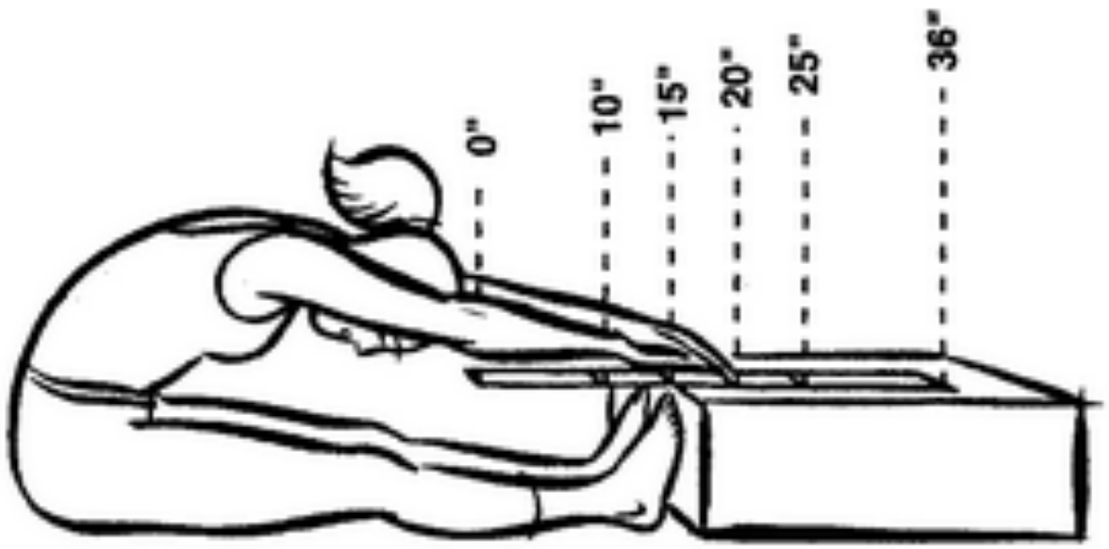
COL5A1: The gene for an enhanced running economy

By: Logan Silber

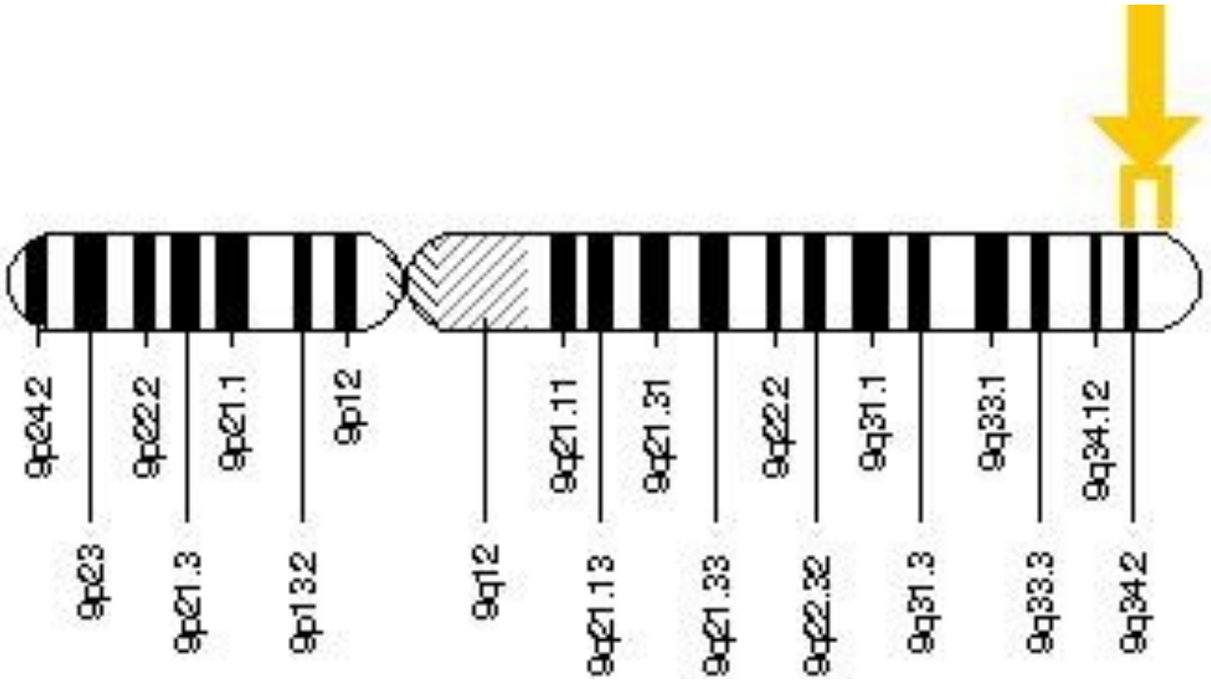
How does COL5A1 promote endurance running?

Reduced flexibility



Enhanced running economy

Where is the mutation in COL5A1?

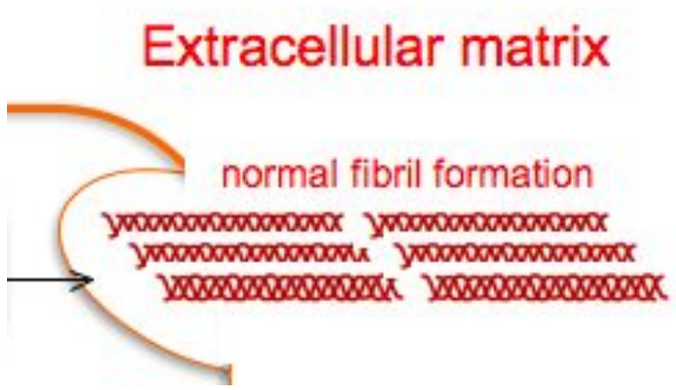


Rs12722

C ⟶ T

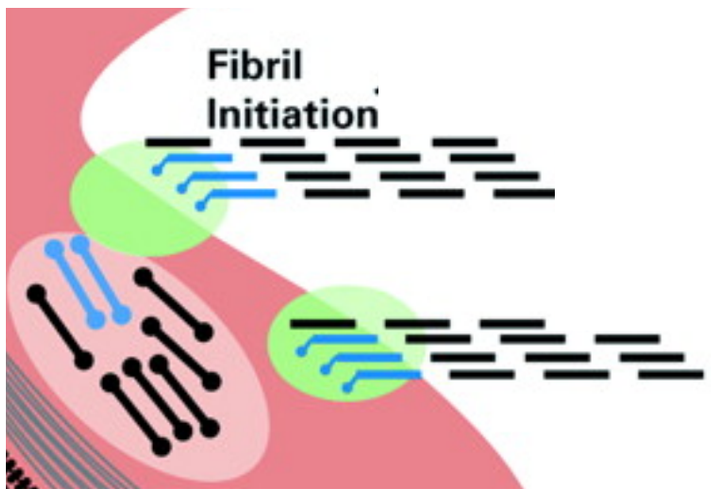
Molecular Function

Extracellular matrix structural constituent



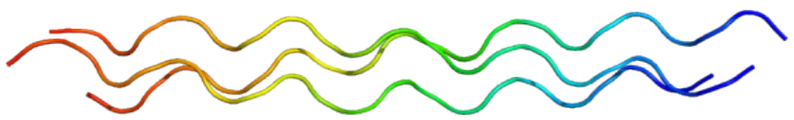
Biological Function

Collagen fibril organization



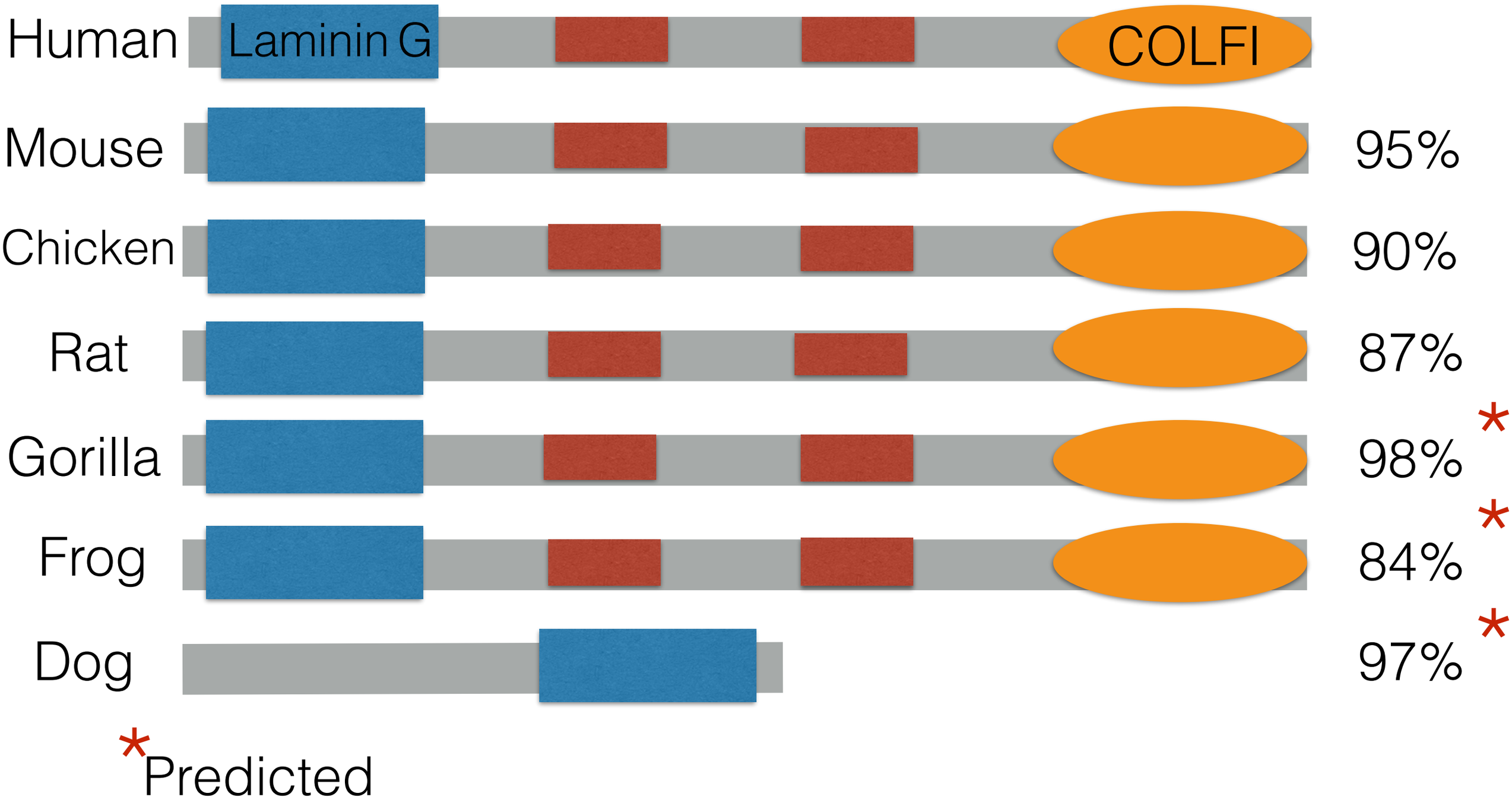
Cellular Component

Collagen subunit

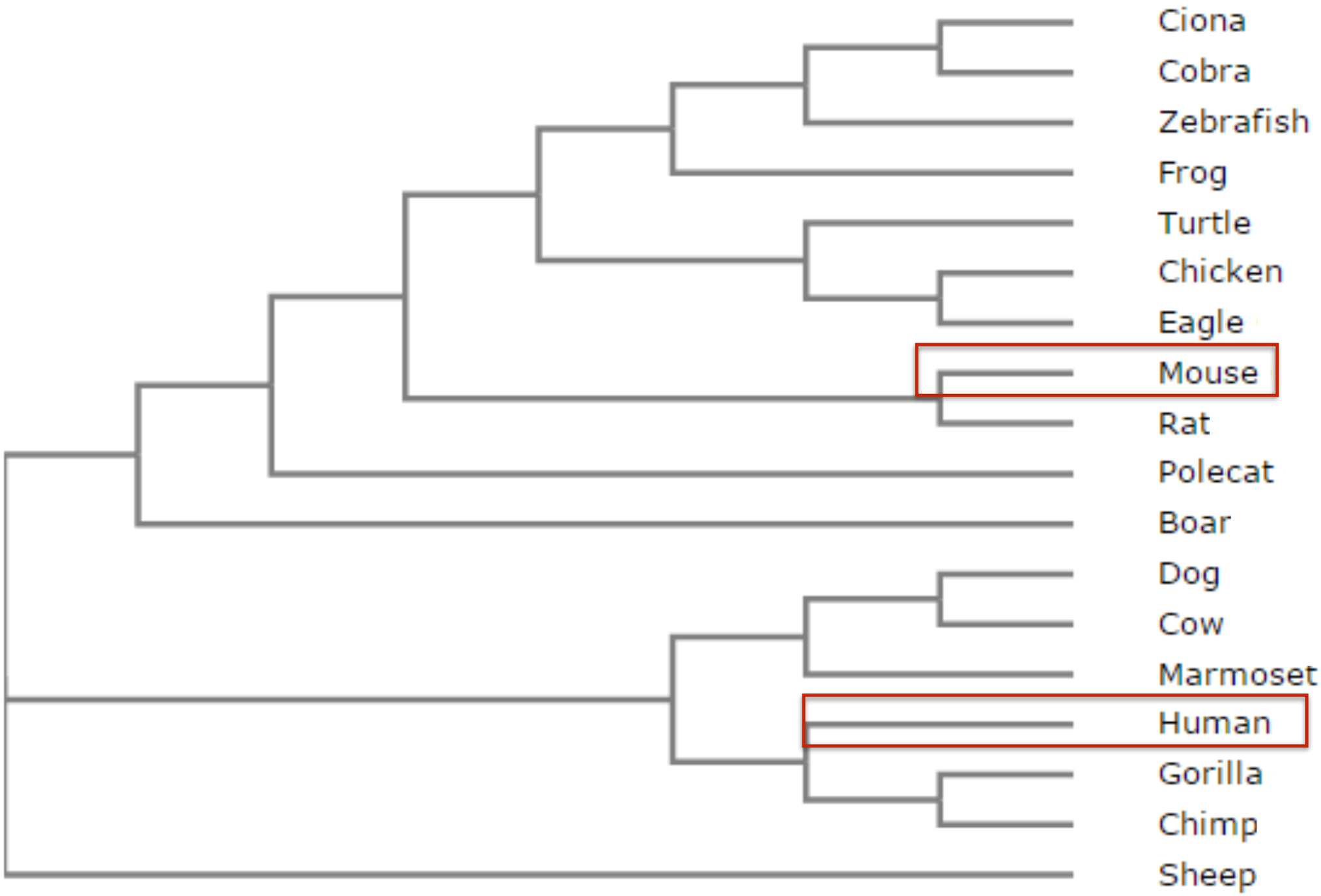


How well conserved is the protein amongst other organisms?

collagen alpha-1(V) chain



What is the phylogeny of the protein amongst other organisms?



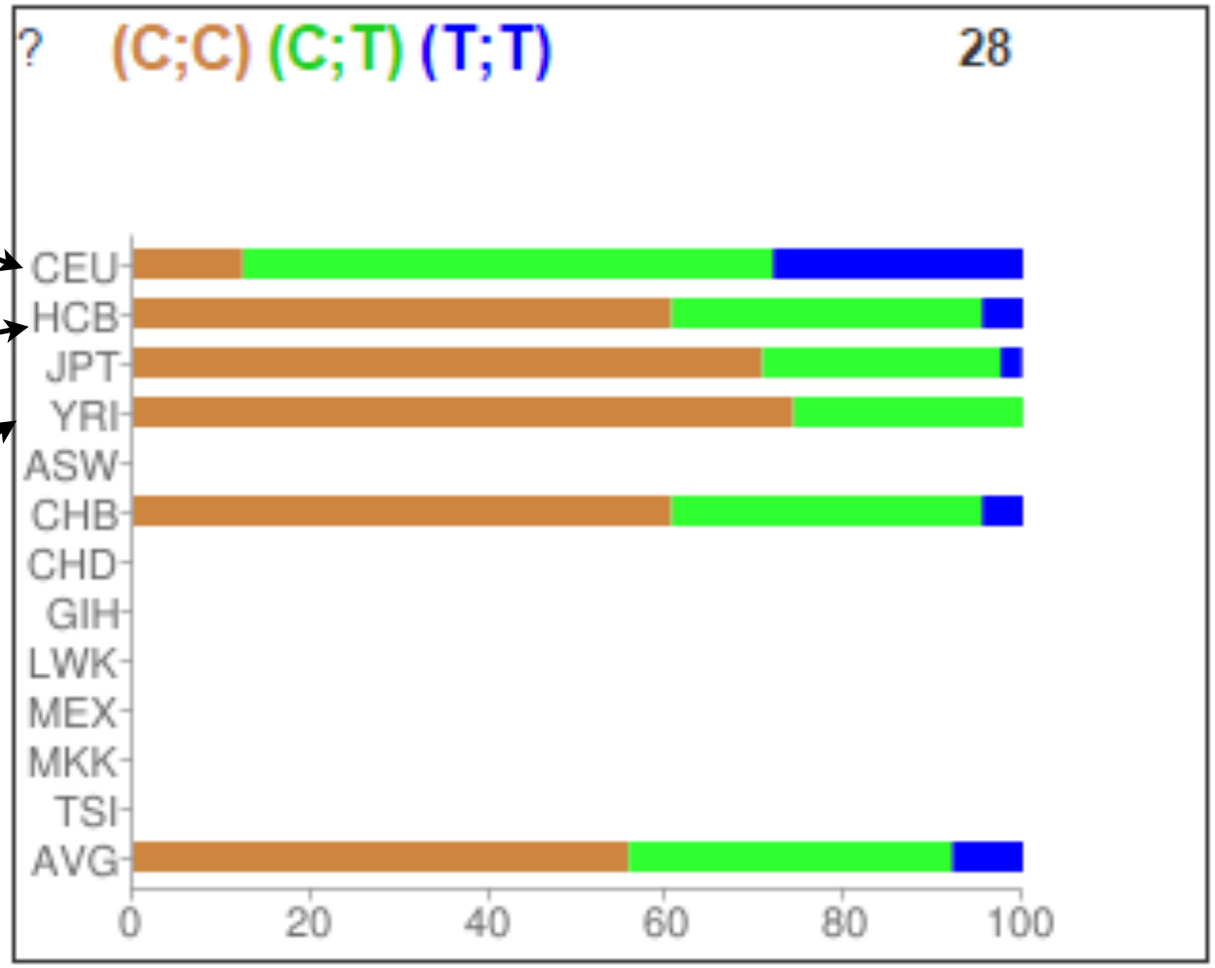
Clustal Omega

What is the prevalence of the rs12722 variant appearing in different ethnic backgrounds?

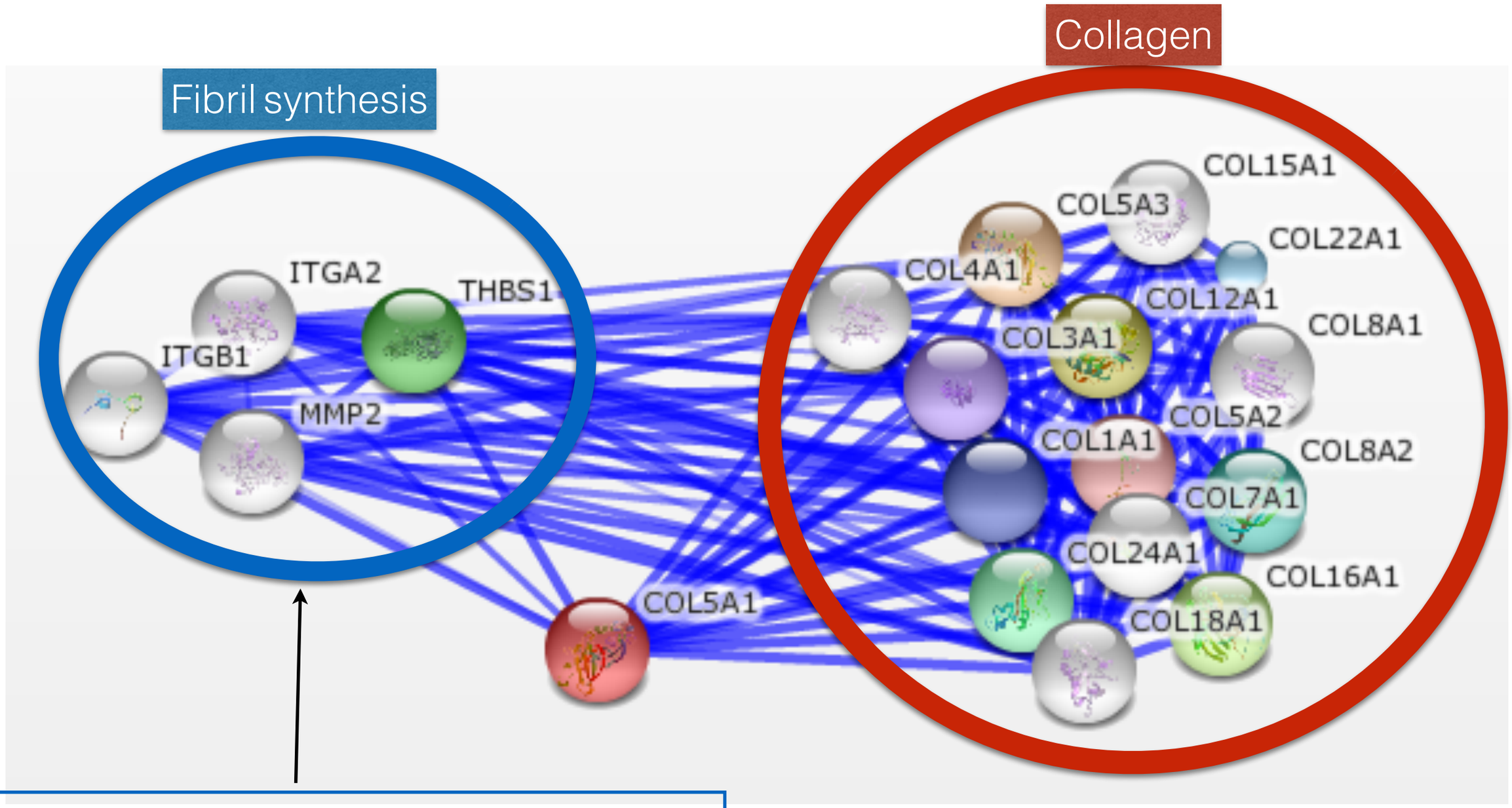
European

Chinese

African



The COL5A1 gene product interacts with proteins needed for collagen fibril synthesis

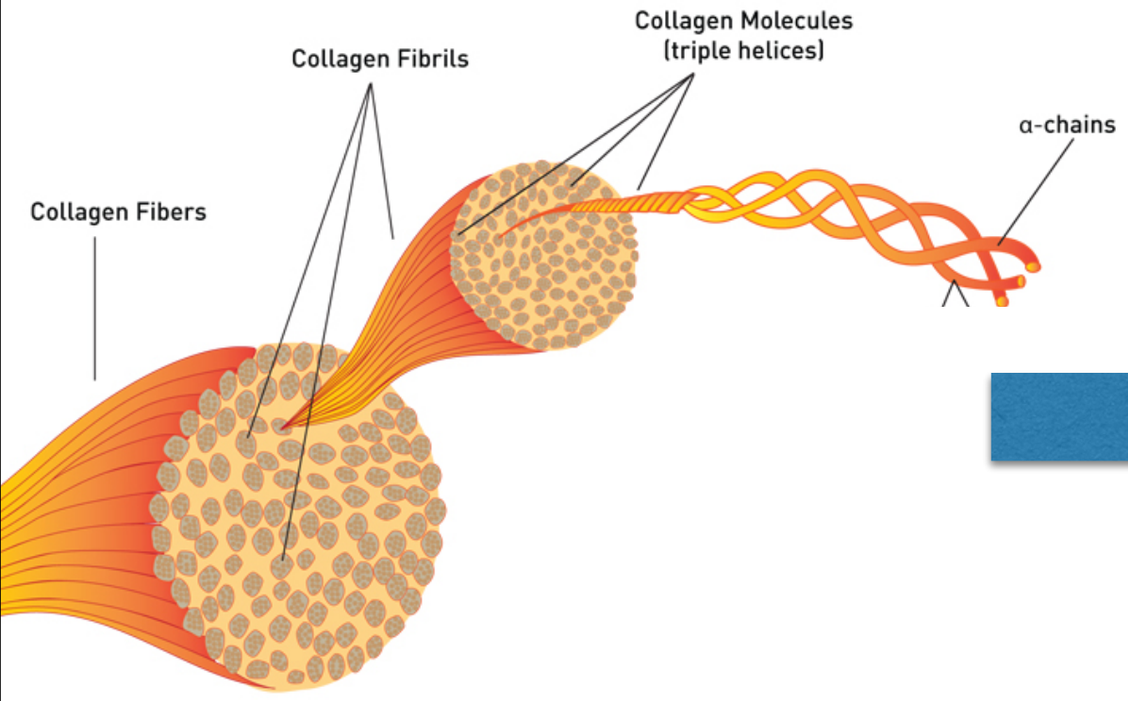


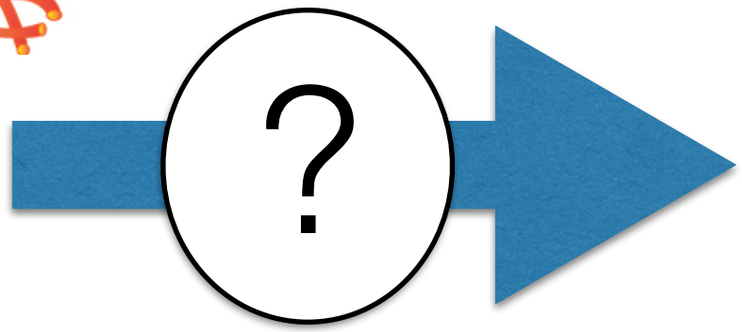
ITGA - Integrin
MMP2 - Collagenase
THBS1 - Thrombospondin 1

STRING

Gap in knowledge

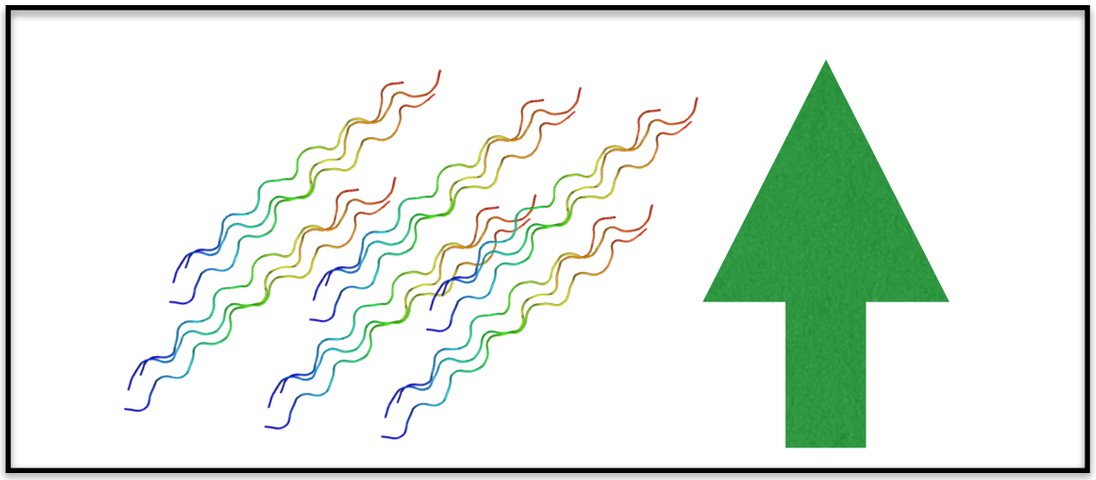
How does the rs12722 gene product differ from the normal COL5A1 gene product so that cellular functionality is affected and an enhanced running economy is produced?





Hypothesis

The rs12722 gene product enhances running economy due to an increase in fibril formation as a result of higher transcription and translation. This will promote extracellular matrix support and therefore create more muscle inflexibility.

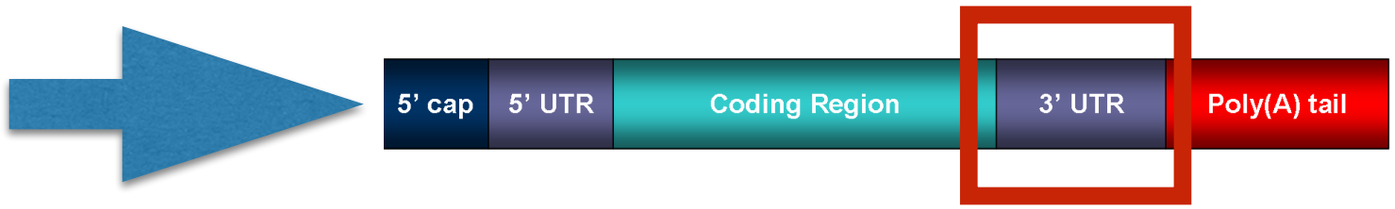


Aim 1: To determine if the SNP is within a DNA motif or if a miRNA exists that would bind with the variant mRNA

Approach: Use DREME and miRBase to see if there is a site being regulated

DREME
Discriminative Regular Expression Motif Elicitation
Version 4.10.0

miRBase



Hypothesis: The mutation is present on a regulatory DNA binding domain or affects the binding of a miRNA to the normal transcript.

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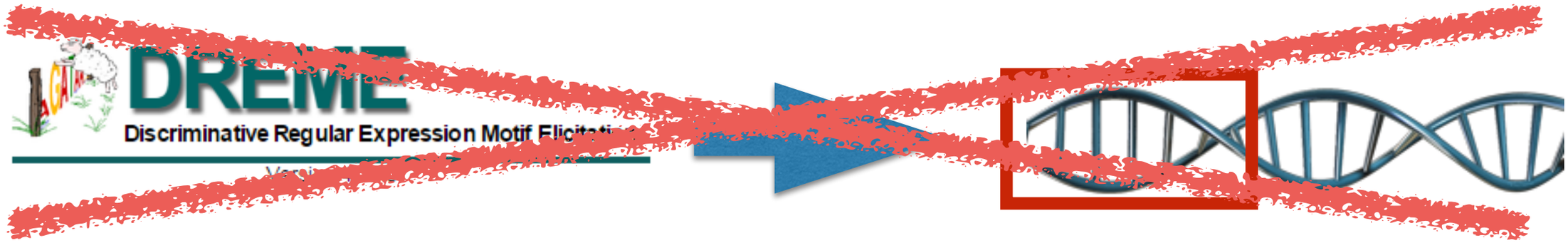

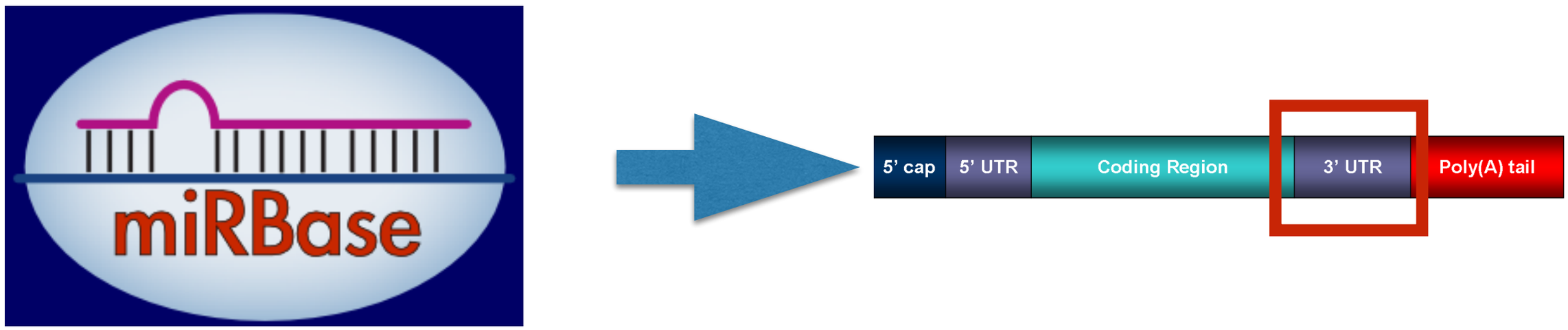

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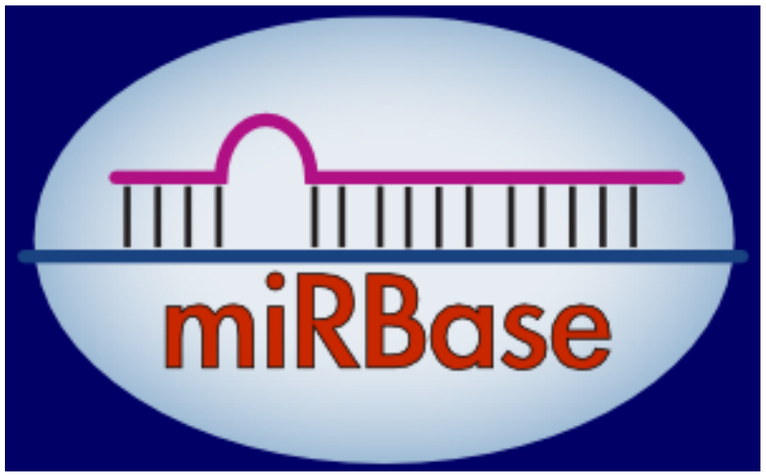
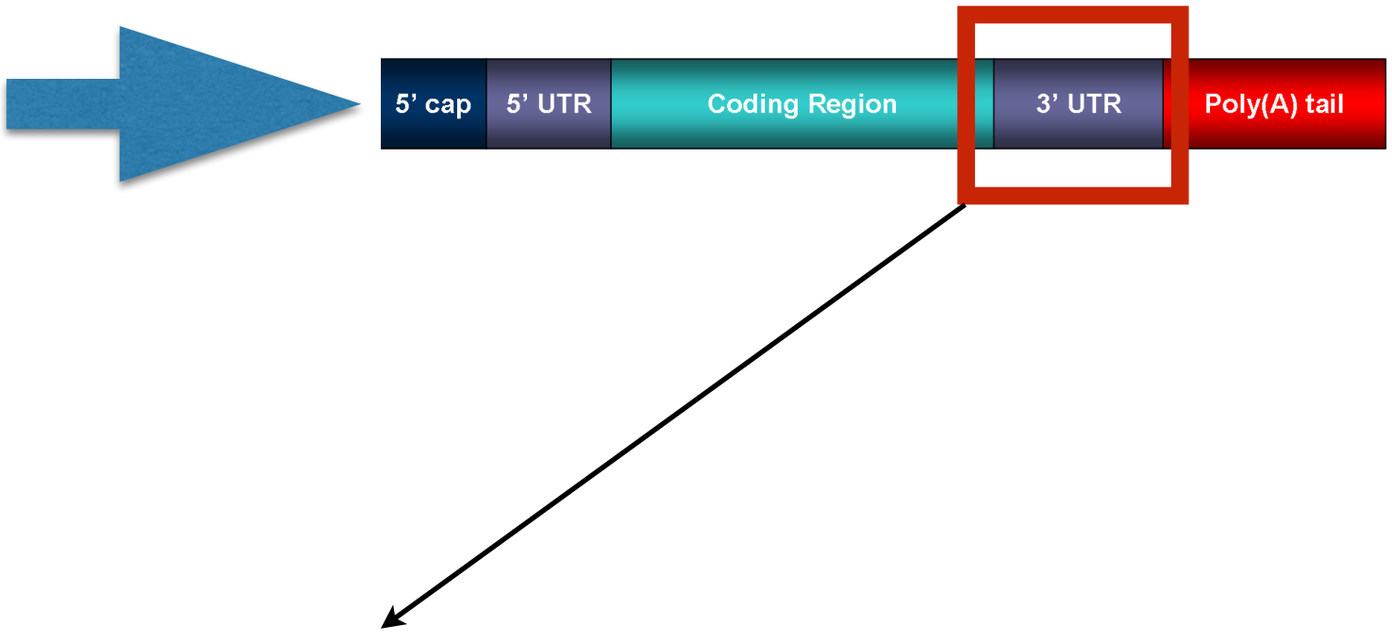
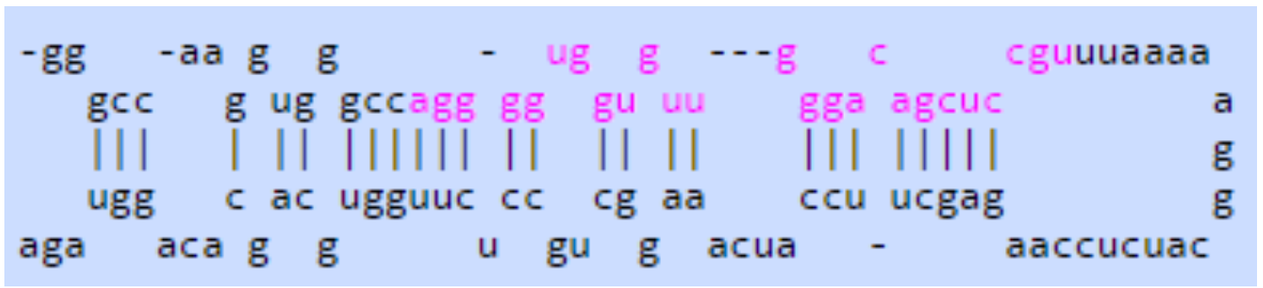




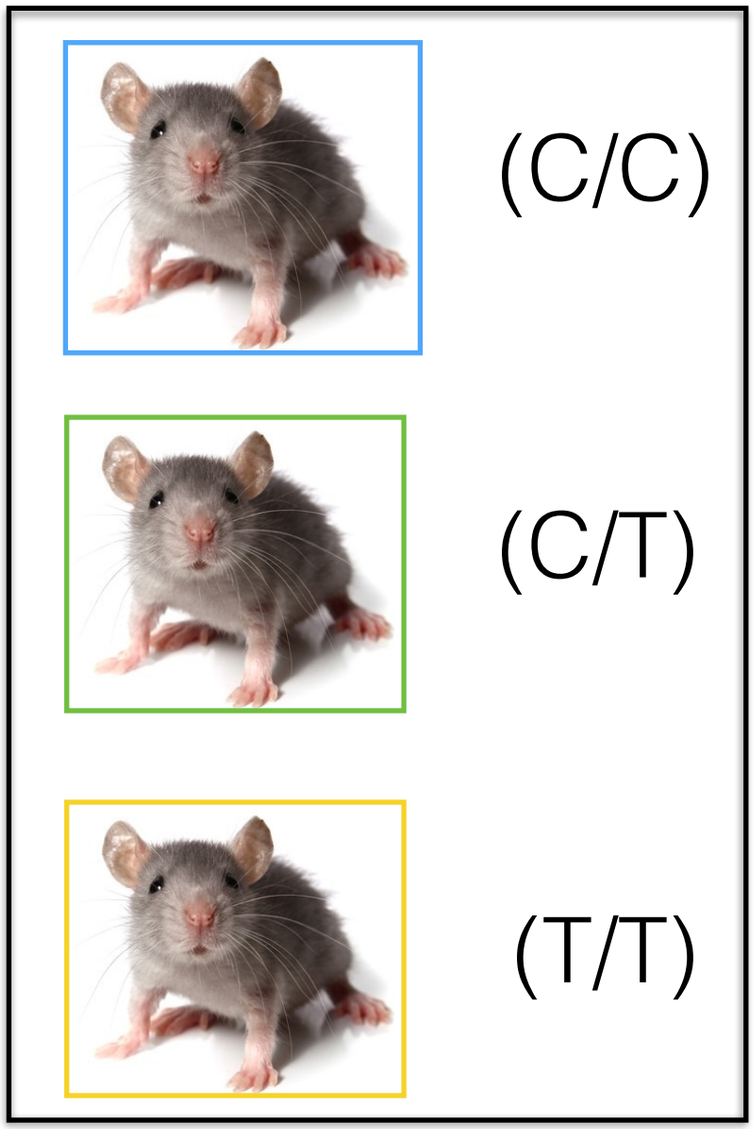


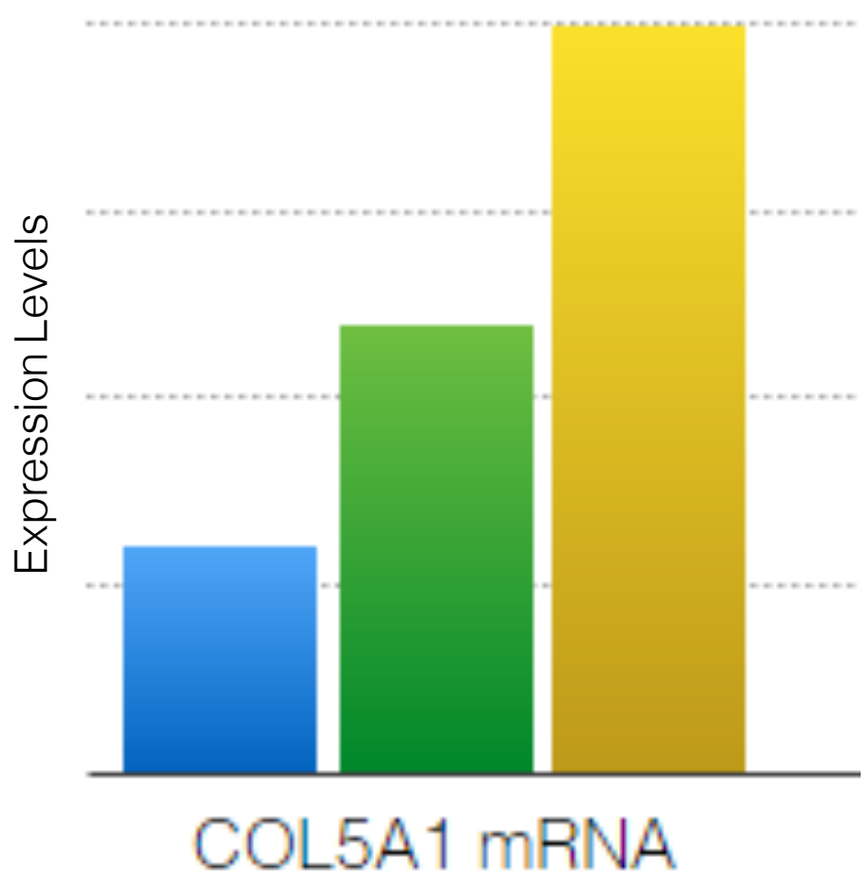
mir-608

Conclusion: More sequencing of miRNA and more deep sequencing of mRNA must be done to confirm interaction

Aim 2: To determine if there are higher levels of rs12722 mRNA compared to normal COL5A1 mRNA in smooth muscle cells

Approach: Creating lines of mice containing the normal human COL5A1 and rs12722 COL5A1 gene and using RNA sequencing to quantify mRNA levels



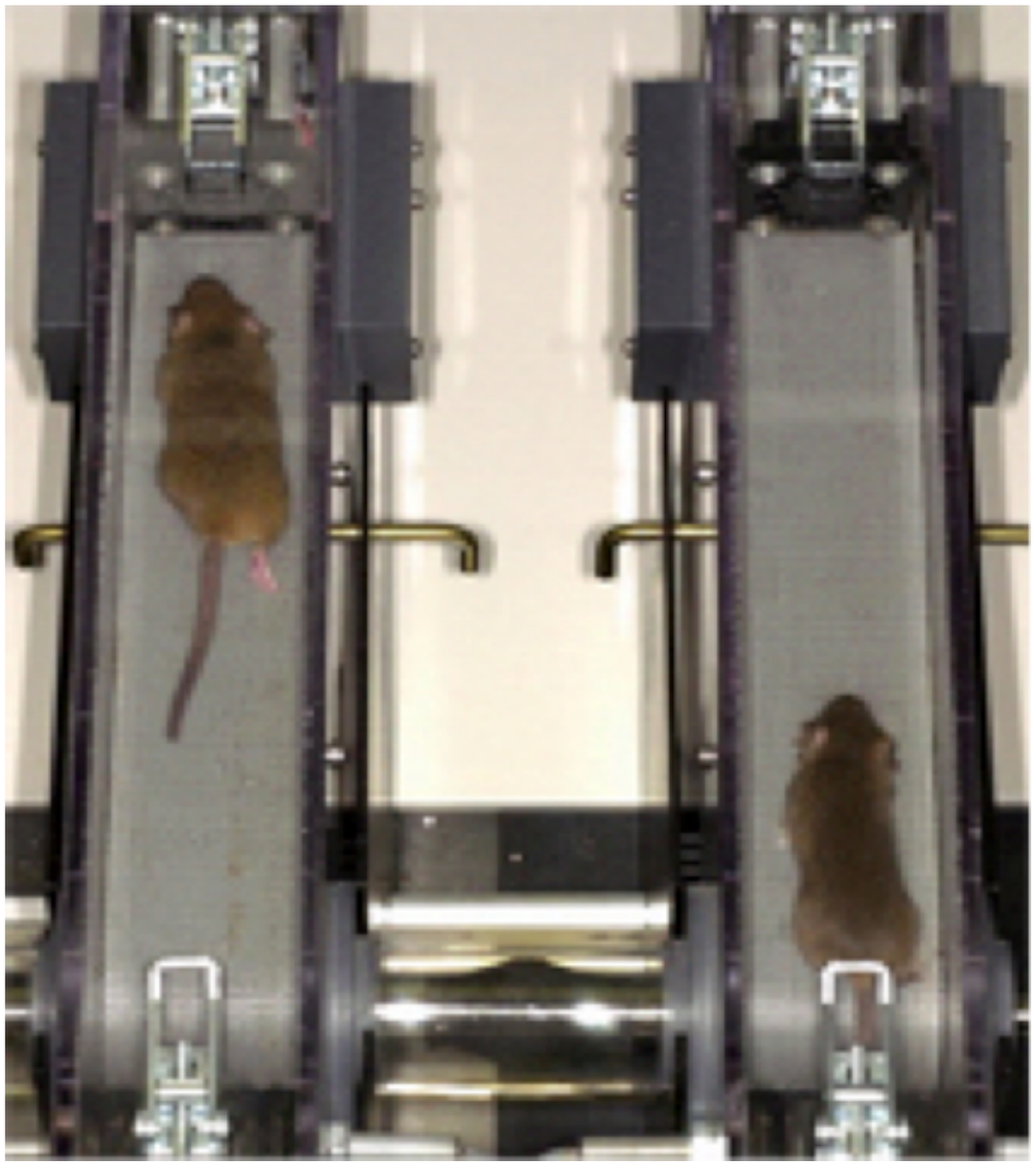


Hypothesis: More rs12722 mRNA will be quantified, which implies creation of more collagen fibrils

Aim 2: To determine if there are higher levels of rs12722 mRNA compared to normal COL5A1 mRNA in smooth muscle cells

Follow up experiment: Mouse Treadmill

Homozygous for rs12722

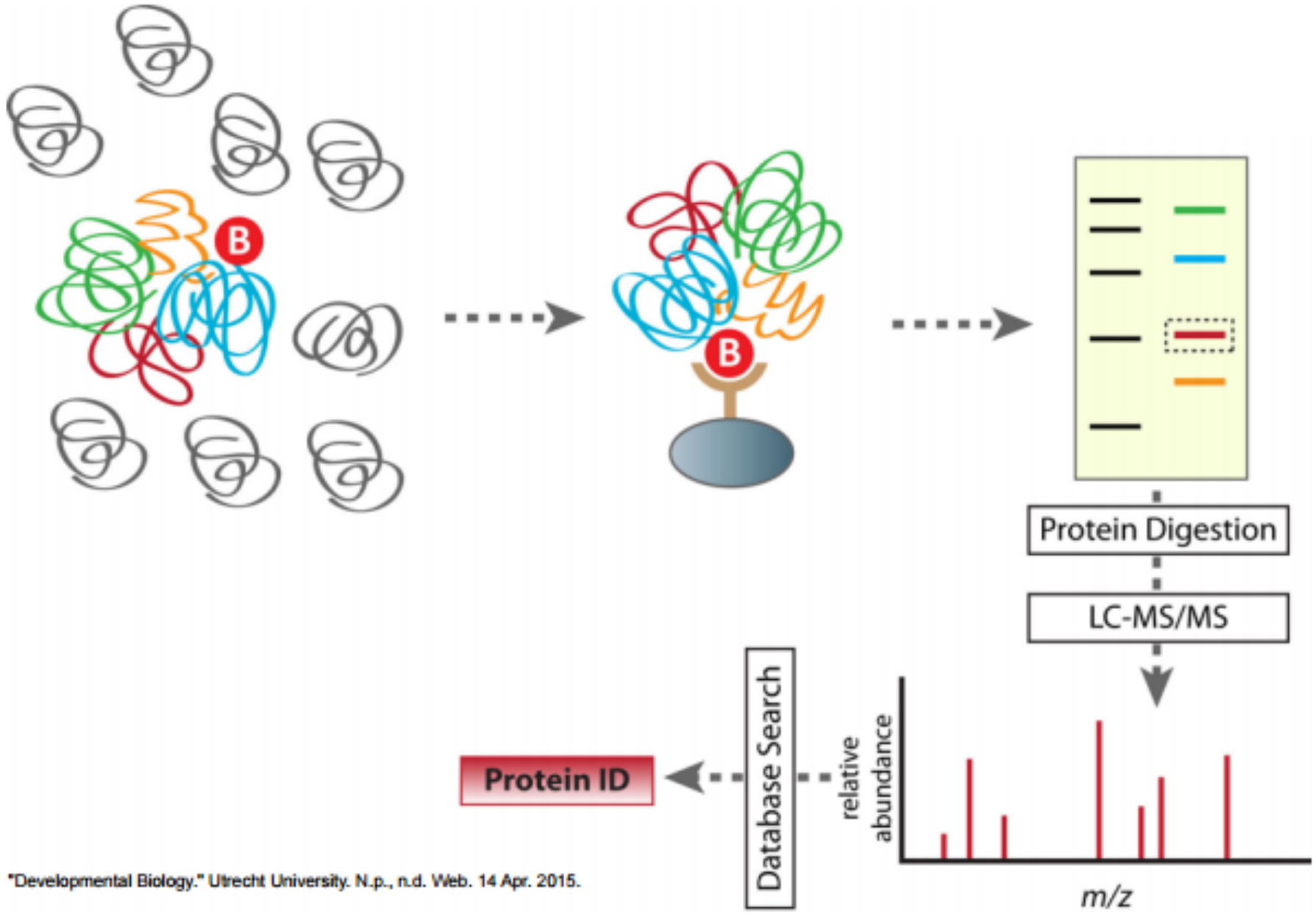


Homozygous for normal COL5A1

Expected: Higher levels of of rs12722 mRNA compared to normal COL5A1 mRNA and mice homozygous for rs12722 can for run longer

Aim 3: To determine if there are any new proteins that interact with rs12722 variant gene product

Approach: Using TAP tag on type V collagen made from rs12722



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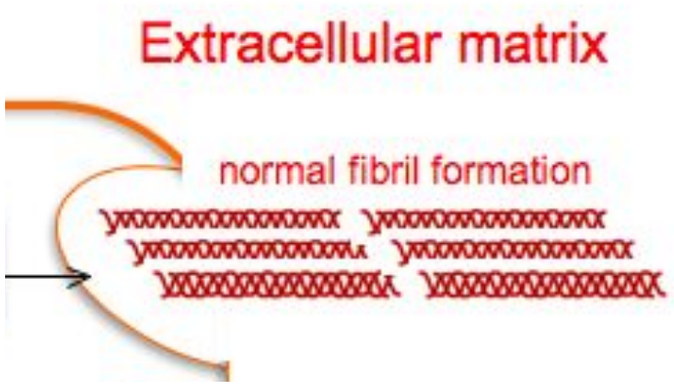
Hypothesis: There is a new protein interaction that promotes collagen fibril initiation or is an extracellular matrix structural constituent

Aim 3: To determine if there are any new proteins that interact with rs12722 variant gene product

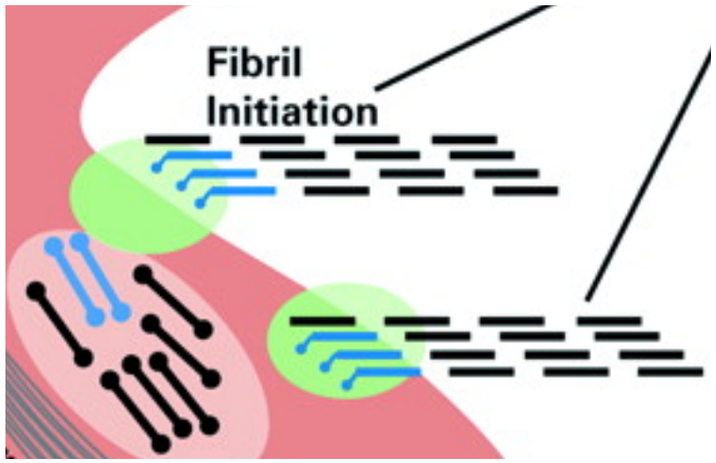
Follow up: Discover ontologies of proteins

GENEONTOLOGY
Unifying Biology

Molecular Function



Biological Function



Expected: There is a new protein interaction that promotes collagen fibril organization or is an extracellular matrix structural constituent

What are some future directions?

Larger studies from marathon participants

Further sequencing of miRNAs

A RT-qPCR experiment on mRNA transcription levels

Yeast two-hybrid specific library approach

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Picture references

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Questions?