Kindler Syndrome

Skin blistering and cancer development

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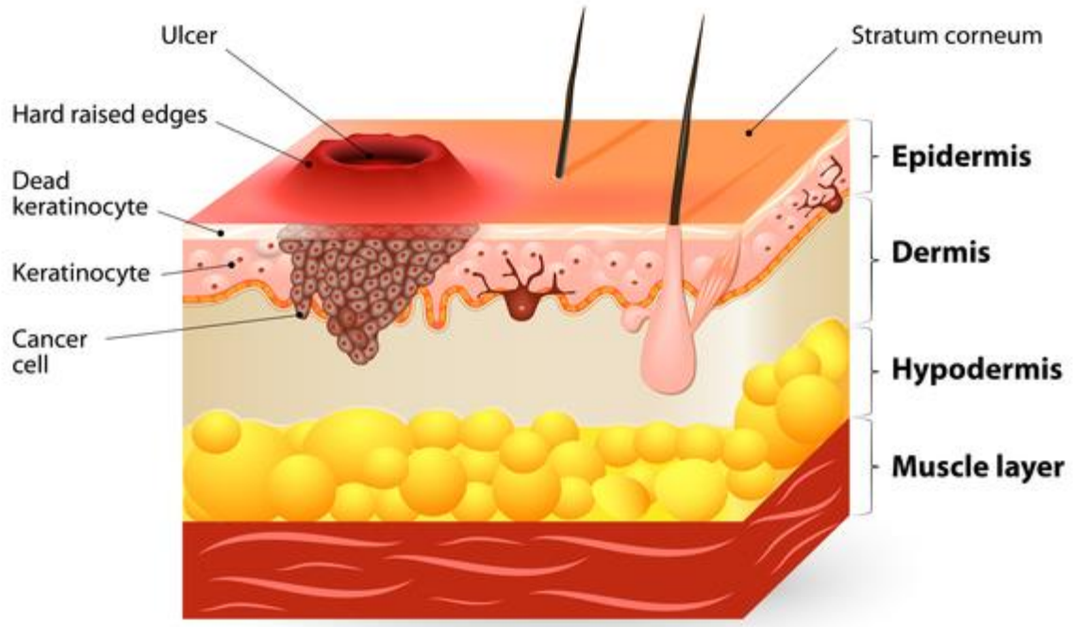
Kindler syndrome is a skin condition with some severe phenotypes. Some of the following images may be graphic.

What is Kindler Syndrome?

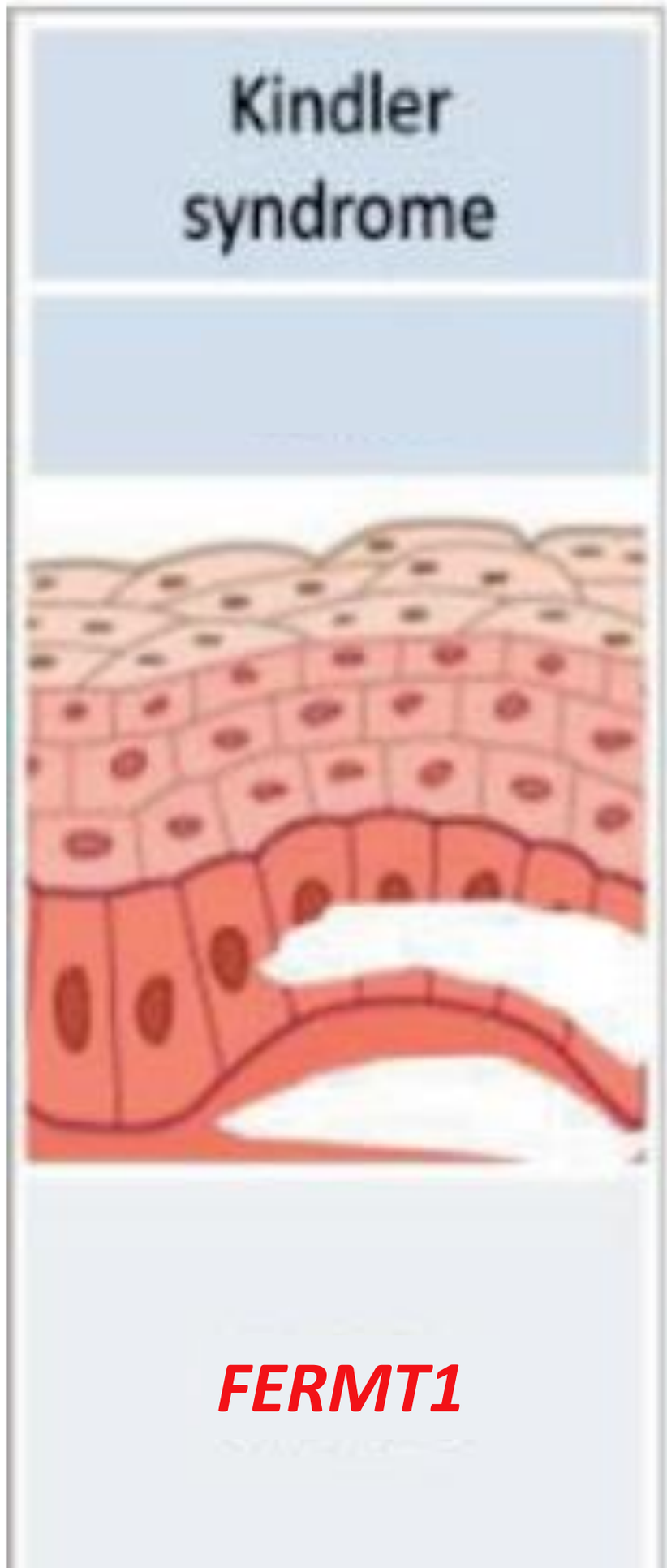
Skin blistering in youth



Squamous-cell carcinoma development later

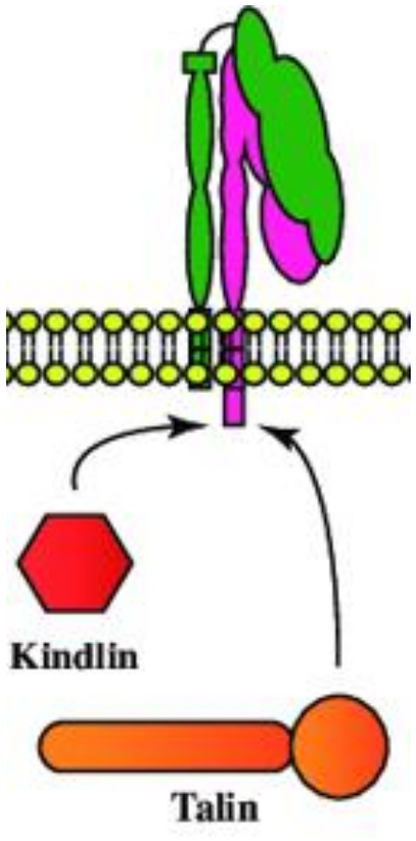
What gene causes Kindler Syndrome?

FERMT1 encodes kindlin-1



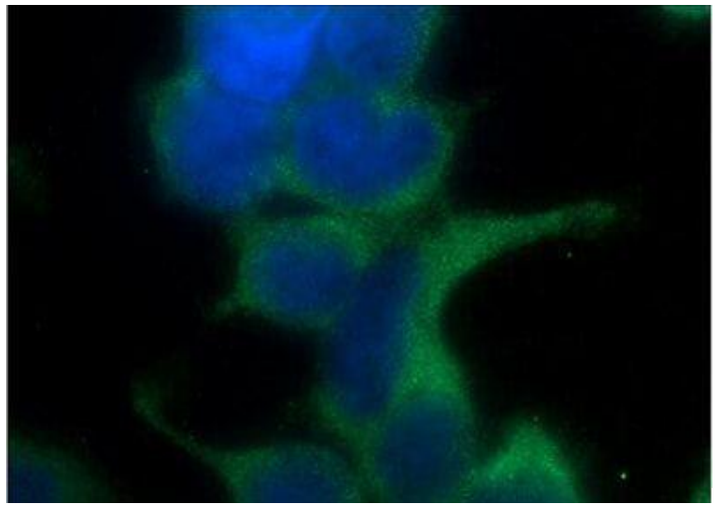
What does FERMT1 do?

Molecular Function



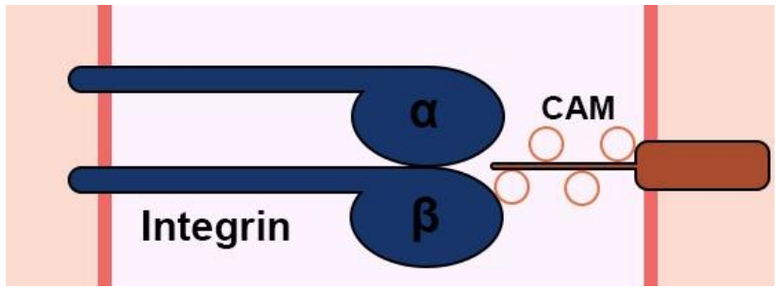
Binds with Talin to Integrin

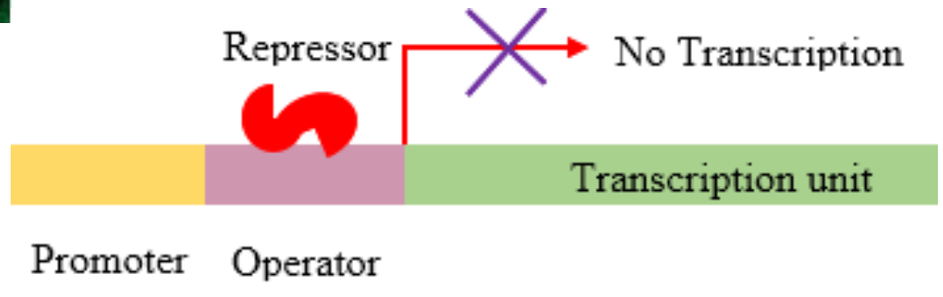
Cellular Component



Kindlin-1 found in cytosol

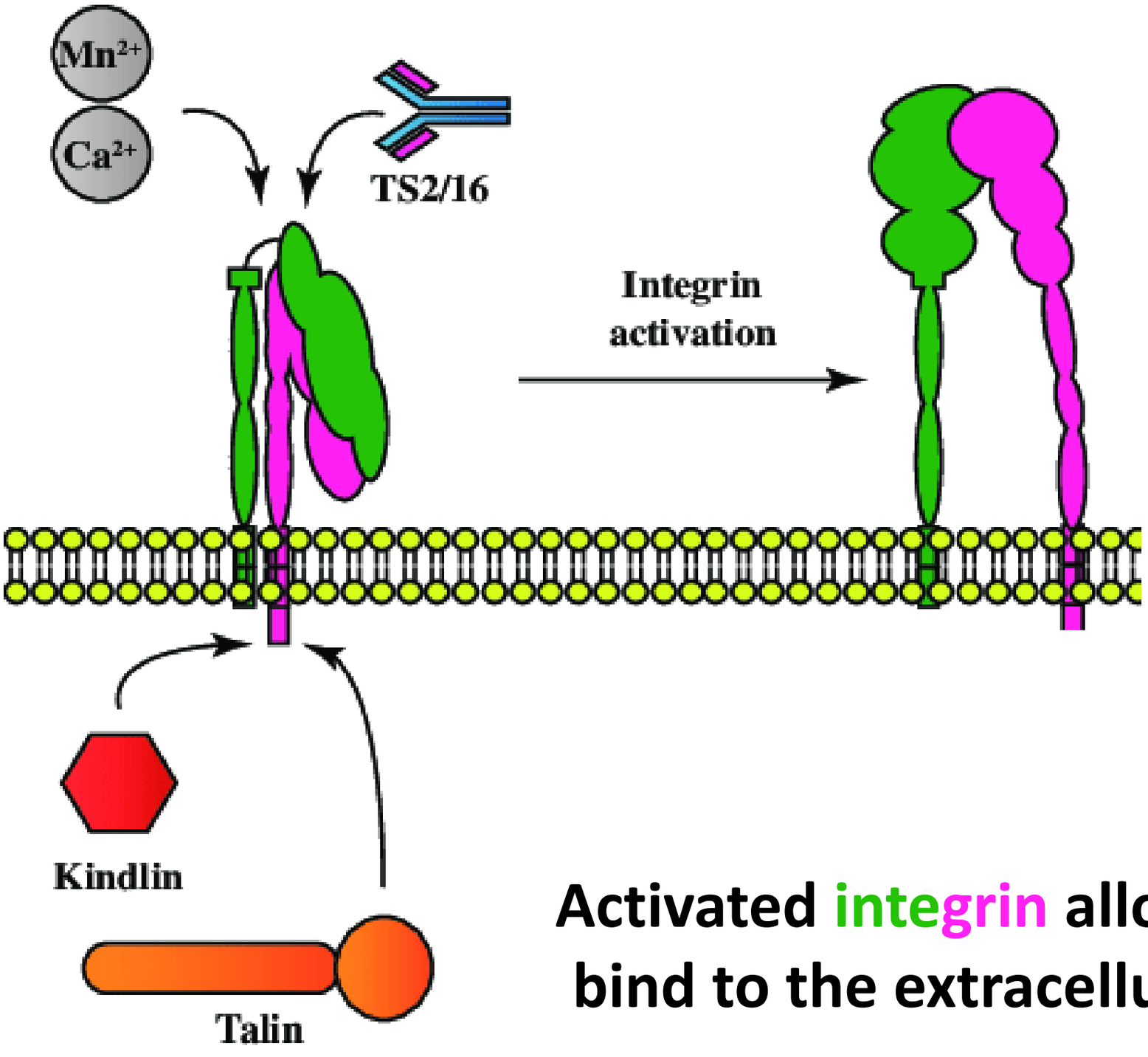
Biological Function





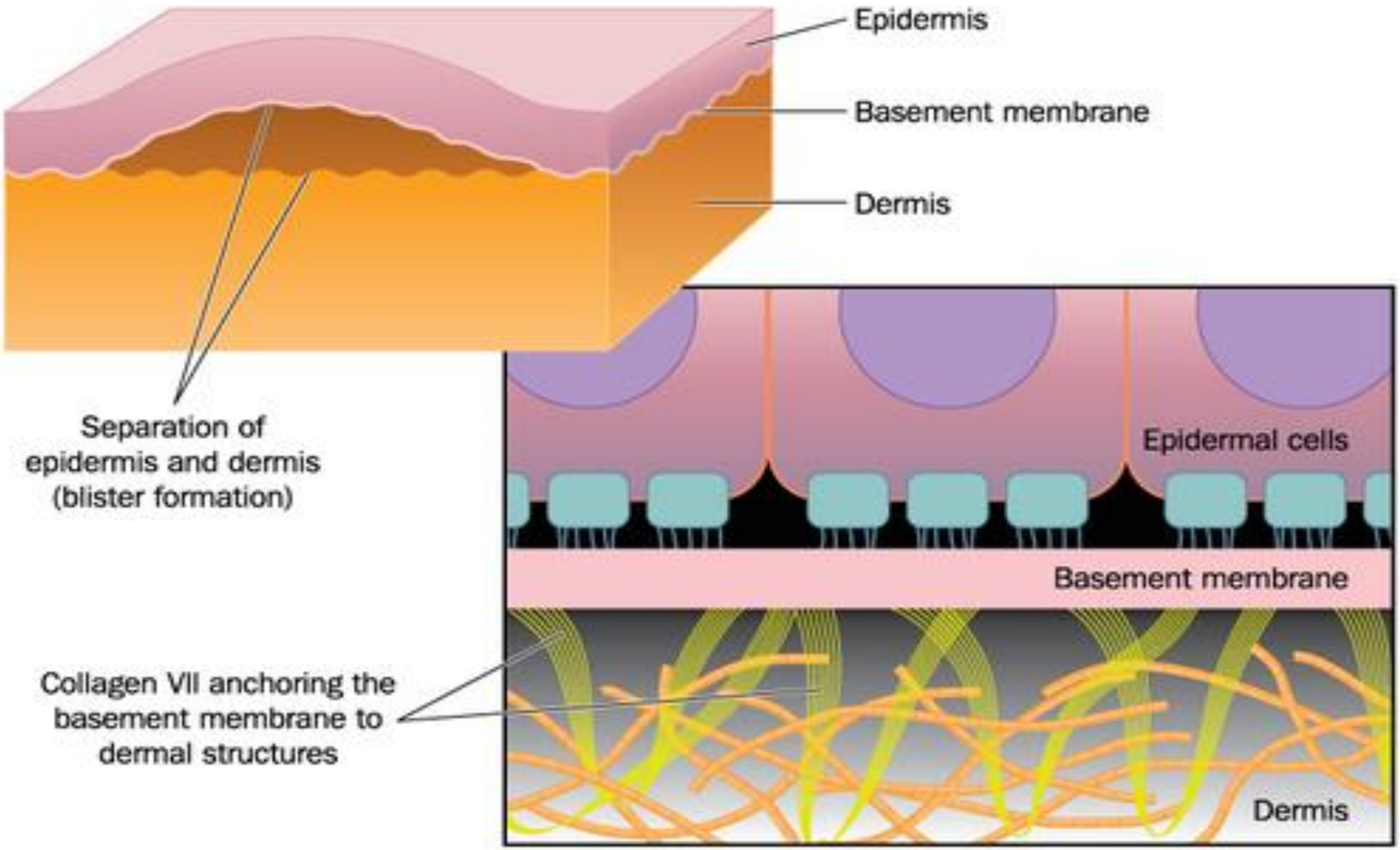
Involved in cell adhesion and negative transcription regulation

Kindlin-1 activates integrin proteins

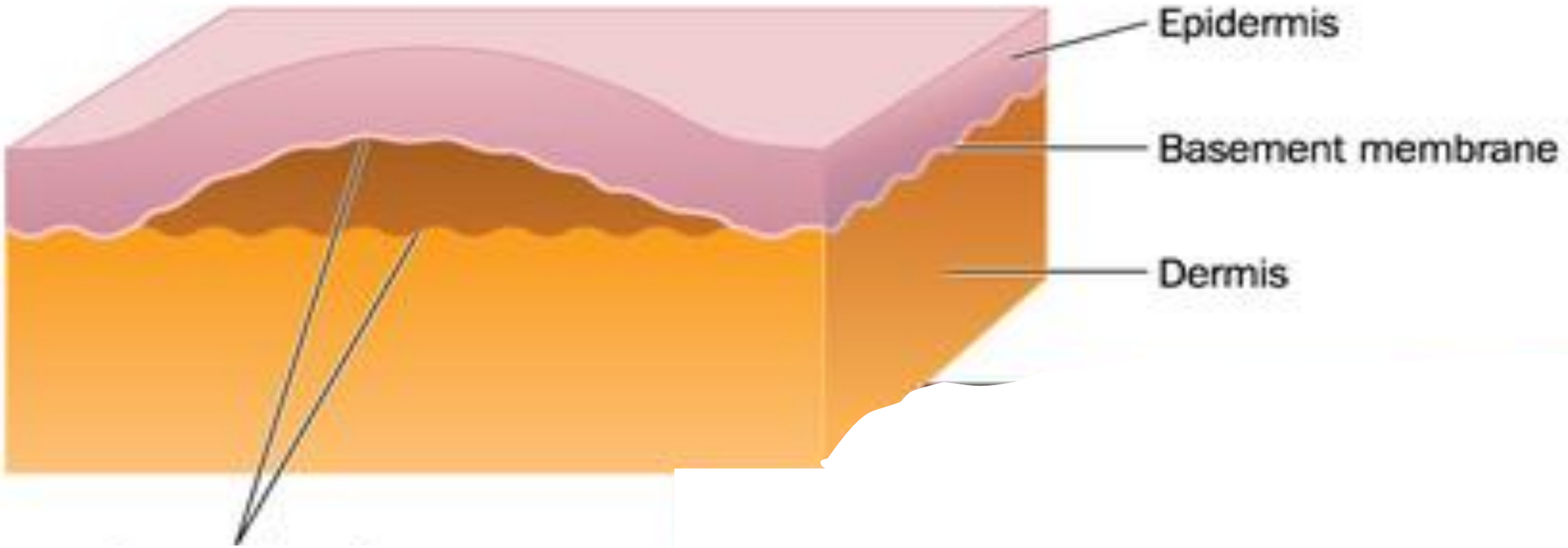


Activated integrin allows cells to bind to the extracellular matrix

What causes Kindler Syndrome?



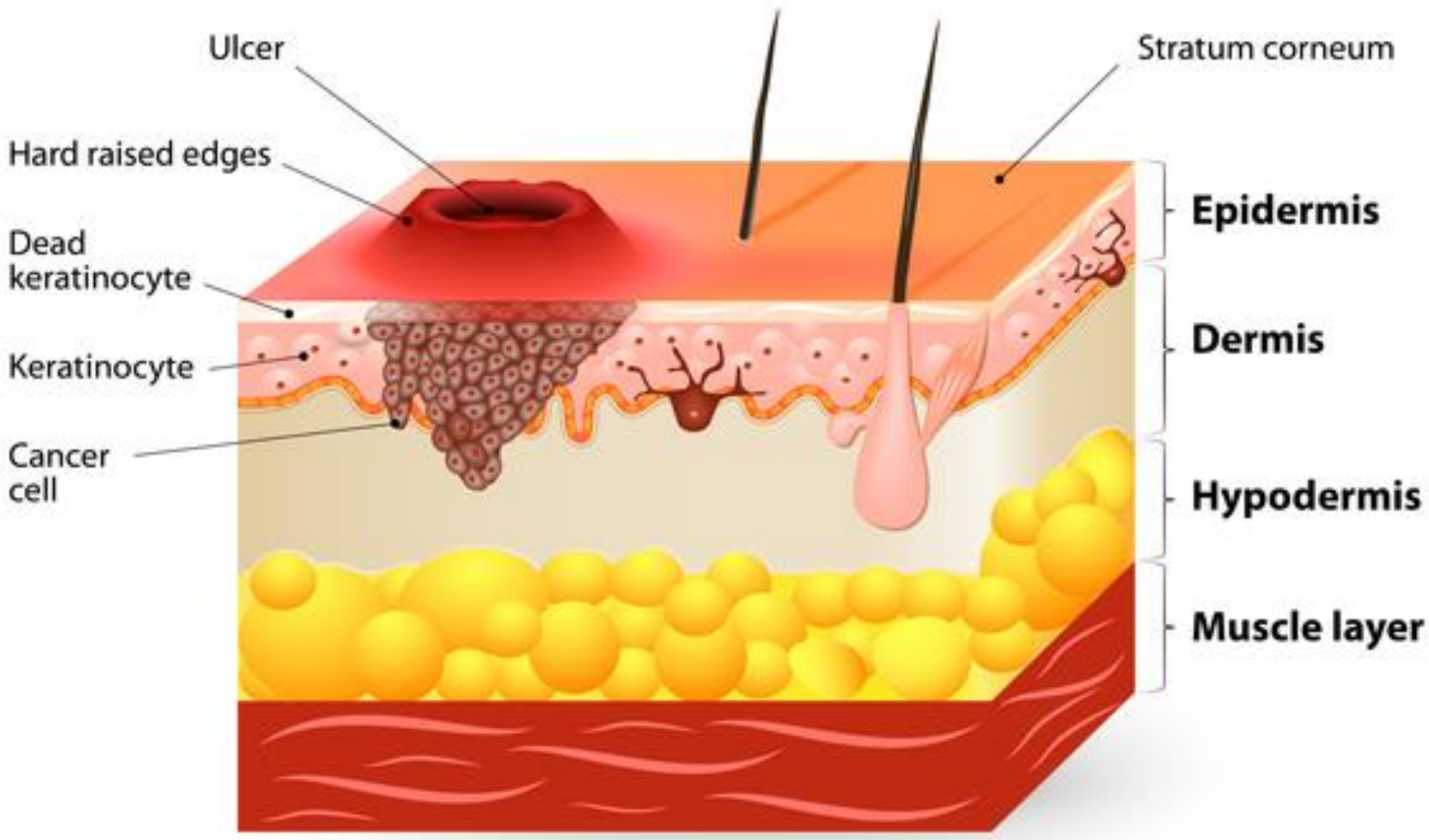
What causes blistering?



Separation of epidermis and dermis (blister formation)

How To Treat Kindler's Syndrome?

What is the gap in knowledge?



Why does Kindler Syndrome lead to development of squamous-cell carcinomas in older patients?

Primary Goal

Determine what FERMT1's role is in cancer development of Kindler Syndrome patients

AIM 1

Identify highly conserved residues of FERMT1

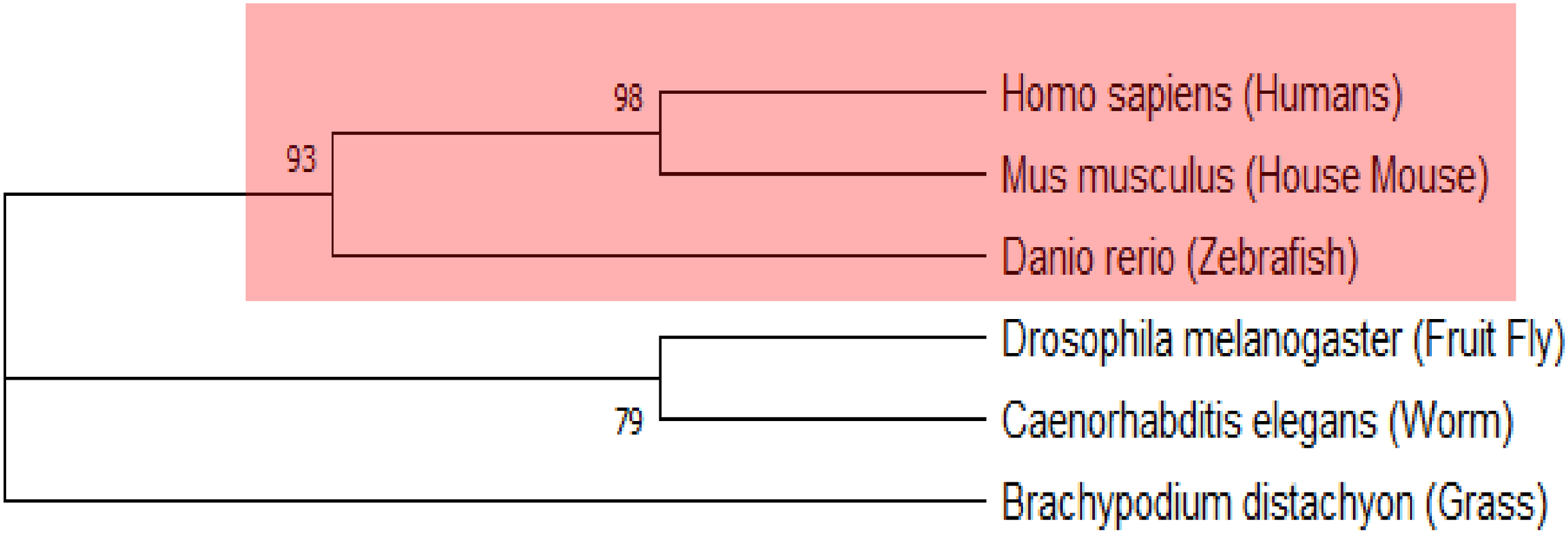
AIM 2

Analyze protein interaction networks

AIM 3

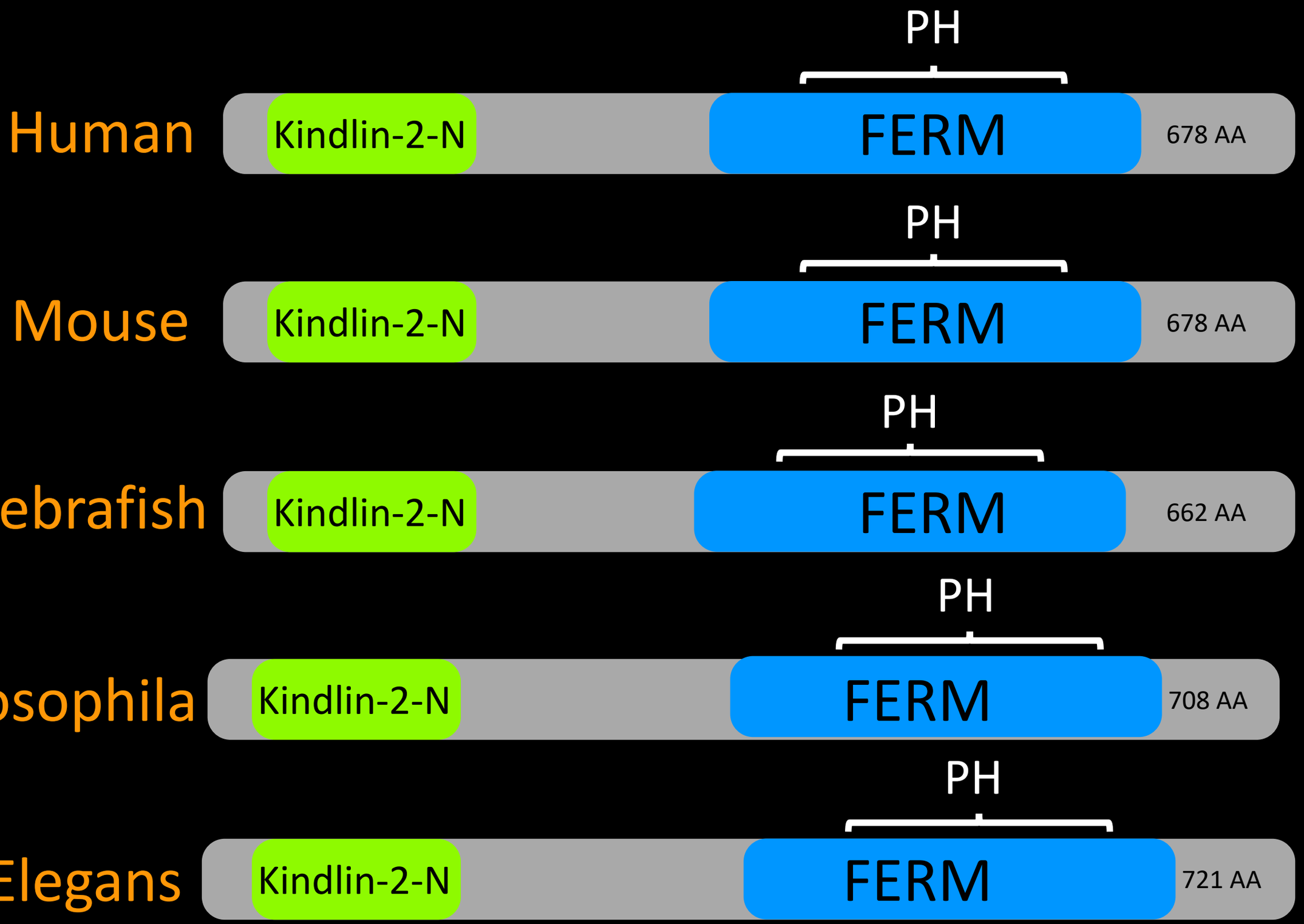
Analyze the transcriptome in FERMT1 mutants

FERMT1 phylogeny

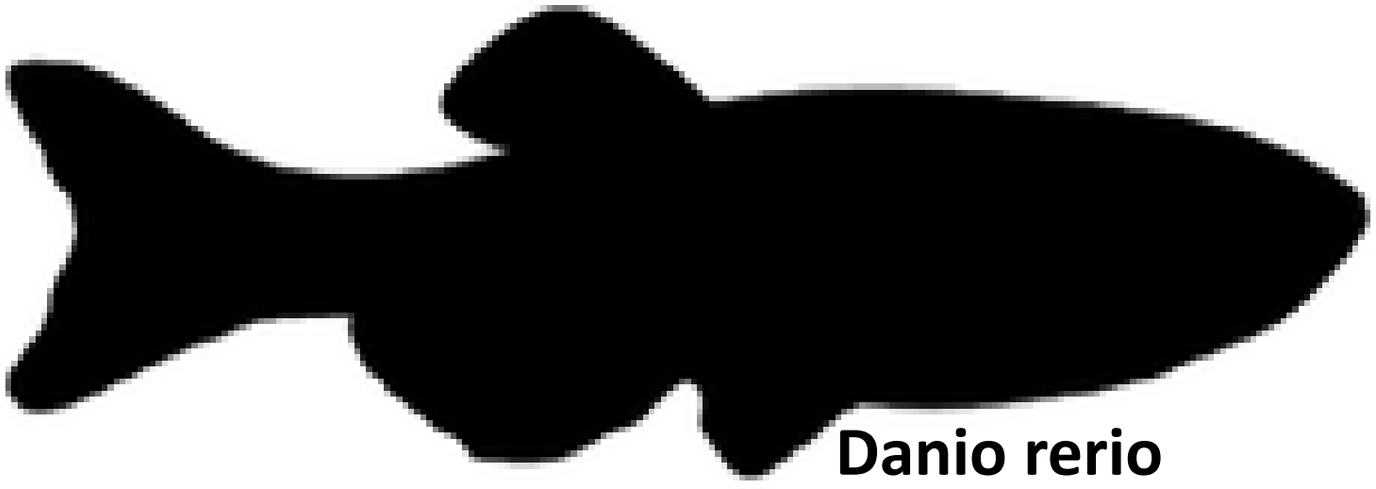


Mice and zebrafish FERMT1 is most closely related to humans

FERMT1 is highly conserved across model organisms



Which model organism will be used?



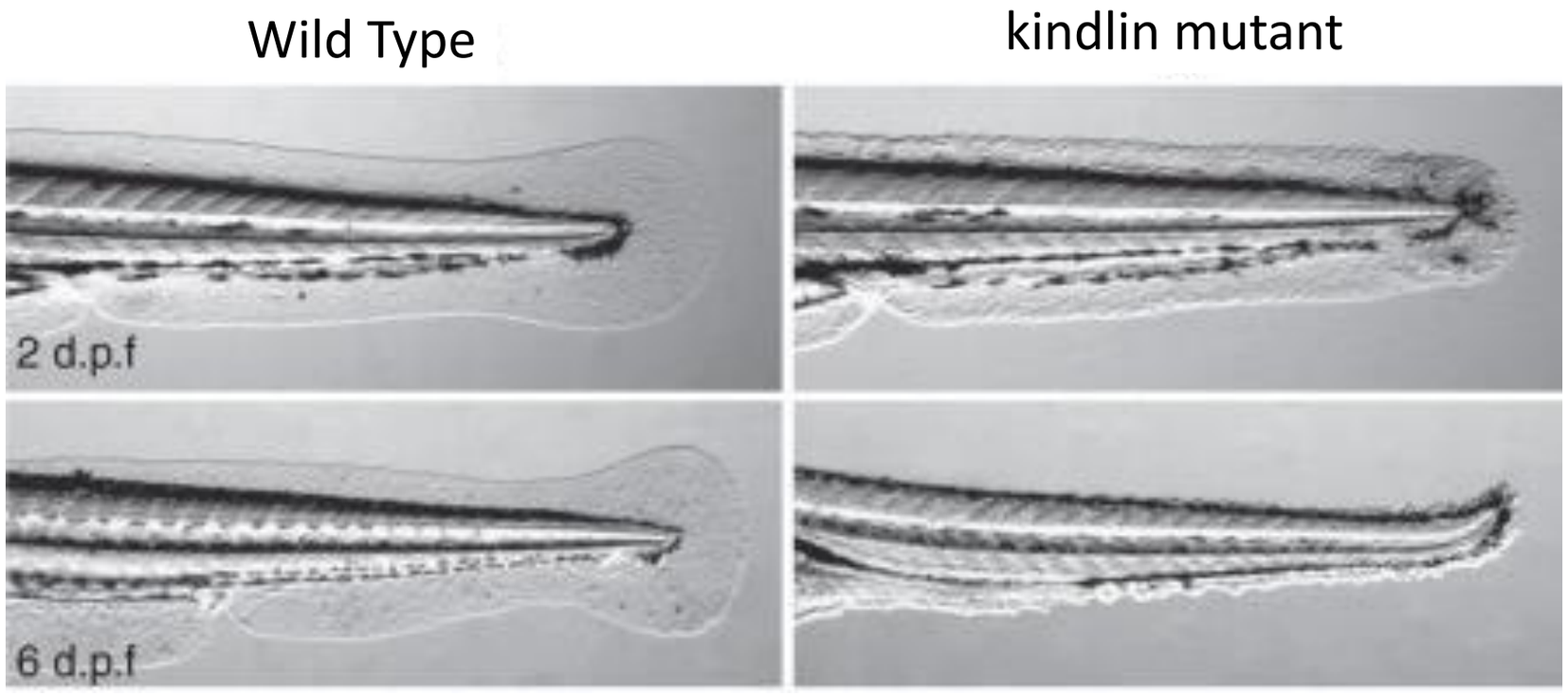
Danio rerio

Inexpensive

Shows phenotype

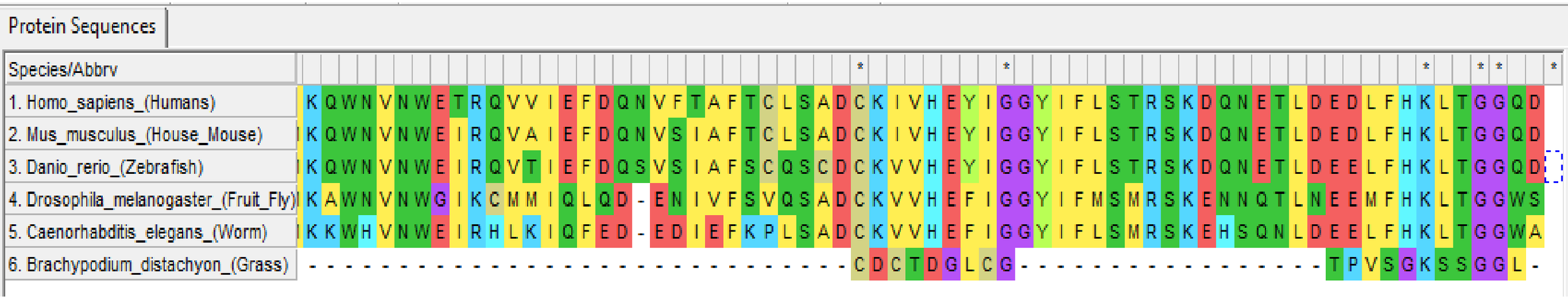
Homologous gene

Similar function



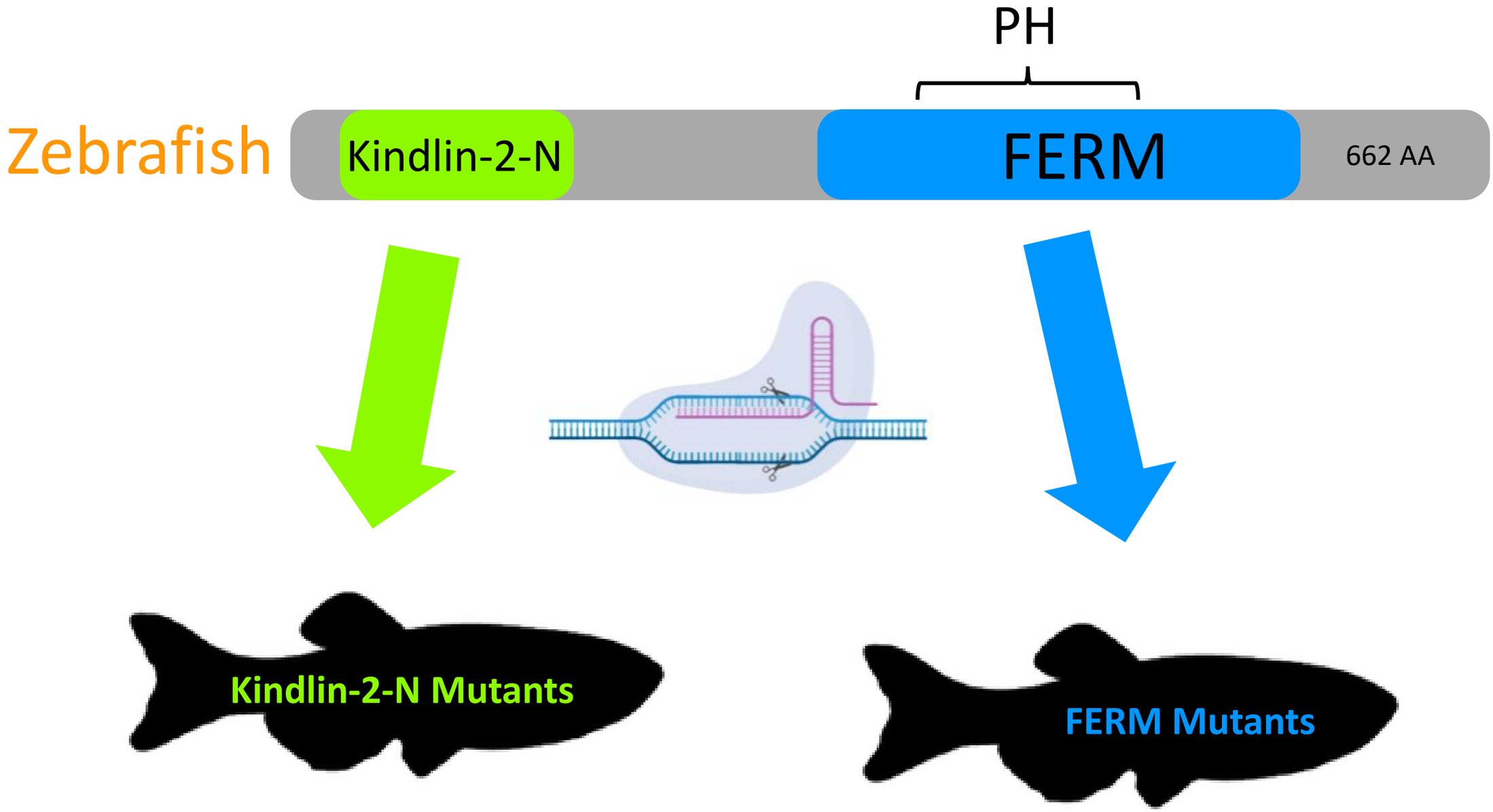
Postel, et. Al 2013

AIM 1: Analyze protein sequence for conserved sights

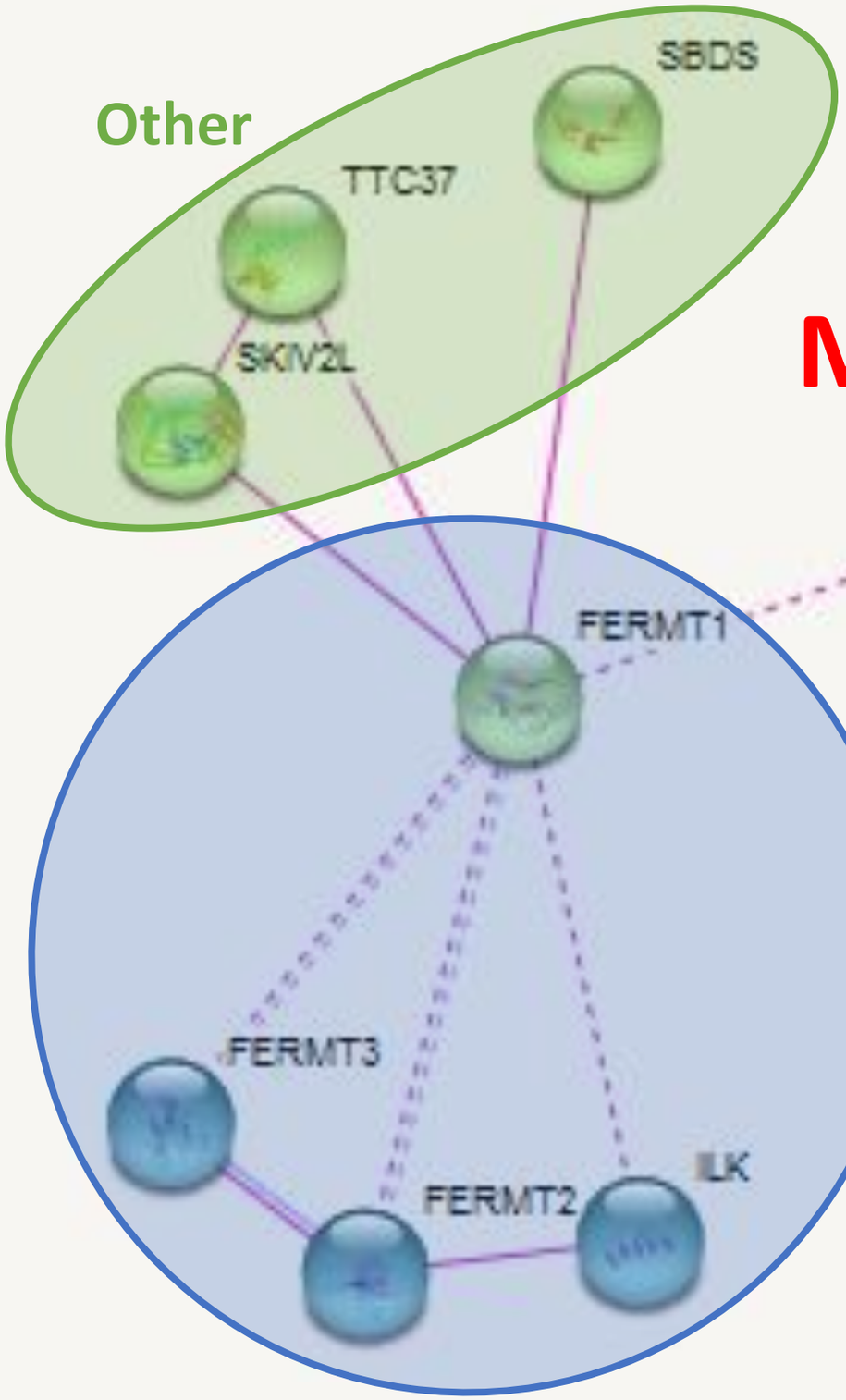


Identify highly conserved regions of the kindlin-1 to be mutated

AIM1: Establishing mutant lines via CRISPR

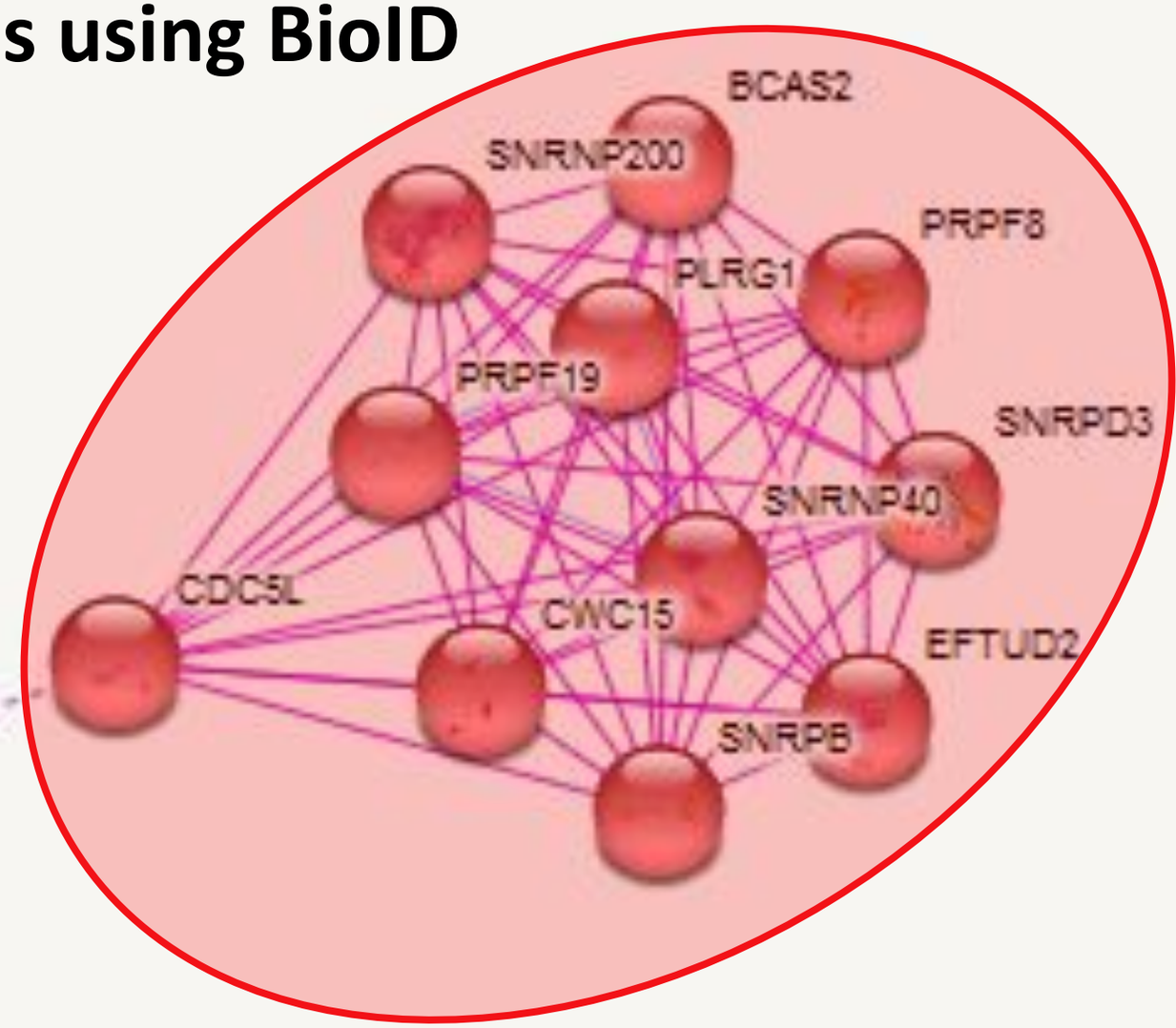


AIM 2: Analyze FERMT1 interactions using BioID



Integrin Mediated Signaling Pathway

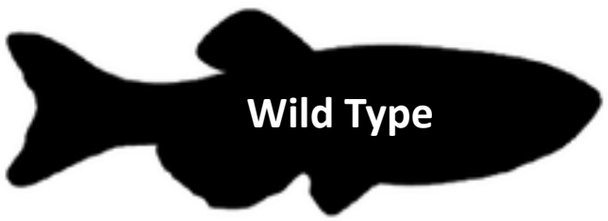
Mutants

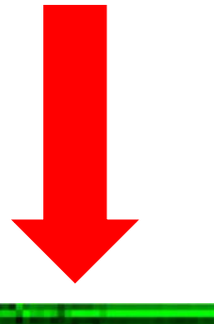


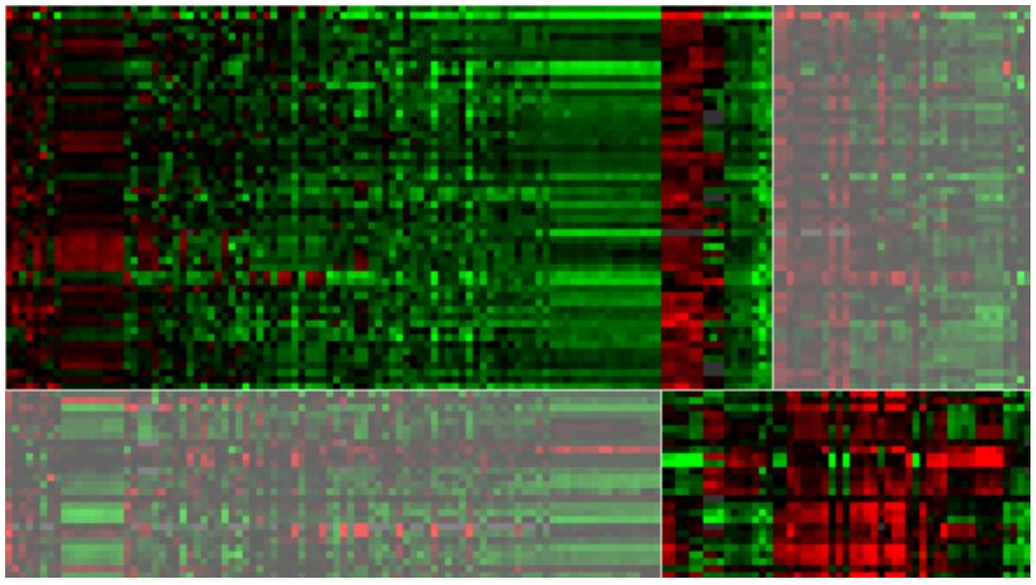
Transcription regulation

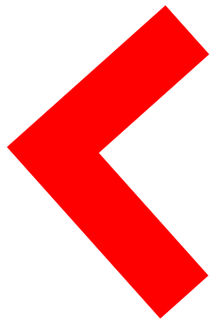
Mutant screens should show disruption of this network

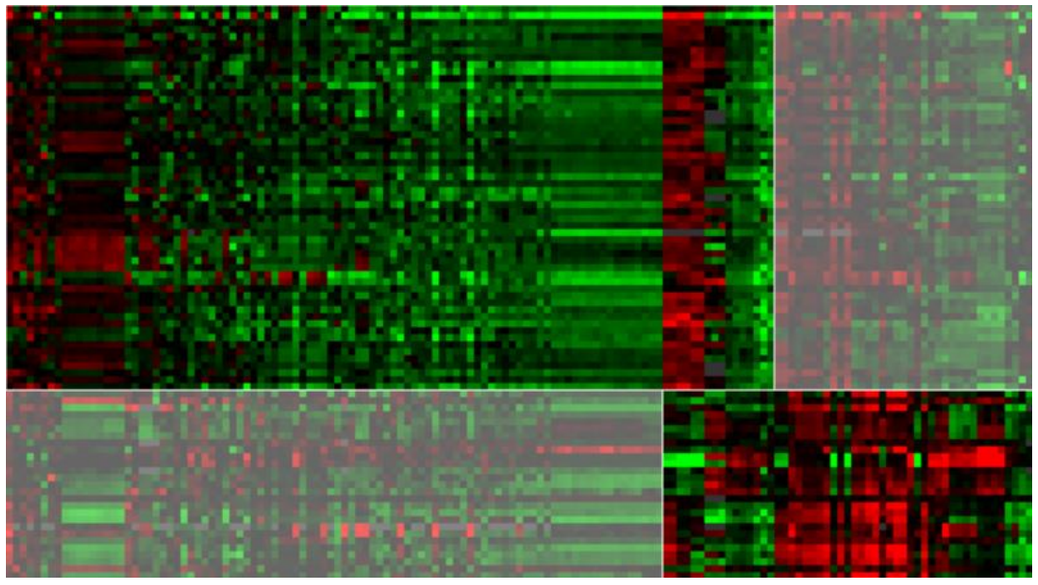
AIM 3: Analyze transcription levels via single-cell RNA-seq





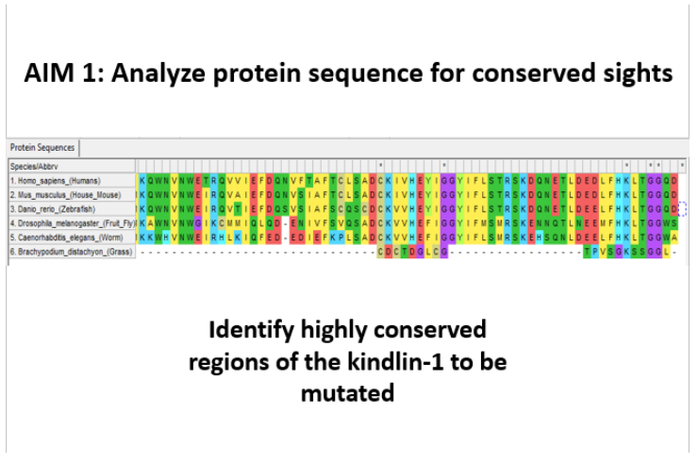




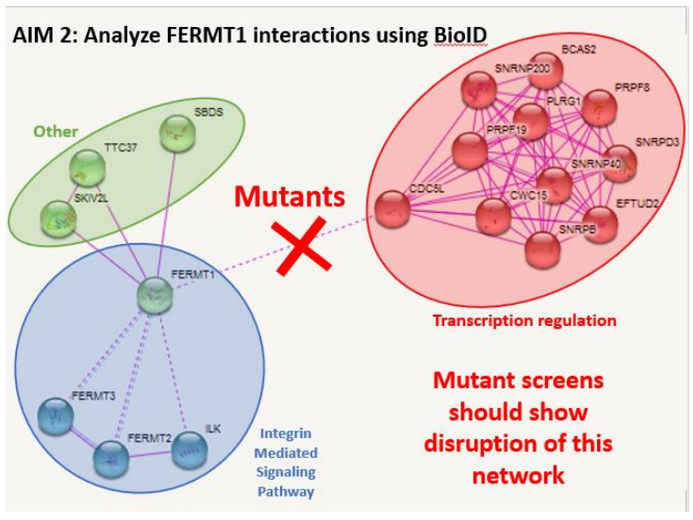


Transcription should be increased in mutant fish

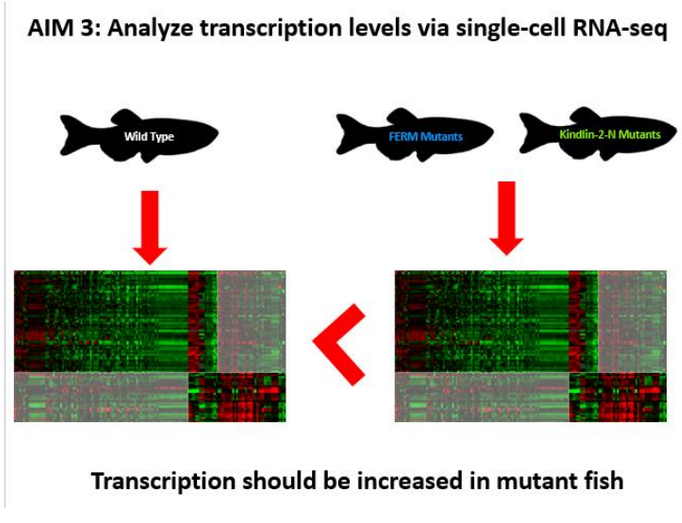
Summary



AIM1: Analyze protein sequence and establish mutant zebrafish lines



AIM2: Analyze protein interaction network of mutants



AIM1: Analyze transcription levels of mutants

References

Epidermis Picture: https://ghr.nlm.nih.gov/condition/kindler-syndrome

Kindler Syndrome picture: https://www.debra.org.uk/uk-funded-projects/sonnenberg-kindler-syndrome
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Kindlin-1 function: https://www.researchgate.net/figure/Molecular-mechanisms-for-integrin-activation-Integrins-exist-in-two-activation-states-on_fig4_323191947
Zebrafish embryo: http://sitn.hms.harvard.edu/art/2014/zebrafish-embryo-development/
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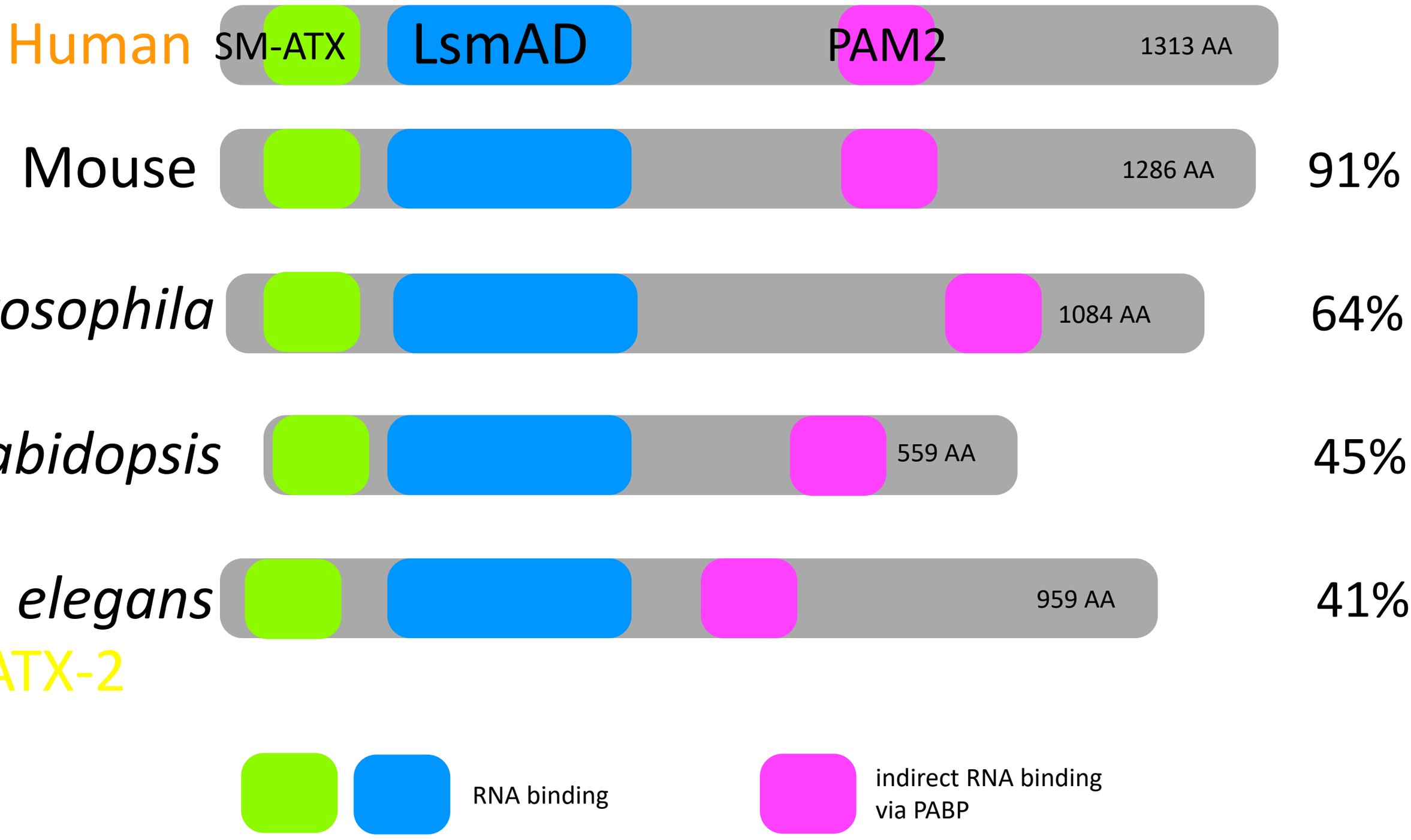
Squamous Cell Carcinoma: https://www.sciencedirect.com/science/article/pii/S1507136716300517

Ataxin-2 is a conserved RNA Binding Protein



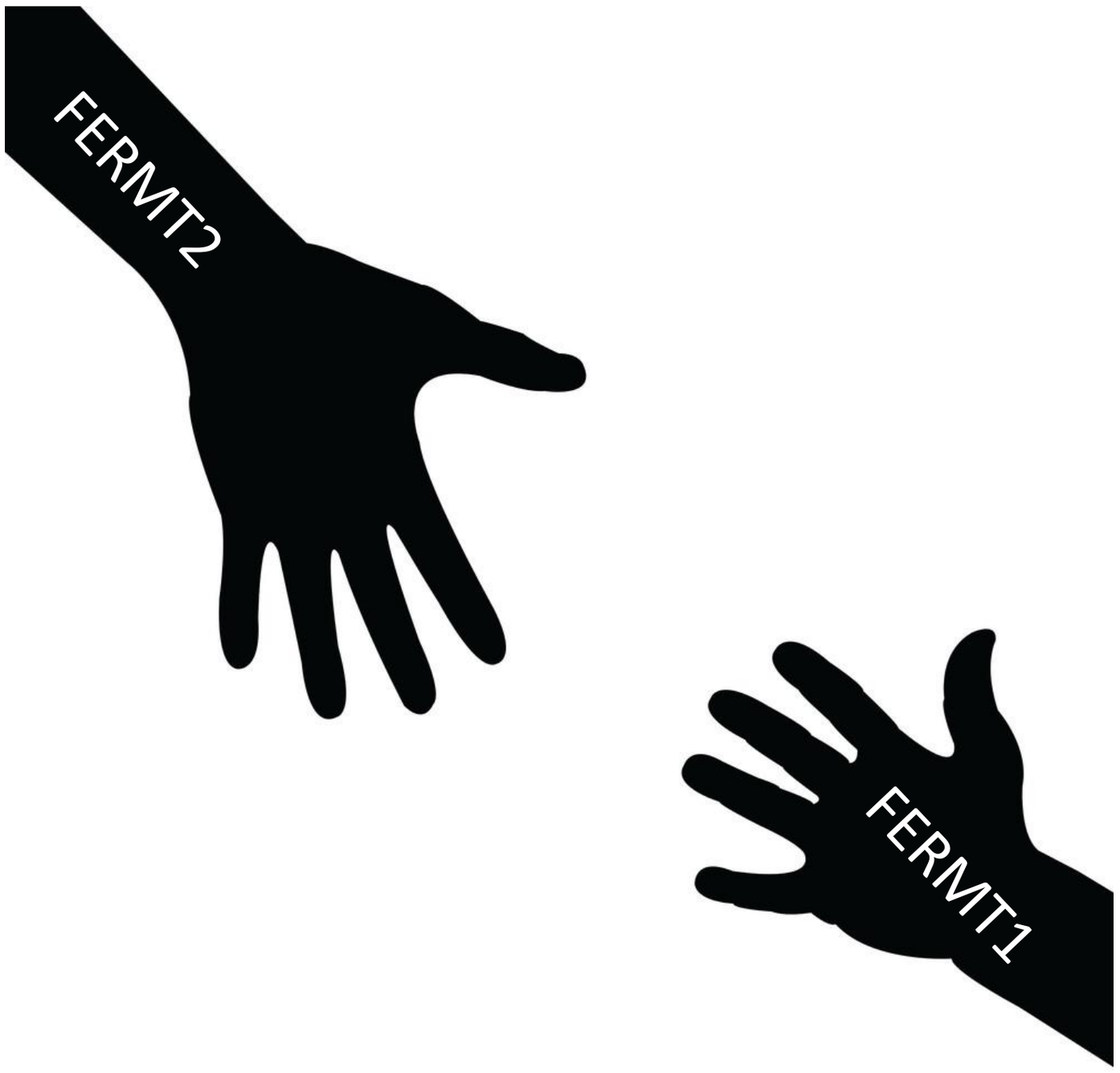
Does timing of kindlin-1 mutation affect phenotype?

WT

Knockdown WT at adolescence

Recovered phenotype?
(No cancer)

How can we recover kindlin-1 function?



YES! Kindlin-2 function recovers function lost by kindlin-1 mutations

How does kindlin-1 expression change over time?