

SEMA5A & Cri du Chat syndrome



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What is Cri du Chat syndrome?

microcephaly

cognitive impairment

respiratory, circulatory, sensory, and skeletal problems

malformed ears

small birth weight

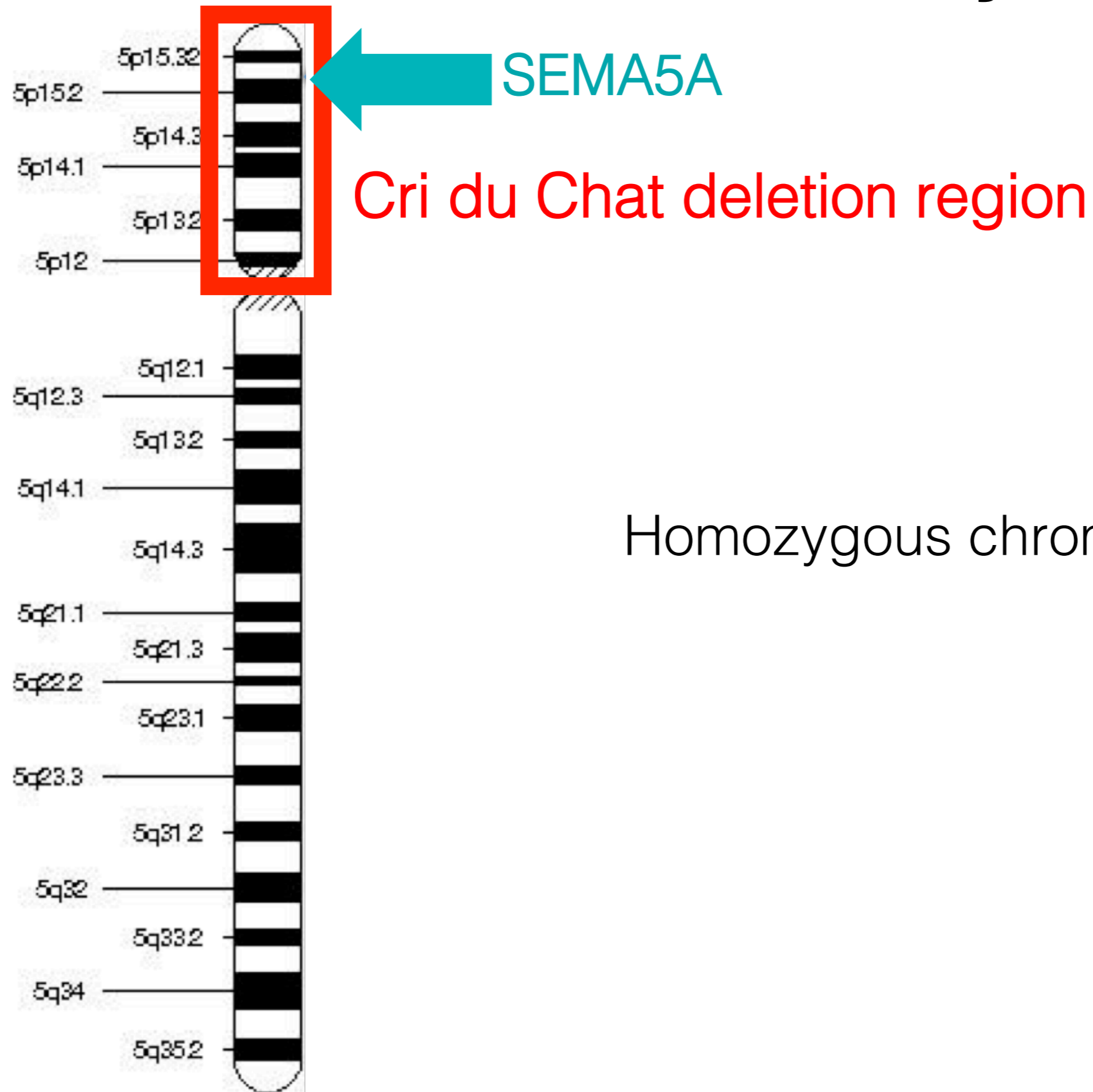
poor muscle tone



Gid's cat-like cry

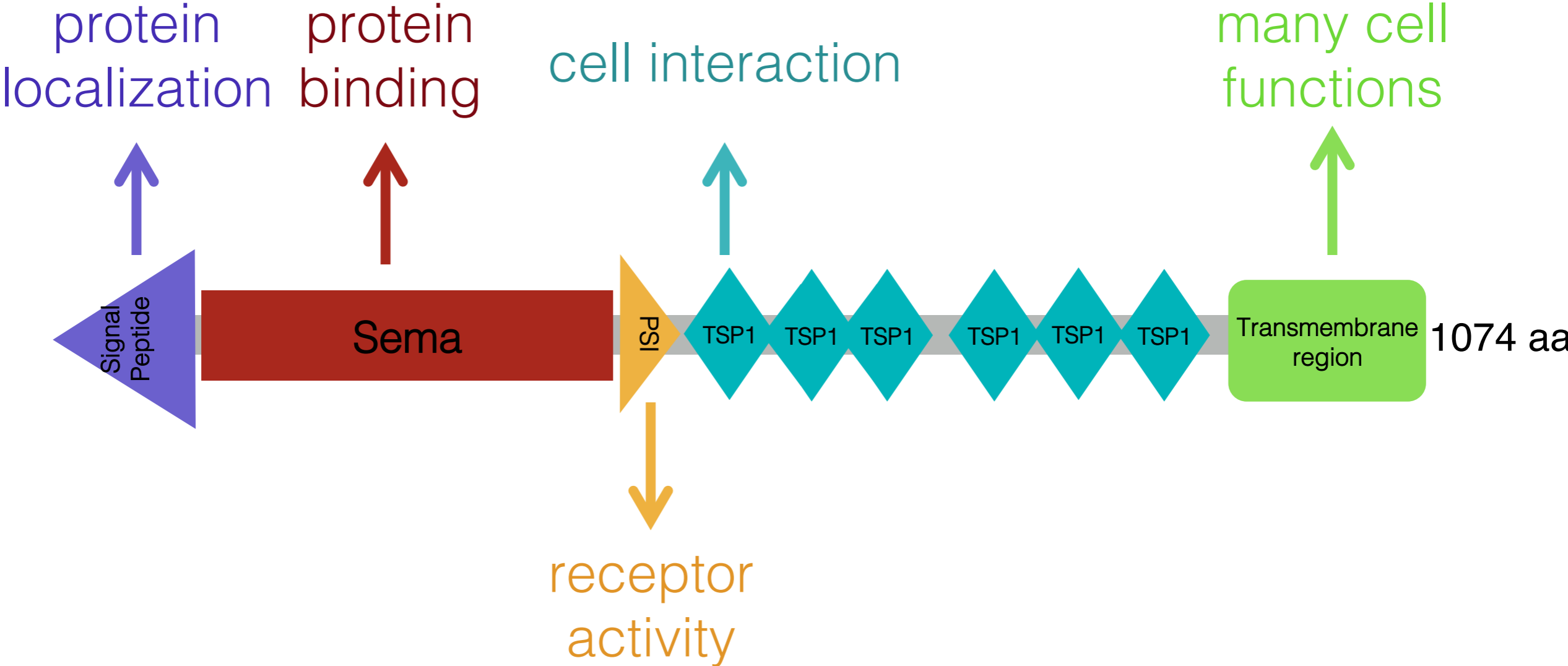
Image: <https://shsgdp.wikispaces.com/file/view/trisomy18a.jpg/134508901/241x288/trisomy18a.jpg>
Audio: <https://www.youtube.com/watch?v=TYQrzFABQHQ>

What causes Cri du Chat syndrome?



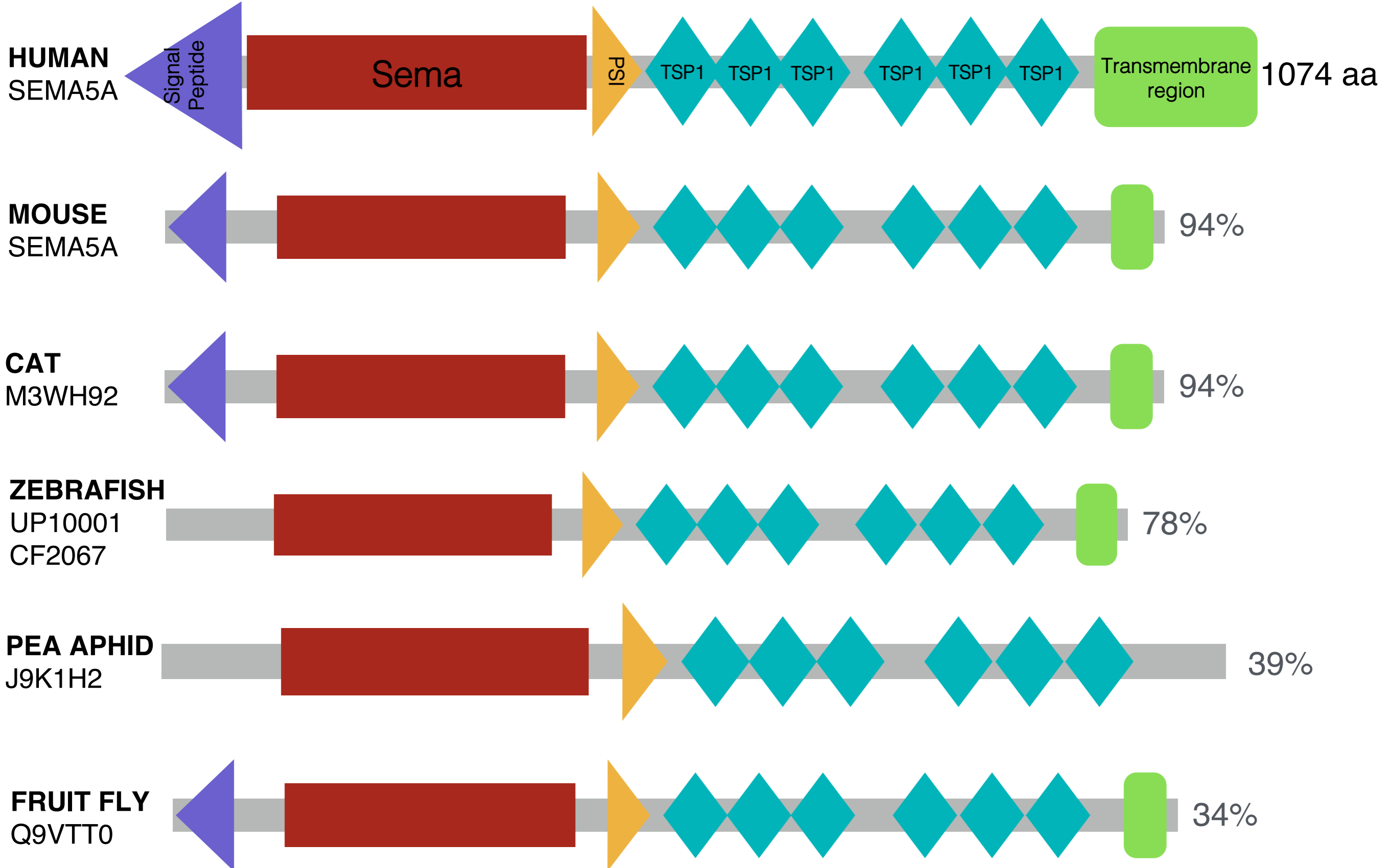
Homozygous chromosomal deletion

What protein domains are in SEMA5A?



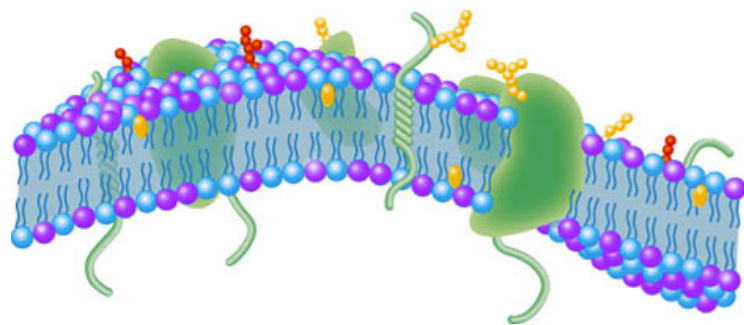
neuron development and vascularization

How well conserved is SEMA5A?



Where and how does SEMA5A function?

Cellular components



cell membrane

Biological processes



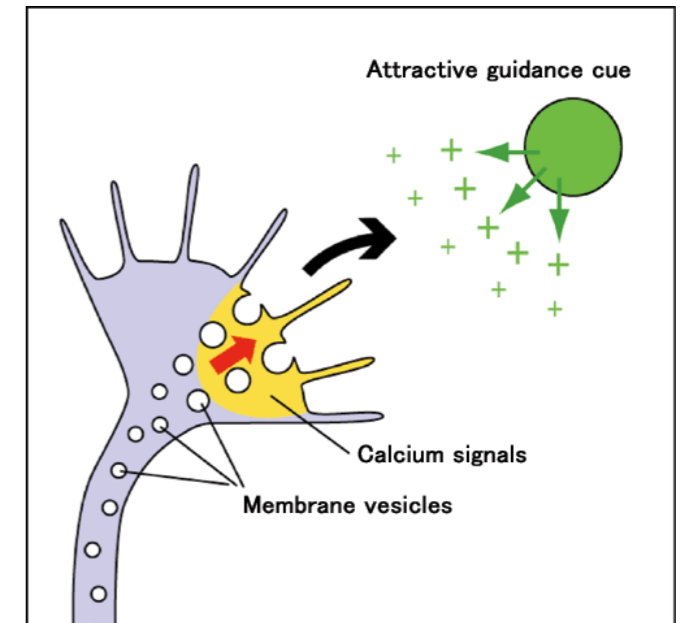
signal transduction

axon guidance

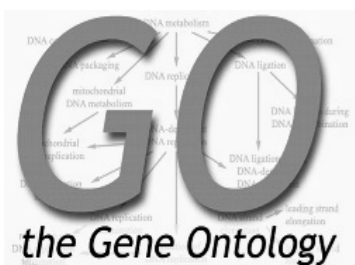
blood vessel patterning

branching morphogenesis

Molecular function



axon guidance receptor

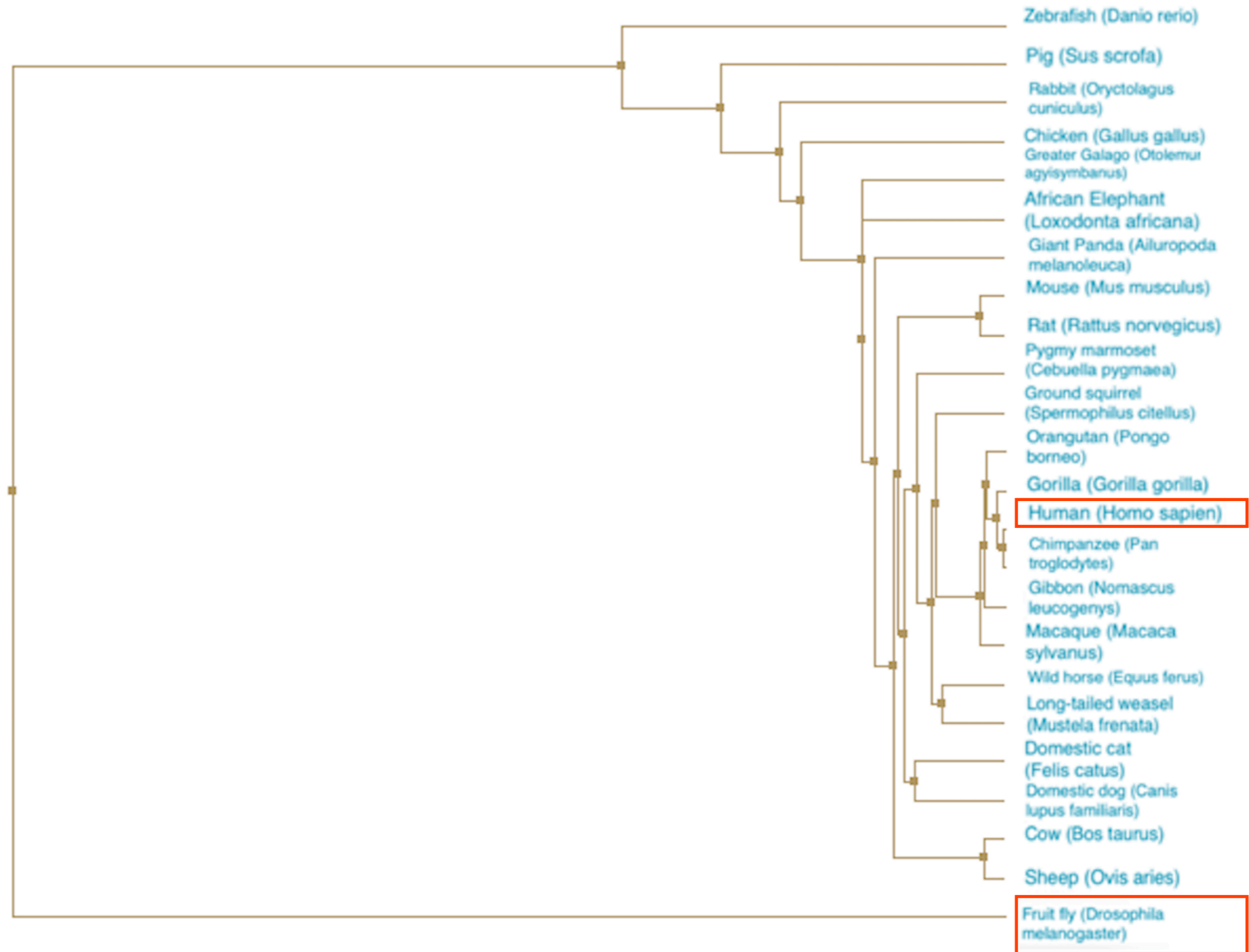


cell membrane: <http://www.scs.illinois.edu/~mlkraft/images/cell%20membrane%20smaller.jpg>

Blood vessels: <https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcRqNadS9MGb0o4SsGV66zJa2d1mzraZjwQPuLoG4D7p1bOygdj->

axon guidance receptor: <http://www.brain.riken.jp/bsi-news/bsinews38/files/research0103-biq-e.gif>

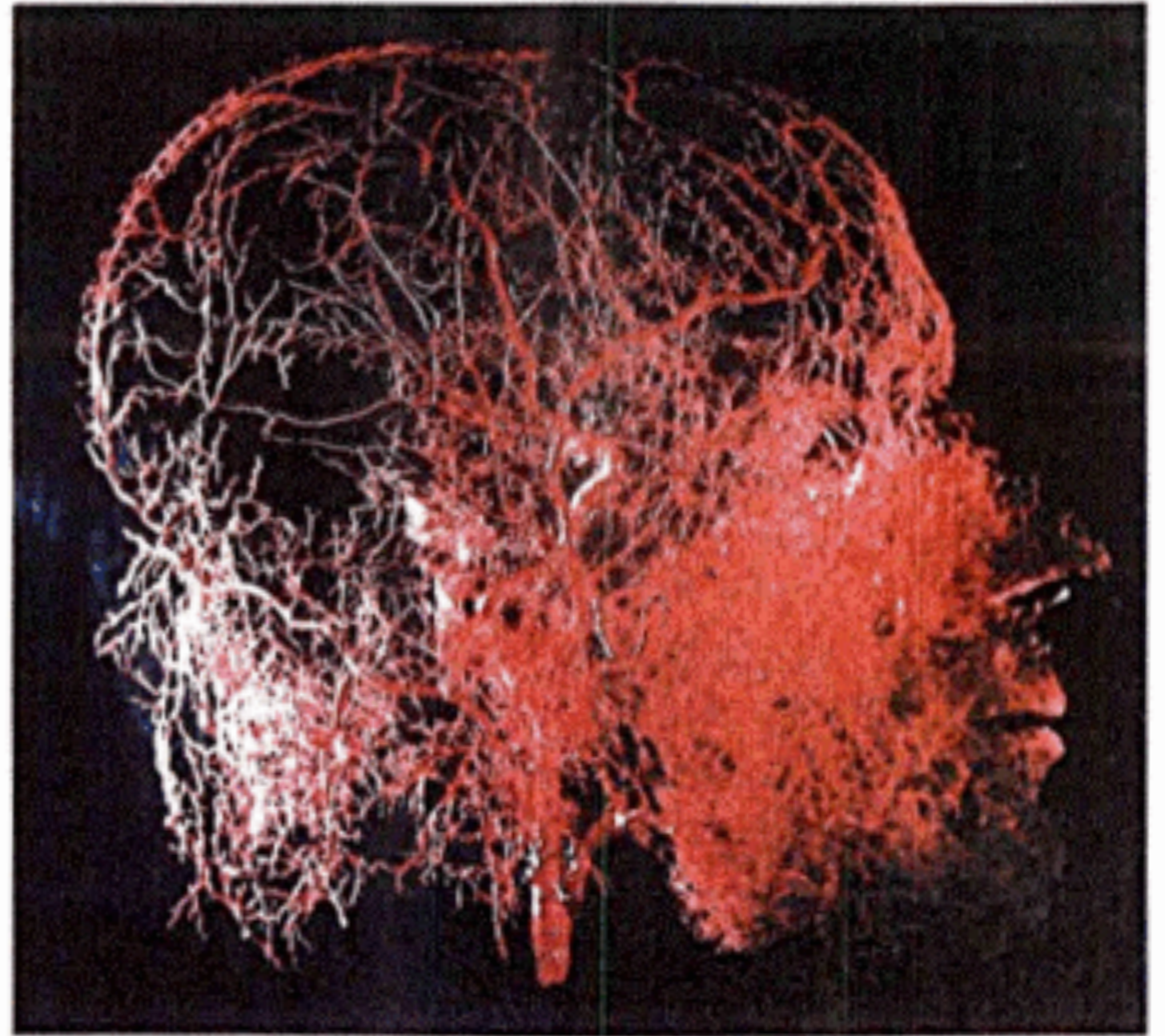
Phylogeny: how well conserved is SEMA5A?



average distance using percent identity

Gap in knowledge: How does SEMA5A function in vascularization?

SEMA5A

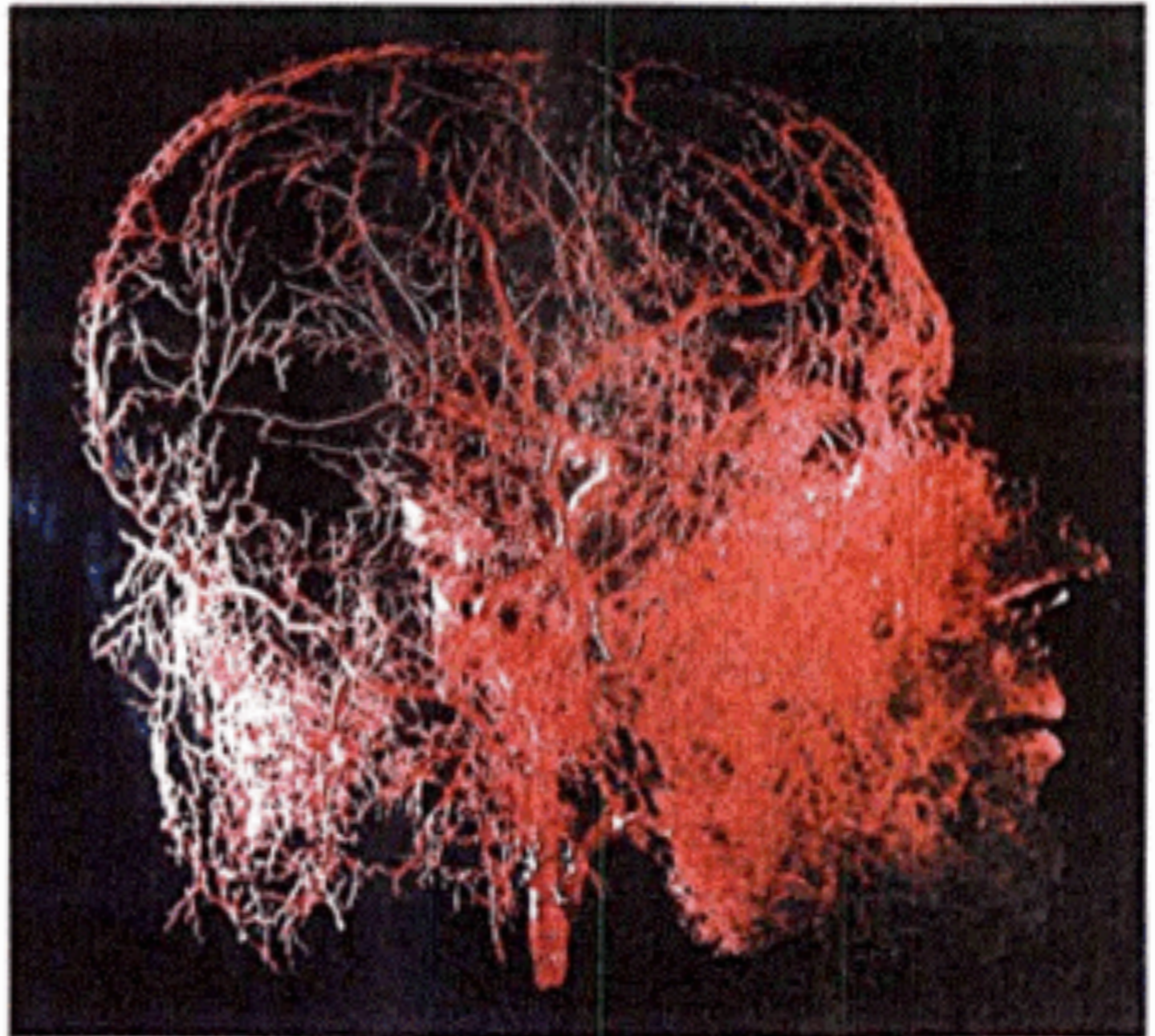


Hypothesis: SEMA5A necessary for localization signal pathways and proper vascular positioning

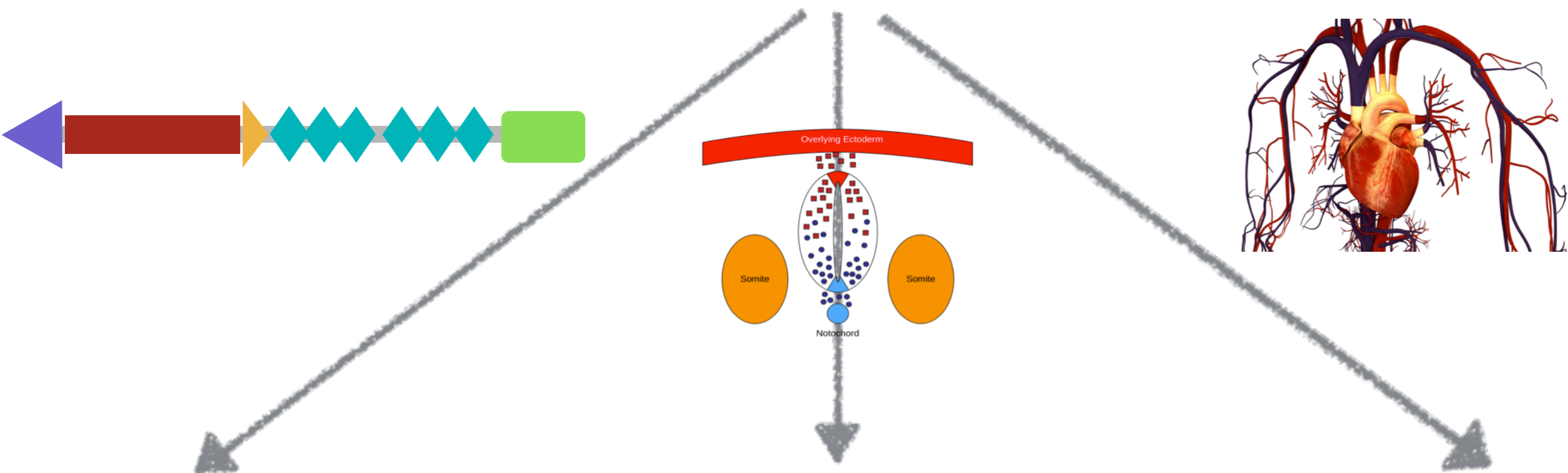
SEMA5A



signal
pathways



Primary goal: Determine the proteomic changes that contribute to abnormal vascularization



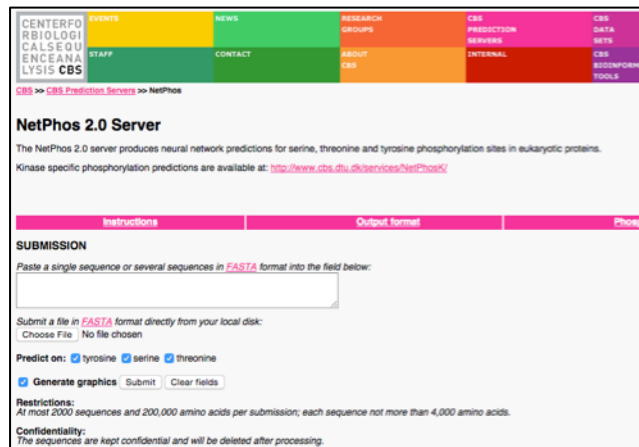
Aim 1: Identify important phosphorylation sites that regulate vascularization

Aim 2: Identify new SEMA5A binding partners that regulate SEMA5A localization

Aim 3: Identify phosphorylation site differences in vascular organisms

Aim 1: Determine predicted and conserved post-translational modifications involved in vascularization

Approach:

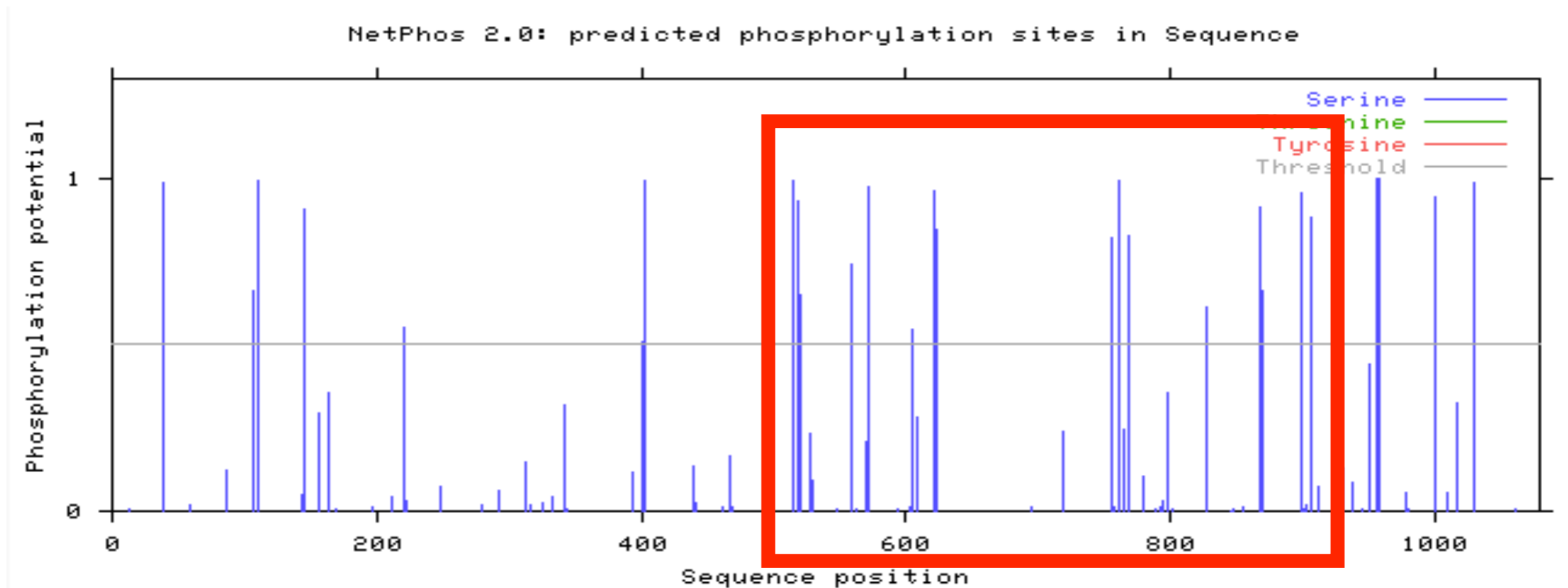


mass
spectrometry

Determine the importance of SEMA5A in vascular patterning

Aim 1 cont.: Determine predicted and conserved post-translational modifications involved in vascularization

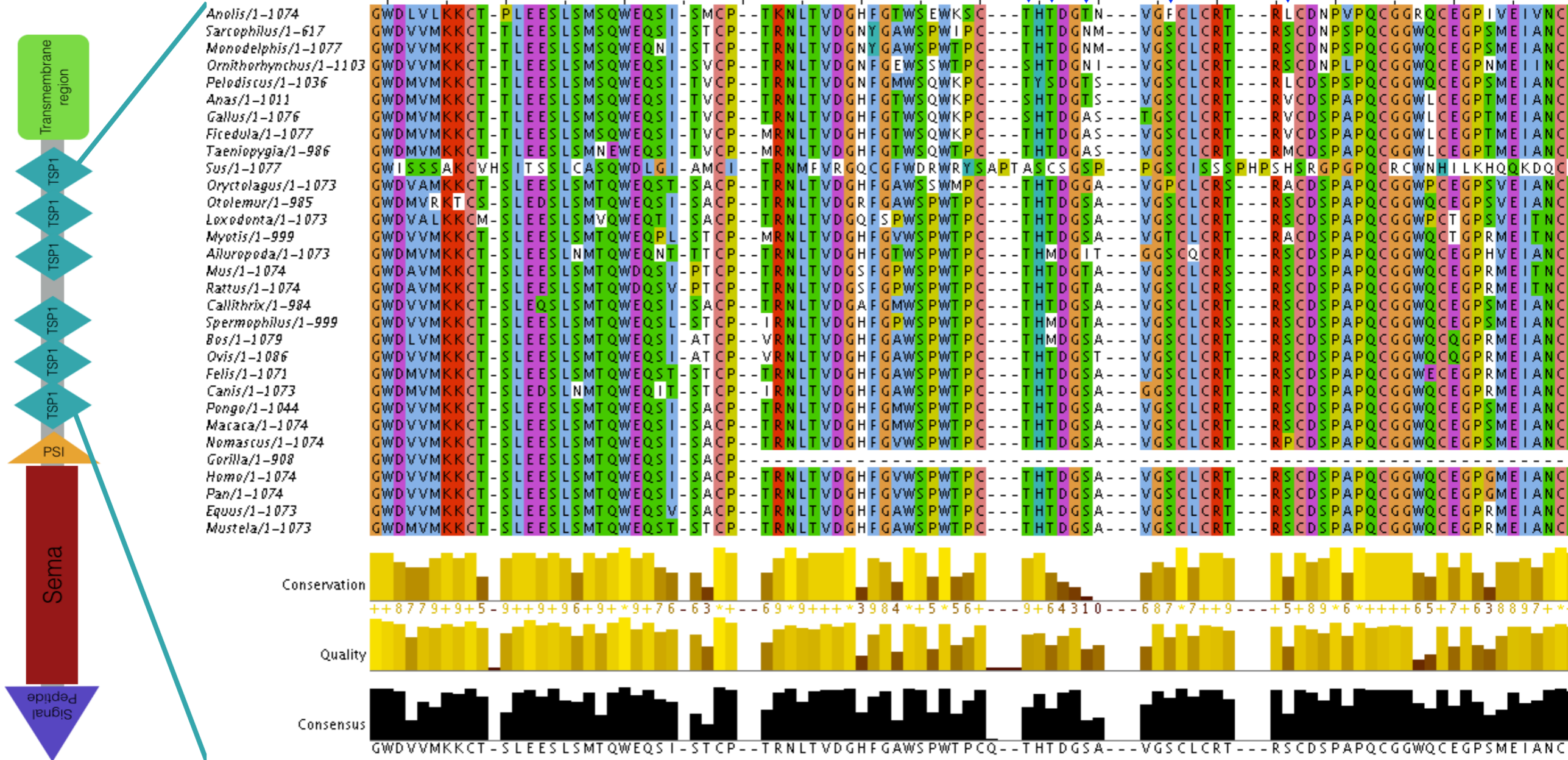
Analysis:



Results: SEMA5A has some highly conserved post-translational modifications

Aim 1 cont.: Determine predicted and conserved post-translational modifications involved in vascularization

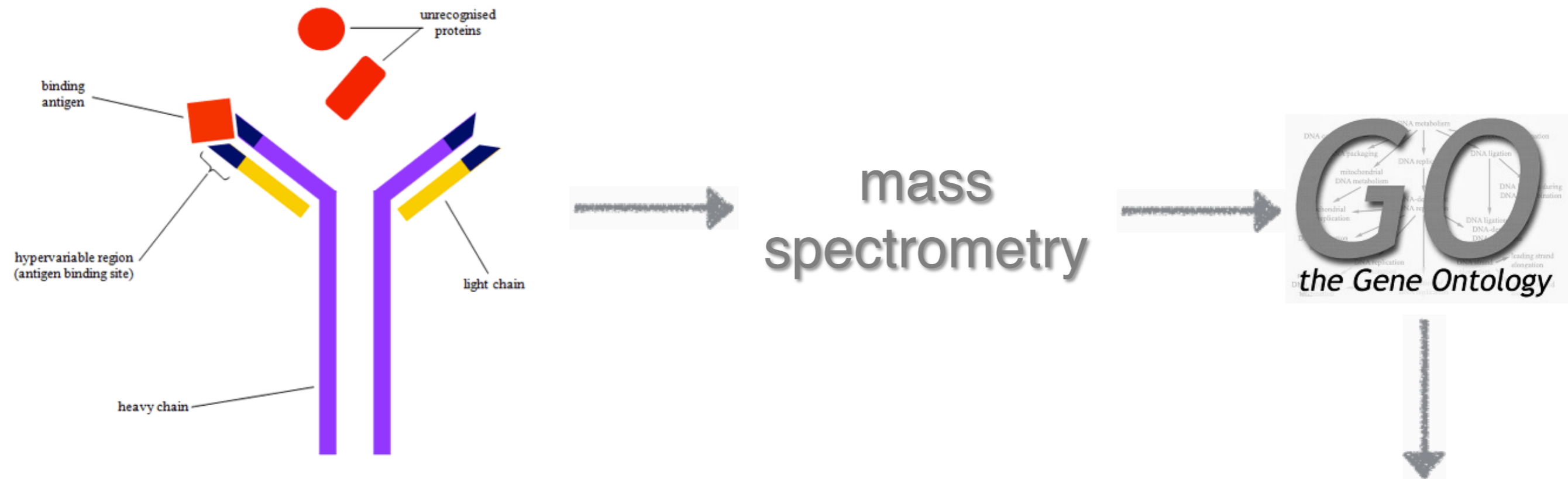
Analysis:



Results: SEMA5A has some highly conserved post-translational modifications

Aim 2: Determine unique protein interactions of SEMA5A that regulate vascularization

Approach:

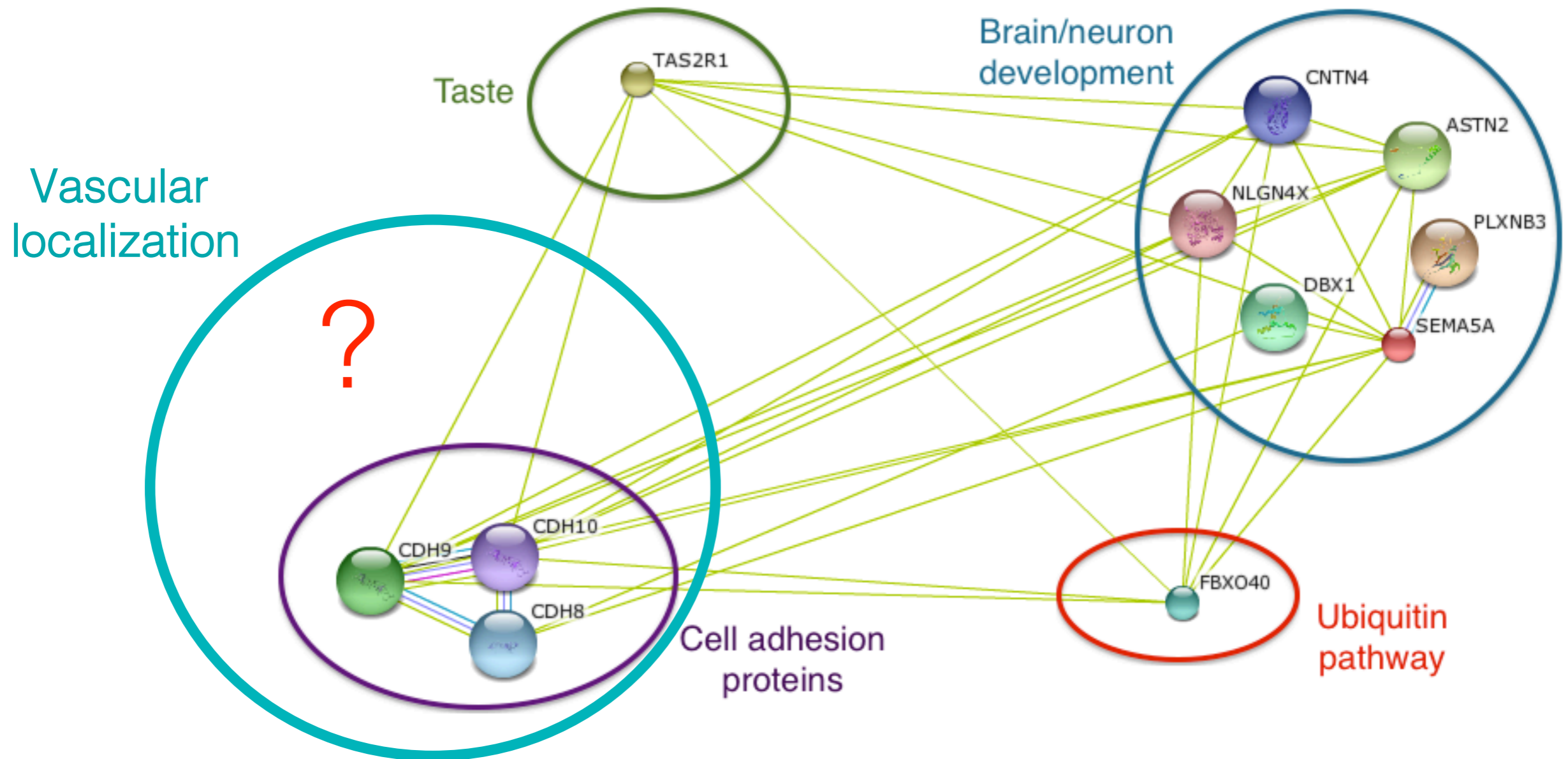


co-immunoprecipitation

Determine the important SEMA5A protein interactions involved in vascular patterning

Aim 2 cont.: Determine unique protein interactions of SEMA5A that regulate vascularization

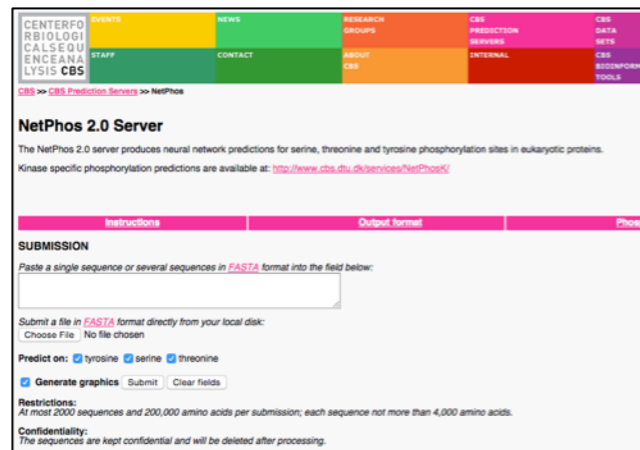
Expected analysis:



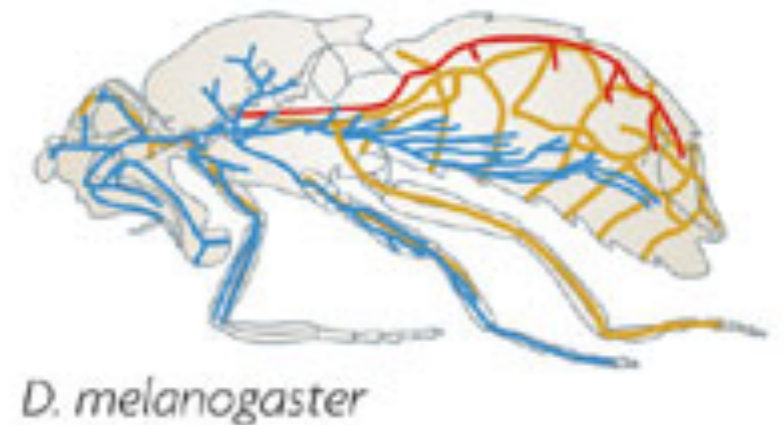
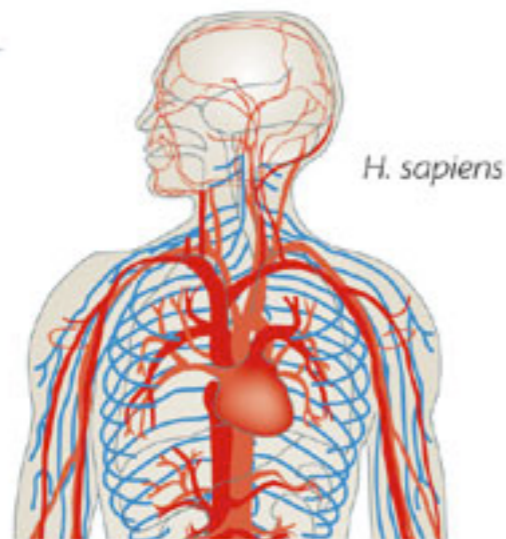
Expected results: SEMA5A will interact with proteins involved in signal pathways for vascular localization

Aim 3: Identify phosphorylation site differences between complex vascular and simple vascular organism

Approach:



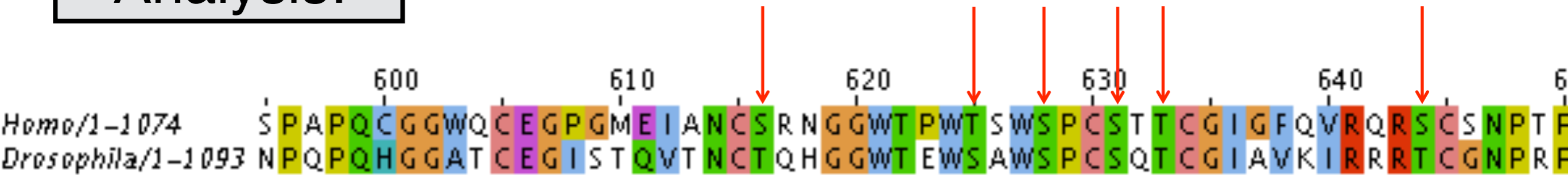
Conservation in phosphorylation sites



Determine the importance of SEMA5A in vascular patterning

Aim 3 cont.: Identify phosphorylation site differences between complex vascular and simple vascular organism

Analysis:



Crispr/cas9

Phosphorylation sites that function in vascularization

Results: some phosphorylation sites are highly conserved between humans and fruit flies

Future directions

Findings: SEMA5A gene is involved in localization signal pathways and is necessary for proper vascular positioning

Yes

No

gene therapy and drug screen for compounds that rescue vascular phenotypes

explore more genes or proteins that are necessary for vascularization

References

- [1] Cerruti Mainardi, P. (2006). Cri du Chat syndrome. *Orphanet Journal of Rare Diseases*, 1, 33. doi:10.1186/1750-1172-1-33.
- [2] Manning, K. (1977). The larynx in the Cri du Chat Syndrome. *The Journal of Laryngology & Otology*, 91(10), 887-892.
- [3] Genetic Science Learning Center (2014, June 22) Cri-du-Chat Syndrome. Learn.Genetics. Retrieved January 28, 2015, from <http://learn.genetics.utah.edu/content/disorders/chromosomal/cdc/>
- [4] Fiore, R., Rahim, B., Christoffels, V., Moorman, A., & Puschel, A. (2005). Inactivation of the Sema5a Gene Results in Embryonic Lethality and Defective Remodeling of the Cranial Vascular System. *Molecular and Cellular Biology*, 25(6), 2310-2319, from <http://mcb.asm.org/content/25/6/2310.full>

