Characterization of a zebrafish peripheral myelin mutant

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Zebrafish provide an ideal system for studying the development of myelinating glia

Myelin insulates axons and allows allows for efficient electrical signaling

Myelin is produced by Schwann cells in the PNS and oligodendrocytes in the CNS

Each stage of Schwann cell developmental can be defined by key developmental markers

Mechanisms of myelination is conserved in jawed, vertebrate organisms

Forward genetic screens uncover genes that regulate myelination in vertebrate systems

A screen conducted at Washington University, St. Louis revealed three novel mutants with reduced myelination.

stl144 homozygous mutants have reduced PNS myelination

- Where is the causative lesion? What gene does it affect?
- At what point in development is this gene necessary?
- What are the developmental effects of disrupting the gene?
  1. Reduced number of Schwann cells
  2. Reduced wrapping by Schwann cells
  3. Reduced number of axons present for wrapping

Whole-genome sequencing analysis pipeline to identify affected gene(s) in stl144

Whole Genome Sequencing of stl144 shows linkage to chromosome 8

Figure 1. Whole genome sequencing of mutants and siblings shows linkage to chromosome 8. Regions of linkage were located using mutant-sibling MAF ratio mapping. 22 candidate genes were identified.

Identifying Carriers of stl144 By Cross

Figure 2. Reduced expression of mbp reveals stl144 homozygous mutants in the progeny of a random in-cross (n=6/23). (A) Use progeny showing no visible deformities. (B) stl144 sibling with wild-type expression of mbp along the plLN (arrow). (C) stl144 +/- mutant with reduced expression of mbp along the plLN.

Acknowledgments

I would like to thank Dr. Sarah Petersen for her guidance and mentorship, as well as the Petersen lab group for their continued support. I thank Becky Gallagher and the Kenyon animal care staff for their excellent maintenance of the Higley Aquaculture Facility.

I thank Nicolas Sanchez in the Monk lab for his troubleshooting of the whole genome sequencing data. Finally, I thank the Monk lab at Washington University, St. Louis for conducting original the forward genetic screen that identified the aforementioned myelin mutants.

This work was generously funded by the Kenyon Summer Science Scholars program.

Future Directions

1. Are neural crest cells present and migrating properly?
   • sox10 marks neural crest cells and can reveal if early development is affected by the mutation.

2. Are axons present and migrating normally?
   • Acetylated microtubules mark PNS axons and can be used to determine if axon development is affected in stl144 mutants.

3. Is the stl144 mutation affecting a GPCR, upstream of cAMP?
   • Rescuing stl144 mutants with forskolin, a cAMP elevator, may reveal the genetic pathway affected by stl144.

Molecular characterization of stl144 mutants may shed light on which candidate gene is most likely responsible for the reduction in PNS myelination.

References


