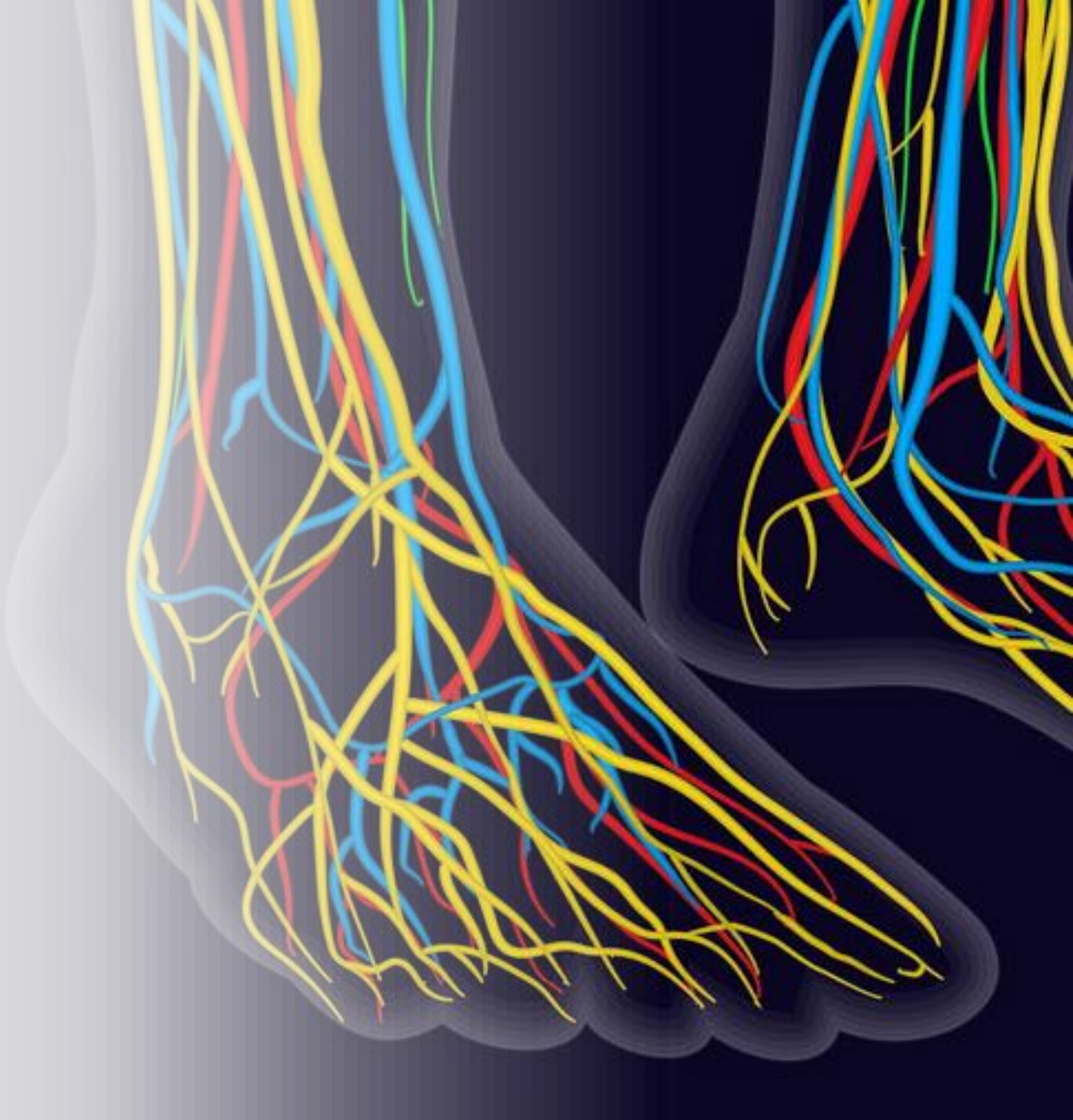
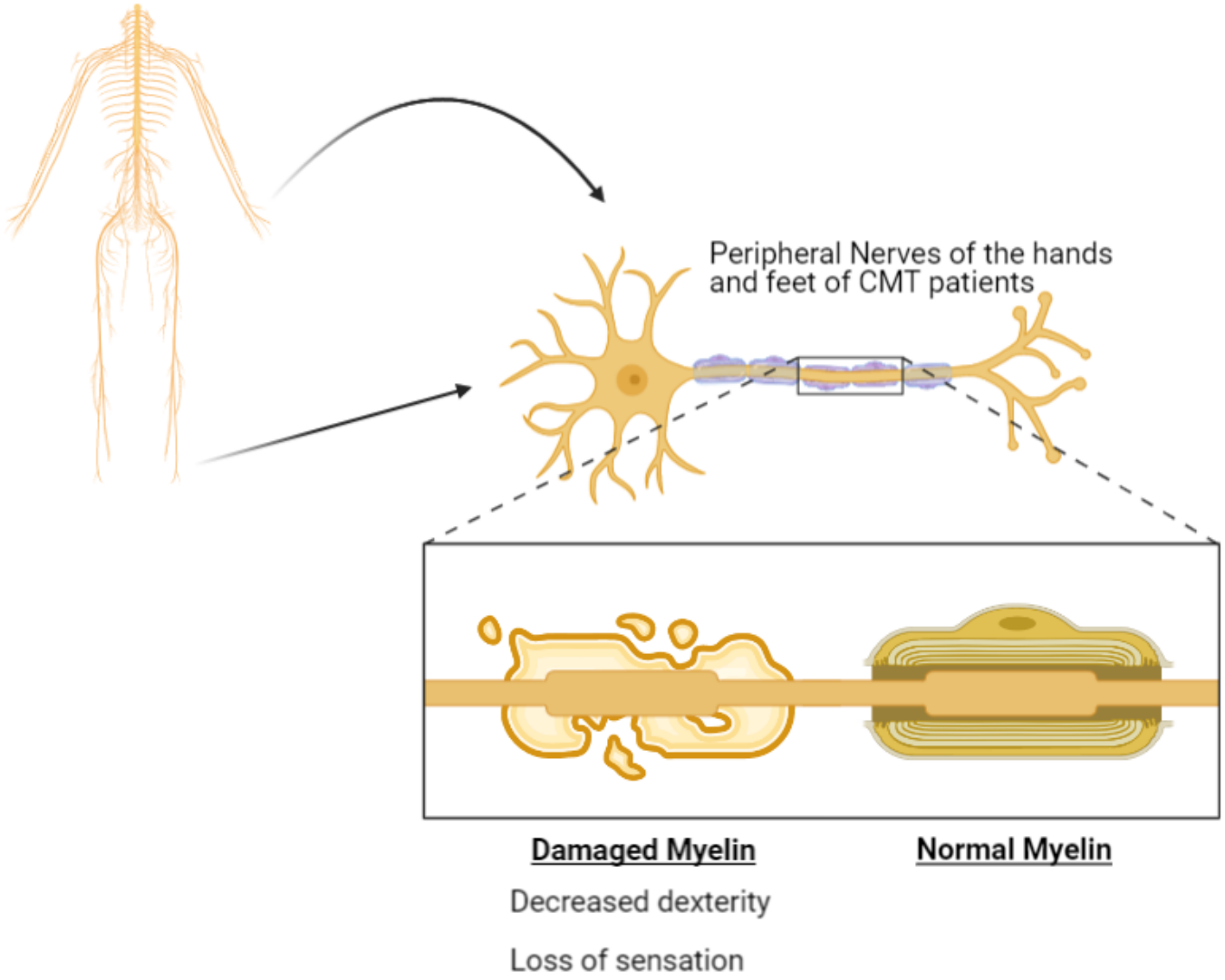
Charcot-Marie-Tooth Disease

Collin Nguyen

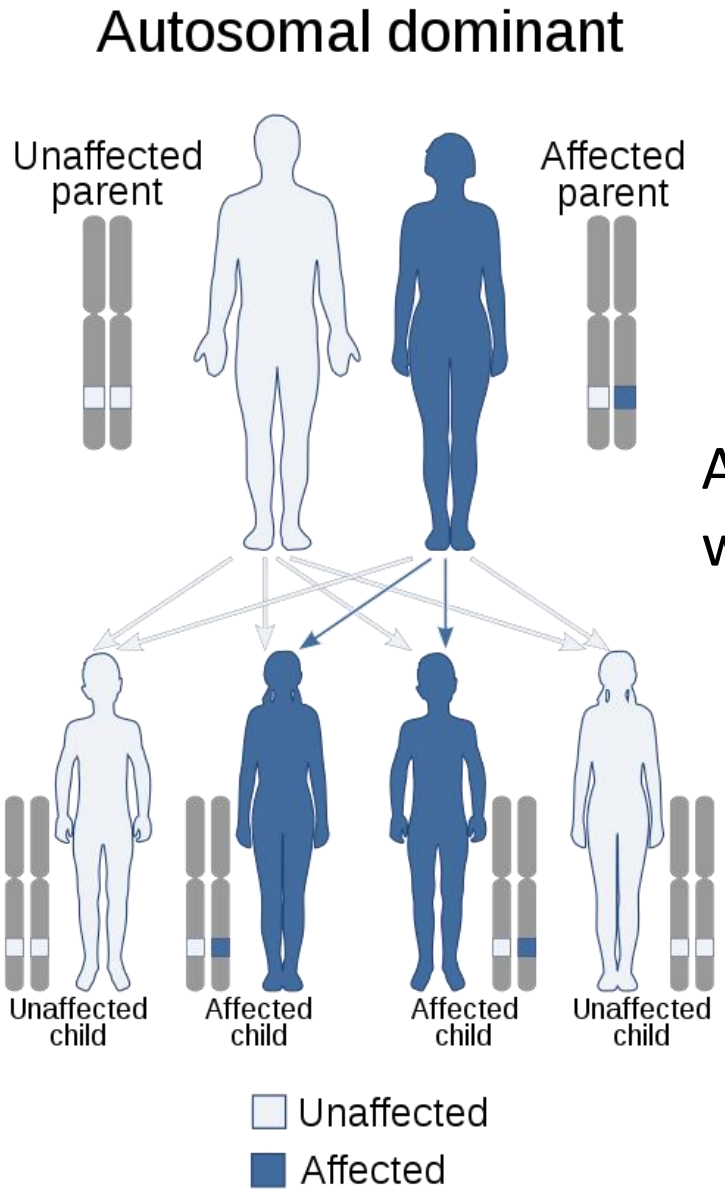


What is Charcot-Marie-Tooth (CMT1A) Disease?



The most common genetic disorder involving the peripheral nervous system

How is CMT1A inherited?



Autosomal dominant inheritance as well as de novo mutations

What are the symptoms of CMT1A?

My hand muscles are shrinking.

My grip is weak and I drop things.

I have a hard time finding shoes that fit.

My arches are high and my toes are curled. ("hammertoes")

I took longer to reach my physical development milestones as a baby.

I trip a lot.

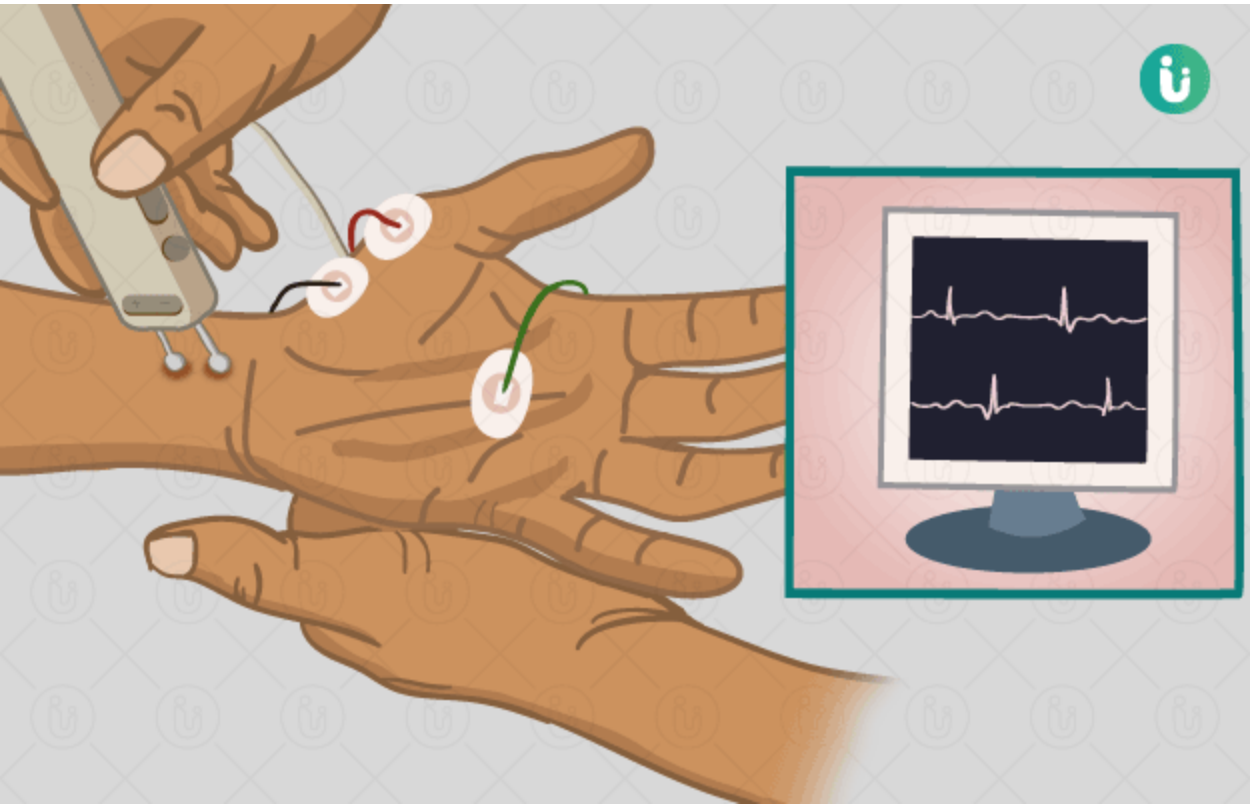
My legs are really skinny.

My ankles give out.

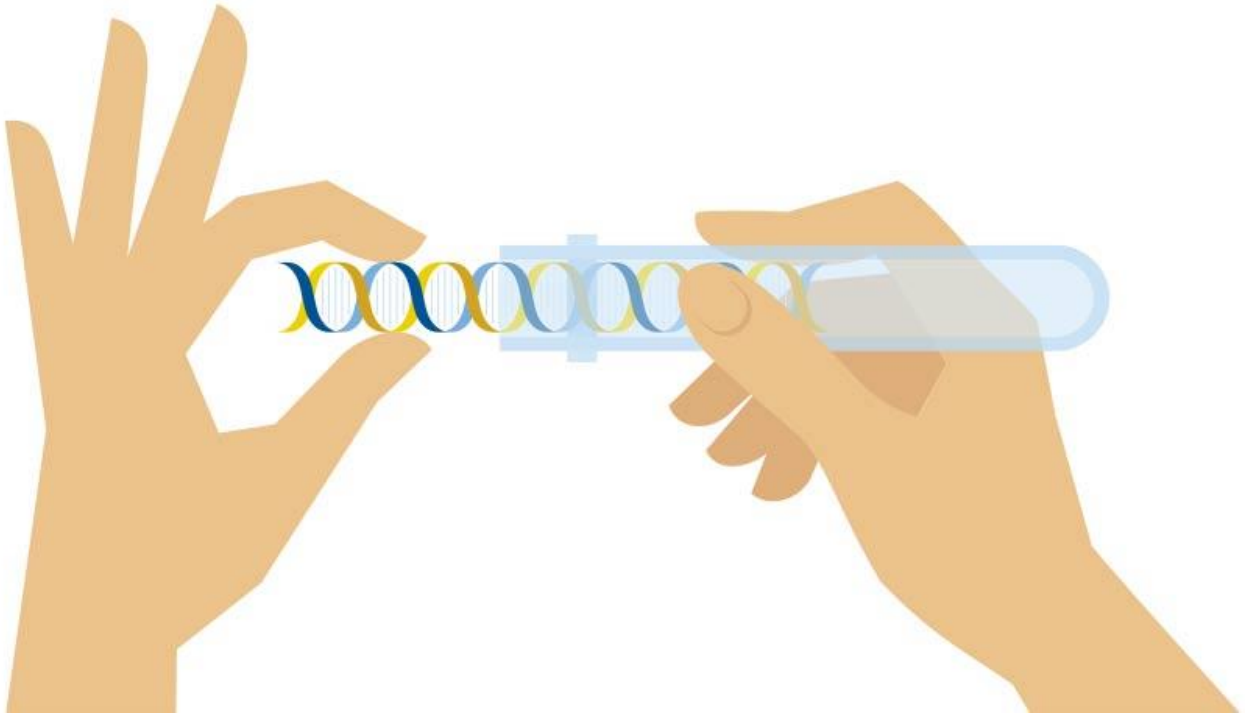
I can't feel my feet very well.

It's hard to lift my feet.

How is CMT1A diagnosed and treated?

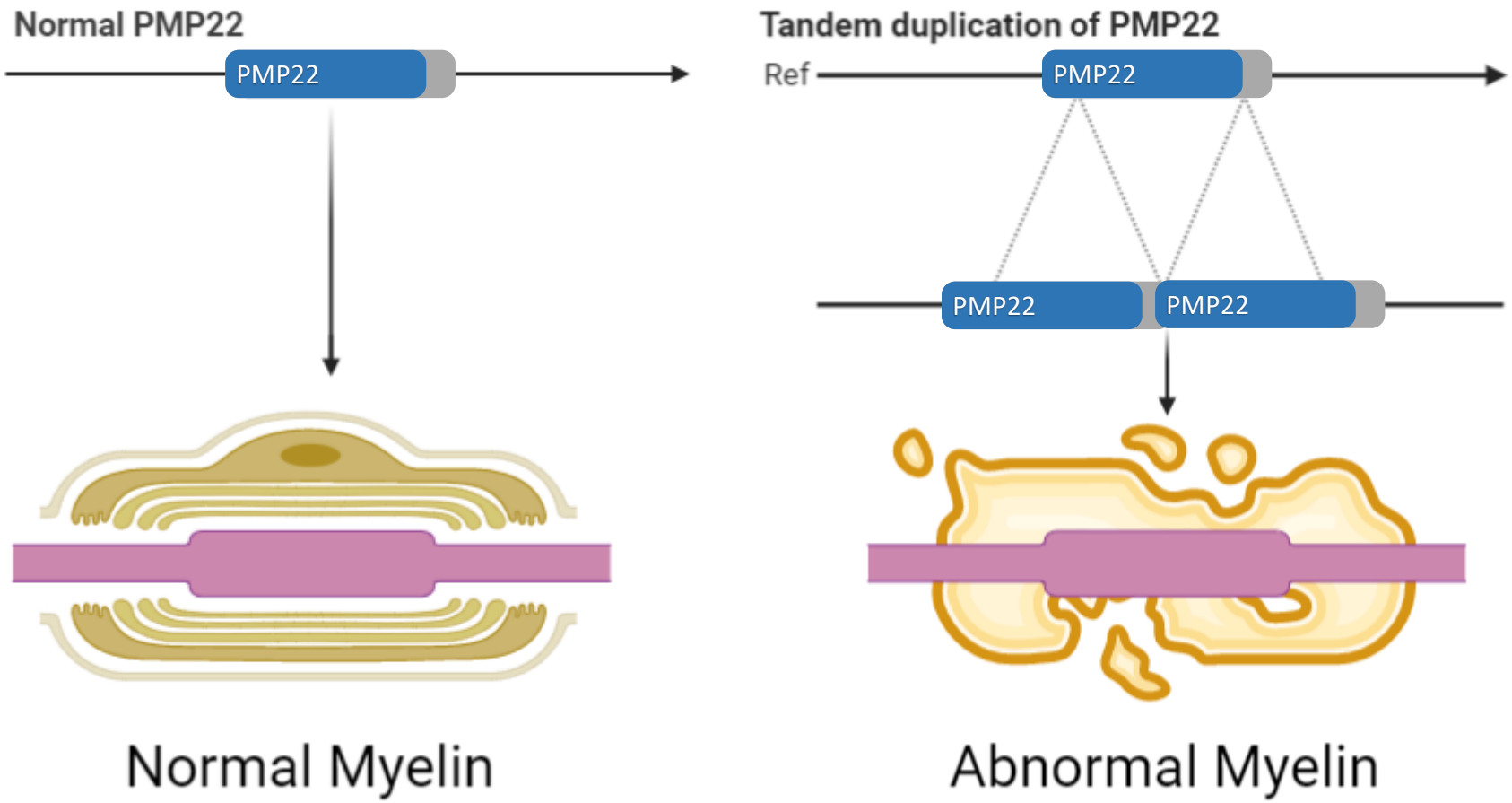


Nerve Conduction Studies

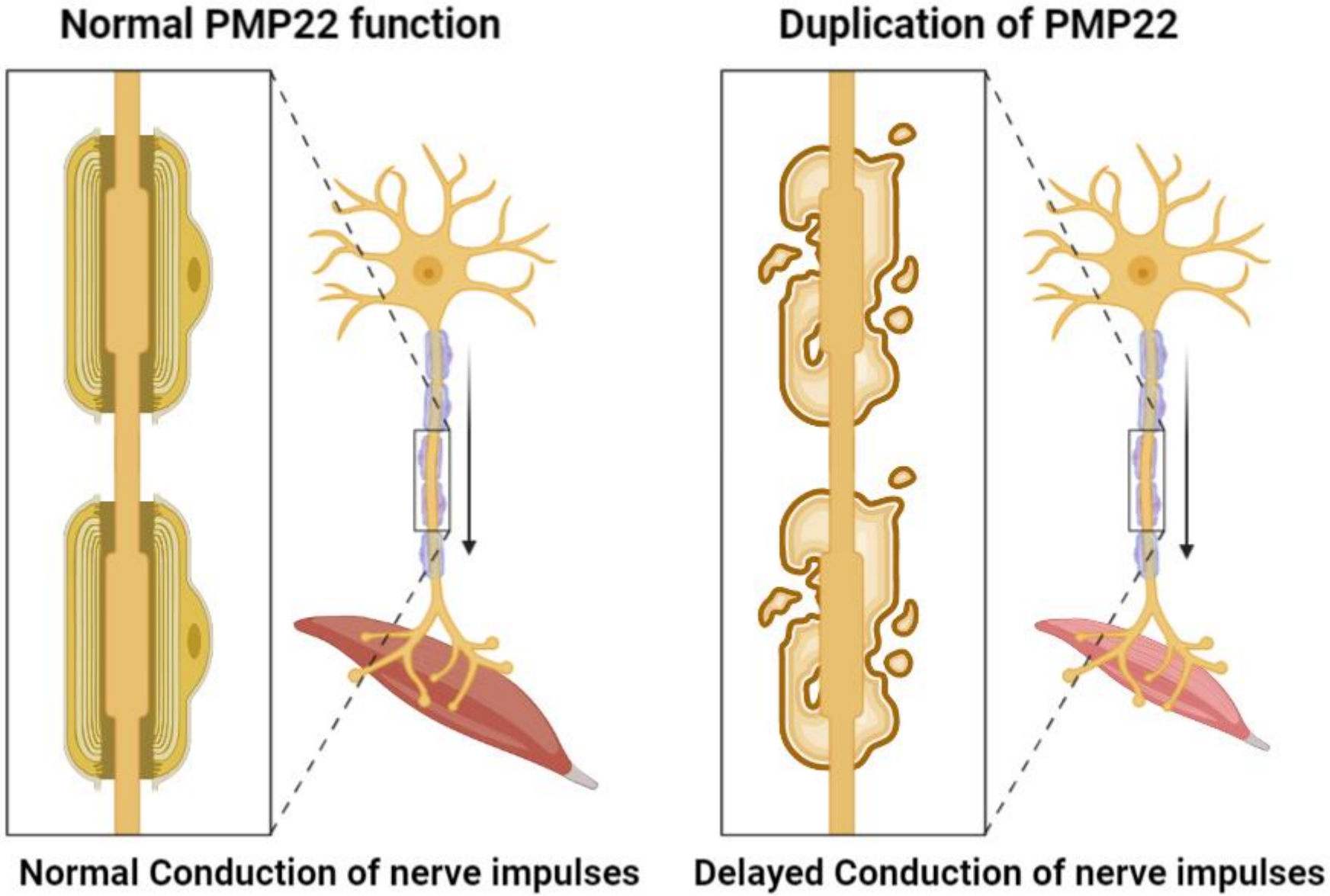


Genetic Testing

What gene is mutated in CMT1A?



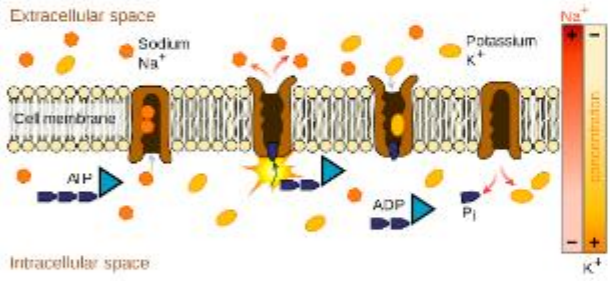
What causes CMT1A symptoms?



How does mutated PMP22 result in abnormal myelination in CMT1A?

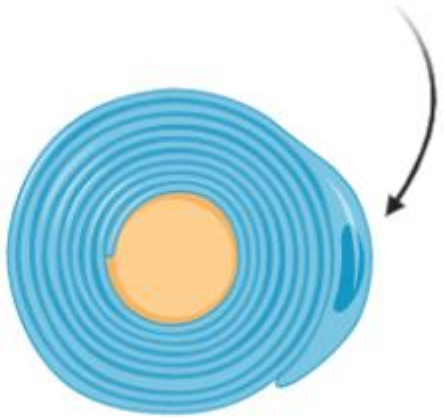
Human PMP22 Claudin 160 AA

Molecular Function



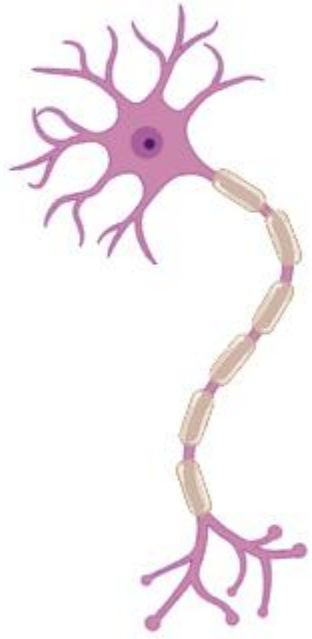
Nucleoside Triphosphatase Activity

Cellular Component



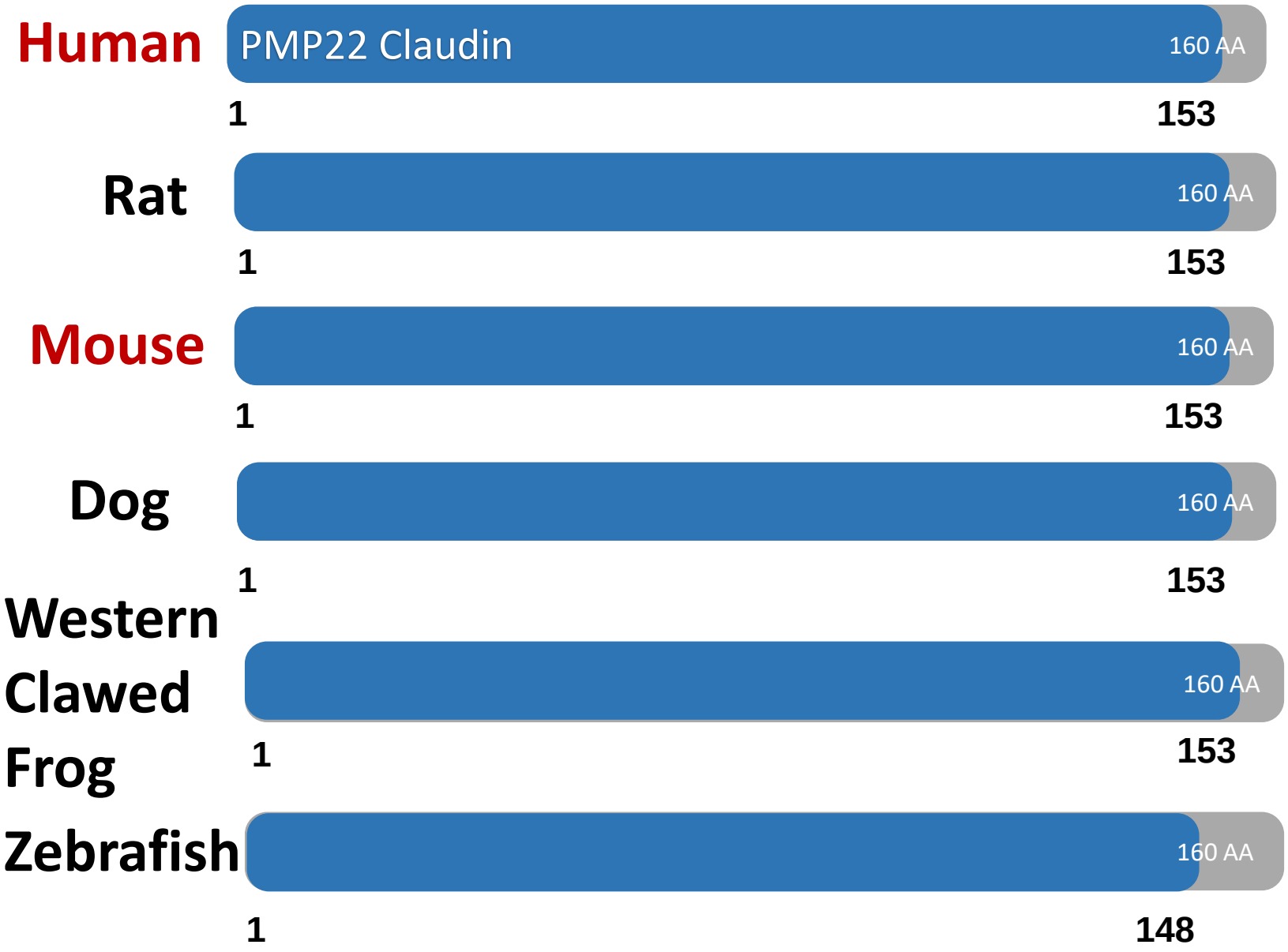
Scwann Cells

Biological Process



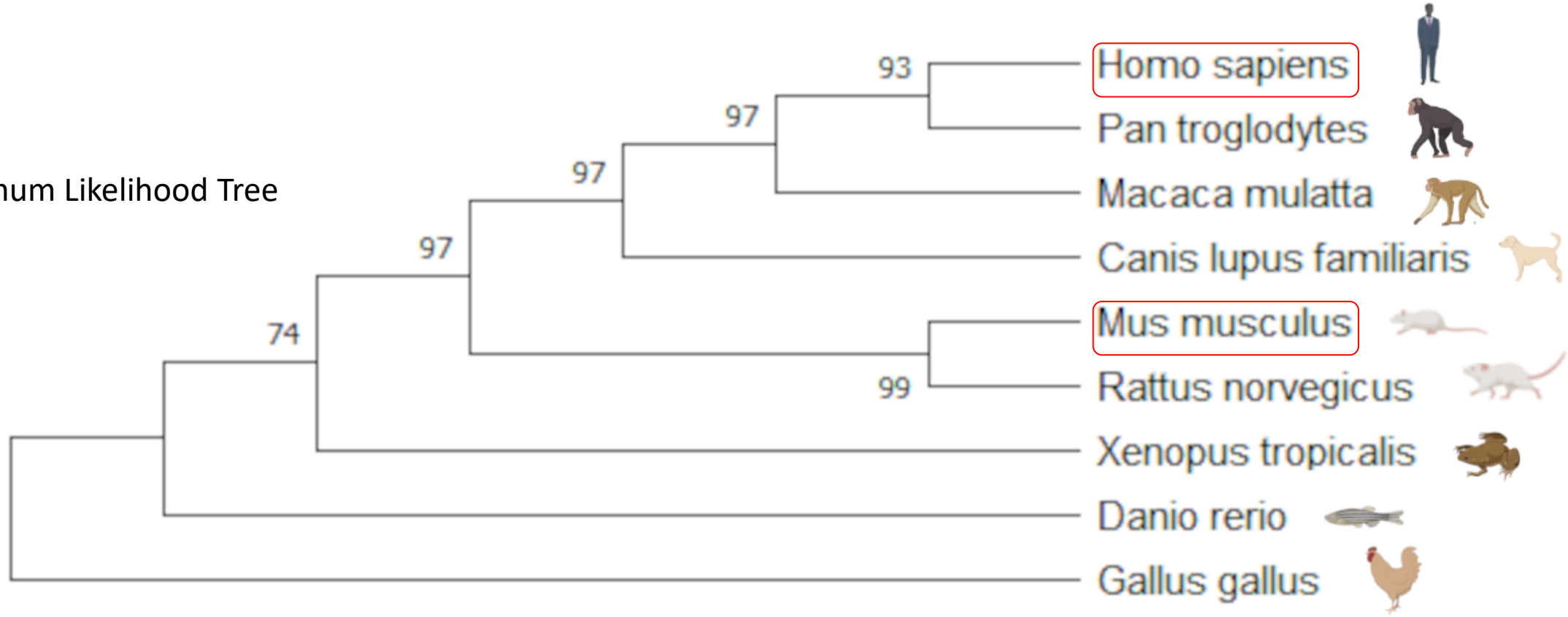
Myelination

What domains are conserved in PMP22?



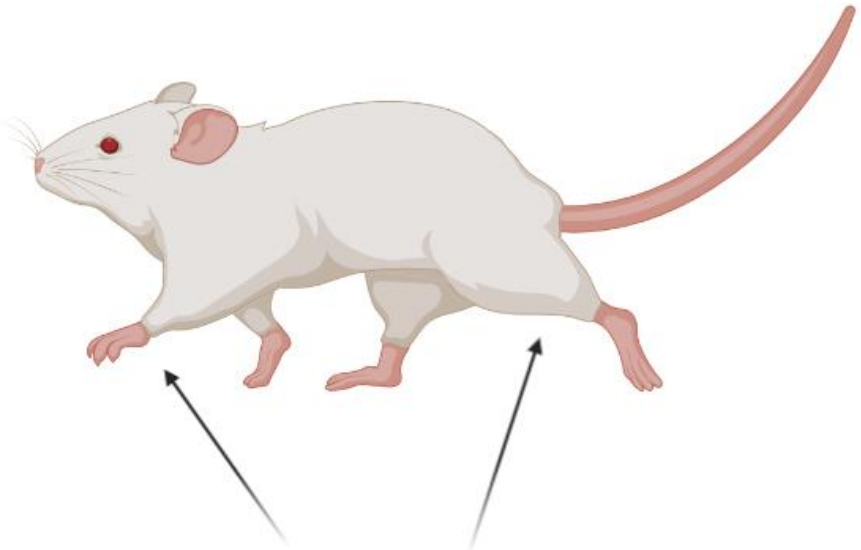
What are the PMP22 homologs?

Maximum Likelihood Tree

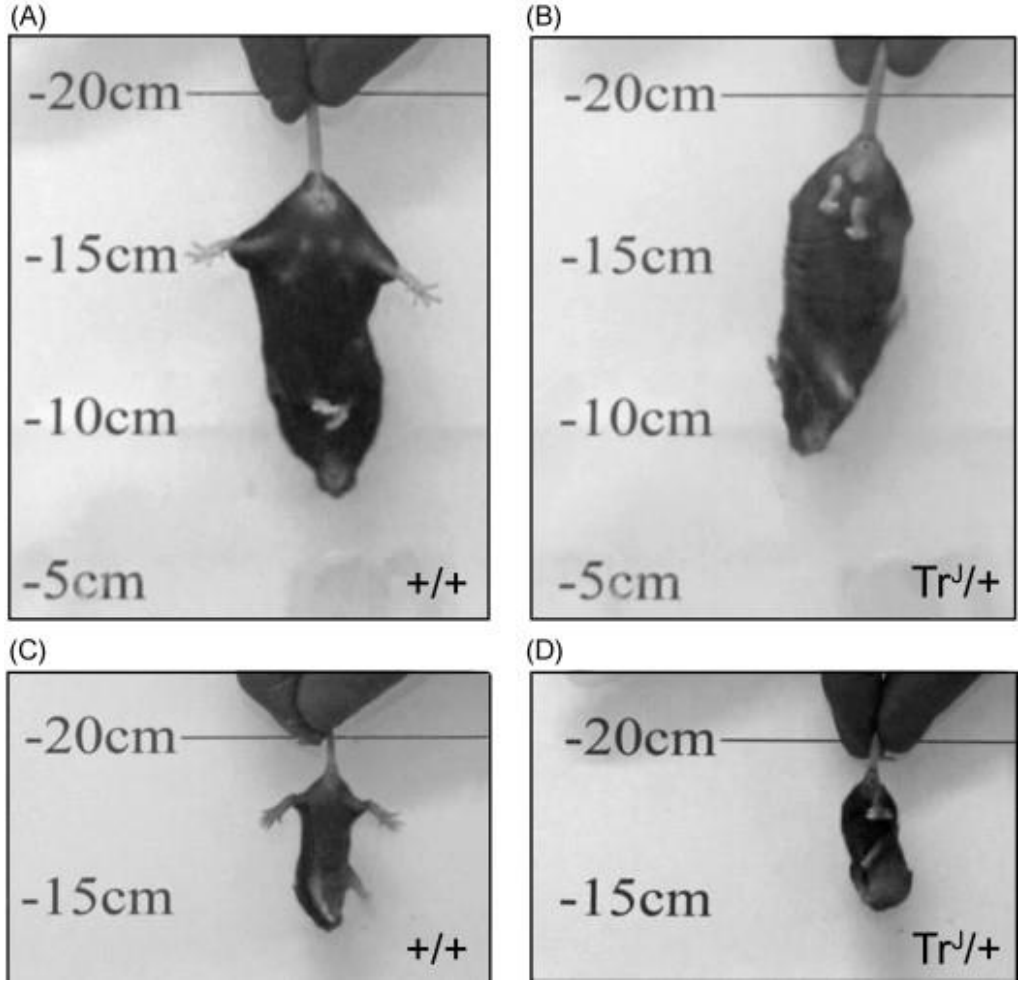


PMP22 has a homolog in mice, an excellent model organism for studying the peripheral nervous system

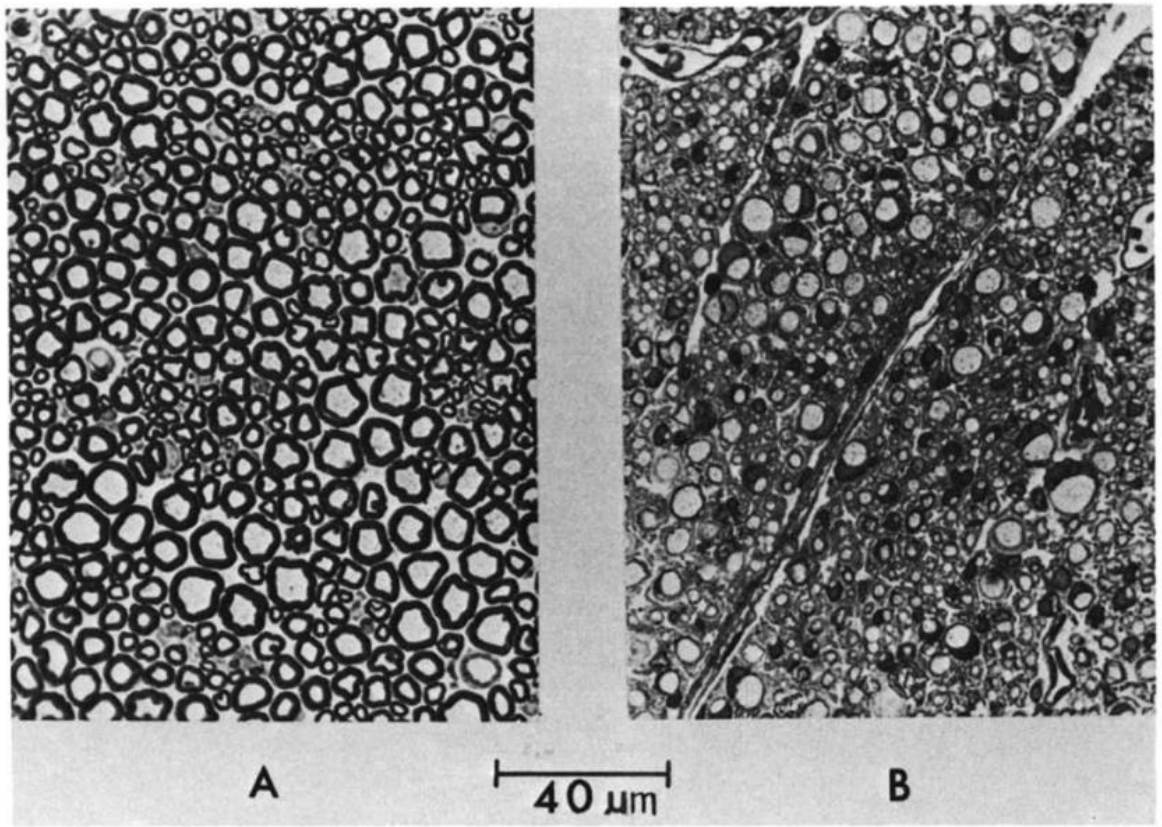
What model organisms can be used to study PMP22?

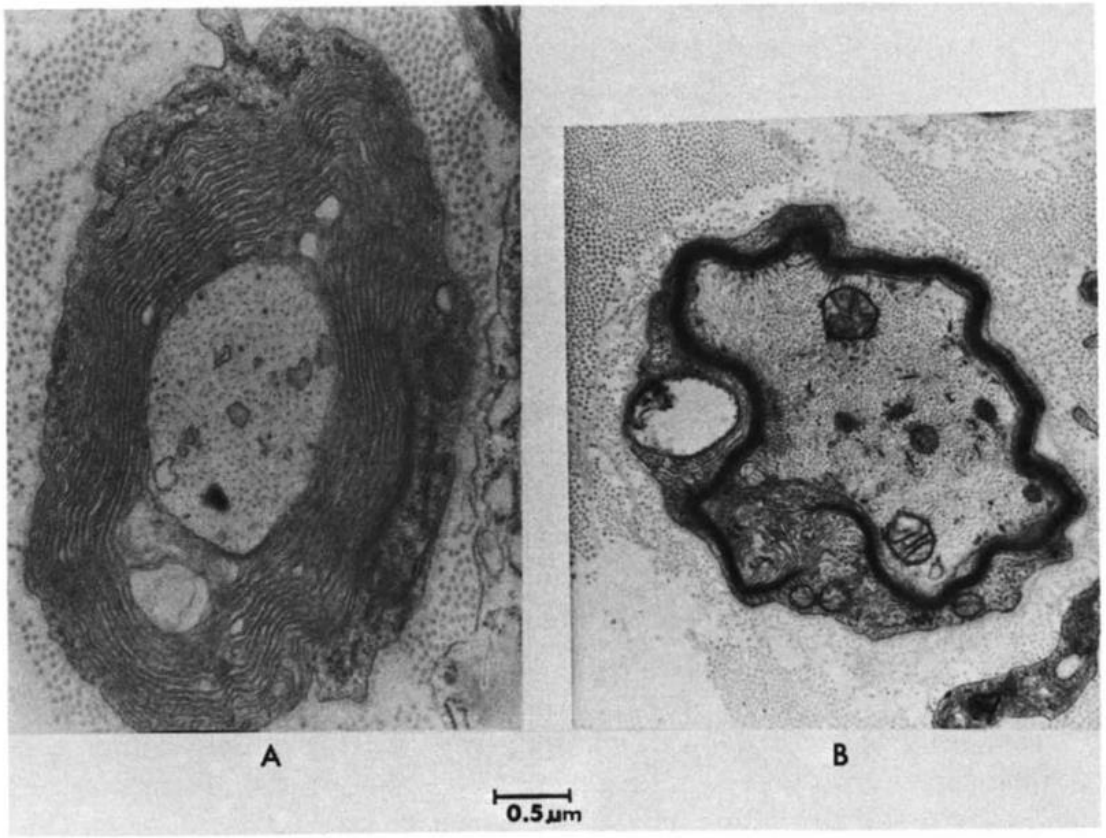


Demyelination results in abnormal gait and tremors of limbs



Why do mice make a great model organism?

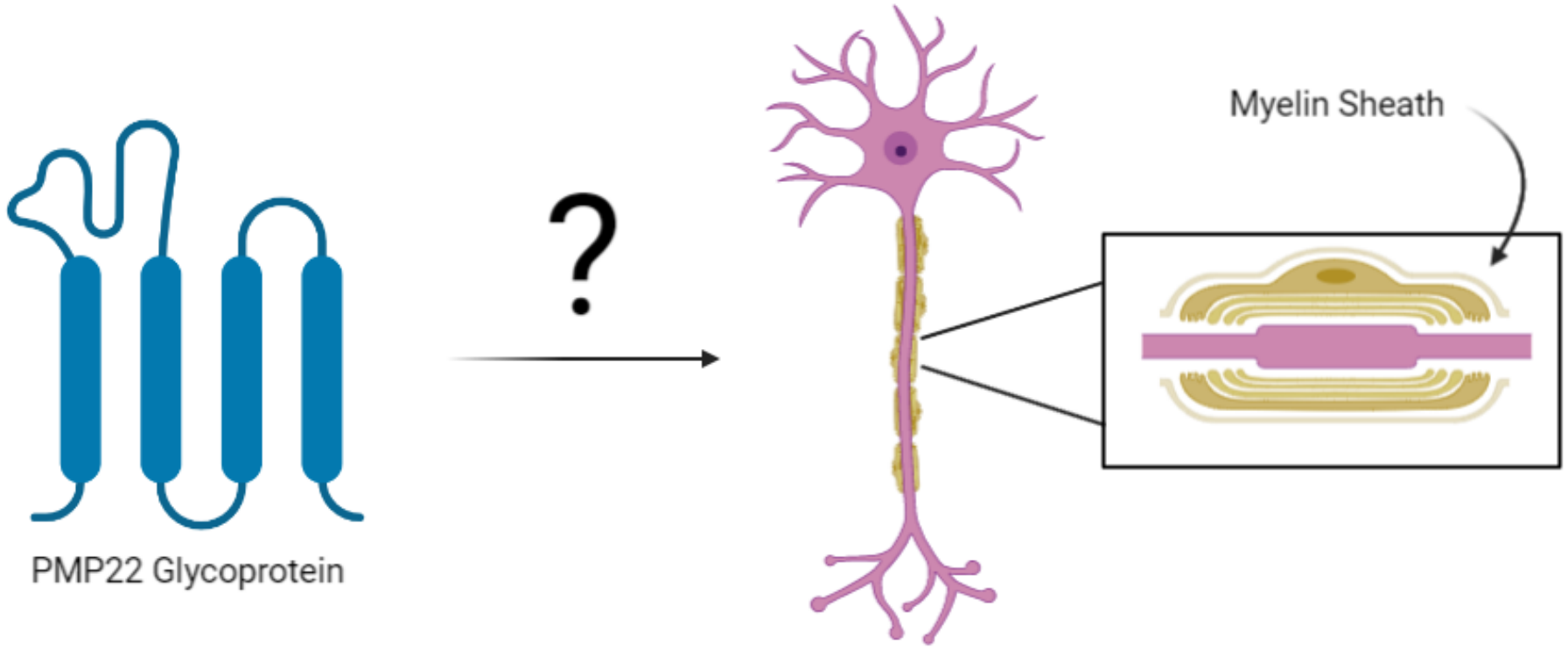




Sciatic nerves and myelin closely resemble human phenotype of CMT1A patients

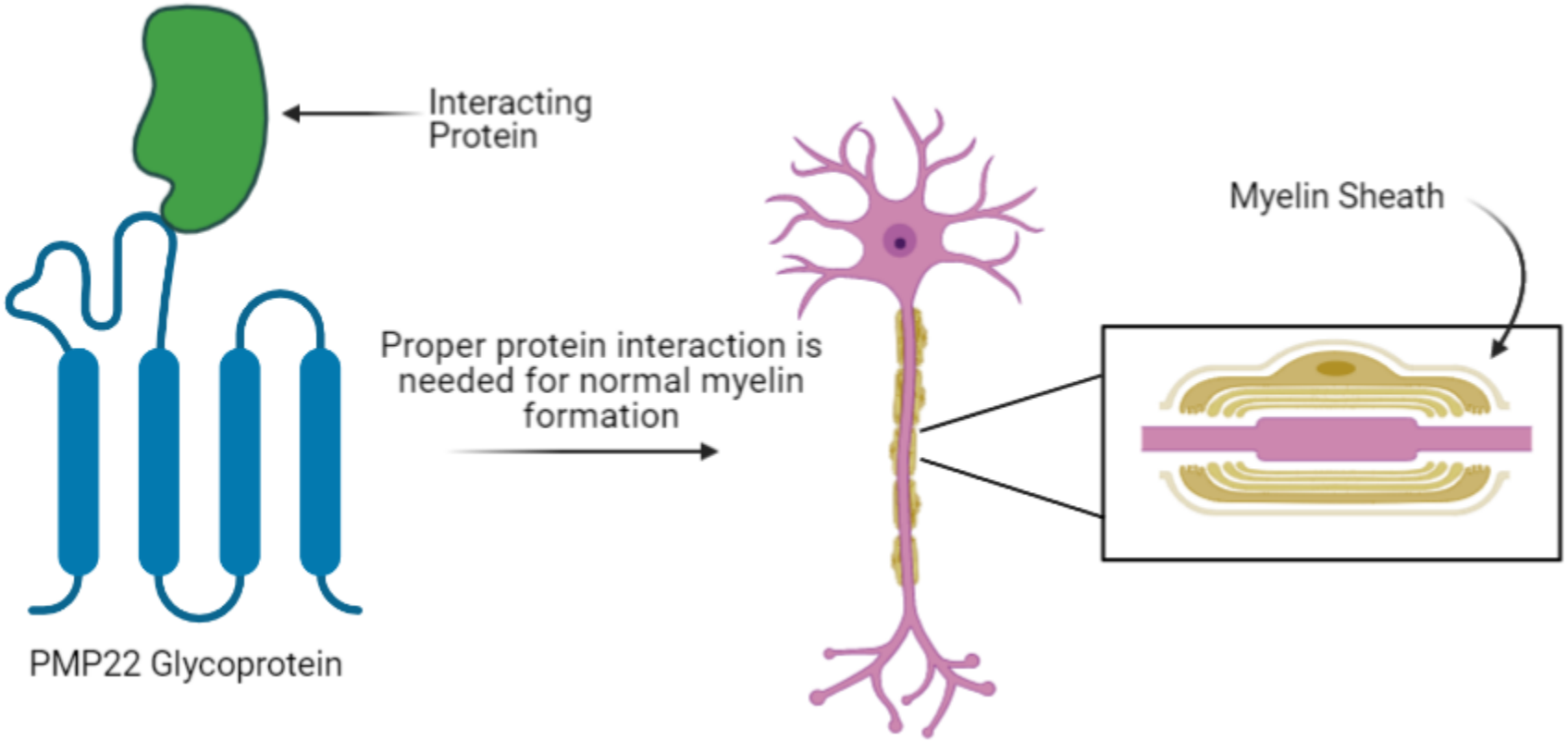
What is the gap in knowledge?

What role does PMP22 play in normal myelin formation?



Specific Aims

Hypothesis: The glycoprotein PMP22 in the peripheral nervous system plays a role in Schwann cell growth regulation and myelination through the protein-protein interactions with other proteins



Specific Aims

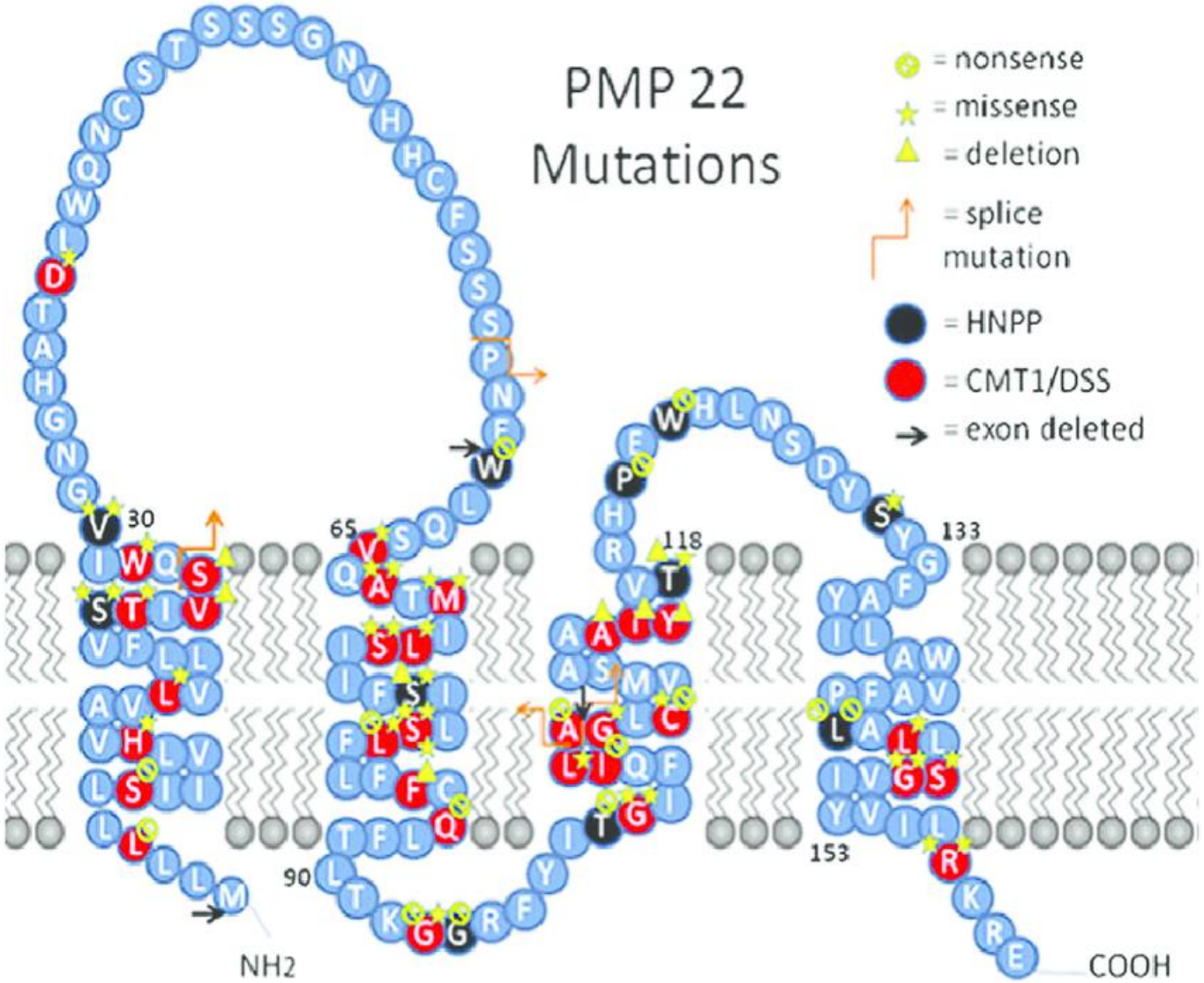
Goal: To determine the role of PMP22 in Schwann cell growth and myelination in the peripheral nervous system

Aim #1: Identify conserved amino acids in PMP22 necessary for the regulation of Schwann cell growth and myelination.

Aim #2: Identify genes that are differentially expressed in in WT and PMP22 mutant myelinating Schwann cells.

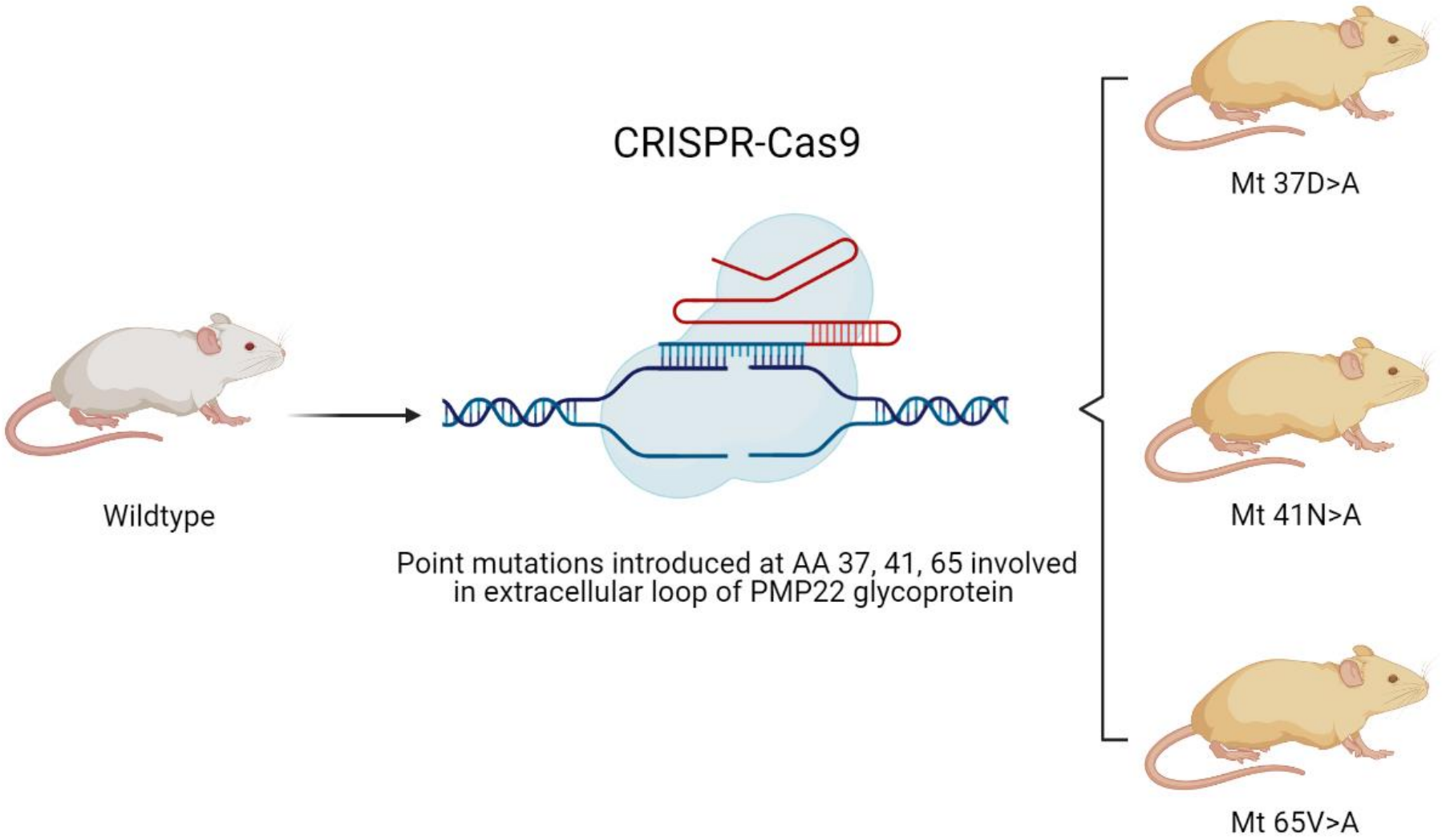
Aim #3: Identify novel proteins important for myelination and cell proliferation.

Aim 1: Conserved amino acids necessary for myelination



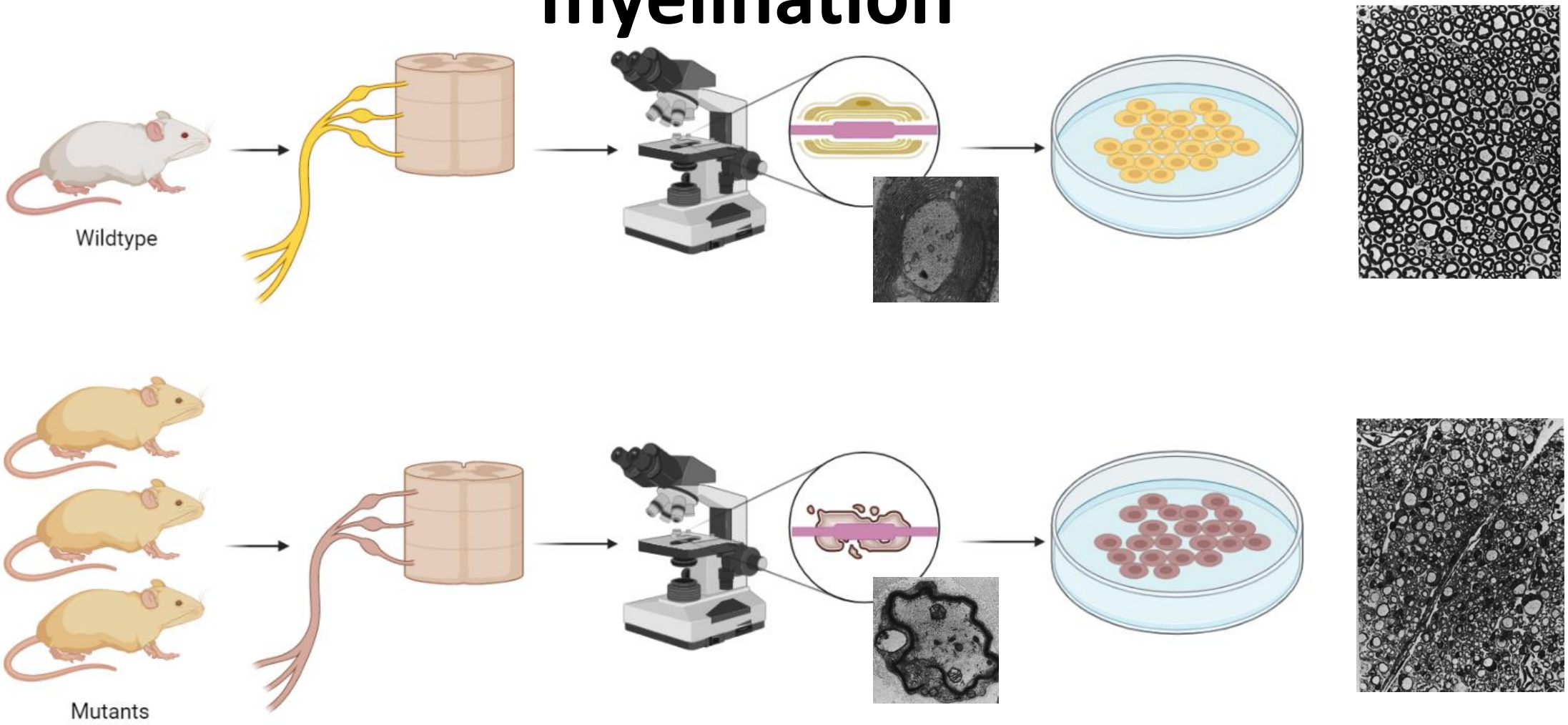
Amino Acids 37, 41, 65 may play a role in proper protein interactions and myelination

Aim 1: Conserved amino acids necessary for myelination



Mutant PMP22 mice can be created using CRISPR-Cas9

Aim 1: Conserved amino acids necessary for myelination



Hypothesis: Mice with mutations in conserved PMP22 amino acids in these extracellular loop regions will show altered Schwann cell growth/proliferation and demyelination in the peripheral nervous system.

Specific Aims

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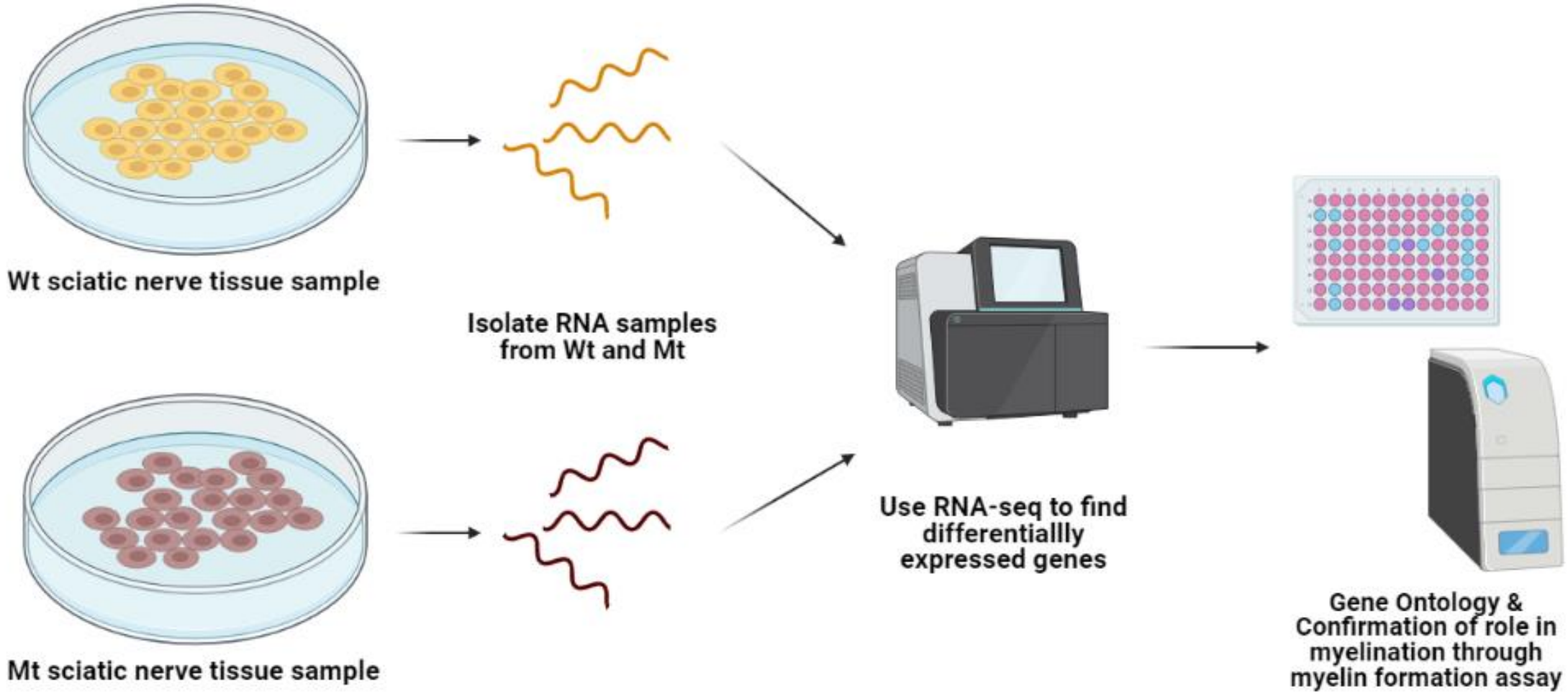
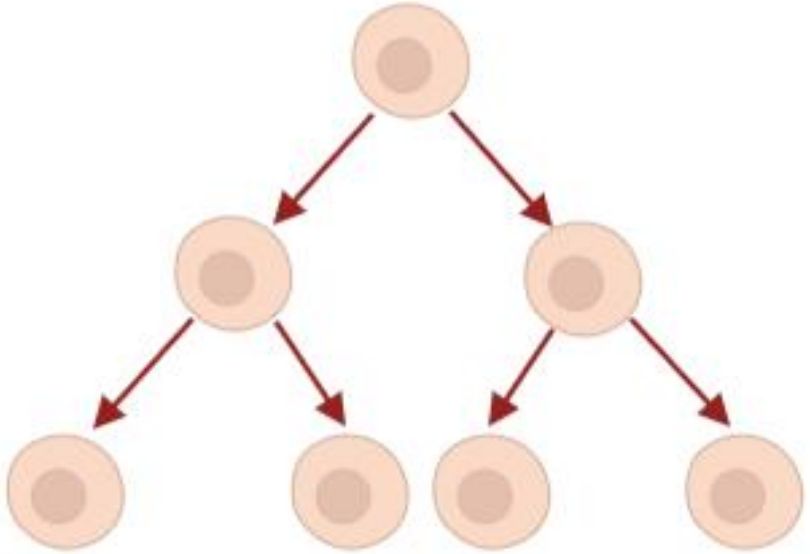
Aim 2: Differential Gene Expression



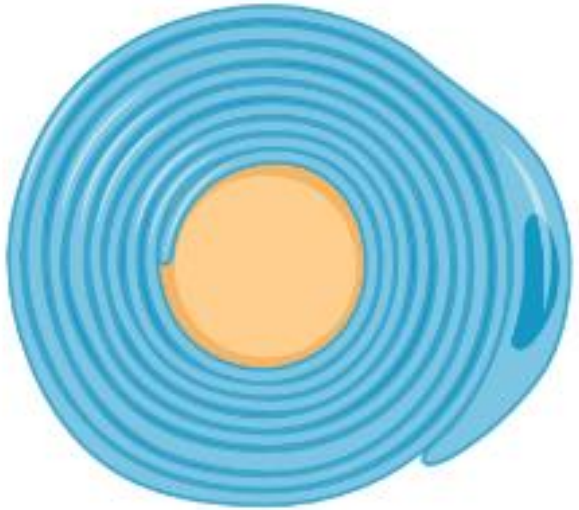
RNA-seq can be used on Wt and Mt RNA in conjunction with GO to find differentially expressed genes related to myelination and can be confirmed via myelin formation assay

Aim 2: Differential Gene Expression

Gene Ontology



(Schwann) Cell Proliferation



Myelination

Hypothesis: Mice with PMP22 mutations will show abnormal levels of gene expression in pathways related to Schwann cell growth/proliferation and myelination.

Specific Aims

Goal: To determine the role of PMP22 in Schwann cell growth and myelination in the peripheral nervous system

Aim #1: Identify conserved amino acids in PMP22 necessary for the regulation of Schwann cell growth and myelination.

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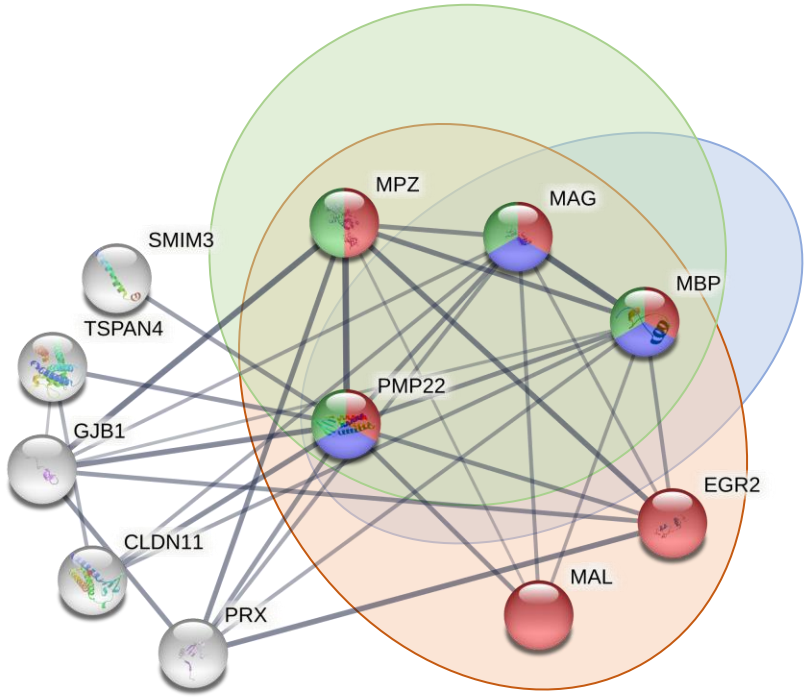
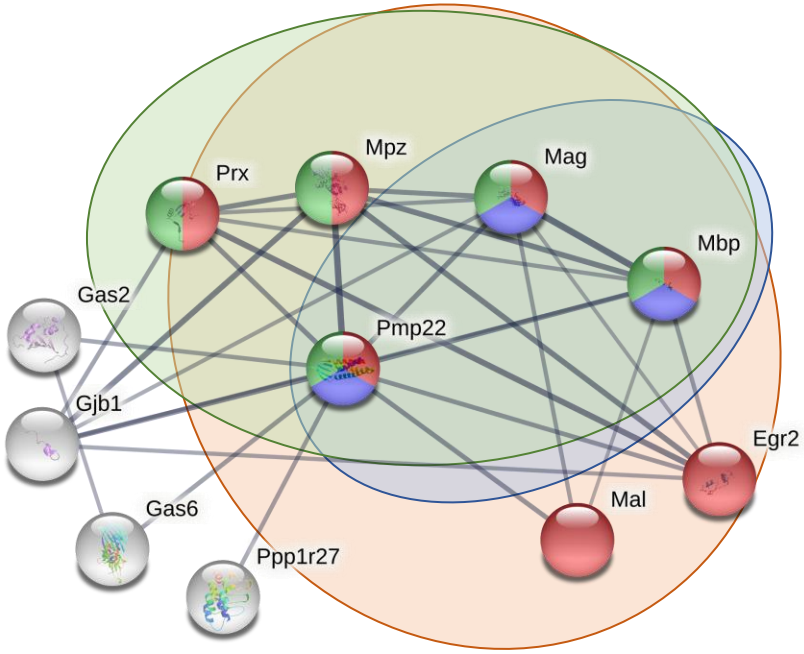
Aim 3: Protein Interactions



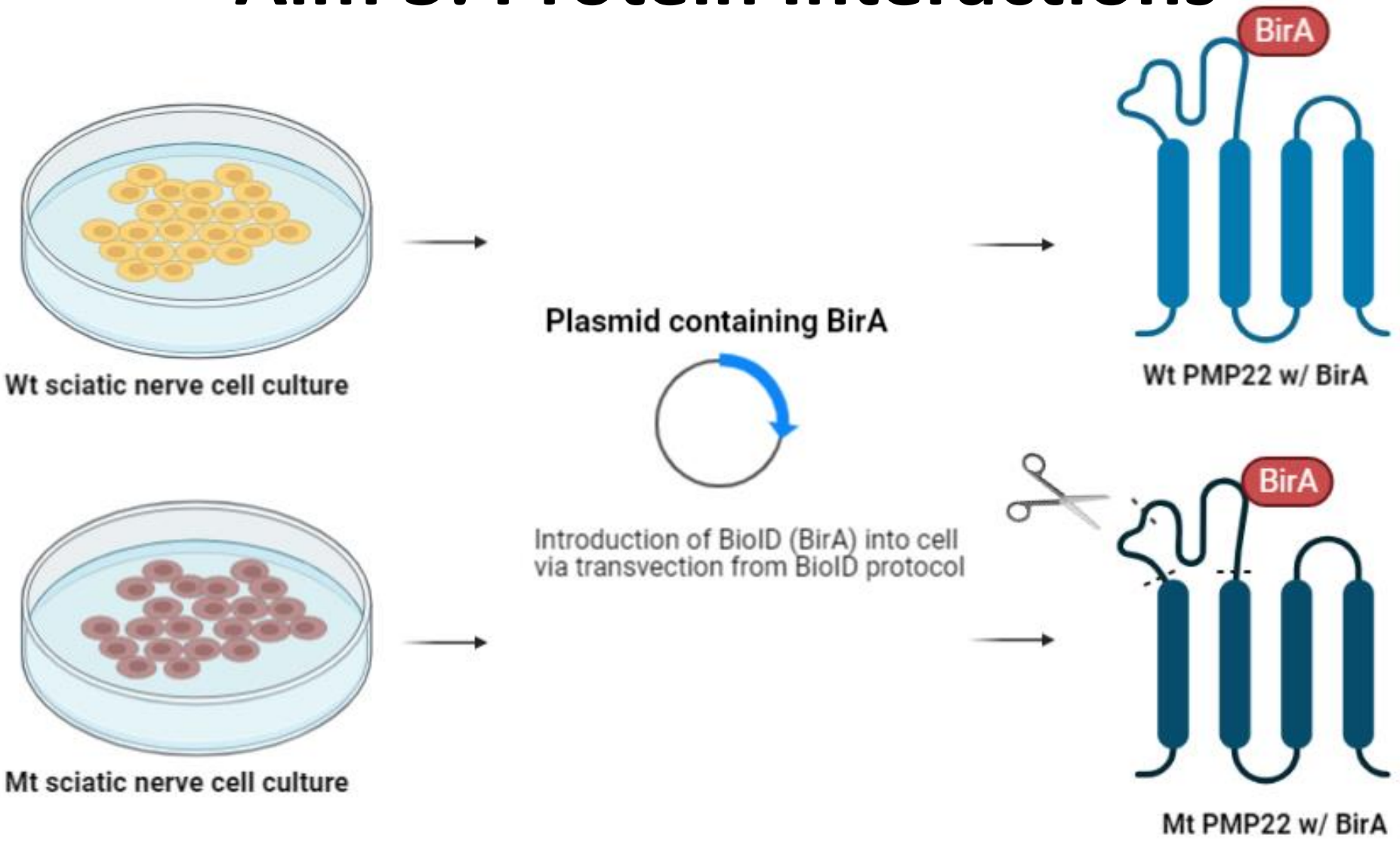
Human



Mouse

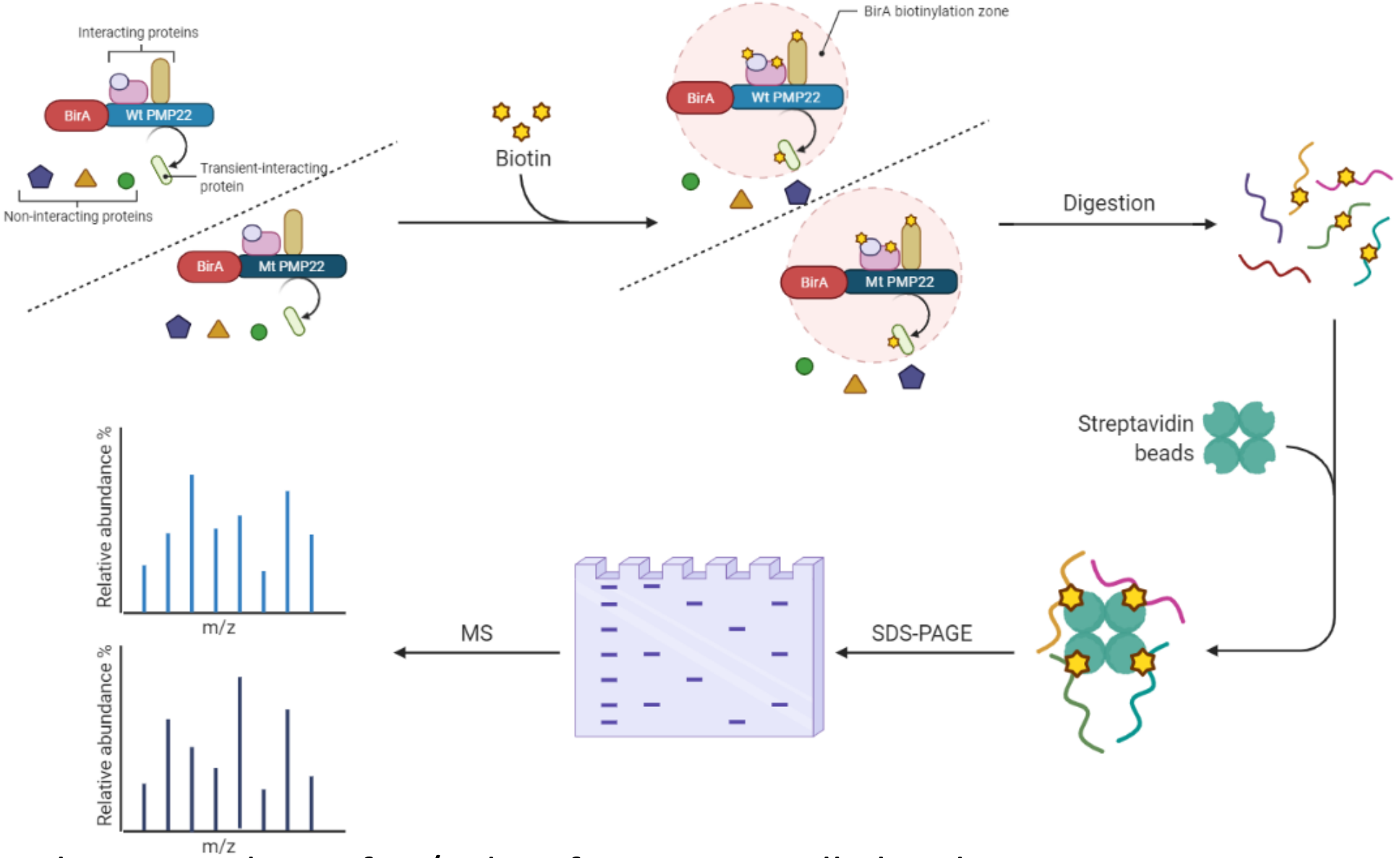
STRING can be used to find already known protein interactions in myelination, compact myelin and myelin sheath

Aim 3: Protein Interactions



Creation of BioID fusion wildtype PMP22 and mutant PMP22 from cell cultures will be made w/ BioID protocol

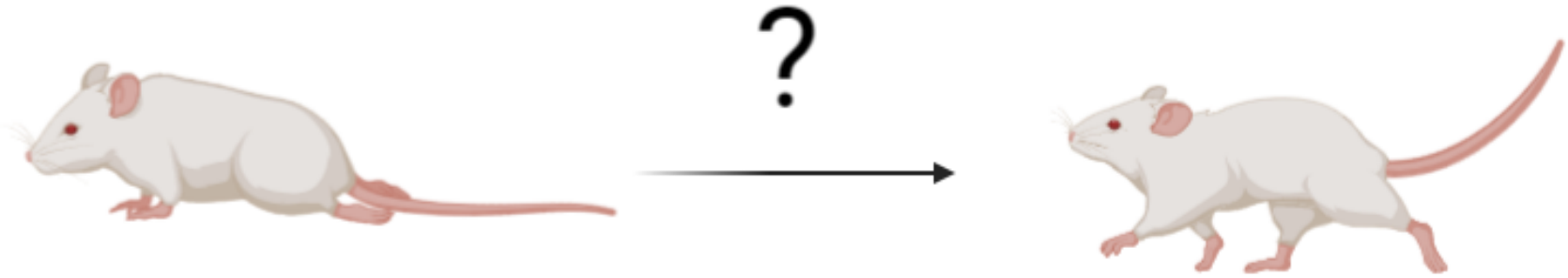
Aim 3: Protein Interactions



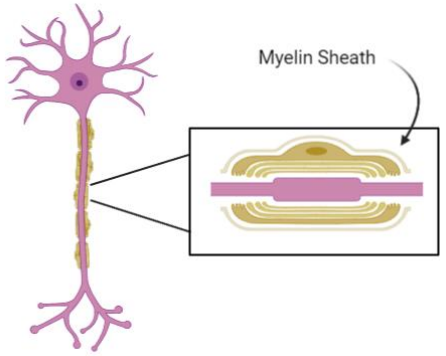
Hypothesis: Analysis of M/Z data from BioID will elucidate new protein interactions and differences between wildtype & mutant PMP22 ability to interact with other proteins

Future Directions?

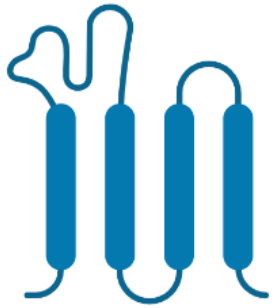
How can alterations in PMP22 associated protein interactions be rescued in vivo?



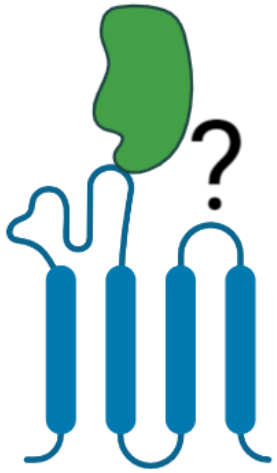
Conclusion



Charcot-Marie-Tooth Type 1A is a genetic disease of the peripheral nervous system resulting in demyelination



There is not cure for Charcot-Marie-Tooth 1A, however PMP22 is implicated in its demyelinating nature despite PMP22's role in myelination being unknown



Improved understanding of the protein interactions between PMP22 and other proteins can elucidate PMP22s role in myelination and contribute to a treatment

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Biorender used to create images

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