Gene & Genome Evolution

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Molecular Biology Reading Group

Introduction

- Natural selection works by applying selective pressure to individuals with different genotype/phenotype
  - But how did genome differences arise in the first place?
- Outline:
  - Generating genome variation
  - Reconstructing phylogeny
  - Human genome

Somatic vs. Germ Cells

- For sexually-reproducing organisms:
  - Germ cell: specialized reproductive cells
  - Somatic cells
- Mutations in the germ line will be passed on
- Mutations in somatic cells only affect individual

Main Mechanisms for Genetic Change (1)

- Mutation within a gene:
  - Substitution or Insert/Deletion of nucleotide(s)
  - Result of mistake in DNA replication or repair
- Gene duplication
  - Whole gene duplicated, then each undergo different genetic change
  - Common in Eukaryotes
- Gene deletion
  - Result from chromosome breakage or repair failure

Main Mechanisms for Genetic Change (1)

- Exon shuffling
  - Hybrid gene formed by combination of different genes
  - Joins occurs at intron, so exons stay intact
- Horizontal (intercellular) transfer
  - Transfer of gene not to progeny, but another existing individual
  - Common in Prokaryotes

Mutation rate (point mutation)

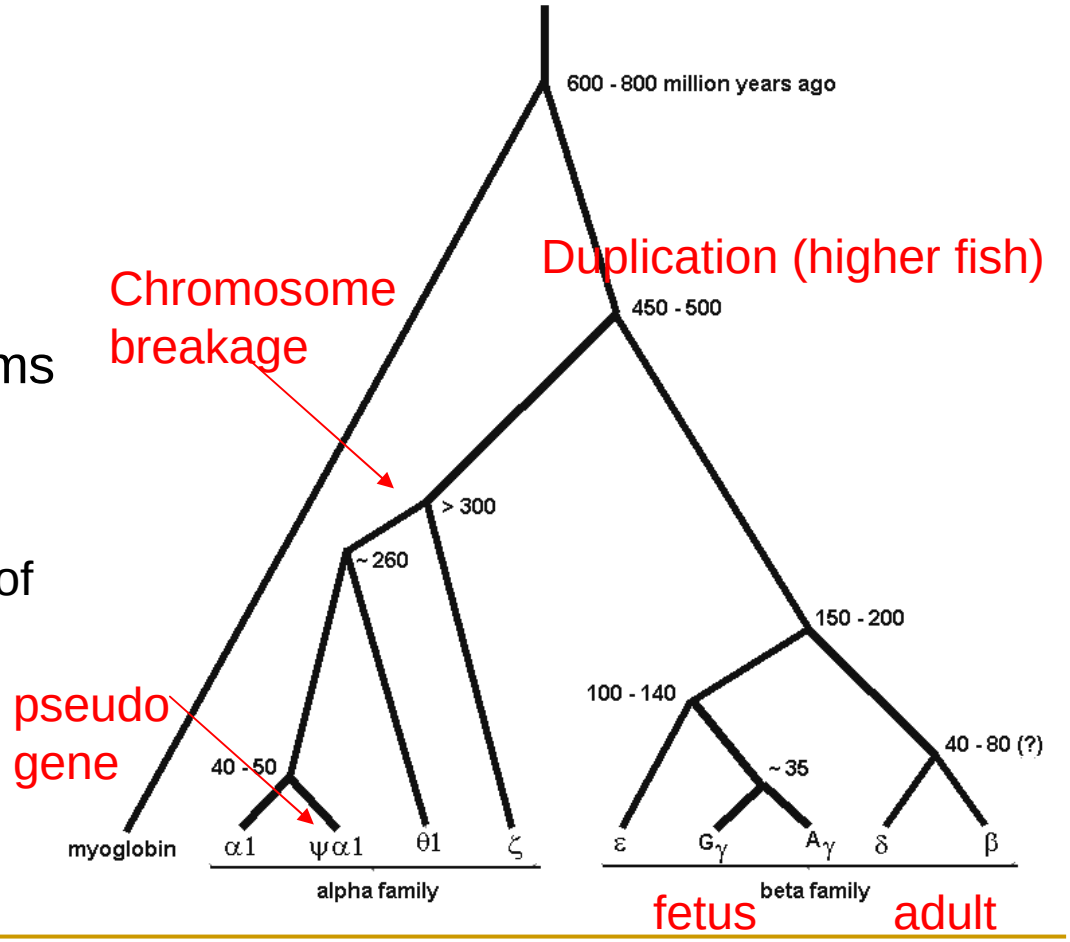
- Eukaryotes:
  - 10^-9 per base, per year
  - 10^-6 ~ 10^-5 per gene, per year
- HIV, Influenza A Virus:
  - 10^-3 ~ 10^-2 per base, per year
  - Mutation occurs every round of replication
- Mutation is the only way new genetic material arise, but are often selectively neutral
  - Genetic drift can be used as evolutionary clock for reconstructing history

Gene Duplication

- One gene can create a family of genes
  - Bacillus subtilis: >50% genes are in families
  - Almost all genes in vertebrates have multiple versions
    - Hypothesis: entire genome duplicated twice early on
- Examples:
  - Different opsins (proteins that detect light at different wavelength) are expressed in different retinal cells
  - Hemoglobin
- After duplication, different copies are free to mutate (without affecting core functionality, probably)

Globin family

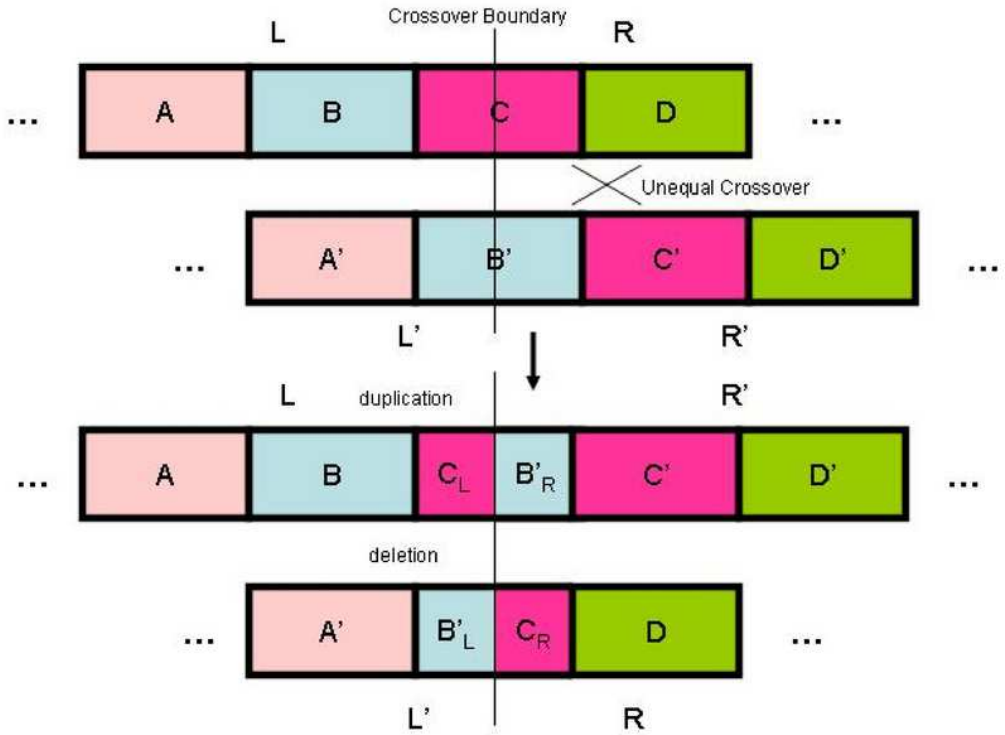
- Most primitive oxygen-carrying molecule in animals:
  - Polypeptide of 150 amino acids
  - Found in marine worms insects, primitive fish
- Higher vertebrates:
  - hemoglobin composed of alpha & beta chains
  - more efficient
  - carries 4 oxygen



http://nitro.biosci.arizona.edu/courses/EEB600A-2003/lectures/lecture25/figs/Globin.gif

What creates gene duplication?

1. Unequal crossover:



2. Whole genome duplication: e.g. in Xenopus frogs
3. Transposons

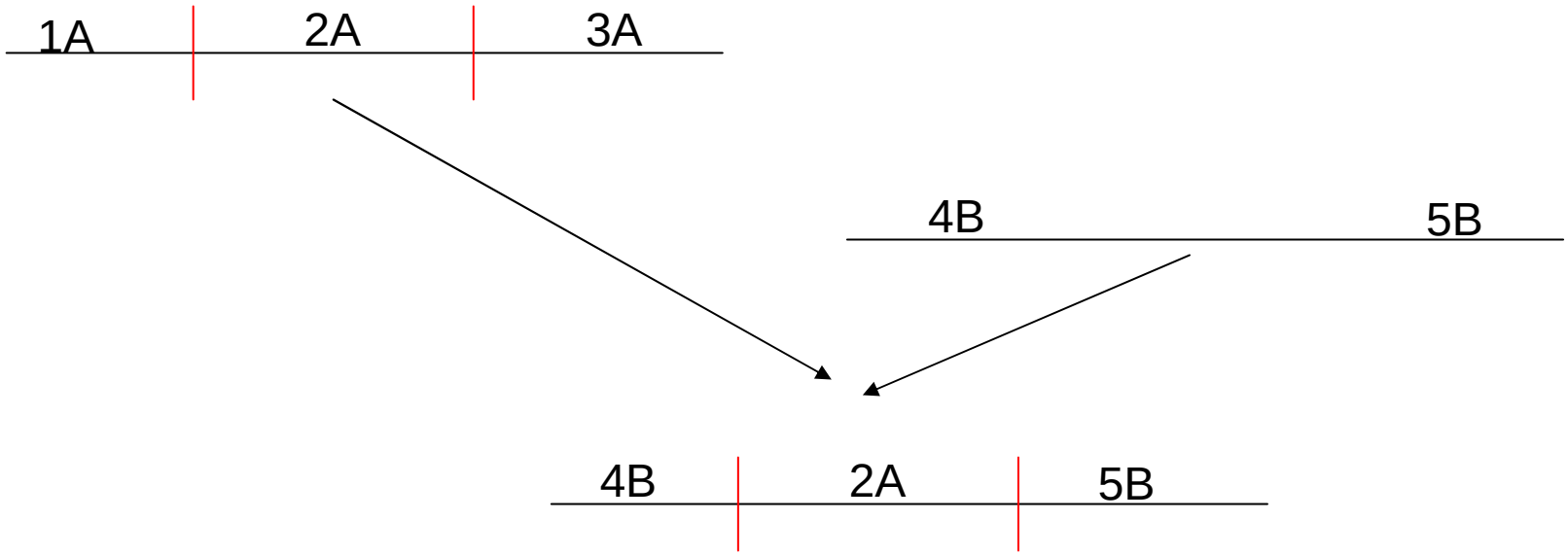
- http://hc.ims.u-tokyo.ac.jp/JSBi/journal/GIW02/GIW02F010/GIW02F010_fig0002l.png

Exon shuffling

- Duplication (unequal crossover) can also happen at intra-gene level:
  - exons are usually short, introns are long, making this process robust
- ~30k genes in human probably arose from combination of a few thousand exons

Genome evolution has been accelerated by transposable elements

- Transposons can carry exons from Gene A to Gene B



Horizontal gene transfer

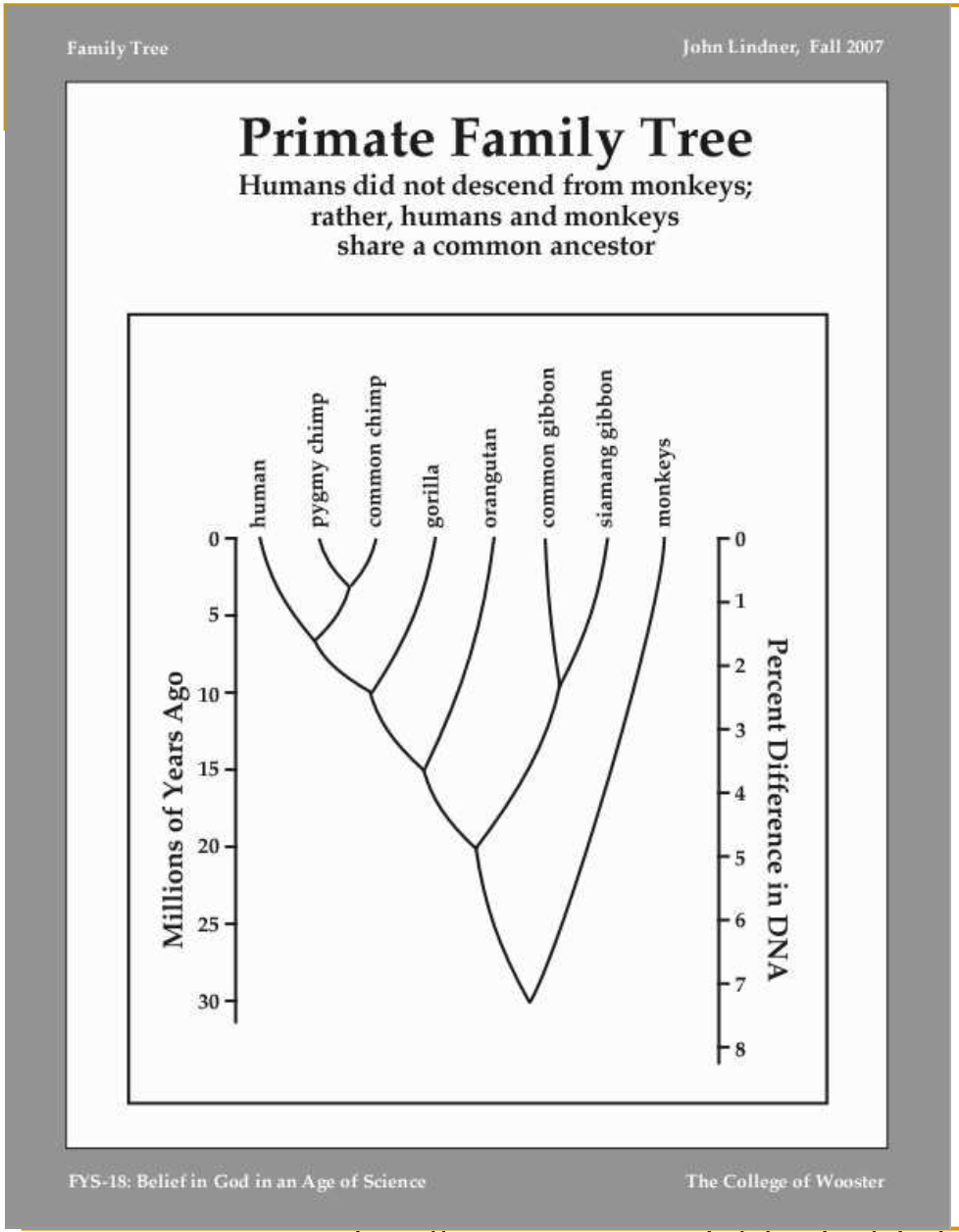
- E Coli:
  - 18% of genome is acquired from another species
- Common way in which bacteria gain antibiotic resistance
- Primordial cells may have been genetically promiscuous
  - Eukaryotes seem more similar to Archae in genes for replication, transcription, translation, but more similar to Eubacteria in genes for metabolic processes

Reconstructing Life's Family Tree

- Homologous genes:
  - Genes that are similar in nucleotide sequence due to common ancestry
  - 50% of human genes are homologous to C elegans or Drosophilia
- Highly conserved genes:
  - E.g. ribosomal RNA → useful for studying distant relationships
  - On the other hand, neutral mutations are useful for studying close organisms.

Amount of gene divergence due to mutation can estimate time of speciation

- Assume:
  - 1 of 10^10 nucleotide mutates in each cell cycle
  - 5% of human genome code for protein and gene regulation; 95% selectively neutral (30k genes)
  - 200 cell division per germ line (from conception to production of egg/sperm)
  - Total DNA in a cell: 6 billion nucleotides
- Then:
  - By mutation, 100 new differences between child and parent.
  - Between two families, the difference is 200 per generation
  - After 150 generations (early civilization): 30k nucleotide differences
  - After 5-10 million years: 1% genome difference (human vs. chimpanzee)



- Both chromosome organization and DNA sequence are similar for human vs. chimpanzee
- 99%+ of the million copies of transposable elements (Alu) are similarly located
- Human chromosome 2 is fusion of 2 chromosomes in chimpanzee, gorilla, orangutan

http://www.wooster.edu/physics/Lindner/FYS2007/FamilyTree.jpg

Human vs. Mouse

- Diverged 75 million years ago
- Same number of genes, but transposon distribution differs
- Centromeres in humans lie at chromosome center; in mouse, at the ends
- 90% of gene can be partitioned and compared directly

Human vs Fish

- Diverged 400 million years ago
- Different size genomes, amount of gene duplication differs
- Most sequence differ (except very high conserved ones)

- Focus on a highly conserved ribosomal RNA gene, which are present in all living species

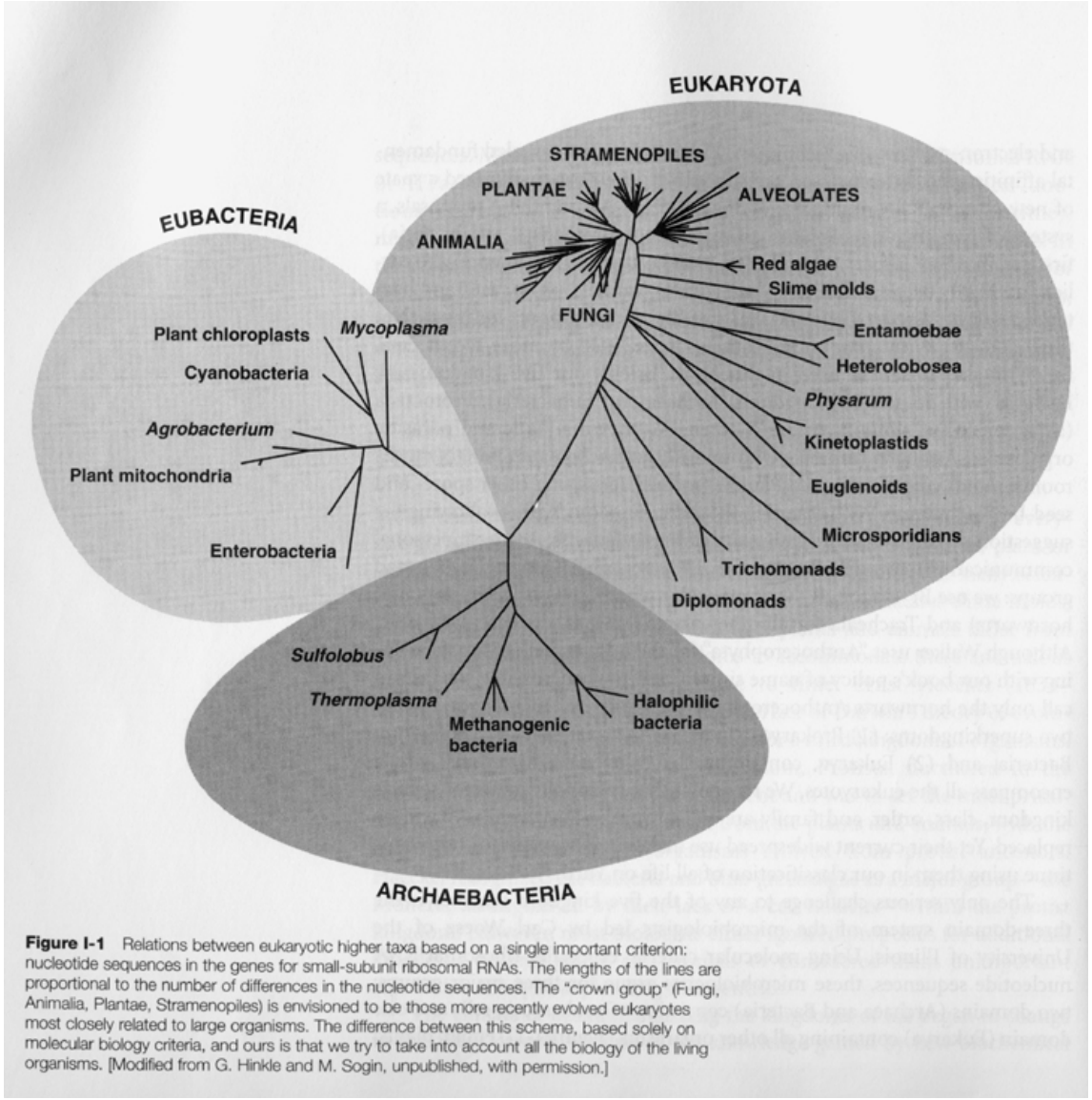


Figure I-1 Relations between eukaryotic higher taxa based on a single important criterion: nucleotide sequences in the genes for small-subunit ribosomal RNAs. The lengths of the lines are proportional to the number of differences in the nucleotide sequences. The "crown group" (Fungi, Animalia, Plantae, Stramenopiles) is envisioned to be those more recently evolved eukaryotes most closely related to large organisms. The difference between this scheme, based solely on molecular biology criteria, and ours is that we try to take into account all the biology of the living organisms. [Modified from G. Hinkle and M. Sogin, unpublished, with permission.]

- http://www.geocities.com/therapeuter2002/treeoflife1.jpg

Human Genome

- 3.2 x 10^9 nucleotide pairs
  - on 22 autosomes & 2 sex chromosomes
  - Suppose each nucleotide is 1mm, then whole genome is 3200km (on average a gene every 300m, for 30m long, but only 1 meter of actual code)
- Individual humans differ by 1 in 1000 nucleotide
  - Human Genome Project includes a variety of individuals
- Characteristics:
  - Little (2%) protein-coding genes
  - Large average gene size of 27k nucleotides (long introns). Only ~1300 nucleotides needed to code average protein
  - Regulatory genes are spread all over

Human genome

"It may resemble your garage/bedroom/fridge/life: highly individualistic, but unkempt; little evidence of organization; much accumulated clutter; and the few patently valuable items indiscriminately, apparently carelessly, scattered throughout."

Single-nucleotide polymorphism (SNP)

- 3 million+ SNP located so far
- 90%+ of all genes contain at least one SNP
- May be linked to specific traits/diseases → active area of medical research
- Variation most likely present at the beginning of human ancestry

CA repeats

- CA are replicated poorly due to slippage during replication
- Individuals may vary by the number of CA repeats
- Used in forensics, paternity identification

Some research frontiers

- Identifying genes in the sea of “junk DNA”
  - E.g. Using comparative genomics
- Understanding regulatory networks
  - Difference between humans and chimps are amplified by the “developmental program”, not just genetic sequence differences
  - Alternative splicing
    - Allows one gene to produce many different proteins
    - 60% human genes undergo this