



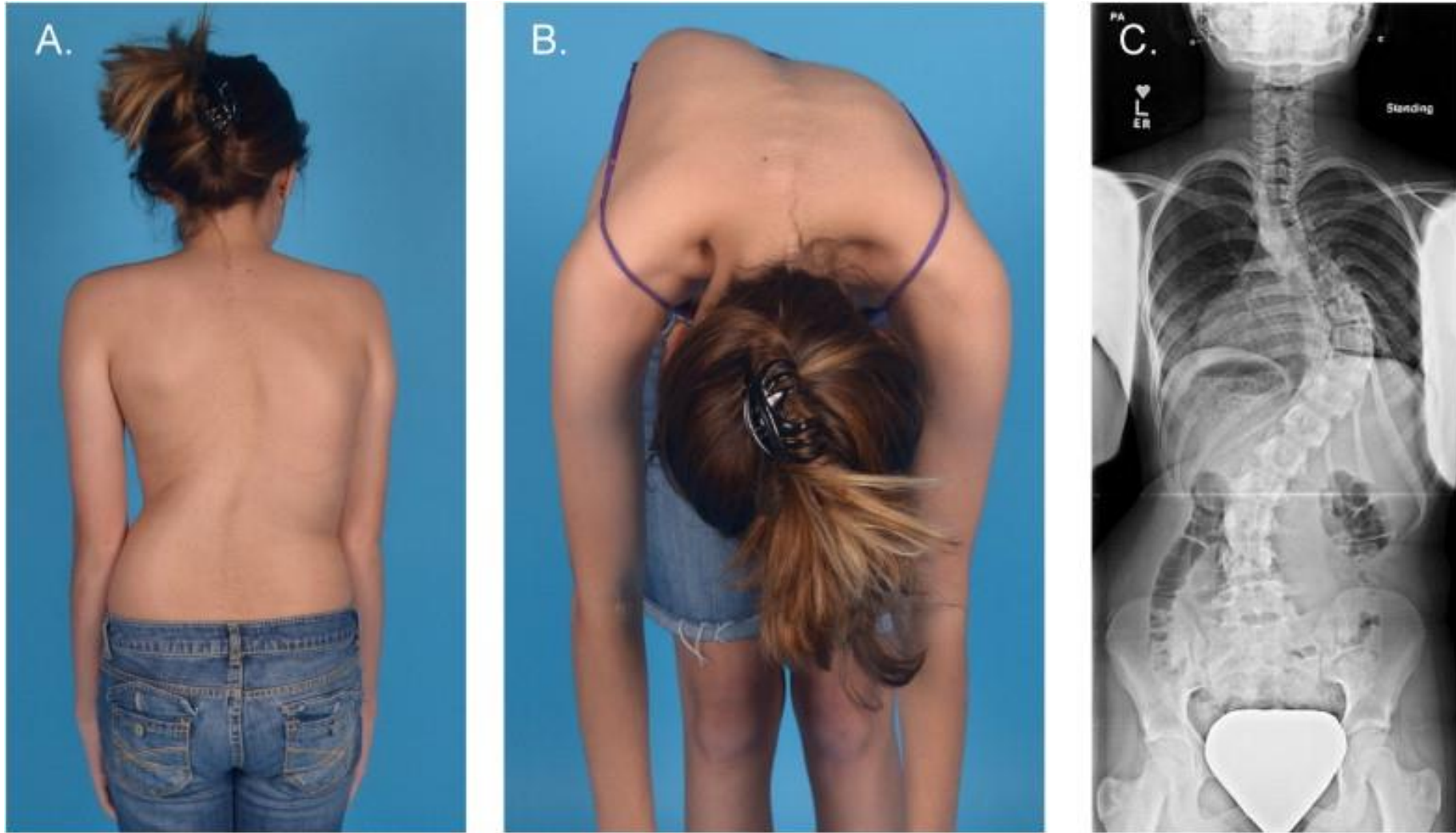
Scoliosis and PTK7



WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

Austin Staudinger

What is scoliosis?



Scoliosis is sideways curvature of the spine in a C- or S-shape

Two **Main Types** of Scoliosis

Congenital scoliosis is present at birth



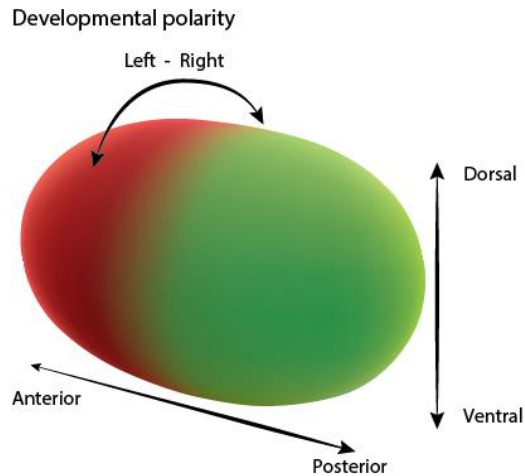
Idiopathic scoliosis starts presenting during adolescence



PTK7 is Linked to Scoliosis

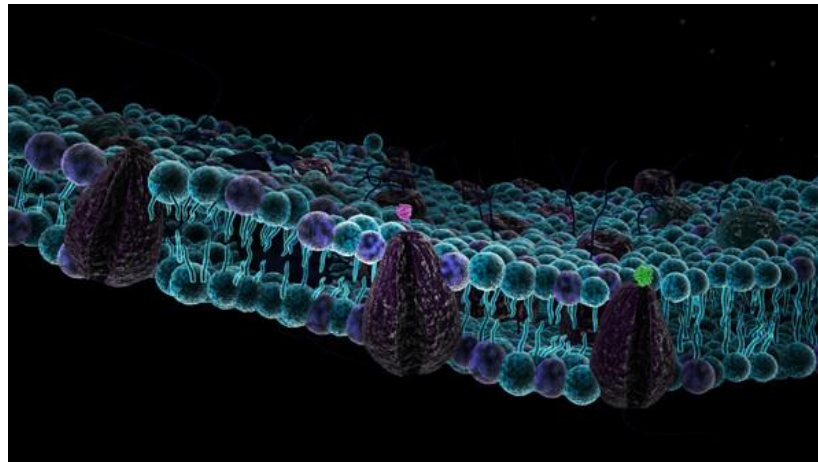


Biological Process



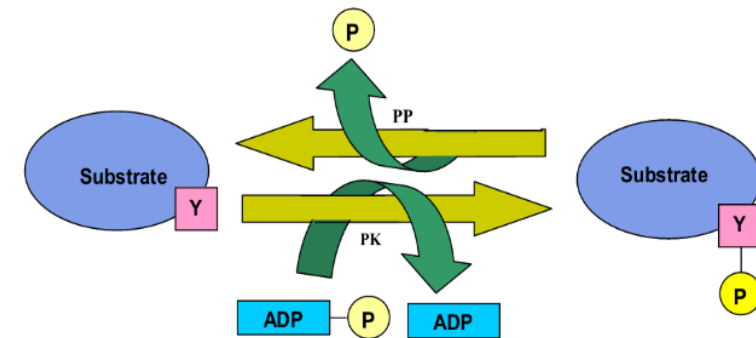
Wnt Activated Planar Cell Polarity Pathway

Cellular Component



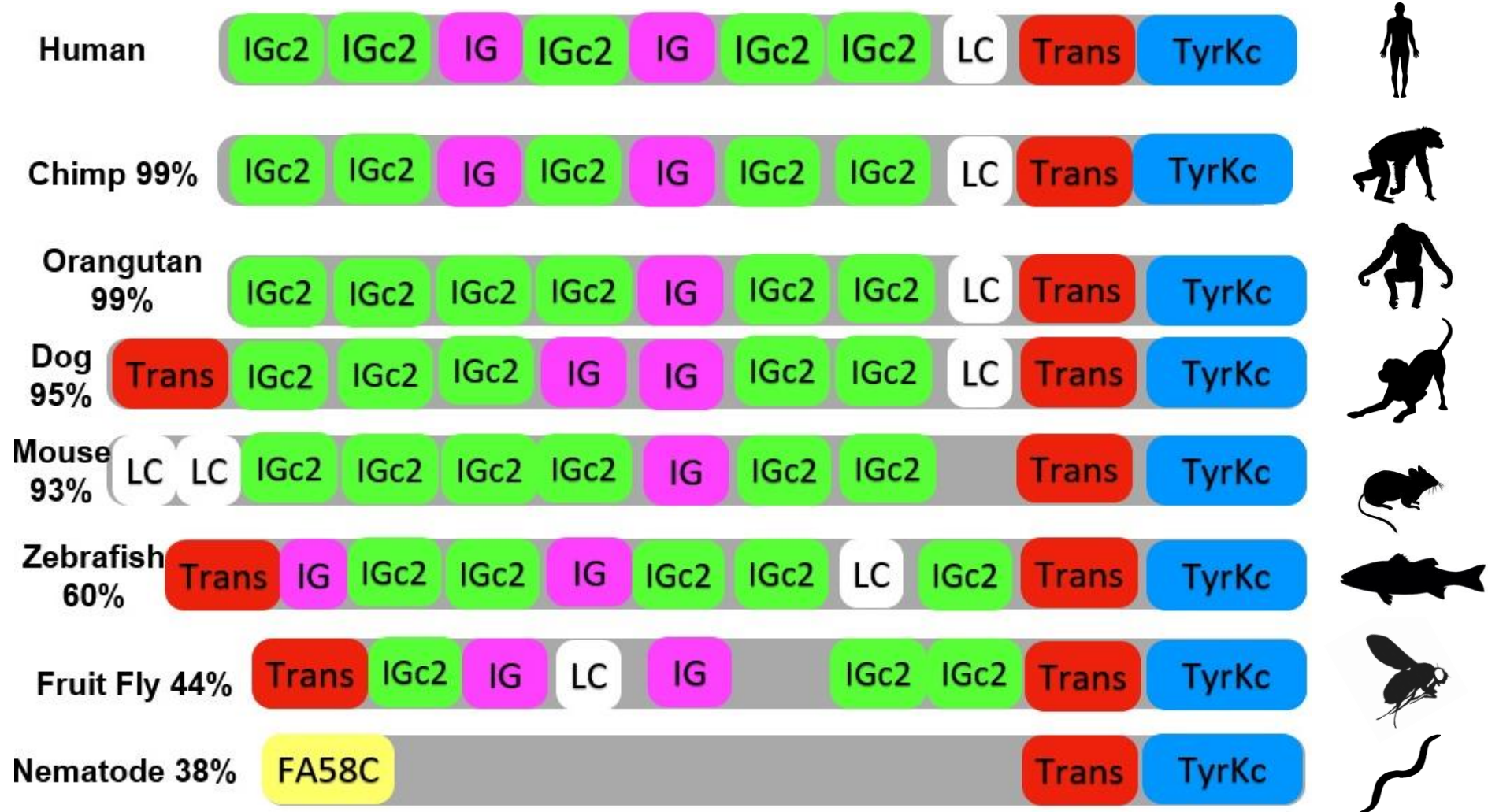
Cell Membrane

Molecular Function

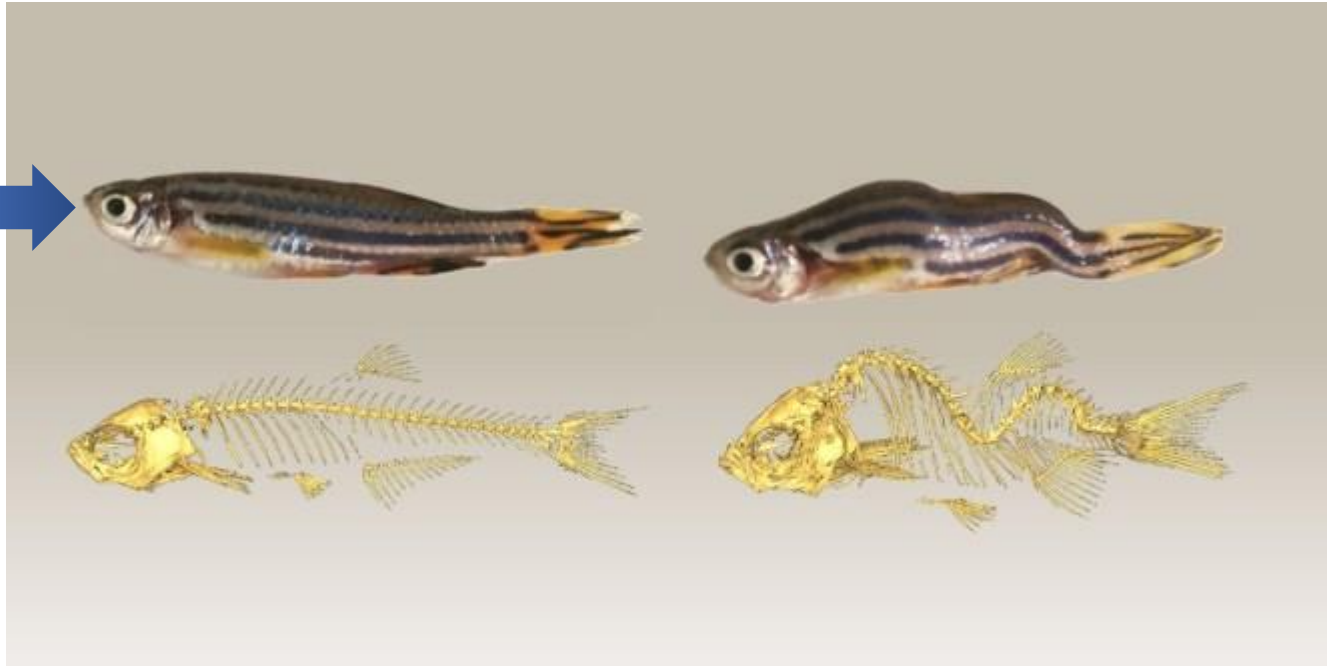


Protein Tyrosine Kinase Activity

PTK7 is Well Conserved

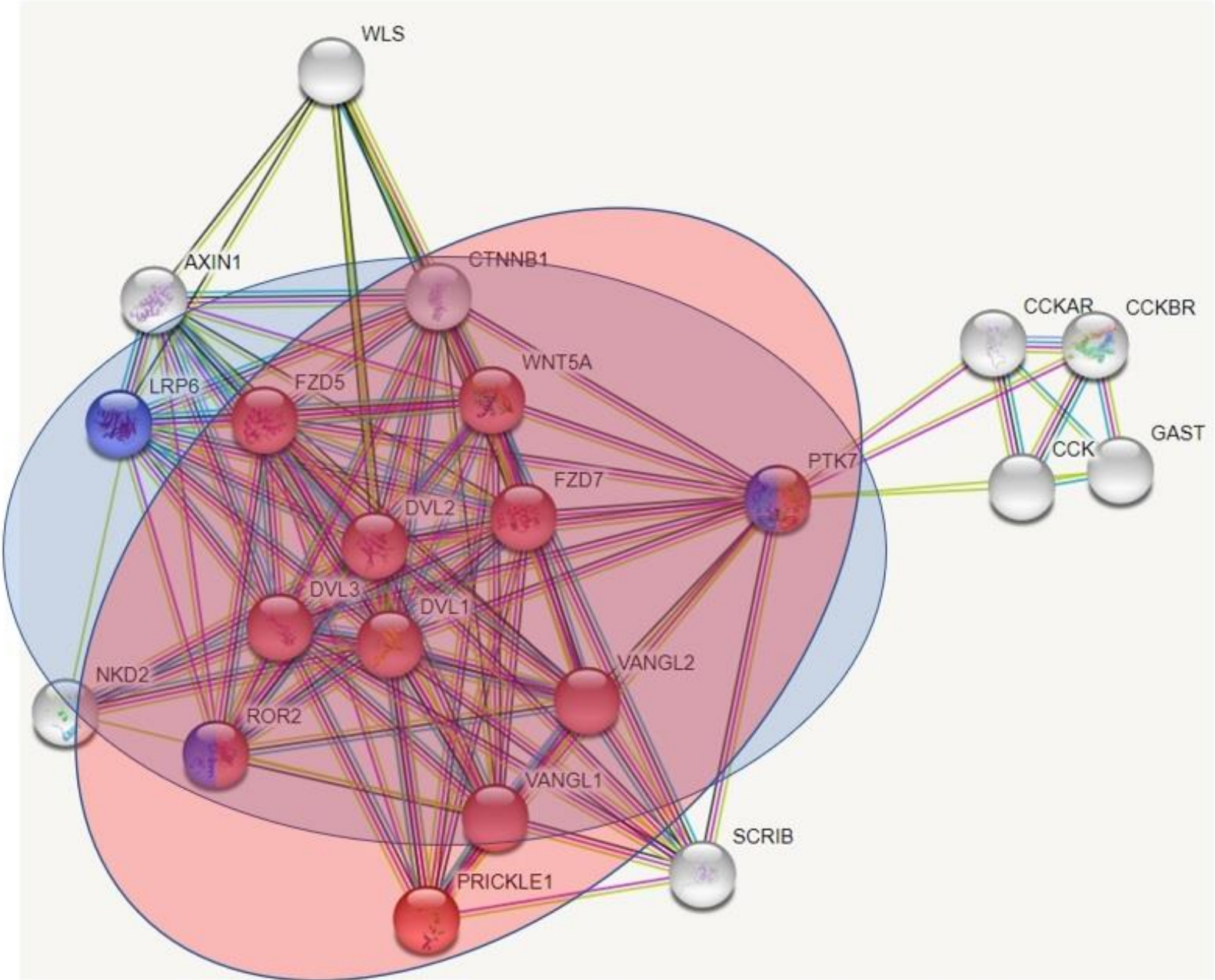
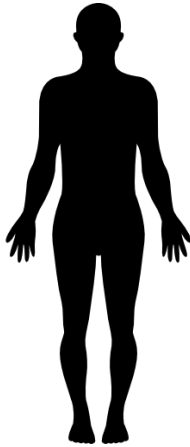


A Good Model for Scoliosis



Pressure from swimming forward is comparable to **gravity** for humans

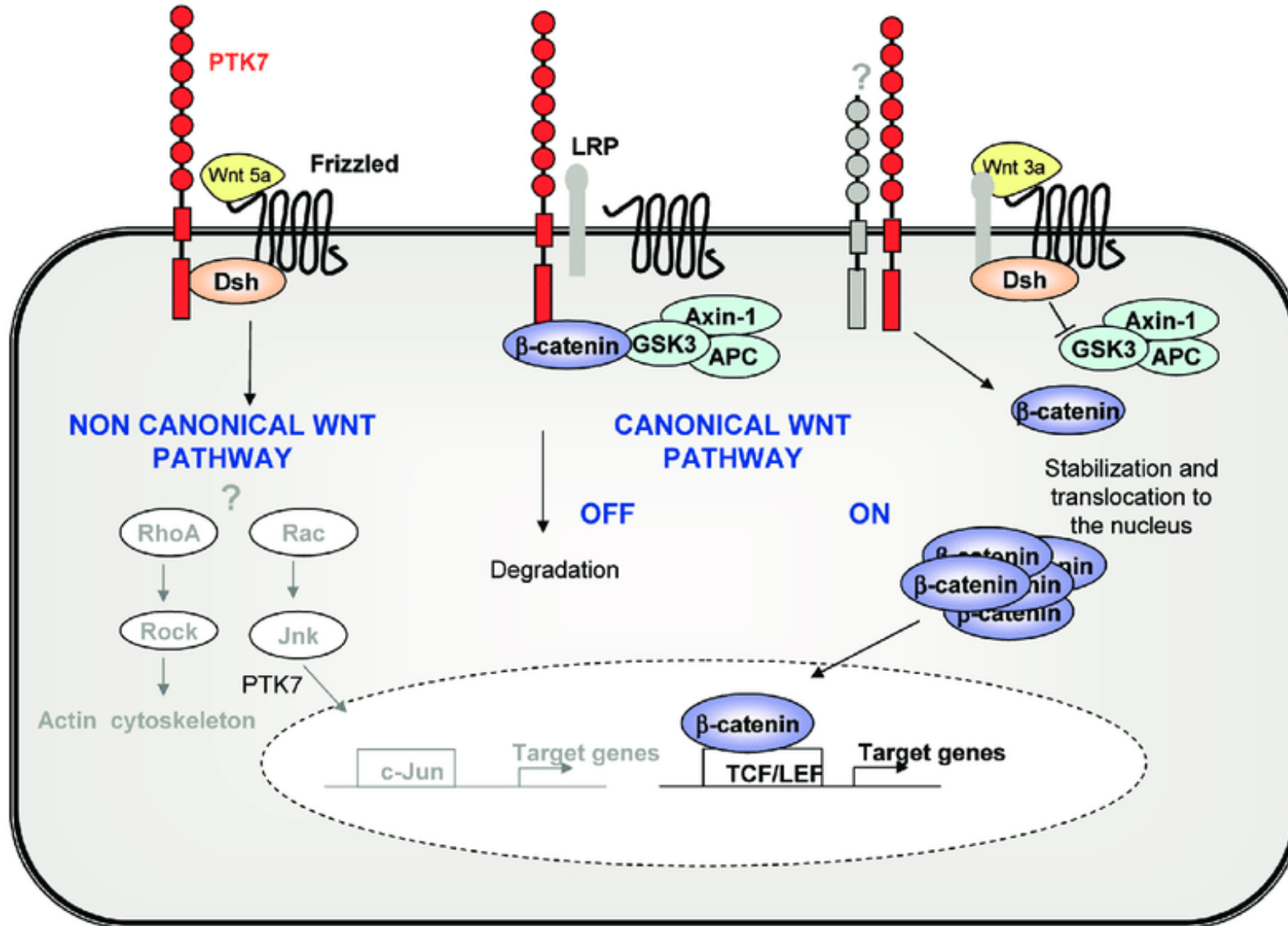
Human PTK7 Protein Interactions



Biological Process:
Wnt/PCP Pathway

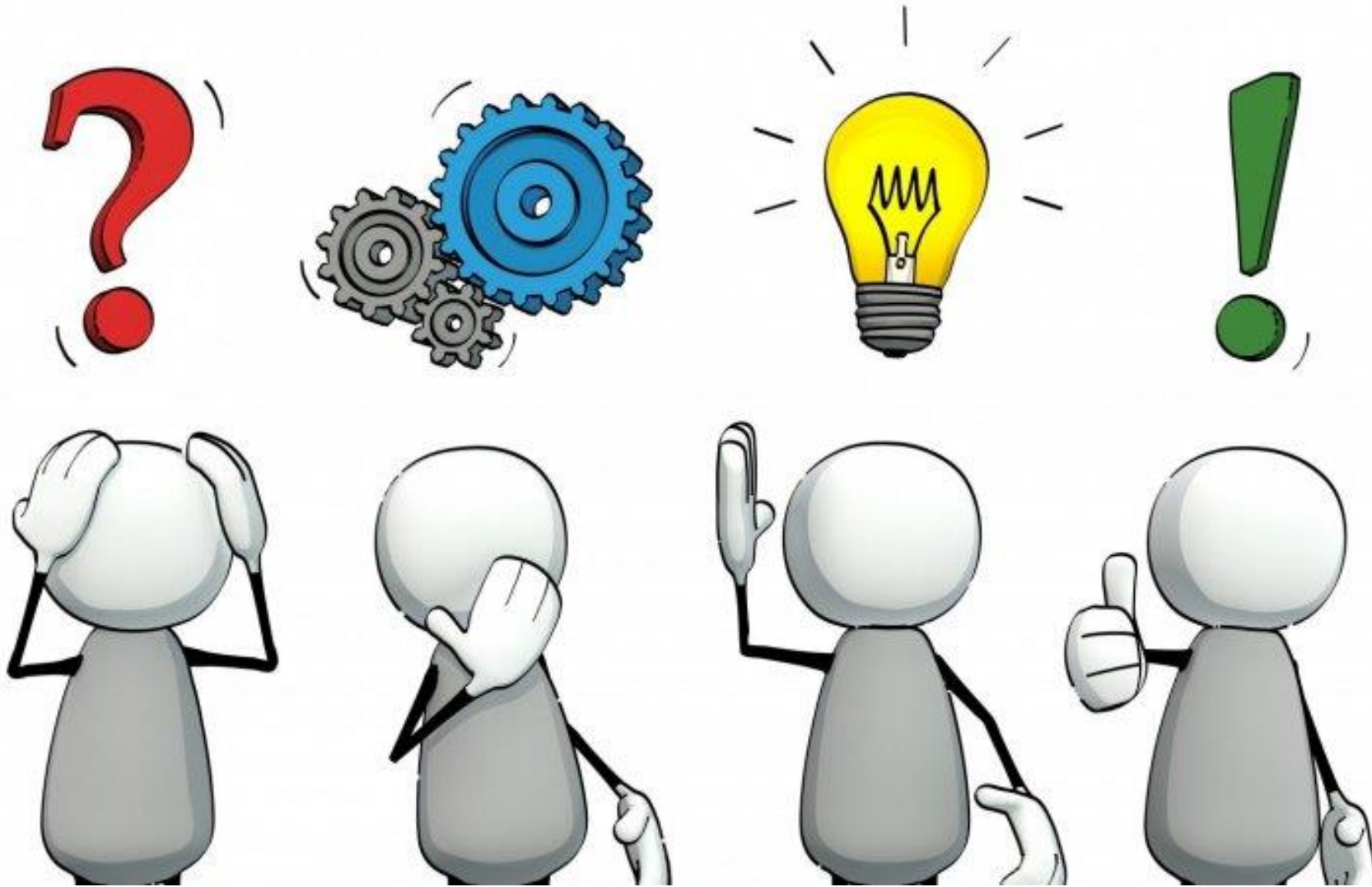
Molecular Function:
Coreceptor Activity

What is the Wnt/PCP signaling pathway?



The Wingless Integrated Planar Cell Polarity Signaling Pathway

What is the gap in knowledge?



It's unclear how PTK7 mutations alter the Wnt/PCP signaling pathway

Primary Goal

Discover how mutated ptk7 alters the Wnt signaling pathway

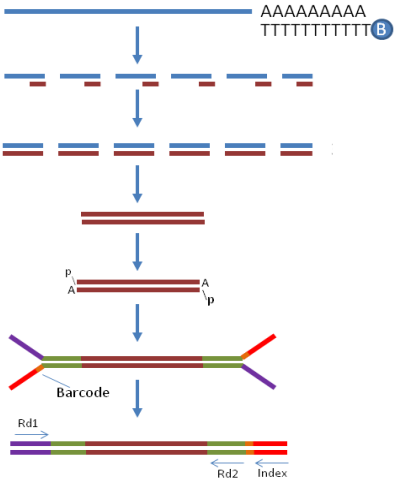
Aim 1

Identify mutations that cause disease phenotype



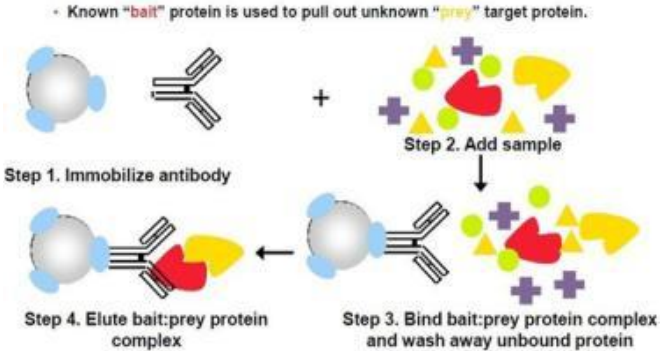
Aim 2

Determine mutant PTK7's ability to regulate skeletal development proteins



Aim 3

Determine mutant PTK7's ability to localize potential Wnt/PCP ligands



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

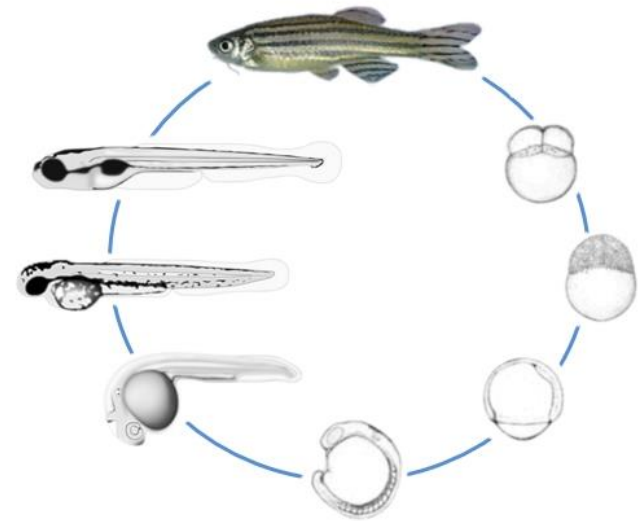


Step 1: Next Generation Sequencing

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

Step 2: Evaluate the phenotypes of variant groups

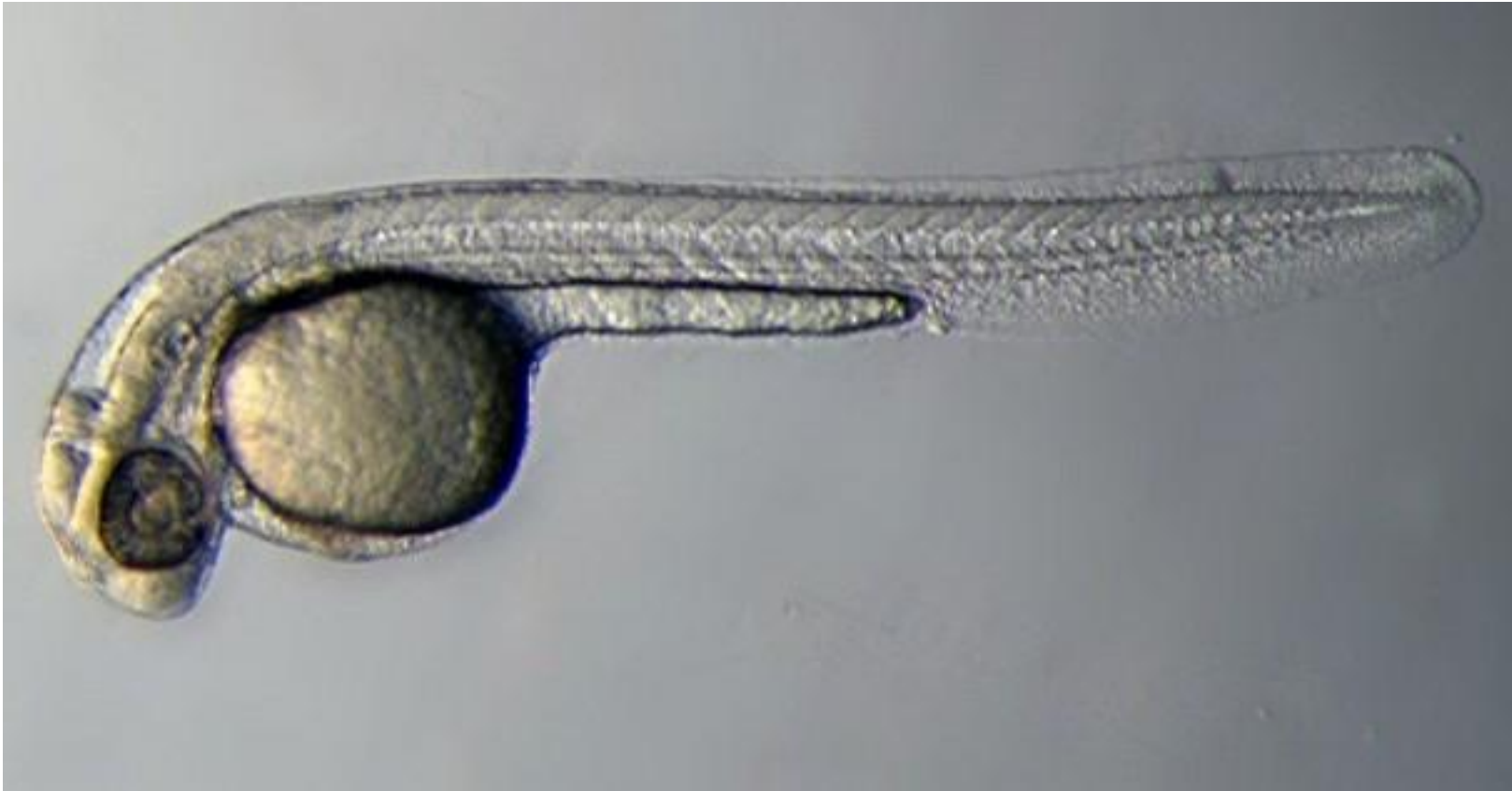
- Larval stage
- Adolescent stage through adulthood



How do you evaluate at the larval stage?

Signs of congenital scoliosis in zebrafish:

Abnormal vertebrae size, shape, and alignment

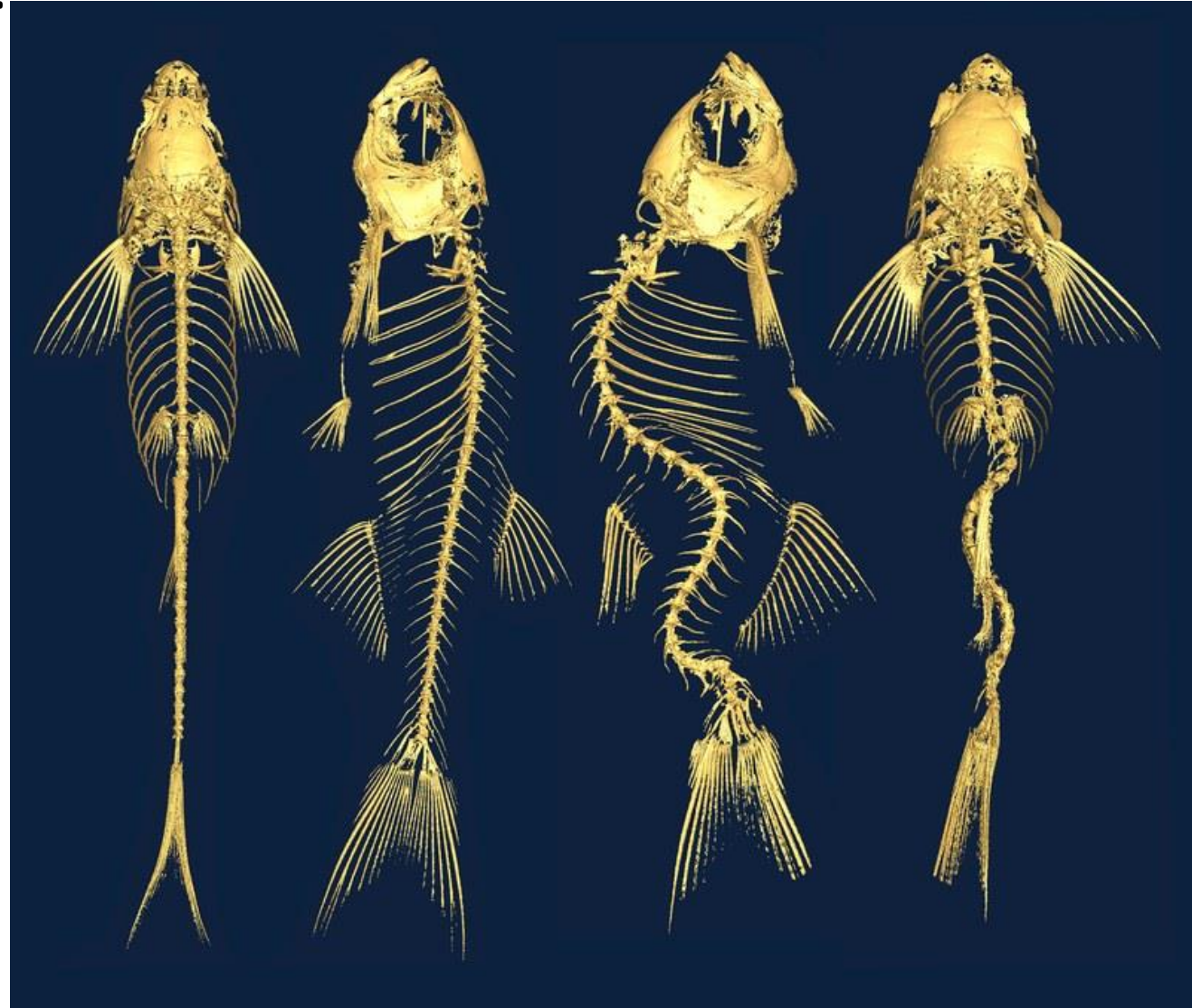


How do you evaluate during adolescence?

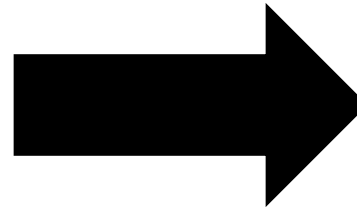
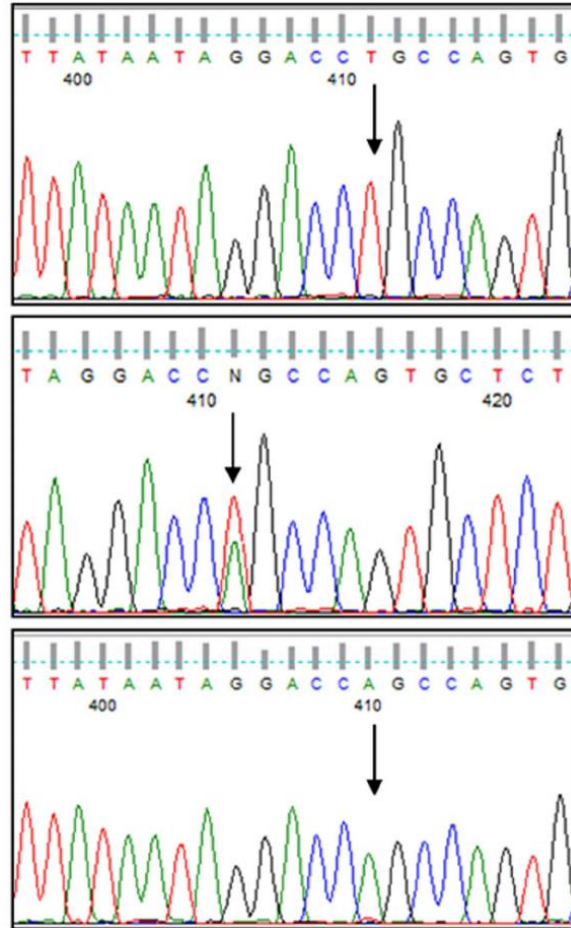
Signs of idiopathic scoliosis in zebrafish:

Abnormal length ratios
(dorsal:ventral and left:right)

Re-examination will track disease progression
through adulthood



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

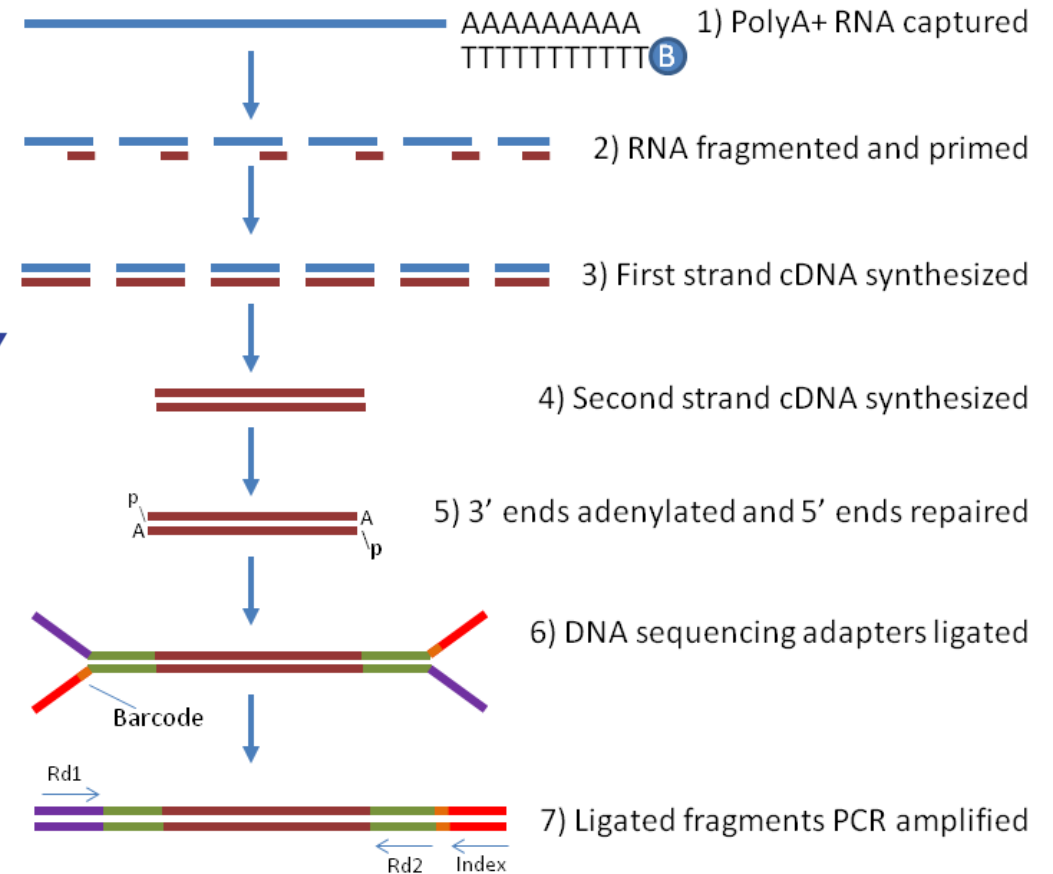


Hypothesis: Next generation sequencing will find multiple sites of variation within the ptk7 gene, some of which will cause scoliosis with varying severity.

Aim 2: Determine if mutant ptk7 is an inefficient regulator of skeletal development proteins.



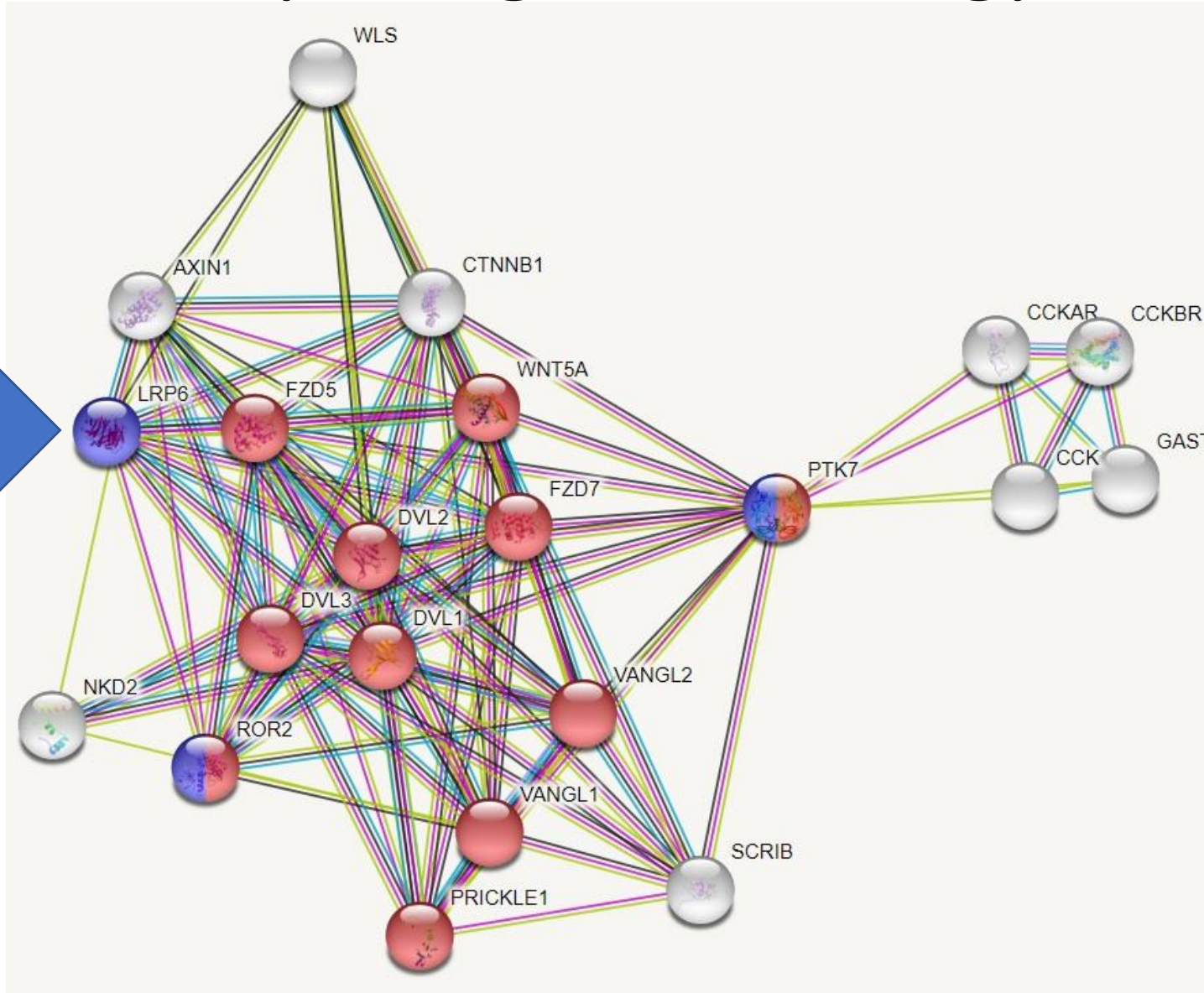
GENEONTOLOGY
Unifying Biology



Approach: Use GO and RNA-seq to measure expression of skeletal proteins in ptk7 mutants

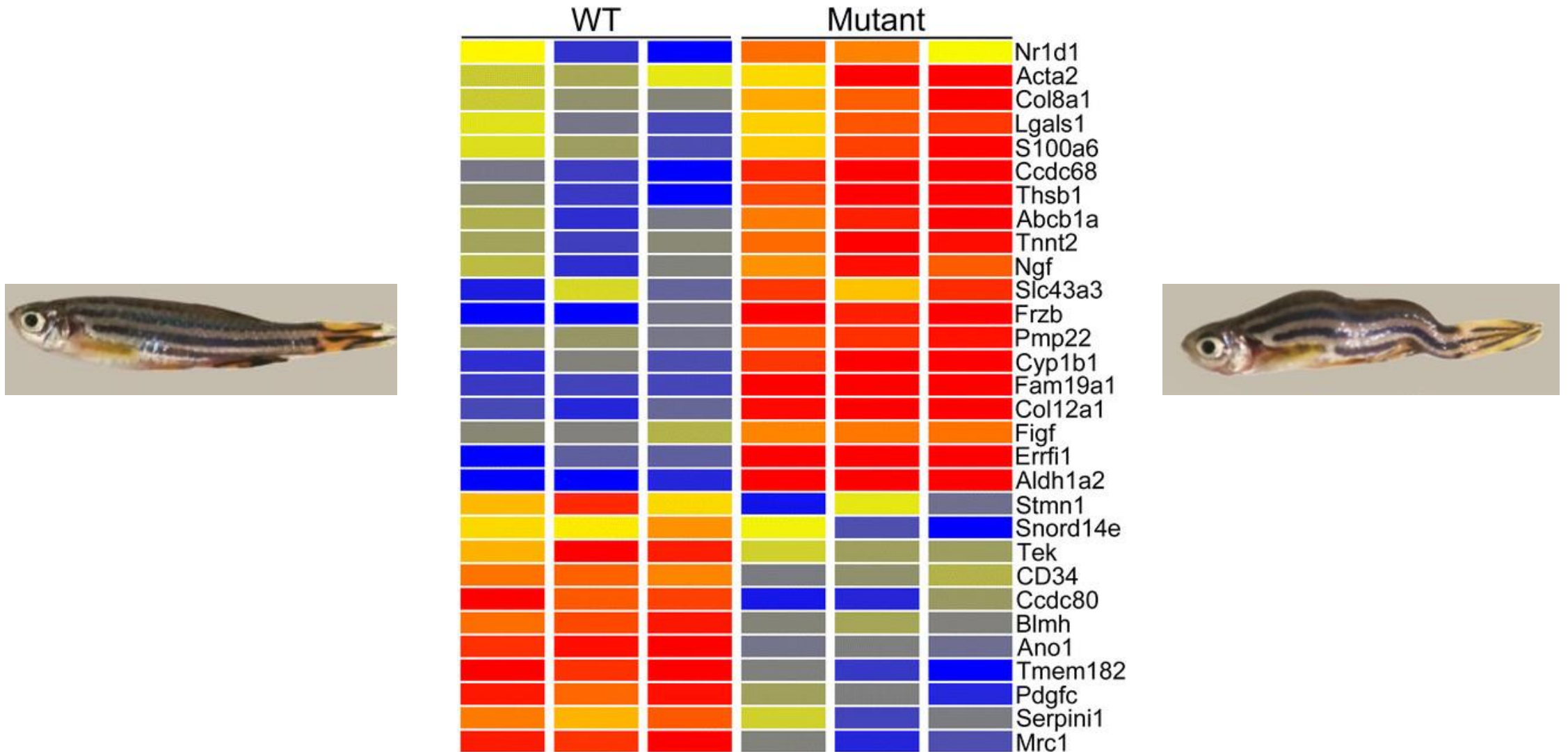
Why use gene ontology?

Coreceptor
Activity
Protein



To identify bone formation genes PTK7 regulates such as LRP6

Why use RNA-sequencing?



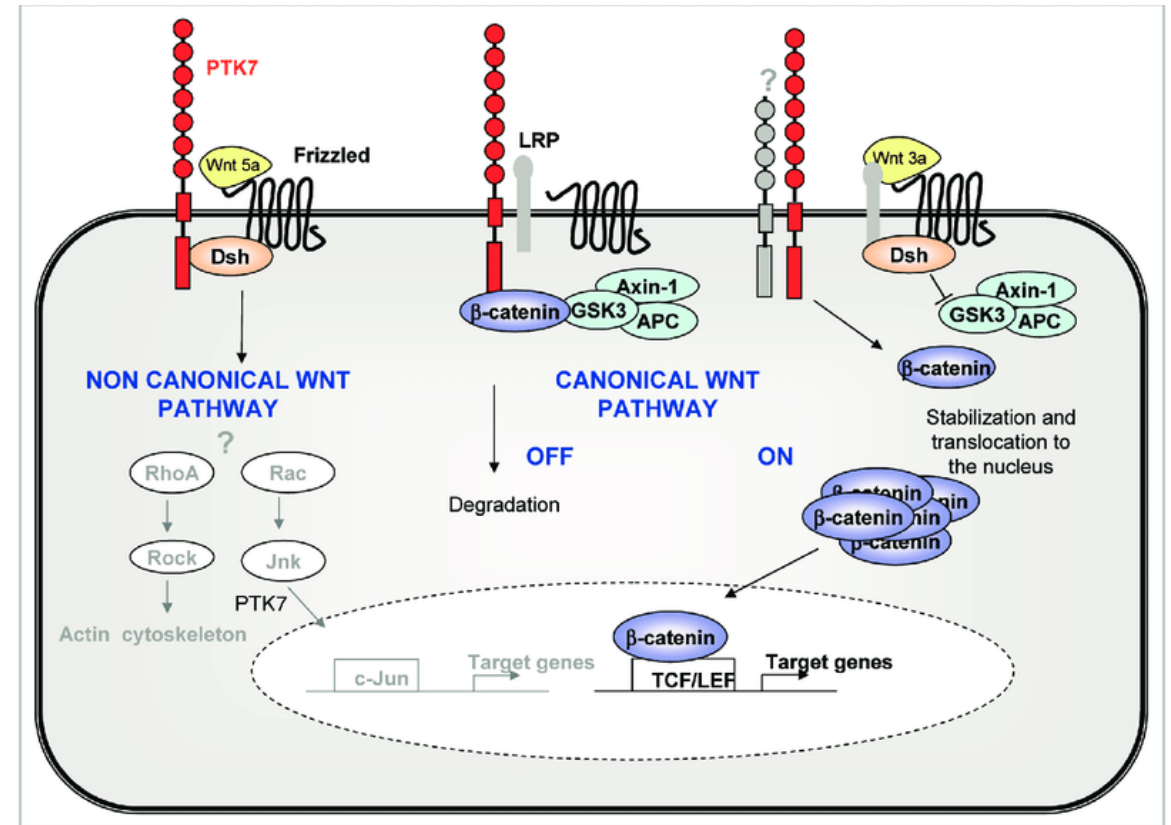
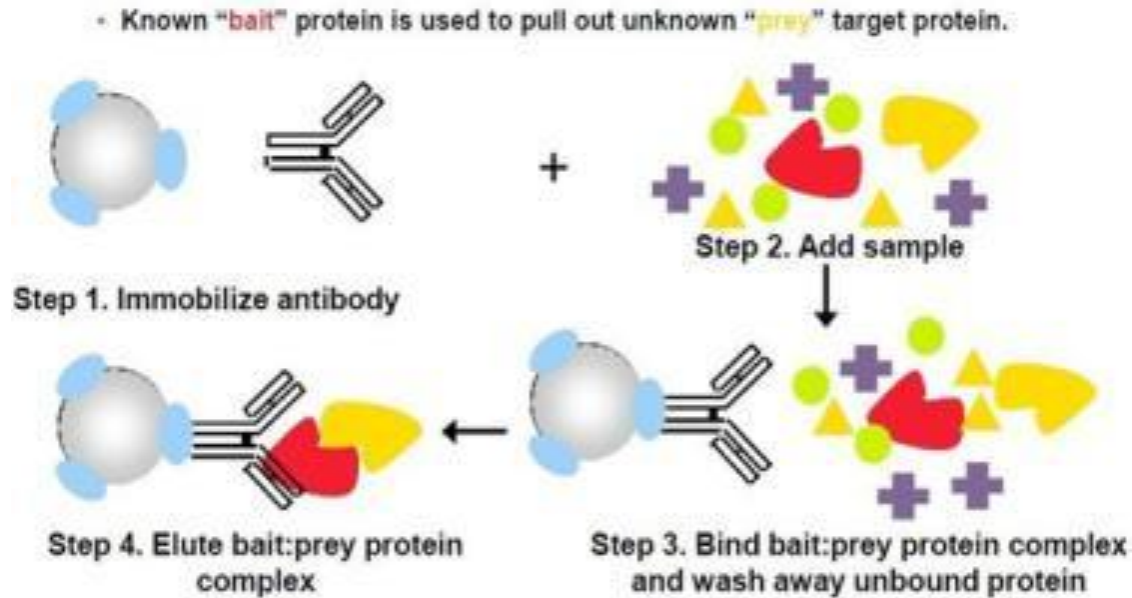
Compare control group transcriptome to mutant transcriptome

Aim 2: Determine if mutant ptk7 is an inefficient regulator of skeletal development proteins.



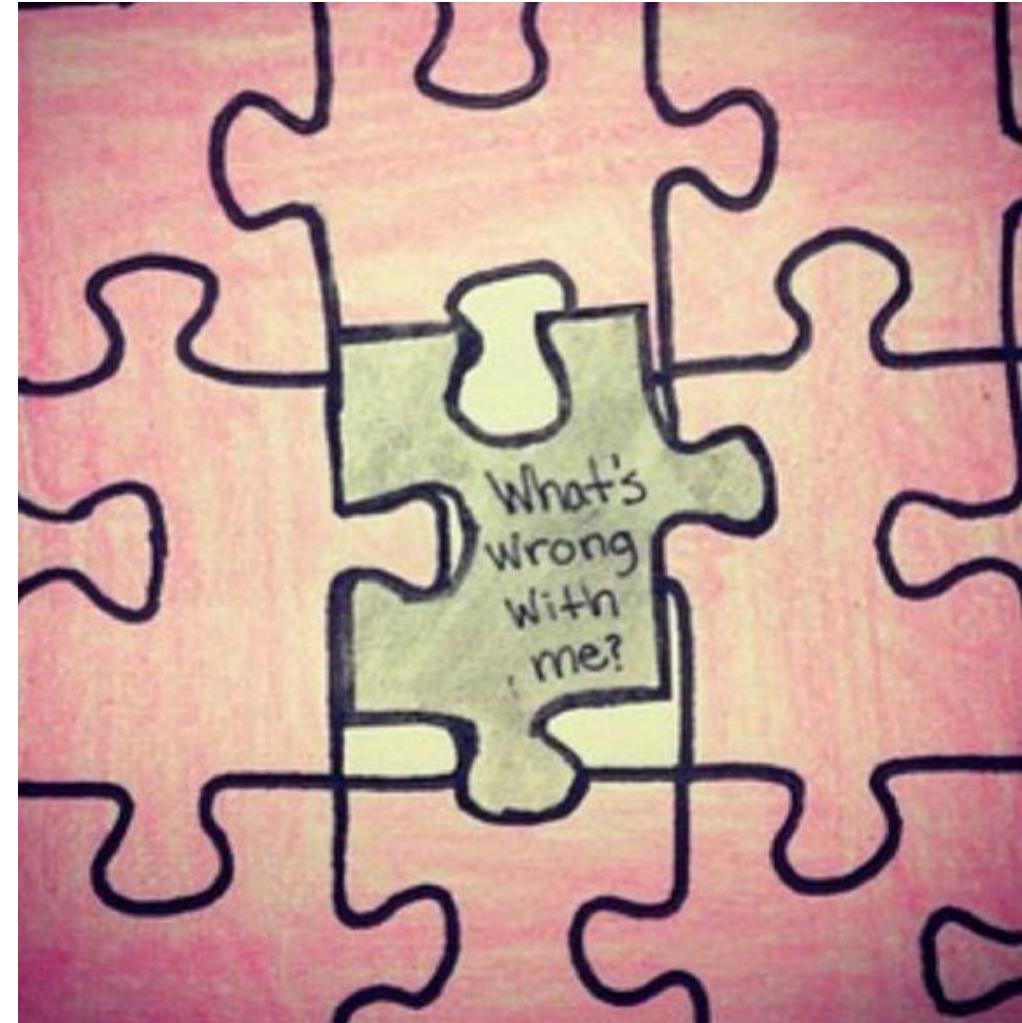
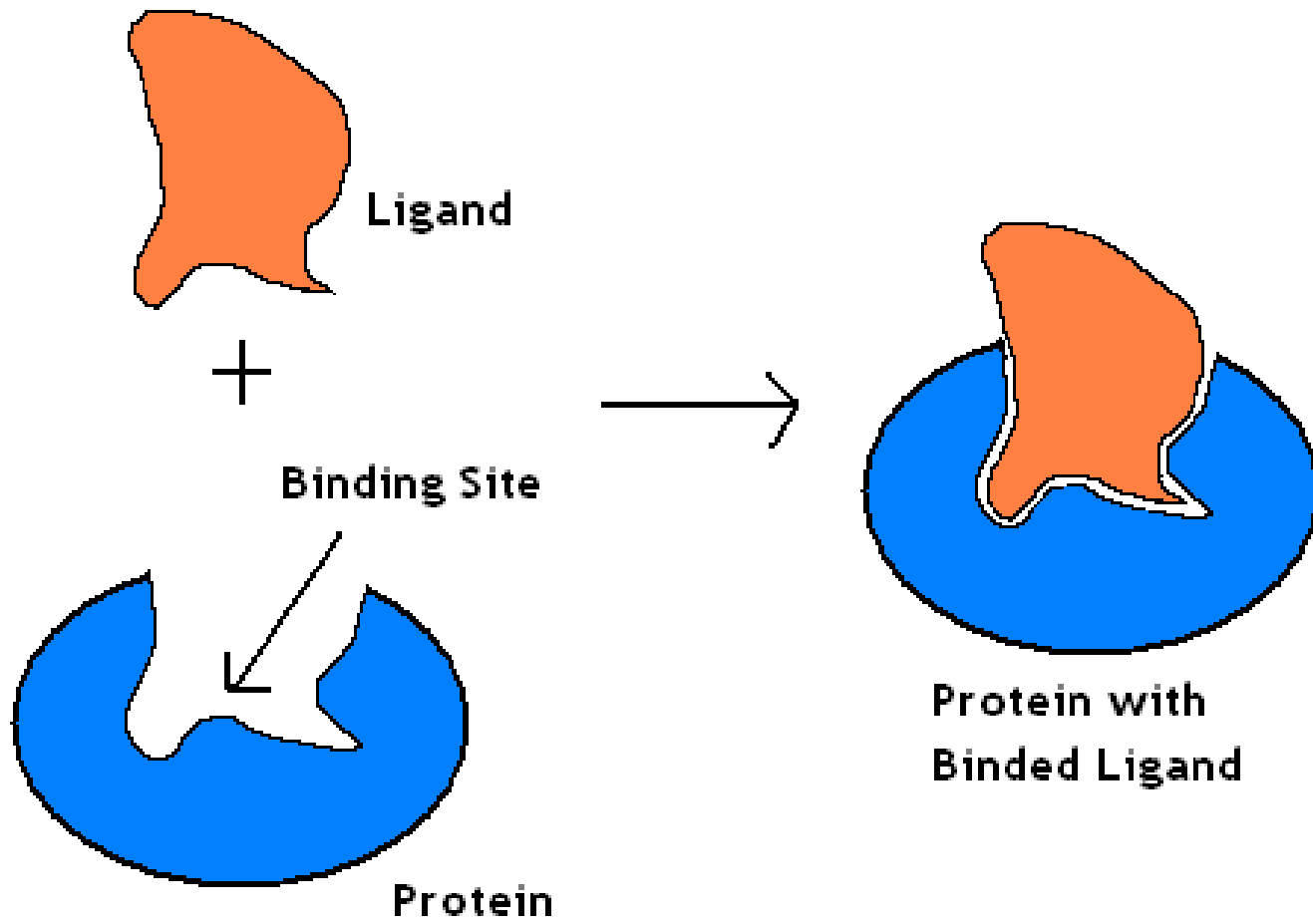
Hypothesis: Bone formation genes will be dysregulated in PTK7 mutants

Aim 3: Determine how well mutant ptk7 can localize potential Wnt/PCP ligands.



Approach: Use Co-IP to determine how well mutant ptk7 binds Dsh

Aim 3: Determine how well mutant ptk7 can localize potential Wnt/PCP ligands.



Hypothesis: Mutant PTK7 will localize less ligands than wild type PTK7

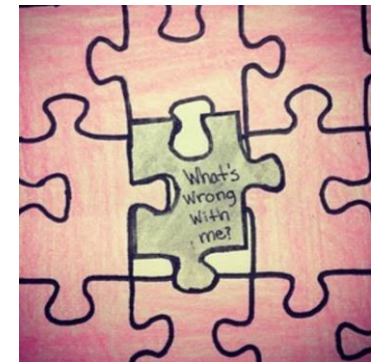
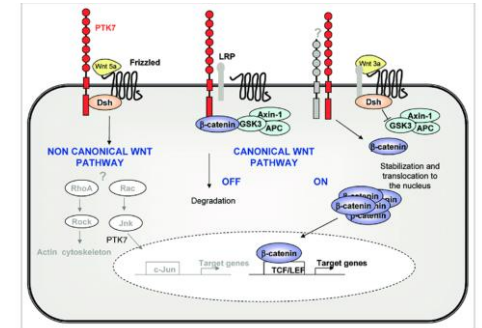
Conclusion

Scoliosis is associated with PTK7 mutations.

PTK7 regulates the Wnt/PCP signaling pathway.

PTK7 interacts with skeletal developmental proteins.

PTK7 mutations hamper its ability to localize Wnt/PCP ligands.



Future Directions

Scoliosis is seen in females about 10 times as often as males

Curvature is typically more severe in females



What is the cause of unequal prevalence and severity of scoliosis between genders?

References

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Any questions?

