Gene duplications

- Models of duplicate gene fate
- Two examples
  - Subfunctionalization
    - Abalone fertilization proteins
  - Neofunctionalization
    - Primate segmental duplication

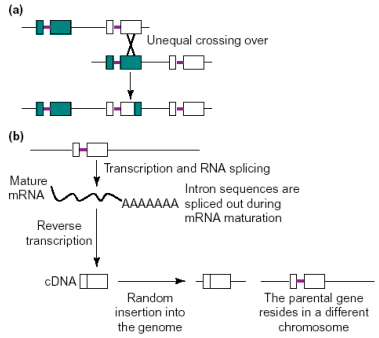
Gene duplication is common (old numbers)

	Total number of genes	Number of duplicate genes (% of duplicate genes)
Bacteria		
Mycoplasma pneumoniae	677	298 (44)
Helicobacter pylori	1590	266 (17)
Haemophilus influenzae	1709	284 (17)
Archaea		
Archaeoglobus fulgidus	2436	719 (30)
Eukarya		
Saccharomyces cerevisiae	6241	1858 (30)
Caenorhabditis elegans	18 424	8971 (49)
Drosophila melanogaster	13 601	5536 (41)
Arabidopsis thaliana	25 498	16 574 (65)
Homo sapiens	40 580[b]	15 343 (38)

How do gene duplications occur

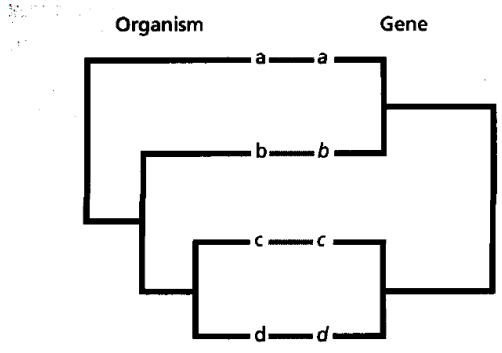
- Unequal crossing over
- Retrotransposition
- Segmental duplications

Two types of gene duplication:

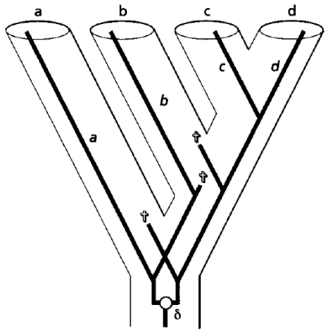


How would you tell difference?

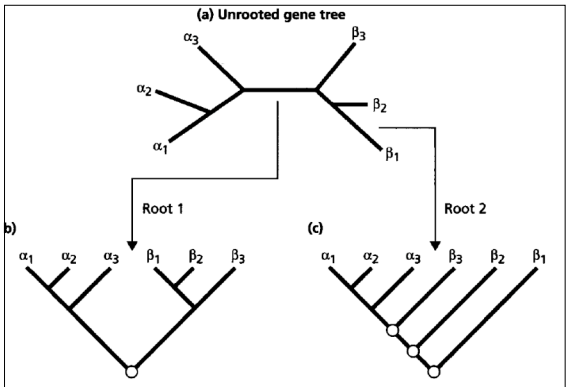
Gene tree and species tress may not be congruent



Gene duplication and loss can explain incorrect phylogeny



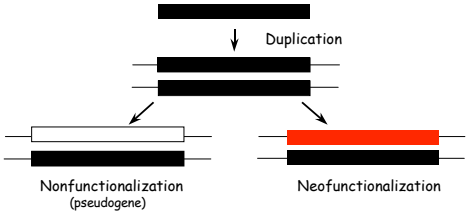
Duplicate genes can be used to root trees



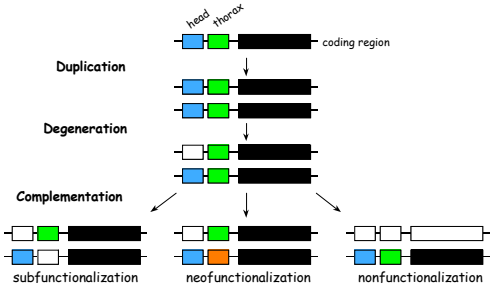
Minimize number of duplication events.

What about origins of new functions?

The Classical Model for the Fates of Duplicate Genes



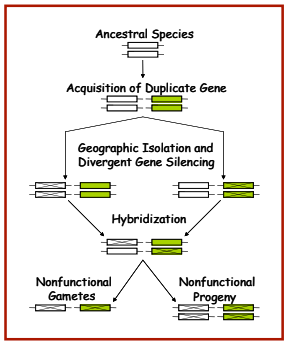
The DDC Model



How would you test for subfunctionalization, neofunctionalization, and nonfunctionalization?

Other models of duplication loss

The stochastic birth and loss of duplicate genes leads to the passive origin of reproductive isolating barriers.



Example of subfuncationalization

- Specialization of function
  - Optimize two pre-existing function

Specialization of function: subfunctionalization

- Ancestral gene has two function.
- Following duplication, adaptive evolution optimizes function for each gene.
- Genes then become non-redundant and fixed in population.

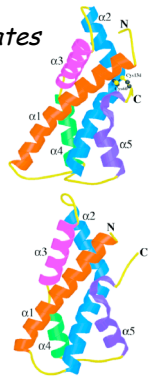
Sp18 and Lysin are Duplicates

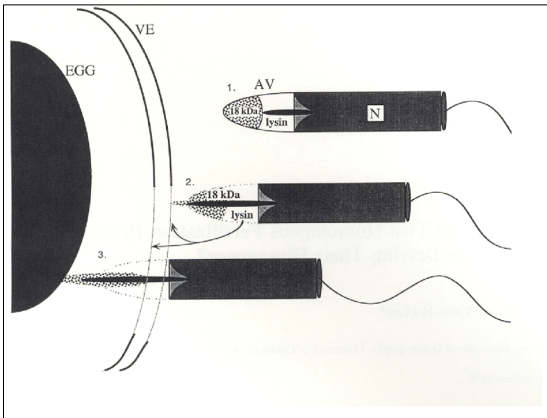
Fusion: Sp18 (≈146AA)

5' 3'

VE Dissolution : Lysin (≈155AA)

5' 3'

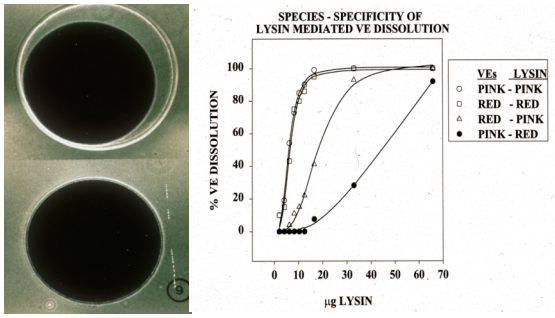




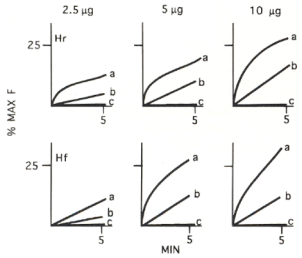
Subfunctionalization hypothesis

- Ancestral abalone had one sperm acrosomal protein that mediated both VE dissolution and fusion
- Gene duplication occurred
  - Lysin specialized for VE dissolution
  - Sp18 specialized for fusion
- Can we test this hypothesis?
  - VE dissolution and fusion assays

The sperm acrosomal protein lysin dissolves the egg vitelline envelope (VE), sp18 has no effect



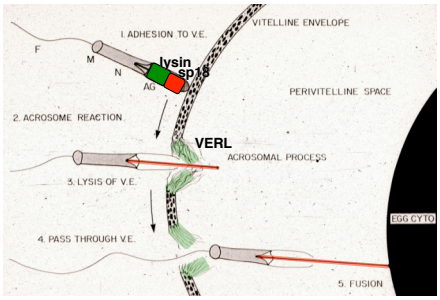
Sp18 better fusagen than lysin:



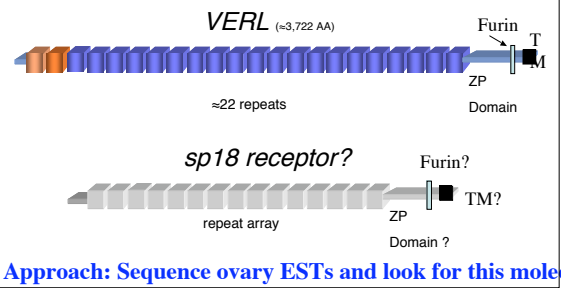
Subfuncationalization

- Lysin and sp18 are duplicates with similar 3D structures and intron/exon boundried.
- Lysin remains efficient at VE dissolution, but has only vestigial fusion ability
- Sp18 potent fusagen, but has lost ability to dissolve VEs
- Can we use this information for further analyses?
  - Egg receptors?

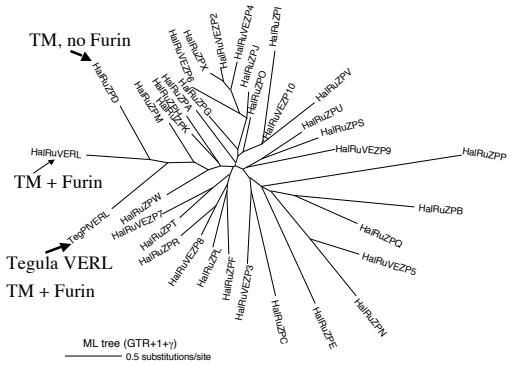
Abalone Fertilization: Lysin receptor elevated, sp18 receptor membrane bound?



Hypothesis: VERL and sp18 receptor are paralogs



Approach: Sequence ovary ESTs and look for this mole

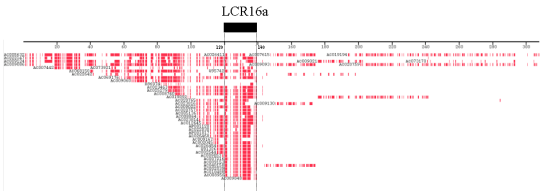


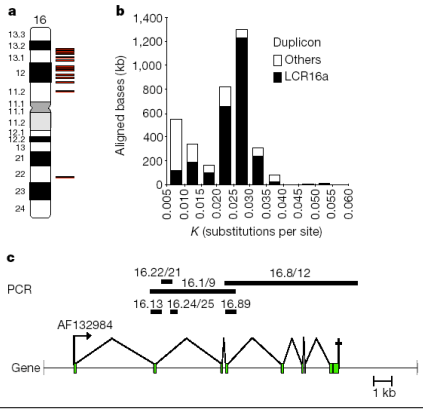
Subfunctionalization

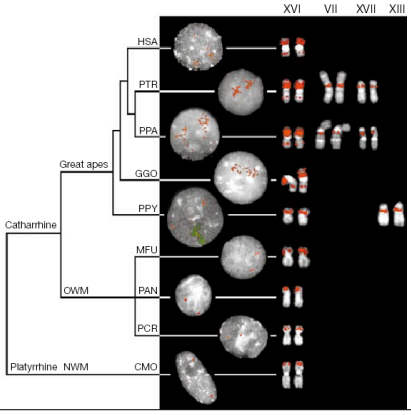
- Gene duplication lead to potential optimization of two preexisting functions
- Knowledge of duplication lead to functional assays and further characterization
  - Fusion/dissolution assays
  - Receptor identification

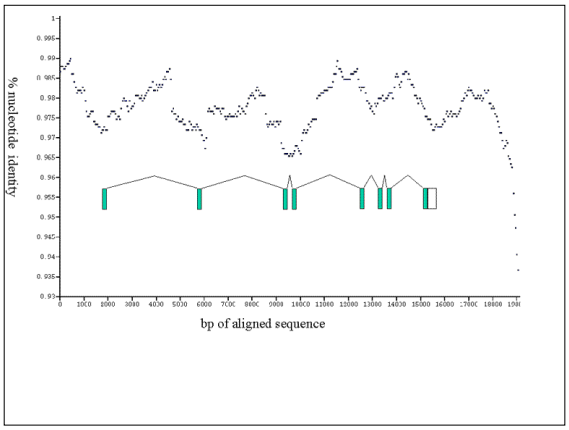
Example Neofunctionalization from human morpheus gene family

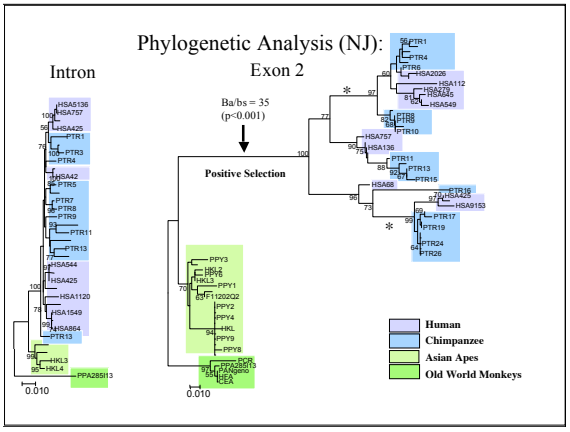
- From heirachical sequencing, complex duplications were found (note: would these be found by shotgun sequencing?)
- Blast these to the complete genome and find locations
- Look at duplications by FISH in other primates and rt-PCR for expression pattern.
- Perform phylogenetic and adaptive evolution studies.





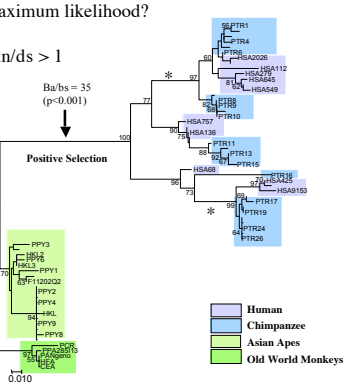






How would test by Maximum likelihood?

Find 9 lineages with dn/ds > 1



Positive Selection: Exon 2

Exon 2	Ka(SE)	Ks(SE)	Ka/Ks	Z value	p
HSA-PTR	0.207 (0.035)	0.042 (0.017)	4.92	3.92	<0.0001
HSA-PPY	0.370 (0.067)	0.087 (0.038)	4.25	3.3	<0.0005
HSA-HKL	0.364 (0.066)	0.091 (0.039)	4.00	3.29	<0.0005
HSA-OW	0.450 (0.081)	0.030 (0.014)	15.00	4.94	<0.00001
PTR-PPY	0.349 (0.063)	0.086 (0.036)	4.05	3.37	<0.0005
PTR-HKL	0.342 (0.061)	0.089 (0.037)	3.84	3.27	<0.0005
PTR-OW	0.434 (0.076)	0.034 (0.014)	12.8	5.00	<0.00001
PPY-HKL	0.026 (0.011)	0.033 (0.022)	0.78	-0.09	0.94
PPY-OW	0.108 (0.067)	0.063 (0.038)	1.71	0.96	0.5
HKL-OW	0.100 (0.030)	0.067 (0.039)	1.49	0.71	0.5
HSA-HSA	0.196 (0.033)	0.038 (0.019)	5.15	4.05	<0.0005
PTR-PTR	0.207 (0.040)	0.046 (0.019)	5.10	3.48	<0.005
PPY-PPY	0.034 (0.013)	0.033 (0.025)	1.03	0.04	
HKL-HKL	0.020 (0.012)	0.040 (0.026)	0.5	-0.95	0.95
OW-OW	0.006 (0.005)	0 (0)	NA	1	0.54

*OW=Cercopithecus aegyptiops, Papio anubis, Papio hamadryas, Macaca fascicularis

HSA = human

PTR = chimp

PPY = orang

HKL = gibbon

OW = old-world monkeys

***Highly significant positive selection during emergence of man and the African apes**

***Neutral / weak purifying selection among the Asian Apes**

How would we analyze these data with ML?
Would any additional information be gained?

Exon 2	Ka(SE)	Ks(SE)	Ka/Ks	Z value	p
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***Highly significant positive selection during emergence of man and the African apes**

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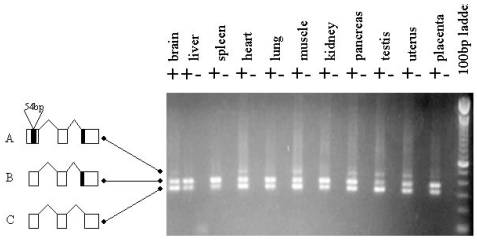
Some copies are obtaining different tissue expression

Non great apes show only testis expression



Conclusions

- Extraordinary plasticity of genome and gene
- Evidence for evolution of recent hominoid gene by duplication and adaptation.
  - Gene not detected in other organisms
- Appears to have gained wide tissue expression in great apes
- Additional examples expected.
  - 5-7% of all human sequences duplicated in last 20Myr.

Ways to identify gene duplicates as orthologs

- Reciprocal best hit Blasts
- Synteny

Reciprocal best hits

- Blast gene of interest from genome A against genome B.
- Find best hit in genome B.
- Take best hit against from genome B and blast against Genome A.
- If oringinal gene of interest is found, then assume orthologs.

Obtaining sequence data

Potential projects