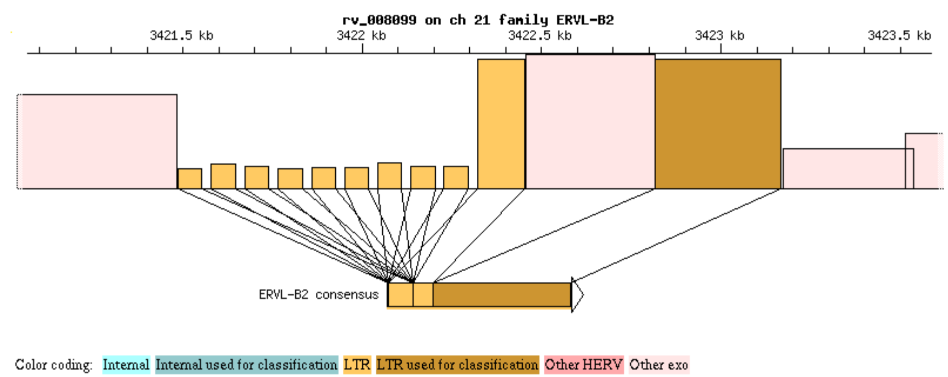


HERV

Human Endogenous Retroviruses (Example of HERV 16)







Other genes that may add to make us humans

An intelligence gene

A gene called *SRGAP2* was duplicated three times. As a result, our ancestors had several copies, some of which could evolve freely. One of the mutated copies turned out to be better than the original. It seems to have caused our brain cells to extrude more spines, allowing them to form more connections.

Added dexterity

Our hands are unusually dextrous, allowing us to make beautiful stone tools and write words. That might be partly down to a bit of DNA called *HACNS1*, which has evolved rapidly since our ancestors split from the ancestors of chimps. We don't know what *HACNS1* does, but it is active in our arms and hands as they develop.

Power to the brain

After the human line split from the chimp line, two genes mutated. *SLC2A1* and *SLC2A4* both build proteins that transport glucose in and out of cells. The tweaks may have taken glucose away from muscles and into the early hominins' brains. The glucose would then have boosted the brains, allowing them to grow bigger.

Lidský genom – etické aspekty

Důvěrnost dat
Patentování genů
Genová terapie (somatické buňky vs. zárodečné buňky)
„Pozitivní“ genové inženýrství

Lidské buňky – etické aspekty

Klonování
Embryonální kmenové buňky

Applications of Molecular Genetics

1. Transgene organisms
   - Microorganisms producing important proteins (enzymes, hormones…)
   - Higher organisms producing important proteins (e.g. in milk)
   - Improved organisms (e.g. for agriculture, bioremediations…)
2. Diagnostics (prenatal, infections…)
3. Forensics (DNA tests)
4. Gene therapy
   - Somatic cells
   - Germinal cells
   - „Positive“ gene engineering
5. Protein engineering