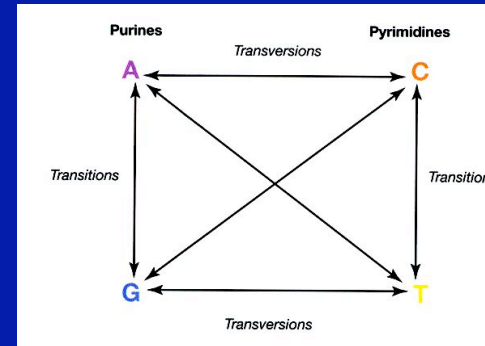


Kinds of mutations

1. Point mutations (change in a single DNA base)
2. Chromosomal mutations
 - Insertions & deletions
 - Inversions
 - Gene duplications
 - Polyploidizations

Mutations at single DNA bases



Transitions are more frequent than transversions

Synonymous ("silent") mutations:

Changes in the 3rd base of a codon that do not change the amino acid of the protein made by that gene (because of redundancy in the genetic code)

Non-synonymous (replacement) mutations:

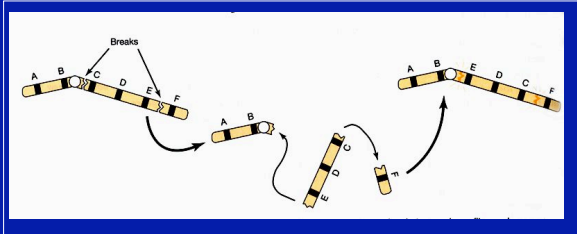
Changes in a DNA sequence that do change an amino acid

Chromosome (karyotype) mutations

- Karyotype: The chromosomal arrangement of an individual (or species)
- Changes in the karyotype
 - Deletions and insertions
 - Inversions
 - Gene duplications
 - Polyploidization

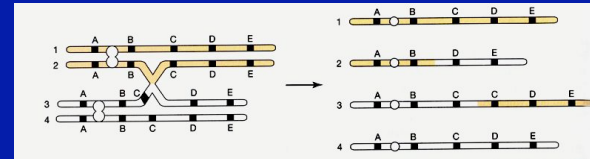
Inversion:

A reversal of the orientation of a part of a chromosome

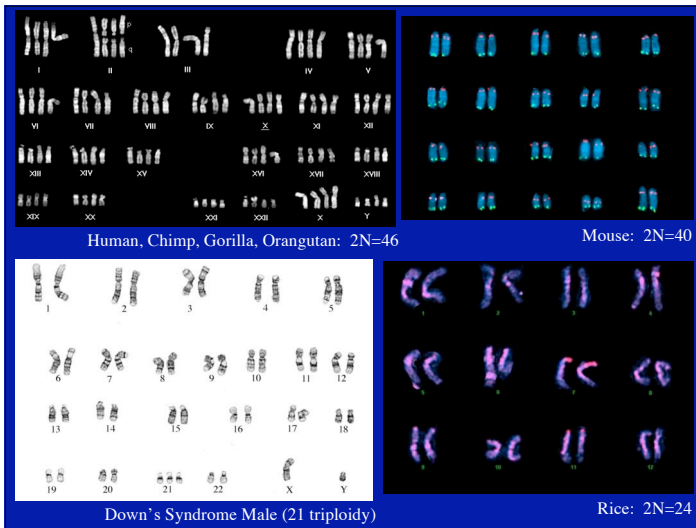


Duplication:

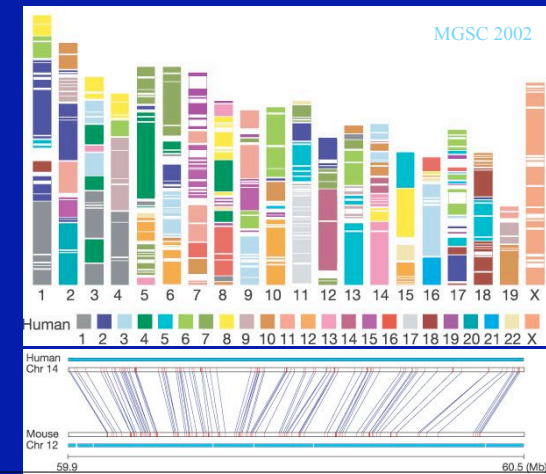
A doubling of a part of a chromosome, of an entire chromosome, or even the whole genome

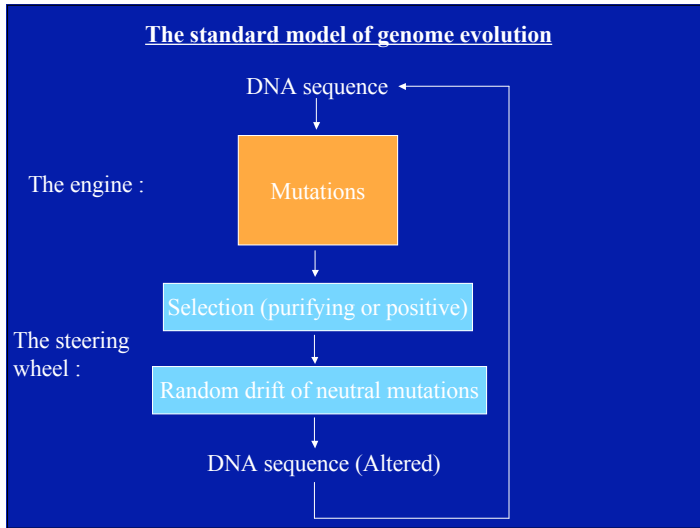


Tandem duplication resulting from unequal crossing-over during meiosis



Synteny between human and mouse





What is the origin of novelty, and diversity?

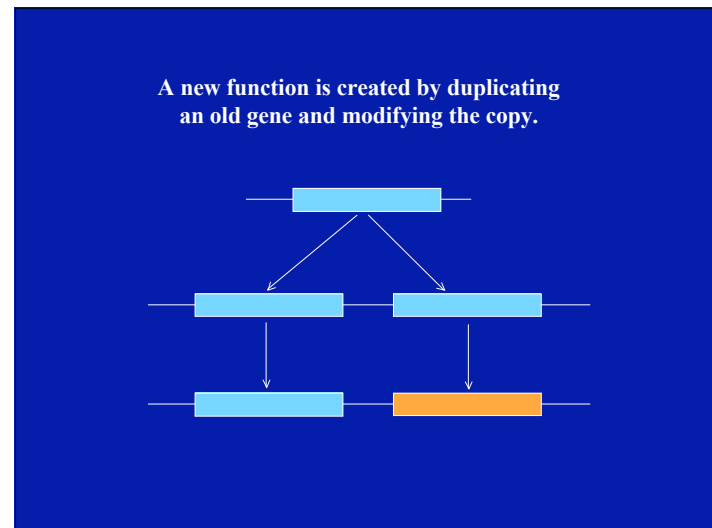
Or, how do you acquire new function while maintaining the old?

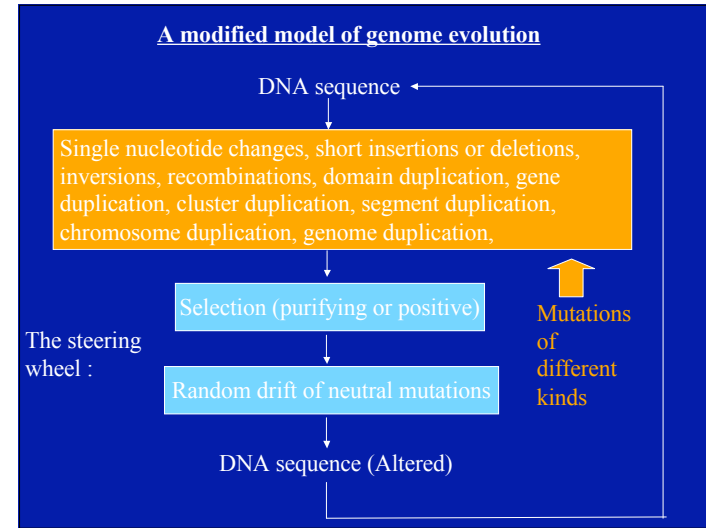
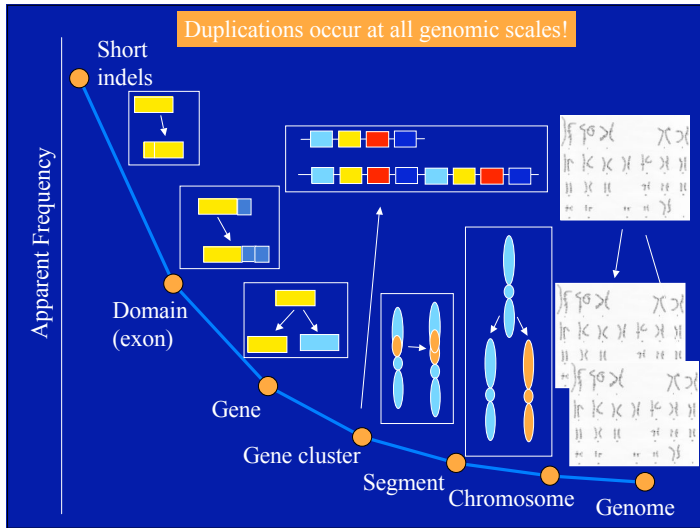
Carroll S.B. et al. From DNA to Diversity (2001) Blackwell Science

Evolution by Gene Duplication
Susumu Ohno, 1970

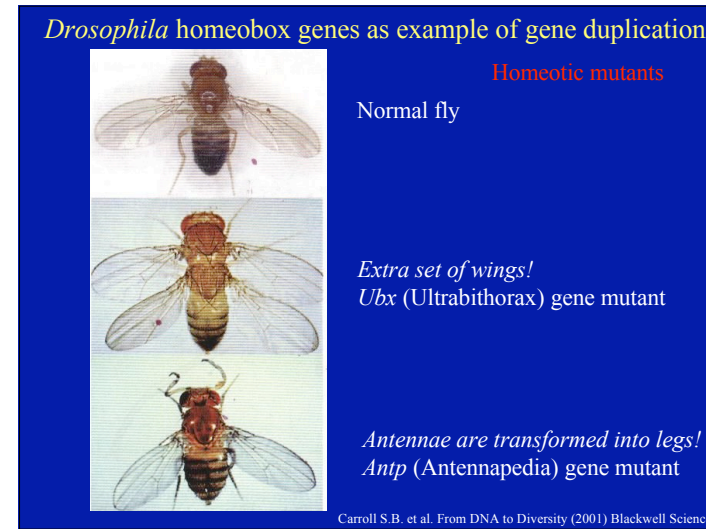
Susumu Ohno

“natural selection merely modified, while redundancy created”

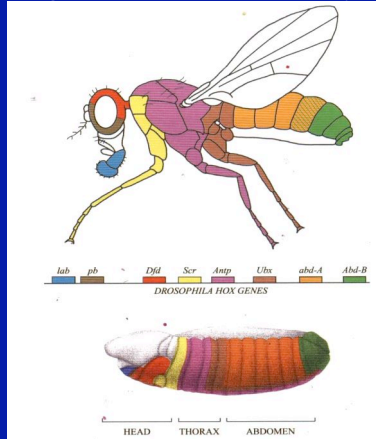




GATCTACCATGAAAAGACTTGTGAATCCAGGAAGAGAGACTGACTGGCAACATGTTA
 GTACAAAAAGATTGGACTGTAACCTAAAAATGATCAAATATGTTTCCCATGCATCA
 CAATGGGAAAGCTCTCTGGAGAGTGAGAGAAGCTTCCAGTTAAGGTGACATTGAAGC
 CCTGAAAGATGAGGAAGAGTTGTATGAGAGTGGGGAGGAAGGGGAGGTGGAGGG
 GGAATGGGCCGGGATGGGATAGCGCAAACCTGCCGGGAAGGGAAACCAGCACTGTAC
 CTGAACAACGAAGATGGCATAATTTGTTTACAGGGAATGGTGAATTAAGTGTGGCAGGA
 TTGTAGACACAGTAATTTGCTTGTATGGAATTTGCCTGAGAGACCTCATTCAGTTTC
 TTTTGTATGCTTTCATCCATCACTGTCCTGTCAAATAGTTTGAACAGGTATAATGAT
 ATAACCCAAAGCATAATATTTCGTTAATTCACAGAATCACATATAGGTGCCACAGT
 CCATTTTATGAATGGAGT**Evolution by Genome Duplication**GATGAAAACCTTAG
 ATGAATGATTGGCGCAGGCTCACCTGGATATTAAGACTGAGTCAAATGTTGGGCTGG
 ACTTAAATGTTTGCCTTGTTCATGAGCACCACATAATGCCTCTCCTATGCAGTTAAGCA
 GGTGACAGAAAAGCCCATGTTTGTCTACTCACACACTTCCGACTGAATGTAATGATG
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 CCTAGTAGCTGAGACTACATGCCTGCACCACCACATCTGGCTAGTTTCTTTTATTTT
 GATGGGGTCTTGTGTGTGGCCAGGCTGGCCACAAATCCTGGTCTCAAGTGATCCTC
 CTCAGCCTCGAAAGTGTGGGATTACAGATGTGAGCCACCACATCTGGCCAGTTTCA
 ATTAATGGTTCATTGTGAAGGATACATCTCAGAAACAGTCAATGAAAAGAGACGTGCA
 GATGCACTGGCTGATGCGCTTAAATGCAAGCACTTGGGACCCCAAGCTGGCAAGTGG



Eight homeobox (*Hox*) genes regulate the identity of regions within the adult and embryo.



Adult

Embryo

Carroll S.B. et al. From DNA to Diversity (2001) Blackwell Science

The *Hox* genes are paralogs with a highly conserved homeobox domain

Multiple alignment of the homeobox domain:

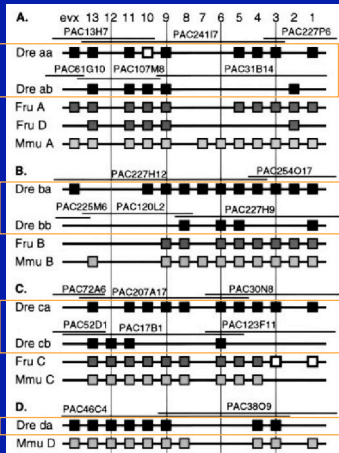
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lab      MNSGRITVFNHQTLELEKEFHFNRYLTRRRRIETAAFLQLNEDVQKIWFQNRMRKQKKRY
pb       PRRERTAVTNQLELEKEFHFNRYLRRRIETAAFLDLTERQKIWFQNRMRKQKKRQI
Dfd      PRRRTAVTRHOLELEKEFHFNRYLRRRIETAAFLDLTERQKIWFQNRMRKQKKEN
Scr      PRRRTAVTRVQLELEKEFHFNRYLRRRIETAAHALCLTERQKIWFQNRMRKQKKEN
Antp     RRRGRQTVTRVQLELEKEFHFNRYLRRRIETAAHALCLTERQKIWFQNRMRKQKKEN
Ubx      RRRGRQTVTRVQLELEKEFHFNRYLRRRIETAAHALCLTERQKIWFQNRMRKQKKEL
abd-A    RRRGRQTVTRVQLELEKEFHFNRYLRRRIETAAHALCLTERQKIWFQNRMRKQKKEL
abd-B    VRRRRTVYKHEQLELEKEFHFNRYLRRRIETAAHALCLTERQKIWFQNRMRKQKKEN
consensus -RRGR-TYR-QTLELEKEFHFNRYLRRRIETAAHALCLTERQKIWFQNRMRK-KKE-
                Helix 1                Helix 2                Helix 3
    
```

The *Hox* genes are transcription regulators and the Homeobox domain is DNA-binding domain.

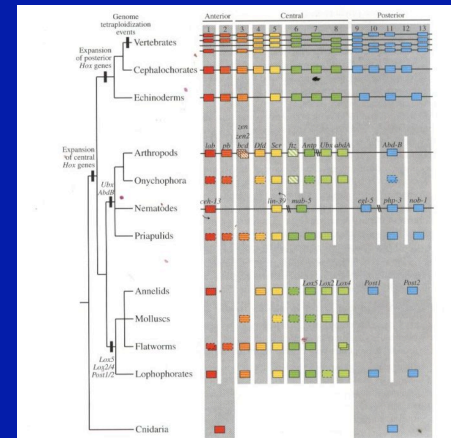
Carroll S.B. et al. From DNA to Diversity (2001) Blackwell Science

At least 7 *Hox* clusters in zebrafish



Amores et al. (1998) Science 282 1711-1714

Evidence 2: Vertebrates have 4 copies of the *Hox* cluster

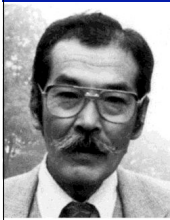


Carroll S.B. et al. From DNA to Diversity (2001) Blackwell Science

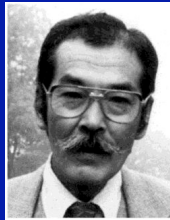
Susumu Ohno and the 2R hypothesis

"It is our contention that the ancestors of reptiles, birds, and mammals have experienced at least one tetraploid evolution either at the stage of fish or at the stage of amphibians" (1970)

"A mammalian ancestor might have gone through at least one round of tetraploid evolution at the stage of fish" (1973)



Susumu Ohno



Susumu Ohno

Distribution of chromosome number in fishes is bi-modal

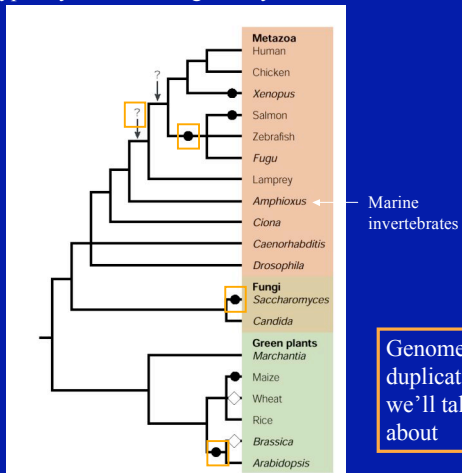
Species	Ploidy	Diploid chromosome number
Tetraodon barb <i>Barbus tetraodon</i>	Diploid	50
Fasciata barb <i>Barbus fasciatus</i>		
Pfütz <i>Rutilus rutilus</i>	50	50
Schleie <i>Tinca tinca</i>		
Döbel <i>Leuciscus cephalus</i>	50	50
Black shark <i>Labeo chrysophekadion</i>		
Barbe <i>Barbus barbus</i>	Tetraploid 100	100
Carp <i>Cyprinus carpio</i>		
Goldfish <i>Carassius auratus</i>	104	104

Evolution by gene duplication, Ohno (1970)

Polyploidy events during eukaryote evolution

One genome duplication at the origin of the vertebrates

Another genome duplication following divergence with lamprey

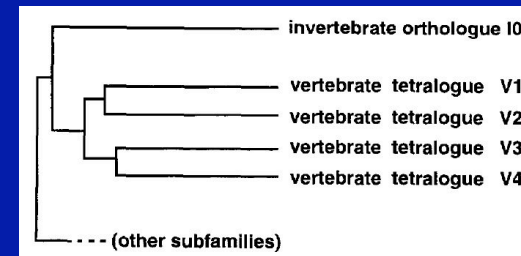


Genome duplications we'll talk about

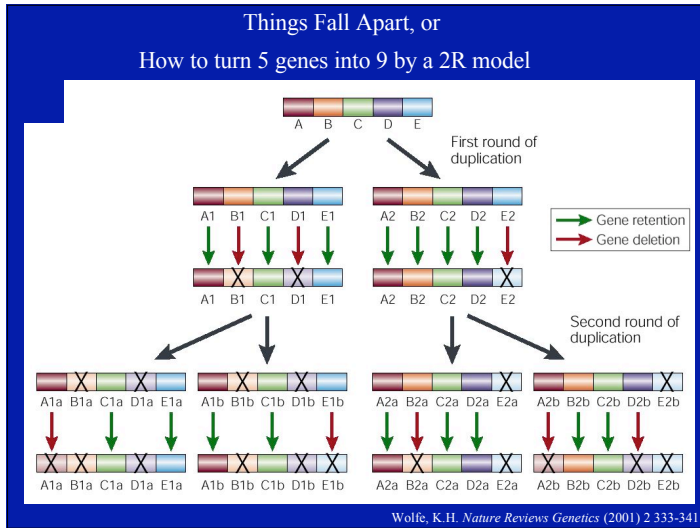
Wolfe, K.H. *Nature Reviews Genetics* (2001) 2 333-341

The "one-to-four" rule:

The human genome contains up to four paralogs of many *Drosophila* genes.



Spring J. *FEBS Letters* 400 (1997) 2-8



The 'one-to-four' rule does not hold up entirely unless we consider independent duplications and deletions

Species	Group	Gene number	Reference
<i>Drosophila melanogaster</i>	Arthropoda	13,500	Adams et al. 2000
<i>Caenorhabditis elegans</i>	Nematode	19,000	The <i>C. elegans</i> Sequencing Consortium 1998
<i>Ciona intestinalis</i>	Urochordata	15,500	Simmen et al. 1998
<i>Fugu rubripes</i>	Actinopterygii	"similar to mammals"	Elgar 1996
<i>Homo sapiens</i>	Mammalia	80,000	Antequera and Bird 1994
		35,000	Ewing and Green 2000; Roest Crolius et al. 2000; Lander et al. 2001; Venter et al. 2001

When the human genome was estimated at 80,000 genes the "one-to-four" hypothesis was reasonable but now that the estimate is at 35,000.

Makalowski W. *Genome Research* (2001) 667-670

The Voltage-gated Sodium (Na⁺) Channels

Single copy in non-chordate animals

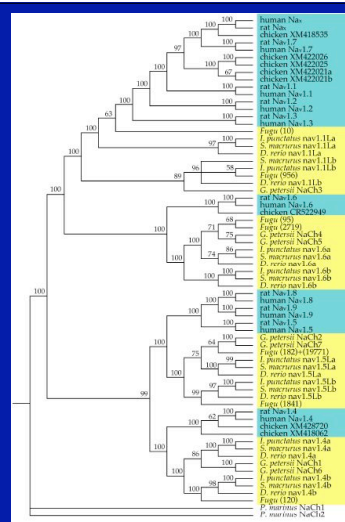
Family of paralogs in vertebrates; up to 11 genes in mammals

Great and highly specific functional diversity

Na _v 1.1	Na _v 1.2	Na _v 1.3	Na _v 1.7	Na _v 1.4	Na _v 1.5	Na _v 1.8	Na _v 1.9	Na _v 1.6
HC 2	HC 2	HC 2	HC 2	HC 17	HC 3	HC 3	HC 3	HC 12
CNS PNS	CNS	embry- onic CNS	PNS	skeletal muscle	heart & skeletal muscle	PNS	PNS	CNS PNS
TNa3 (1.1/2/3/ 7a)	TNa4 (1.1/2/3/ 7b)	TNa1 (1.4a)	TNa6 (1.4b)	TNa2 (1.5/8/9b)	TNa7 (1.5/8/9a)	TNa5 (1.6a)	TNa8 (1.6b)	
nervous system	nervous system	Adult skeletal muscle	Early and adult skeletal muscle; electric organ in <i>S.m.</i>	Early and adult heart	Early CNS, PNS, and skeletal muscle; adult heart	CNS and PNS	CNS and PNS	

Eight sodium channel genes in teleosts exist on different chromosomes, and appear to have arisen through chromosomal or whole-genome duplication

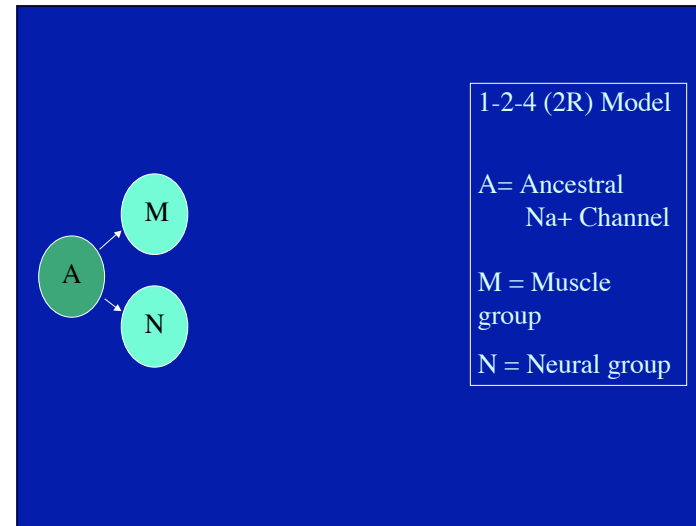
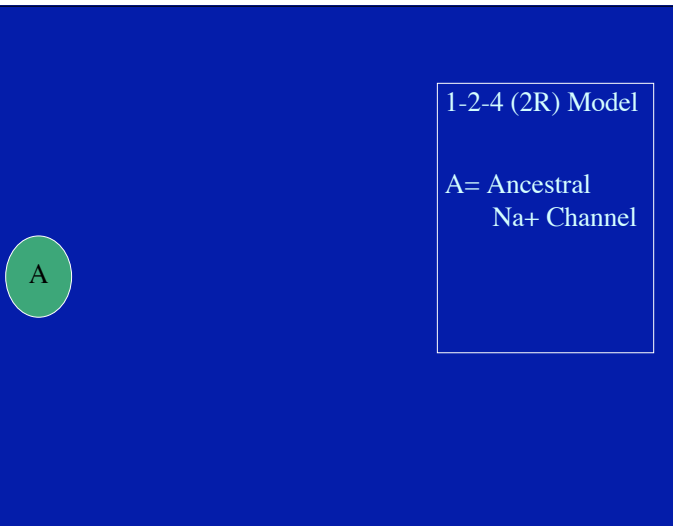
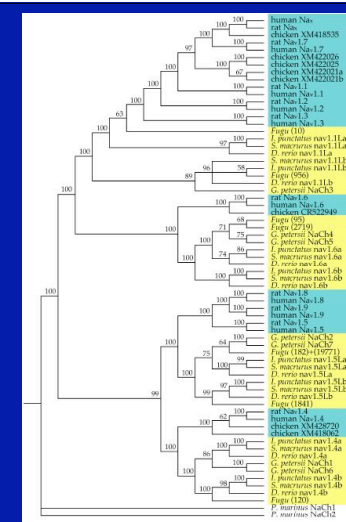
In contrast, ten sodium channel genes in mammals exist on only four chromosomes, and appear to have arisen through tandem duplications

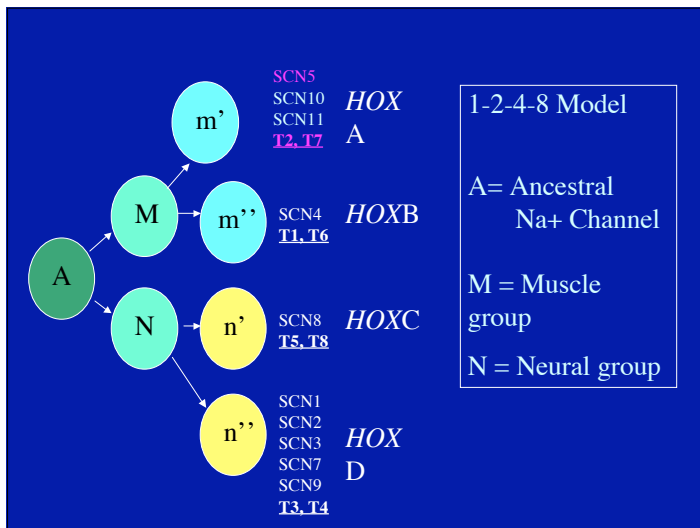
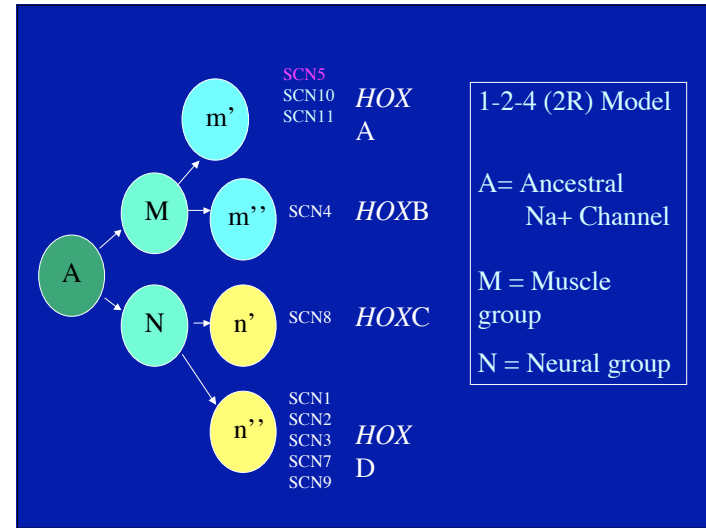
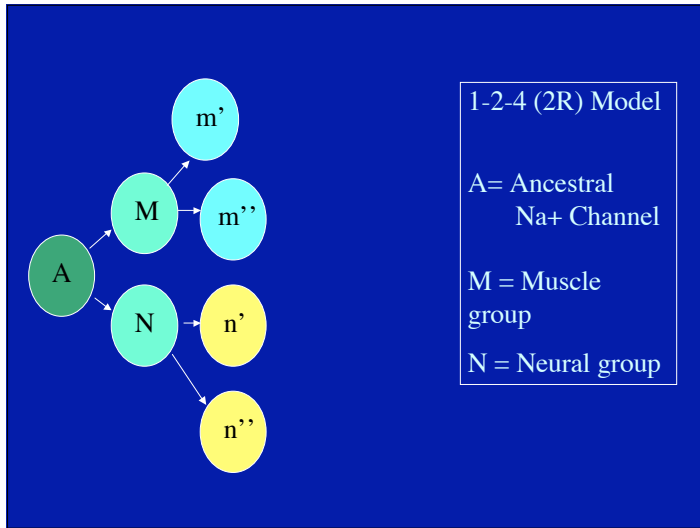


8 genes in fish
10 genes in mammals

How to make comparisons between genes? Have to understand difference between

Gene orthologs
Gene paralogs
(orthologous genes, vs. paralogous genes)



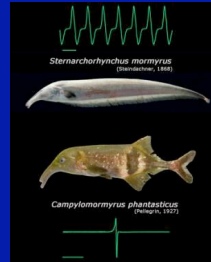


What does the phylogeny of Na⁺ channels tell us about gene orthology in vertebrates?

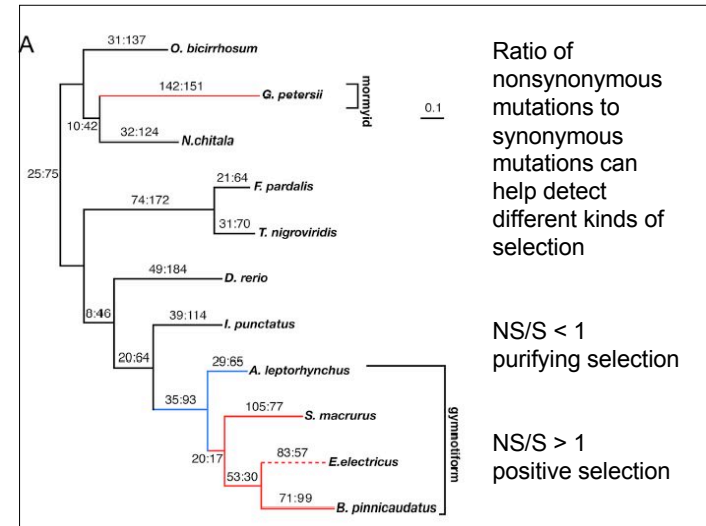
Mammalian	Teleost	Expression
SCN 5, SCN10, SCN11	T2 and T7	Heart [and PNS in mammals]
SCN4	T1 and T6	Skeletal Muscle, and EO in some fish
SCN8	T5 and T8	Brain/CNS
SCN1, SCN2, SCN3, SCN7, SCN9	T3 and T4	CNS/PNS [and heart in mammals]

Evolution of novel gene function:

Two evolutionarily independent lineages of weakly-electric fish co-opted the same sodium channel gene ortholog to “build” a novel structure: the electric organ.



Mammalian	Teleost	Expression
SCN4	T1 and T6	Skeletal Muscle, and EO in some fish



Purifying selection:

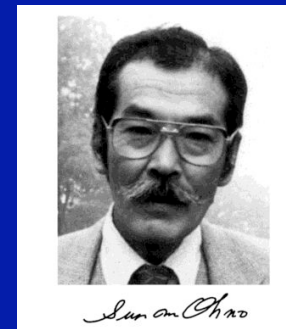
selection *for* an existing allele (DNA sequence), and *against* other mutations at the same locus. Nonsynonymous mutations selected against, but synonymous ones can accumulate

Positive selection:

selection that favors new mutations, to fixation -- especially when the rate of fixations of nonsynonymous mutations exceeds the rate of fixation of neutral (synonymous) mutations

Evolution by Gene Duplication

Susumu Ohno, 1970



“natural selection merely modified, while redundancy created”