Idiopathic scoliosis affects 3% of adolescents worldwide, and is characterized by the spine being curved sideways in a C- or S-shape. This curvature causes back pain, and the asymmetric ribcage often puts pressure on the lungs and heart2. Mutations in the protein-tyrosine kinase-7 (*ptk7*) gene are associated with idiopathic and congenital scoliosis. Ptk7 is a critical regulator of the Wnt (Wingless/Integrated) signal transduction pathway, which generates waves of traveling gene expression along the posterior body axis during early embryonic development3. *Due to a lack of model organisms with spine structure sufficiently similar to humans, the details of the interaction between ptk7 variants and the Wnt signaling pathway remain unclear3.*

I **hypothesize** that ptk7 variants lead to scoliosis by altering the regulation of several proteins to collectively act as an on/off switch for the Wnt signal transduction pathway. The **long-term goal** of this study is to further our understanding of the details regarding the underlying mechanism of scoliosis pathogenesis. The **objective** is to utilize the zebrafish model to uncover the role of ptk7 in the Wnt signaling pathway. The zebrafish is a good model organism for this study because the cranial-to-caudal pressure from swimming forward is comparable to the downward pressure gravity imposes on humans while exacerbating scoliosis3.

**Aim 1: Identify novel mutations in the ptk7 gene that cause idiopathic or congenital scoliosis.**

**Hypothesis:** I expect to find multiple sites of variation within the ptk7 gene, some of which will cause the scoliosis phenotype.

**Approach:** I will use next generation sequencing to locate several ptk7 variants in zebrafish. It will then be determined whether or not each variant actually contributes to the scoliosis phenotype. Each variant will have a group of zebrafish to be examined during the larvae stage for signs of congenital scoliosis such as abnormal vertebrae size, shape, or alignment. Variant groups that do not display congenital scoliosis will then have their dorsal:ventral and left:right length ratios calculated during adolescence to detect for idiopathic scoliosis. Groups that begin displaying idiopathic scoliosis will be re-examined at several stages to measure the severity of disease progression for that variant. It will also be noted which variants never develop scoliosis.

**Rationale:** To better understand how ptk7 variants cause scoliosis, it is imperative to know which domains the mutations that cause each type of scoliosis are in, and it will be beneficial to determine which variants cause the most deleterious curvature.

1. Grimes DT, Boswell CW, Morante NF, Henkelman RM, Burdine RD, Ciruna B. Science. 2016 Jun 10;352(6291):1341-1344.
2. <https://www.mayoclinic.org/diseases-conditions/scoliosis/symptoms-causes/syc-20350716>
3. Hayes M, Gao X, Yu LX, Paria N, Henkelman RM, Wise CA, Ciruna B. Nat Commun. 2014 Sep 3;5:4777.