GENETICS AND MOLECULAR BIOLOGY FOR ENVIRONMENTAL ANALYSIS

MOLECULAR ECOLOGY

LESSON 16: COMPARATIVE GENOMICS

Prof. Alberto Pallavicini

pallavic@units.it

COMPARATIVE GENOMICS

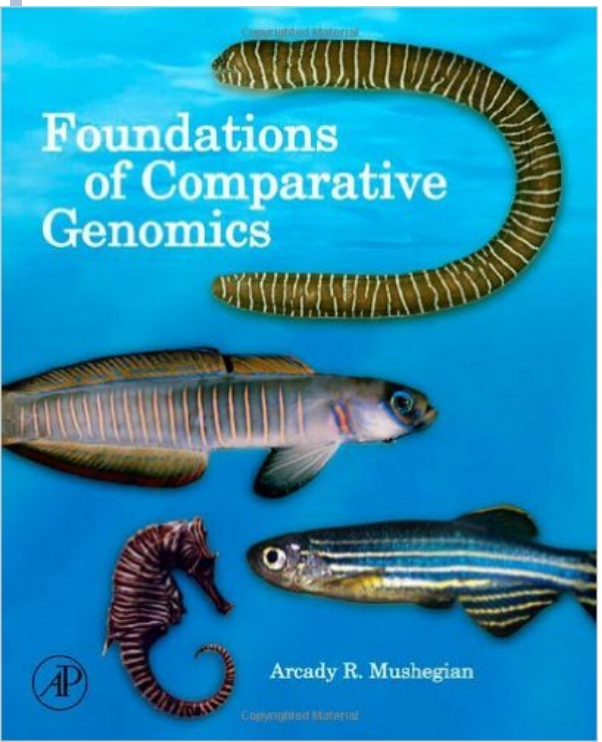
- Once the genome of a species is elucidated, partly or completely, the researcher is able to analyse the properties that characterize the genome as a whole.

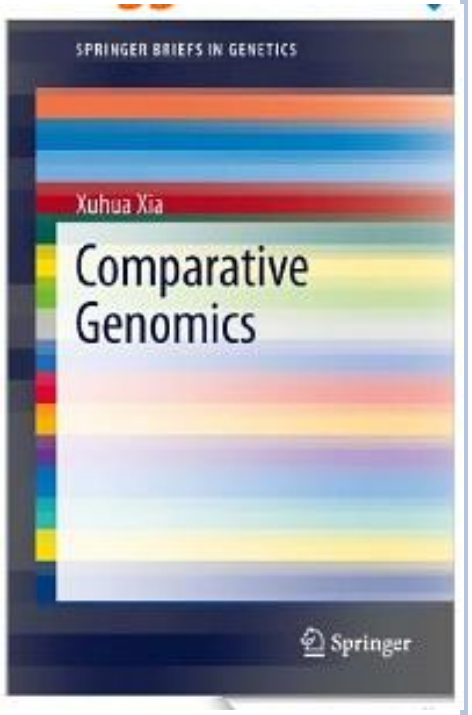
- This is usually not done in isolation, but in comparison with other species, and therefore this part of genome science is called ***comparative genomics*.**

- The term *structural genomics*—the study of genome sequences, genetic and physical maps, and so on—is also appropriate here, as a contrast with functional genomics

COMPARATIVE GENOMICS

- Comparative genomics is now a recognized subdiscipline of genome science with dedicated handbooks. The field is closely related to molecular phylogenetics.





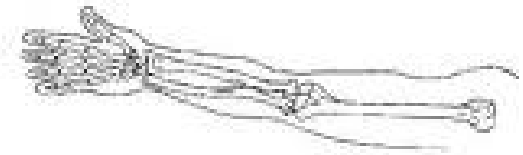
- Because by far the greatest number of completely sequenced genomes are from prokaryotes, comparative genomics proceeded at a tremendous pace, especially in microbiology.

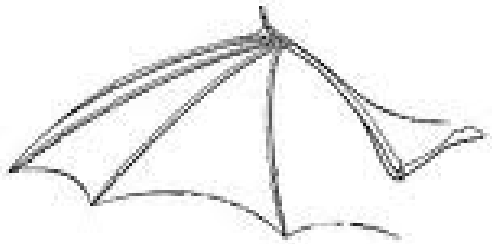
- Comparison of genomes has shed new light on the microbial species concept and on the genes associated with specific phenotypes such as physiological functions or specific resistances

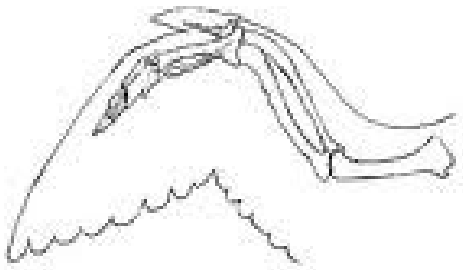
COMPARATIVE GENOMIC ANALYSIS AS A TOOL FOR BIOLOGICAL DISCOVERY

- Biology is a discipline rooted in comparisons.
- **Comparative physiology** has assembled a detailed catalogue of the *biological similarities* and *differences* between species, revealing insights into how life has adapted to fill a wide range of environmental niches.

Comparative genomic analysis as a tool for biological discovery



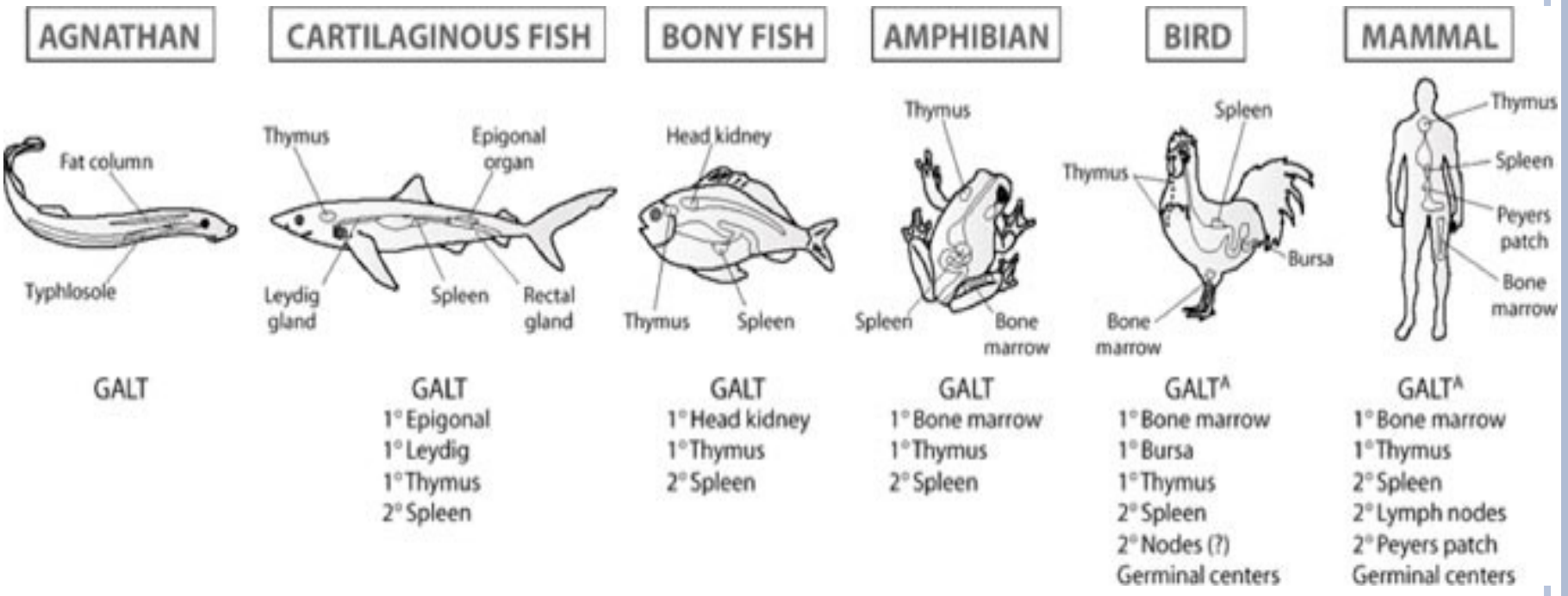




- For example, following the initial budding of limbs in every vertebrate embryo, some develop to become legs (mammals), wings (birds), fins (fish) or even atrophy into vestigial structures (some reptiles, such as snakes).

Comparative genomic analysis as a tool for biological discovery

- *Comparative studies* in anatomy, biochemistry, pharmacology, immunology and cell biology have provided the *fundamental paradigms* from which each discipline has grown.



Comparative genomic analysis as a tool for biological discovery

- *Genomics is the most recent branch of biology to employ comparison-based strategies.*

At the foundation of the evolutionary relationship of all vertebrates is conserved genetic information in the form of DNA sequence, which is assumed to underlie homologous functional and anatomical similarities between species.

Comparative genomic analysis as a tool for biological discovery

- **Technological progress in DNA sequencing has resulted in the generation of a large dataset of genomic sequence information.**
- In the las 20 years, draft genome sequence has become available for hundreds of vertebrates (not only human, mouse, rat, zebrafish and two pufferfish *Fugu rubripes* and *Tetraodon nigroviridis*)

http://www.ensembl.org/index.html

Rattus norvegicus	RGSC v3.4	July 6, 2006
Macaca mulatta (rhesus macaque)	1.1	June 23, 2006
Caenorhabditis elegans	WS150	May 11, 2006
Mus musculus	36.1	May 8, 2006
Drosophila melanogaster	4.3	April 19, 2006
Tribolium castaneum (red flour beetle)	1.1	April 18, 2006
Homo sapiens	36.1	March 9, 2006
Dictyostelium discoideum	1.1	November 22, 2005
Arabidopsis thaliana	TAIR6.0	November 21, 2005
Bos taurus (cow)	2.1	October 12, 2005
Canis familiaris (dog)	2.1	September 8, 2005
Strongylocentrotus purpuratus (sea urchin)	1.1	August 17, 2005
Danio rerio (zebrafish)	Zv4	July 5, 2005
Anopheles gambiae (mosquito)	2.2	June 30, 2005
Apis mellifera (bee)	2.1	May 31, 2005
Pan troglodytes (chimpanzee)	1.1	November 23, 2004
Gallus gallus (chicken)	1.1	August 11, 2004

The Human Genome

The Human Genome

The Human Genome Project generated an unprecedented amount of knowledge about human genetics. Explore human genome resources, browse the human genome sequence using the Map Viewer, find gene information in Entrez Gene, and access information on genetic disorders in OMIM.

CCDS Database

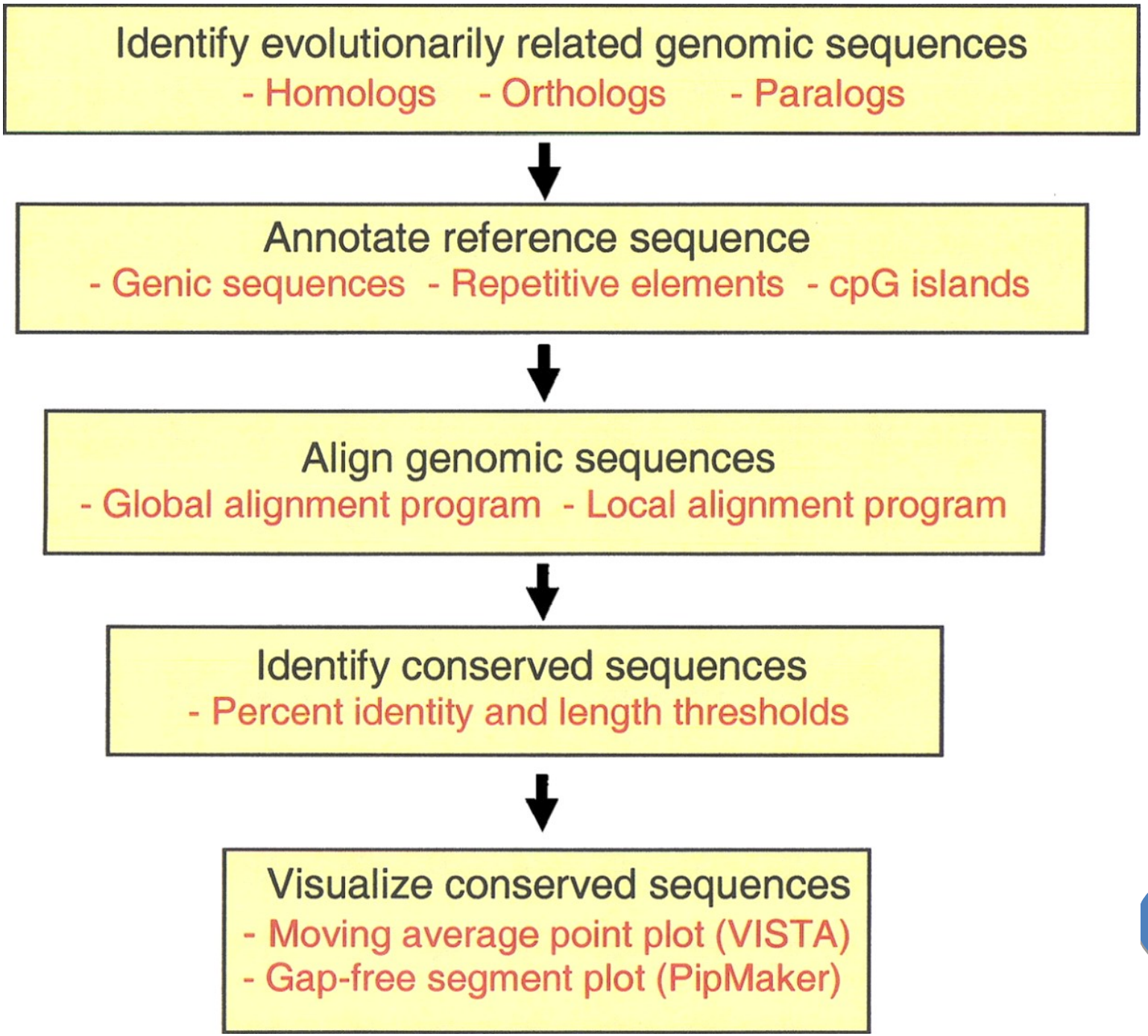
The new Consensus CDS (CCDS) project is a collaborative effort to identify a core set of human protein coding regions that are consistently annotated and of high quality. **More...**

Genome Resources
BLAST
Map Viewer
Genome Project DB

- Arabidopsis B M P
- Aspergillus G B M P
- Bee G B M P
- Beetle NEW G B M P
- Cat G B M P
- Chicken G B M P
- Chimpanzee G B M P
- Cow G B M P
- Dictyostelium G B M P
- Dog G B M P
- Frog G B P
- Fruit Fly G B M P
- Human G B M P
- Malaria B M P
- Mosquito B M P
- Mouse G B M P
- Nematode G B M P
- Pig G B M P
- Rabbit G B P
- Rat G B M P
- Rhesus macaque NEW G B M P
- Sea Urchin G B M P
- Sheep G B M P
- Yeast (Saccharomyces) G B M P
- Zebrafish G B M P

Comparative genomic analysis as a tool for biological discovery

- The sudden wealth of sequence data has allowed **whole genome alignments** to compare and contrast the evolution and content of vertebrate genomes.
- Such comparative strategies have identified pockets of DNA sequences conserved over evolutionary time, and such evolutionary conservation has been a powerful guide in sorting **functional** from **non-functional** DNA


Identify evolutionarily related genomic sequences
- Homologs - Orthologs - Paralogs
Annotate reference sequence
- Genic sequences - Repetitive elements - cpG islands
Align genomic sequences
- Global alignment program - Local alignment program
Identify conserved sequences
- Percent identity and length thresholds
Visualize conserved sequences
- Moving average point plot (VISTA)
- Gap-free segment plot (PipMaker)

GENOME SIZE

- Usually the size of a genome is known with some accuracy before its complete sequence is elucidated, because genome size is essential knowledge for optimal construction of a genomic library and the design of a genome-sequencing project.

- Genome size may be estimated using biochemical methods or flow cytometry and is usually expressed in picograms of the haploid genome per cell. This is easily converted to nucleotides by the general formula $G = 0.987 \times 10^9 C$, where G is genome size in base-pairs and C is genome size in pg (roughly, 1 pg is equivalent to 1000 Mbp).

GENOME SIZE AND NUMBER OF GENES FOR ORGANISMS WITH COMPLETELY SEQUENCED GENOMES

Species	Total size of the genome (kbp)	Estimated no. of protein-encoding genes
Bacteriophage φX174	5.4	10
Mycoplasma genitalium	580	468
Methanococcus jannaschii	1665	1738
Haemophilus influenzae	1830	1743
Escherichia coli	4639	4288
Agrobacterium tumefaciens	5670	5419
Pseudomonas aeruginosa	6264	5570
Saccharomyces cerevisiae	12 610	6128
Caenorhabditis elegans	95 500	18 424
Drosophila melanogaster	123 000	13 601
Arabidopsis thaliana	125 000	25 498
Oryza sativa	466 000	50 820

MINIMAL NUMBER OF GENES

- increase of genome size going from viruses to prokaryotes, and further to unicellular eukaryotes and multicellular eukaryotes.

- **The minimal number of genes required for an autonomous self-replicating entity** was estimated by Graur and Li (2000) as 256 (based on a comparison of prokaryotic genomes) or 254 (based on a review of knockout studies). This is about half the number of genes in *Mycoplasma genitalium*, which has 468 genes, the lowest number of any independently living organism.

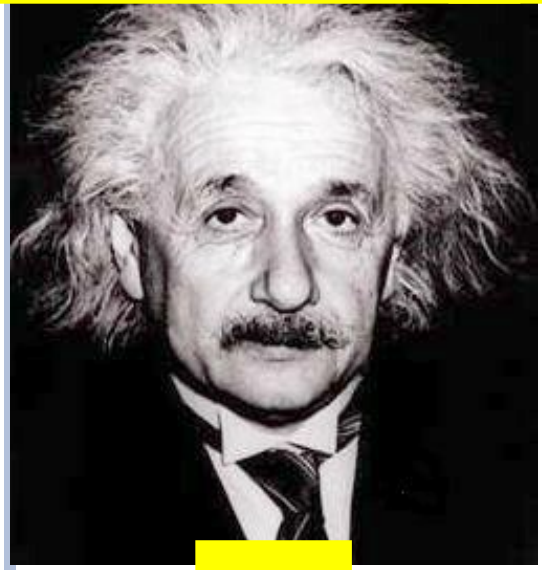
GENOME MINIATURIZATION

- reduction of the genome in endosymbiotic organisms and parasites. In the ultimate endosymbiotic entity, the mitochondrion, many genes were lost compared to its alpha-proteobacterial ancestor, partly due to deleting functions that were not necessary in the symbiotic lifestyle, and partly due to migration of genes to the nuclear genome of the host.

THE 3 GENOMIC PARADOXES

K-value paradox: Complexity does not correlate with chromosome number.

Homo sapien ***Lysandra atlantica*** ***hioglossum reticulatu***

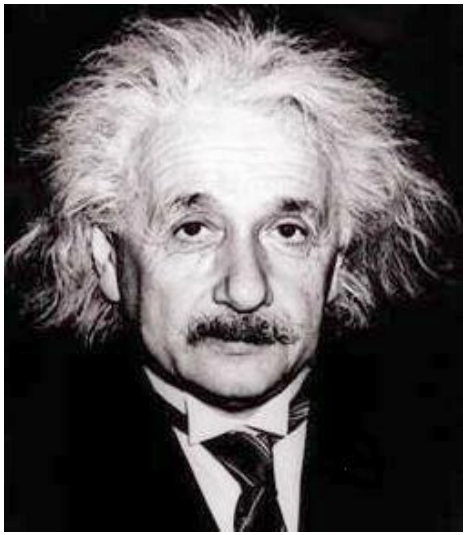


46

250

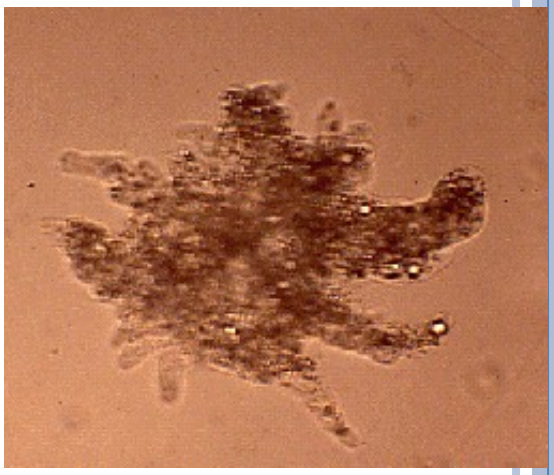
~1260

C-value paradox: Complexity does not correlate with genome size.



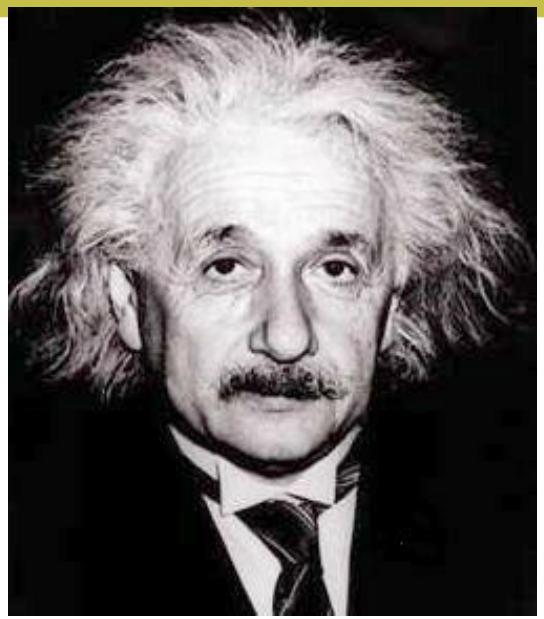
3.4 X 10^9 bp
Homo sapiens

1.5 X 10^{10} bp
Allium cepa



6.8 X 10^{11} bp
Amoeba dubia

N-value paradox: Complexity does not correlate with gene number.



~21,000 genes

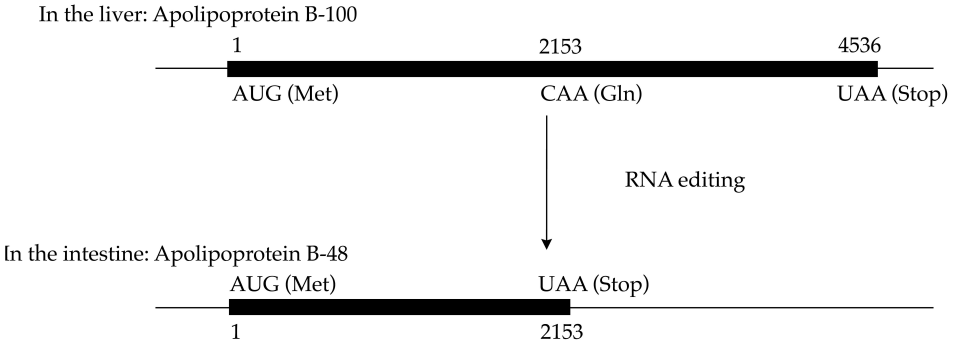
~25,000 genes

~60,000 genes

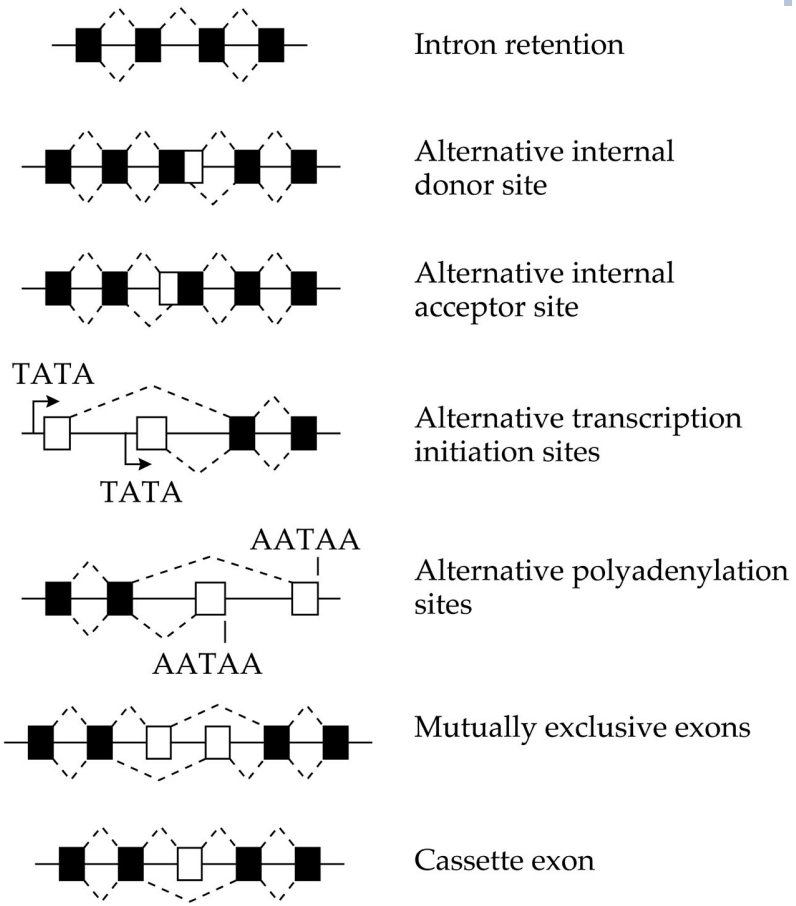
POSSIBLE SOLUTIONS:

Solution 1 to the N-value paradox:

Many protein-encoding genes produce more than one protein product (e.g., by alternative splicing or by RNA editing).

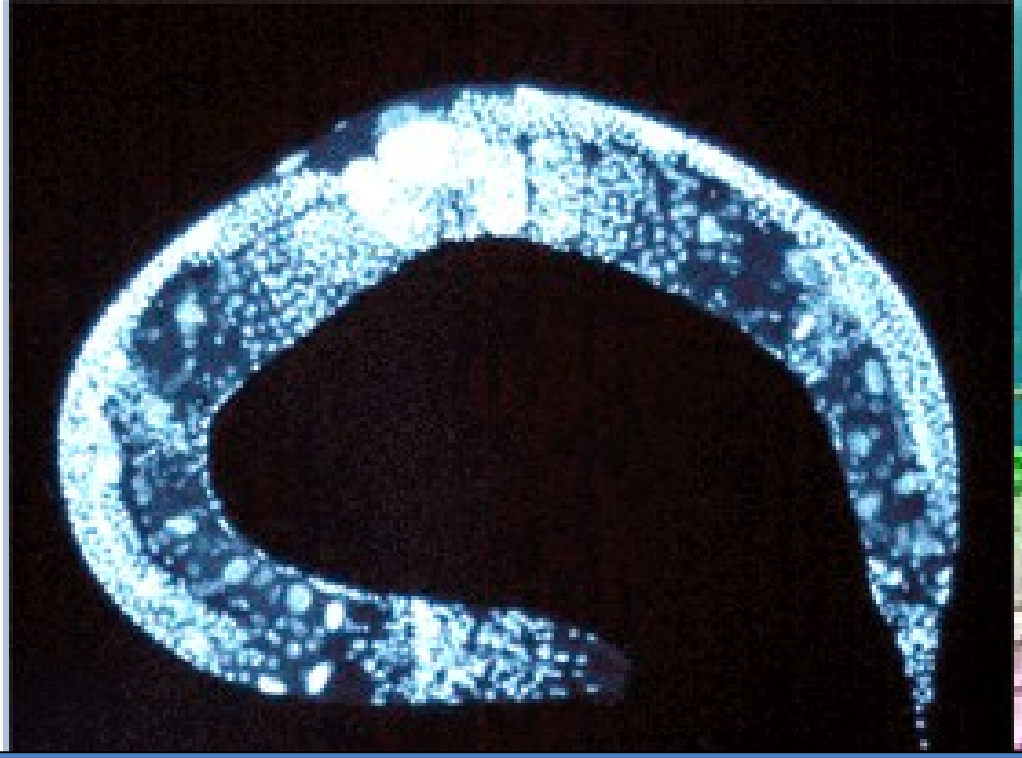


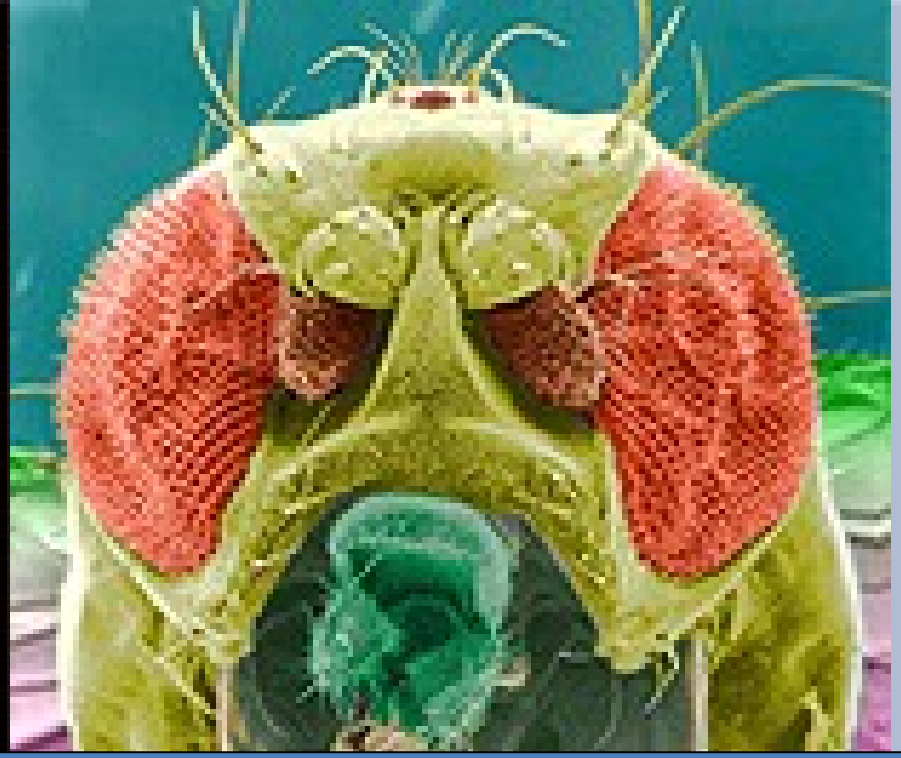
RNA editing



Alternative splicing

The combinatorial use of RNA editing and alternative splicing probably causes the human proteome to be 5-10 times larger than that of *Drosophila* or *Caenorhabditis*.





♀ ♂

959 cells 1,031 cells

19,000 genes

$\sim 10^8$ cells

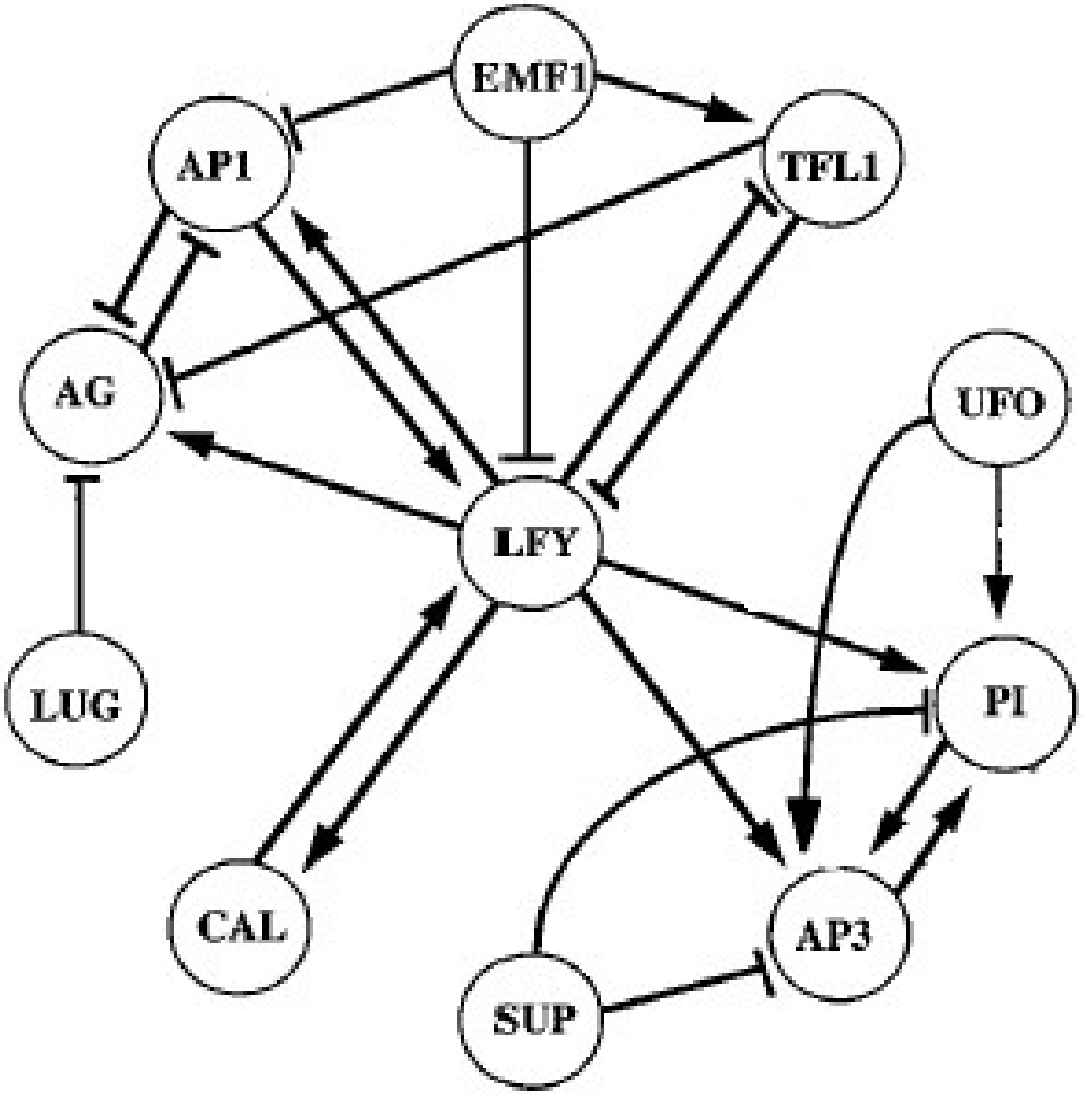
13,600 genes

Solution 2 to the N-value paradox:

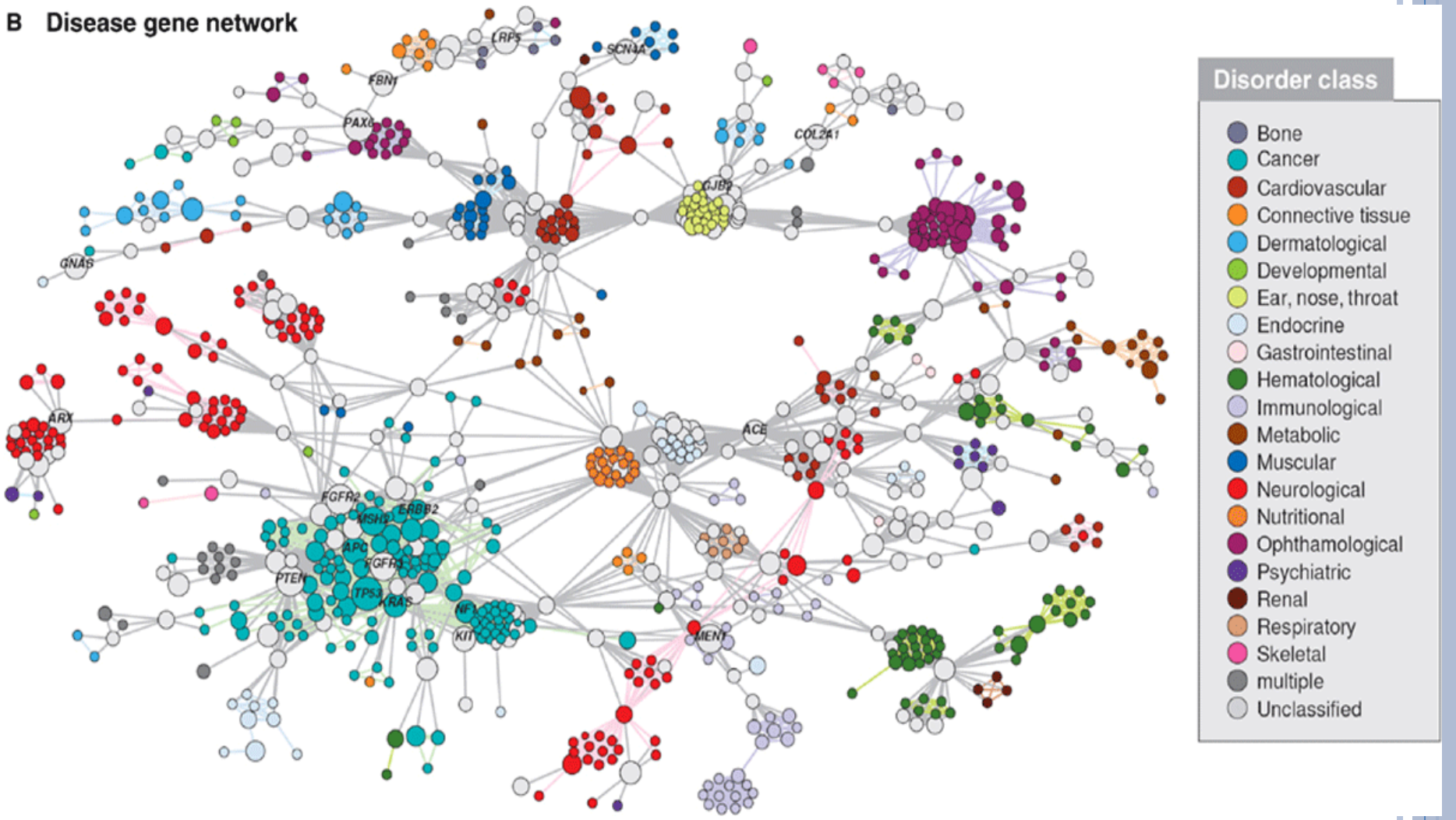
We are counting the wrong things, we should count other genetic elements (e.g., small RNAs).

Solution 3 to the N-value paradox:

We should look at connectivity rather than at nodes.



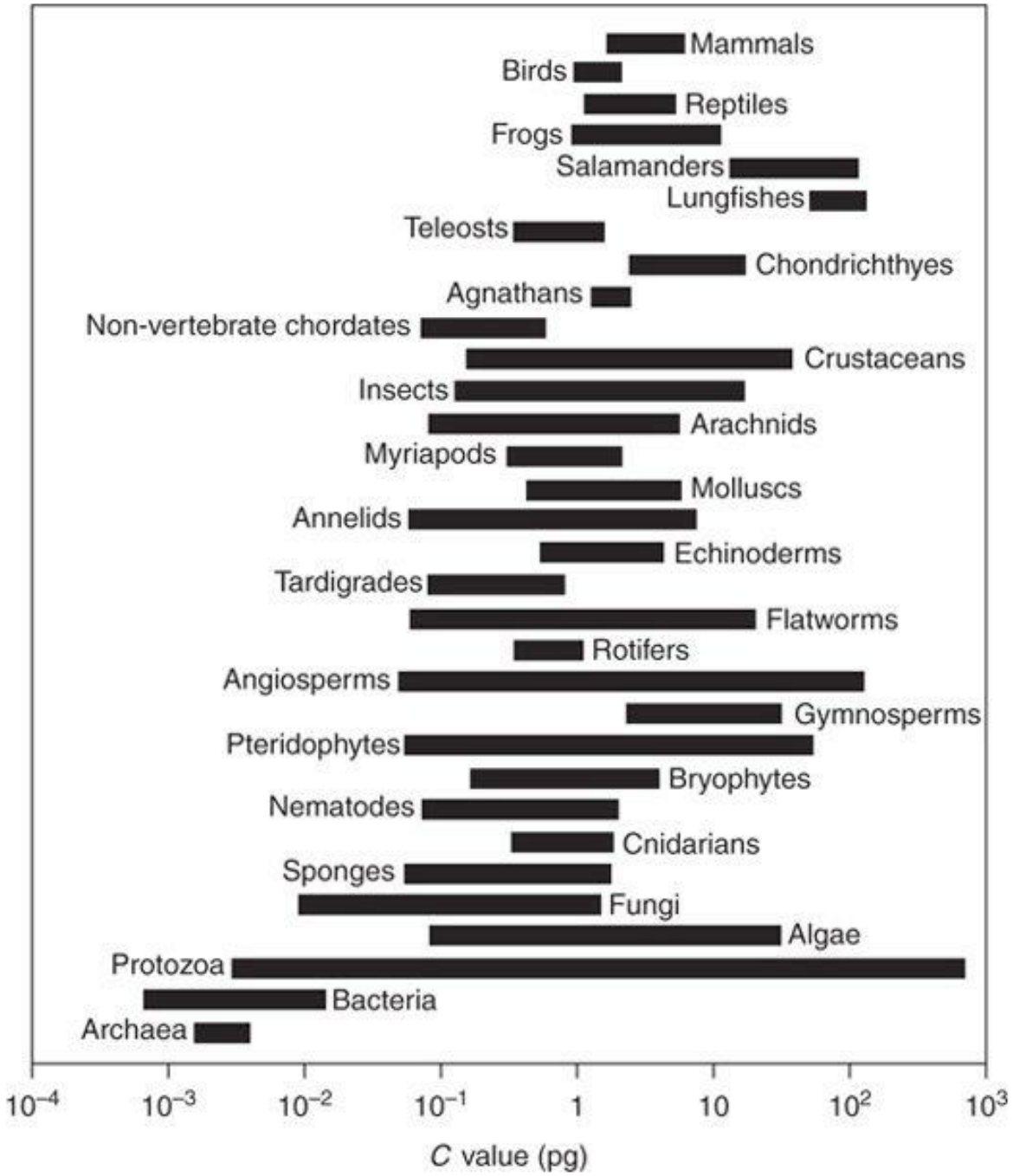
L. Mendoza and E. R. Alvarez-Buylla. 1998. Dynamics of the genetic regulatory network for *Arabidopsis thaliana* flower morphogenesis. J. Theor. Biol. 193:307-319.



- Disease gene network. Each node is a single gene, and any two genes are connected if implicated in the same disorder. In this network map, the size of each node is proportional to the number of specific

Range of C-values in various eukaryotic taxa

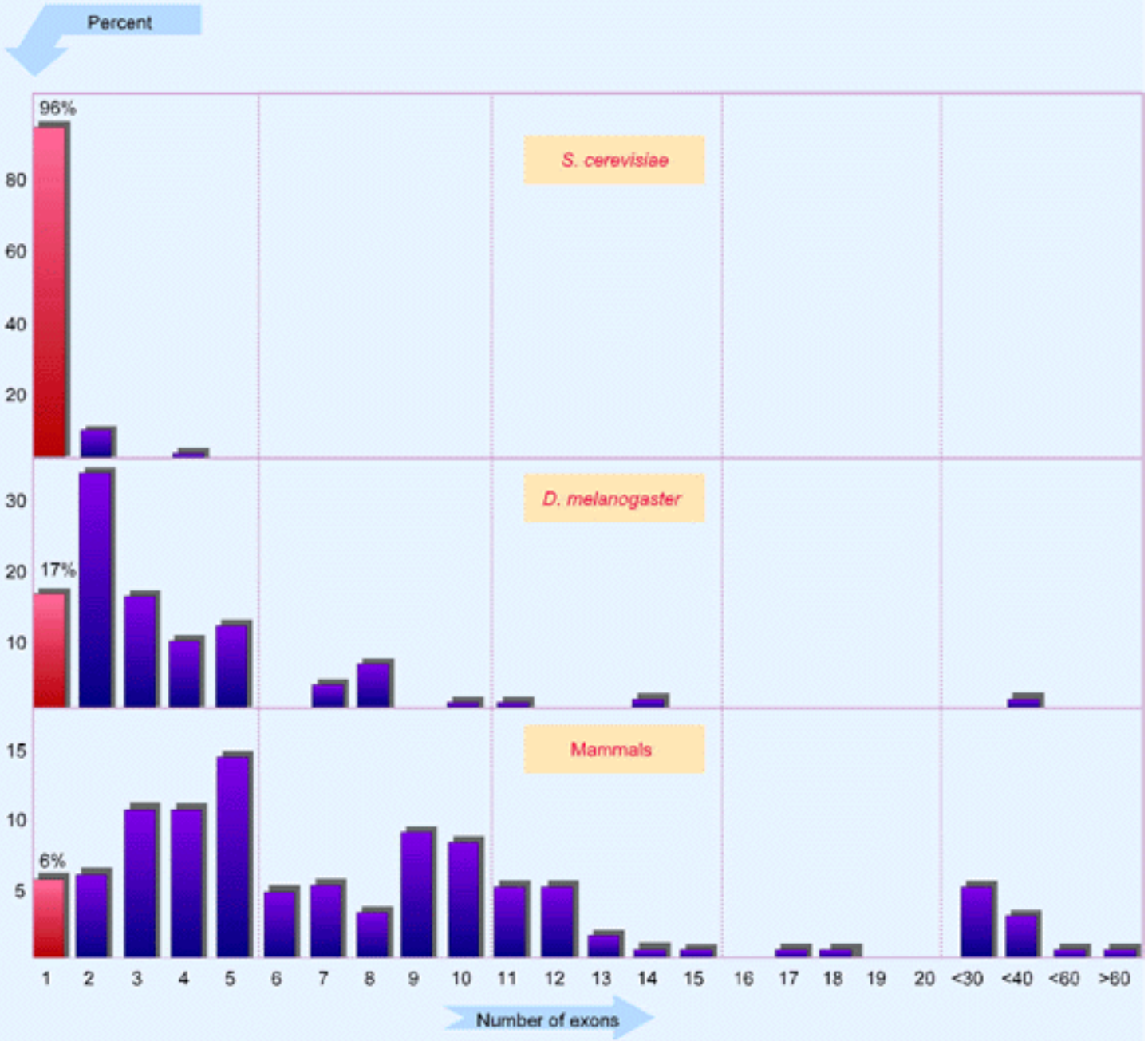
Taxon	Genome size range (Kb)			Ratio (highest/lowest)
Eukaryotes	2,300	-	686,000,000	298,261
Amoebae	35,300	-	686,000,000	19,433
Fungi	8,800	-	1,470,000	167
Animals	49,000	-	139,000,000	2,837
Sponges	49,000	-	53,900	1
Molluscs	421,000	-	5,290,000	13
Crustaceans	686,000	-	22,100,000	32
Insects	98,000	-	7,350,000	75
Bony fishes	340,000	-	139,000,000	409
Amphibians	931,000	-	84,300,000	91
Reptiles	1,230,000	-	5,340,000	4
Birds	1,670,000	-	2,250,000	1
Mammals	1,700,000	-	6,700,000	4
Plants	50,000	-	307,000,000	6,140


Mammals
Birds
Reptiles
Frogs
Salamanders
Lungfishes
Teleosts
Chondrichthyes
Agnathans
Non-vertebrate chordates
Crustaceans
Insects
Arachnids
Myriapods
Molluscs
Annelids
Echinoderms
Tardigrades
Flatworms
Rotifers
Angiosperms
Gymnosperms
Pteridophytes
Bryophytes
Nematodes
Cnidarians
Sponges
Fungi
Algae
Protozoa
Bacteria
Archaea
10^{-4}
10^{-3}
10^{-2}
10^{-1}
1
10
10^{2}
10^{3}
C value (pg)

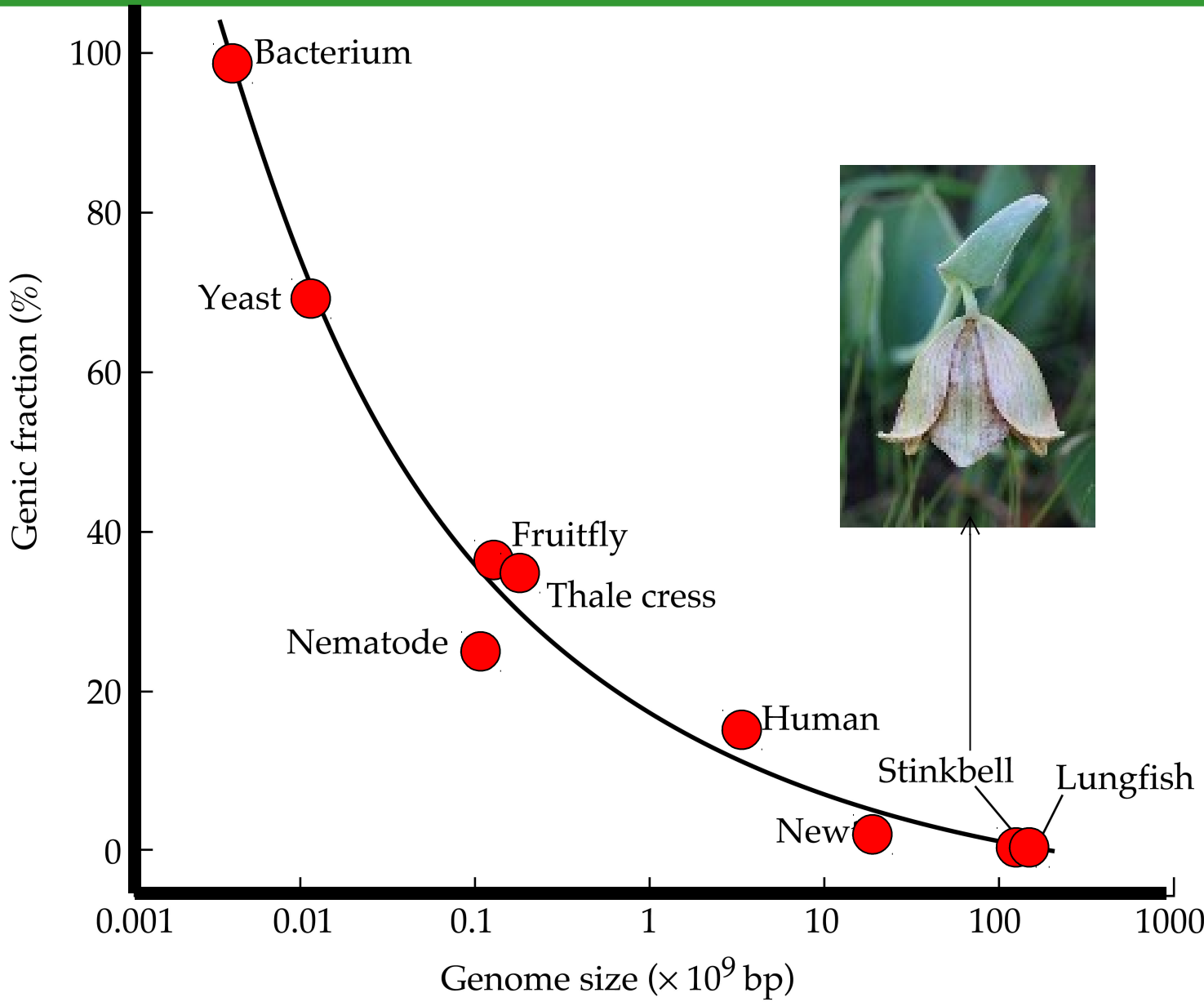
If the variation in C-values is attributed to genes, it can be due to interspecific differences in

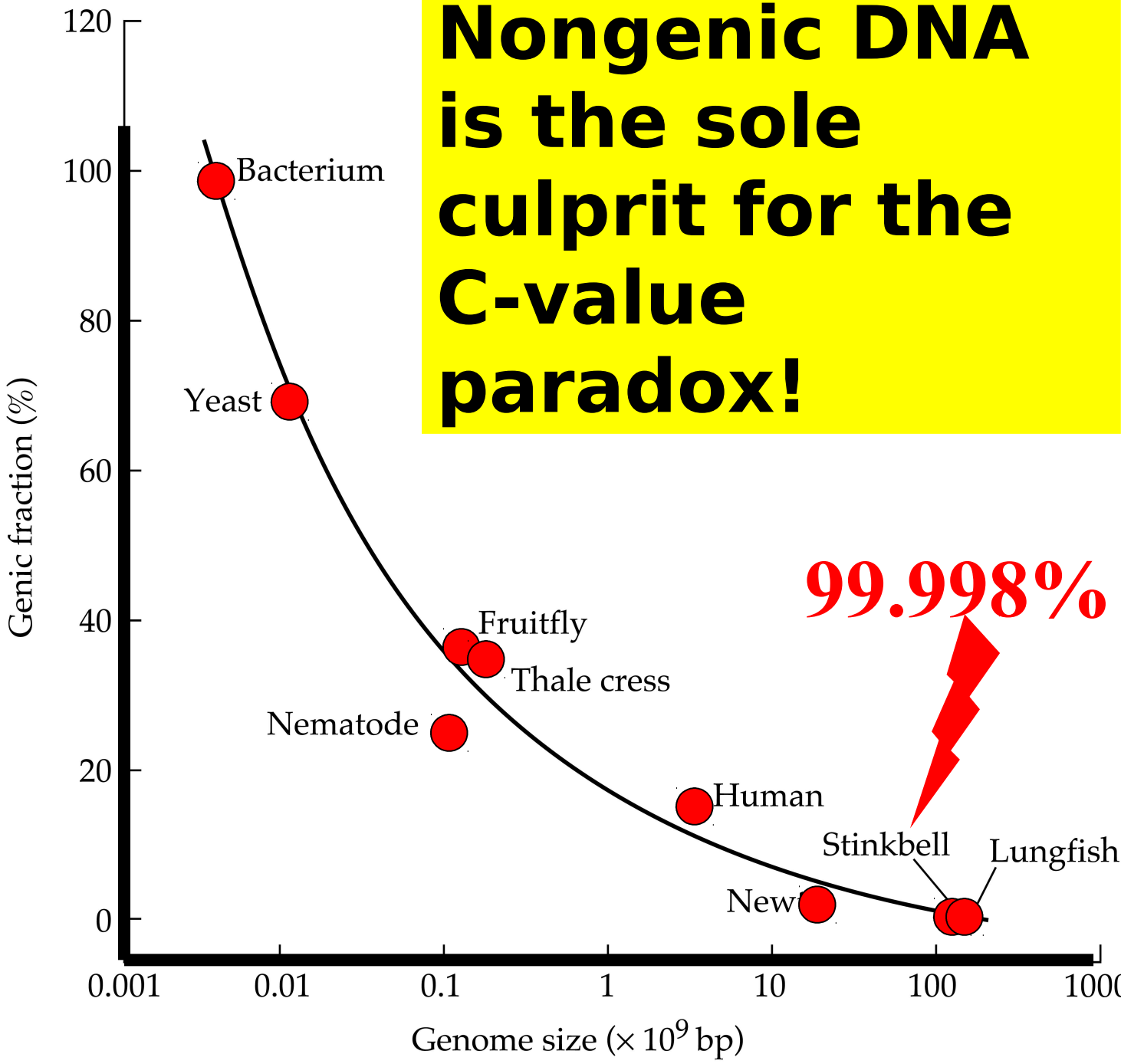
(1) the number of protein-coding genes
(2) the size of proteins
(3) the size of protein-coding genes
(4) the number and sizes of genes other than protein-coding ones.

The number of protein-coding genes in eukaryotes is thought to vary over a 50-fold range. This variation is insufficient to explain the 300,000-fold variation in nuclear-DNA content.


Percent
96%
S. cerevisiae
80
60
40
20
D. melanogaster
30
20
17%
10
Mammals
15
10
6%
5
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
<30
<40
<60
>60
Number of exons

The **bigger** the genome, the **smaller** the genic fraction




Nongenic DNA is the sole culprit for the C-value paradox!
99.998%
Genic fraction (%)
120
100
80
60
40
20
0
Bacterium
Yeast
Fruitfly
Thale cress
Nematode
Human
Stinkbell
Lungfish
Newt
0.001
0.01
0.1
1
10
100
1000
Genome size (× 10^9 bp)

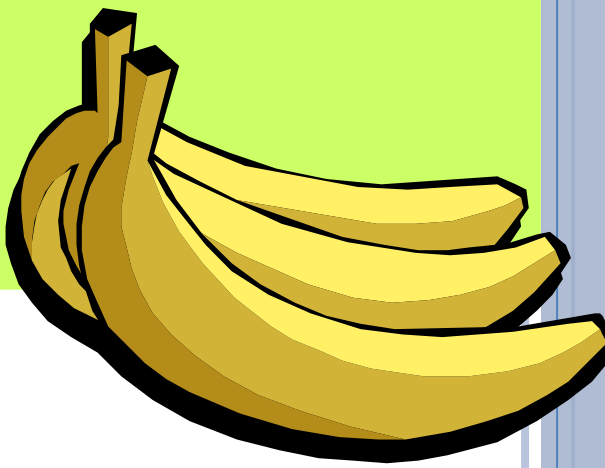
Genome increase:

(1) global increases, i.e., the entire genome or a major part of it is duplicated
(2) regional increases, i.e., a particular sequence is multiplied to generate repetitive DNA.

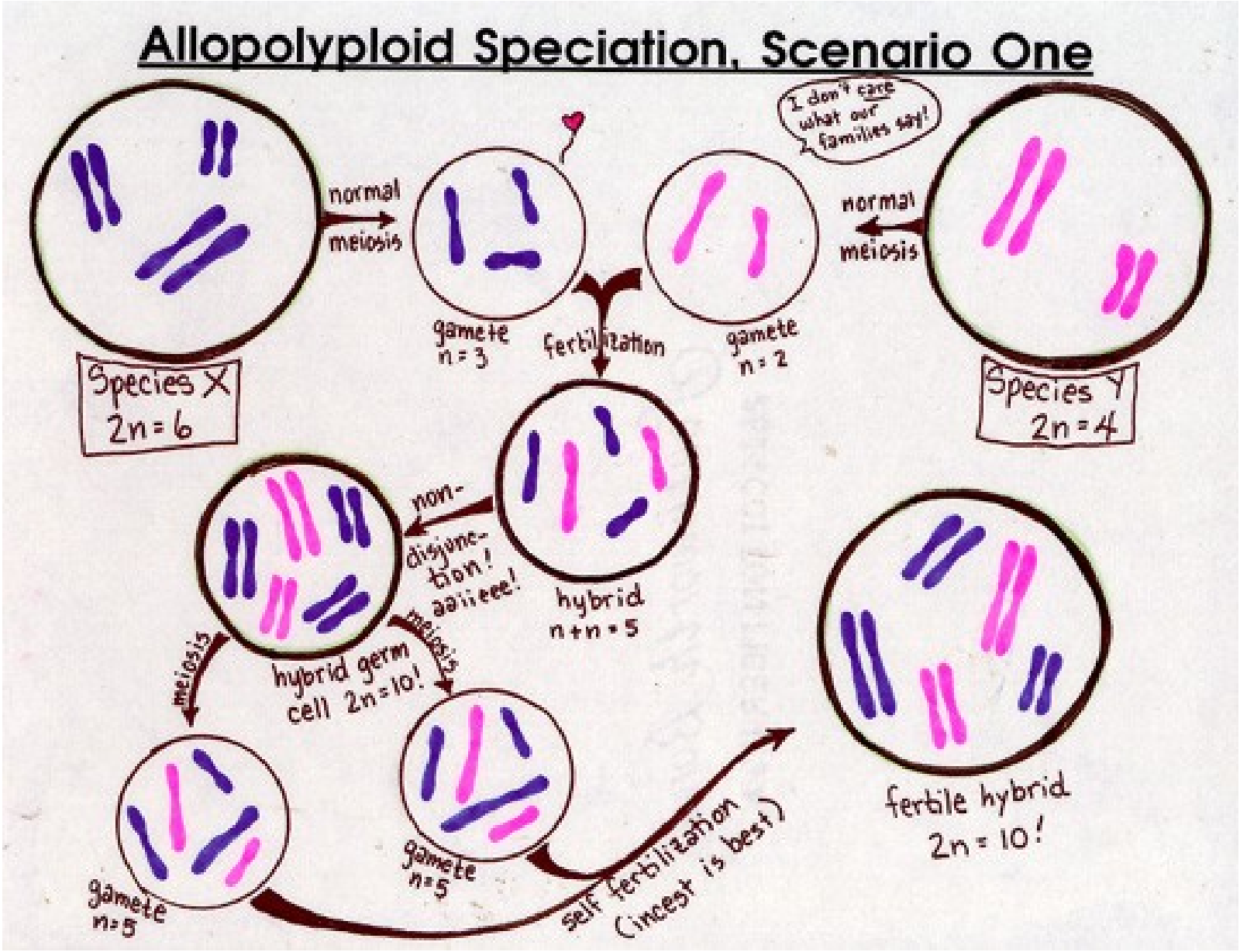
MECHANISMS FOR GLOBAL INCREASES IN GENOME SIZE

Polyploidization = the addition of one or more complete sets of chromosomes to the original set.

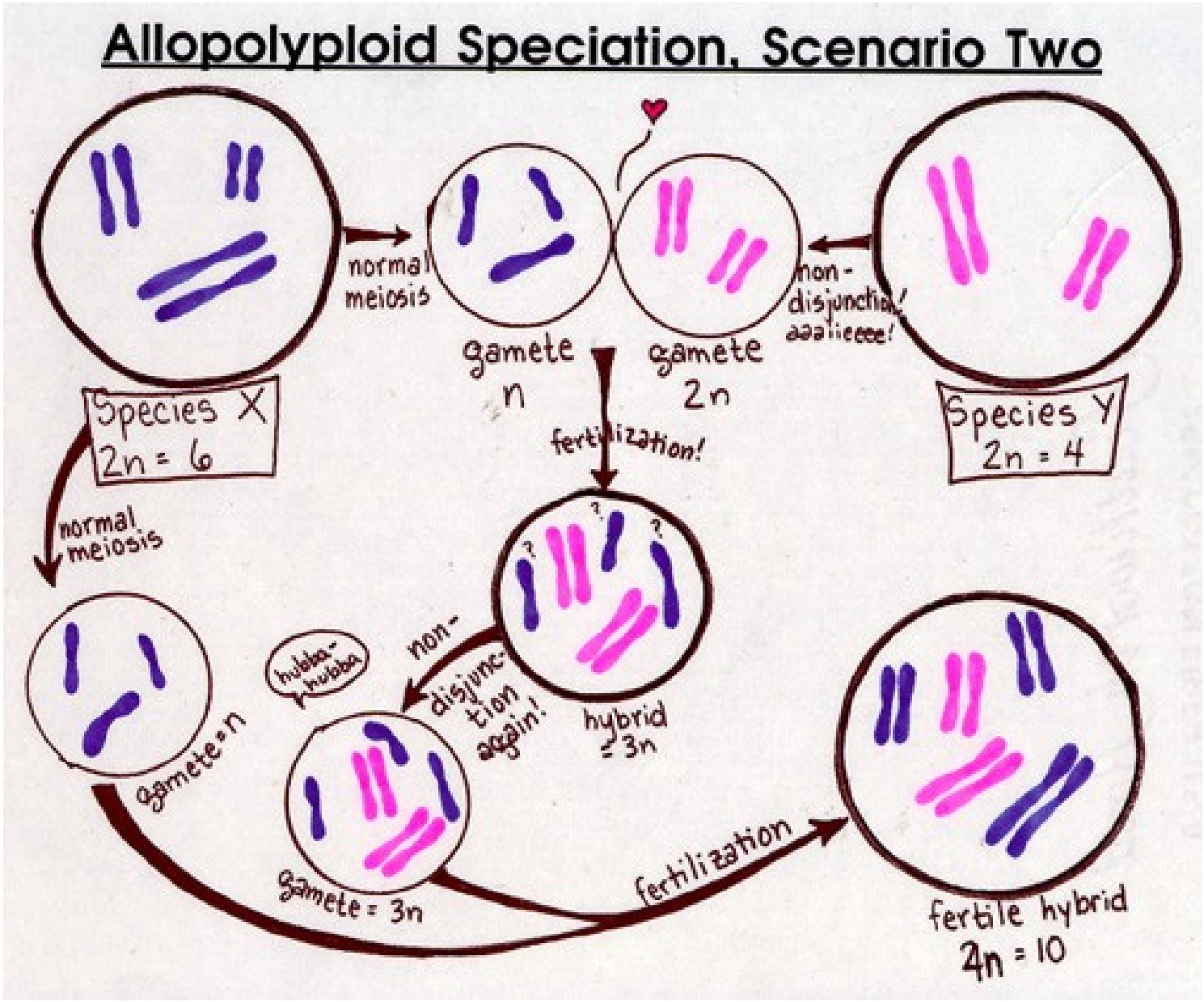
An organism with an odd number of autosomes cannot undergo meiosis or reproduce sexually.



allopolyploidy

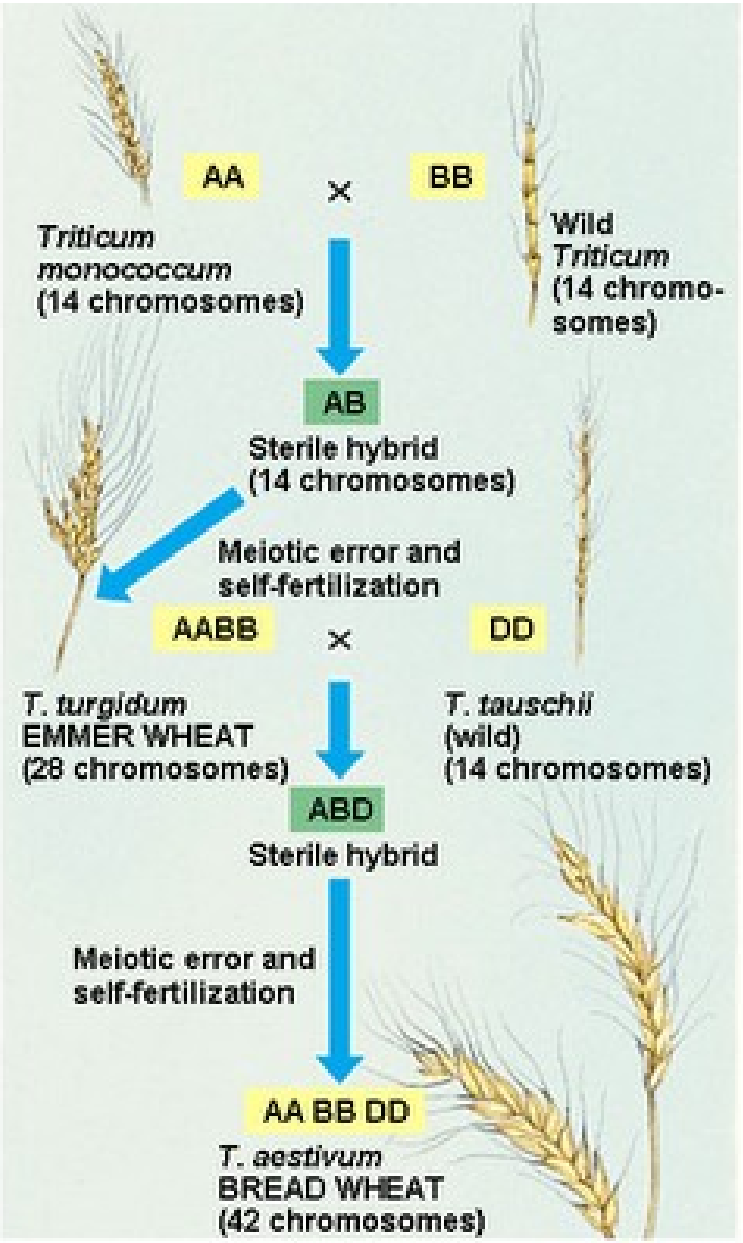


allopolyploidy



Following polyploidization, a very rapid process of duplicate-gene loss ensues.

Allohexaploid *Triticum aestivum* originated about 10,000 years ago. In this very short time, many of its triplicated loci have been silenced.



The proportion of enzymes produced by triplicate, duplicate, and single loci is 57%, 25%, and 18%, respectively.

https://www.nature.com/news/small-group-scoops-international-effort-to-sequence-huge-wheat-genome-1.22924

https://academic.oup.com/gigascience/article/6/11/1/4561661

NATURE | NEWS

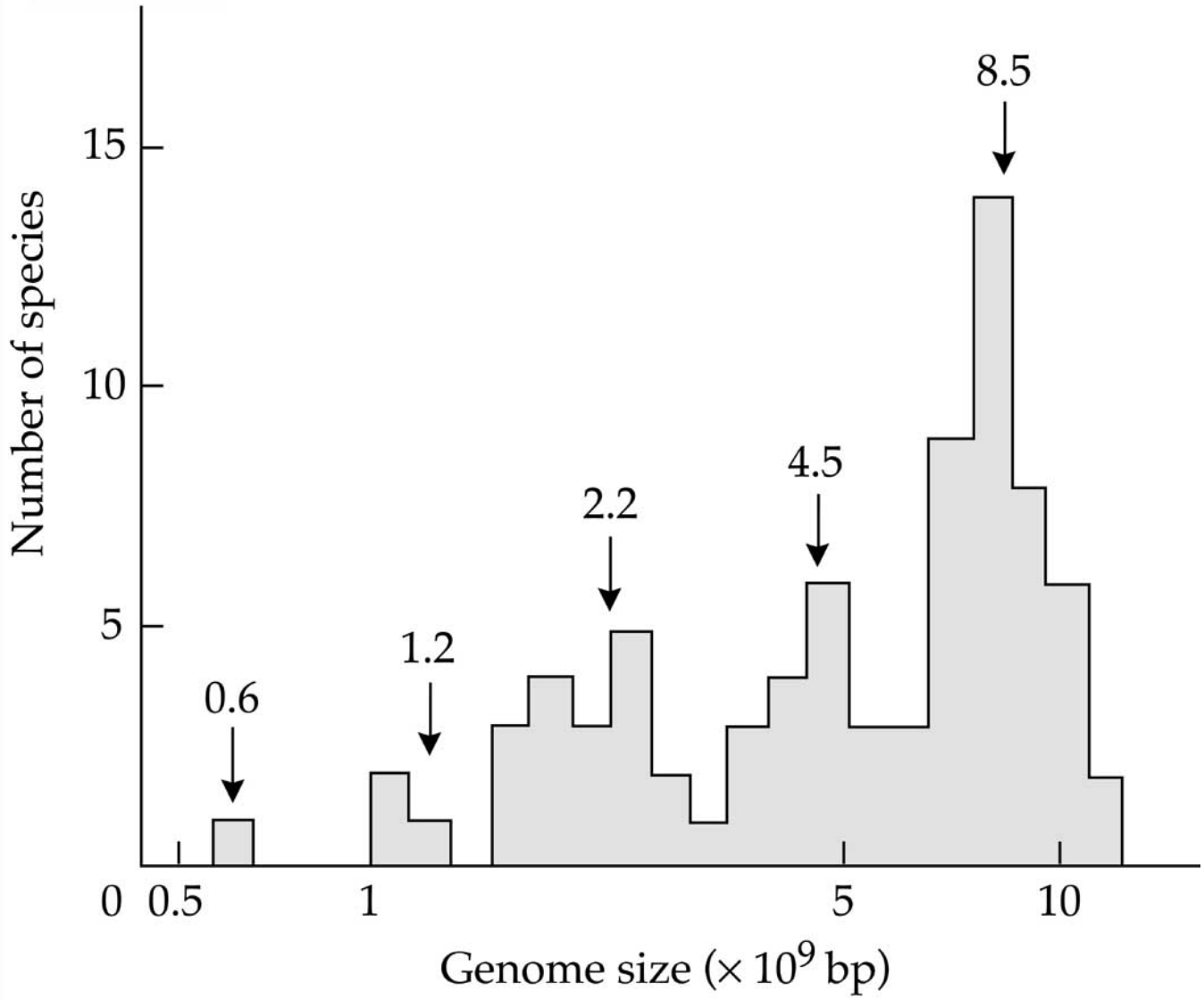
Small group scoops international effort to sequence huge wheat genome

Just six scientists conquer one of the most complicated genomes ever read.

Ewen Callaway

31 October 2017

During evolution autopolyploidy & allopolyploidy becomes cryptopolyploidy.



Genome sizes in 80 grass species (Poaceae).

Nature (2004) 431:988-993.

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83–321

Trends

Megabase deletions of gene deserts result in viable mice

Marcelo A. Nóbrega*, Yiwen Zhu*, Ingrid Plajzer-Frick, Veena Afzal & Edward M. Rubin

DOE Joint Genome Institute Walnut Creek, California 94598, USA, and Genomics Division Lawrence Berkeley National Laboratory Berkeley, California 94720, USA

* These authors contributed equally to this work

The functional importance of the roughly 98% of mammalian genomes not corresponding to protein coding sequences remains largely undetermined[1]. Here we show that some large-scale deletions of the non-coding DNA referred to as gene deserts[2–4]

Duplicazioni dell'intero genoma

Paleoploidia.

Serve come prova la presenza, nell'intero genoma, di coppie di geni omologhi che *si presentano nello stesso ordine;* o l'evidenza di un «orologio molecolare» che indica uguali tempi di divergenza in molte coppie di omologhi.

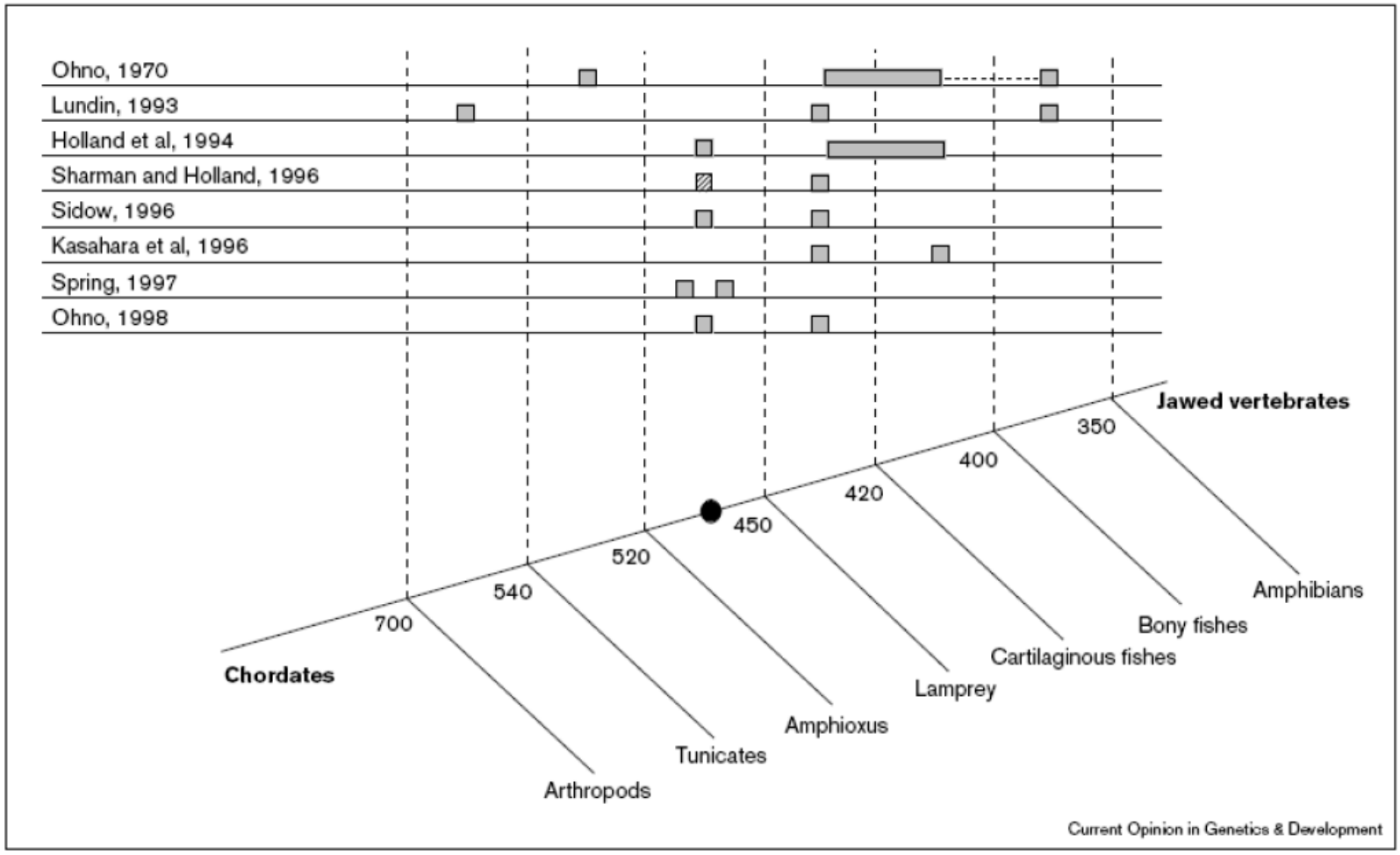
Yeast

Il genoma del lievito subì una duplicazione circa 10^8 anni fa. Gli effetti sono oscurati dai successivi riarrangiamenti cromosomici e dalla massiva perdita di materiale duplicato.

Comunque il genoma del lievito contiene 55 regioni duplicate, lunghe in media 55 kb, che coprono insieme il ~ 50% del genoma e comprendono 376 coppie di geni omologhi.

Come si originano le novità evolutive: duplicazioni genomiche

2R Hypothesis Susumu Ohno



Da Skrabanek L, Wolfe KH. 1998

Come si originano le novità evolutive: duplicazioni genomiche

2R Hypothesis

1R: il genoma raddoppia, **2R**: il genoma quadruplica (aggiungiamo una fish-specific genome duplication: **3R** per la linea dei pesci)

Ancora molta discussione sul numero e la datazione delle duplicazioni

Si vedono delle tracce della 2R (esempio: geni Hox), ma altre sono cancellate da eventi successivi

Come si originano le novità evolutive: duplicazioni genomiche

2R Hypothesis

Si vedono delle tracce della 2R (esempio: geni Hox)

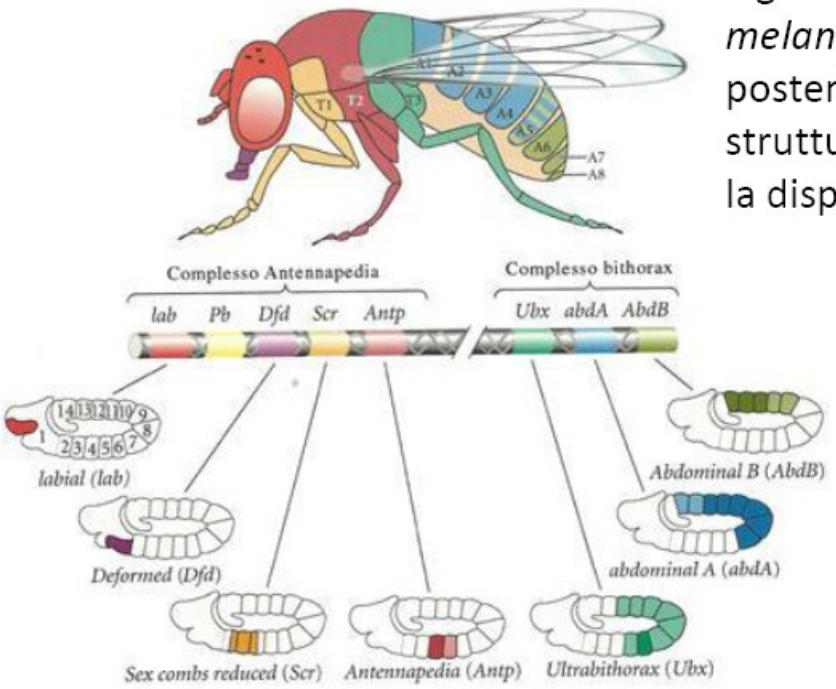
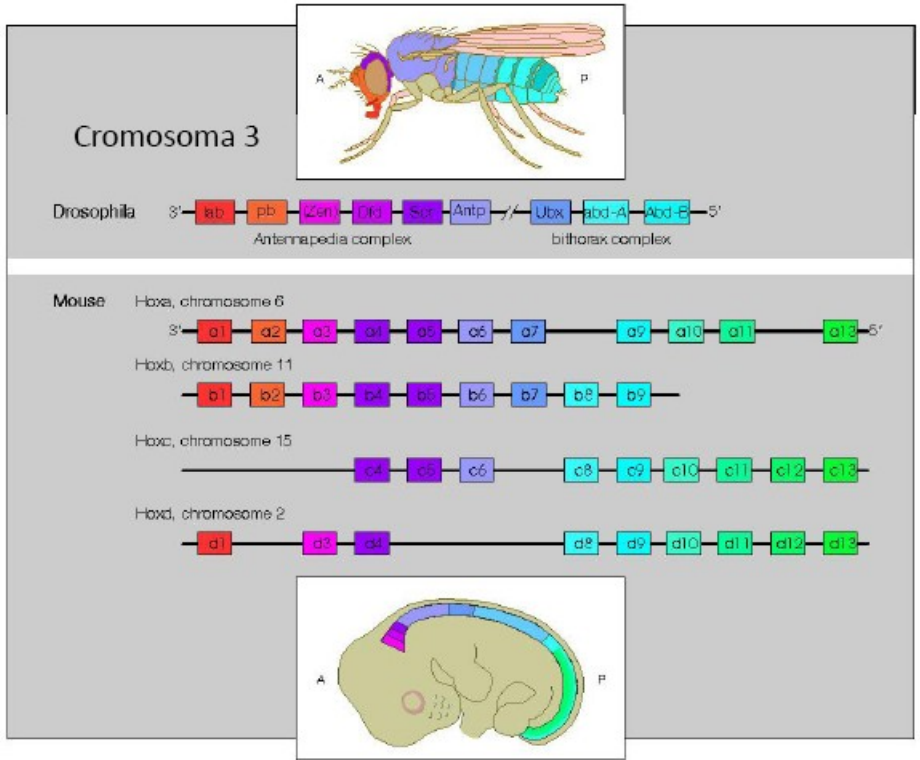


Fig. 9.10: L' espressione dei geni Hox nell'embrione di *D. melanogaster* (in basso) in specifici domini dell'asse antero-posteriore del corpo definisce la posizione di specifiche strutture lungo lo stesso asse nell'adulto (in alto). Al centro la disposizione dei geni Hox sul cromosoma



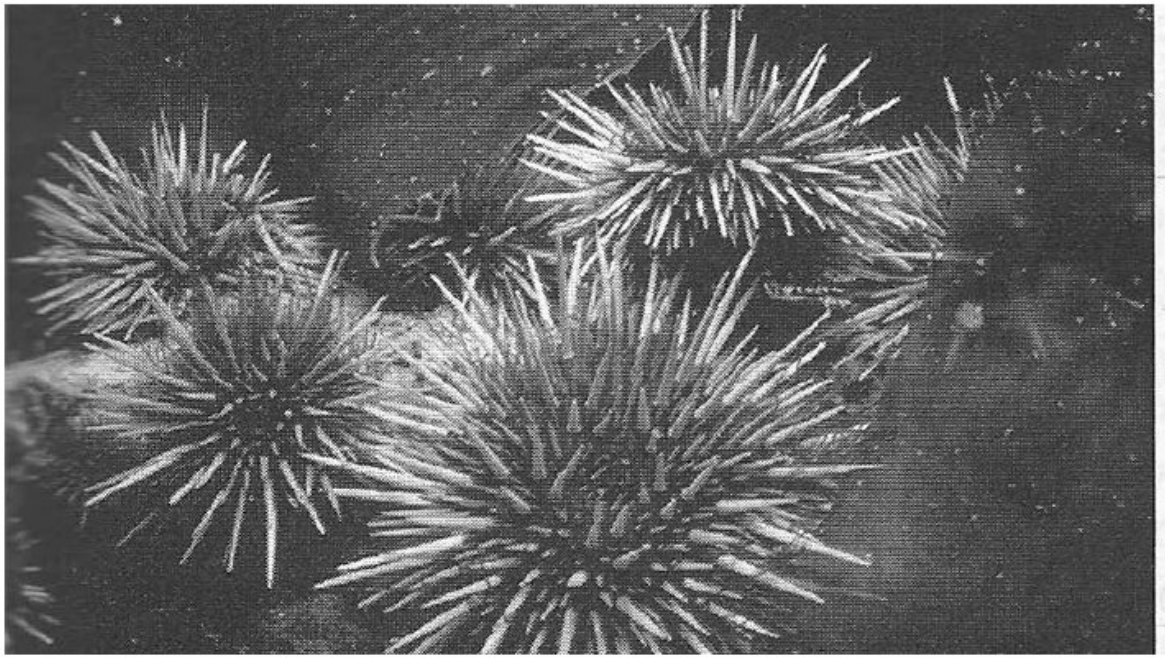
>Complessità
>Nr geni omeotici

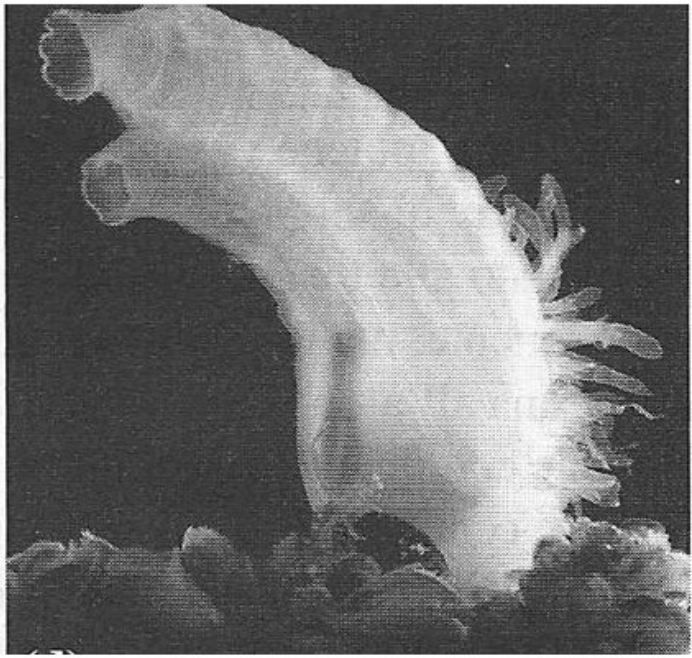
4 clusters nei vertebrati
Geni con similarità di sequenza con quelli di Drosophila

Come si originano le novità evolutive: duplicazioni genomiche

2R Hypothesis

Si vedono delle tracce della 2R (esempio: sequenziamento di genomi)



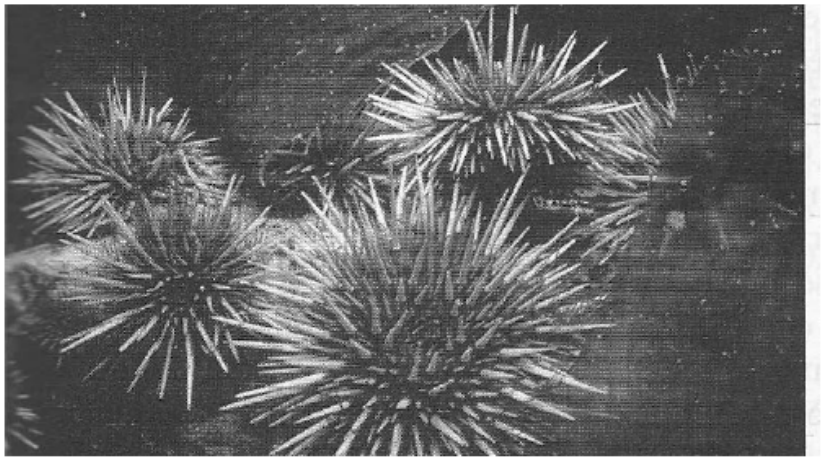


Il sequenziamento dei genomi di riccio di mare (*Strongylocentrotus purpuratus*, echinoderma) e dell'ascidia (*Ciona intestinalis*, tunicato) mostrano numerosi geni in **proporzione 1 a 4 rispetto agli omologhi vertebrati**

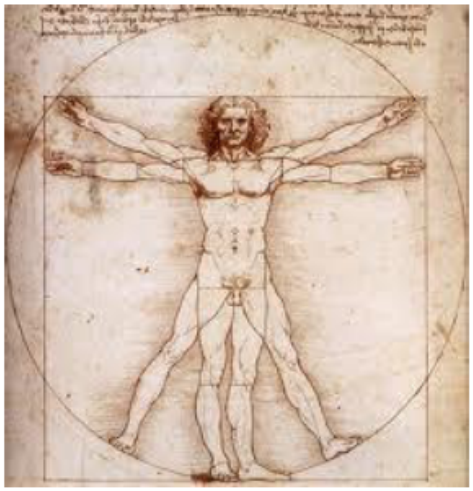
Come si originano le novità evolutive: duplicazioni genomiche

2R Hypothesis

Tuttavia....



~ 23.000 geni



~ 24.000 geni

Nel complesso il riccio di mare ha tanti geni quanti l'uomo: **dopo le duplicazioni genomiche molte copie non sopravvivono come geni funzionanti**

Nelle piante

Il sequenziamento del genoma di *A. thaliana* ha rilevato almeno 2 duplicazioni genomiche.

La maggior parte delle piante sono poliploidi.

In studi condotti sulla flora artica, si è osservato che la frazione di specie vegetali diploidi e poliploidi aumenta all'aumentare della latitudine.

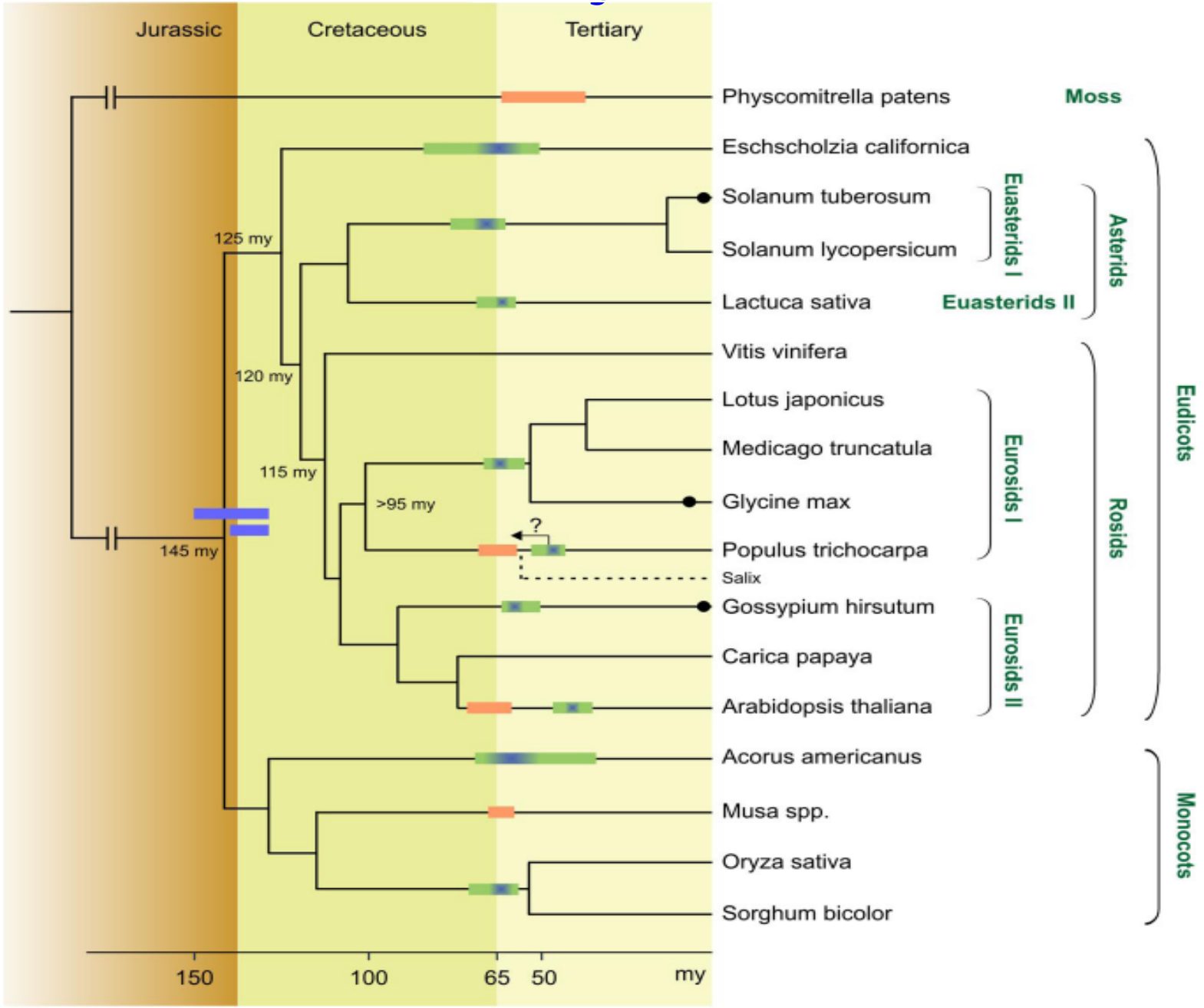
Plants with double genomes might have had a better chance to survive the Cretaceous–Tertiary extinction event

http://www.pnas.org/content/106/14/5737.long

Jeffrey A. Fawcett[a,b,1], Steven Maere[a,b,1], an

[a]Department of Plant Systems Biology, Flanders Institute
Ghent University, 9052 Gent, Belgium

Communicated by Marc C. E. Van Montagu, Ghent Univ

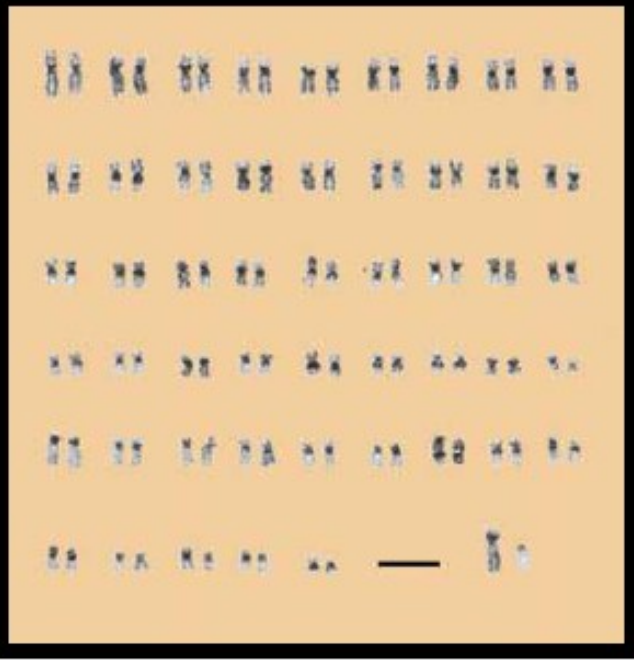


POLIPLOIDIA NEI MAMMIFERI


Tympanoctomys barrerae

Nel 1999 viene identificato un mammifero poliploide, il topo rosso di Mendoza (Argentina), 4N= 102.

Il successo evolutivo di questa specie poliploide è legato al mantenimento di un unico set di cromosomi sessuali XY.



Gene order

In genetics, two loci are called *syntenic* if they are located on the same chromosome.

In genomics, however, the term *synteny* is used to indicate a situation where a series of genes is arranged in the same order on different genomes

GENE ORDER

- In any genome, genes are found to be organized in clusters and these clusters sometimes maintain the same order across species, even across groups as far apart as mammals and fish.

- Well-known examples of synteny are histone genes, *Hox* gene clusters, and the genes of the major histocompatibility complex (MHC). There are also large synteny blocks, covering hundreds of kilobase pairs, between the genomes of rice and *Arabidopsis*

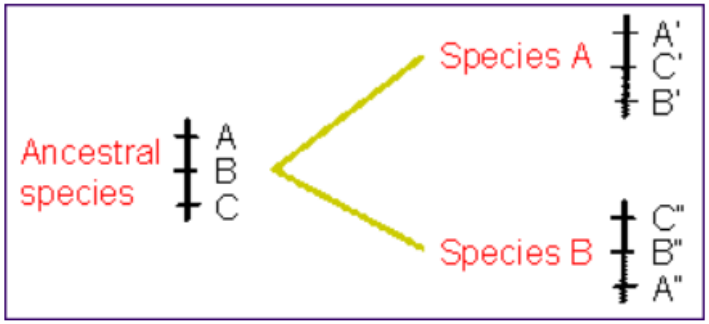
- **Synteny analysis is an important tool in comparative genomics**. The relative order of genes in one species can provide clues about the presence or even the function of genes in another species.

- Similarly, by looking at the order of genes in a cluster, one can discover genes by homology to another species that were missed by automatic gene-finding algorithms.

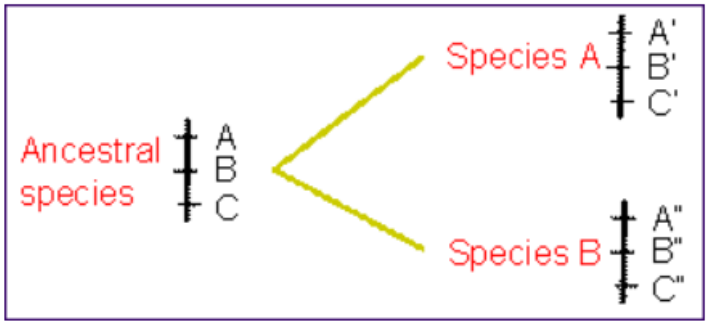
- How could such blocks of gene order be maintained while other regions of the genome are reshuffled extensively by recombination?

- How can it be that some genes are free to move through the genome while others are tied, for millions of years, to the same neighbours?

Syntenic* = a set of loci in two different species which is located on the same chromosome in each (not necessarily in the same order).



Collinear = a set of loci in two different species which are located on the same chromosome in each, and are conserved in the same order.



* Synteny now has the same meaning as collinear, despite the different origins of the terms

Come differiscono i genomi

Similarità e differenze tra sequenze genomiche compaiono

(1) ai livelli di singole basi;

(2) al livello di geni;

(3) in blocchi su scala maggiore; e

(4) al livello di interi genomi che hanno subito duplicazioni complete.

Come si originano le novità evolutive: geni *de novo*

Origine da sequenze non codificanti

DOI: 10.1534/genetics.107.084491

De Novo Origination of a New Protein-Coding Gene in *Saccharomyces cerevisiae*

Jing Cai,*,†,1 Ruoping Zhao,*,1 Huifeng Jiang*,† and Wen Wang*,2

ABSTRACT

Origination of new genes is an important mechanism generating genetic novelties during the evolution of an organism. Processes of creating new genes using preexisting genes as the raw materials are well characterized, such as exon shuffling, gene duplication, retroposition, gene fusion, and fission. However, the process of how a new gene is *de novo* created from noncoding sequence is largely unknown. On the basis of genome comparison among yeast species, we have identified a new *de novo* protein-coding gene, *BSC4* in *Saccharomyces cerevisiae*. The *BSC4* gene has an open reading frame (ORF) encoding a 132-amino-acid-long peptide, while there is no homologous ORF in all the sequenced genomes of other fungal species, including its closely related species such as *S. paradoxus* and *S. mikatae*. The functional protein-coding feature of the *BSC4* gene in *S. cerevisiae* is supported by population genetics, expression, proteomics, and synthetic lethal data. The evidence suggests that *BSC4* may be involved in the DNA repair pathway during the stationary phase of *S. cerevisiae* and contribute to the robustness of *S. cerevisiae*, when shifted to a nutrient-poor environment. Because the corresponding noncoding sequences in *S. paradoxus*, *S. mikatae*, and *S. bayanus* also transcribe, we propose that a new *de novo* protein-coding gene may have evolved from a previously expressed noncoding sequence.

Come si originano le novità evolutive: geni *de novo*

Origine da sequenze non codificanti

Letter

On the origin of new genes in *Drosophila*

Qi Zhou,[1,2,4] Guojie Zhang,[1,2,3,4] Yue Zhang,[1,4] Shiyu Xu,[1] Ruoping Zhao,[1] Zubing Zhan,[1,2] Xin Li,[1,2] Yun Ding,[1,2] Shuang Yang,[1,3] and Wen Wang[1,5]

Several mechanisms have been proposed to account for the origination of new genes. Despite extensive case studies, the general principles governing this fundamental process are still unclear at the whole-genome level. Here, we unveil genome-wide patterns for the mutational mechanisms leading to new genes and their subsequent lineage-specific evolution at different time nodes in the *Drosophila melanogaster* species subgroup. We find that (1) tandem gene duplication has generated ~80% of the nascent duplicates that are limited to single species (*D. melanogaster* or *Drosophila yakuba*); (2) the most abundant new genes shared by multiple species (44.1%) are dispersed duplicates, and are more likely to be retained and be functional; (3) de novo gene origination from noncoding sequences plays an unexpectedly important role during the origin of new genes, and is responsible for 11.9% of the new genes; (4) retroposition is also an important mechanism, and had generated ~10% of the new genes; (5) ~30% of the new genes in the *D. melanogaster* species complex recruited various genomic sequences and formed chimeric gene structures, suggesting structure innovation as an important way to help fixation of new genes; and (6) the rate of the origin of new functional genes is estimated to be five to 11 genes per million years in the *D. melanogaster* subgroup. Finally, we survey gene frequencies among 19 globally derived strains for *D. melanogaster*-specific new genes and reveal that 44.4% of them show copy number polymorphisms within a population. In conclusion, we provide a panoramic picture for the origin of new genes in *Drosophila* species.

Genome Research
www.genome.org

18:1446–1455 ©2008

Duplicazioni

Specie	Geni duplicati (%)
Bacteria (batteri)	
Mycoplasma pneumoniae	44
Helicobacter pylori	17
Haemophilus influenzae	17
Archaea (archei)	
Archaeoglobus fulgidus	30
Eukarya (eucarioti)	
Saccharomyces cerevisiae	30
Caenorhabditis elegans	49
Drosophila melanogaster	41
Arabidopsis thaliana	65
Homo sapiens	38

Da: J. Zhang, *Evolution by gene duplication: an update*, «Trends Ecol. Evol.», 18 (2003), pp. 292-298.

Duplicazione genica: destino dei geni duplicati

1. Tutte le copie mantengono la stessa funzione.

2. Alcune copie scompaiono.

3. Alcune copie evolvono con una nuova funzione.

Duplicazione genica: destino dei geni duplicati

1. Tutte le copie mantengono la stessa funzione.

Numbers of rRNA and tRNA genes per haploid genome in various organisms

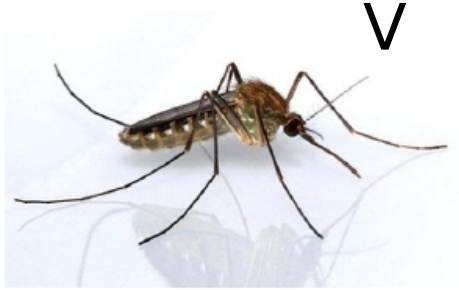
Genome Source	Number of rRNA sets	Number of tRNA genes[a]	Approximate genome size (bp)
Human mitochondrion	1	22	2×10^4
Nicotiana tabacum chloroplast	2	37	2×10^5
Escherichia coli	7	~ 100	4×10^6
Neurospora crassa	~ 100	~ 2,600	2×10^7
Saccharomyces cerevisiae	~ 140	~ 360	5×10^7
Caenorhabditis elegans	~ 55	~ 300	8×10^7
Tetrahymena thermophila	1	~ 800[c]	2×10^8
Drosophila melanogaster	120-240	590-900	2×10^8
Physarum polycephalum	80-280	~ 1,050	5×10^8
Euglena gracilis	800-1,000	~ 740	2×10^9
Human	~ 300	~ 1,300	3×10^9
Rattus norvegicus	150-170	~ 6,500	3×10^9
Xenopus laevis	500-760	6,500-7,800	8×10^9

Duplicazione genica: destino dei geni duplicati

1. Tutte le copie mantengono la stessa funzione.

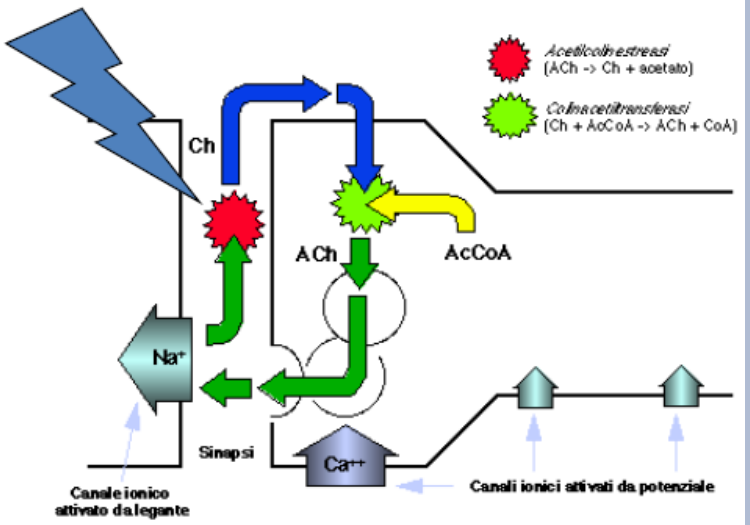
CNV

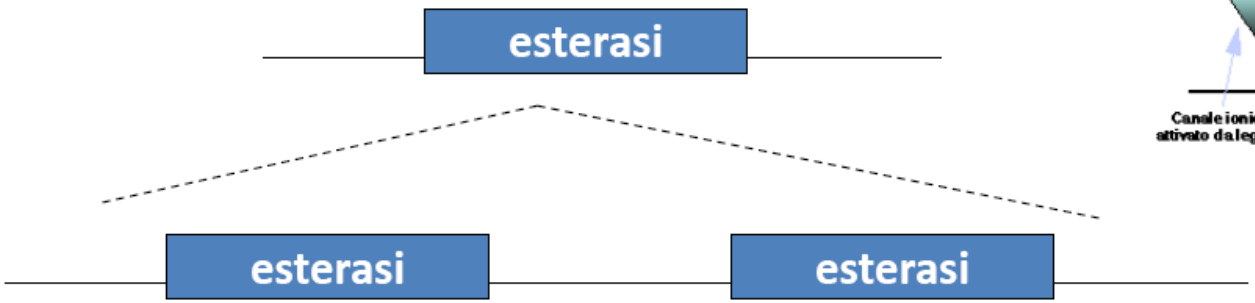
Resistenza ai pesticidi: **zanzare**



Organofosfati: neurotossine che colpiscono il SN degli insetti

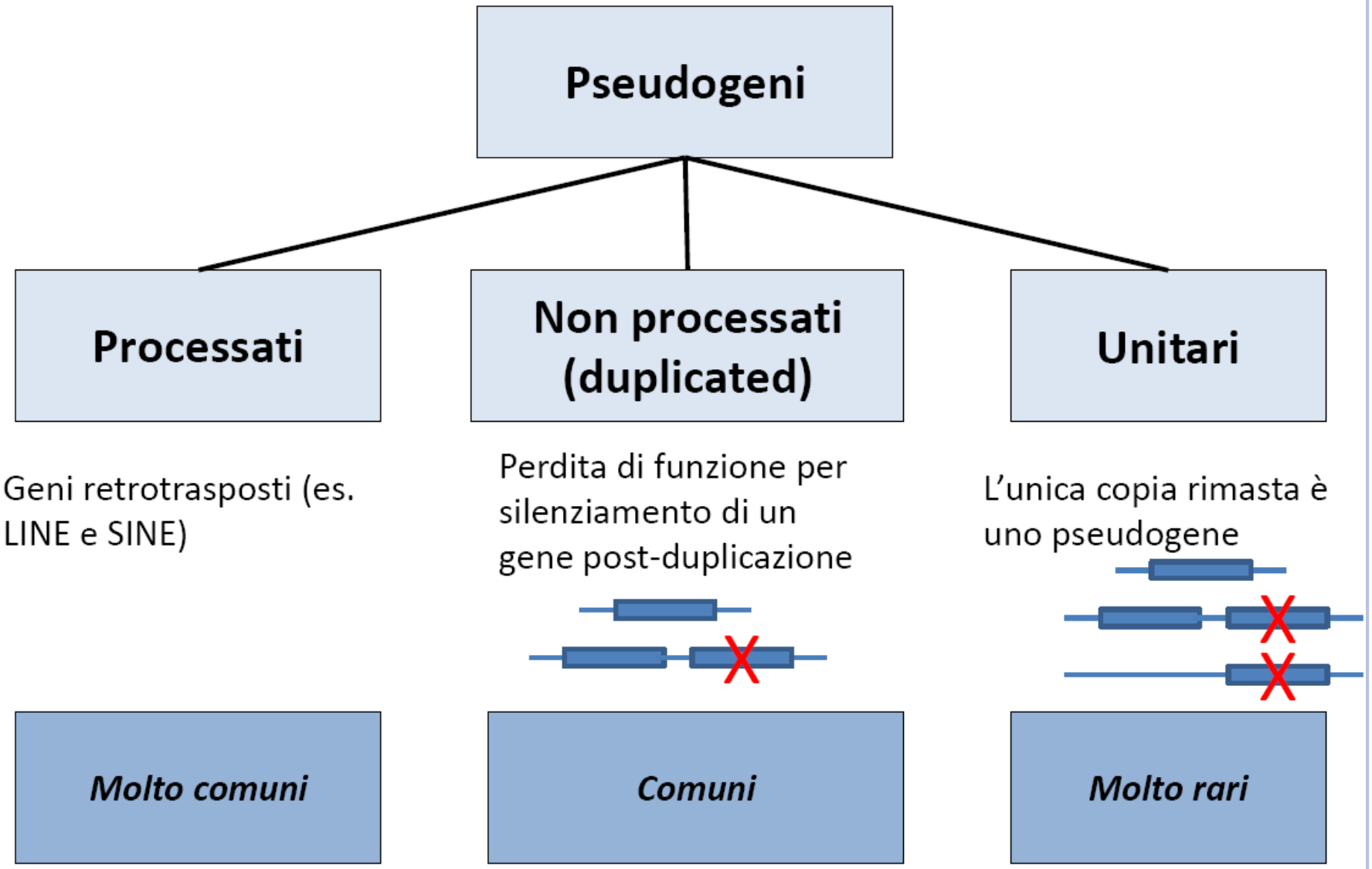
Resistenza:
Amplificazione del gene dell'Esterasi che blocca il pesticida prima dell'arrivo al terminale nervoso





Duplicazione genica: destino dei geni duplicati

2. Alcune copie scompaiono.



COPY NUMBER VARIATION

- se paragoniamo il genoma di due individui, troveremo una differenza media di duplicazioni segmentali per circa 20 milioni di paia di basi, che risultano cioe' presenti nel primo e assenti nel secondo o viceversa.
- http://www.nature.com/nature/journal/v444/n7118/abs/nature05329.html

Global variation in copy number in the human genome

Richard Redon[1], Shumpei Ishikawa[2,3], Karen R. Fitch[4], Lars Feuk[5,6], George H. Perry[7], T. Daniel Andrews[1], Heike Fiegler[1], Michael H. Shapero[4], Andrew R. Carson[5,6], Wenwei Chen[4], Eun Kyung Cho[7], Stephanie Dallaire[7], Jennifer L. Freeman[7], Juan R. González[8], Mònica Gratacòs[8], Jing Huang[4], Dimitrios Kalaitzopoulos[1], Daisuke Komura[3], Jeffrey R. MacDonald[5], Christian R. Marshall[5,6], Rui Mei[4], Lyndal Montgomery[1], Kunihiro Nishimura[2], Kohji Okamura[5,6], Fan Shen[4], Martin J. Somerville[9], Joelle Tchinda[7], Armand Valsesia[1], Cara Woodwark[1], Fengtang Yang[1], Junjun Zhang[5], Tatiana Zerjal[1], Jane Zhang[4], Lluis Armengol[8], Donald F. Conrad[10], Xavier Estivill[8,11], Chris Tyler-Smith[1], Nigel P. Carter[1], Hiroyuki Aburatani[2,12], Charles Lee[7,13], Keith W. Jones[4], Stephen W. Scherer[5,6] & Matthew E. Hurles[1]

Copy number variation (CNV) of DNA sequences is functionally significant but has yet to be fully ascertained. We have constructed a first-generation CNV map of the human genome through the study of 270 individuals from four populations with ancestry in Europe, Africa or Asia (the HapMap collection). DNA from these individuals was screened for CNV using two complementary technologies: single-nucleotide polymorphism (SNP) genotyping arrays, and clone-based comparative genomic hybridization. A total of 1,447 copy number variable regions (CNVRs), which can encompass overlapping or adjacent gains or losses, covering 360 megabases (12% of the genome) were identified in these populations. These CNVRs contained hundreds of genes, disease loci, functional elements and segmental duplications. Notably, the CNVRs encompassed more nucleotide content per genome than SNPs, underscoring the importance of CNV in genetic diversity and evolution. The data obtained delineate linkage disequilibrium patterns for many CNVs, and reveal marked variation in copy number among populations. We also demonstrate the utility of this resource for genetic disease studies.

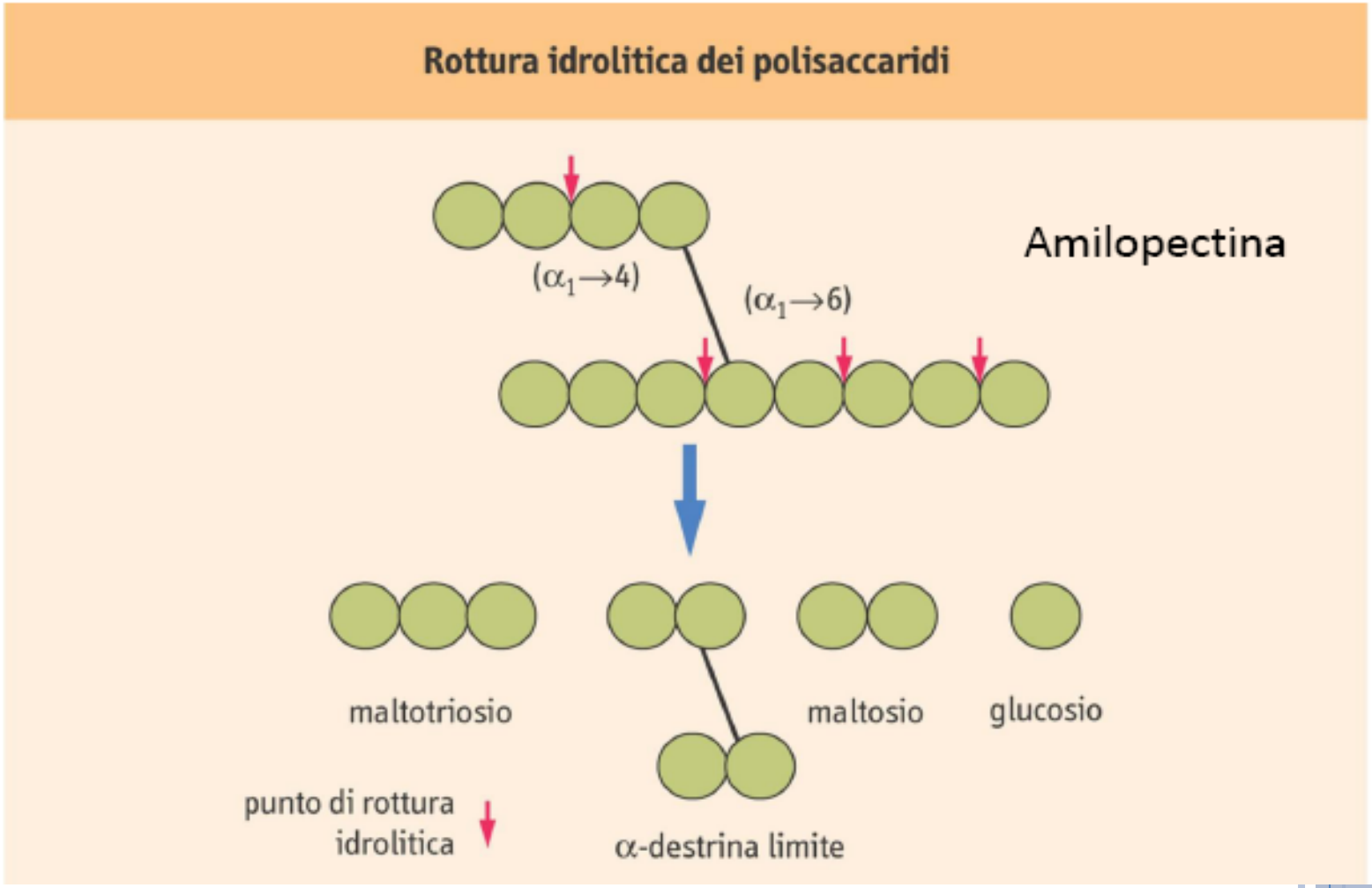
Evolutionary genetics: You are what you ate

http://www.nature.com/nature/journal/v449/n7159/full/449155a.html

It is hard to think of anyone who doesn't like starchy foods such as pasta, chips, rice or bread. But certain populations, for example hunter–gatherers living in the rainforests or near the Arctic circle, have historically existed on a diet rich in protein and low in starch.

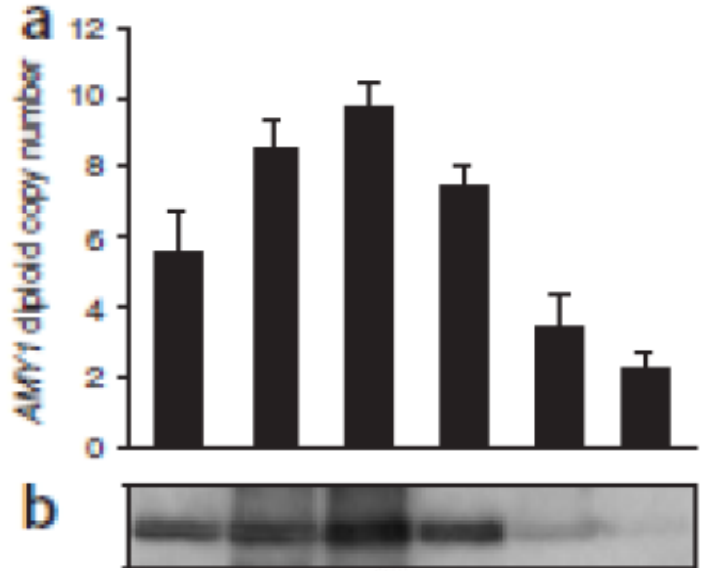
AMILASI

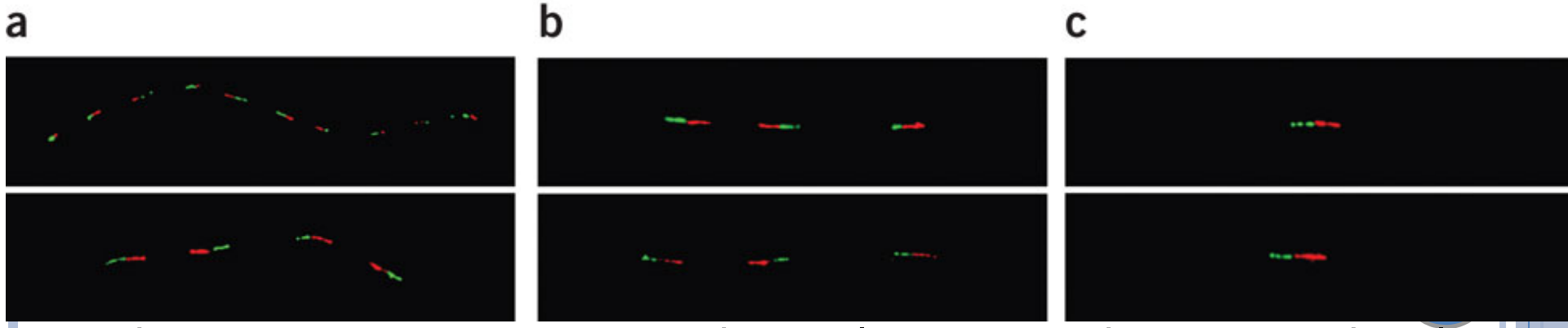
2 forme isoenzimatiche
alfa-amilasi salivare o ptialina
alfa-amilasi pancreatica



•Il gene per l'amilasi salivare *AMY1* è presente in copia multipla nel genoma
• il numero di copie varia tra gli individui e tra le popolazioni
e corrisponde all'espressione della proteina nella saliva

a) Numero di copie del gene in diversi individui

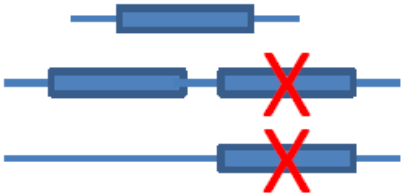




- http://www.nature.com/ng/journal/v39/n10/abs/ng2123.html

Duplicazione genica: destino dei geni duplicati

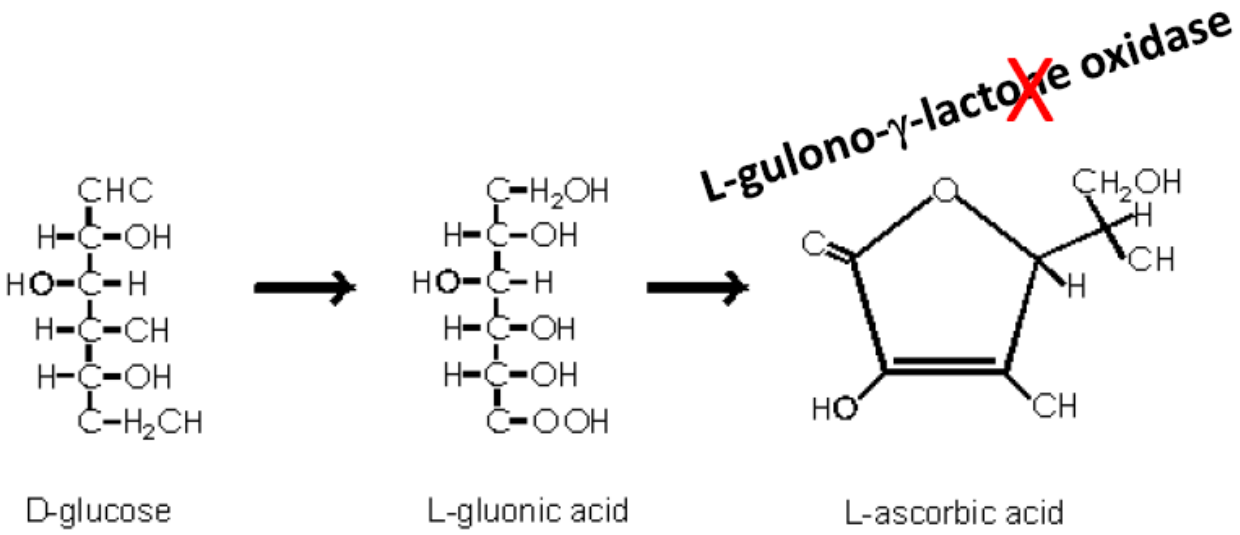
2. Alcune copie scompaiono. Pseudogeni unitari



Come si può fissare in una popolazione la perdita di un gene?
Per deriva se la selezione è rilassata

Ipoascorbemia o scrobuto = incapacità di sintetisi dell'acido ascorbico

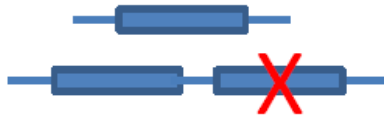
Cavie
Uomo si ammalano di scorbuto se non assumo acido ascorbico (vitamina C)
Trote



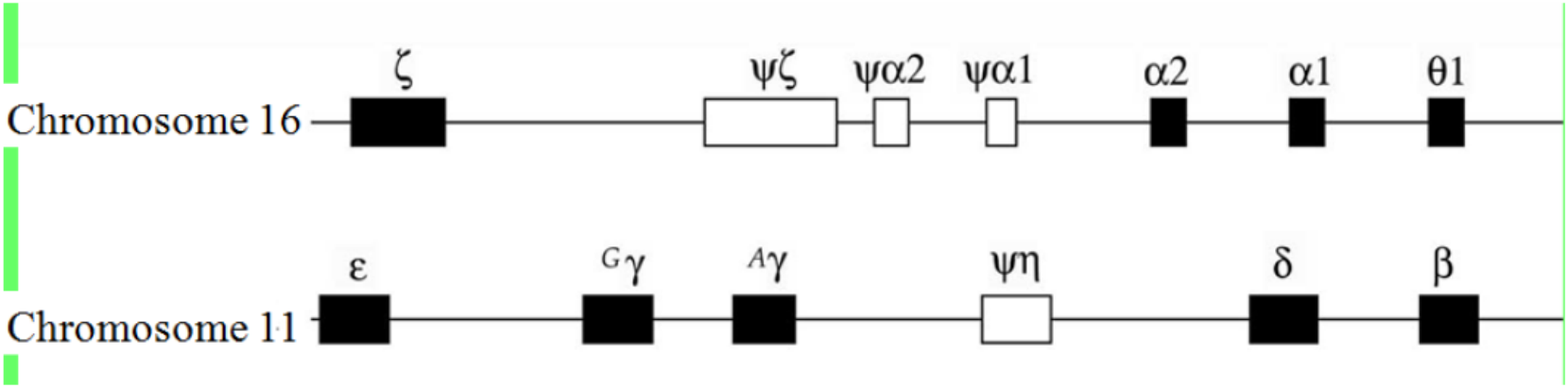
Lo pseudogene non ha una controparte funzionante: pseudogene unitario
Mutazioni diverse in uomo e cavia: perdita di funzione in momenti diversi

Duplicazione genica: destino dei geni duplicati

2. Alcune copie scompaiono. Pseudogeni non processati



Molti esempi nelle globine



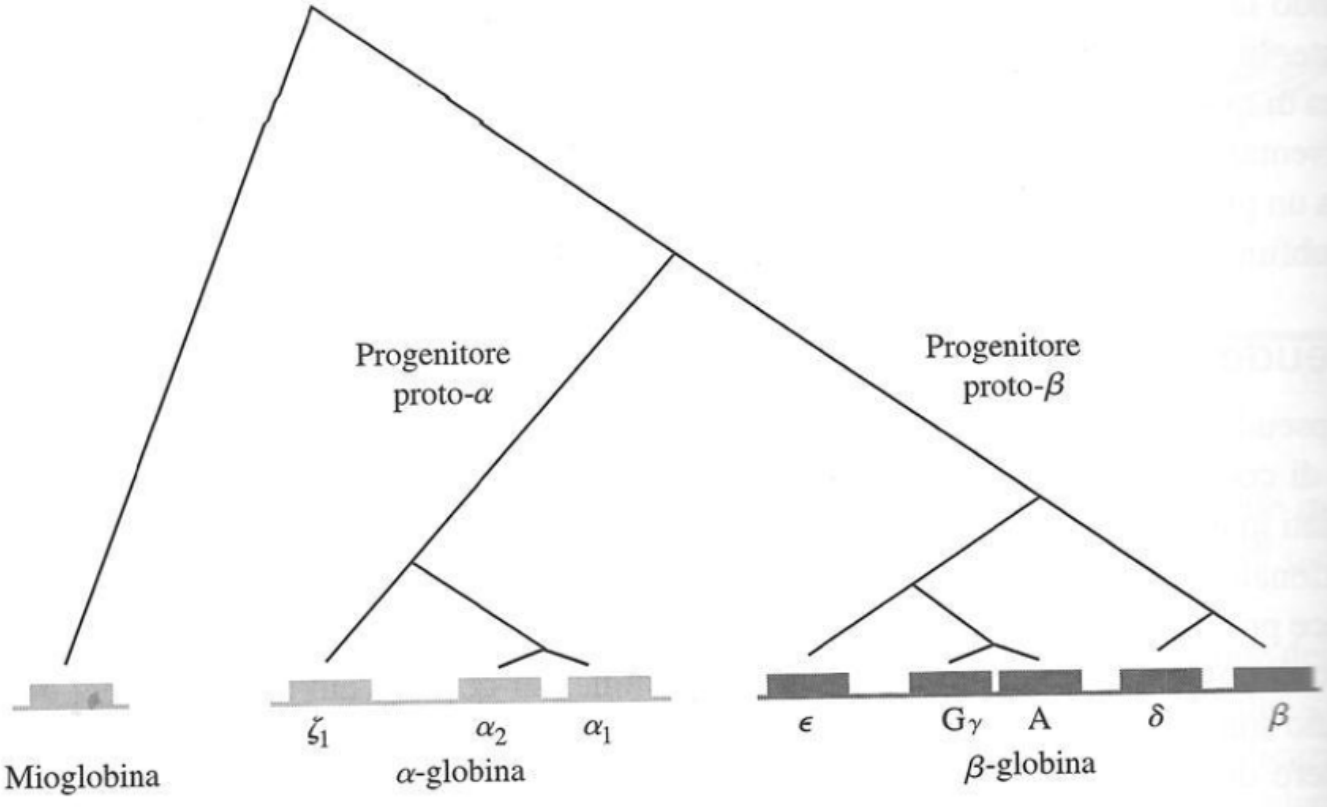
Pseudogene	TATA box	Init. codon	Frame shift	Premature stop	Essential amino acid	Splice GT/AG	Stop codon	Polyadenilation signal AATAAA
Human ψα1		+	+	+	+	+	+	+
Human ψζ1				+				
Mouse ψα3	+		+	+		+		
Mouse ψα4			+		+			
Mouse βh3	?	+	+	+	+	+	?	?
Goat $\psi\beta^x$	+		+	+	+	+	+	+
Goat $\psi\beta^z$	+		+	+	+	+	+	+
Rabbit ψβ2			+	+	+	+		

Duplicazione genica: destino dei geni duplicati

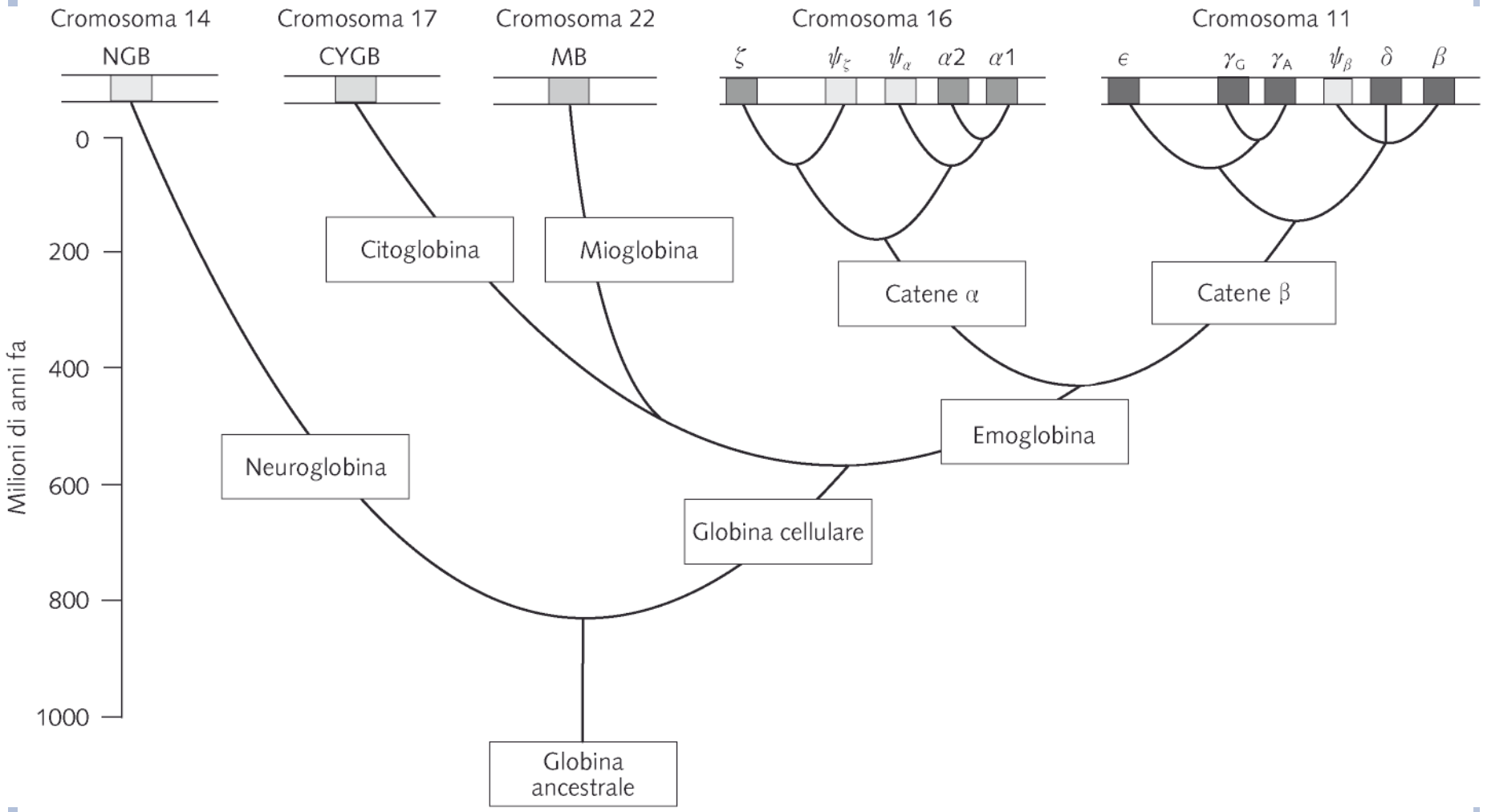
3. Alcune copie evolvono con una nuova funzione.

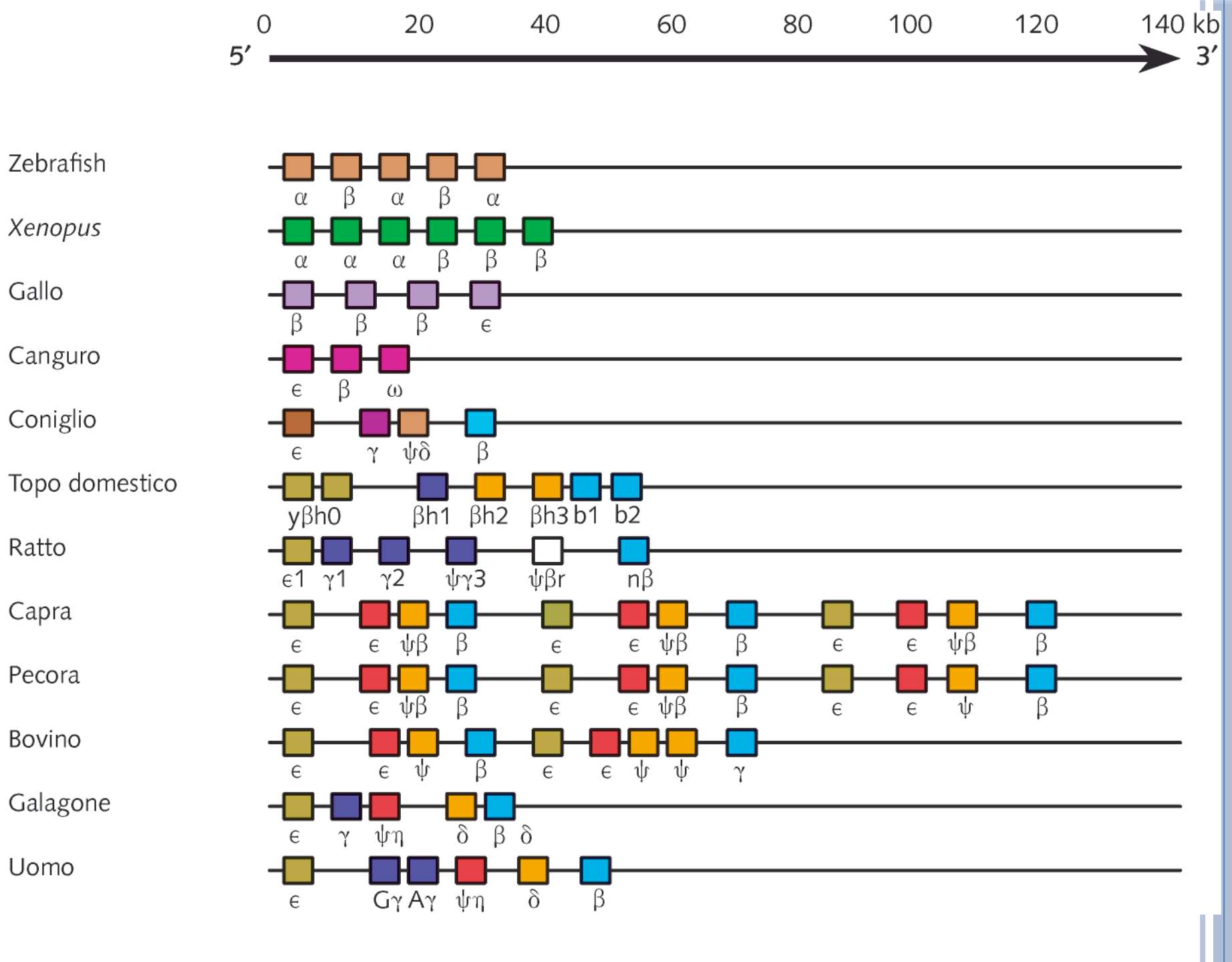
Rosso e blu sono PARALOGHI

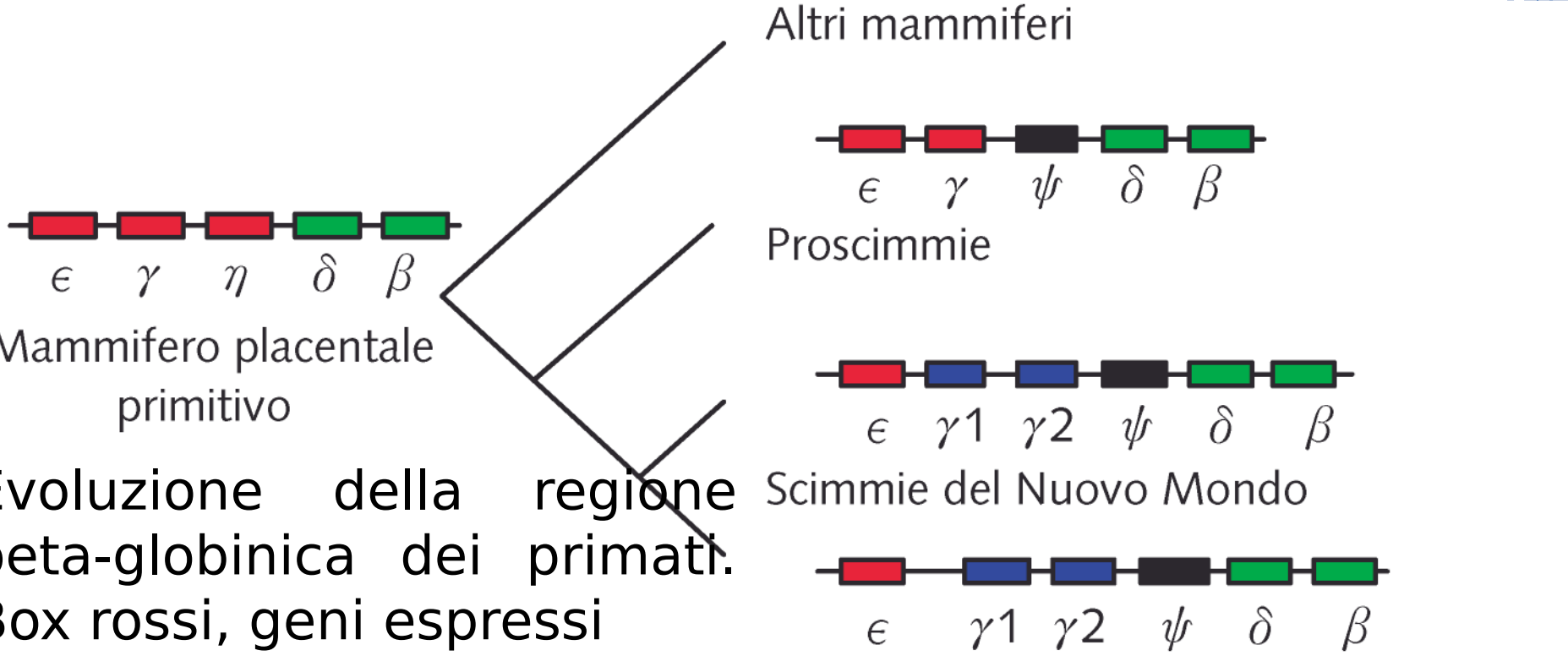
Figura 7.9
Vi sono, per esempio nella nostra specie, diversi geni per le globine, probabilmente derivati da duplicazioni avvenute nel passato. Questo albero mostra la "storia" dei geni per le globine, che spiega la presenza dei paraloghi.



Duplicazioni




0
20
40
60
80
100
120
140 kb
5′
3′
Zebrafish
α β α β α
Xenopus
α α α β β β
Gallo
β β β ε
Canguro
ε β ω
Coniglio
ε γ ψδ β
Topo domestico
yβh0 βh1 βh2 βh3 b1 b2
Ratto
ε1 γ1 γ2 ψγ3 ψβr nβ
Capra
ε ε ψβ β ε ε ψβ β ε ε ψβ β
Pecora
ε ε ψβ β ε ε ψβ β ε ε ψ β
Bovino
ε ε ψ β ε ε ψ ψ γ
Galagone
ε γ ψη δ β δ
Uomo
ε Gγ Aγ ψη δ β



Evoluzione della regione beta-globinica dei primati. Box rossi, geni espressi a livello embrionale; box verdi, geni espressi a livello post-embrionale; box blu, geni espressi a livello fetale; box neri, pseudogeni.

Espansioni delle famiglie

I recettori accoppiati a proteine C (GPCR) sono una grande famiglia dì proteine transmembrana che intervengono nella trasduzione dei segnali nelle cellule.

Hanno in comune una struttura contenente 7 eliche transmembrana, disposte in una topologia comune.

Questa famiglia ha la stessa età degli eucarioti ed è grande ed eterogenea.

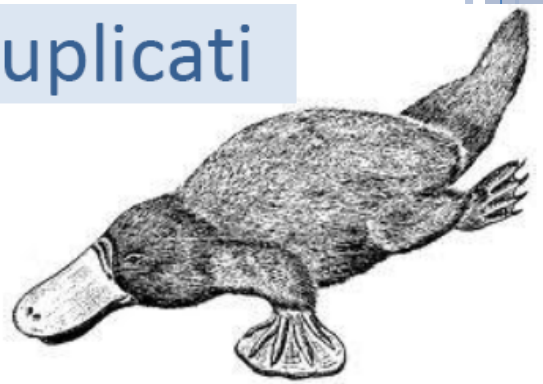
I genomi dei mammiferi contengono circa 1500 – 2000 GPCR, che costituiscono circa il 3 - 5% del genoma.

Il genoma umano ha circa 1000 geni per i **recettori olfattivi**, di cui soltanto il 40% sono attivi. Il genoma murino ne ha circa 1300, di cui l'80% sono attivi.

Duplicazione genica: destino dei geni duplicati

3. Alcune copie evolvono con una nuova funzione.

Novità evolutiva nell'ornitorinco: capacità di produrre veleno



Vol 453|8 May 2008|doi:10.1038/nature06936 nature

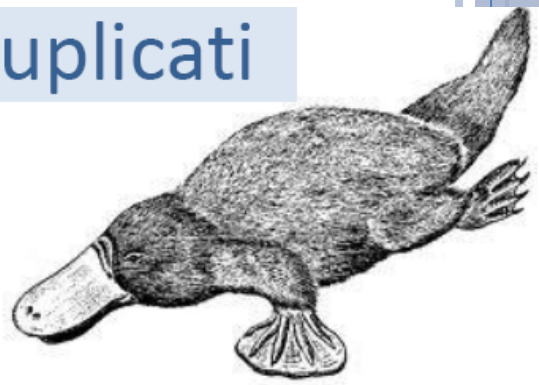
ARTICLES

Genome analysis of the platypus reveals unique signatures of evolution

A list of authors and their affiliations appears at the end of the paper

We present a draft genome sequence of the platypus, *Ornithorhynchus anatinus*. This monotreme exhibits a fascinating combination of reptilian and mammalian characters. For example, platypuses have a coat of fur adapted to an aquatic lifestyle; platypus females lactate, yet lay eggs; and males are equipped with venom similar to that of reptiles. Analysis of the first monotreme genome aligned these features with genetic innovations. We find that reptile and platypus venom proteins have been co-opted independently from the same gene families; milk protein genes are conserved despite platypuses laying eggs; and immune gene family expansions are directly related to platypus biology. Expansions of protein, non-protein-coding RNA and microRNA families, as well as repeat elements, are identified. Sequencing of this genome now provides a valuable resource for deep mammalian comparative analyses, as well as for monotreme biology and conservation.

Duplicazione genica: destino dei geni duplicati



3. Alcune copie evolvono con una nuova funzione.

Le proteine del veleno derivano da copie duplicate neofunzionalizzate di geni già presenti nel genoma.

Una duplicazione simile ma indipendente si osserva nei rettili (convergenza evolutiva!)

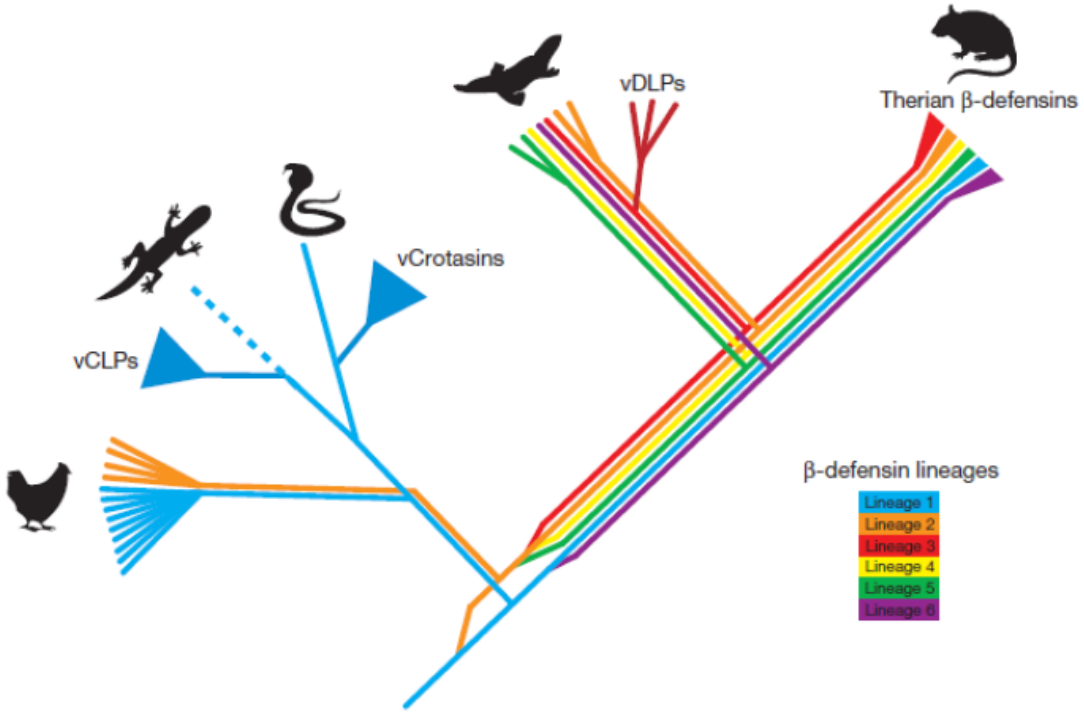


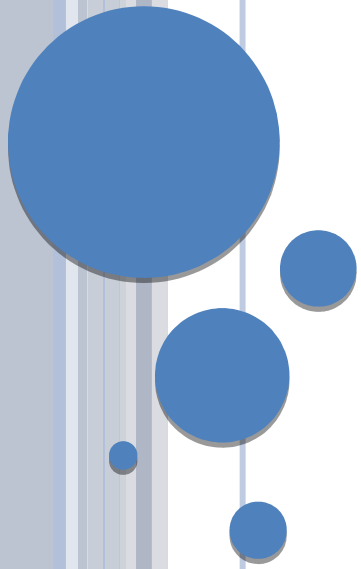
Figure 4 | The evolution of β-defensin peptides in platypus venom gland. The diagram illustrates separate gene duplications in different parts of the phylogeny for platypus venom defensin-like peptides (vDLPs), for lizard venom crotamine-like peptides (vCLPs) and for snake venom crotamines. These venom proteins have thus been co-opted from pre-existing non-toxin homologues independently in platypus and in lizards and snakes[48].

Duplicazioni su larga scala

I genomi di molte specie contengono duplicazioni di regioni multigeniche, la cui lunghezza varia da specie a specie.

- Le duplicazioni segmentali su grande scala sono una componente importante nella differenza tra genoma dell'uomo e genoma dello scimpanzé, interessando circa il 2,7% del genoma.

DETECTING SELECTION PRESSURE



Detecting selection pressure

```
S1 AAG ACT GCC GGG CGT ATT
S2 AAA ACA GCA GGA CGA ATC
```

```
S1 K T A G R I
S2 K T A G R I
```

Synonymous = 6

Non-synonymous = 0

Purifying selection:

Non-synonymous << Synonymous substitutions

★ **Histones**

```
S1 AAG ACT GCC GGG CGT ATT
S2 AAA ACA GAC GGA CAT ATG
```

```
S1 K T A G R I
S2 K T D G H M
```

Synonymous = 3

Non-synonymous = 3

Neutral selection:

Non-synonymous = Synonymous substitutions

```
S1 AAG ACT GCC GGG CGT ATT
S2 AAT ATT GAC GAG CAT ATG
```

```
S1 K T A G R I
S2 N I D E H M
```

Synonymous = 0

Non-synonymous = 6

Positive (Darwinian) selection :
Non-synonymous >> Synonymous substitutions

★ **Host-pathogen arm-race**

The Ka/Ks ratio

Ks

Synonymous substitution rate

Ka

Non-synonymous substitution rate

Assume: Ks = neutral rate of evolution

- **Purifying selection: Ka/Ks < 1**
- **Neutral selection: Ka/Ks = 1**
- **Positive selection: Ka/Ks > 1**

Selection against silent substitutions

Human	GAG	GCT	GCC	GGG	CGT	ATT
Mouse	GGC	ACT	GCC	GGG	CGT	ATT
Dog	GGG	ACT	GCC	GGG	CGT	ATT

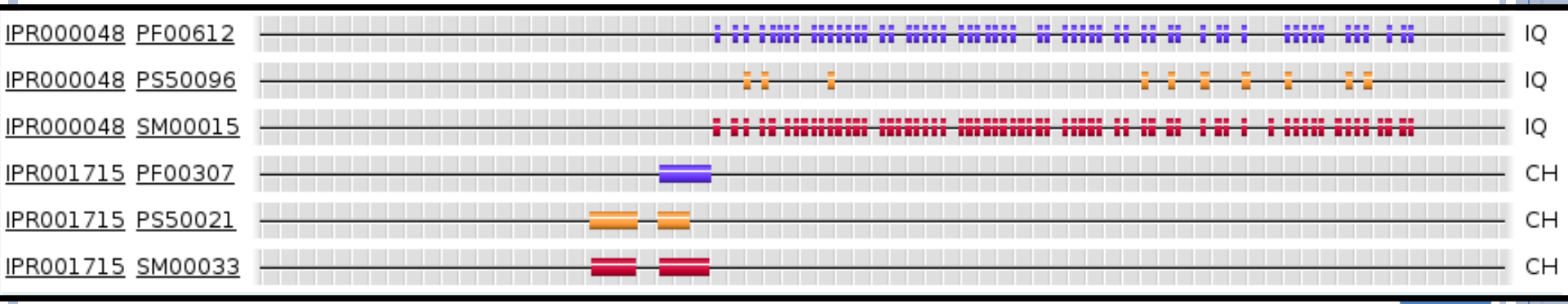
- ✓ RNA stability
- ✓ Exonic splicing regulatory sequences
- ✓ RNA editing
- ✓ Overlapping genes
- ✓ Codon bias and GC content
- ✓ Translational efficiency
- ✓ Protein folding

Reviewed in
Chamary, Parmley, and Hurst
Nature Reviews Genetics (2006)

Struttura e domini di ASPM Important for neurogenenesis

http://www.genecards.org/cgi-bin/carddisp.pl?gene=ASPM

- **ASPM è una proteina di 3477 aa** e contiene:
  - un dominio di legame-ai-microtubuli N-terminale
  - 2 domini CH (Calponin-homology, legame con l'actina)
  - 39 motivi ripetuti Ile-Gln (IQ)
  - 1 regione C-terminale con funzione ignota.



Struttura e domini di ASPM

- Inoltre, **ASPM presenta 28 esoni.**
- Domanda:

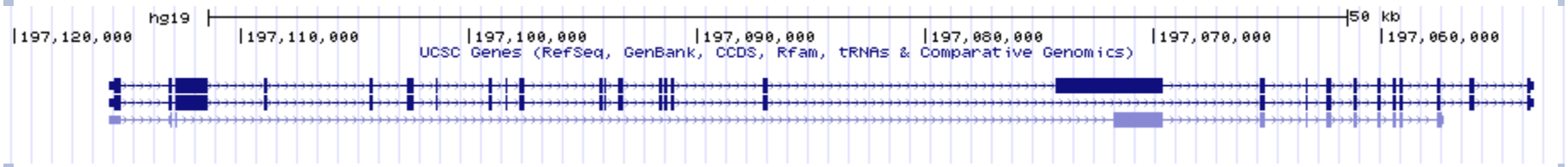
l'evoluzione di ASPM è costante per tutta la proteina?

O alcuni domini sono più conservati?

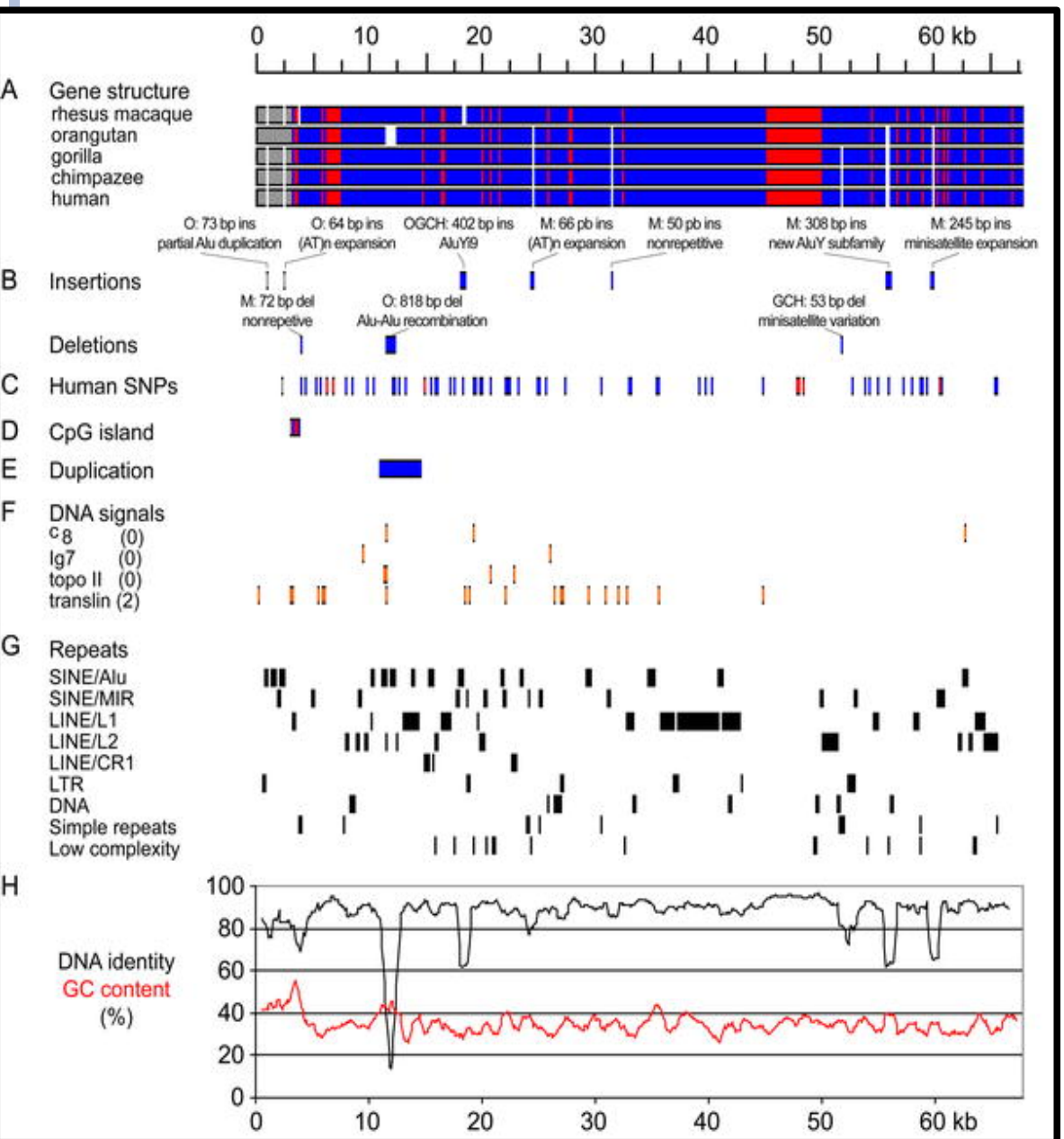
-> '*Accelerated Evolution of the ASPM Gene Controlling Brain Size Begins Prior to Human Expansion*',

Kouprina et al.

http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.0020126

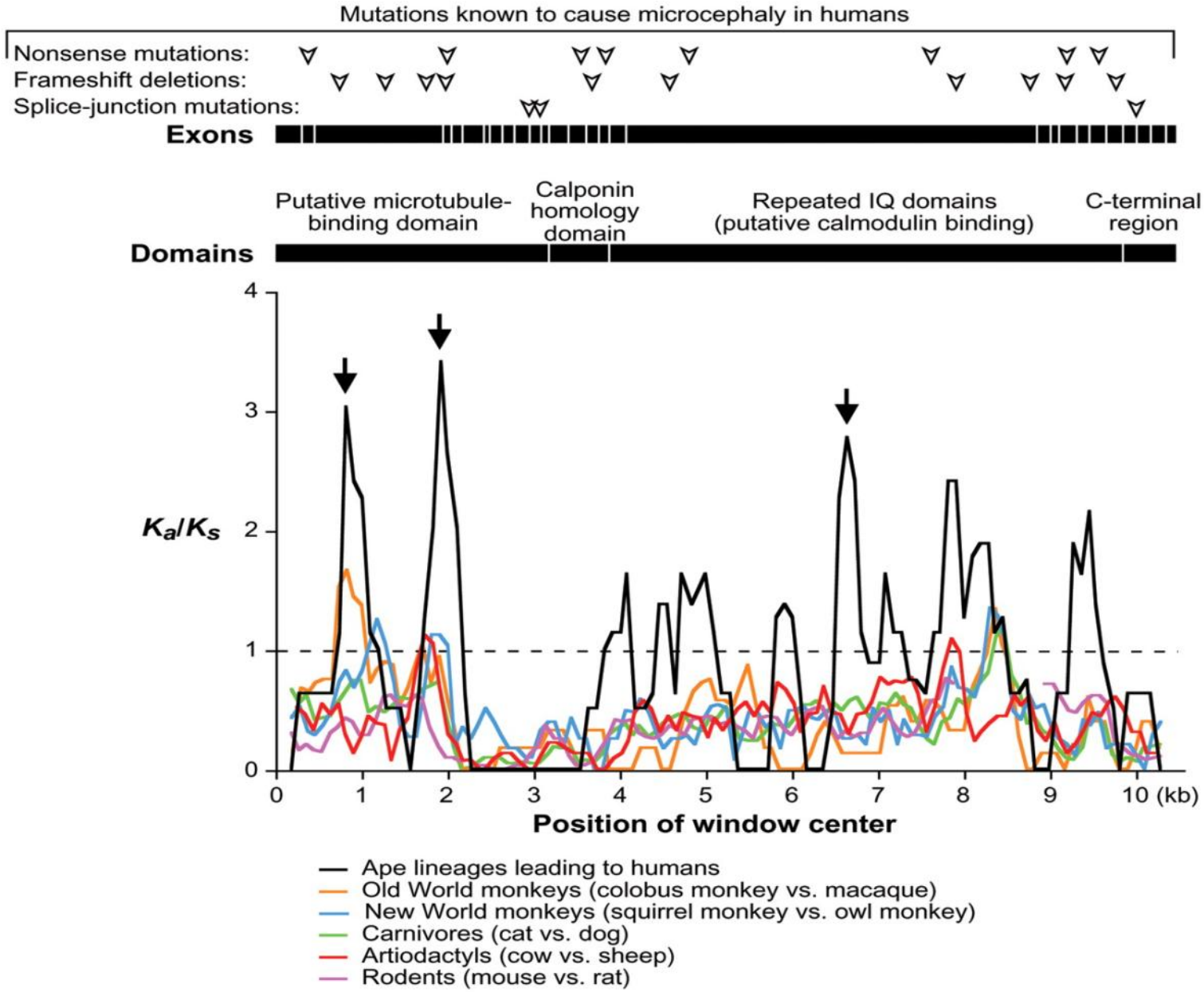


Evoluzione di ASPM



- Nella figura è mostrato l'allineamento tra le copie di ASPM di uomo, macaco, orango, gorilla, scimpanzè.
- Le delezioni più grandi avvengono nelle zone non codificanti (in blu), mentre il resto è conservato.

Figure 3. Sliding-window analysis of Ka/Ks along the ASPM coding region.



Evans P D et al. Hum. Mol. Genet. 2004;13:489-494

In conclusione:

- ASPM è un gene coinvolto nella mitosi dei neuroni del cervello, che ha subito forte selezione positiva nell'uomo, specie nelle regioni a IQ e nell'esone 18.
- La sua selezione comincia addirittura prima della separazione tra uomo e scimmie.
- Studi recenti hanno identificato **una variante positiva (A44871G)** evolutasi 5800 +/- 5000 anni fa.

Positive selection at the ASPM gene coincides with brain size enlargements in cetaceans

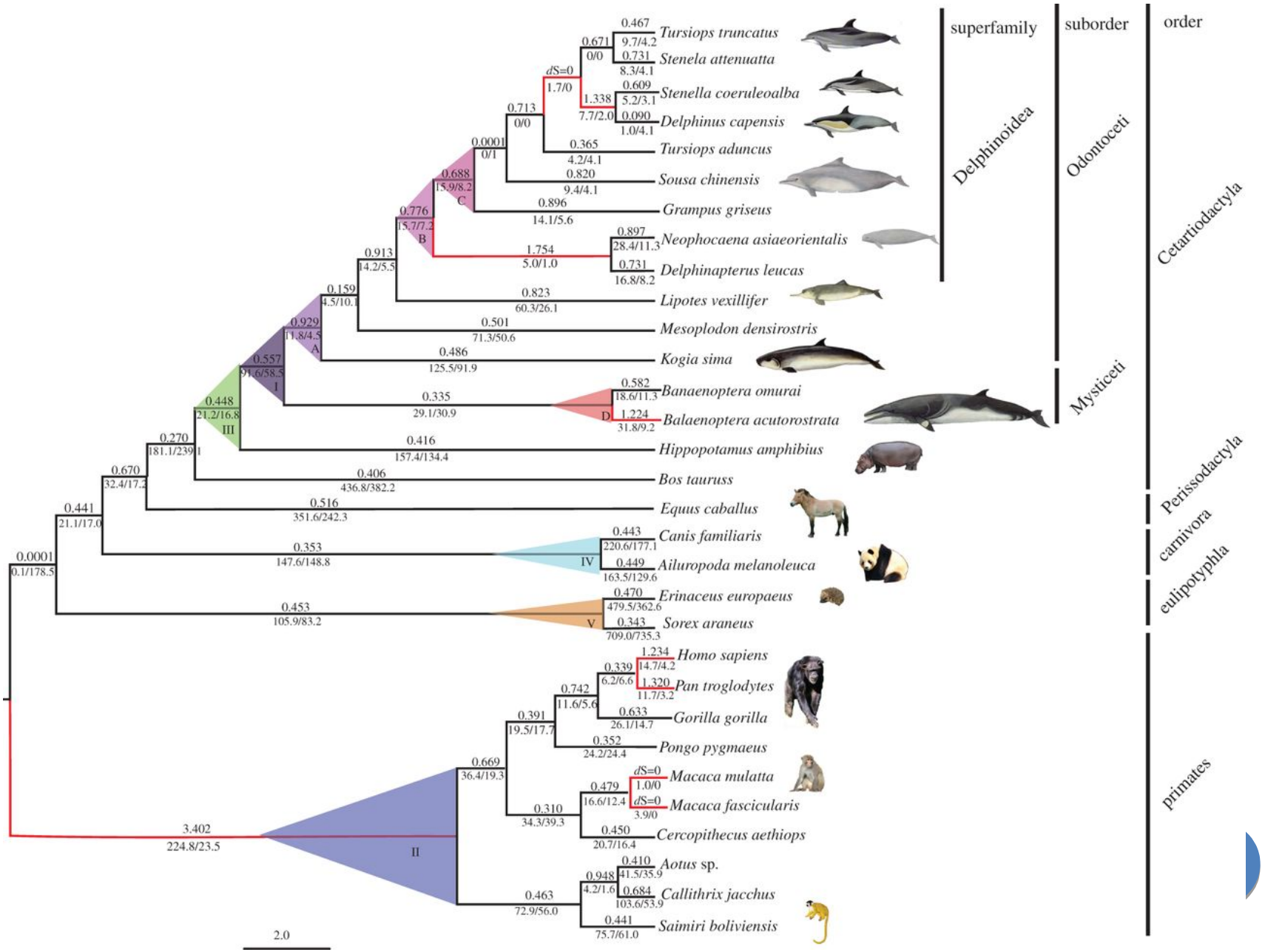
Shixia Xu, Yuan Chen, Yuefeng Cheng, Dan Yang, Xuming Zhou, Junxiao Xu, Kaiya Zhou and Guang Yang*

+ Author Affiliations

*Author for correspondence (gyang@njnu.edu.cn).

Abstract

The enlargement of cetacean brain size represents an enigmatic event in mammalian evolution, yet its genetic basis remains poorly explored. One candidate gene associated with brain size evolution is the abnormal spindle-like microcephaly associated (ASPM), as mutations in this gene cause severe reductions in the cortical size of humans. Here, we investigated the ASPM gene in representative cetacean lineages and previously published sequences from other mammals to test whether the expansion of the cetacean brain matched adaptive ASPM evolution patterns. Our analyses yielded significant evidence of positive selection on the ASPM gene during cetacean evolution, especially for the Odontoceti and Delphinoidea lineages. These molecular patterns were associated with two major events of relative brain size enlargement in odontocetes and delphinoids. It is of particular interest to find that positive selection was restricted to cetaceans and primates, two distant lineages both characterized by a massive expansion of brain size. This result is suggestive of convergent molecular evolution, although no site-specific convergence at the amino acid level was found.


Tursiops truncatus
Stenella attenuatta
Stenella coeruleoalba
Delphinus capensis
Tursiops aduncus
Sousa chinensis
Grampus griseus
Neophocaena asiaeorientalis
Delphinapterus leucas
Lipotes vexillifer
Mesoplodon densirostris
Kogia sima
Banaenoptera omurai
Balaenoptera acutorostrata
Hippopotamus amphibius
Bos tauruss
Equus caballus
Canis familiaris
Ailuropoda melanoleuca
Erinaceus europaeus
Sorex araneus
Homo sapiens
Pan troglodytes
Gorilla gorilla
Pongo pygmaeus
Macaca mulatta
Macaca fascicularis
Cercopithecus aethiops
Aotus sp.
Callithrix jacchus
Saimiri boliviensis
superfamily
suborder
order
Delphinoidea
Odontoceti
Mysticeti
Cetartiodactyla
Perissodactyla
carnivora
eulipotyphla
primates
2.0

Science 9 September 2005:
Vol. 309 no. 5741 pp. 1717-1720
DOI: 10.1126/science.1113722

REPORT

Microcephalin, a Gene Regulating Brain Size, Continues to Evolve Adaptively in Humans

Patrick D. Evans[1,2], Sandra L. Gilbert[1], Nitzan Mekel-Bobrov[1,2], Eric J. Vallender[1,2], Jeffrey R. Anderson[1], Leila M. Vaez-Azizi[1], Sarah A. Tishkoff[4], Richard R. Hudson[3], Bruce T. Lahn[1,*]

+ Author Affiliations

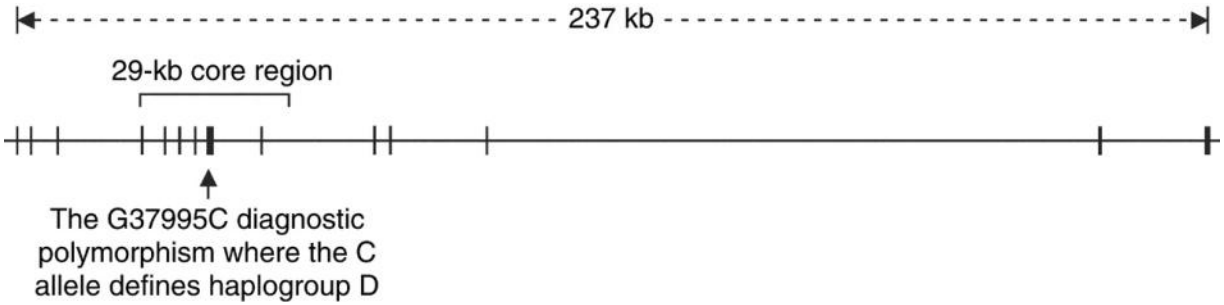
* To whom correspondence should be addressed. E-mail: blahn@bsd.uchicago.edu

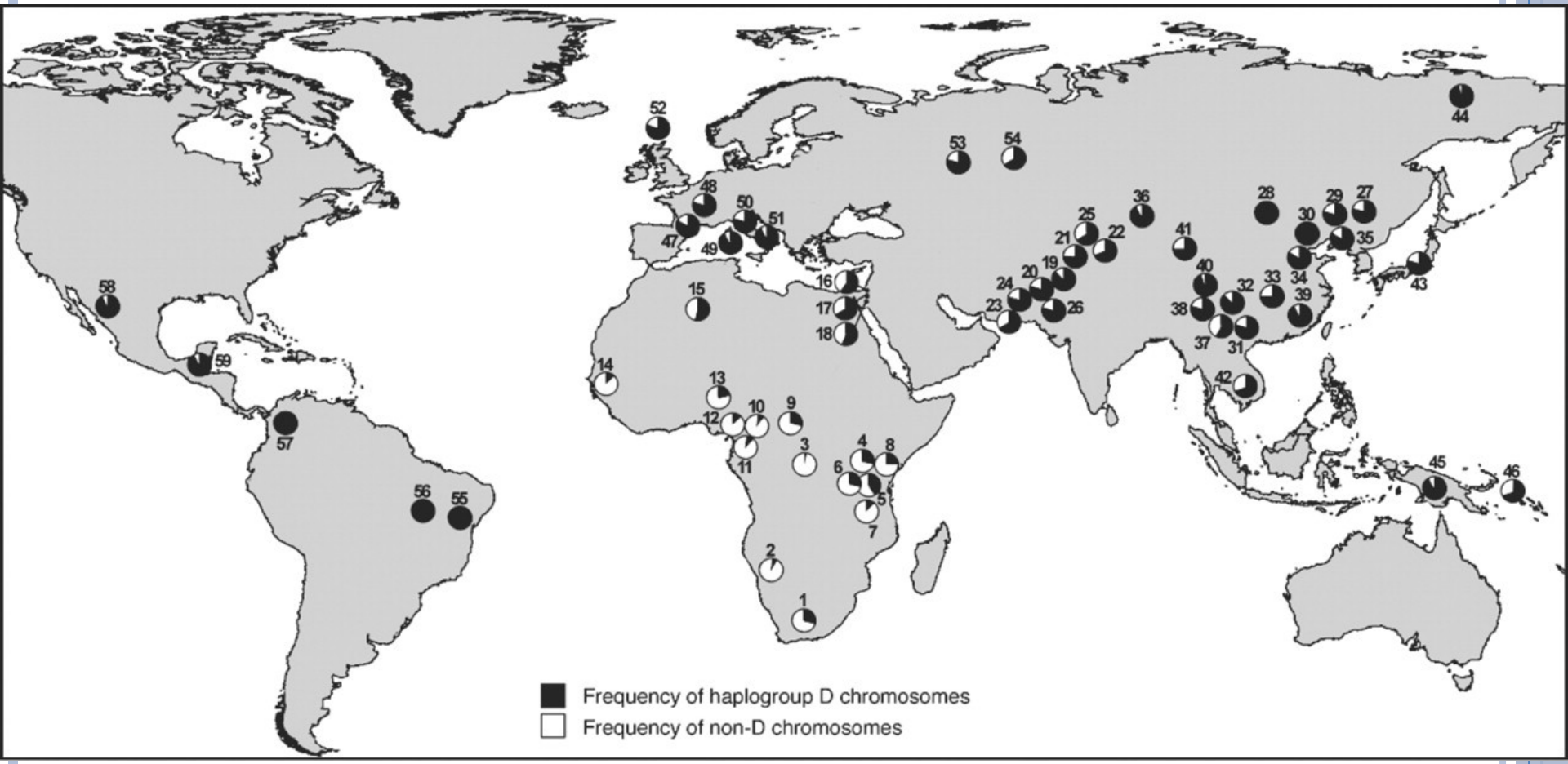
ABSTRACT

The gene *Microcephalin* (*MCPH1*) regulates brain size and has evolved under strong positive selection in the human evolutionary lineage. We show that one genetic variant of *Microcephalin* in modern humans, which arose ~37,000 years ago, increased in frequency too rapidly to be compatible with neutral drift. This indicates that it has spread under strong positive selection, although the exact nature of the selection is unknown. The finding that an important brain gene has continued to evolve adaptively in anatomically modern humans suggests the ongoing evolutionary plasticity of the human brain. It also makes *Microcephalin* an attractive candidate locus for studying the genetics of human variation in brain-related phenotypes.

The most distinct trait of *Homo sapiens* is the exceptional size and complexity of the brain (1, 2). Several recent studies have linked specific genes to the evolution of the human brain (3–12). One of these is *Microcephalin* (7, 8); mutations in this gene cause primary microcephaly [MCPH; Online Mendelian Inheritance in Man (OMIM) accession 251200] (13, 14). MCPH is defined clinically as severe reductions in brain size coupled with mental retardation, but remarkably, an overall retention of normal brain structure and a lack of overt abnormalities outside of the nervous system (15–17). This led to the notion that the brains of MCPH patients function normally for their size and that genes underlying MCPH are specific developmental regulators of brain size (15–17).

Microcephalin





- *Microcephalin* and *ASPM* are genes involved in regulating brain size
- A variant of *Microcephalin* has reached very high frequencies in non-Sub-Saharan Africans in the last 37,000 years.
- A variant of *ASPM* has reached very high frequencies especially in Caucasoids but also in some southern Mongoloids and Australoids in the last 5,800 years.
-

It is almost inconceivable that these two factors were caused by random factors (drift).

Therefore *selection* has acted on these two genes, favoring the new *Microcephalin* variant in non-Sub-Saharan Africans and the *ASPM* especially in Caucasoids, but also to a lesser extent in some southern Mongoloid and Australoid groups.

We know absolutely nothing about what the new *Microcephalin* and *ASPM* variants actually do. What we *do* know is that they confer some substantial advantage that has caused them to grow in numbers. Perhaps, they confer some cognitive or behavioral ability.

Il Gene FOXP2

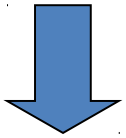
Si è osservato che due diverse mutazioni in questo gene sono associate a disordini nello sviluppo del linguaggio:

R553H (KE Family) → Mutazione missense che porta ad una condizione che colpisce il sistema del linguaggio, della scrittura e della comunicazione. Gli individui affetti hanno problemi nella pronuncia delle parole, non hanno il controllo della grammatica, non riescono ad avere particolari movimenti delle labbra e della lingua, e non capiscono bene la scrittura ☾ malattia ad eredità autosomica dominante.

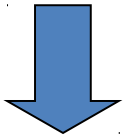
R328X → Il gene è interrotto da una traslocazione che coinvolge i cromosomi 5 e 7, che porta a disordini del linguaggio simili a quelli sopra elencati. (No relazioni familiari)

2 mutazioni uomo-specifiche :

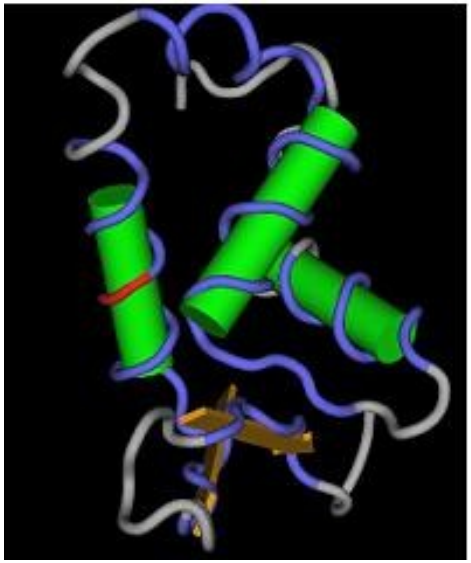
- In posizione 303 (da treonina ad asparagina)
- In posizione 325 (da asparagina a serina)



sito per la fosforilazione ☾ cambio nella struttura secondaria predetta. La fosforilazione di questo FT può essere un importante meccanismo che media la regolazione trascrizionale



Nuova sequenza genica ☾ aumento n° proteine ☾ perfezionamento bocca e laringe ☾ articolazione di suoni complessi



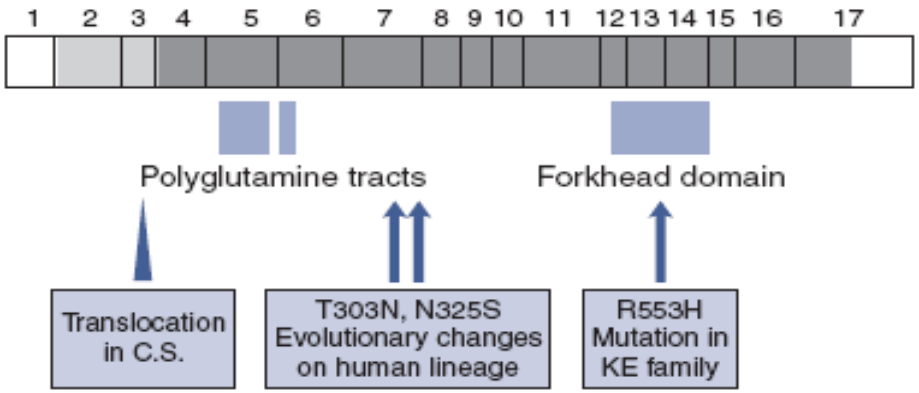
La Proteina FOXP2

In rosso è mostrata la posizione della mutazione dell' aa 325

Il gene Foxp2 (cromosoma 7)

Proteina Foxp2 :

- costituita da 715 aa
- fattore di trascrizione
- contiene una regione ricca di poli-glutammine
- è tra il 5% delle proteine più conservate
- mostra particolari similitudini in tutti i primati

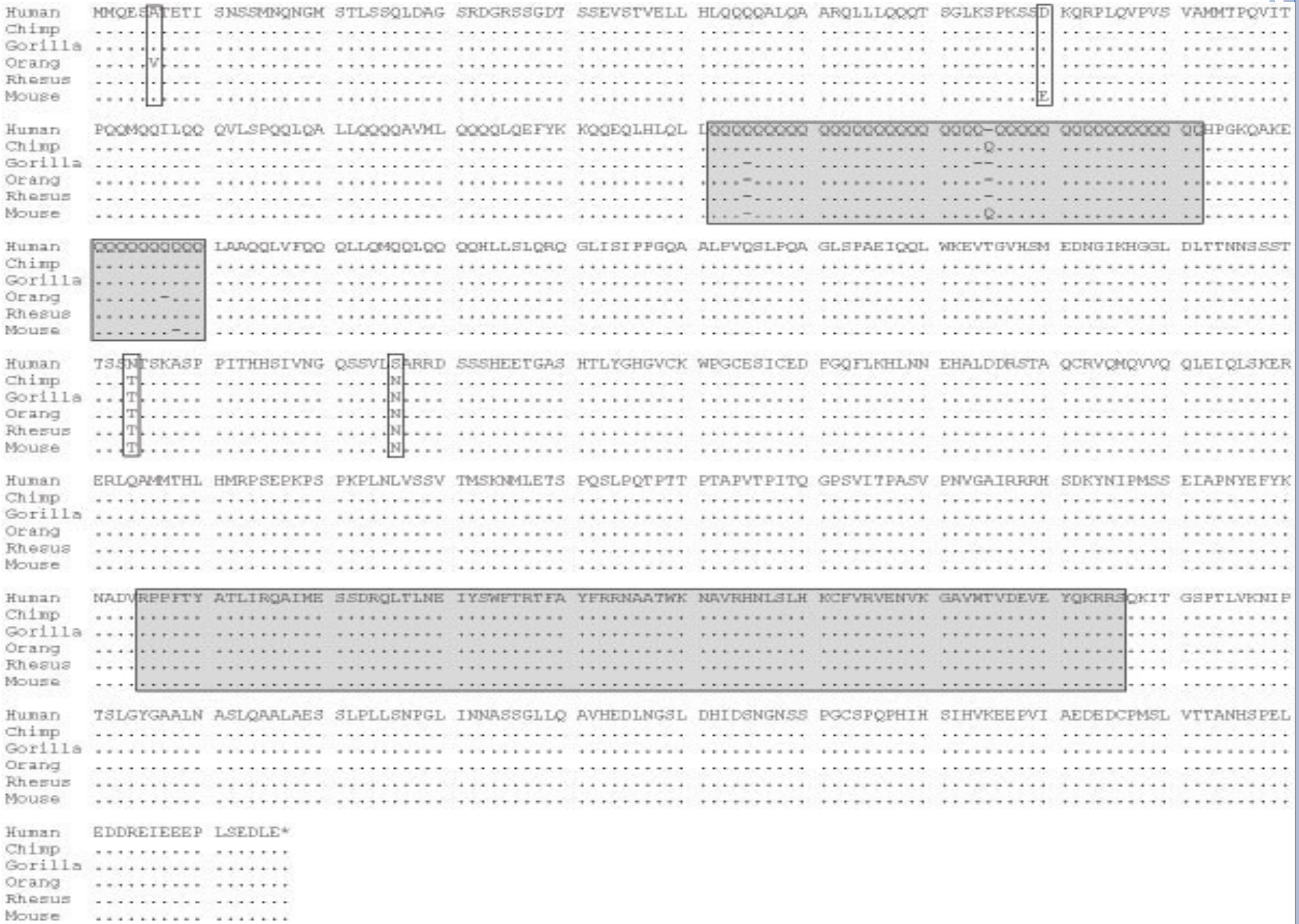


Data la capacità di legare il DNA, le proteine Fox si comportano da fattori di trascrizione e risultano essere direttamente coinvolte nella regolazione dell'espressione di geni target correlati per esempio allo sviluppo embrionale e al controllo metabolico.

Nello specifico il dominio di binding al DNA di Foxp2 è mutato negli individui affetti da deficit nella comunicazione orale.

Il gene Foxp2 è localizzato nel braccio lungo del cromosoma 7 (7q31).

Allineamento di sequenze aminoacidiche di Foxp2



Non solo gli uomini, ma anche gli scimpanzè, altri primati e perfino i topi dispongono del gene Foxp2.

Qual è allora il particolare che ci differenzia dalle altre specie e ci permette di parlare?

Il gene del linguaggio (Svante Paabo et al.) ha subito una mutazione che si è fissata nella nostra specie circa 120-200 mila anni fa.

Grazie alle proteine prodotte in più dalla nuova sequenza genica, bocca e laringe si sono perfezionate tanto da permettere l´articolazione di suoni complessi.

Dal confronto tra i geni Foxp2 dello scimpanzè, del gorilla, dell´orango, del macaco rhesus e del topo, tenuto conto delle varie differenze, è stata dedotta l´evoluzione genetica delle specie.

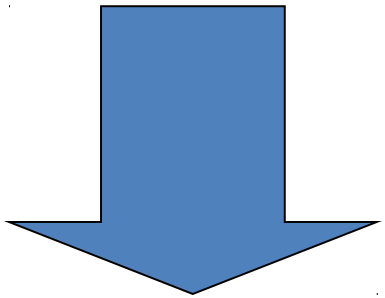
Subito dietro all´uomo nella scala evoluzionistica, ci sono scimpanzè (capaci secondo molti scienziati di comunicare a gesti), gorilla e macaco. Più distaccati orango e topi.

Nessuna variazione genetica è invece apparsa fra uomini di diversa origine etnica.

Le persone con una sola copia di questo gene funzionante hanno problemi non solo nell´articolare il linguaggio, ma anche nel comprenderlo, nel seguire le regole grammaticali e nel muovere i muscoli del viso.

Per studiare se i 2 cambiamenti aminoacidici codificati dall'esone 7 sono polimorfici negli umani, è stato sequenziato questo esone in 44 cromosomi umani presi da distinte popolazioni di tutto il mondo

In nessuno di questi casi si osservò la presenza di polimorfismi e/o sostituzioni aminoacidiche ☾ nessuna variazione genetica apparsa fra uomini di diversa origine etnica



FISSAZIONE

(120.000-200.000 ANNI FA)

La miosina

Stedman et al. (2004) the loss of the sarcomeric **MYOSIN gene MYH16** in the human lineage lead to smaller masticatory muscles. They estimated that mutation that lead to the inactivation **(a two base pair deletion)** occurred **2.4 MYA** right before Homo ergaster/erectus showed up in Africa.

This period that followed was marked by **a strong increase in cranial capacity**.

The authors put up the hypothesis that the loss of that gene removed an evolutionary constrain on brain size in the genus homo.

Pattern di gracializzazione dell'apparato masticatorio associato ad un simultaneo processo di encefalizzazione accelerata

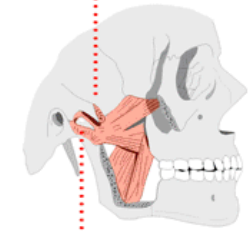
Mutazione porta a riduzione della taglia delle fibre muscolari e degli interi muscoli masticatori.

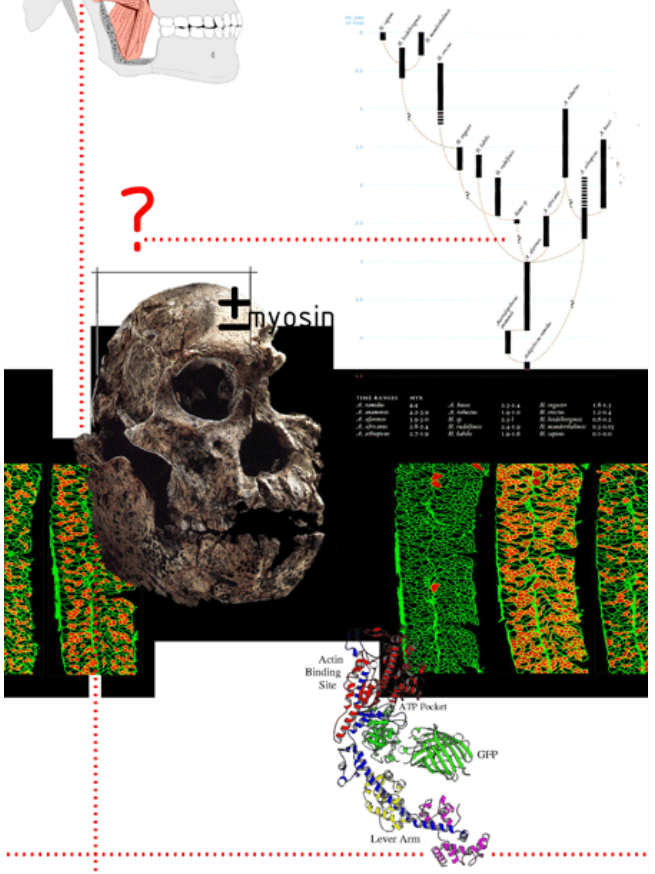
MYH16 evoluzione sotto pressione di selezione negativa in tutte le linee ancestrali eccetto che in quella che ha portato direttamente a *H. sapiens*

NEWS

However Perry et al. (2005) estimated that the MYH16 gene has been lost 5.3 MYA, long before the genus homo appeared. They also find conflicting estimates of nonsynonymous fixation rates across different regions of this gene, revealing a complex pattern inconsistent with a simple model of pseudogene evolution for human MYH16.

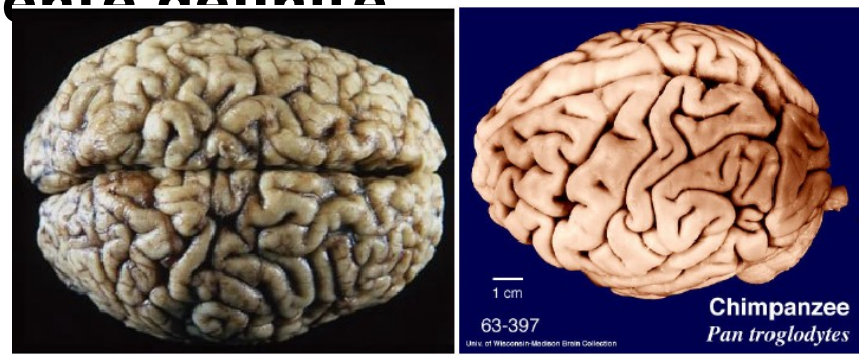
Figure 1 News of chews — the jaw muscles of apes, such as this mountain gorilla, and humans could reflect a profound evolutionary divergence.





Pattern di crescita dello scheletro craniofacciale può essere radicalmente alterato cambiando l'anatomia dei muscoli. La riduzione della taglia dei muscoli masticatori e della forza di contrazione come risultato della mutazione MYH16 negli antenati potrebbe aver avuto un considerevole impatto sulla morfologia del cranio. Questi effetti potrebbero aver incluso una riduzione di stress attorno alle ossa della scatola cranica, permettendo loro di diventare più larghe.

Il cervello delle grandi antropomorfe è suddiviso in due emisferi e quattro lobi, come quello umani, ma presenta una superficie neocorticale minore ("più liscia") e un numero più limitato di aree funzionalmente definite



Le zone deputate al linguaggio sono in *H. sapiens* l'**AREA DI BROCA**, che presiede alla **COMBINAZIONE DEI FONEMI IN PAROLE** e **l'AREA DI WERNICKE**, che presiede **ALL'IDENTIFICAZIONE E SELEZIONE DEI SUONI VERBALI.**

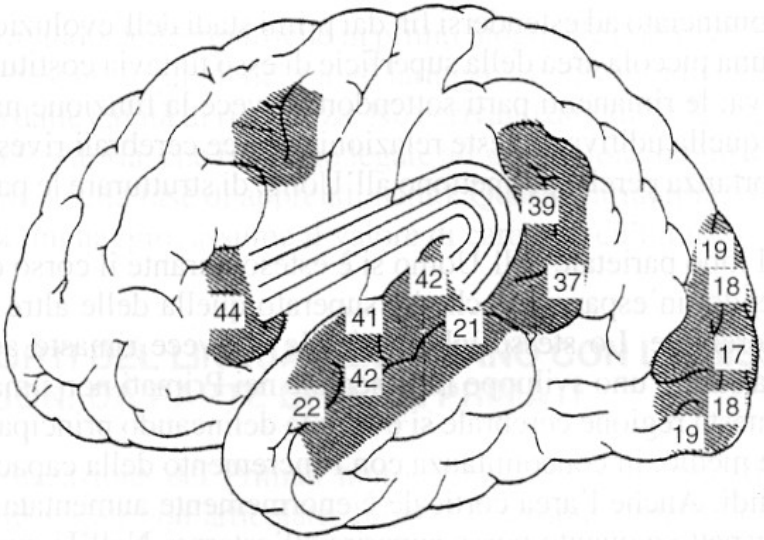


Fig. V.4. Le aree del linguaggio nell'Uomo. L'area di Broca (*area 44*) nella corteccia frontale è connessa con l'area di Wernicke (*area 42*) nella corteccia temporale da un fascio interlobulare: il fascicolo arcuato. È rappresentata anche l'area della circonvoluzione angolare (*area 39*) che funge da stazione intermedia fra aree occipitali visive (*aree 17, 18 e 19*) e aree uditive (*aree 41, 42, 21 e 22*).

lobi frontale e temporo-parietale

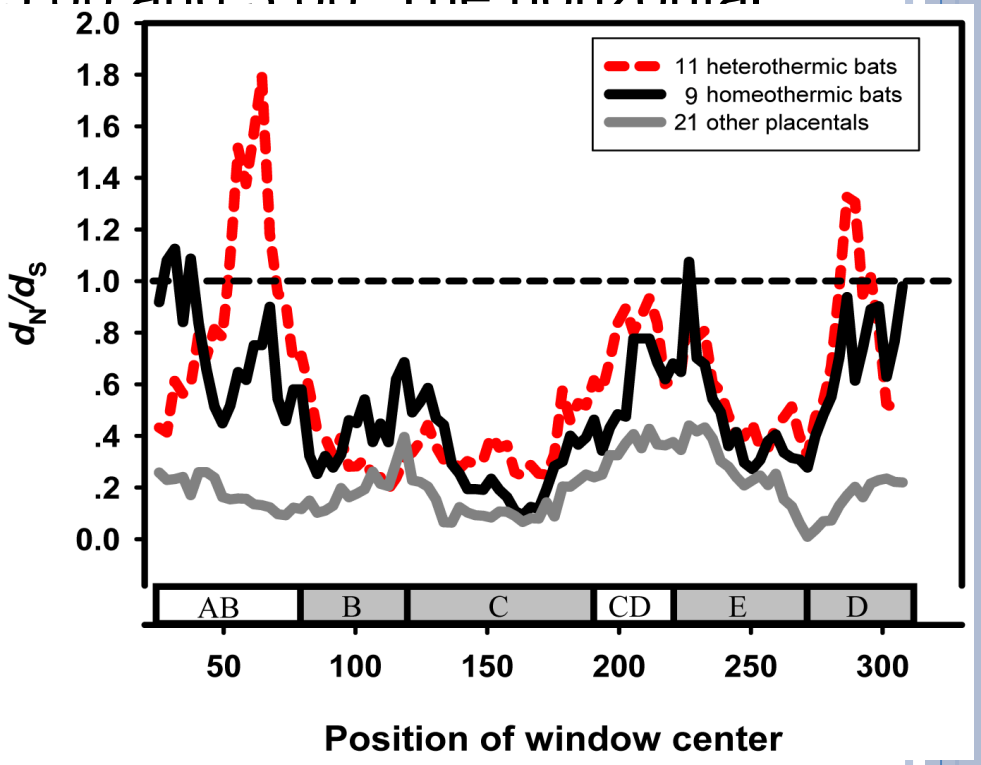
Queste aree **rappresentano strutture interamente nuove del cervello umano.** Sono fra le ultime a mielinare, molti mesi dopo la nascita, questo **non significa che siano esclusive dell'Uomo**, ma che solo di recente e solo nell'uomo hanno assunto una precisa specializzazione funzionale, evidenziata anatomicamente dalla dimensione dei solchi che le delimitano.

Adaptive evolution of Leptin in heterothermic bats.

Heterothermy (hibernation and daily torpor) is a key strategy that animals use to survive in harsh conditions and is widely employed by bats, which are found in diverse habitats and climates. Bats comprise more than 20% of all mammals and although heterothermy occurs in divergent lineages of bats, suggesting it might be an ancestral condition, its evolutionary history is complicated by complex phylogeographic patterns. Here, we use Leptin, which regulates lipid metabolism and is crucial for thermogenesis of hibernators, as molecular marker and combine physiological, molecular and biochemical analyses to explore the possible evolutionary history of heterothermy in bat


Monotremata* Δ (H; Geiser and Körtner 2010)
Paucituberculata (T; ?)
Didelphimorphia* (H/T; Geiser 1998)
Dasyuromorphia (T; Geiser and Körtner 2010)
Diprotodontia (H/T; Geiser and Körtner 2010)
Peramelemorphia
Notoryctemorphia (T; Withers et al. 2000)
Macroscelidea (T; Geiser 1998)
Eulipotyphla (H/T; Geiser 1998)
Cetartiodactyla*
Perissodactyla*
Carnivora* (T;Geiser 1998)
Pteropodidae* Δ (T; Geiser and Stawski 2011)
Rhinolophidae* (H/T; Lyman 1970, Geiser and Stawski 2011)
Hipposideridae* (H/T; Lyman 1970, Geiser and Stawski 2011)
Rhinopomatidae* (T; Geiser and Stawski 2011)
Megadermatidae (T; Geiser and Stawski 2011)
Craseonycteridae
Emballonuridae* (H/T; Lyman 1970, Geiser and Stawski 2011)
Nycteridae
Natalidae (T; Geiser and Stawski 2011)
Miniopteridae* (H; Lyman 1970)
Vespertilionidae* (H/T; Geiser and Körtner 2010)
Molossidae* (H/T; Lyman 1970, Geiser and Stawski 2011)
Myzopodidae
Mystacinidae (H; Lyman 1970, Geiser and Stawski 2011)
Phyllostomidae* (T; Geiser and Stawski 2011)
Mormoopidae* (T; ?)
Thyropteridae
Noctilionidae (T; ?)
Furipteridae
Scandentia
Primates* (H/T; Geiser 1998)
Dermoptera
Rodentia* (H/T; Geiser 1998, Geiser and Körtner 2010)
Lagomorpha
Homeothermy
Hibernation
Torpor
Hibernation and Torpor

- Sliding window analysis of Nei-Gojobori estimates.dN/dS of 21 other placentals, 14 heterothermic bats and 6 hoemothermic bats. In each case is compared to a gene schematic showing the loop (white) and helix (gray) domains, with the window size and step size were fixed at 45 bp and 3 bp. The horizontal broken line identifies ω = 1.



http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0027189