Pseudogenes

Alan R. Rogers

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Outline

- Dead genes
- Vitamin C
- Urate oxidase
- ψMYH16
- GBA
- Globins

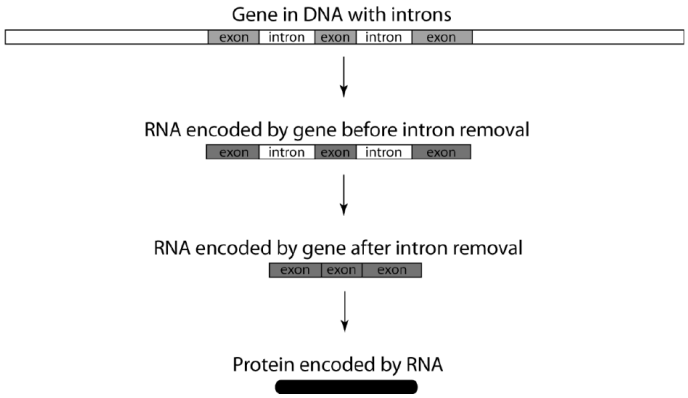
Pseudo-genes

- Genes are DNA sequences that code for protein.
- Some genes are broken and cannot make protein.
- What are such genes for?

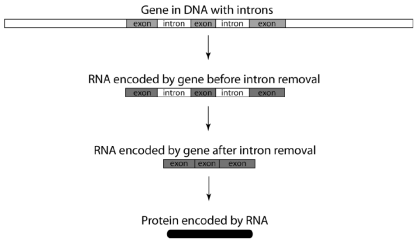
The genetic code (DNA version)

First Position	Second Position A	Second Position G	Second Position T	Second Position C	Third Position	
A	Phe	Ser	Tyr	Cys	A	(adenine)
	Phe	Ser	Tyr	Cys	G	(guanine)
	Leu	Ser	STOP	STOP	T	(thymine)
	Leu	Ser	STOP	Trp	C	(cytosine)
G	Leu	Pro	His	Arg	A	
	Leu	Pro	His	Arg	G	
	Leu	Pro	Gln	Arg	T	
	Leu	Pro	Gln	Arg	C	
T	Ile	Thr	Asn	Ser	A	
	Ile	Thr	Asn	Ser	G	
	Ile	Thr	Lys	Arg	T	
	Met	Thr	Lys	Arg	C	
C	Val	Ala	Asp	Gly	A	
	Val	Ala	Asp	Gly	G	
	Val	Ala	Glu	Gly	T	
	Val	Ala	Glu	Gly	C	

What is a gene?



What is a gene?



Some necessary components

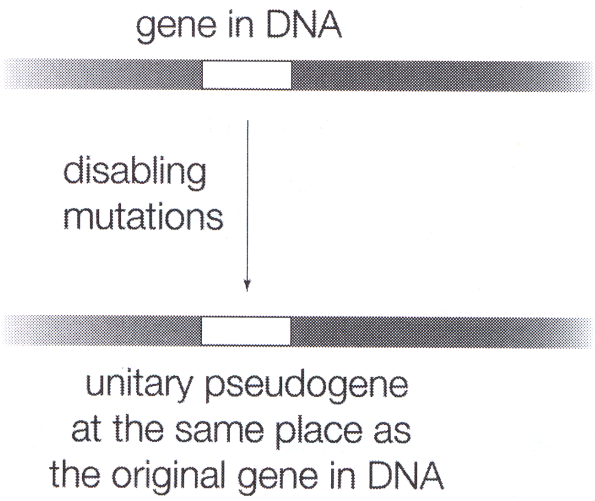
1. promoter: binding site for enzyme that translates DNA into RNA
2. start codon: usually AUG
3. splice sites for removing introns
4. stop codon

If any of these break, the gene no longer makes protein.

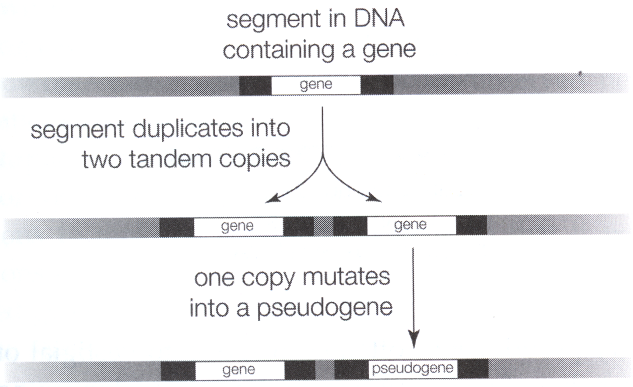
How genes get silenced

- Mutation destroys promoter.
- Mutation creates a stop codon in middle of coding sequence.
- Frame-shift mutation: insert sequence whose length isn't a multiple of 3.
- Retrotransposition: DNA $\rightarrow$ mRNA $\rightarrow$ DNA.

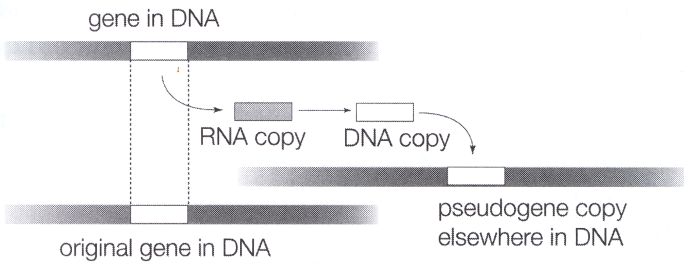
A unitary pseudogene



A duplication pseudogene



A retropseudogene



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Vitamin C, or ascorbic acid

- Essential in human diets.
- Otherwise. . . scurvy
- Yet most animals don't need it.

Why don't other animals need ascorbic acid?

- They make it in their livers
- Involves enzyme L-gulonolactone oxidase (GULO for short)
- We lack this enzyme.
- Why?

Why don't we make the GULO enzyme?

- Perhaps there is some adaptive reason.
  - Some have suggested a role in extending lifespan.
- However: although we lack the enzyme, we all carry the gene that makes it.
- Ours is just broken.

The ψGULO pseudogene

- We all carry the ψGULO gene in our DNA
- At the same position as the working copies in other animals.
- Yet our copies make no GULO enzyme. . . They are broken.
- We evolved from ancestors whose metabolized food differently.

Objection: perhaps ψGULO has some undiscovered function.

Response: Suppose you saw someone using a broken pocketknife to tighten a screw. What would you conclude?

1. It's a screwdriver, and any resemblance to a pocketknife is coincidental.
2. It was built as a pocketknife, even if it now drives screws.

In the same way, the structure of ψGULO proves it was built to make the GULO enzyme, whatever its current function.

What are we doing with such a gene?

Shared ancestry

- Humans, apes and monkeys share the ψGULO pseudogene.
- Even the damage that inactivated these genes is shared across species.
- Humans, apes, and monkeys evolved from a common ancestor.

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Urate oxidase (UOX)

- Enzyme that metabolizes uric acid.
- Humans lack enzyme $\Rightarrow$ have lots of uric acid.
- Causes gout: uric acid crystals form in joints.
- An antioxidant: may slow aging.
- Although we lack the enzyme, we carry a broken copy of the gene that makes it.
- So do chimpanzees, gorillas, orangutans, and gibbons.

The mutation that broke our UOX gene

$$\overbrace{\text{gct}}^{\text{Arg}} \rightarrow \overbrace{\text{act}}^{\text{Stop}}$$

- Chimpanzees, gorillas, and orangutans have same mutation.
- Gibbons also lack urate oxidase, but their gene is damaged in a different way.
- Gibbons lost UOX independently.

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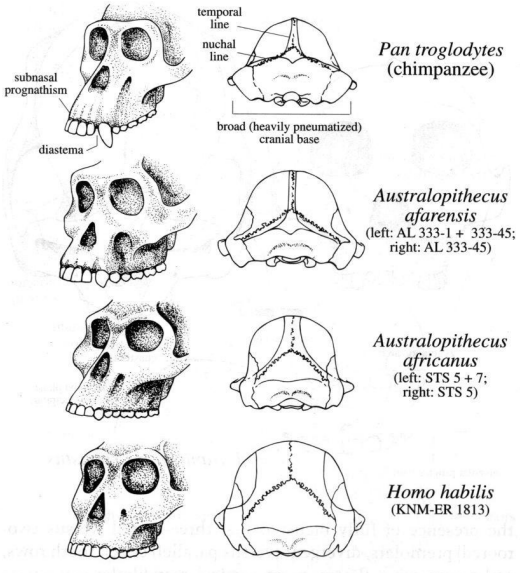
MYH16: a protein in jaw muscle

- Useful for brief, powerful bite.
- Present in carnivores.
- Lost in some herbivores.
- Present in chimps and gorillas.
- Lost in humans within past 4 my.

Effect of losing MYH16

- Evidence: knockout experiments with similar proteins in mice.
- Loss of gene causes 50% reduction in muscle mass.
- Is there evidence of such a reduction in hominin fossils?



- Temporalis muscle goes to top of head in chimp.
- Same true of *A afarensis*,
- and of *A africanus*.
- Muscle much smaller in *Homo habilis*.
- Was this when we lost MYH16?
- We can use DNA to find out.

Neutral mutations and selected mutations

Selectively neutral mutations Some mutations have no effect on codons or other functional parts of chromosome.

Selectively relevant mutations Do affect functional DNA.

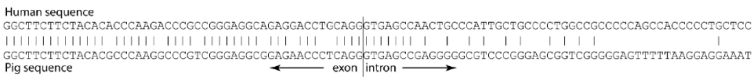
Most selected mutations are harmful and are removed by selection.

Rate of molecular evolution is fastest in DNA that has no function.

The 3rd codon position is often free to vary

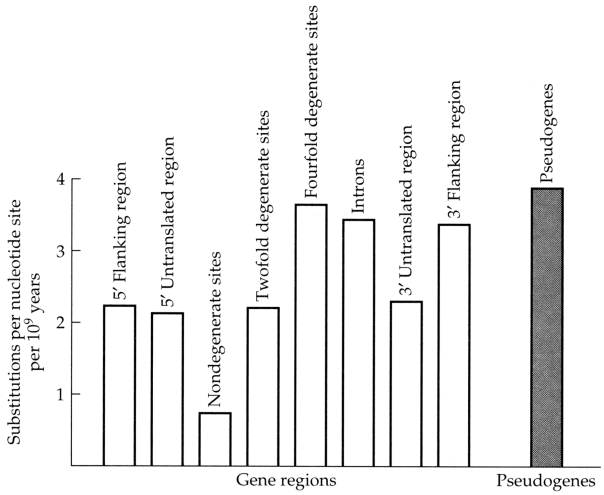
First Position	Second Position				Third Position	
	A	G	T	C		
A	Phe	Ser	Tyr	Cys	A	(adenine)
	Phe	Ser	Tyr	Cys	G	(guanine)
	Leu	Ser	STOP	STOP	T	(thymine)
	Leu	Ser	STOP	Trp	C	(cytosine)
G	Leu	Pro	His	Arg	A	
	Leu	Pro	His	Arg	G	
	Leu	Pro	Gln	Arg	T	
	Leu	Pro	Gln	Arg	C	
T	Ile	Thr	Asn	Ser	A	
	Ile	Thr	Asn	Ser	G	
	Ile	Thr	Lys	Arg	T	
	Met	Thr	Lys	Arg	C	
C	Val	Ala	Asp	Gly	A	
	Val	Ala	Asp	Gly	G	
	Val	Ala	Glu	Gly	T	
	Val	Ala	Glu	Gly	C	

Pig and human insulin genes



- Left portion (exon) is functional—codes for protein
- Right portion (intron) isn't.
- Vertical lines show idential nucleotides in human and pig.
- There are more differences in intron than in exon.
- Nonfunctional DNA evolves faster.

Pseudogenes evolve faster than functional genes



Rate of change in ψMYH16 estimates date of loss.

- Before it was silenced, MYH16 evolved at a rate similar to that in animals with functional copies of the gene.
- After it was silenced, it evolved like a pseudogene.
- Implied date of loss: 0–2.7 my (95% confidence interval, Huff 2008)

Implications of ψMYH16

- *Homo habilis* was the first hominin to use stone tools.
- It appears that jaw muscles were reduced at the same time.
- Having tools, there was less need for the brief powerful bite.

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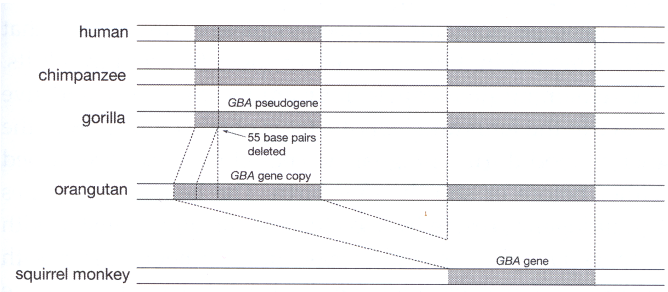
Glucocerebrosidase (GBA)



- Single-copy functional gene in monkey.
- Functional duplicate in orangutan
- Duplication pseudo-gene in human, chimp, gorilla, caused by frame-shift mutation.

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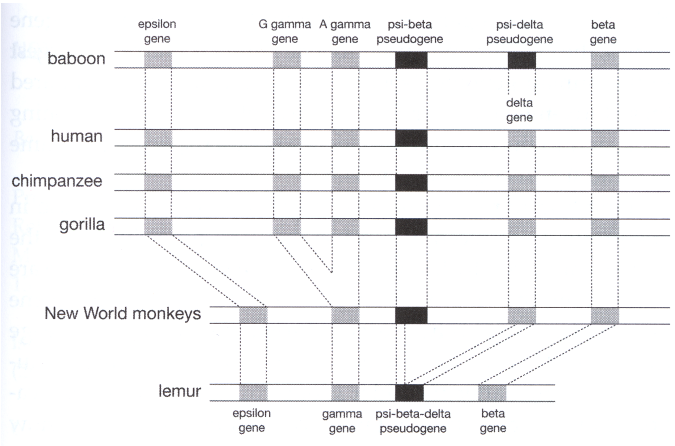
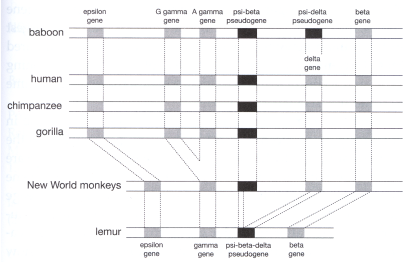
βglobins



History of βglobins



- $\psi\beta$globin: killed long ago; 30% mutated
- human, chimp, gorilla, baboon similar

- apes and OW monkeys: $\gamma \rightarrow G\gamma$ and $A\gamma$.
- baboon: δglobin mutated to pseudogene
- lemur: deletion merged $\psi\beta$ and δ