

Effects of Aging and Gene Dosage on Vertebral Column Regularity



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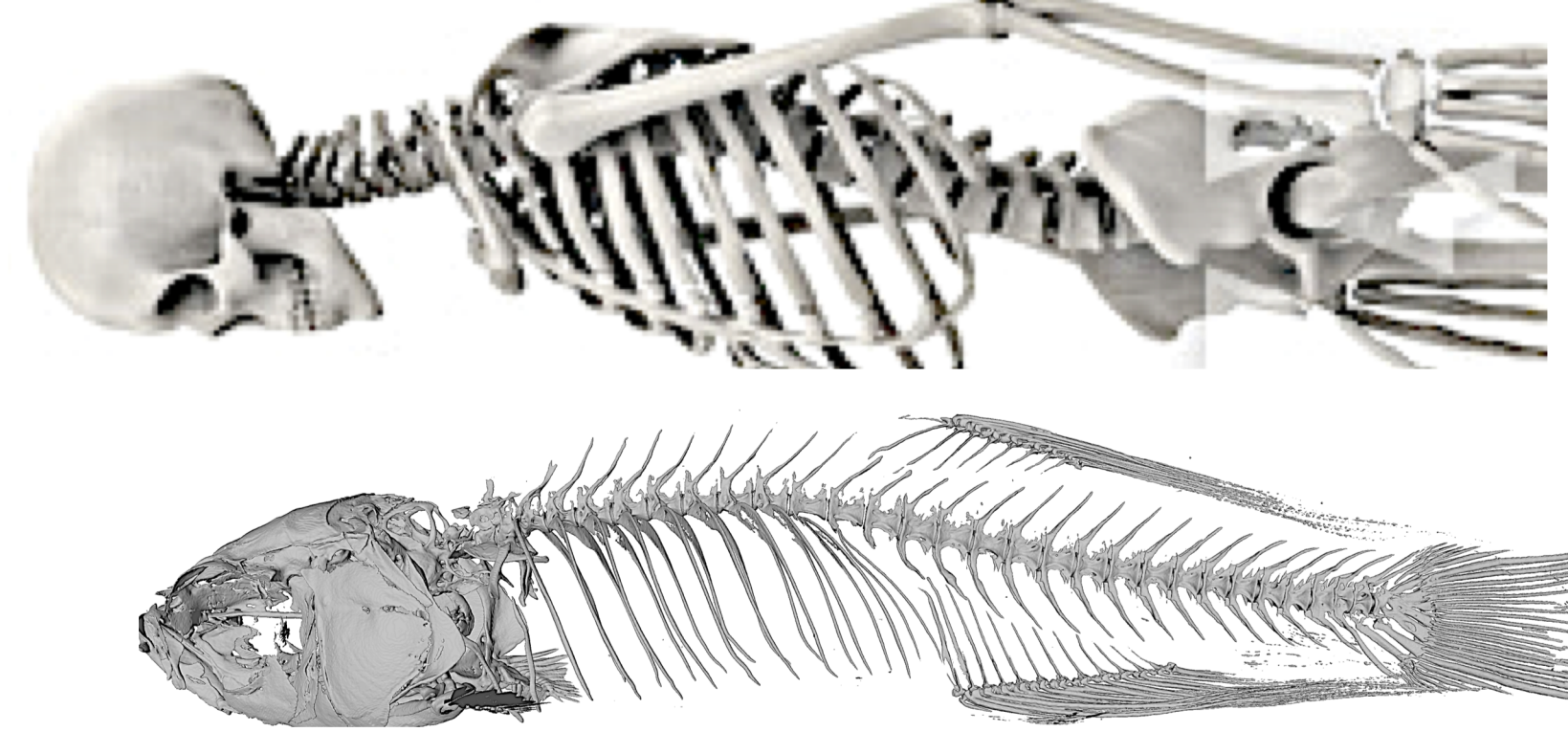
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Introduction

Mild spine disorders that appear later in life are often diagnosed as idiopathic, meaning that the cause of the deformity is unknown and isn't thought to be congenital, or apparent from birth.

Here, we are using zebrafish to study minor (perhaps overlookable) vertebral length defects caused by flaws in development due to gene dosage of Tbx6 and heat shock stress. We propose these subtle defects may become exacerbated over the process of aging and present as spine disorder in adulthood— thus providing a congenital explanation for a spinal condition that would otherwise be dismissed as idiopathic.

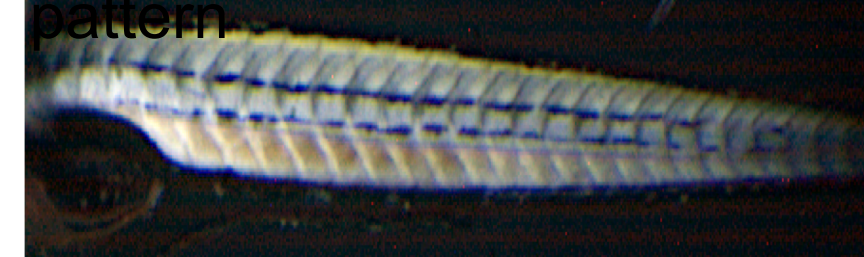


Tbx6 Gene Dosage Effects

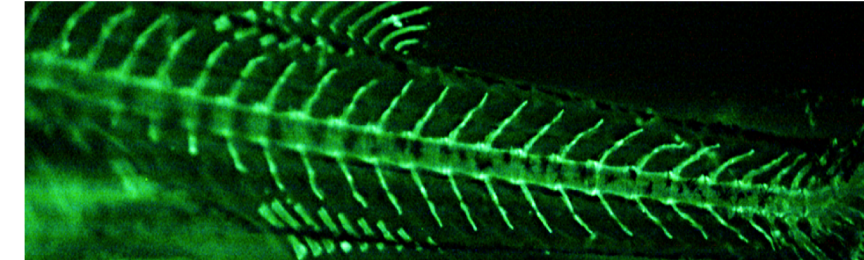
Tbx6 +/+

- Normal segmentation of the vertebrae and somites (embryonic segmental structures that help to pattern muscle, bone, and skin)

Somites in regular segmental



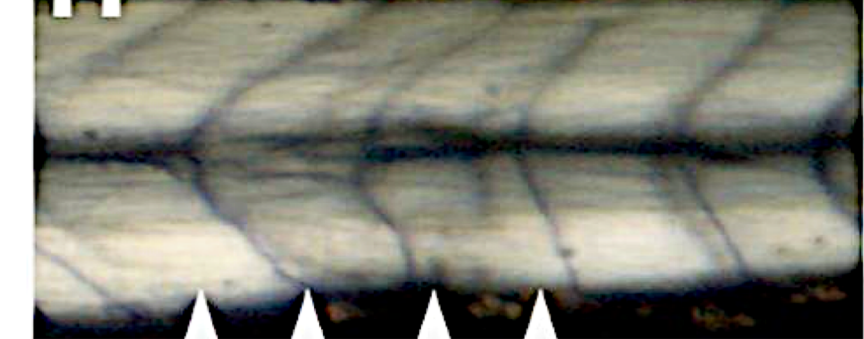
Juvenile spine in regular segmental pattern



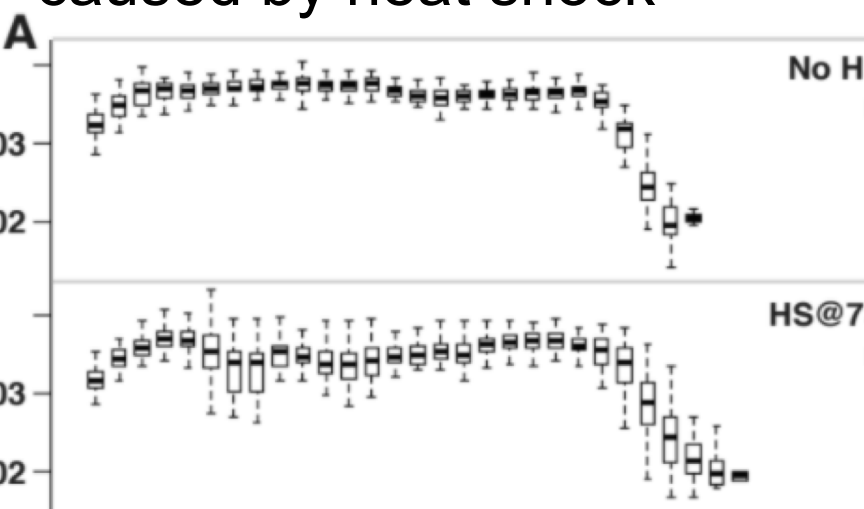
Tbx6 +/-

- More susceptible to stress-related defects compared to Tbx6 +/+.

Somite border defects caused by heat shock



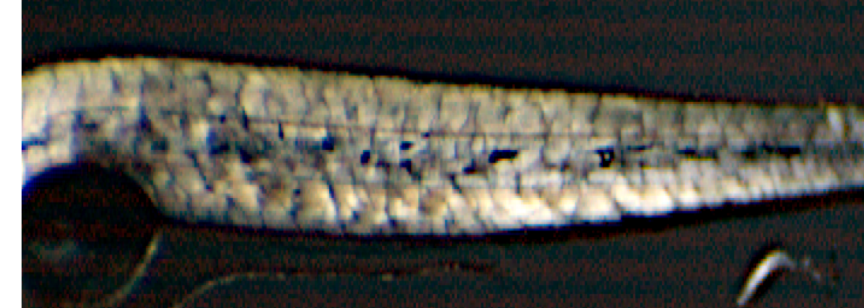
Localized vertebral length defects caused by heat shock



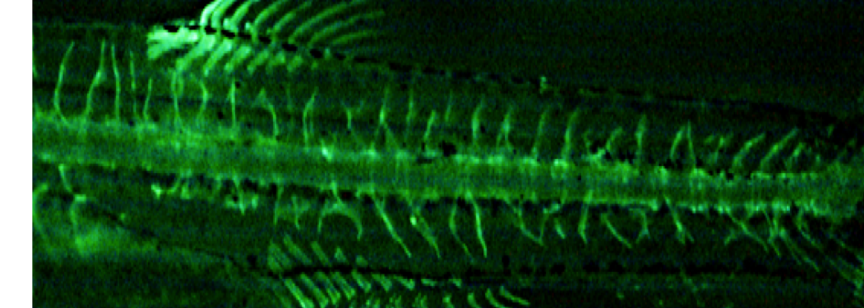
Tbx6 -/-

- Do not form somites and have severe vertebral defects

Loss of somite patterning



Loss of normal vertebral patterning

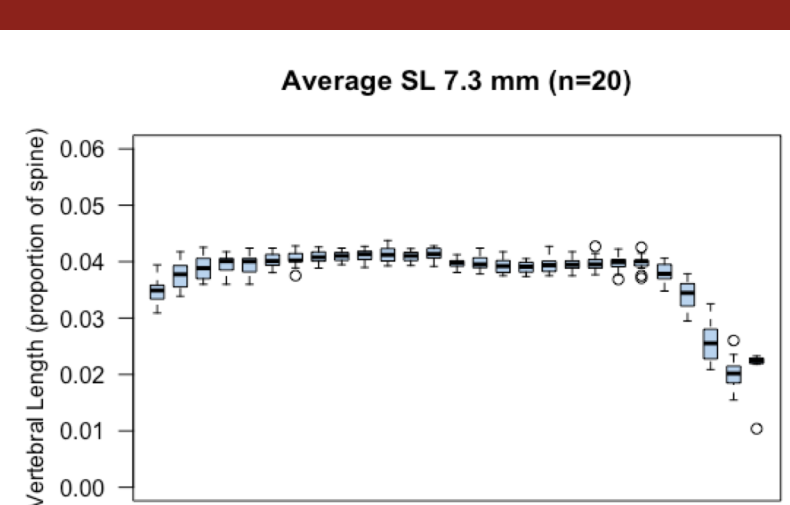


Vertebral Length Regularity

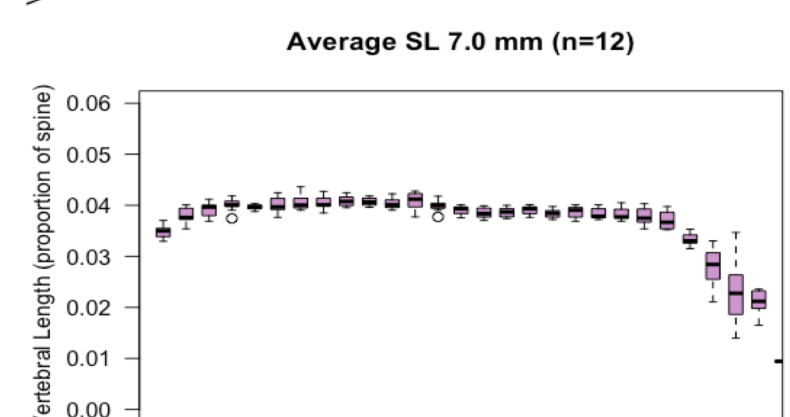
Juvenile

Adult

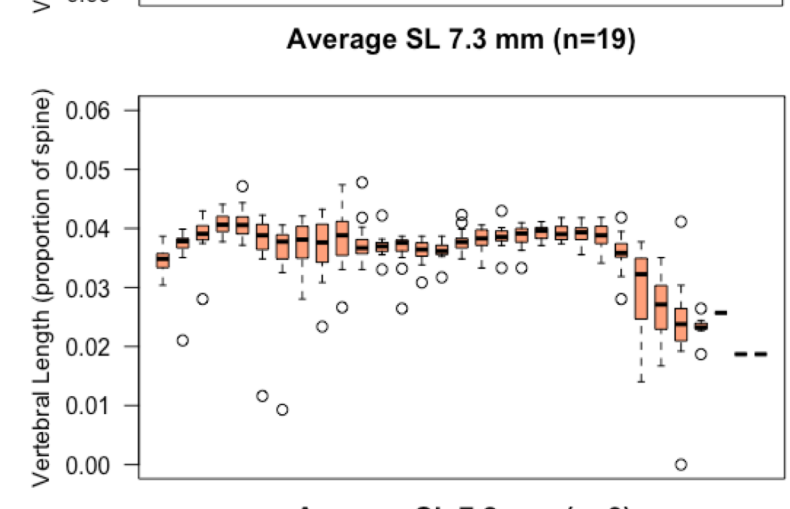
Tbx6 +/+



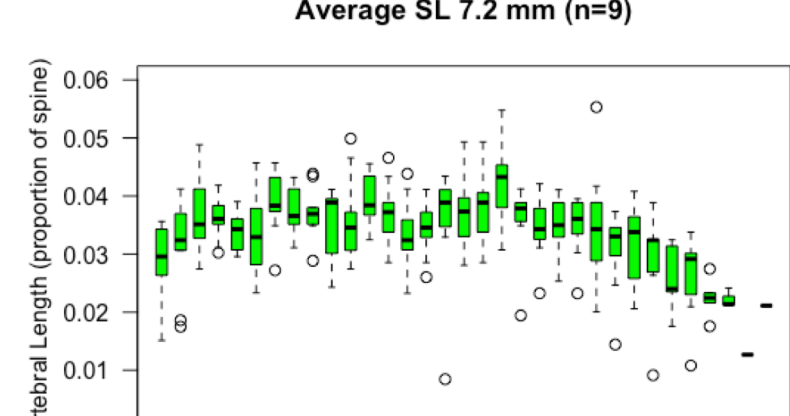
Tbx6 +/-



Heat Shock Tbx6 +/-



Tbx6 -/-



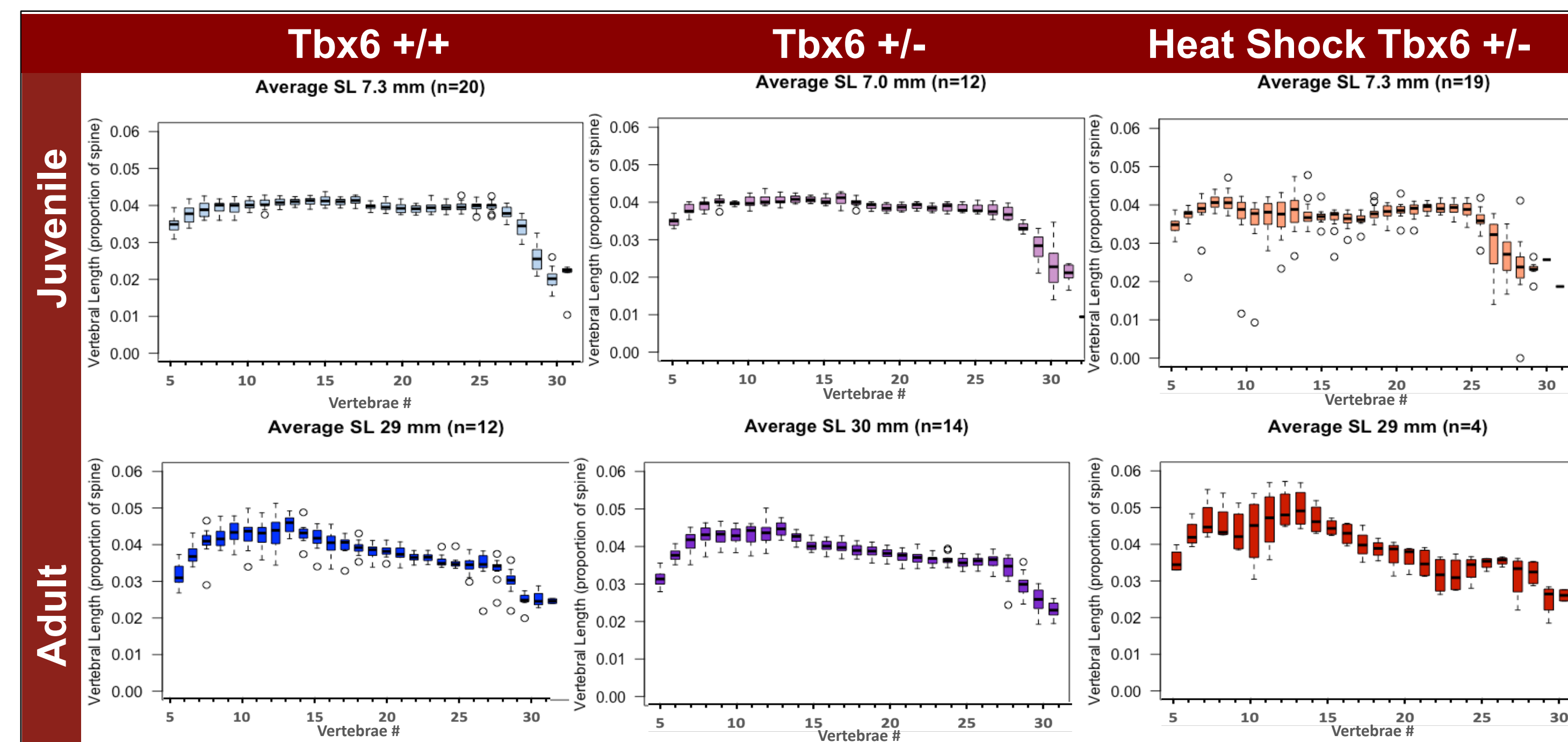
Aging Effects



Phenotype Color Key

Juvenile Tbx6 +/+	Juvenile Tbx6 +/-	Juvenile Heat Shock Tbx6 +/-	Juvenile Tbx6 -/-
Adult Tbx6 +/+	Adult Tbx6 +/-	Adult Heat Shock Tbx6 +/-	Adult Tbx6 -/-

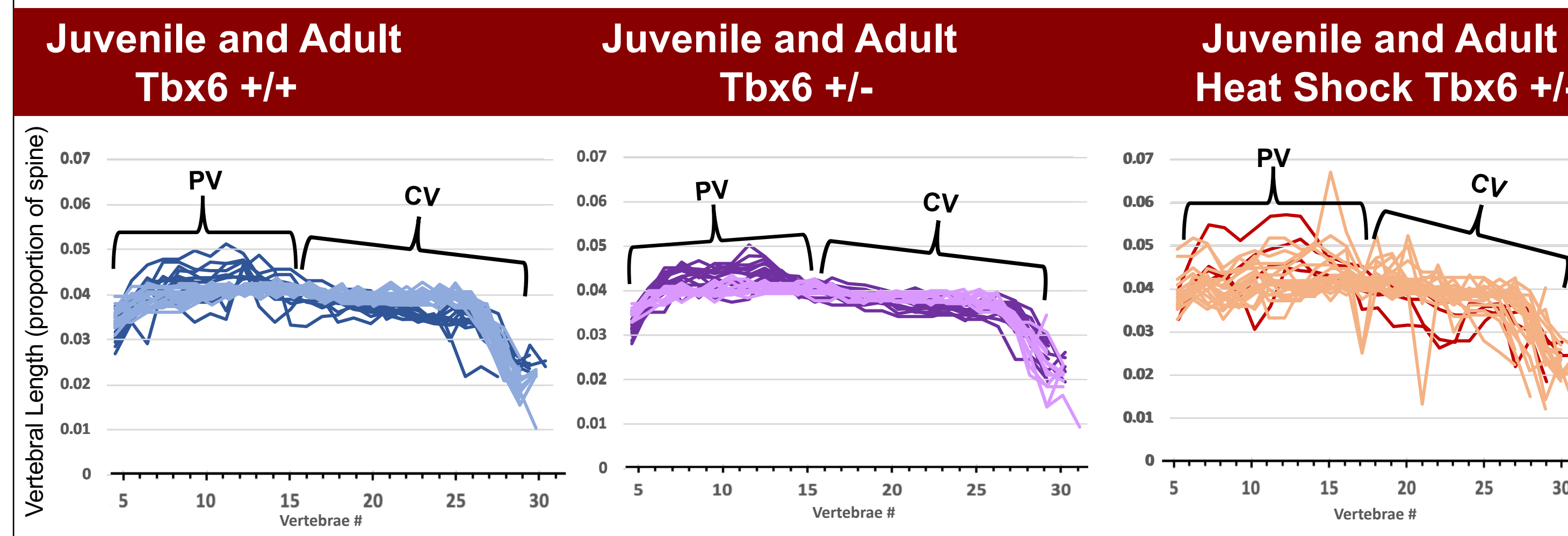
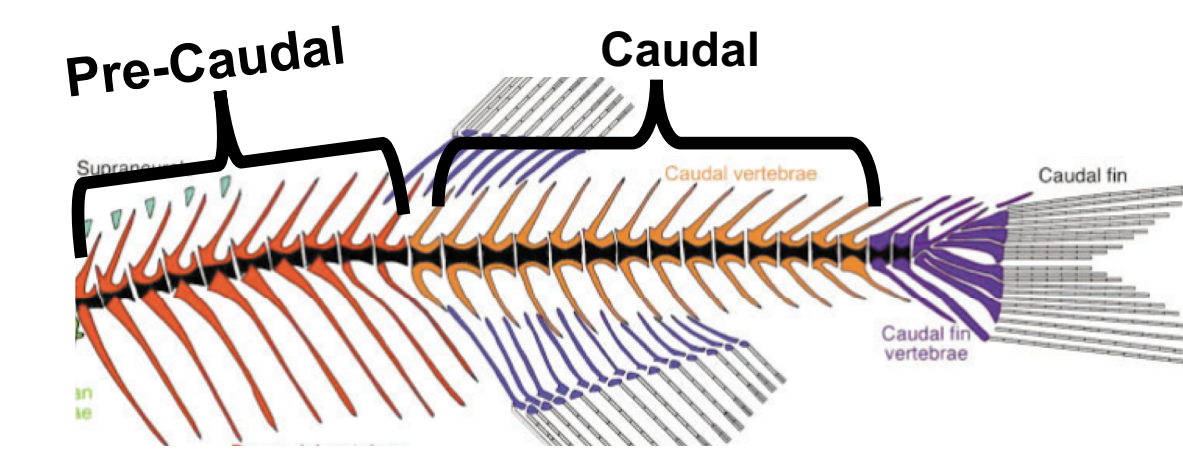
1. Adult individuals may have more vertebral length variability than juveniles in the anterior half of the spine



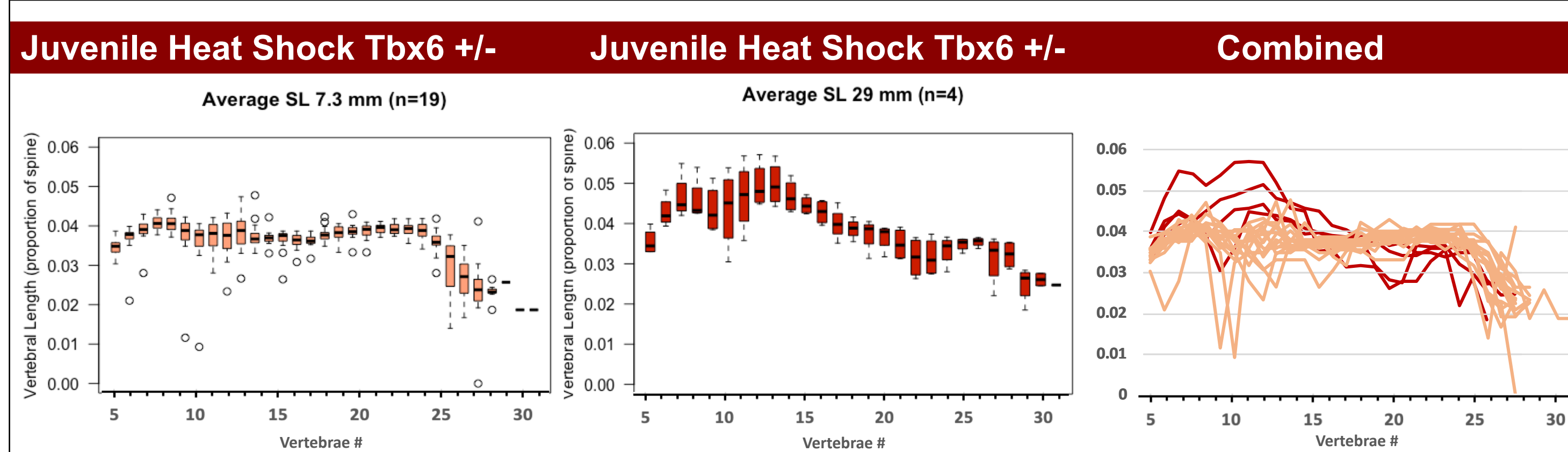
2. Precaudal Vertebrae and Caudal Vertebrae undergo differential growth rates

Pre-Caudal Vertebrae (PV) = "Thoracic" rib-bearing, #5-14

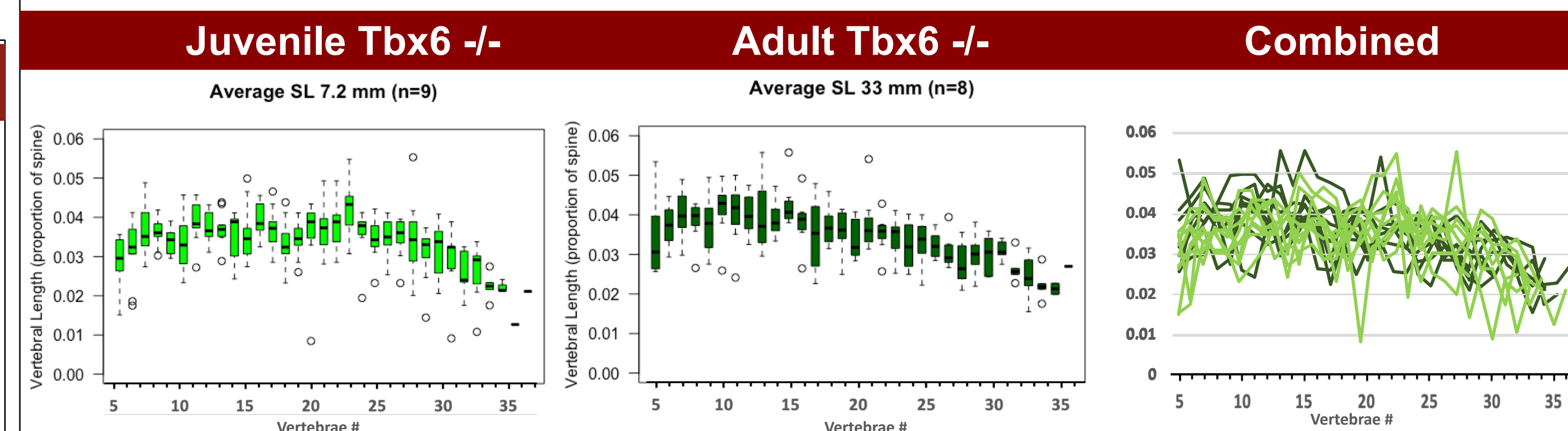
Caudal Vertebrae (CV) = "Lumbar", lower back, #15-28



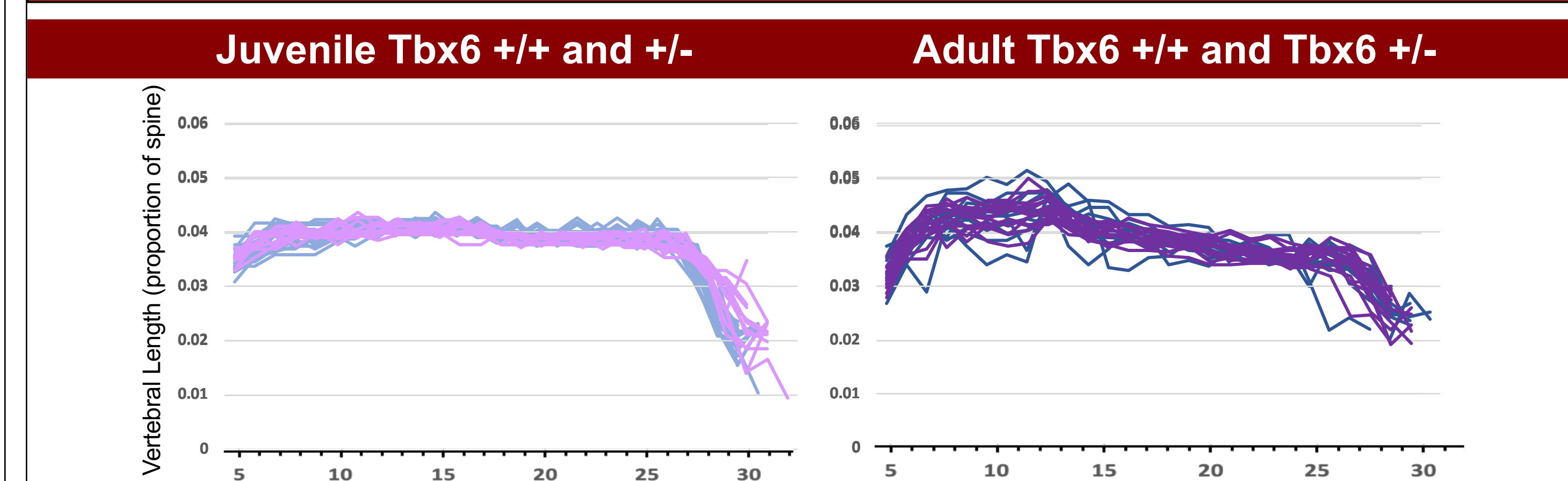
3. Heat shock-induced vertebral length variability increases into adulthood in a localized manner



4. Homozygous loss of Tbx6 causes vertebral length variability that remains stable over age



5. The stress of aging does not have a differential effect on Tbx6 +/+ and Tbx6 +/-



Conclusions

Aging in combination with differential gene dosage of Tbx6 and heat shock stress have an assortment of effects on the vertebral column:

- Aging increases anterior vertebrae length variability in adult Tbx6 +/+, +/-, and heat shock +/-
- it appears that overtime, PV get proportionally larger and CV get proportionally smaller suggesting differential growth rates of those vertebrae
- In Tbx6 -/- individuals, the variability appears to remain constant through age
- While stress has been shown to affect Tbx6 +/- more than Tbx6 +/+, this is not the case with aging.
- Heat shocked Tbx6 +/- individuals' vertebral defects persist and may also worsen through adulthood

Future Directions

- In this project we model "middle-aged" spines, it would be interesting to study an "elderly" sample as well
- We observe lateral spine curvature in aged fish, and we are interested in studying these individuals as models for scoliosis
- Tbx6 -/- individuals display many musculoskeletal defects that we are interested in studying, including: vertebral polarity defects, severe rib deformities, and muscle patterning errors.

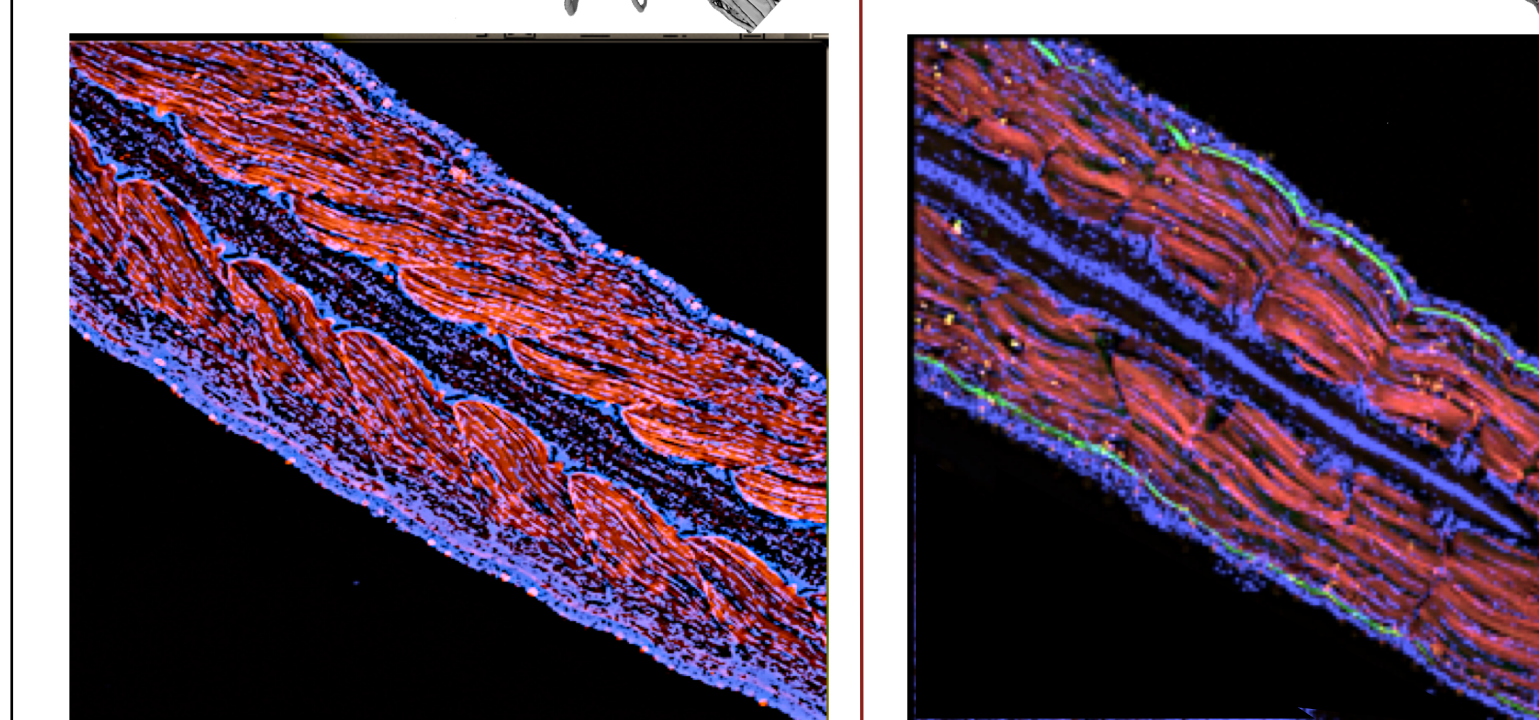
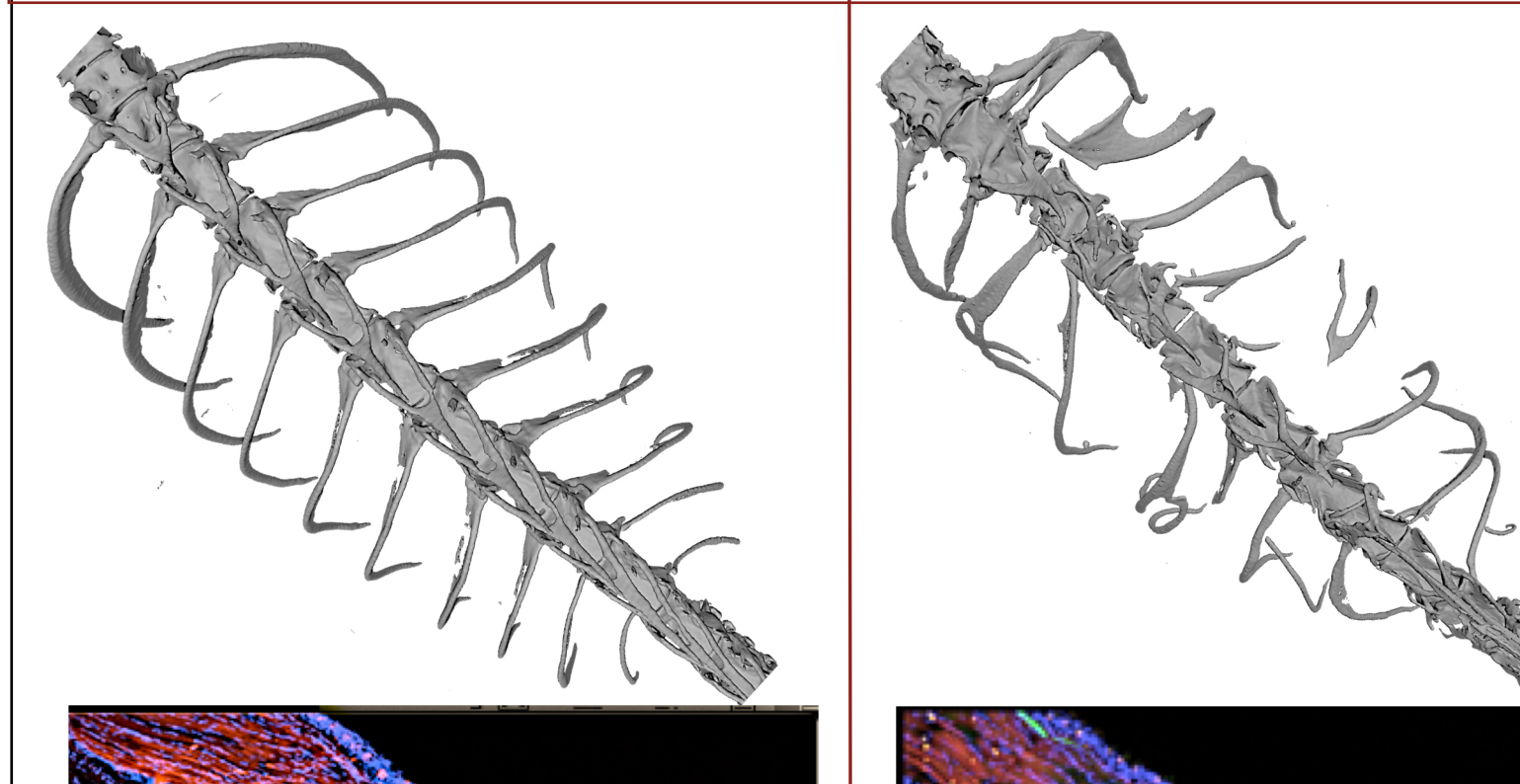
Model for Scoliosis



Tbx6 -/- Musculoskeletal Defects:

Tbx6 +/+, +/-

Tbx6 -/-



Acknowledgments

Thank you first to my right hand man Sarah Shehreen, as well as Kevin Serra (who provided the juvenile data) and Stephen Devoto, for their continued guidance, curiosity, and enthusiasm. Thank you to Christina Vyzas for setting us on this vertebral length journey, and thank you Daniel Youngstrom for the μ CT scans of the adult fish that allowed us to partake on this virtual adventure.

For info about our Methods, please see Sarah for an informative poster!

