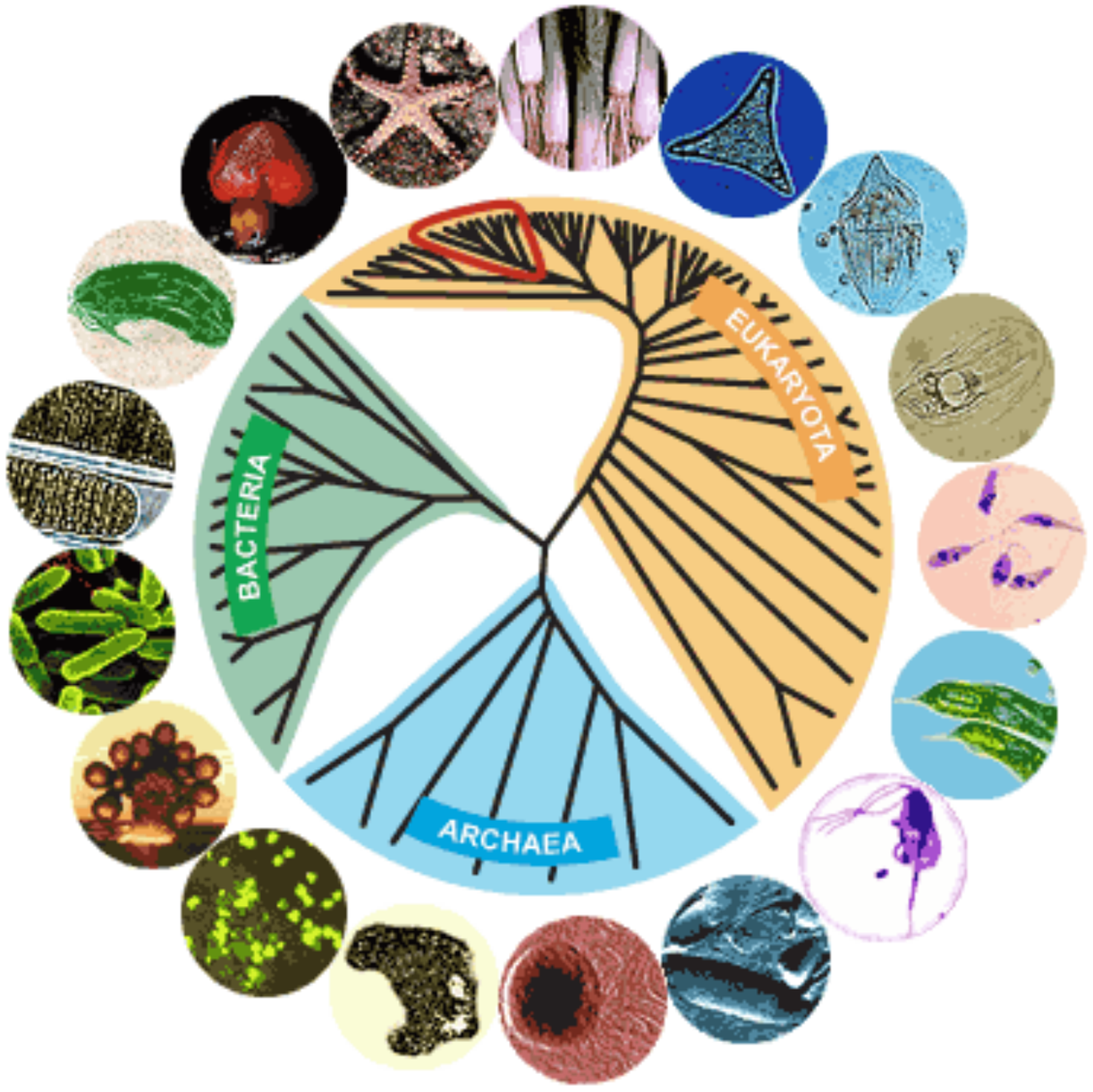
Phylogeny of SNCA

Tessa Bachinski and Rose Rogers

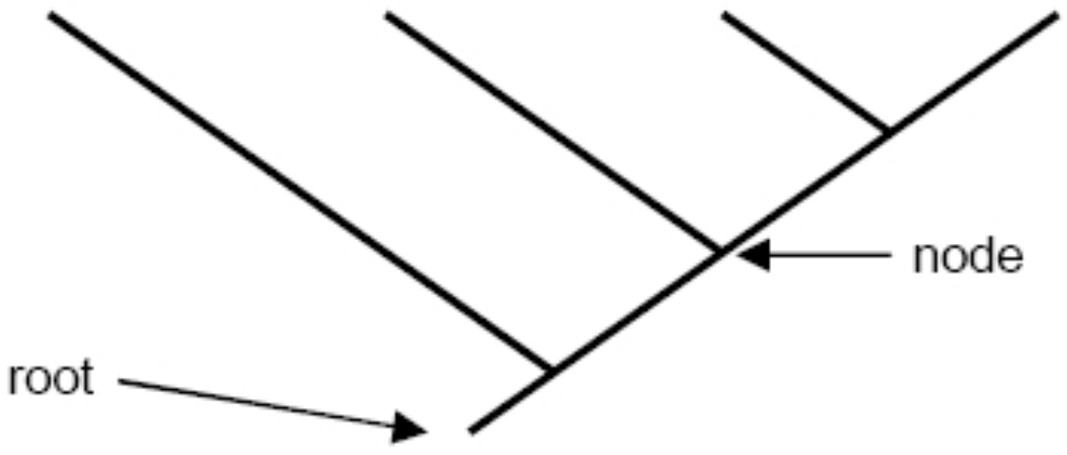
What is Phylogeny?

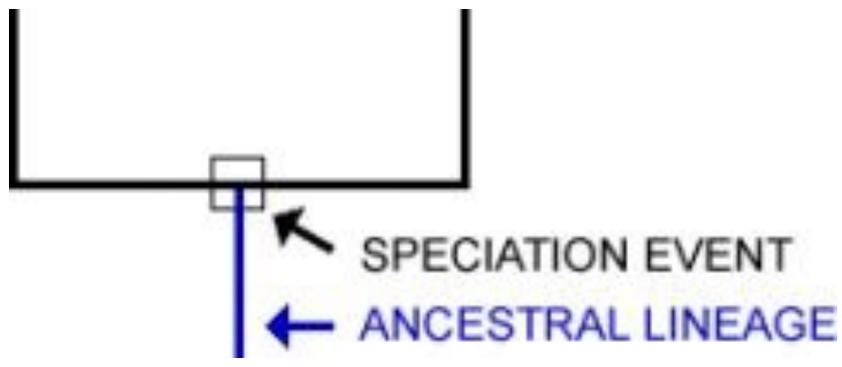


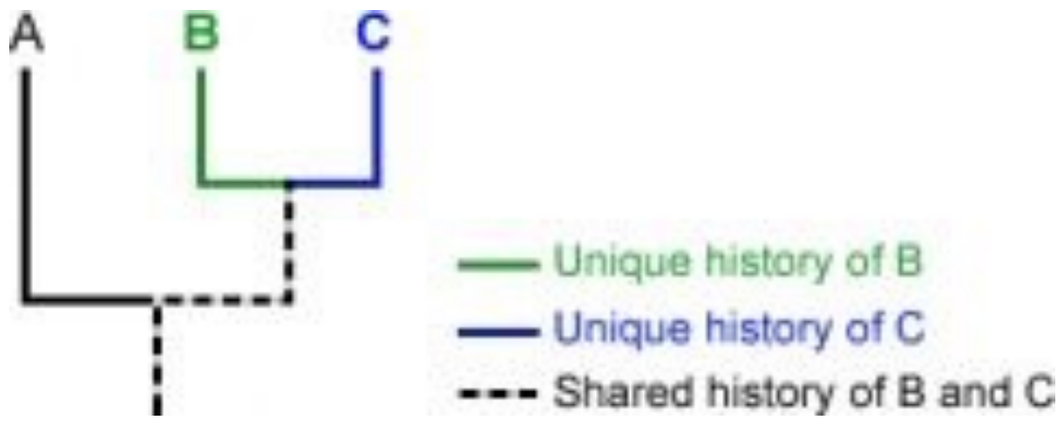
Analysis of relationships in varying aspects of biology

Source: University of California Museum of Paleontology's Understanding Evolution (http://evolution.berkeley.edu)

Phylogeny Basics







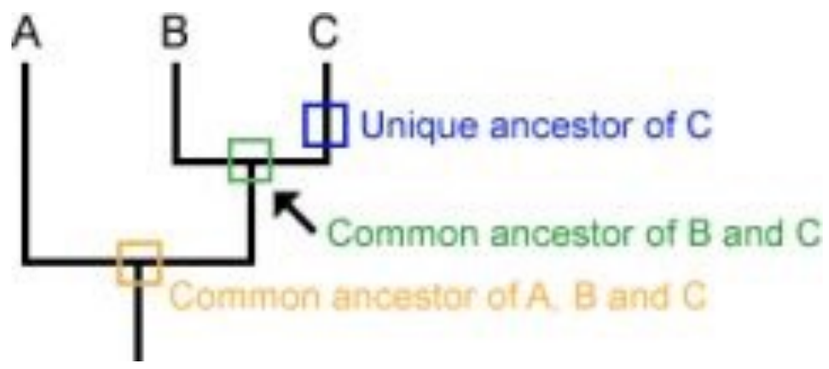
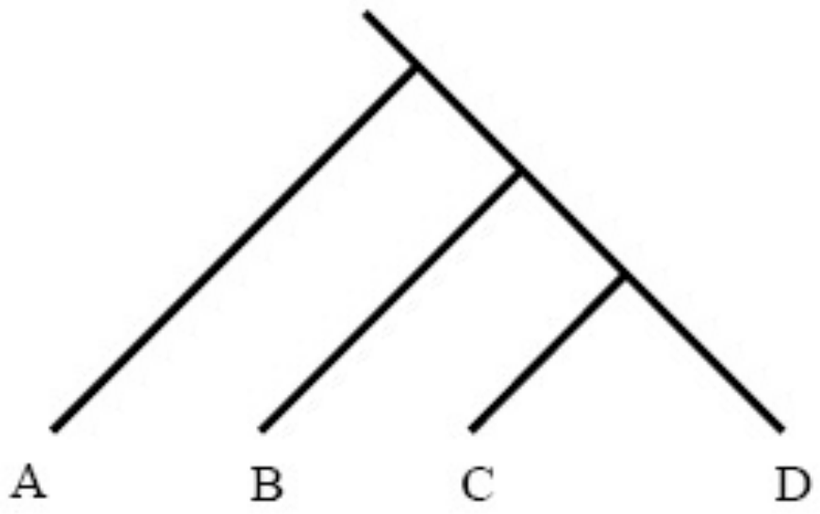
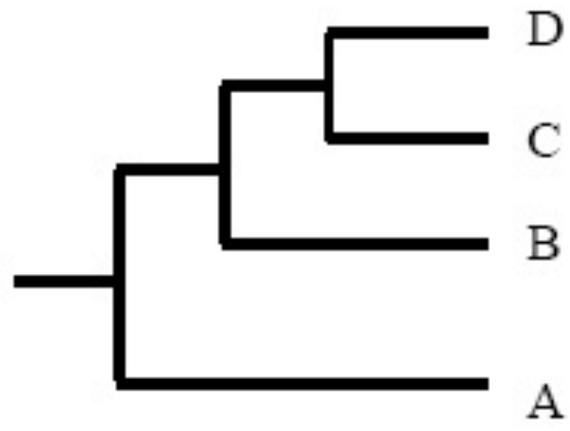
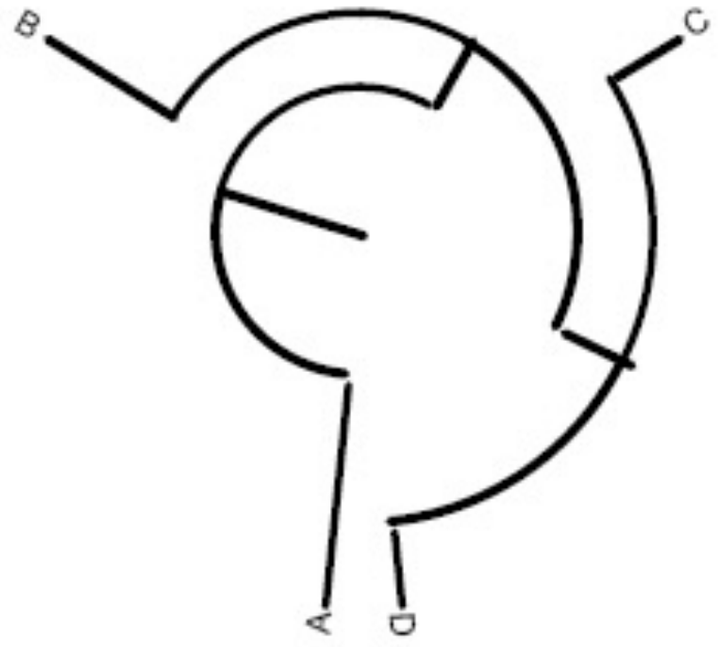


Image 1: Baum, D. Reading a Phylogenetic Tree:The Meaning of Monophyletic Groups
Images 2-3: University of California Museum of Paleontology's Understanding Evolution (http://evolution.berkeley.edu)

Are these trees different?

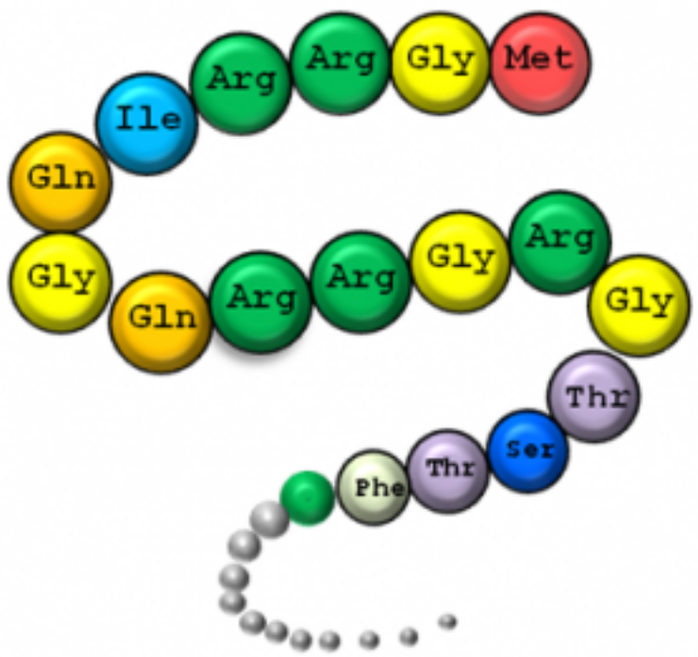






Source: Baum, D. Reading a Phylogenetic Tree:The Meaning of Monophyletic Groups

What kind of data can be used to make phylogeny trees?



Features

Proteins/ Biochemical Markers

DNA

Image 1:https://thumbs.dreamstime.com/z/backbone-fossil-fish-macro-photo-54090281.jpg
Image 2: http://userscontent2.emaze.com/images/2dfa0fd0-0b4f-4f43-a435-8a78be1cf2eb/974647e9-312f-458b-9559-3513779effda.PNG
Image 3: https://www.sciencemag.org/sites/default/files/styles/inline__450w__no_aspect/public/DNA_16x9_0.jpg?itok=gs07u06o

How do you decide what goes where?

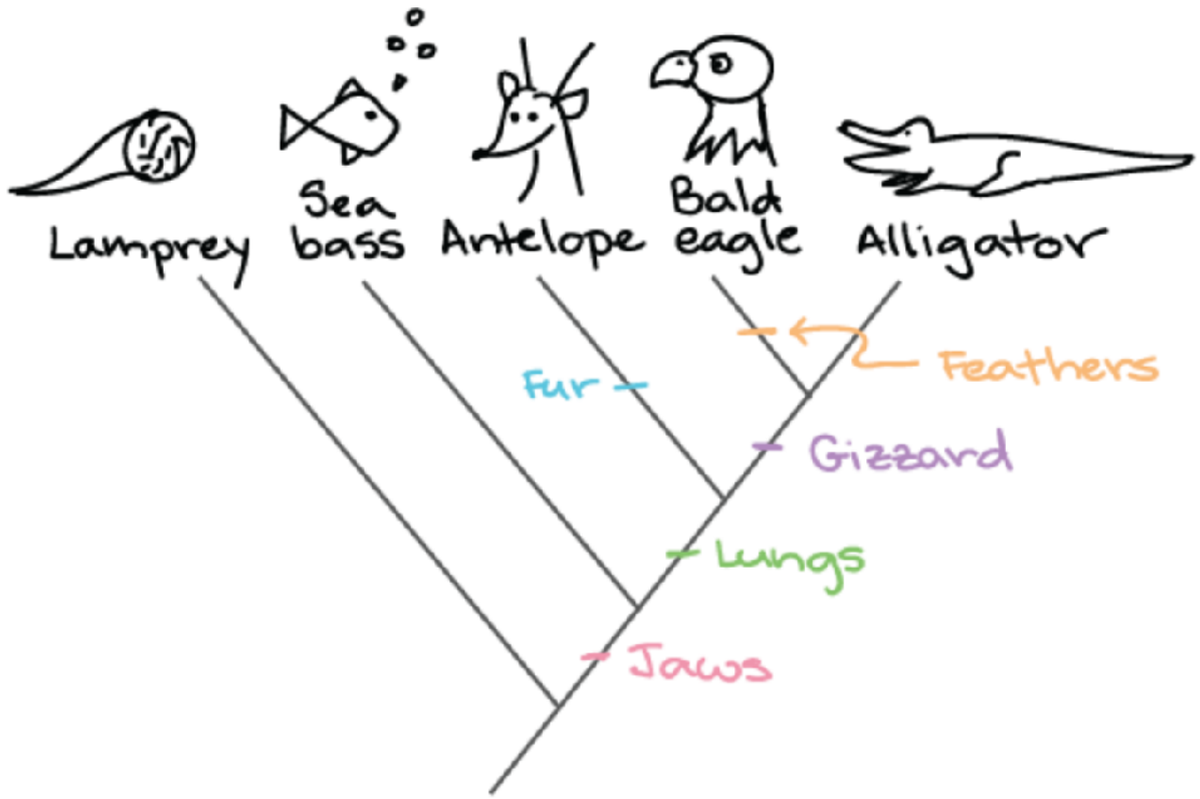
Character Based

Distance Based

Image 1:https://i1.wp.com/mvslim.com/wp-content/uploads/2016/02/384b1c8c-09c2-4db6-8f89-8aa85e7ca0f0.jpg?fit=758%2C474&ssl=1
Image 2: https://images.unsplash.com/photo-1432753759888-b30b2bdac995?ixlib=rb-1.2.1&ixid=eyJhcHBfaWQiOjEyMDd9&w=1000&q=80

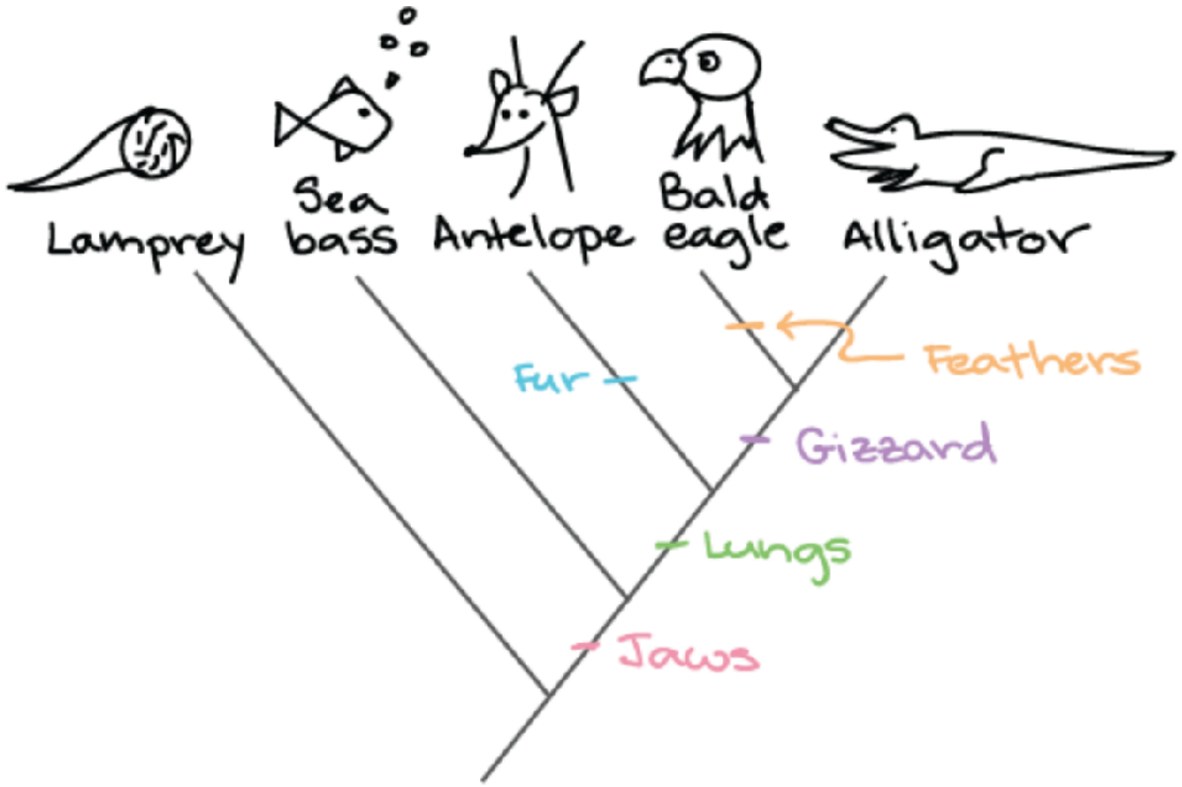
How do you build a tree with character based methods?

Feature	Lamprey	Antelope	Bald eagle	Alligator	Sea bass
Lungs	0	+	+	+	0
Jaws	0	+	+	+	+
Feathers	0	0	+	0	0
Gizzard	0	0	+	+	0
Fur	0	+	0	0	0

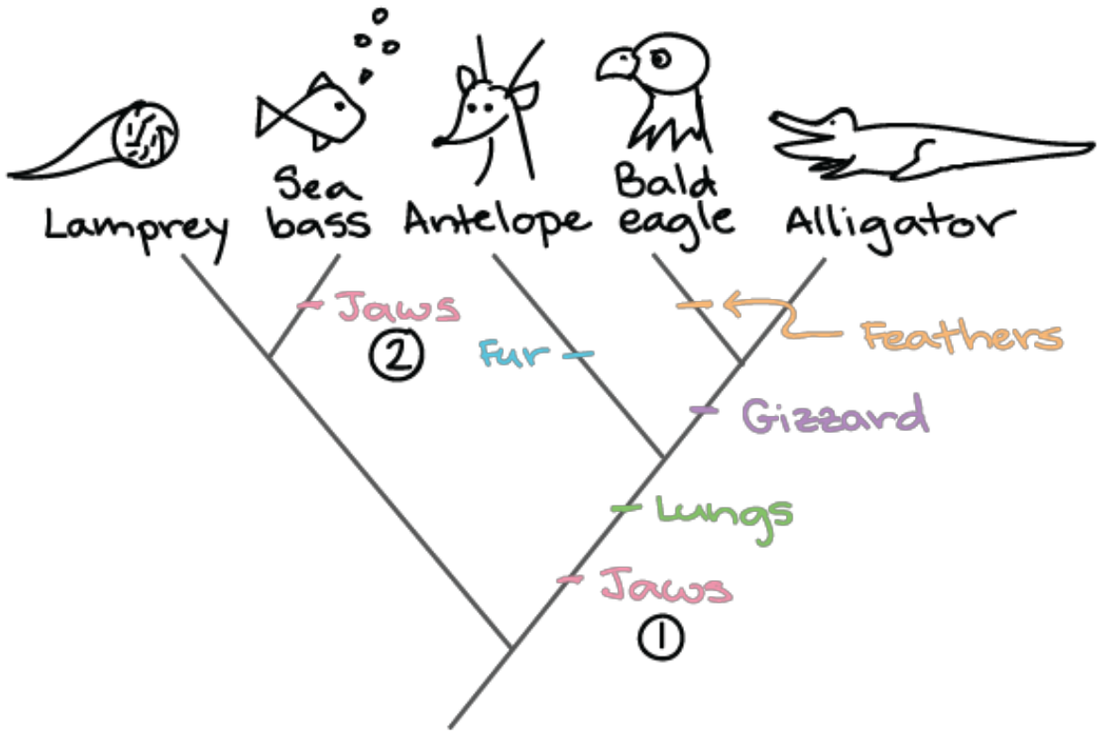


Images: Khan Academy

Maximum Likelihood



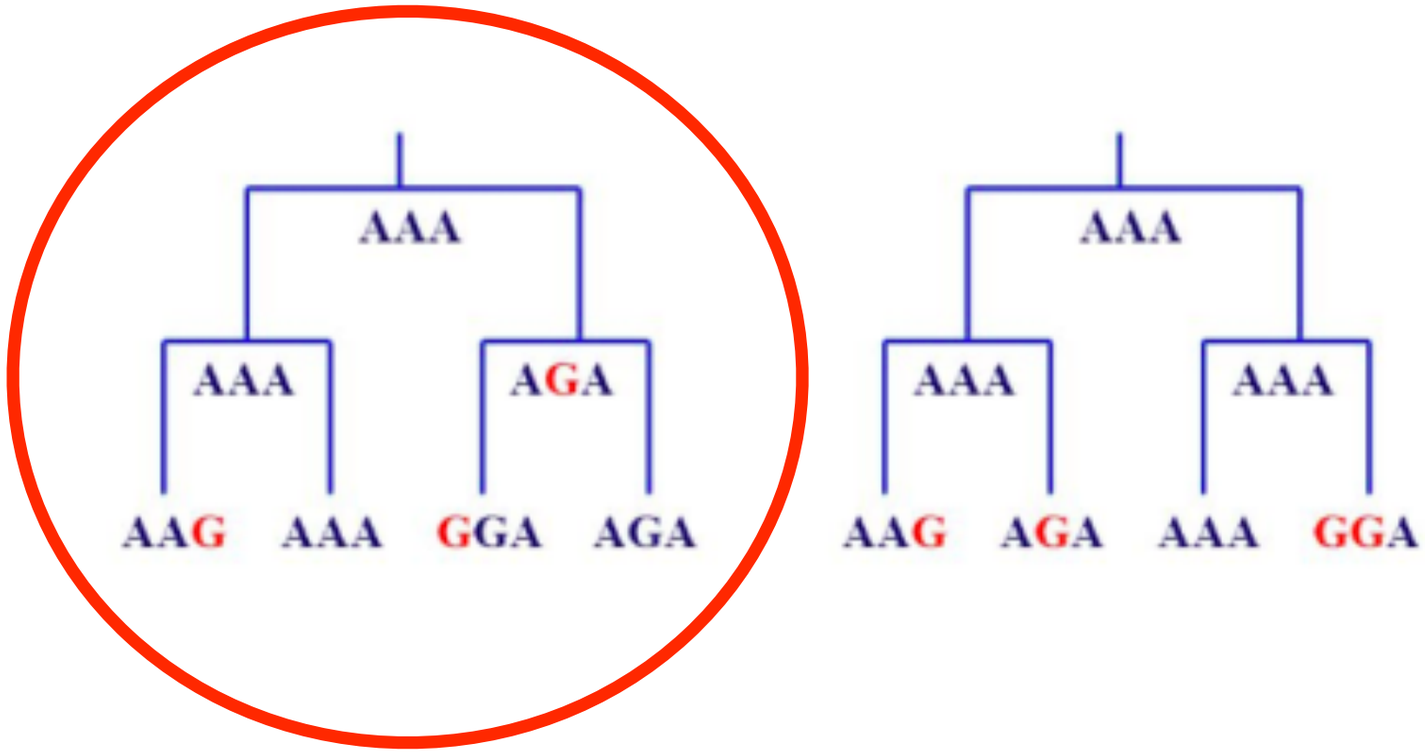
VS



What was more likely to happen?

Images: Khan Academy

Maximum Parsimony



Parsimony requires the fewest changes to get from a common ancestral sequence to the current sequences

How do we use DNA?

Source: Howard Hughs Medical Institute

Step 1: Align

```
T  ATGGCGCTGGCATACTGAGC
T A    GCGCAGGCATACTGAGC
T A    GCGCAGGGATACTGAGC
TTATGGCGCTGGCATTCTGAGC
```

Step 2: Find the SNPs

```
GCTGGCATACTGAGC
GCAGGCATACTGAGC
GCAGGGATACTGAGC
GCTGGCATTCTGAGC
```

Step 3: Find the Indels

```
T  ATGGCGC
T A   GCGC
T A   GCGC
TTATGGCGC
```

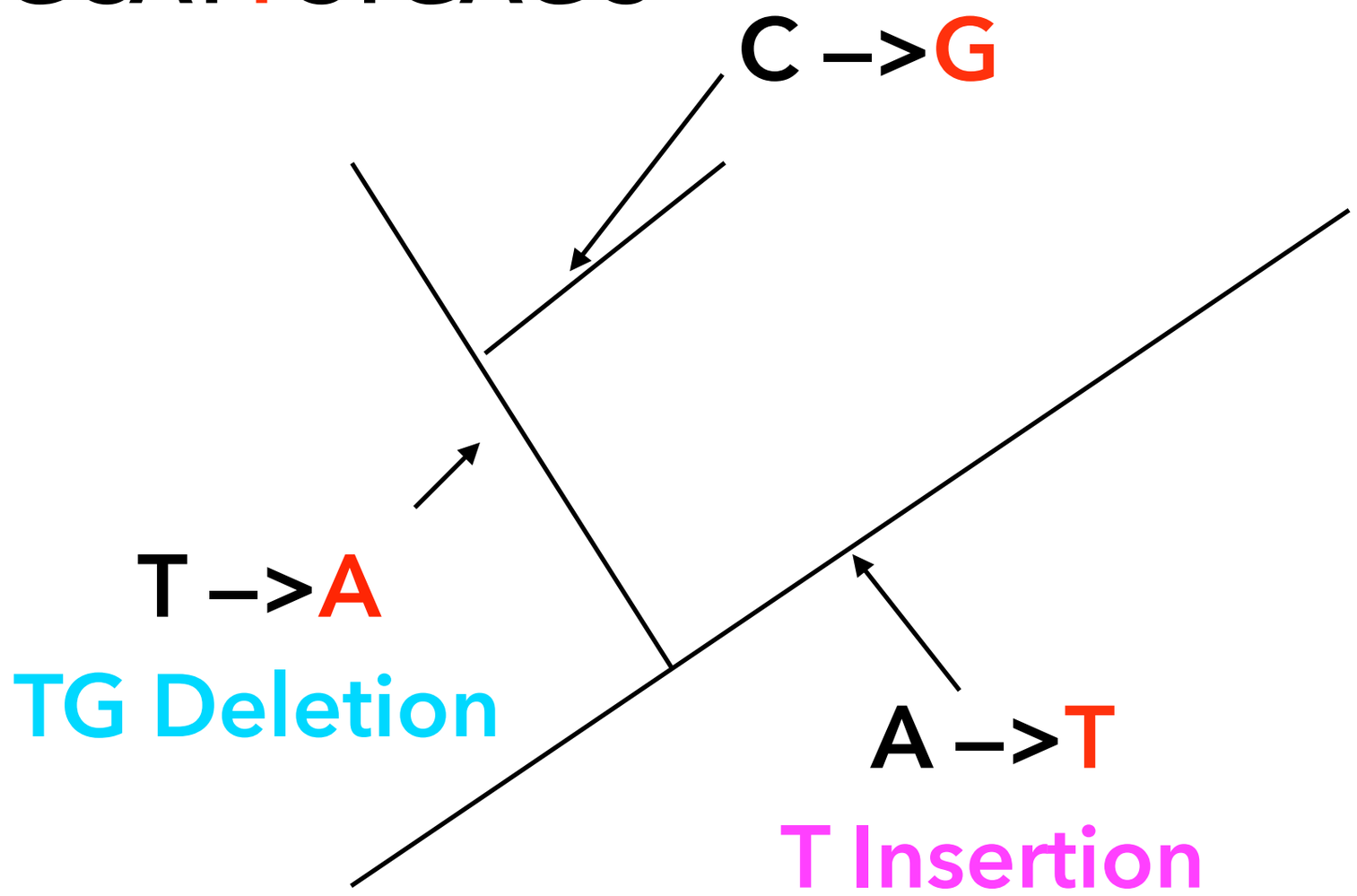
How do we use that information to build a tree?

T ATGGCGCTGGCATACTGAGC

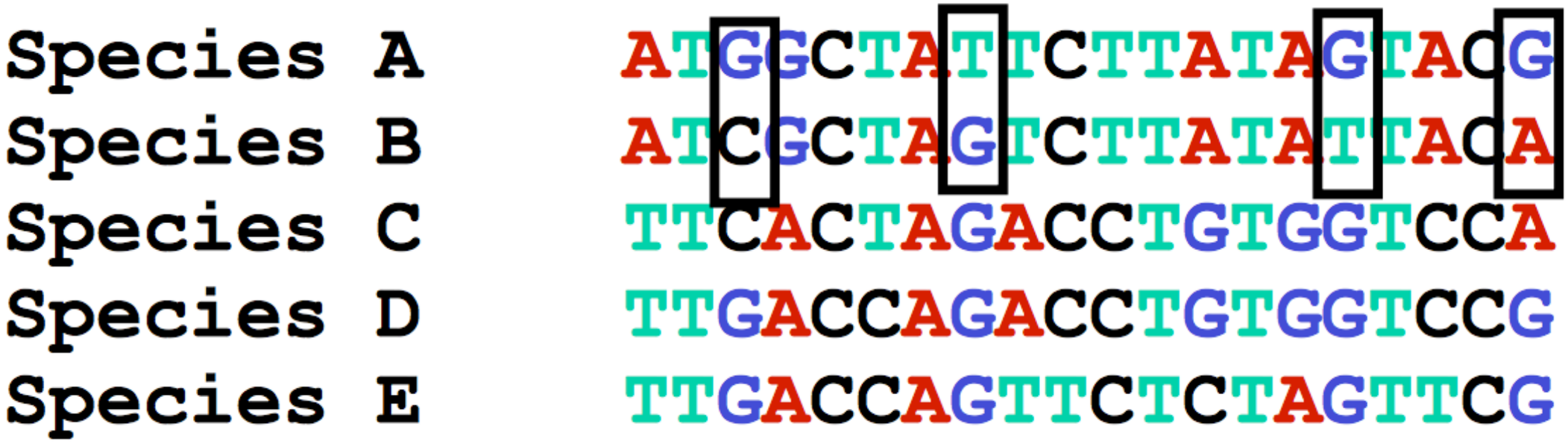
T A GCGCAGGCATACTGAGC

T A GCGCAGGGATACTGAGC

TTATGGCGCTGGCATTCTGAGC



How do we use distance methods to determine trees?



$$= \frac{\text{NUMBER OF CHANGES}}{\text{TOTAL LENGTH}}$$

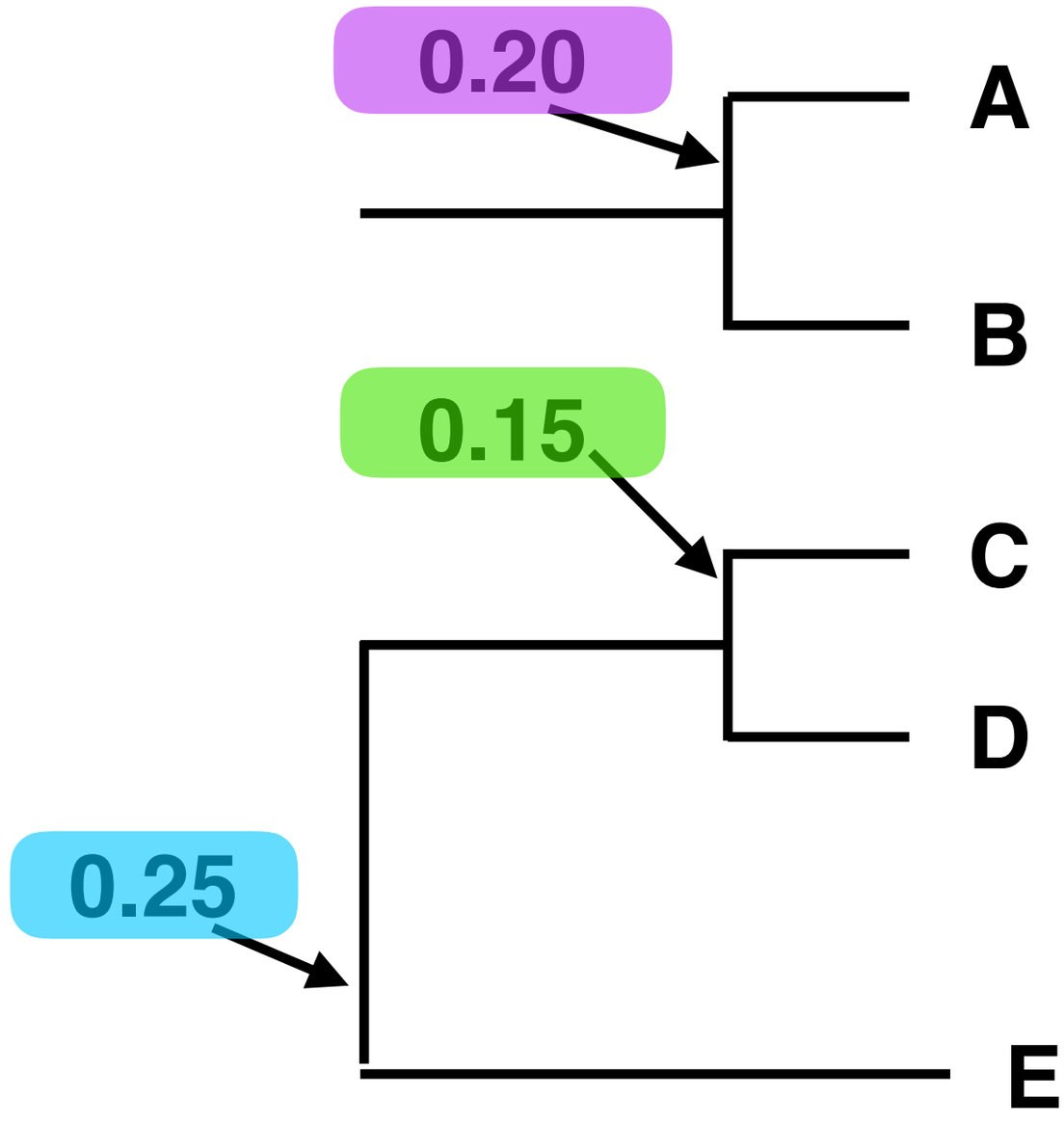
Source:rpi.edu

Distance Matrix Method - Neighbor Joining

	A	B	C	D	E
Species A	----	0.20	0.50	0.45	0.40
Species B		----	0.40	0.55	0.50
Species C			----	0.15	0.40
Species D				----	0.25
Species E					----

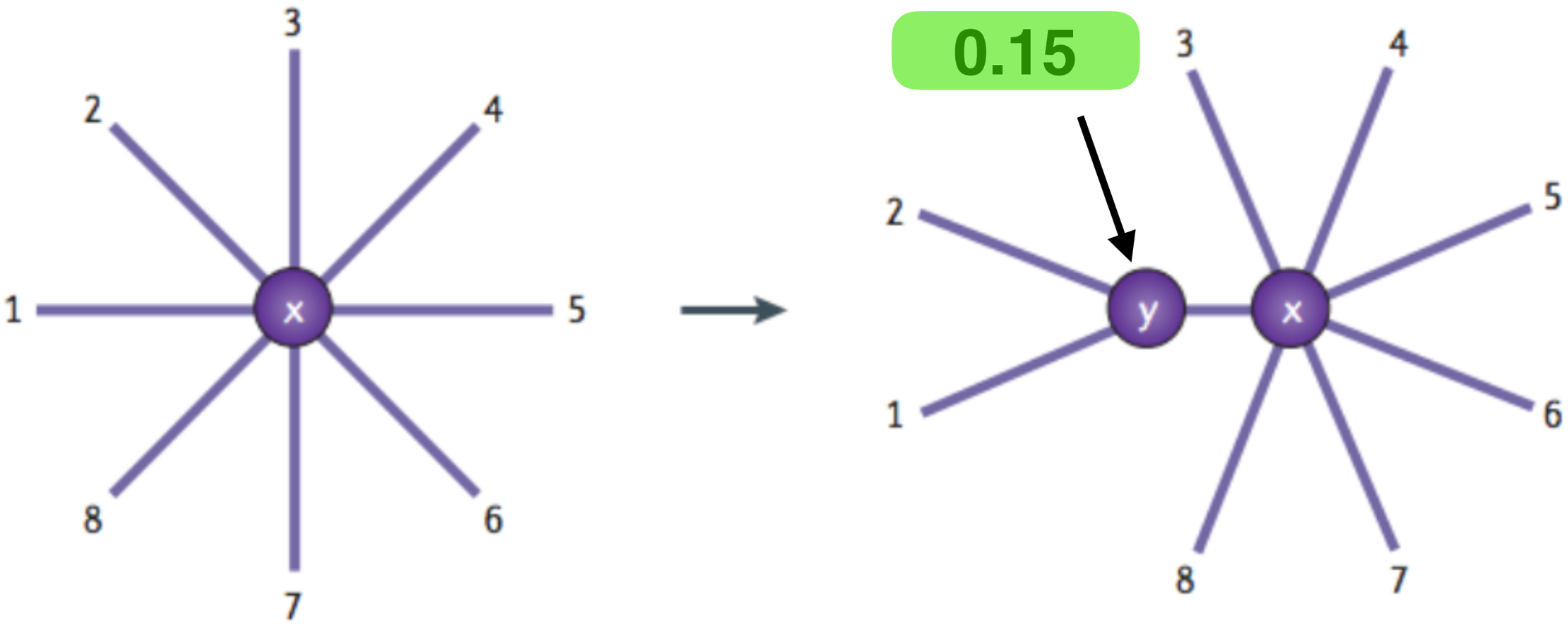
Source:rpi.edu

How do you use the numbers to build a tree?



Source:rpi.edu

How do you use the numbers to build a tree?



Source:Yang, Z. Molecular phylogenetics: principles and practice

What are advantages and disadvantages of each method?

Character Based

Easy to see and calculate (computer/hand)

May require assumptions

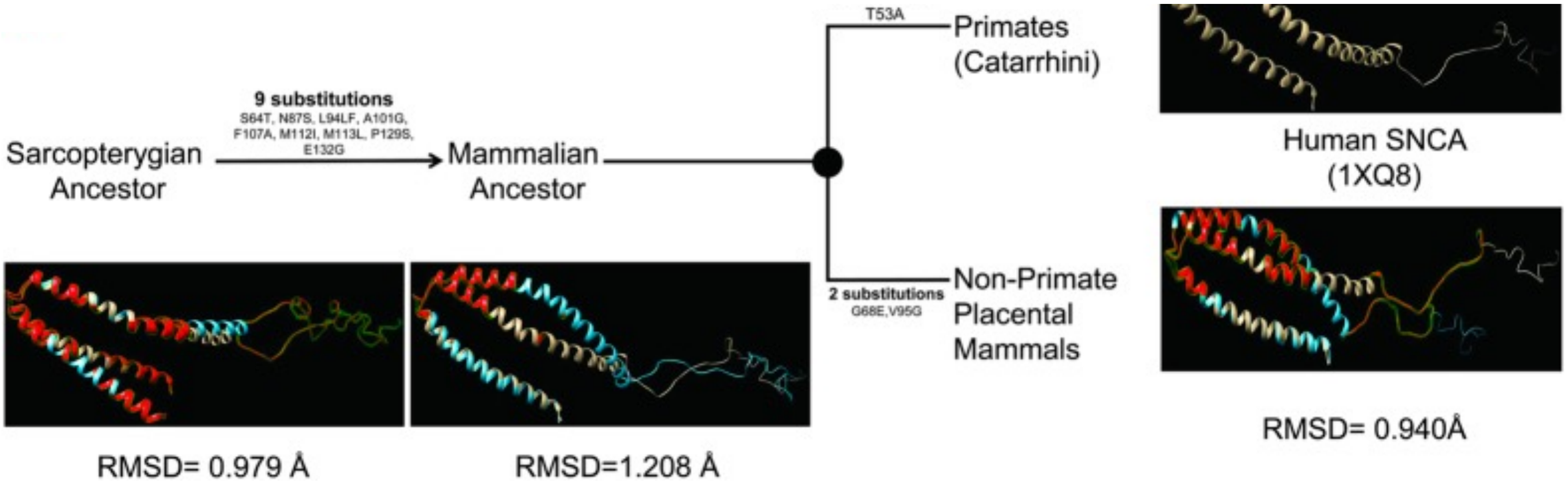
Distance Based

Very quick and easy to compute

Not good if there is poor alignment

Very distant things are hard to calculate

Why do I need this?



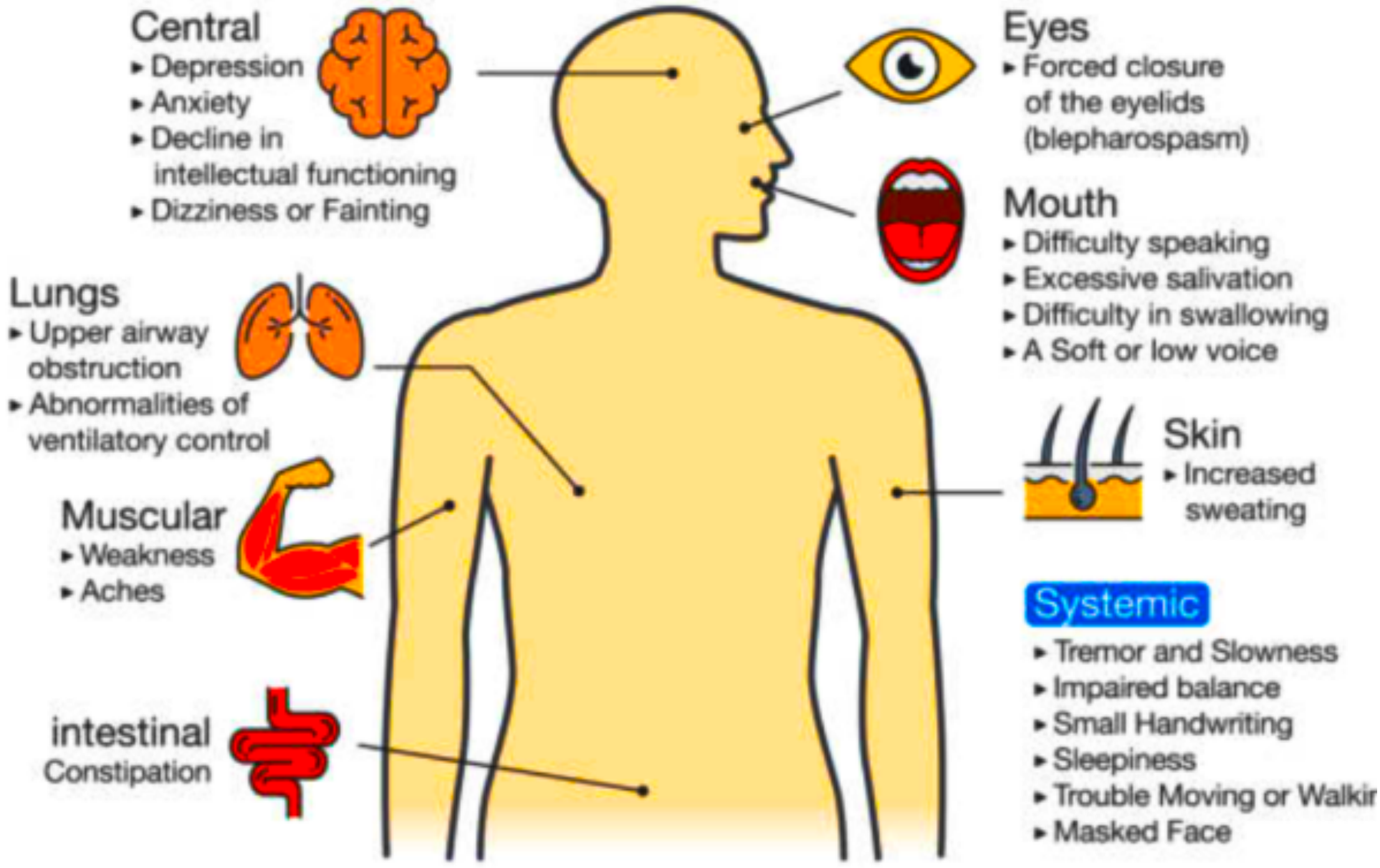
Population Genetics
Evolution
Gene Tracking

Source: Siddiqui IJ, Pervaiz N, Abbasi AA. The Parkinson Disease gene SNCA: Evolutionary and structural insights with pathological implication

What is Parkinson’s Disease?

Source: https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcTax4g1o4ZJufQx6wSCHwMG2MGeBDYIfeJfhICWmEfCqvkRlCwNhw

Symptoms



Source: https://www.americaninhomecare.com/wp-content/uploads/2018/04/Screen-Shot-2018-04-23-at-8.16.44-AM-604x485.png

On a molecular level, what leads to Parkinson's Disease?

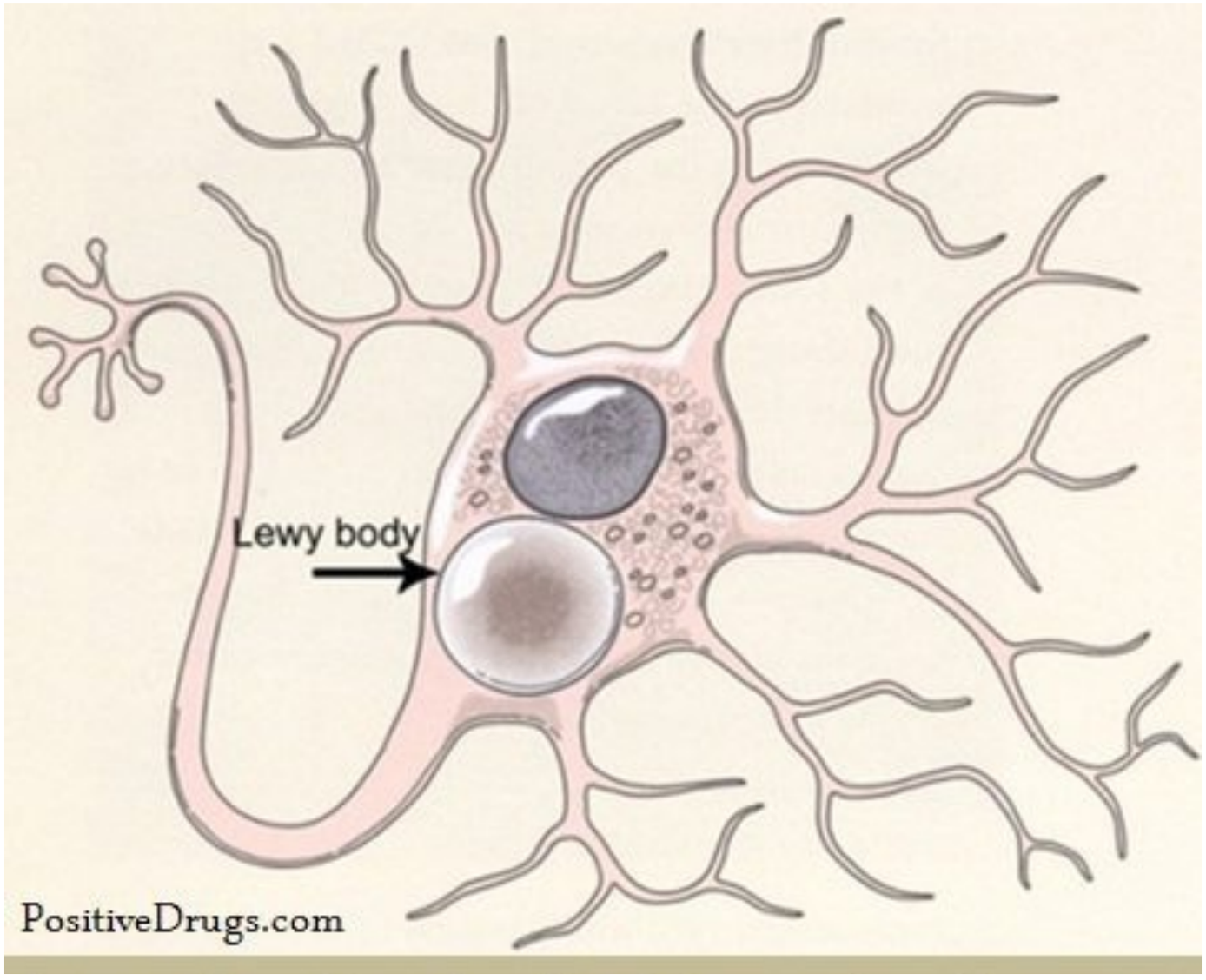


Image: http://positivedrugs.com/wp-content/uploads/2013/11/Lewy-bodies-in-Parkinsons-disease.jpg

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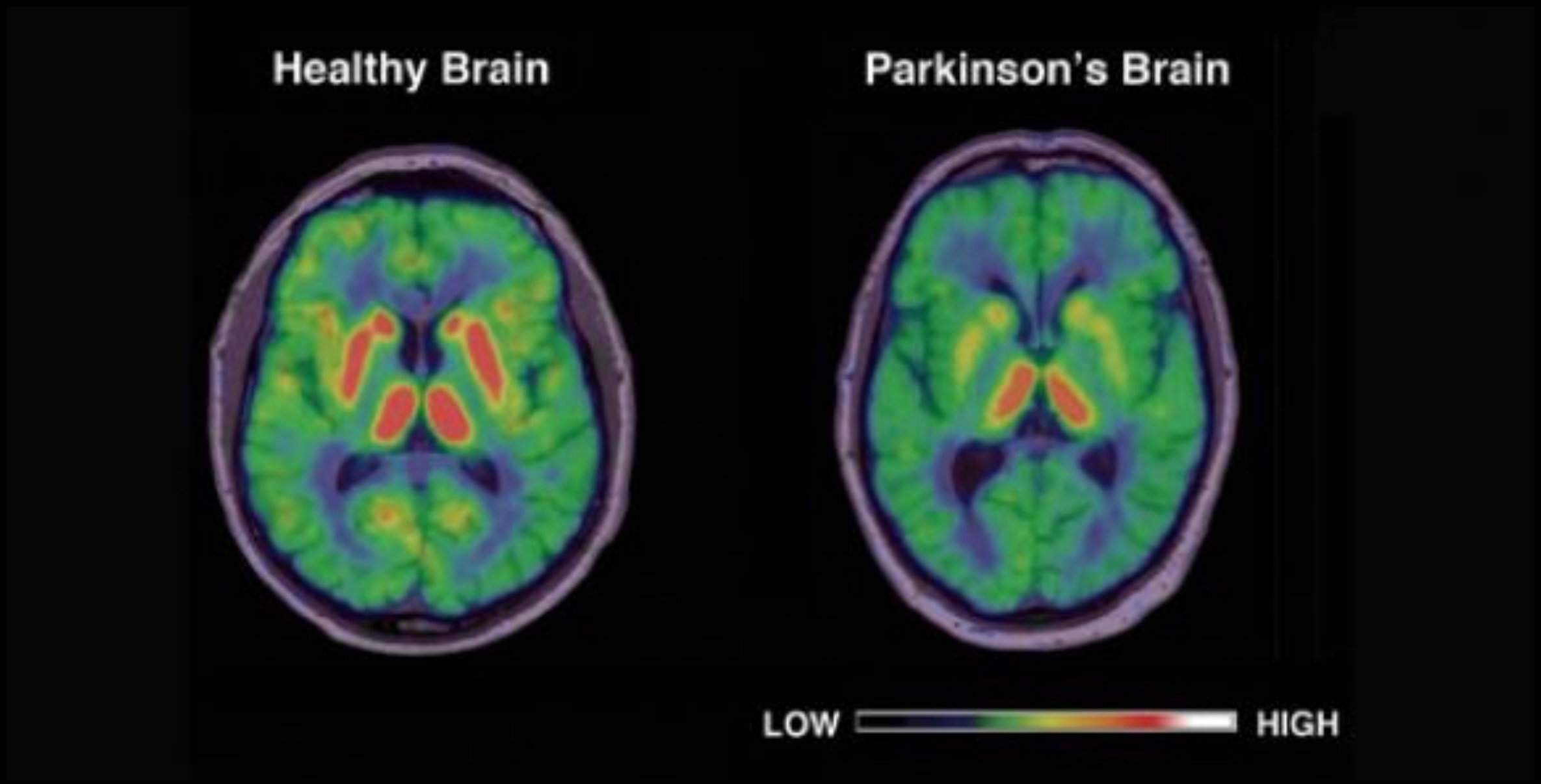
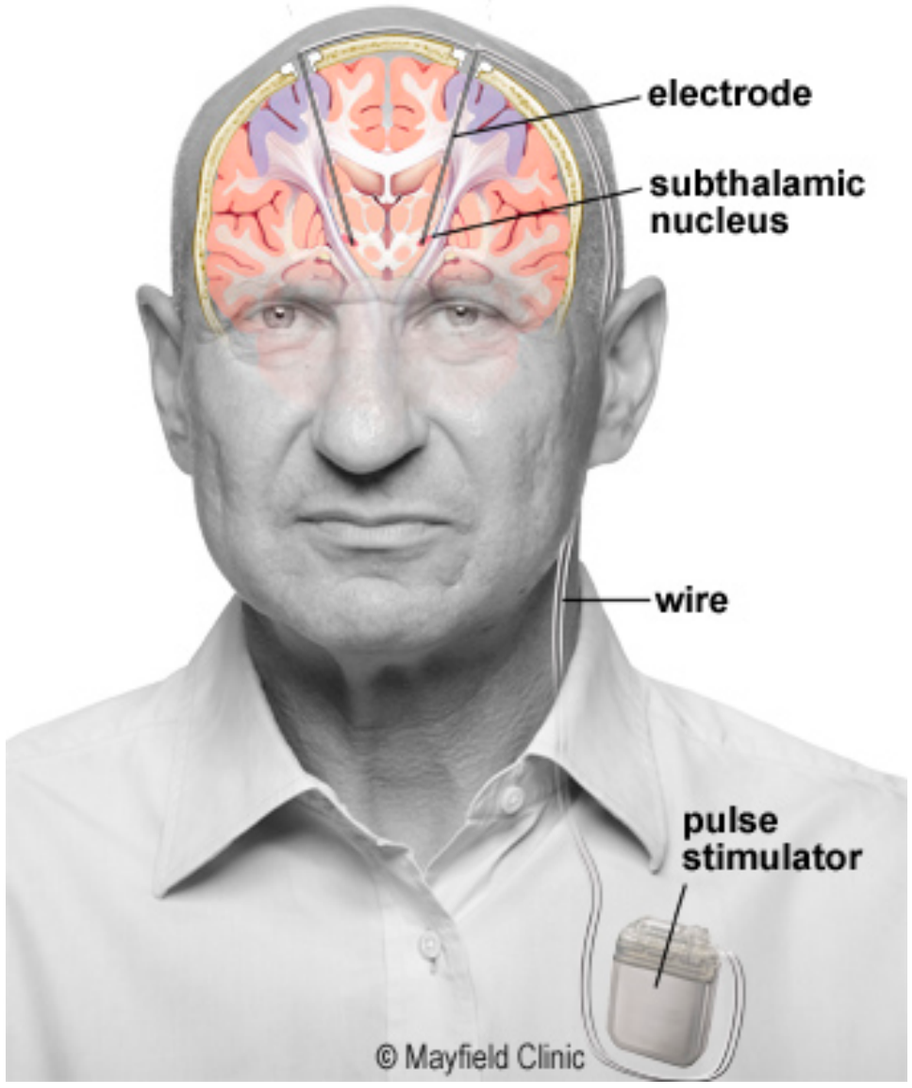


Image: https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&ved=2ahUKEwil2cbB2LLgAhUC4YMKHceqAtoQjRx6BAgBEAU&url=https%3A%2F%2Fwww.parkinsonsneurochallenge.org%2Fsarasota-parkinsons-disease-resources%2Fsarasota-what-is-parkinsons-disease.html&psig=AOvVaw3enZf8Q-OEYHP-hvQ161n7&ust=1549938694312654

Treatments



Medicine Image:https://www.preventionlane.org/wp-content/uploads/2015/09/pill-bottle.jpg
Brain Image: https://dbmmu5j6lxew.cloudfront.net/pe-dbs_fig1.jpg
Yoga Image:https://sunshineyogashack.com/wp-content/uploads/bb-plugin/cache/9N1A6695-circle.jpg
Food Image:https://previews.123rf.com/images/dusanzidar/dusanzidar1703/dusanzidar170300042/75076205-selection-of-healthy-food-on-white-background-healthy-diet-foods-for-heart-cholesterol-and-diabetes-.jpg
Clinical Trial Image:https://i1.wp.com/www.skepticalraptor.com/blog/wp-content/uploads/2017/12/hpv-vaccine-clinical-trials.jpg?fit=768%2C467&ssl=1

SCIENTIFIC REPORTS

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The Parkinson Disease gene SNCA: Evolutionary and structural insights with pathological implication

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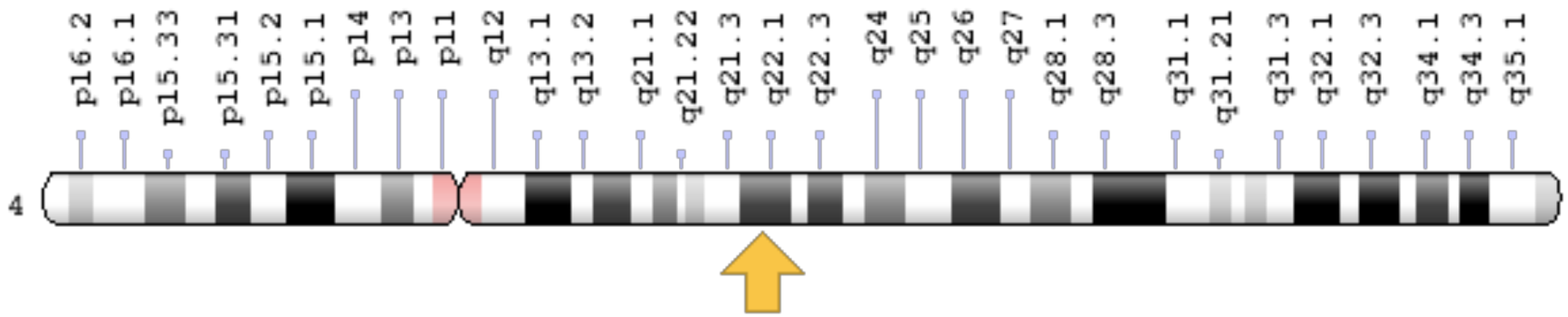
Irum Javaid Siddiqui, Nashaiman Pervaiz & Amir Ali Abbasi

After Alzheimer, Parkinson's disease (PD) is the second most common neurodegenerative disorder. Alpha synuclein (SNCA) is deemed as a major component of Lewy bodies, a neuropathological feature

What is SNCA?



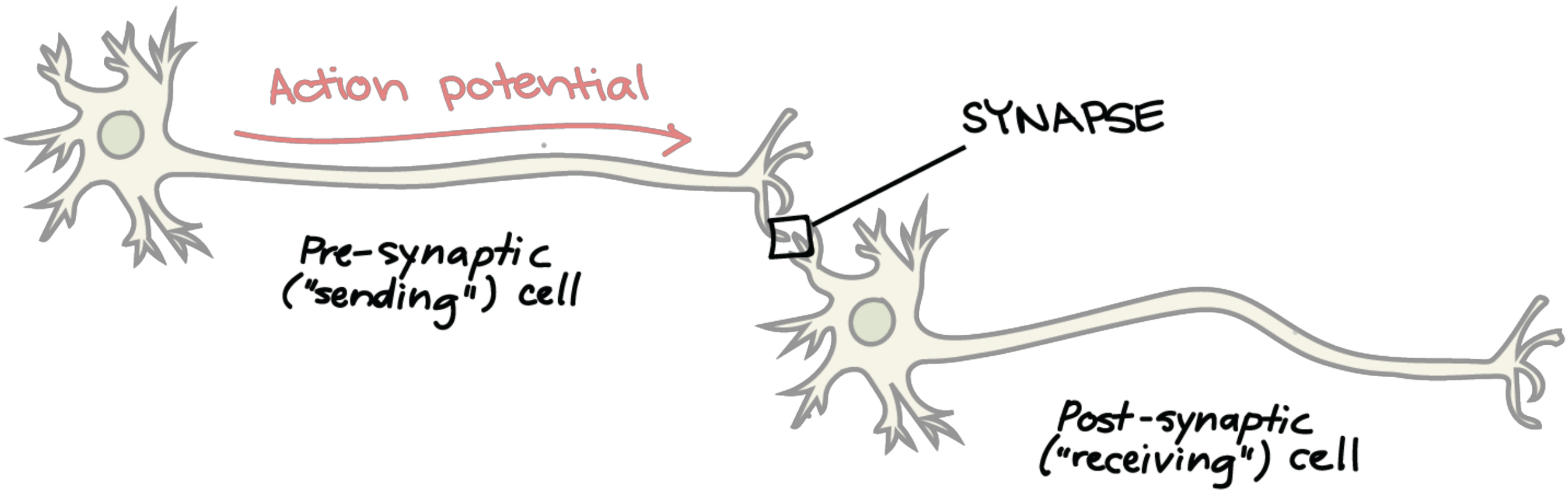
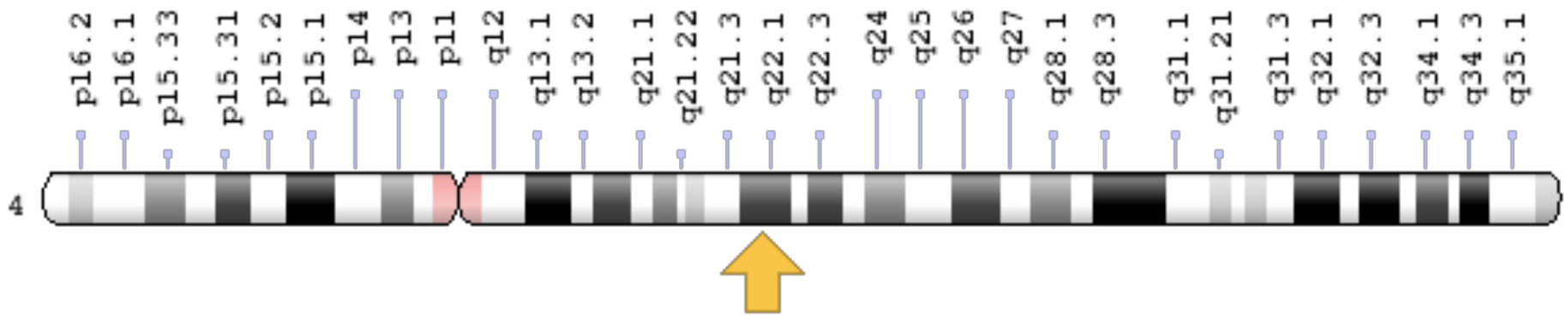


Image 1: https://ghr.nlm.nih.gov/gene/SNCA#location
Image 2: https://www.khanacademy.org/science/biology/human-biology/neuron-nervous-system/a/the-synapse

What is SNCA?



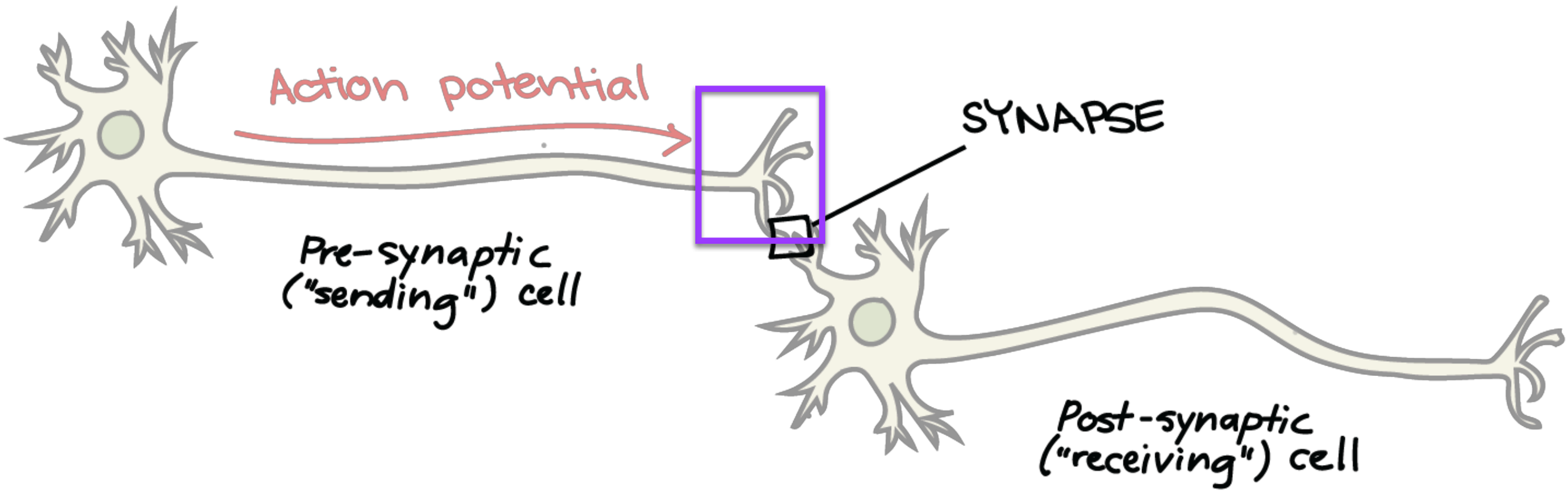
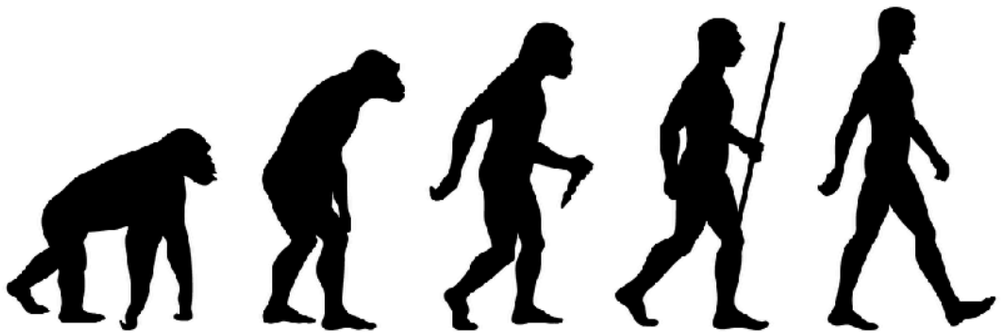


Image 1: https://ghr.nlm.nih.gov/gene/SNCA#location
Image 2: https://www.khanacademy.org/science/biology/human-biology/neuron-nervous-system/a/the-synapse

How can studying phylogeny characterize SNCA function?



Evolutionary Rate

+

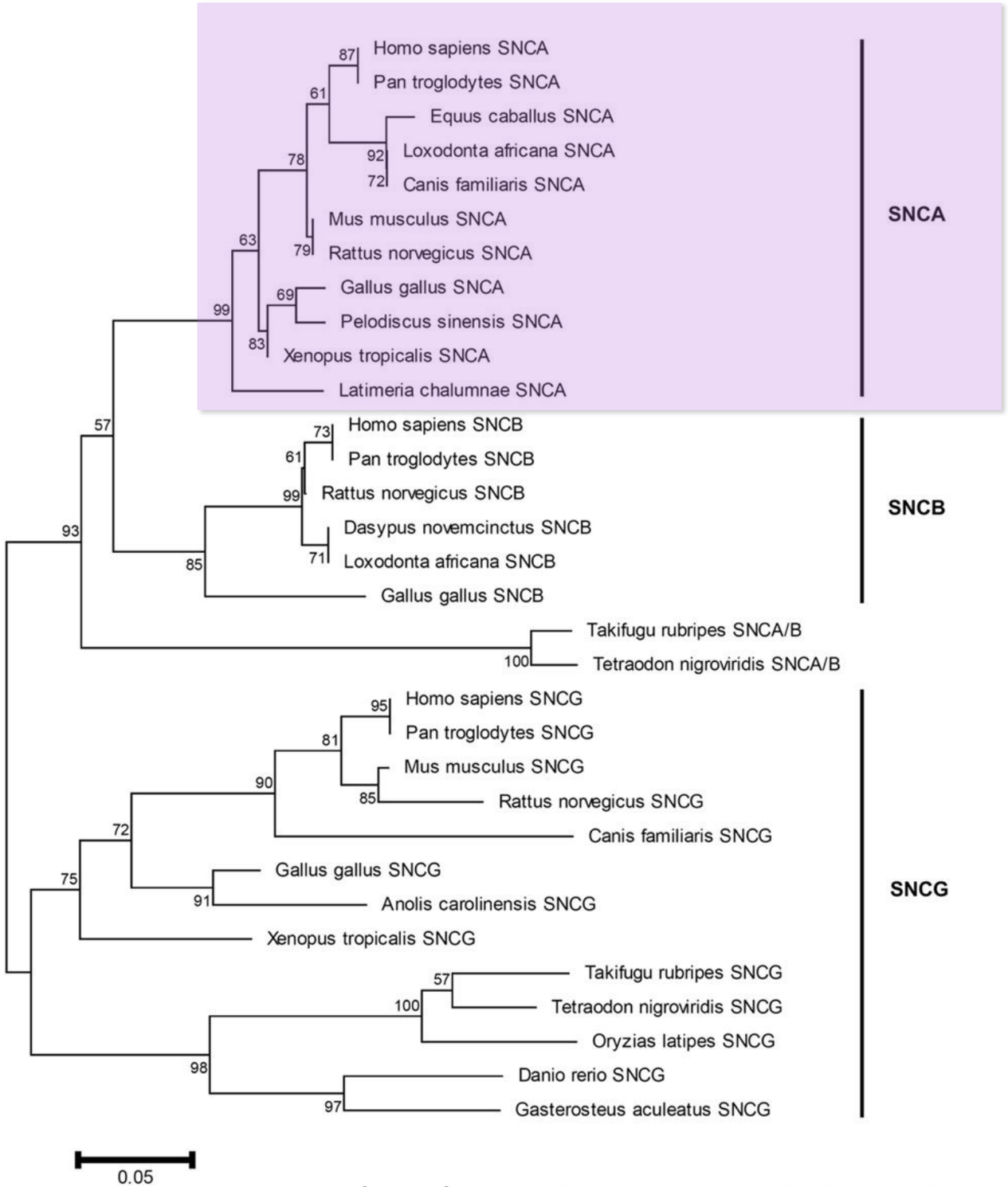
Structural Information

=

Functional Changes

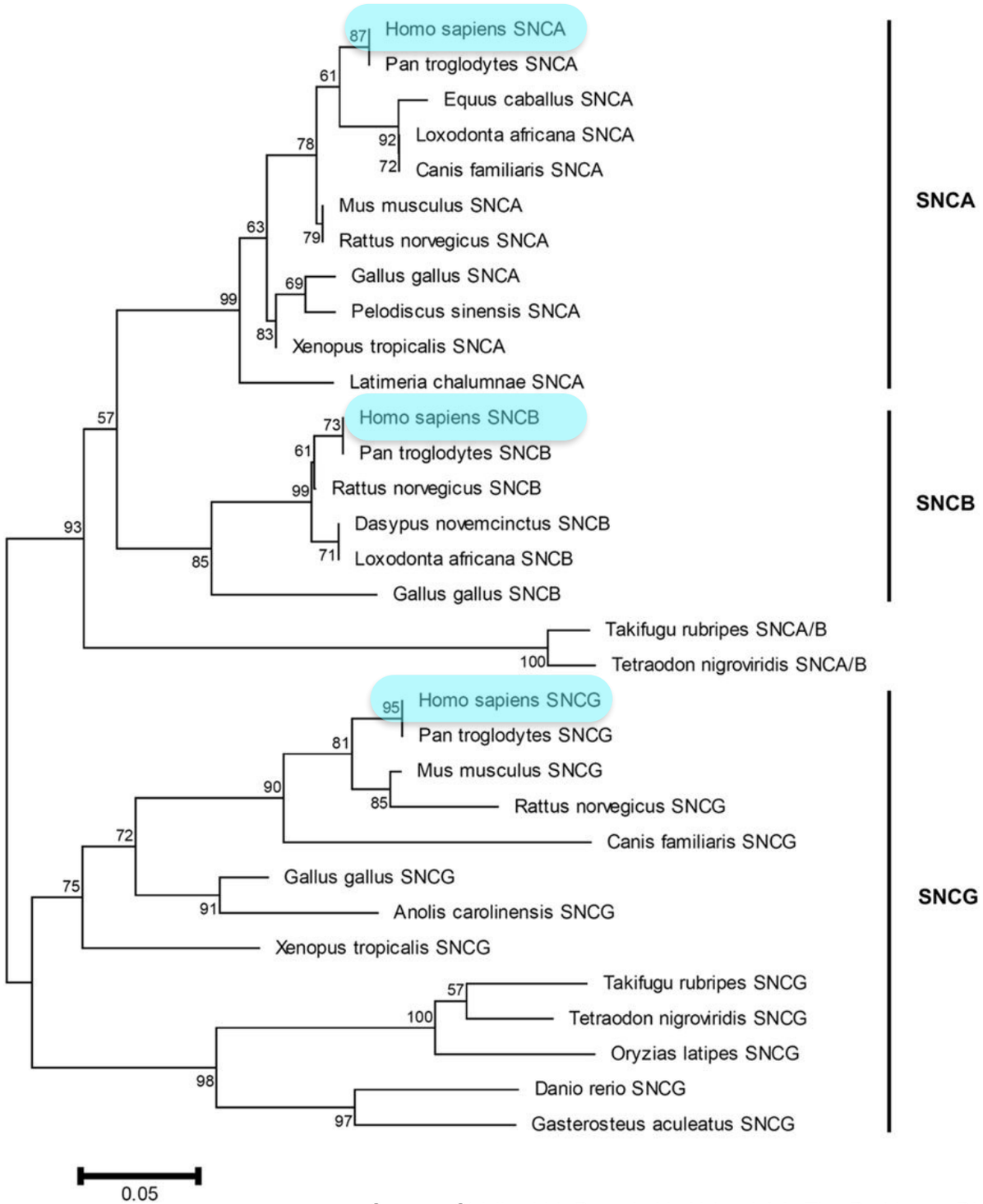
Image 1:http://blogs.discovermagazine.com/d-brief/2018/08/09/human-evolution-changes-caused-mental-disorders/
Image 2:https://sutherlands.com/d/Building-Materials/2

What are the orthologs of SNCA?



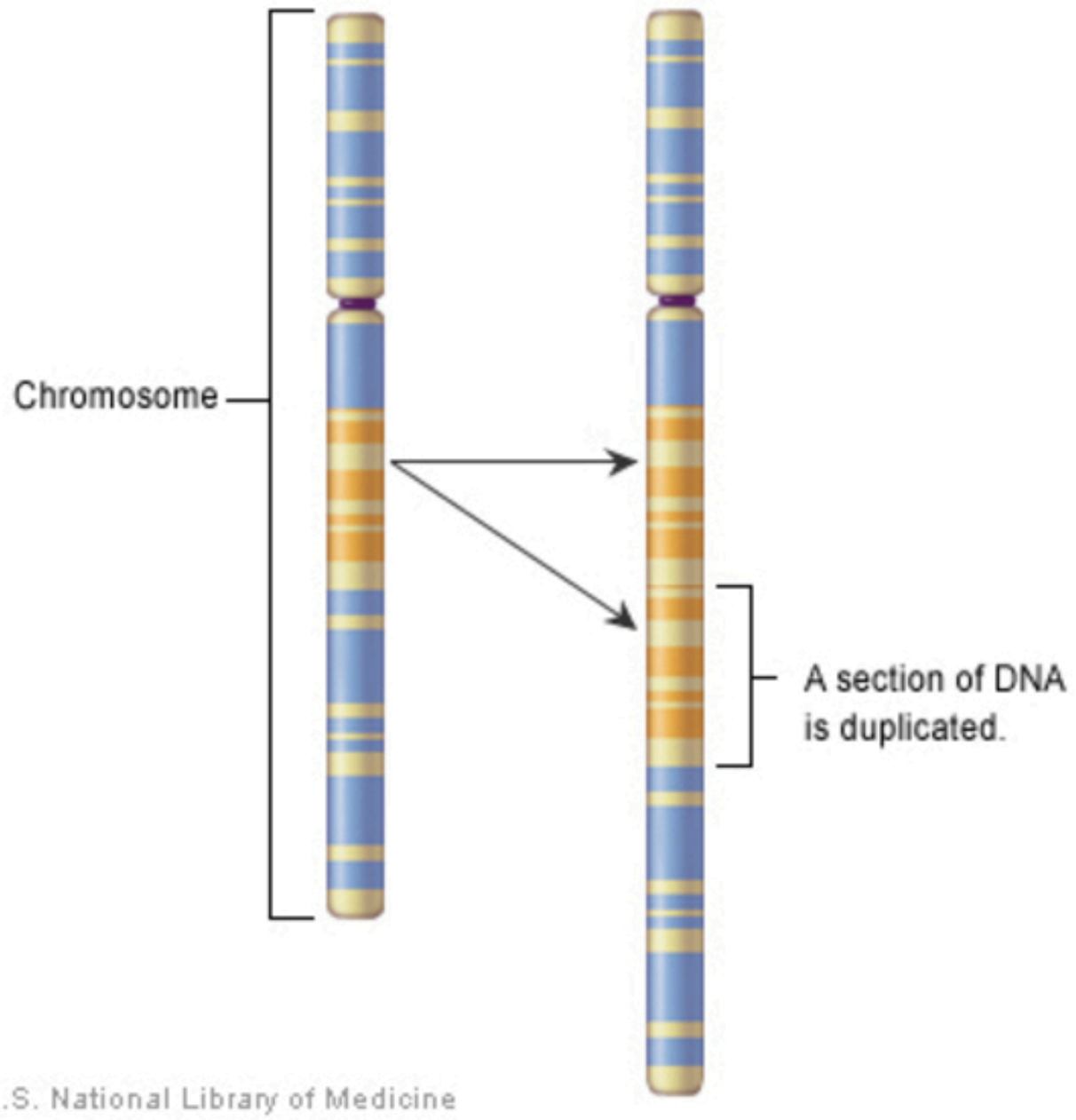
Source: Siddiqui IJ, Pervaiz N, Abbasi AA. The Parkinson Disease gene SNCA: Evolutionary and structural insights with pathological implication

What are the paralogs of SNCA?



Source: Siddiqui IJ, Pervaiz N, Abbasi AA. The Parkinson Disease gene SNCA: Evolutionary and structural insights with pathological implication

What is Gene Duplication?



Gene duplications are important for genetic diversity and speciation.

Image:http://www.daviddarling.info/encyclopedia/D/duplication.html

What happens when a gene is duplicated?

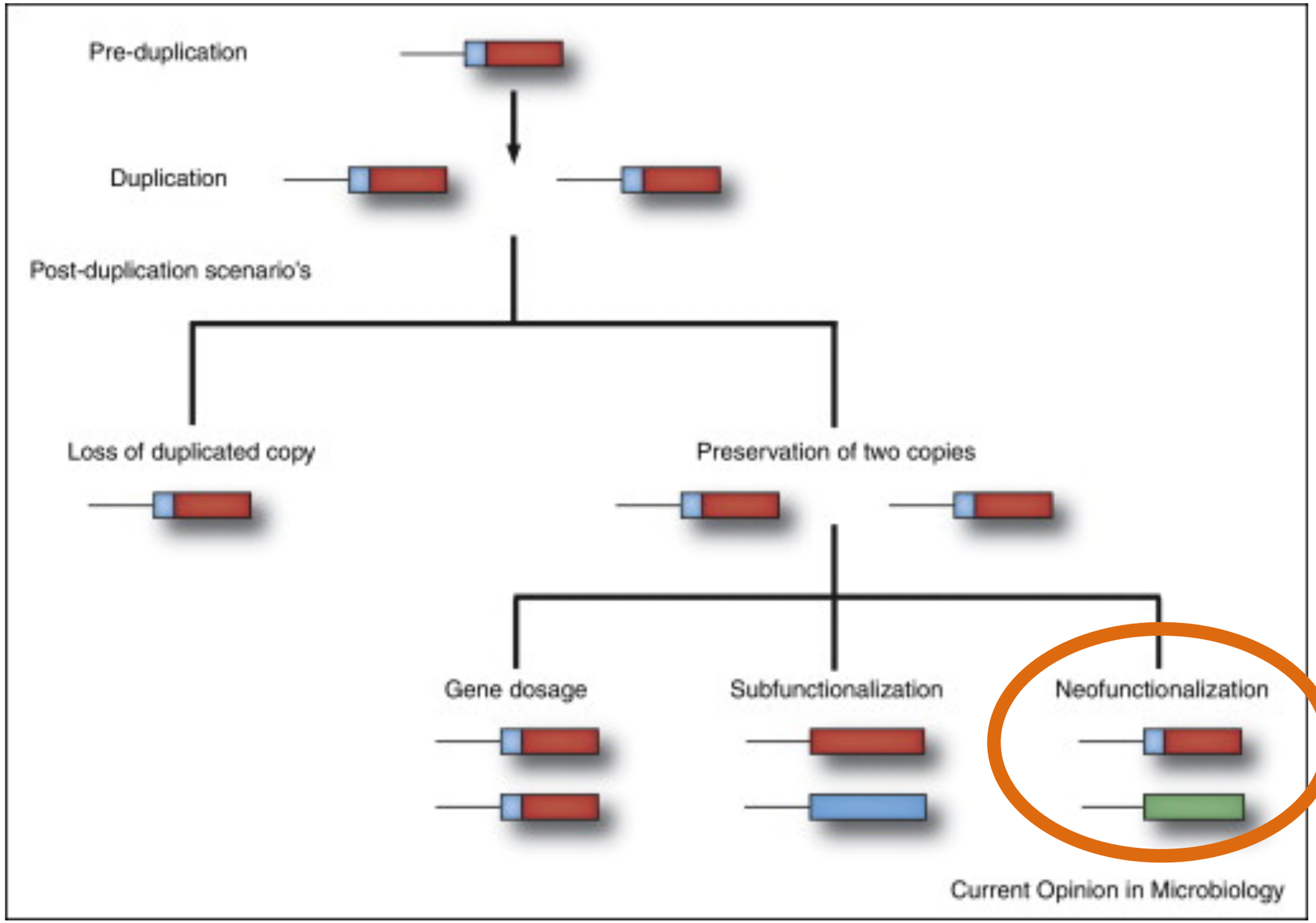
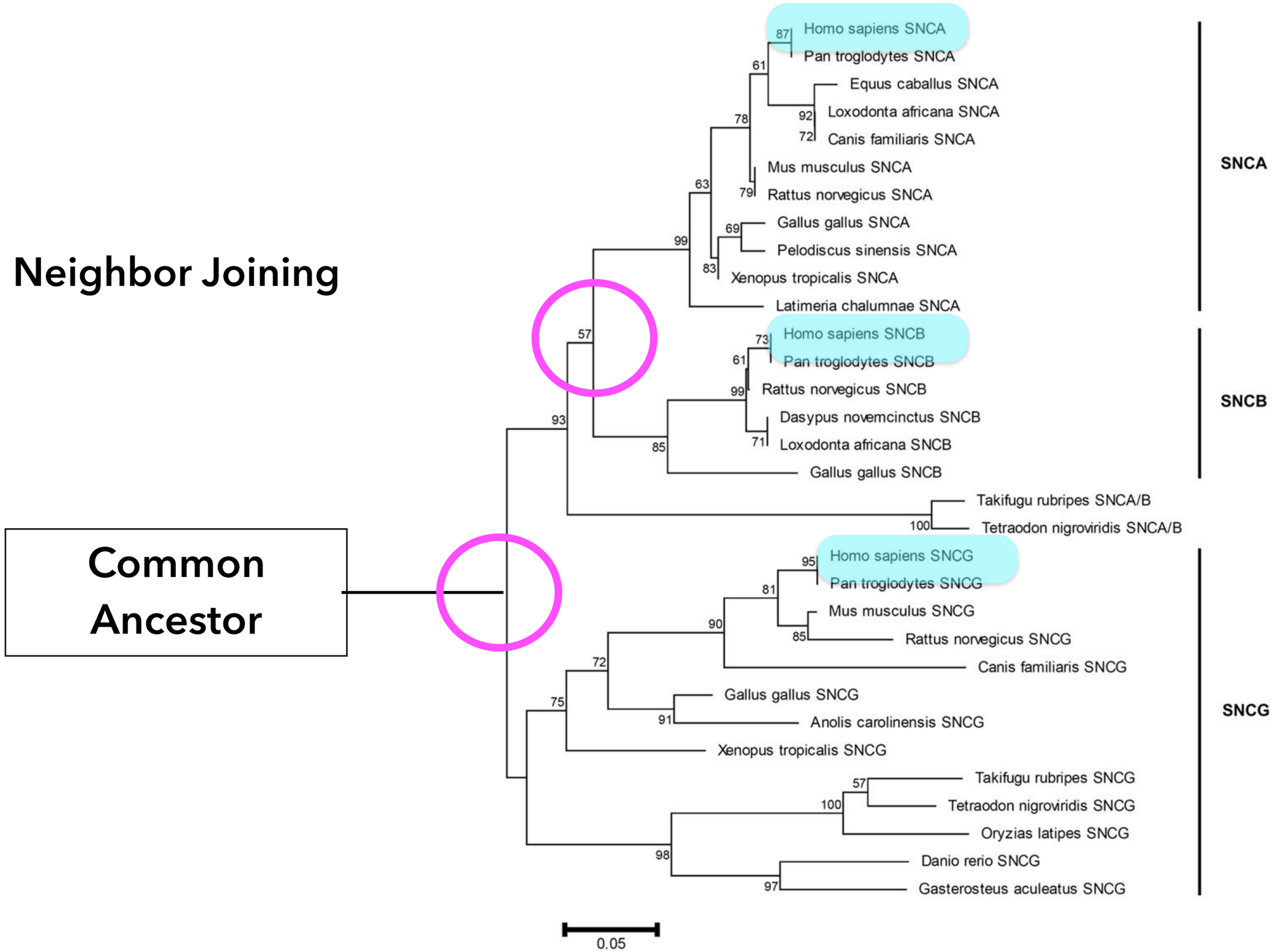


Image:https://www.researchgate.net/figure/Possible-fates-of-duplicated-genes-The-most-common-outcome-of-gene-duplication-is-loss_fig3_280391130

How did gene duplication affect the evolution of SNCA?

Neighbor Joining

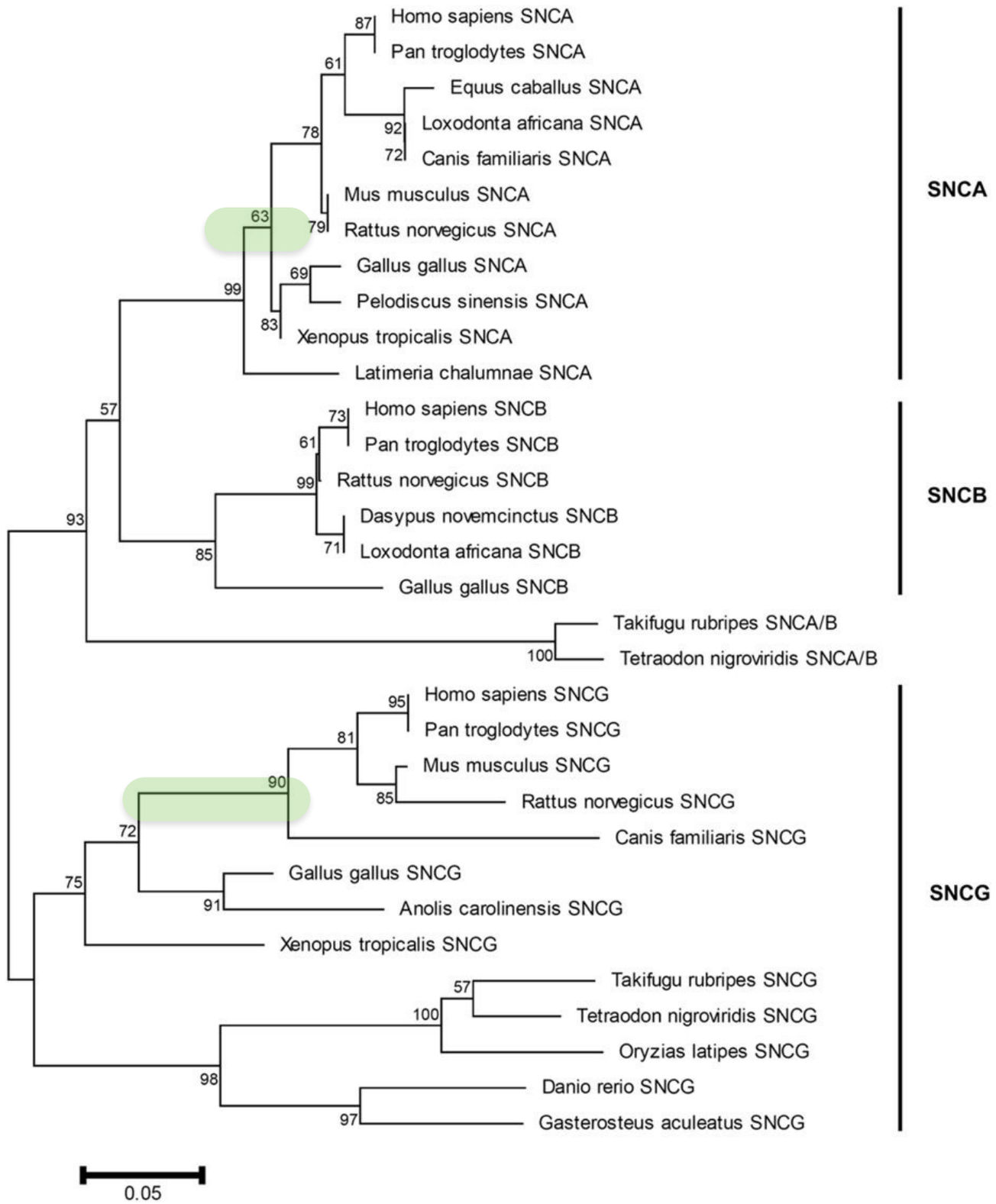
Common Ancestor



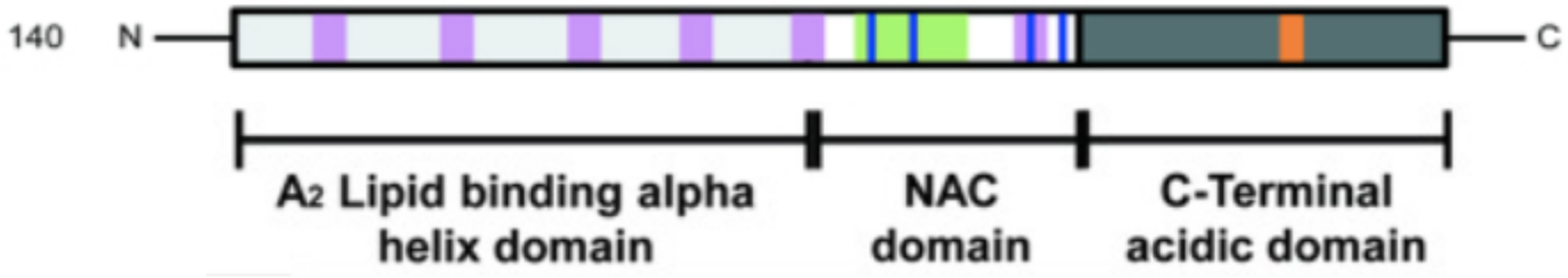
What else does the phylogenic tree tell us?

SNCG evolved fastest.

Note: Only vertebrates are represented.



What does the human SNCA protein look like?



KXKEGV - Interaction with Phospolipids

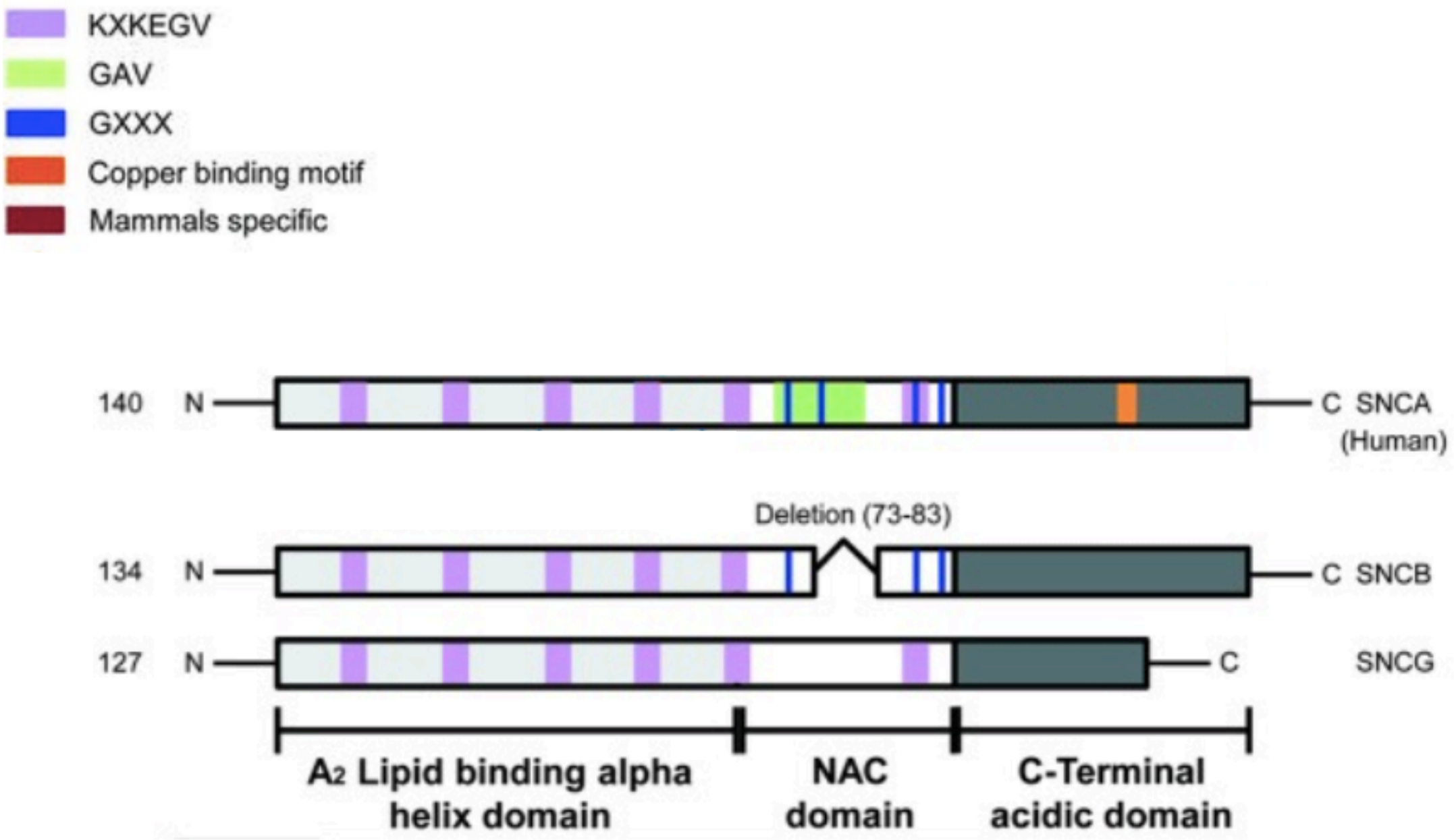
GAV - SNCA Aggregation and Fibrillation

GXXX

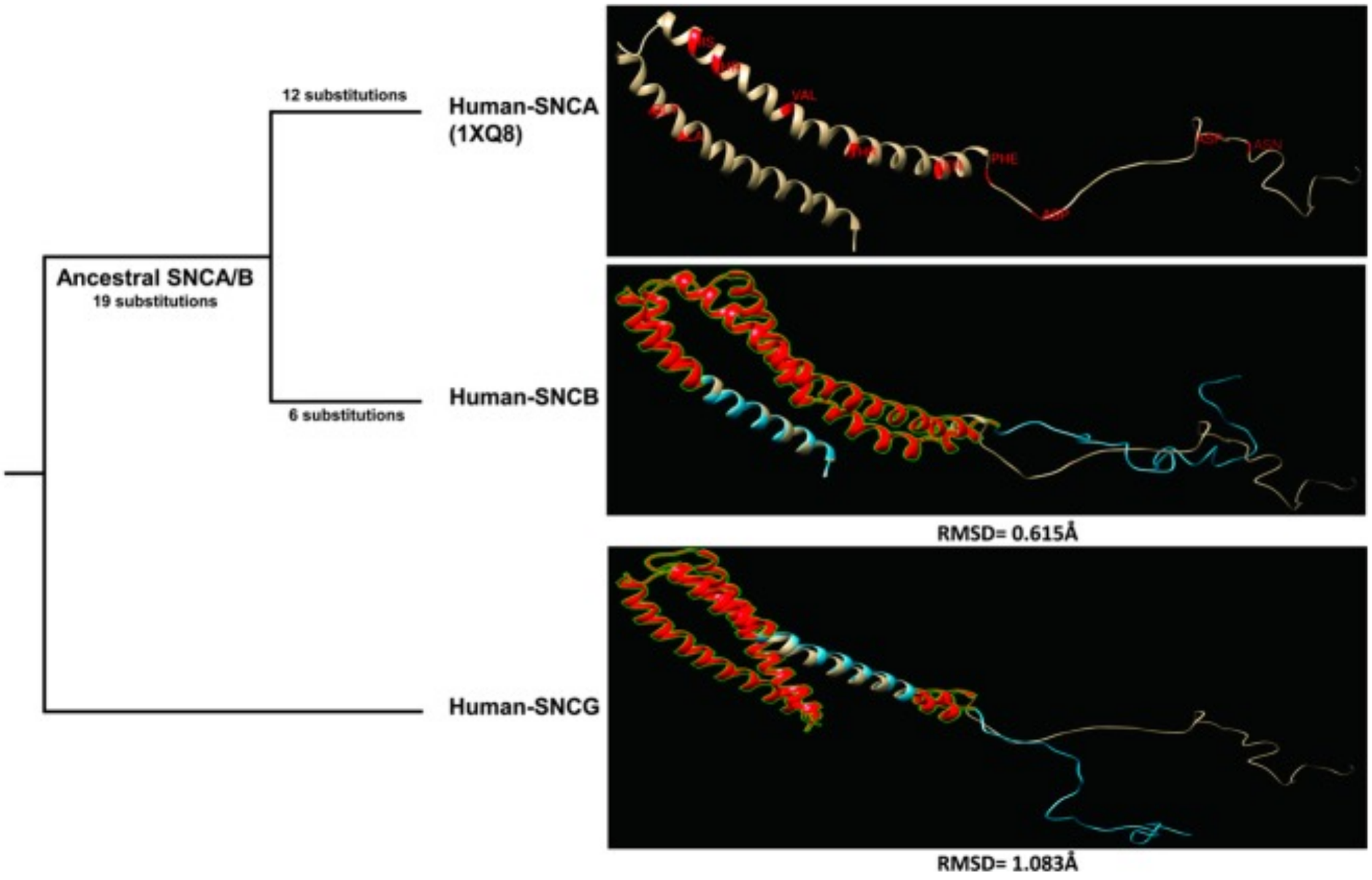
Copper binding motif - Accelerates Aggregation and Implicated in Pathology

Mammals specific

What do SNCA paralogs look like?

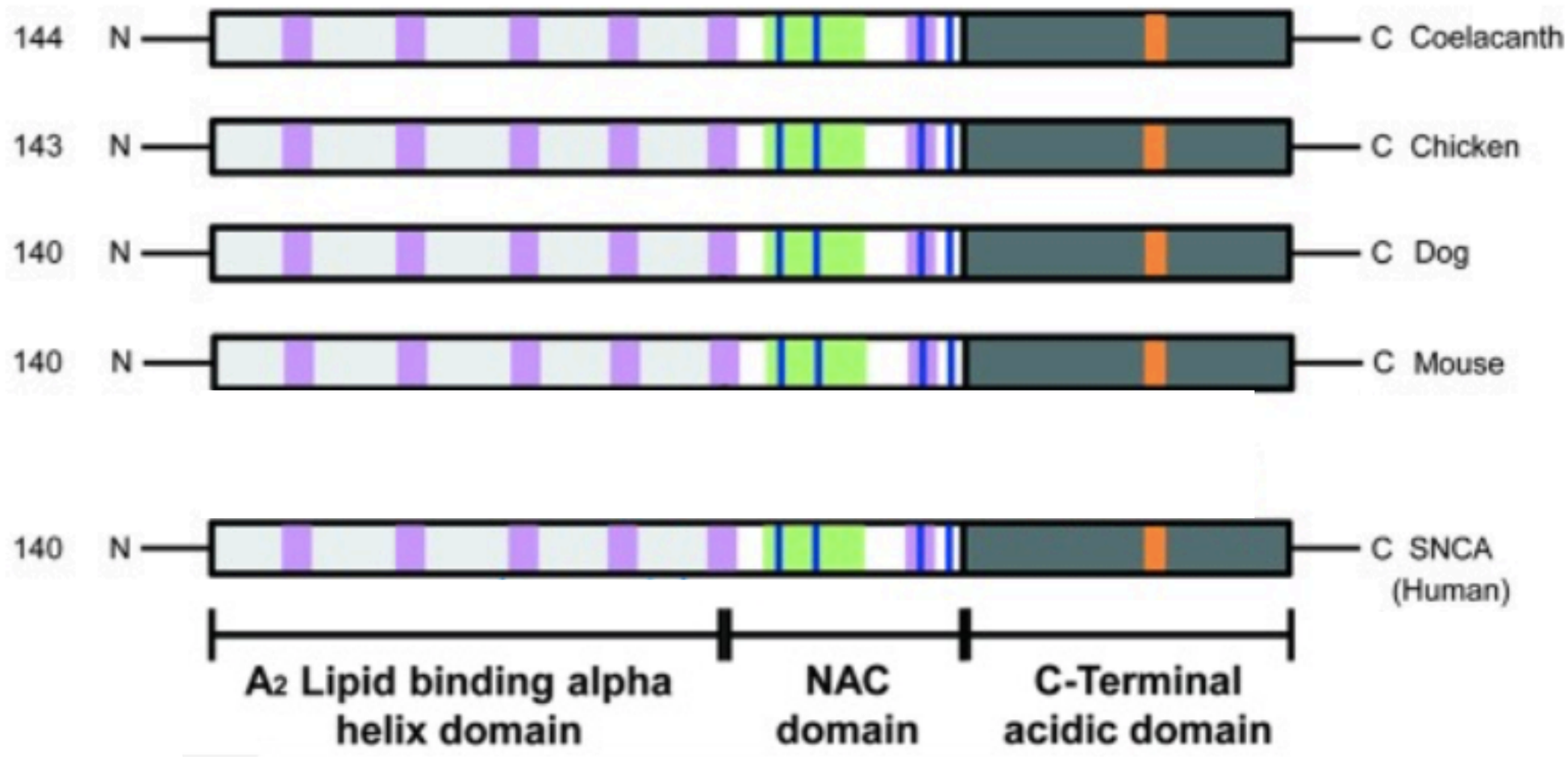


How do SNCA paralogs compare structurally?



Despite high sequence homology, SNCB and SNCG are highly deviant from SNCA in the lipid binding and NAC domains.

What do SNCA orthologs look like?



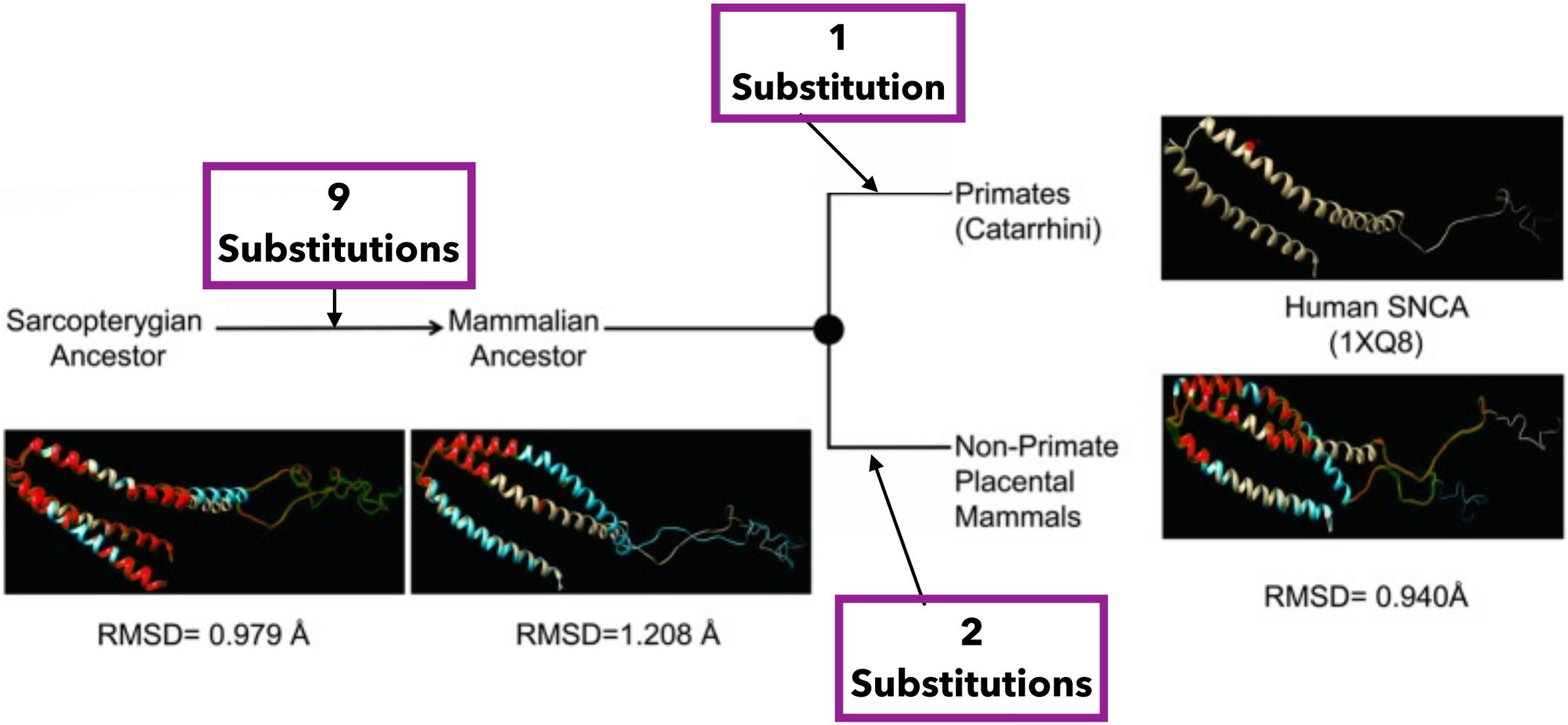
SNCA structure is highly conserved among orthologs.

How are the orthologs different?

Amino Acid Position	Ancestral	Mammal Replacement	Non-Primate Mammal Replacement	Primate Replacement	Preference	Stability Impact
53	T			A	none	-
64	S	T			+	-
68	G		E		-	-
87	N	S			+	-
94	L	F			none	-
95	V		G		-	-
101	A	G			none	-
107	F	A			-	-
112	M	I			+	-
113	M	L			+	-
129	P	S			-	+
132	E	G			-	-

12 total SNCA amino acid changes have occurred since divergence of SNCA.

What did the structural evolution of the orthologs look like?

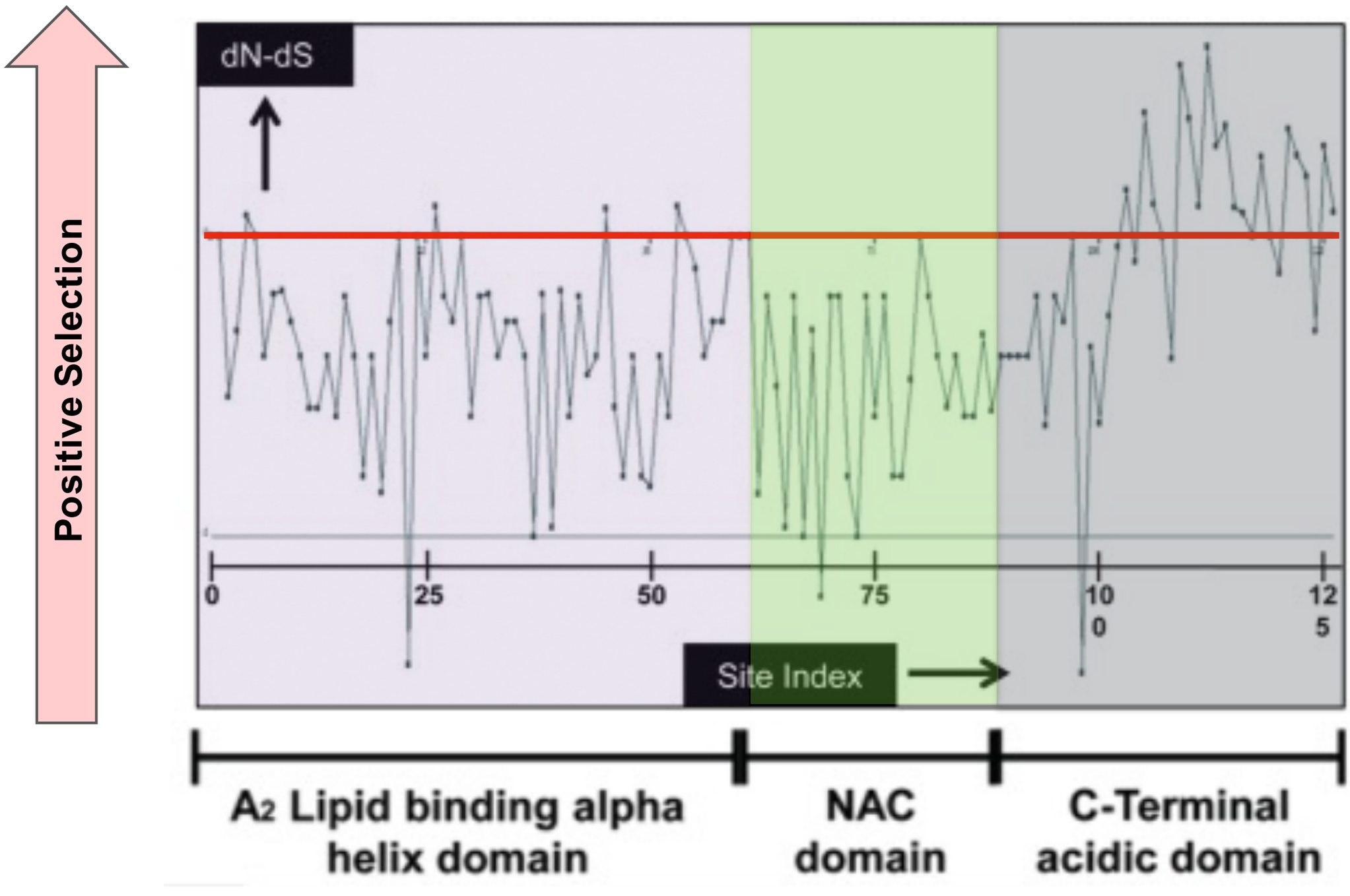


Are these amino acid changes good or bad?

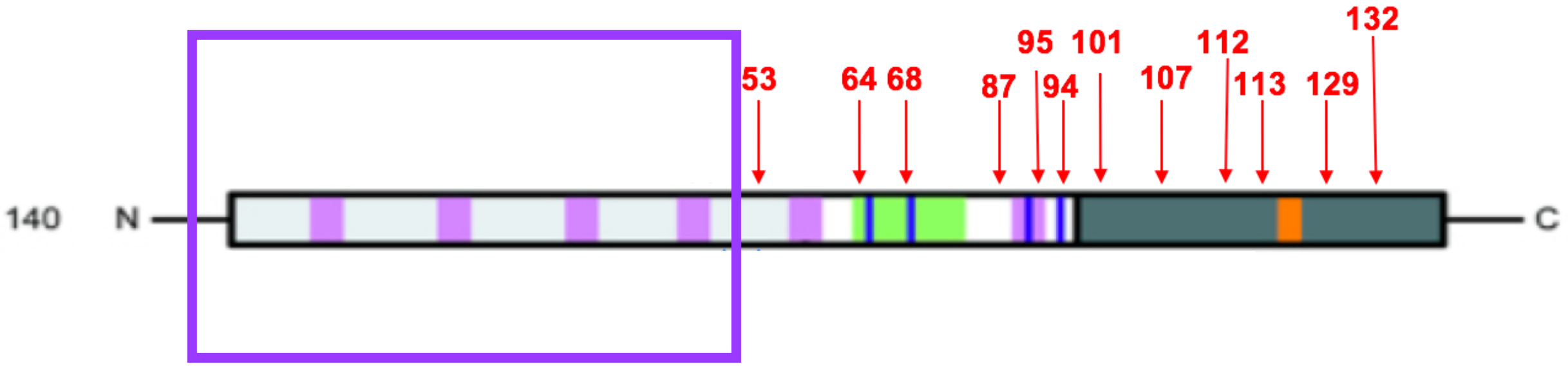
Amino Acid Position	Ancestral	Mammal Replacement	Non-Primate Mammal Replacement	Primate Replacement	Preference	Stability Impact
53	T			A	none	-
64	S	T			+	-
68	G		E		-	-
87	N	S			+	-
94	L	F			none	-
95	V		G		-	-
101	A	G			none	-
107	F	A			-	-
112	M	I			+	-
113	M	L			+	-
129	P	S			-	+
132	E	G			-	-

12 total SNCA amino acid changes have occurred since divergence of SNCA.

Are the mutations seen in SNCA selected for?



What do these changes mean for the protein?



What region of the protein is most important?

Comparison between lineages	Major change in backbone torsion angles (residue no)	Critical region
Primates ↔ Non Primate Placental Mammals	32–44,47–58 64–74 92–113	(32–58) Lipid Binding Domain
Primates ↔ Mammalian Ancestor	37–58 70	
Primates ↔ Sarcopterygian Ancestor	8–12,14,15,18,24,25, 29–47, 50–55, 58 65–77 93–107, 109–140	

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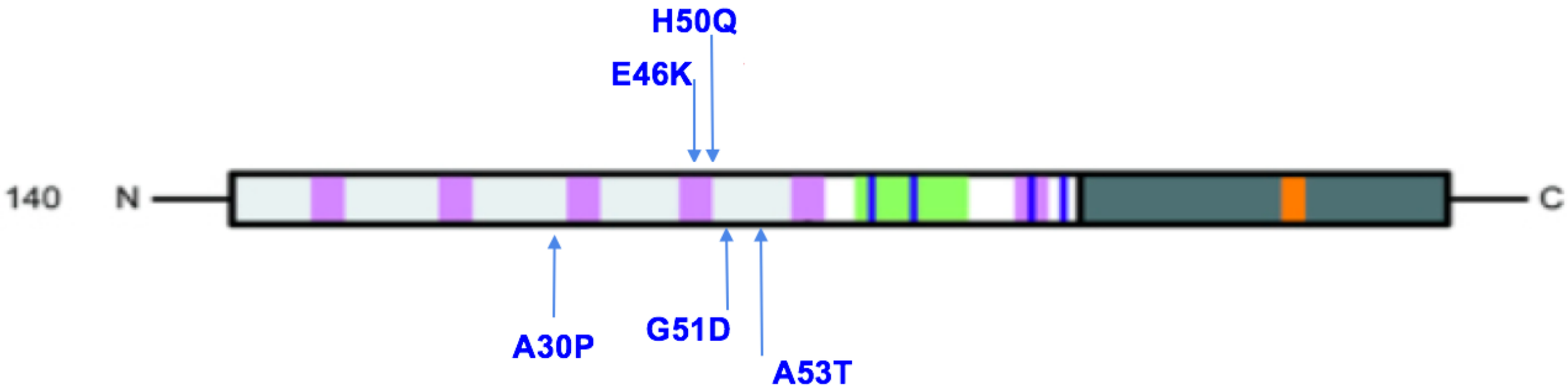
	65–77	
	93–107, 109–140	

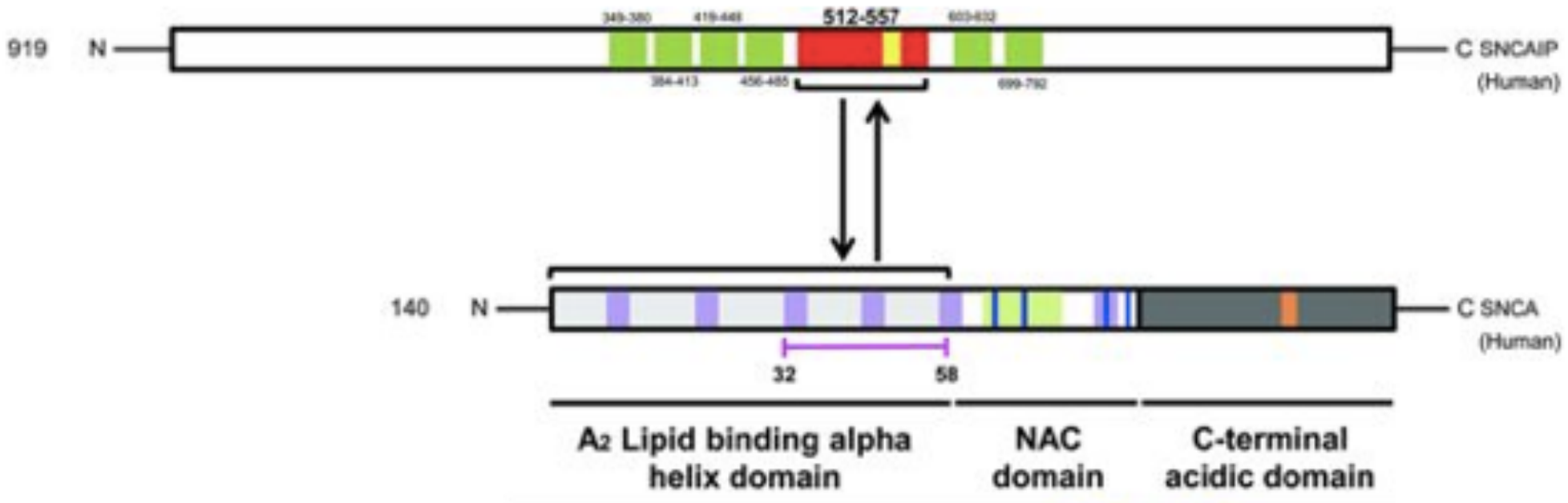
The lipid binding domain undergoes constant structural evolution despite high sequence conservation.

What does the critical region mean for Parkinson's Disease?



All of the mutations have different structural effects, but all cause high deviance in the critical region (32-58).

Why is the critical region so important?

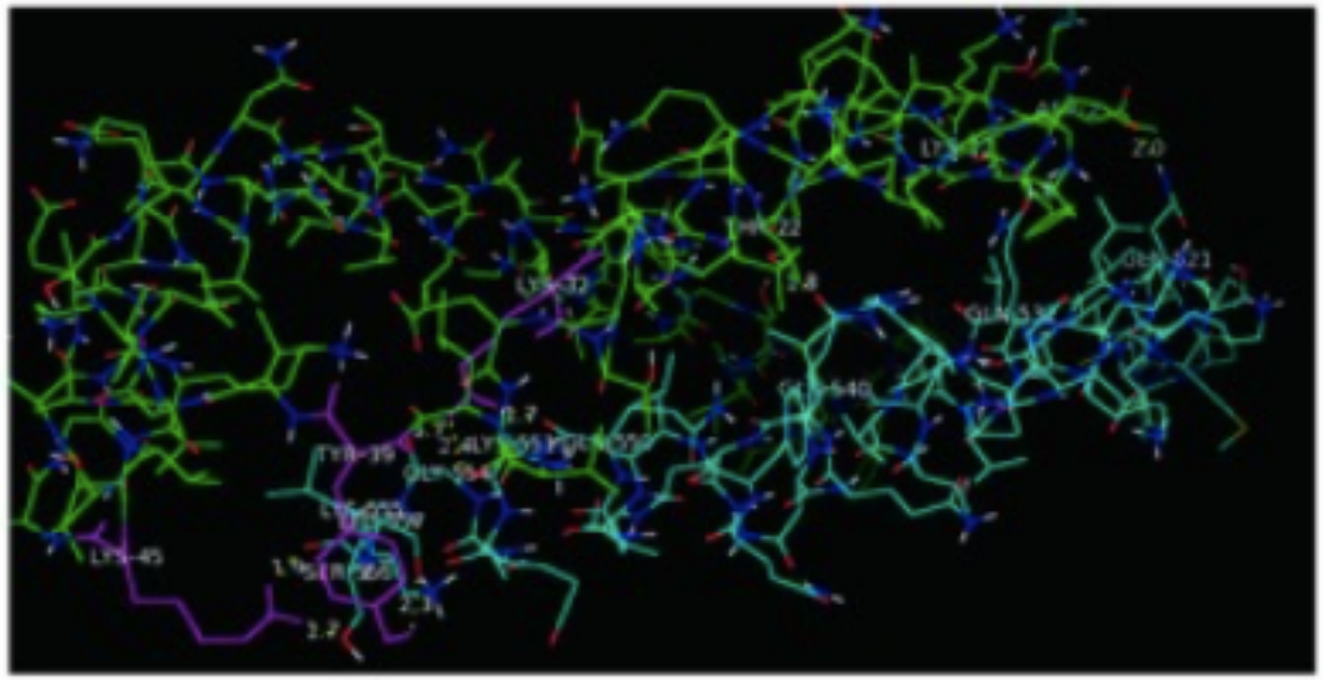


Synphilin-1 Coiled-Coil Domain

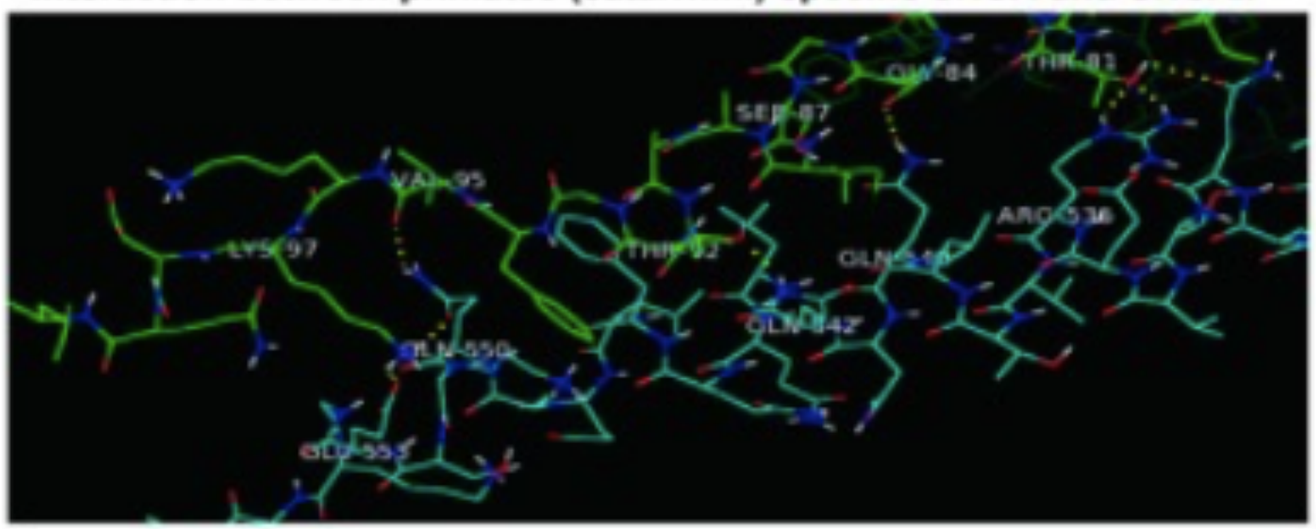
Critical Region (32-58)

Synphilin-1 interacts with SNCA at the synapse to facilitate its function.

How does this interaction differ as a result of mutation?

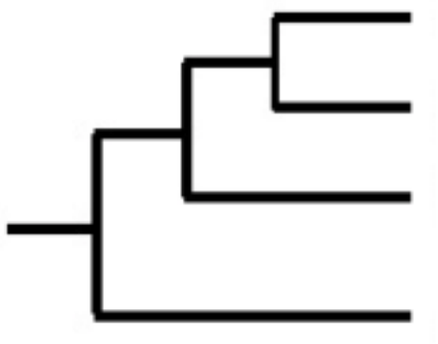


Interaction between primates (catarrhini) specific SNCA and SNCAIP



Interaction between mutant SNCA-A30P and SNCAIP

Summary



Phylogenic analysis indicates the N-terminal sequence of SNCA is highly conserved and changes to the sequence are selected against.

Structural analysis identified the lipid binding domain as critical for the maintenance of SNCA's function

Interaction analysis identified this critical region as paramount to SNCA synaptic function as well as a promising therapeutic target.

Image 1:Source: Baum, D. Reading a Phylogenetic Tree:The Meaning of Monophyletic Groups
Image 2: https://www.shutterstock.com/search/blueprint
Image 3:https://www.sciencebuddies.org/science-fair-projects/project-ideas/HumBio_p045/human-biology-health/pills

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