

LIFEFEST 2026

Nashville



**SDH Research and Clinical Trials - SDH-Deficient GIST:
Using the awesome power of yeast genetics
to remove the uncertainty of VUS**

Dr. Michael Heinrich

2026 Life Fest Conference

SDH-Deficient GIST:

**Using the awesome power of yeast genetics
to remove the uncertainty of VUS**

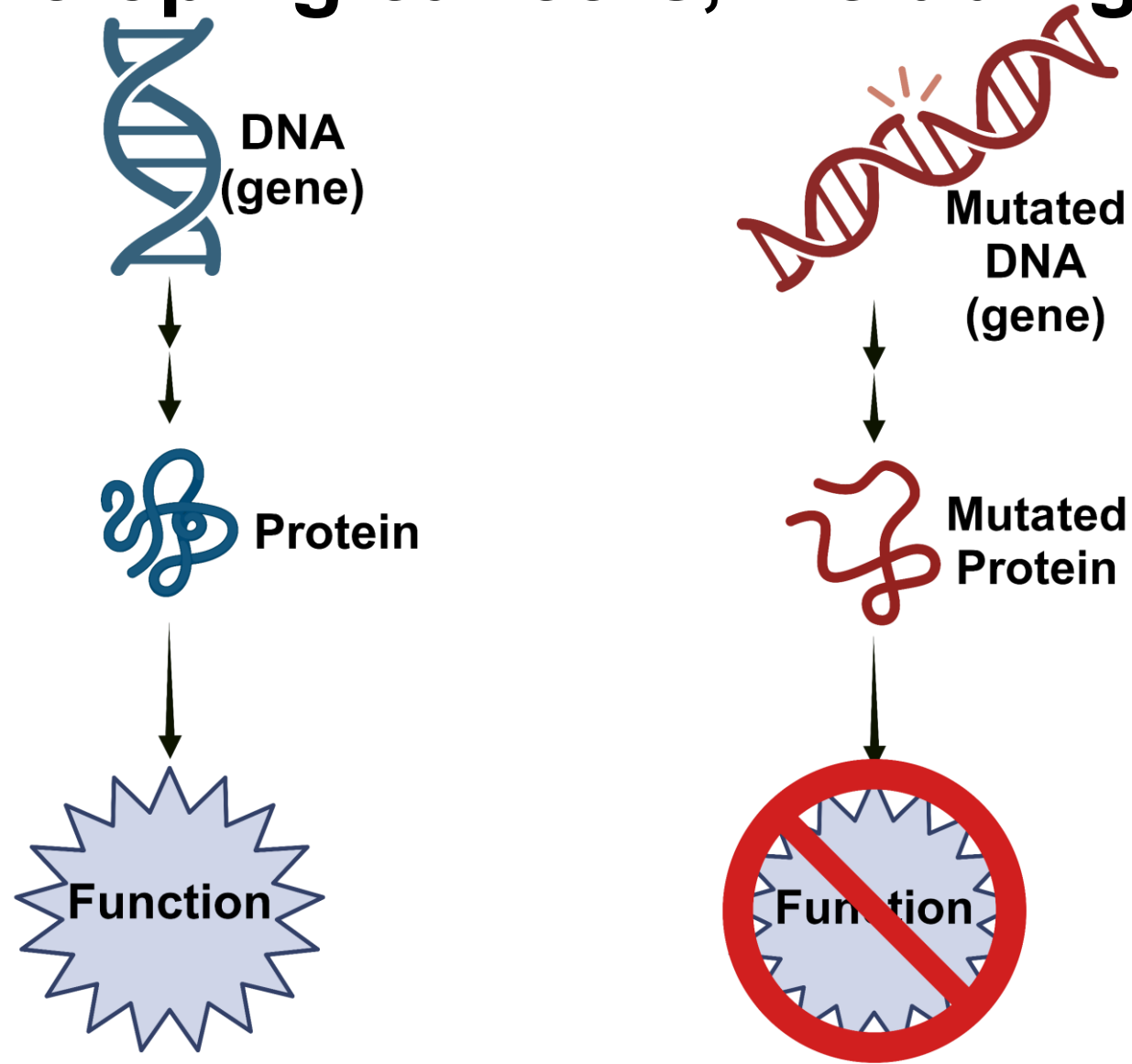
Christine Robbins, PhD

(Resident Yeast Specialist)

Michael Heinrich, MD

(Yeast enthusiast)

Mutations in various genes can increase the chance of developing cancers, including GIST



GIST Tumor Genetics: Oncogenes vs. Tumor Suppressor Genes



1 gain-of
function (GOF)
event



Oncogenes
1 GOF mutation
Examples: KIT, PDGFRA



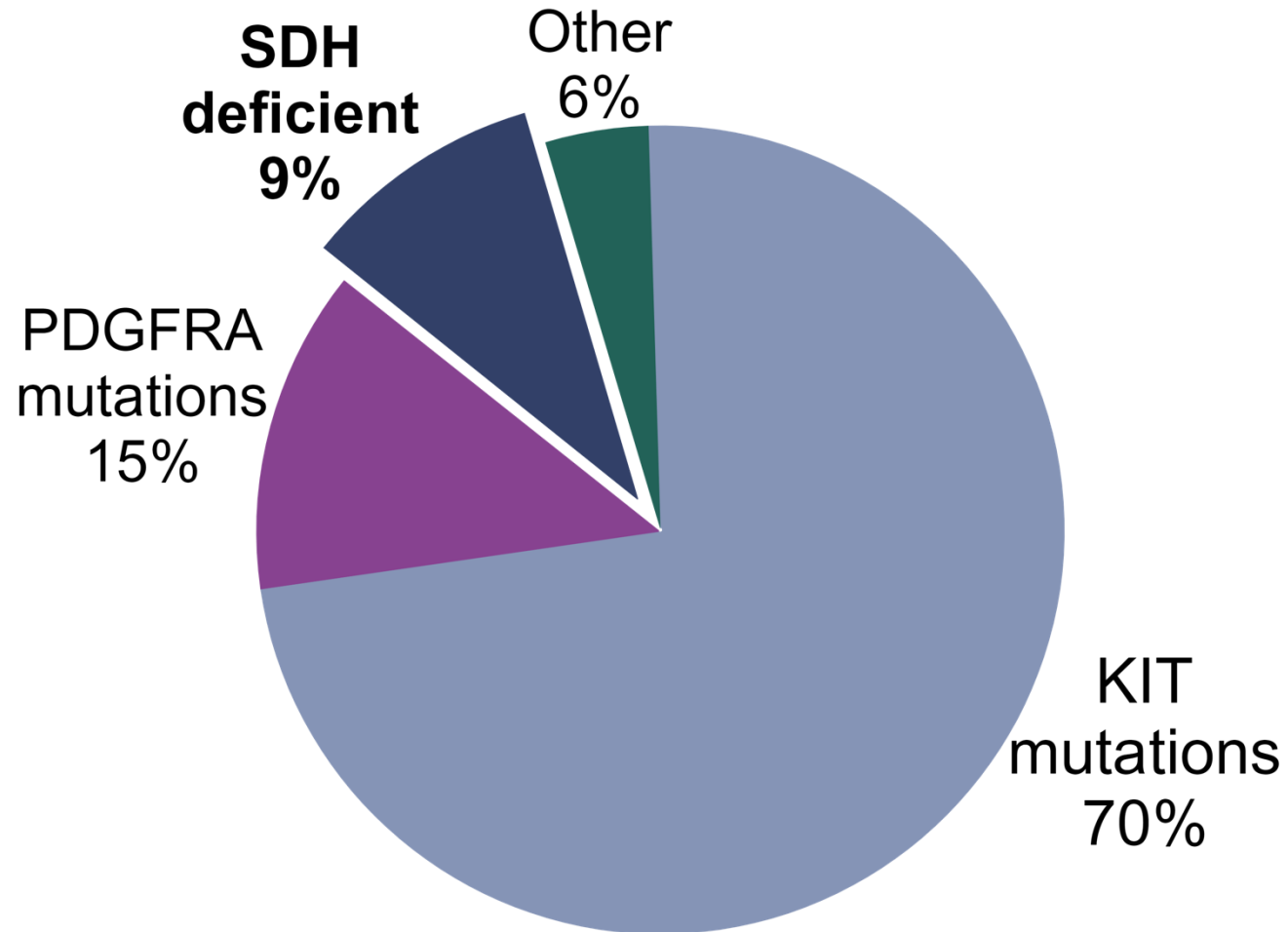
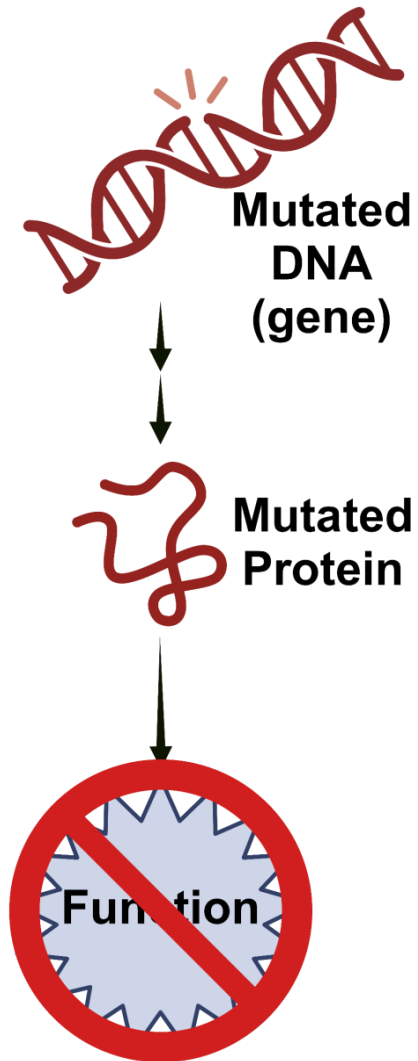
2 loss of function
(LOF) events



Tumor Suppressor Genes
2 LOF mutations
Examples: SDHA/B/C/D



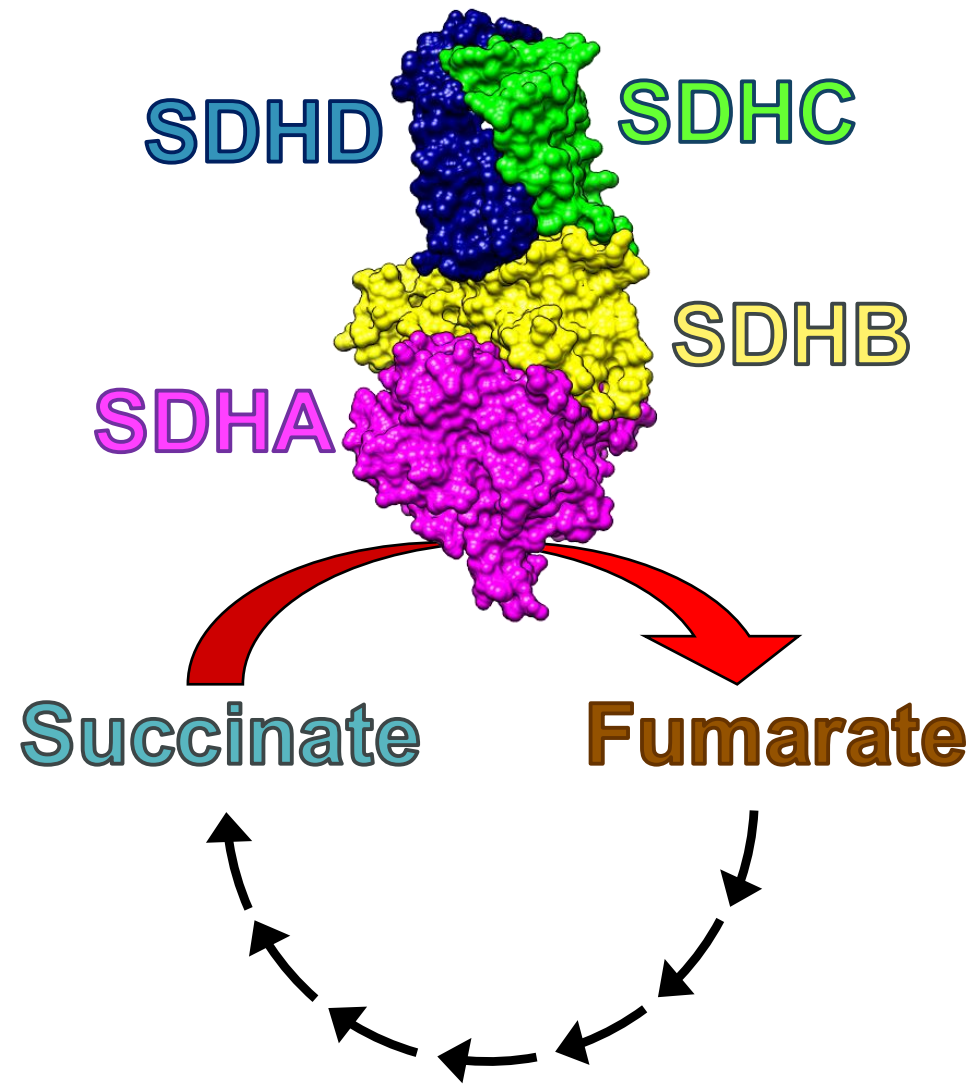
Mutations in various genes can increase the chance of developing cancers, including GIST



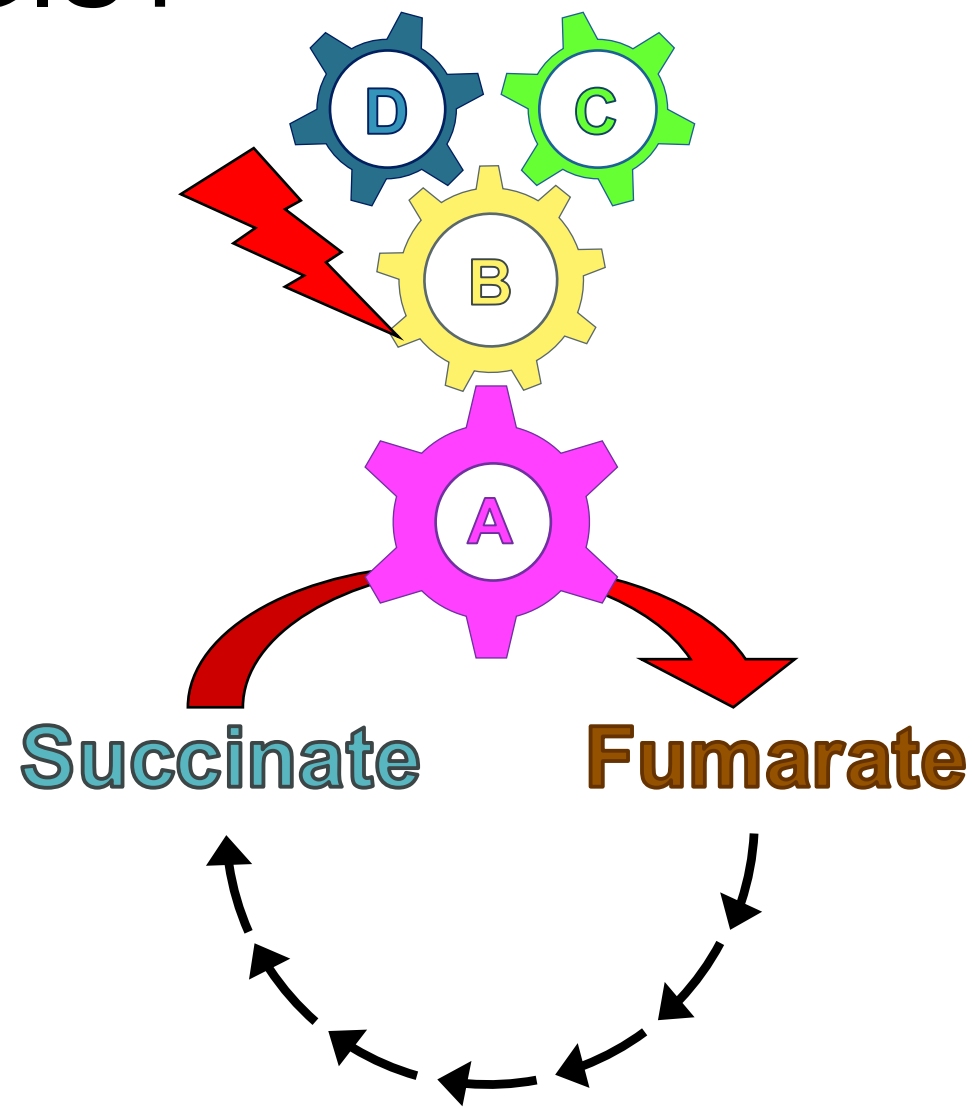
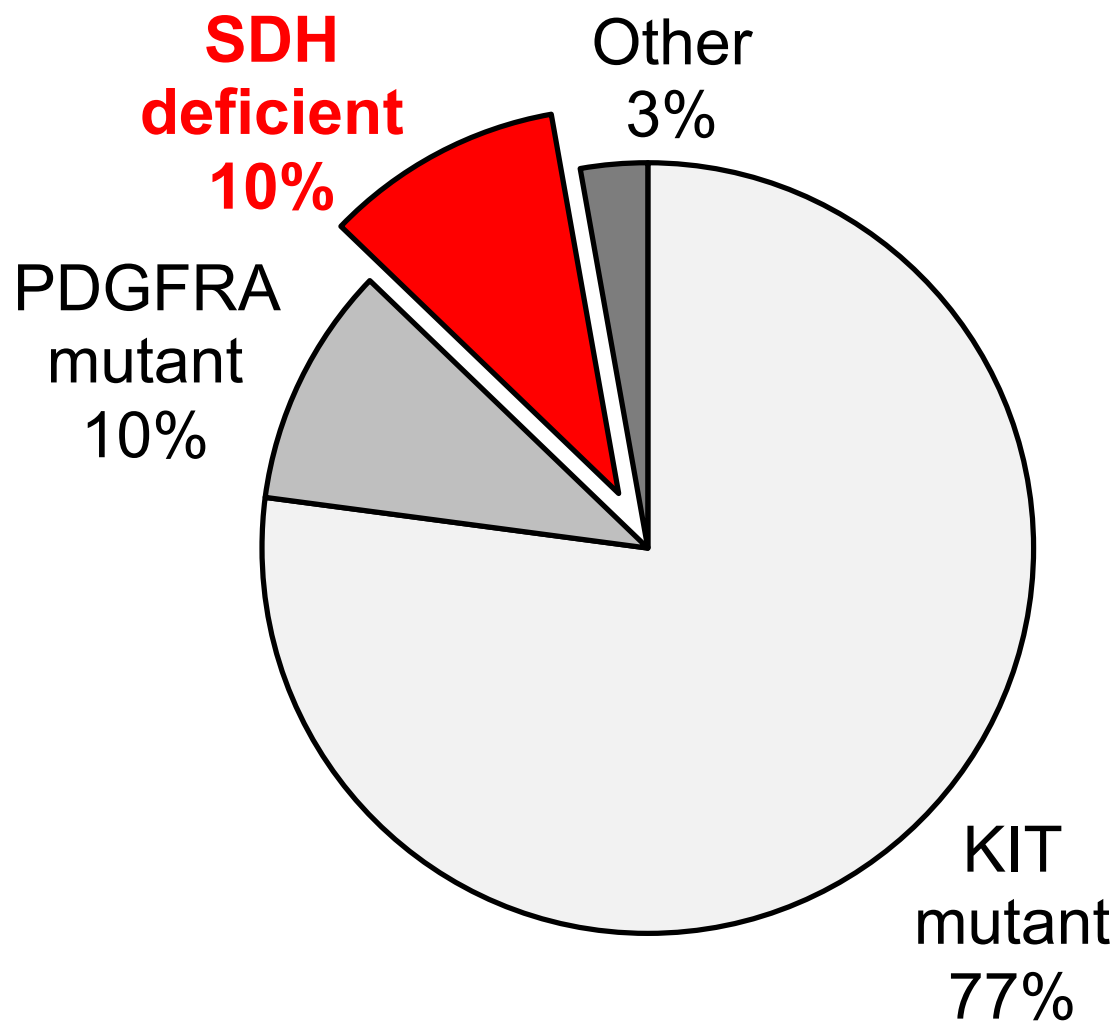
What is “SDH” and what does it do?

Succinate Dehydrogenase (SDH)

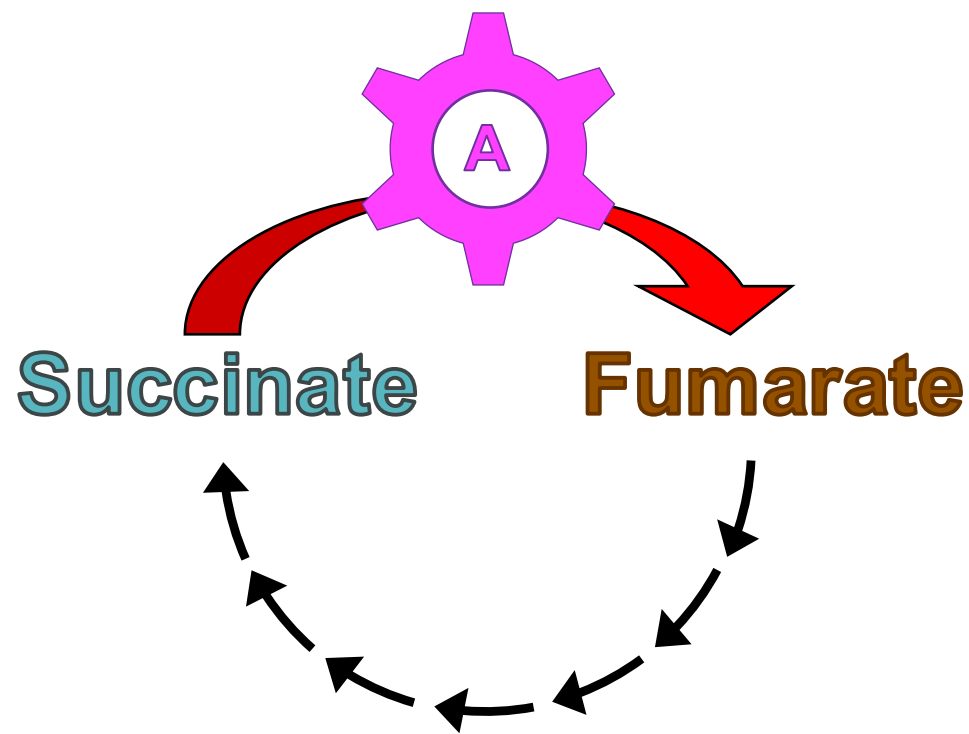
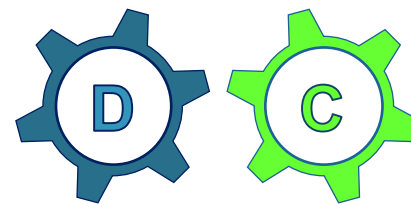
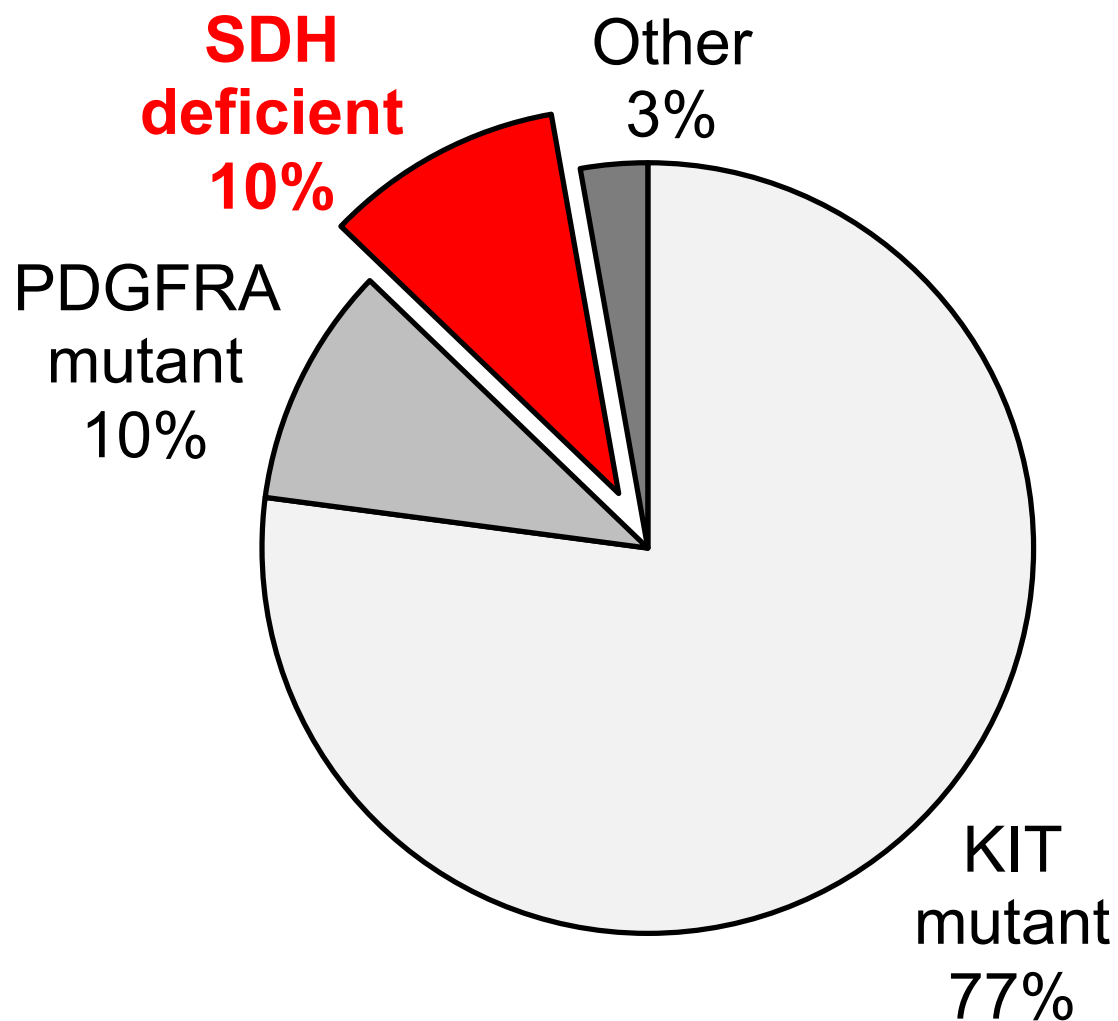
- Enzyme complex made of 4 subunits
- Located in mitochondria
- Important for normal metabolism



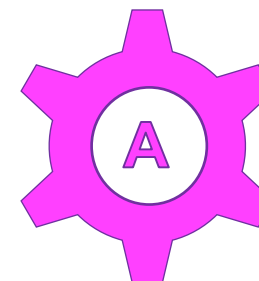
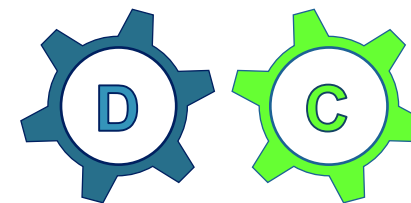
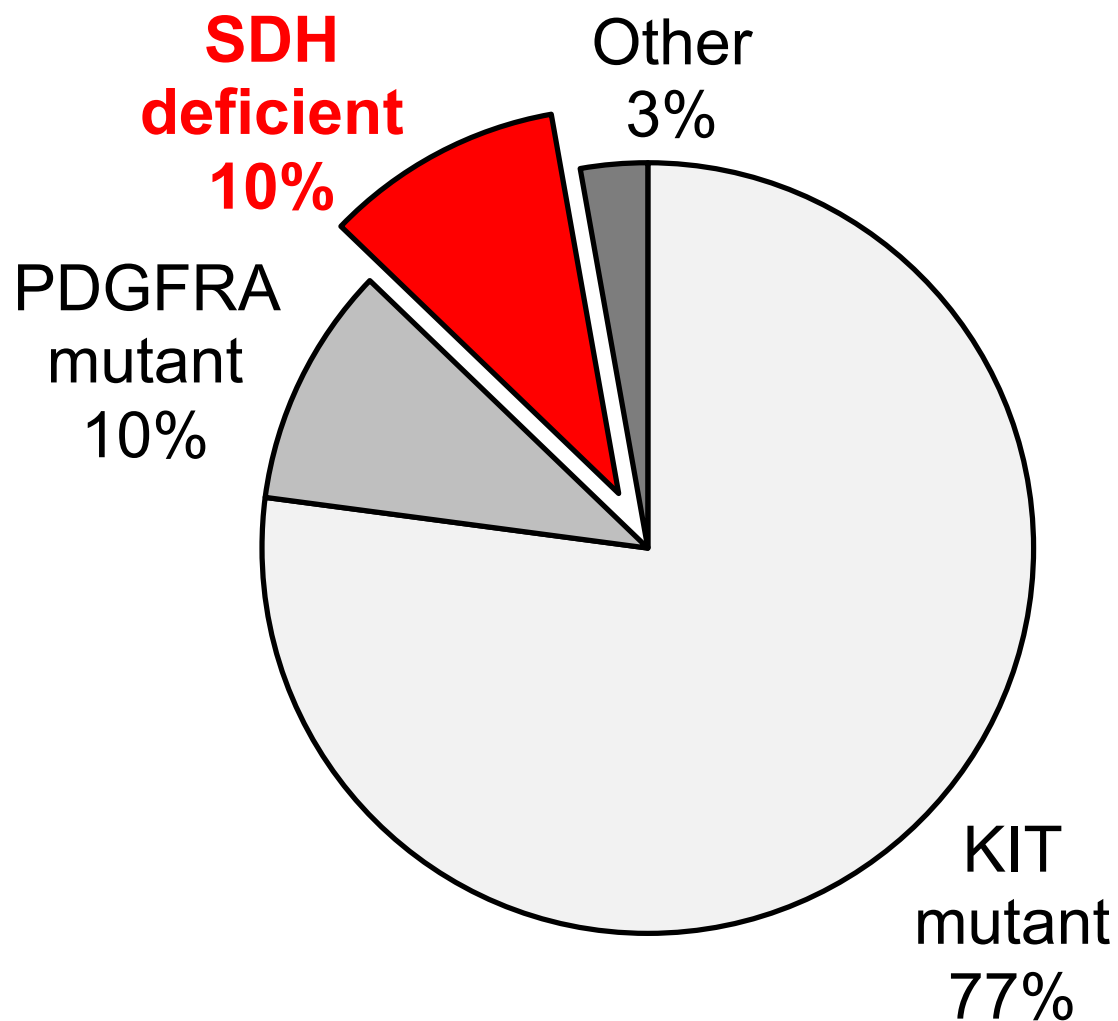
Loss of SDH function is the most common cause of non-KIT/PDGFRα related GIST



Loss of SDH function is the most common cause of non-KIT/PDGFRα related GIST



Loss of SDH function is the most common cause of non-KIT/PDGFRα related GIST

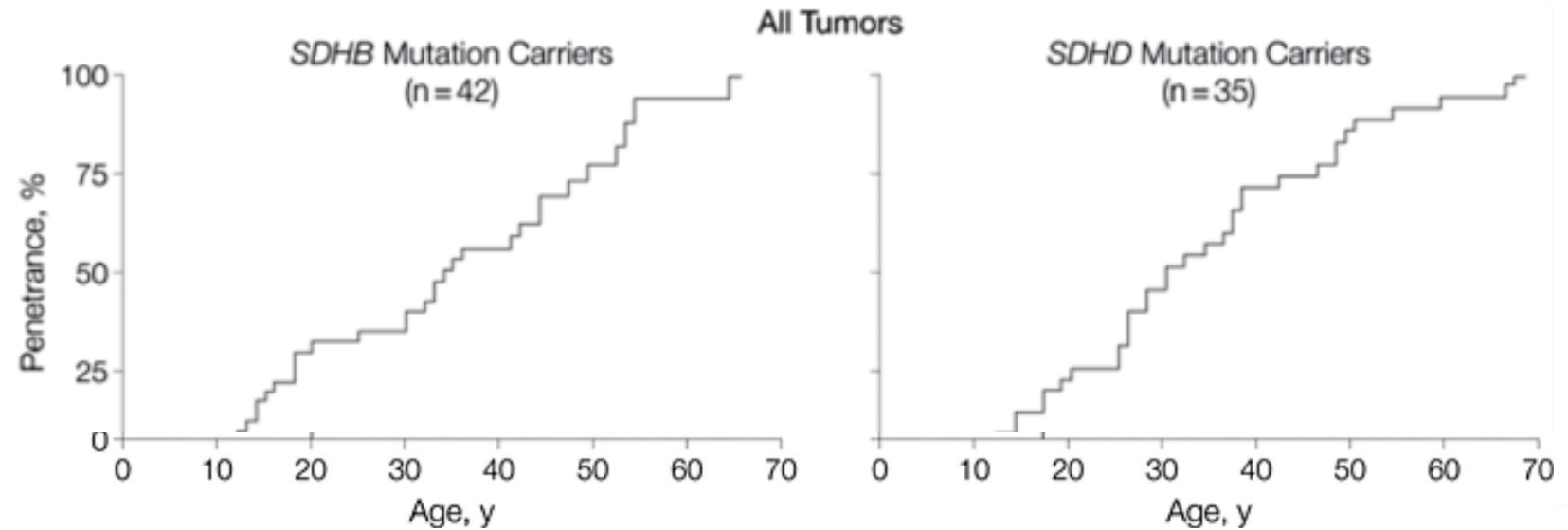
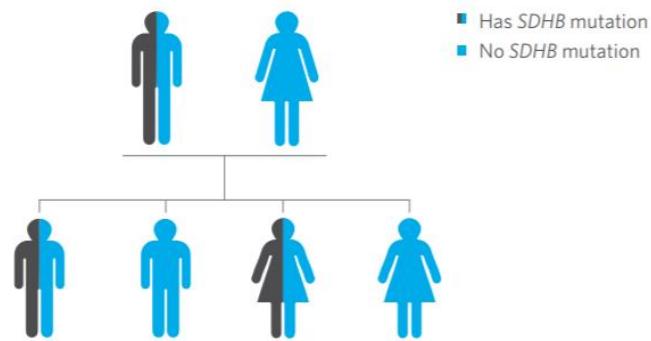


Succinate

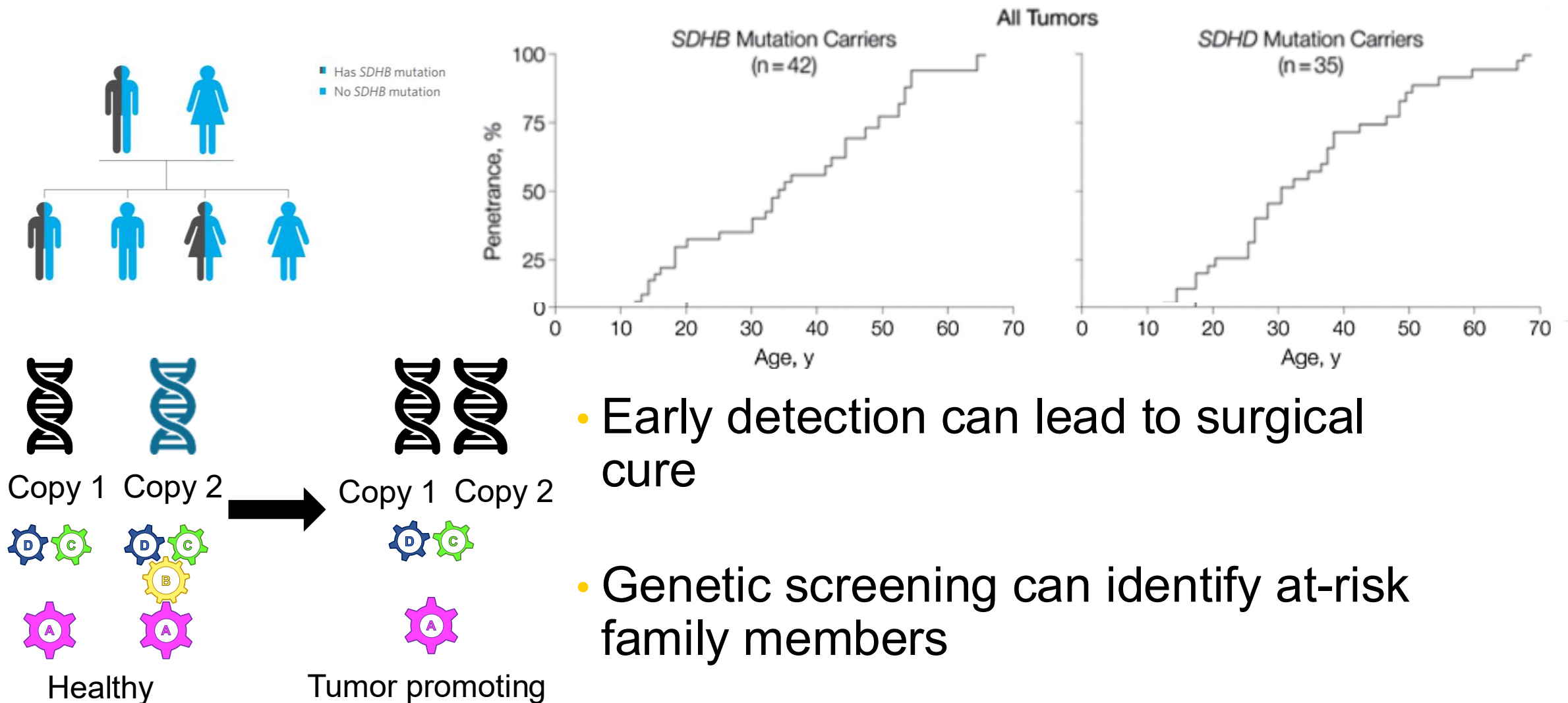


Cancer

Inheriting a loss-of-function SDH mutation results in high life-time risk for SDH-deficient cancers

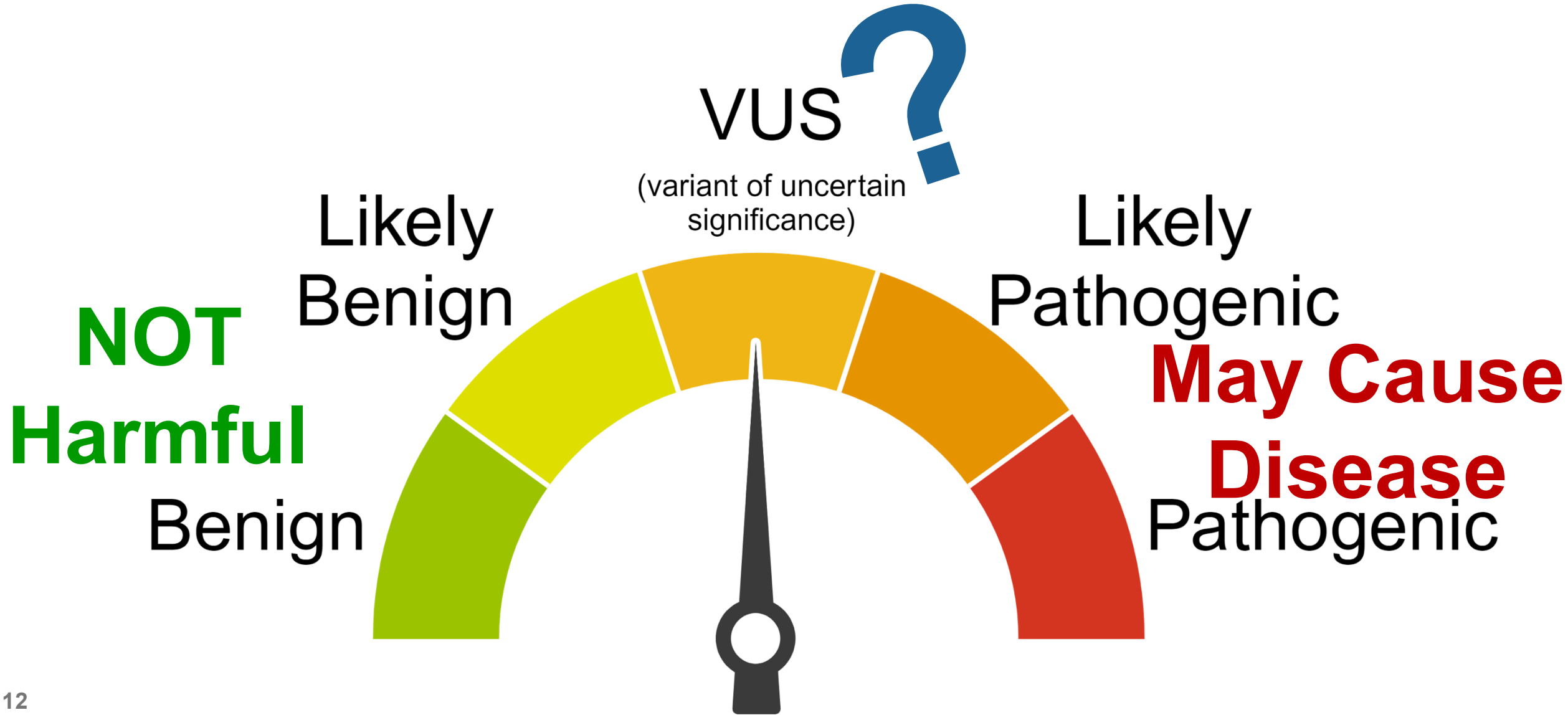


Inheriting a **loss-of-function** SDH mutation results in high life-time risk for SDH-deficient cancers

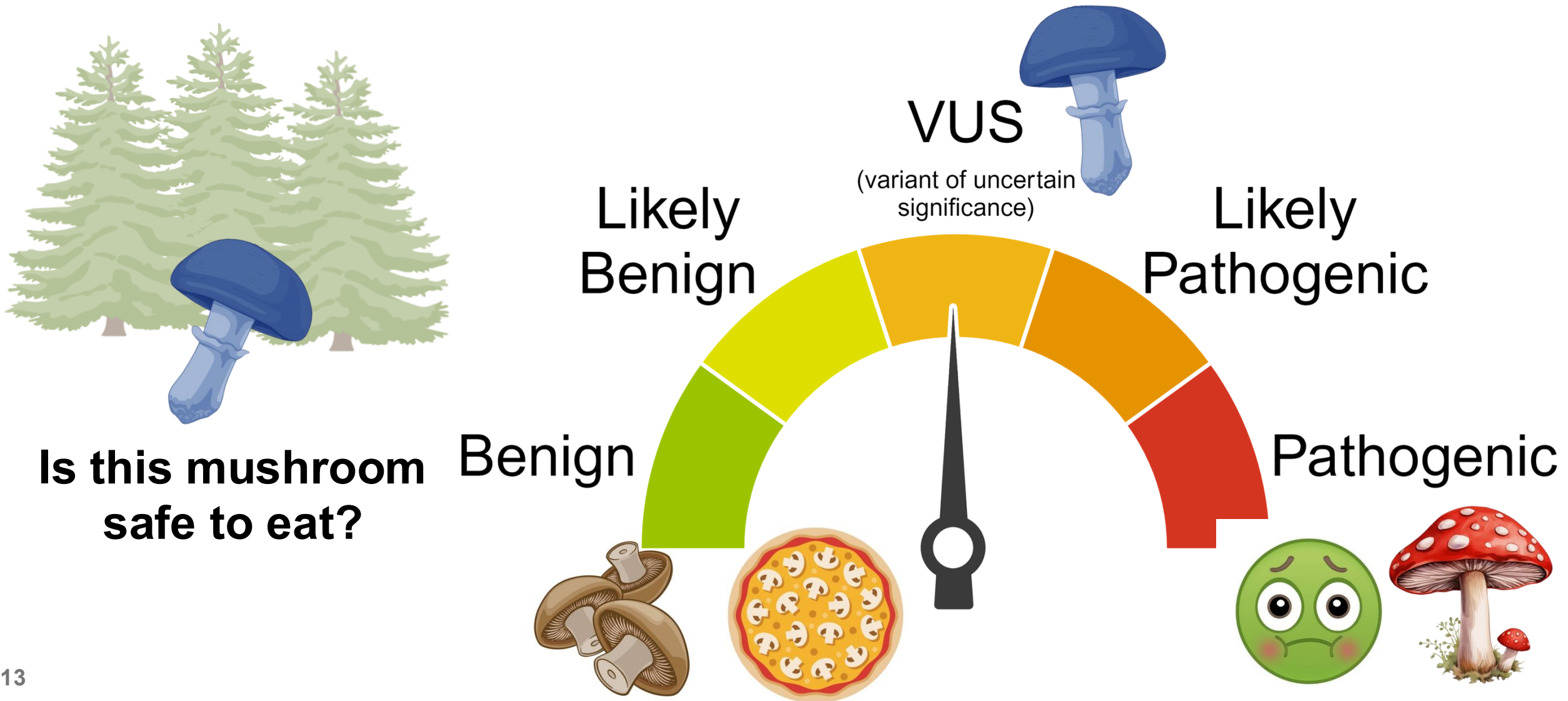


- Early detection can lead to surgical cure
- Genetic screening can identify at-risk family members

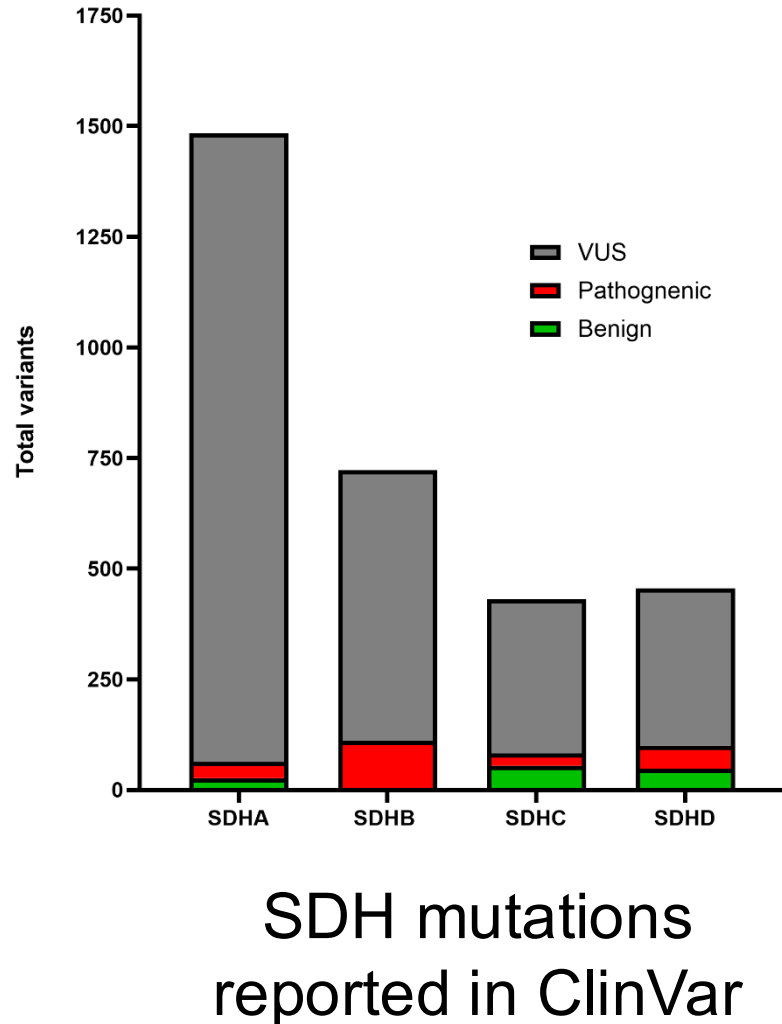
Not all mutations are problematic



When a mutation is a VUS, we don't know *YET* if it might cause problems



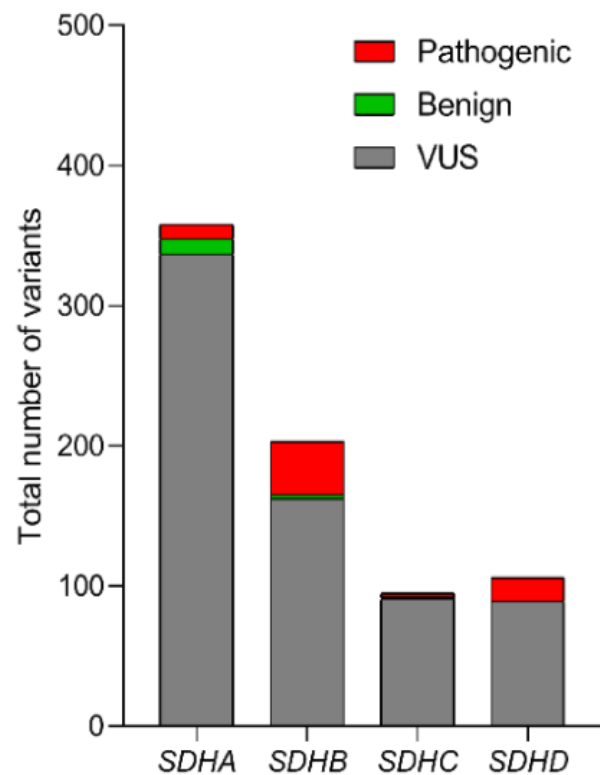
Most SDH mutations are variants of unknown significance (VUS)



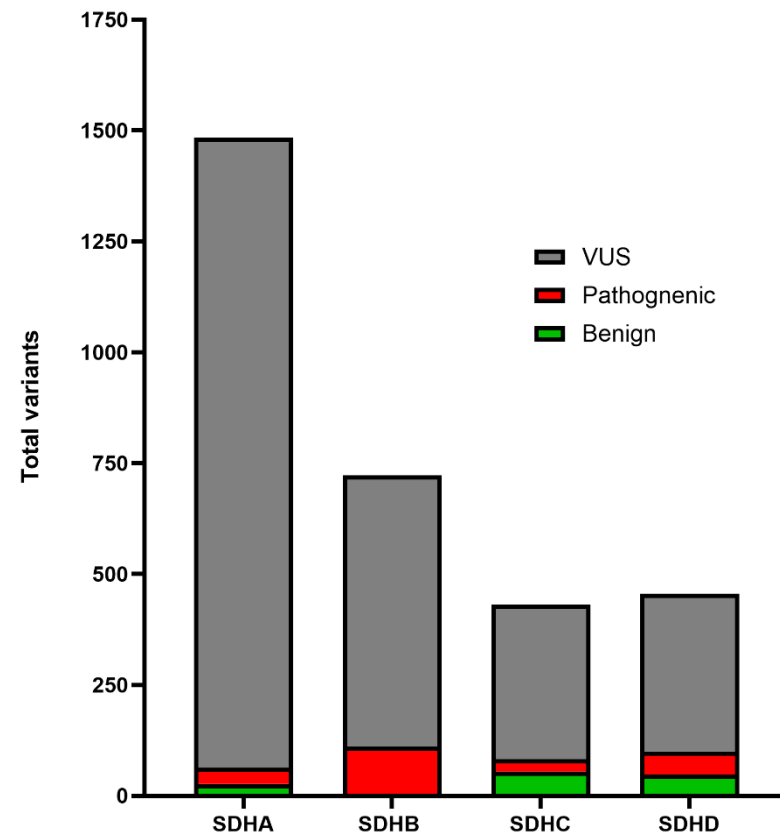
Tumor risk **cannot** be determined, and screening is **not** recommended for patients with SDH VUS

Family screening **not** recommended for relatives of a patient with a SDH VUS

VUS problem is worsening over time



Life Fest 2020

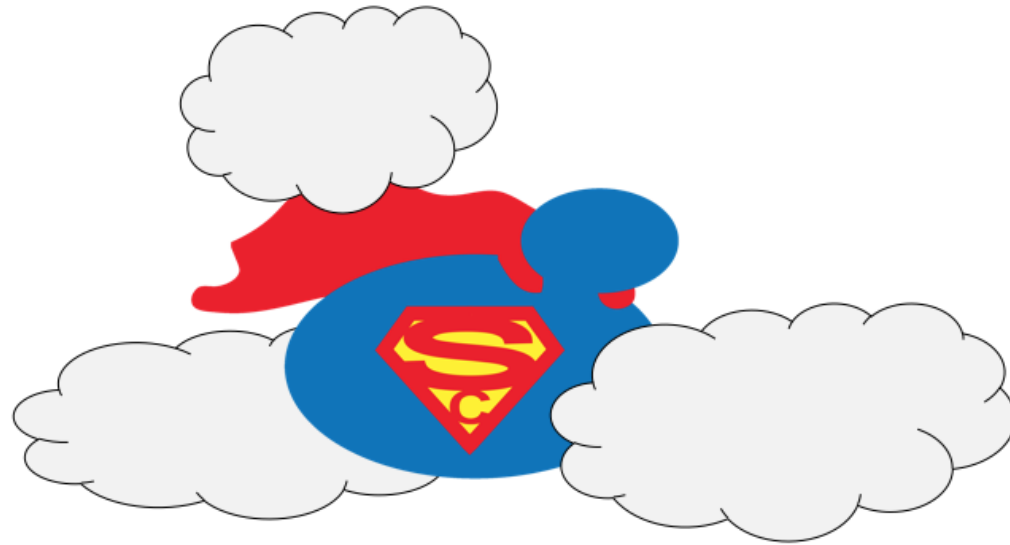


Life Fest 2026

Scientists must test new mushrooms and mutations to see if they are benign or pathogenic

Understanding the significance of VUS mutations will allow for better diagnostic tools and early detection of disease

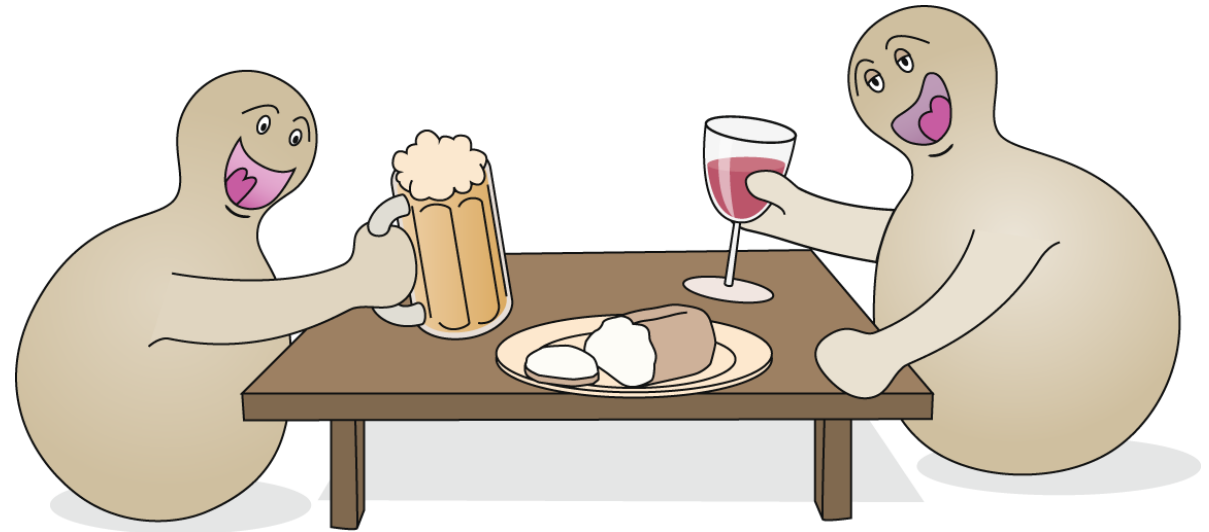
**My laboratory is using the awesome power of yeast genetics
to remove the uncertainty**



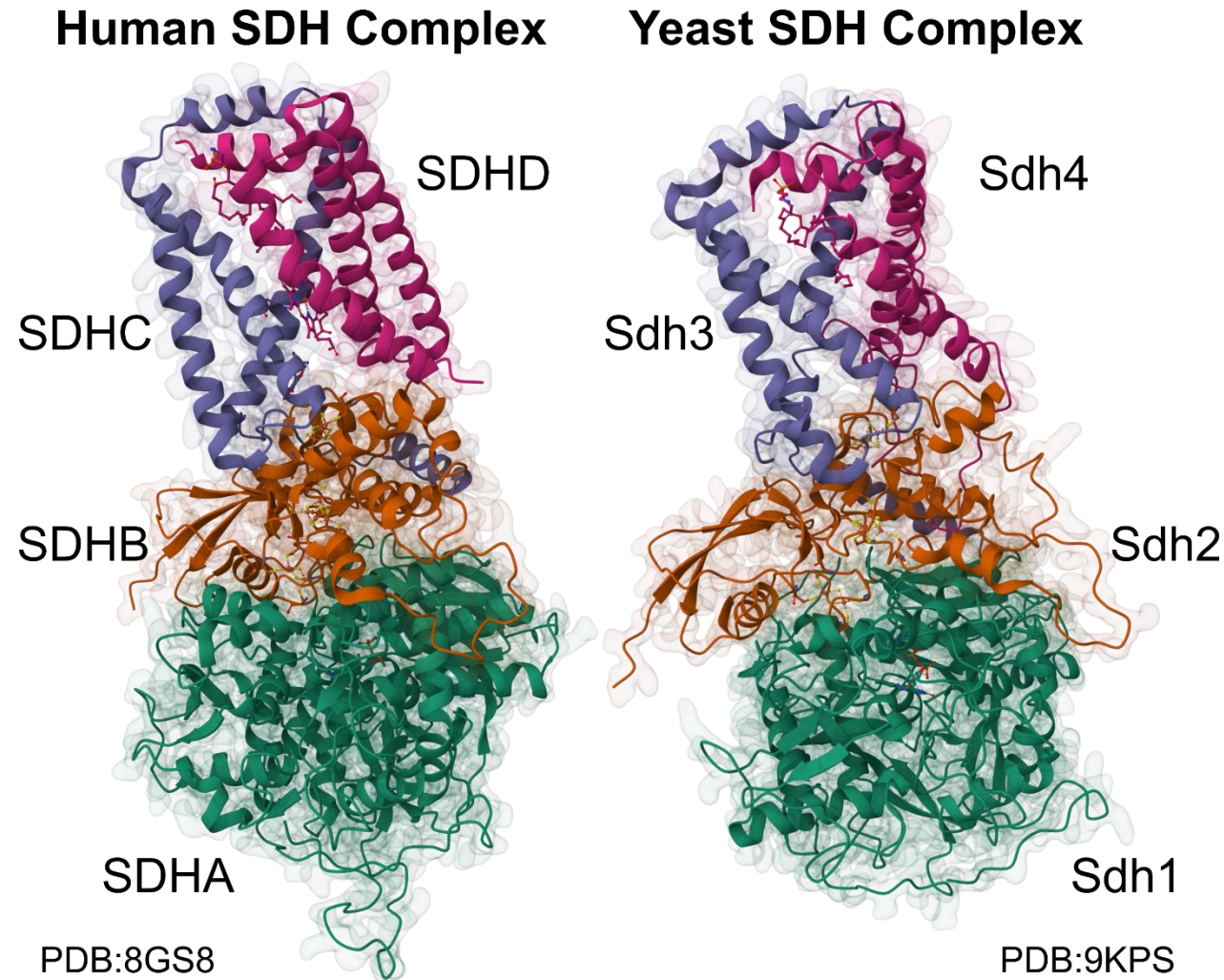
Saccharomyces cerevisiae, the yeast used in bread baking and beer making

Why use yeast to model human disease?

- ❖ Yeast share many processes with human cells (including SDH)
- ❖ It is easier, faster, and cheaper to make and study mutations in yeast
- ❖ We can easily screen for mitochondria (SDH) function based on what we feed them

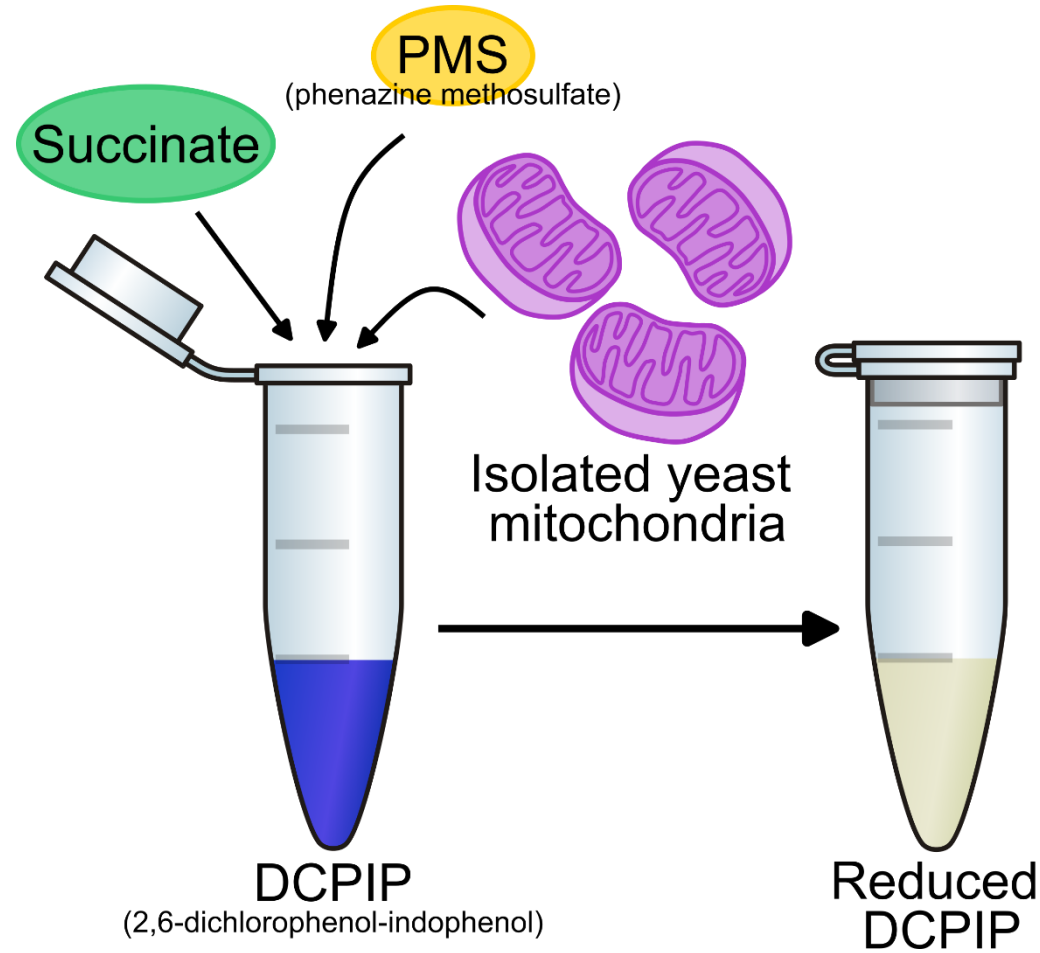


Yeast and Human SDH complexes are similar in both structure and function

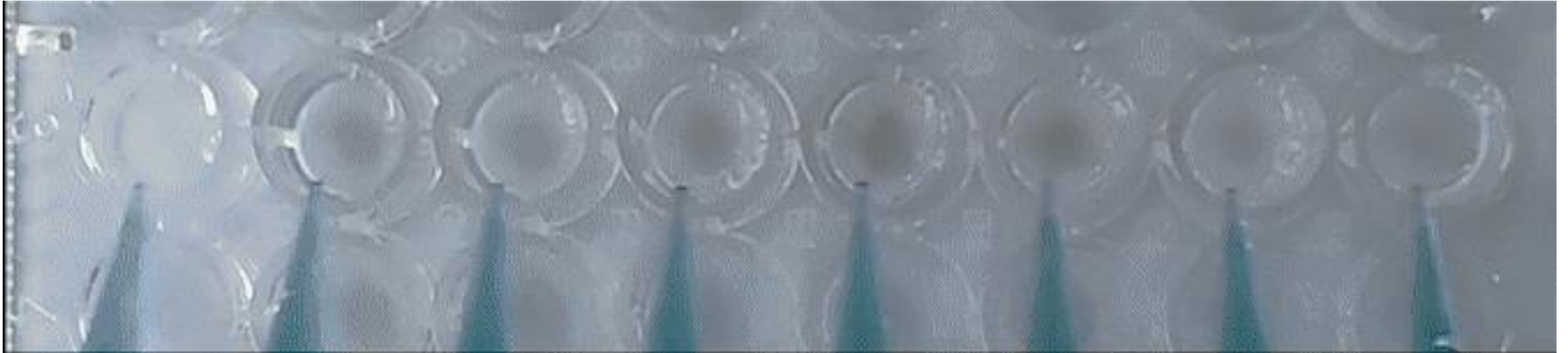


**In the lab, there are a few ways we can measure if the
SDH complex is functional**

We can measure SDH enzyme activity using a color changing assay

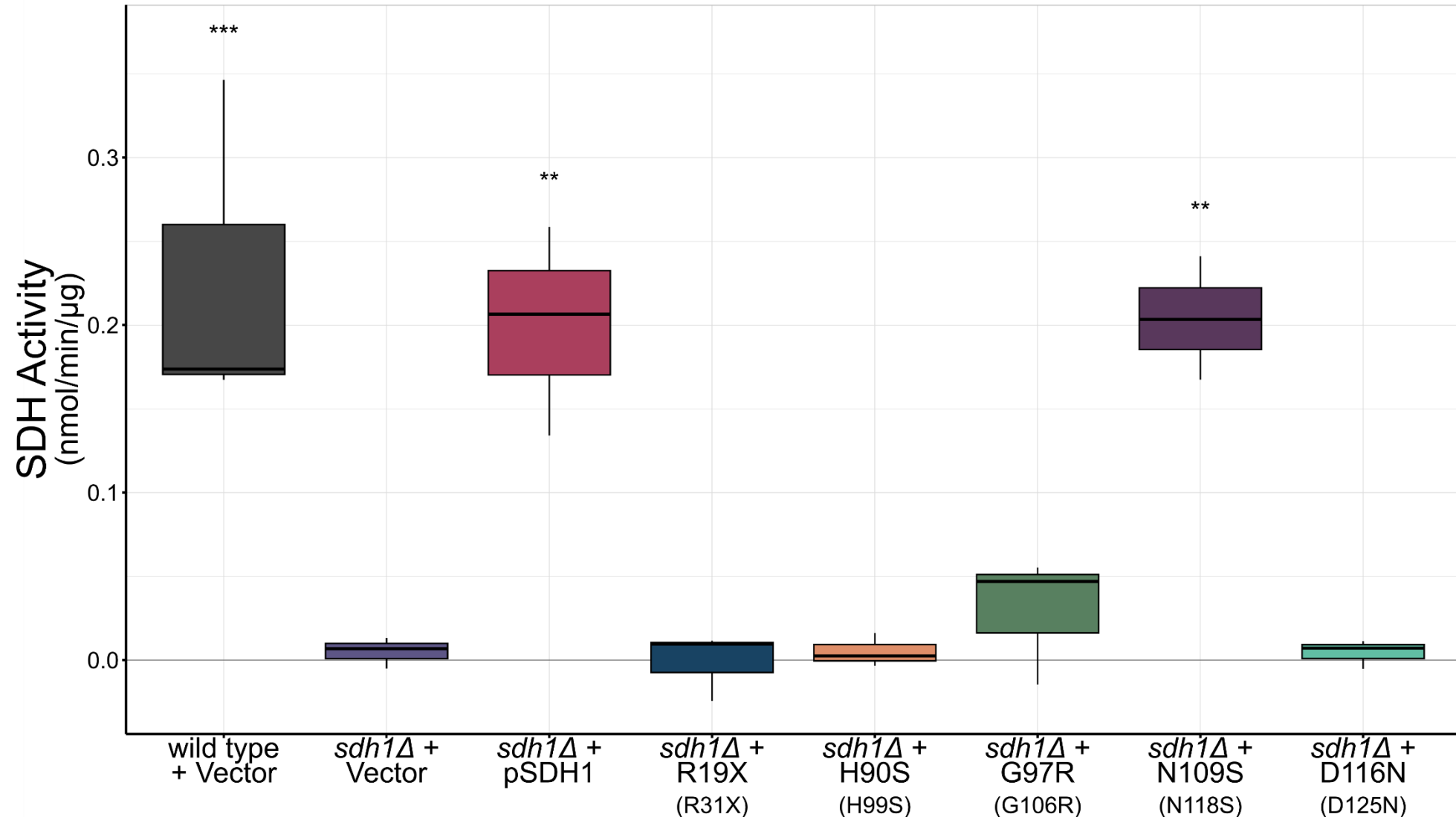


We can measure SDH enzyme activity using a color changing assay

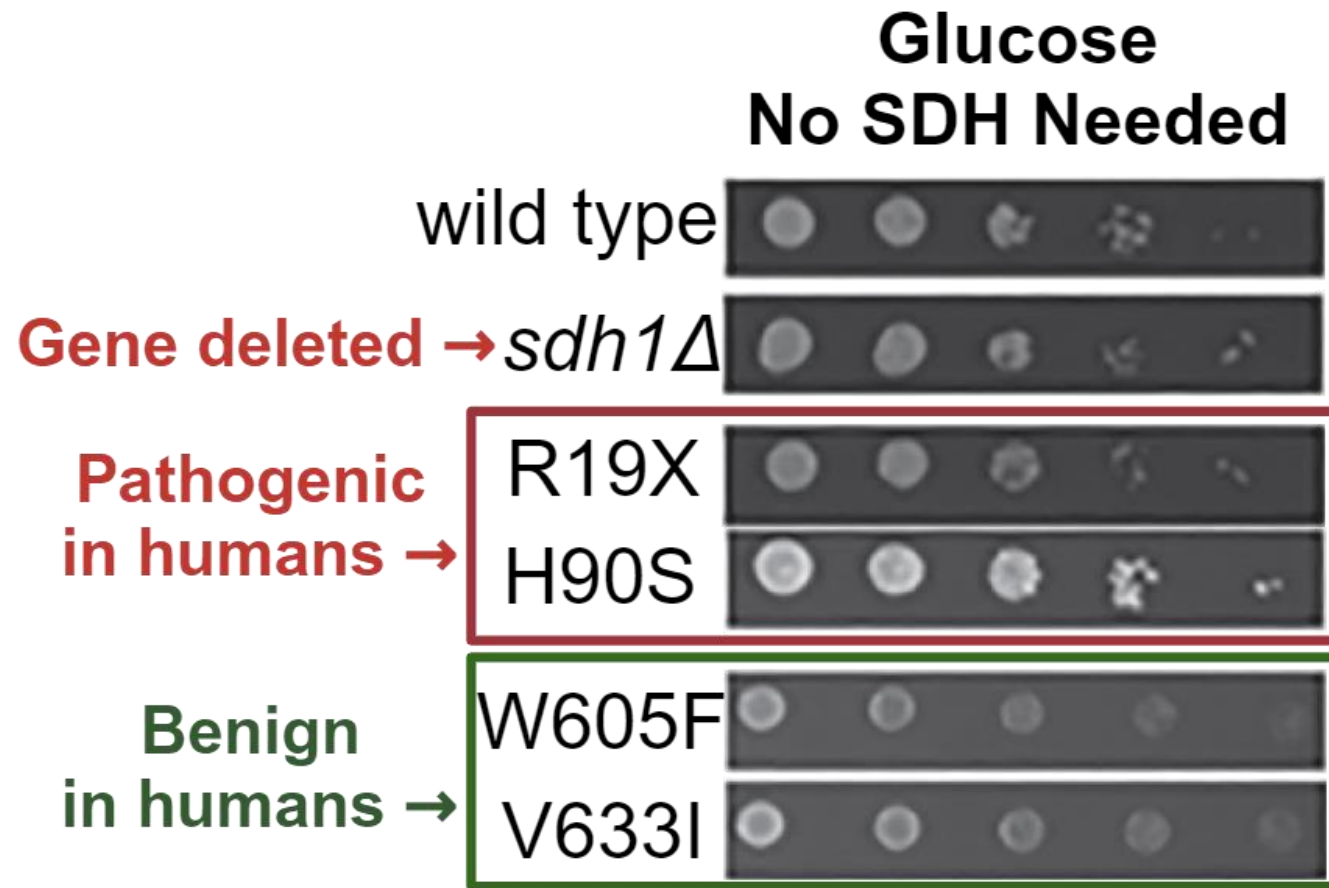


<u>Strain</u>	wild type	<i>sdh1</i> Δ	Δ+pSDH1	Δ+ R19X	Δ+H90S	Δ+ G97R	Δ+N109S	Δ+D116N
<u>SDH</u>								

We can measure SDH enzyme activity using a color changing assay



We can also determine SDH function based on growth



SDH mutant yeast fed Glycerol:
Growth = Benign No Growth = Pathogenic

We want to determine the pathogenicity of all possible mutations in SDH1 (SDHA in humans)

Sdh1 Protein (~620 amino acids)



We want to determine the pathogenicity of all possible mutations in SDH1 (SDHA in humans)



How are we going to manage to mutate every amino acid to every other amino acid?

Sdh1 Protein (~620 amino acids)

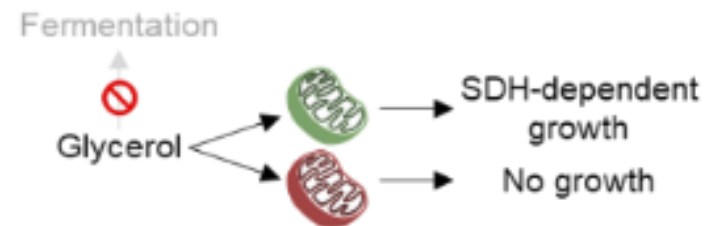
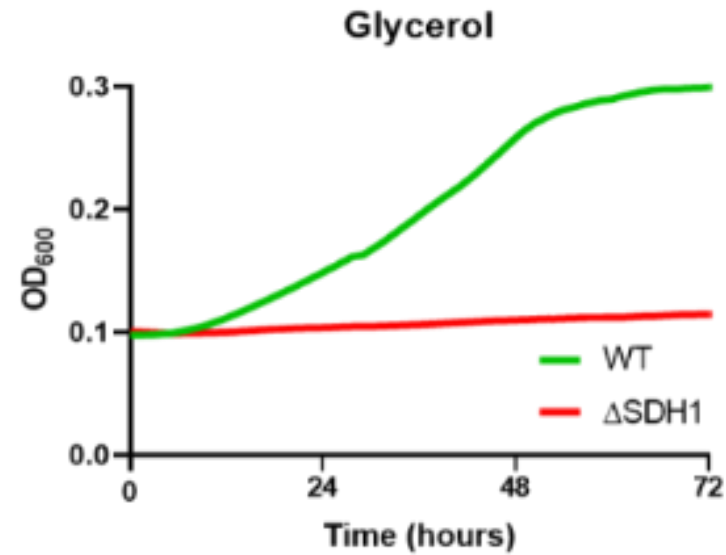
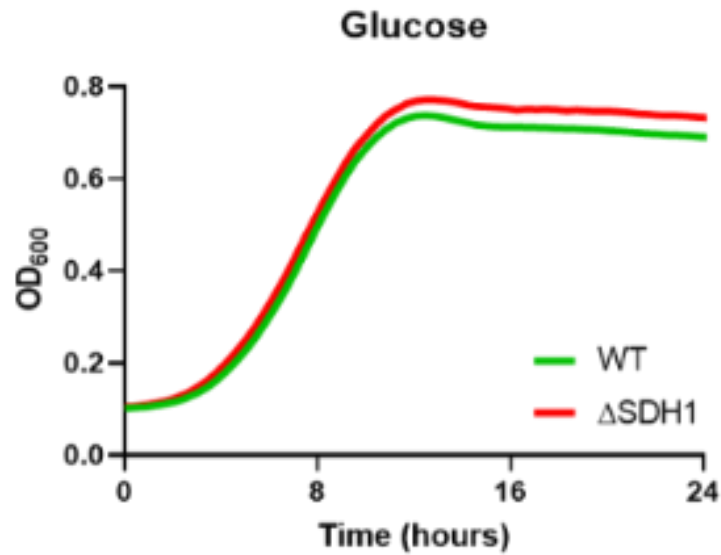


Mutation Mushrooms

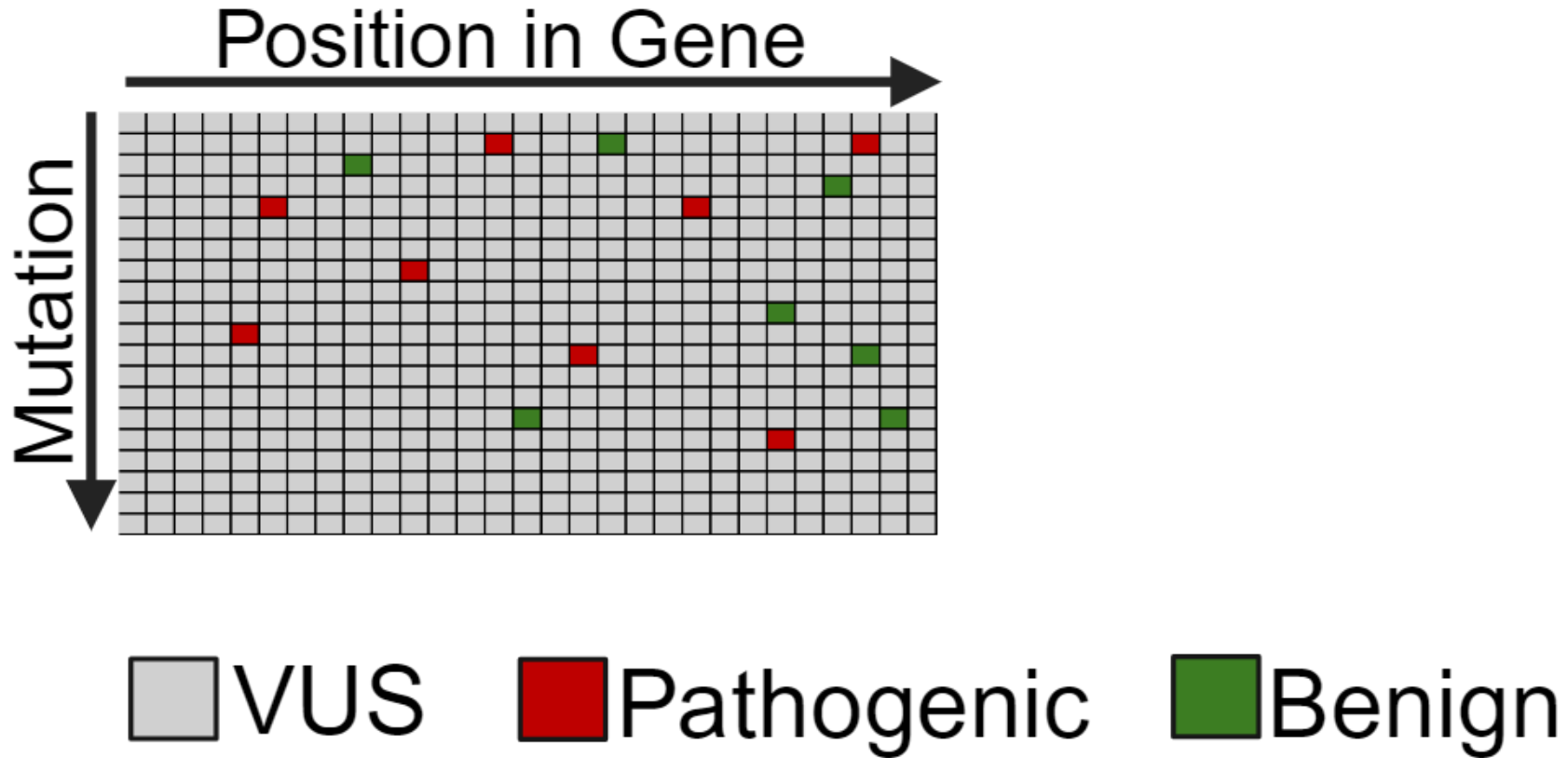


Transfer mutations into yeast
Each cell has only 1 mutation

Metabolic selection in glycerol depletes cells with LOF mutations



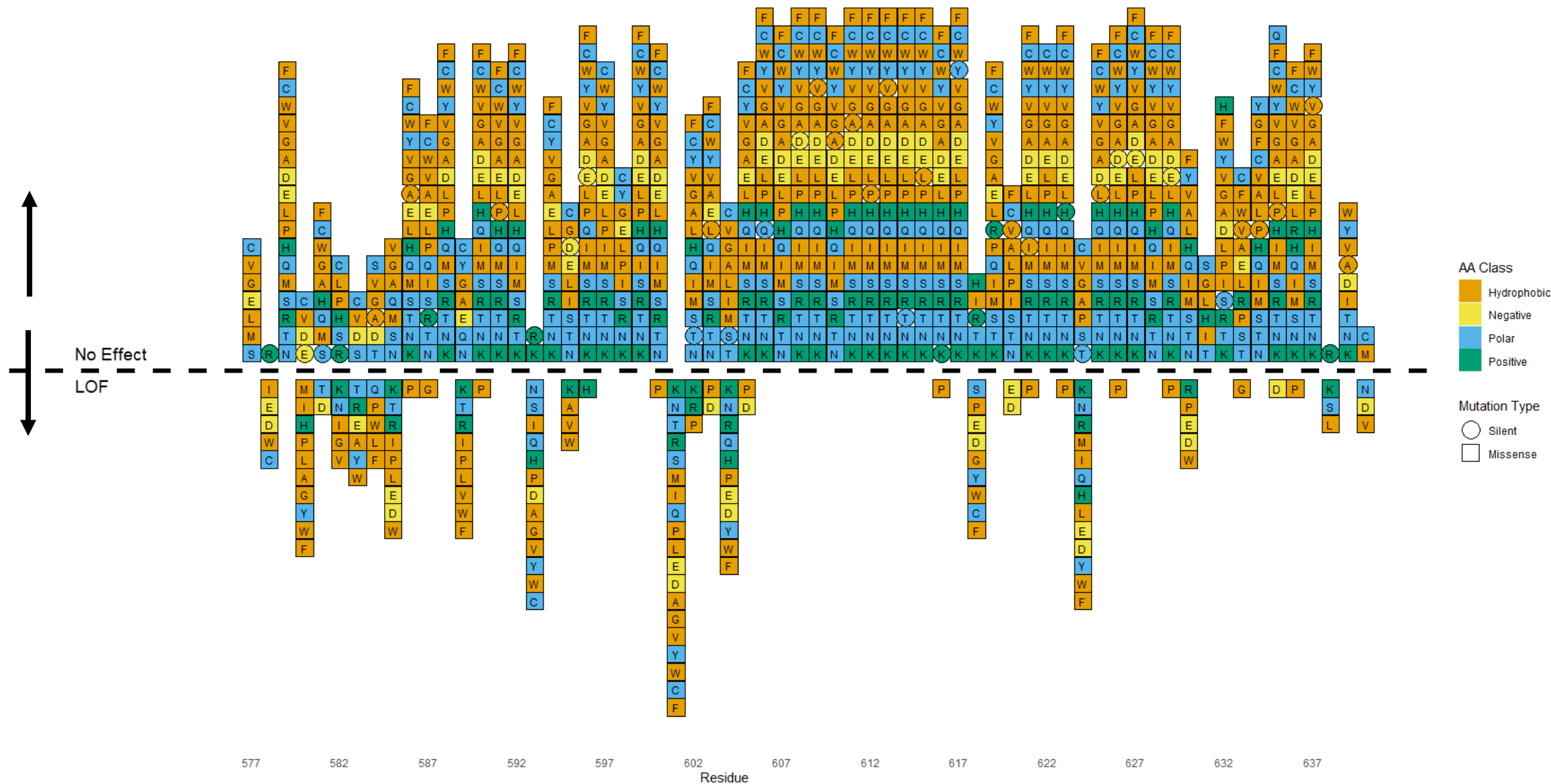
When we make all of our mutations, we will know what is pathogenic or benign



Identifying which VUS are pathogenic or benign can be an excellent diagnostic tool and can guide the development of more effective treatment.

Actual Data!

Mutation Map



Thank You!!!!

Questions?

Funding



KNIGHT
CANCER
Institute



robbinsch@ohsu.edu

heinrich@ohsu.edu



Update on GIST Research Studies

Heinrich laboratory



KNIGHT
CANCER
Institute

Deep Mutational Scanning to Identify SDH Variants Associated With GIST

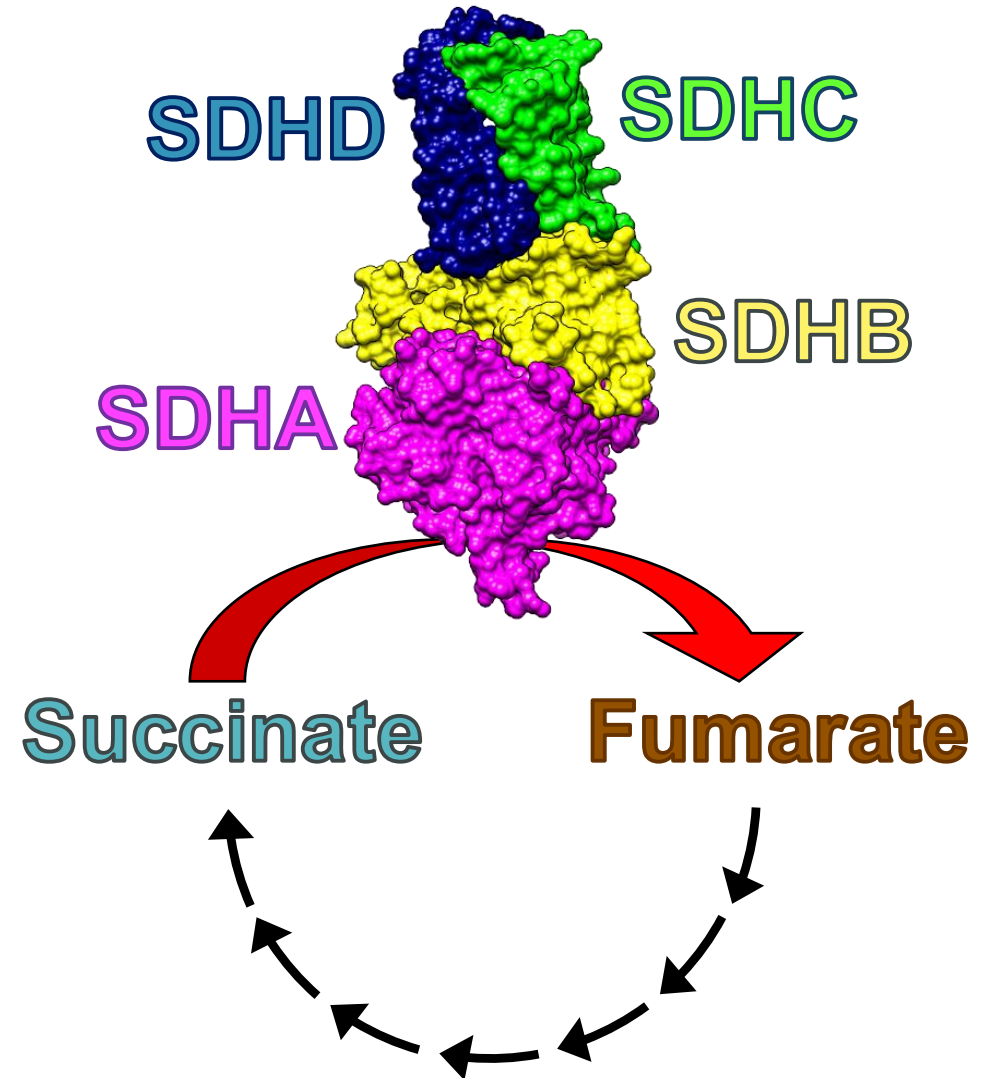
Jason Kent

Graduate Student – Heinrich Lab
Cell & Developmental Biology – OHSU

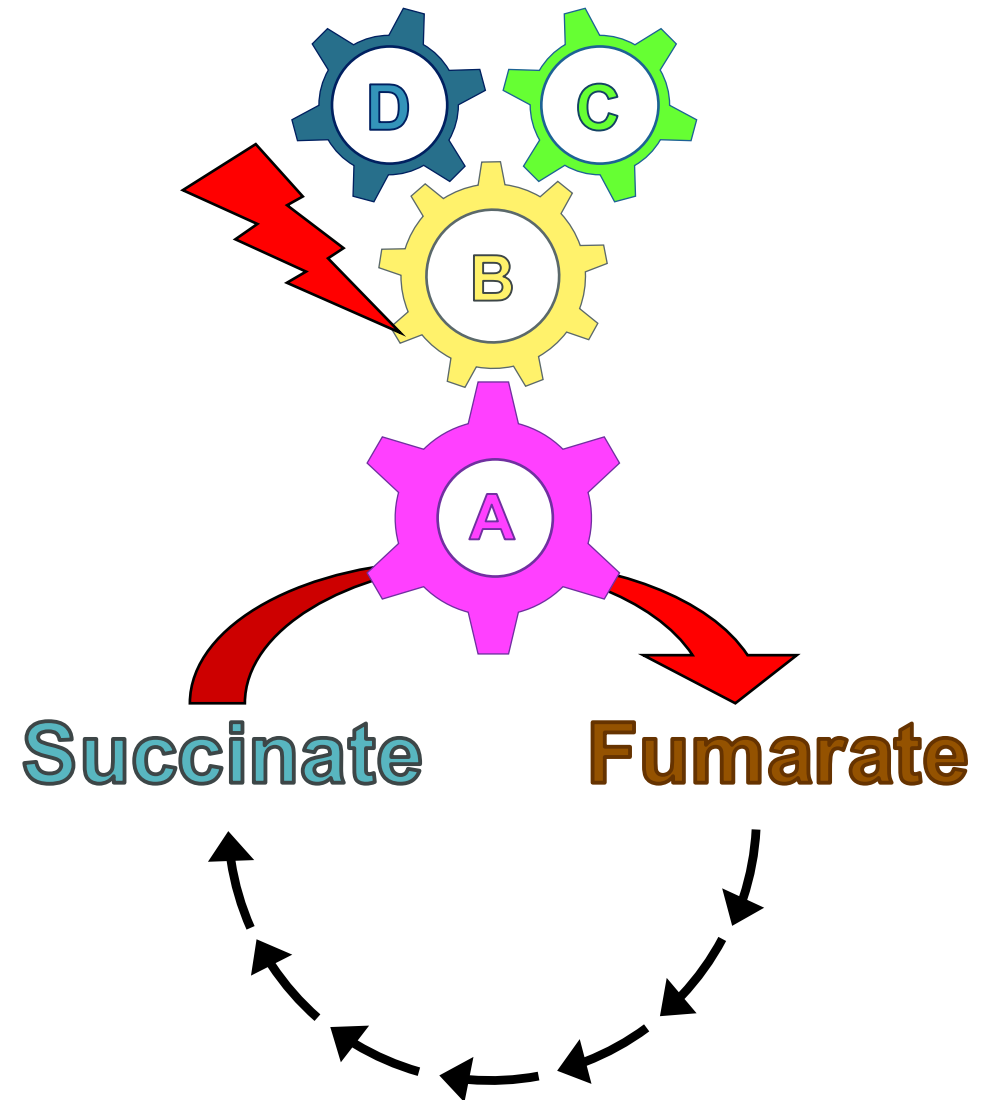
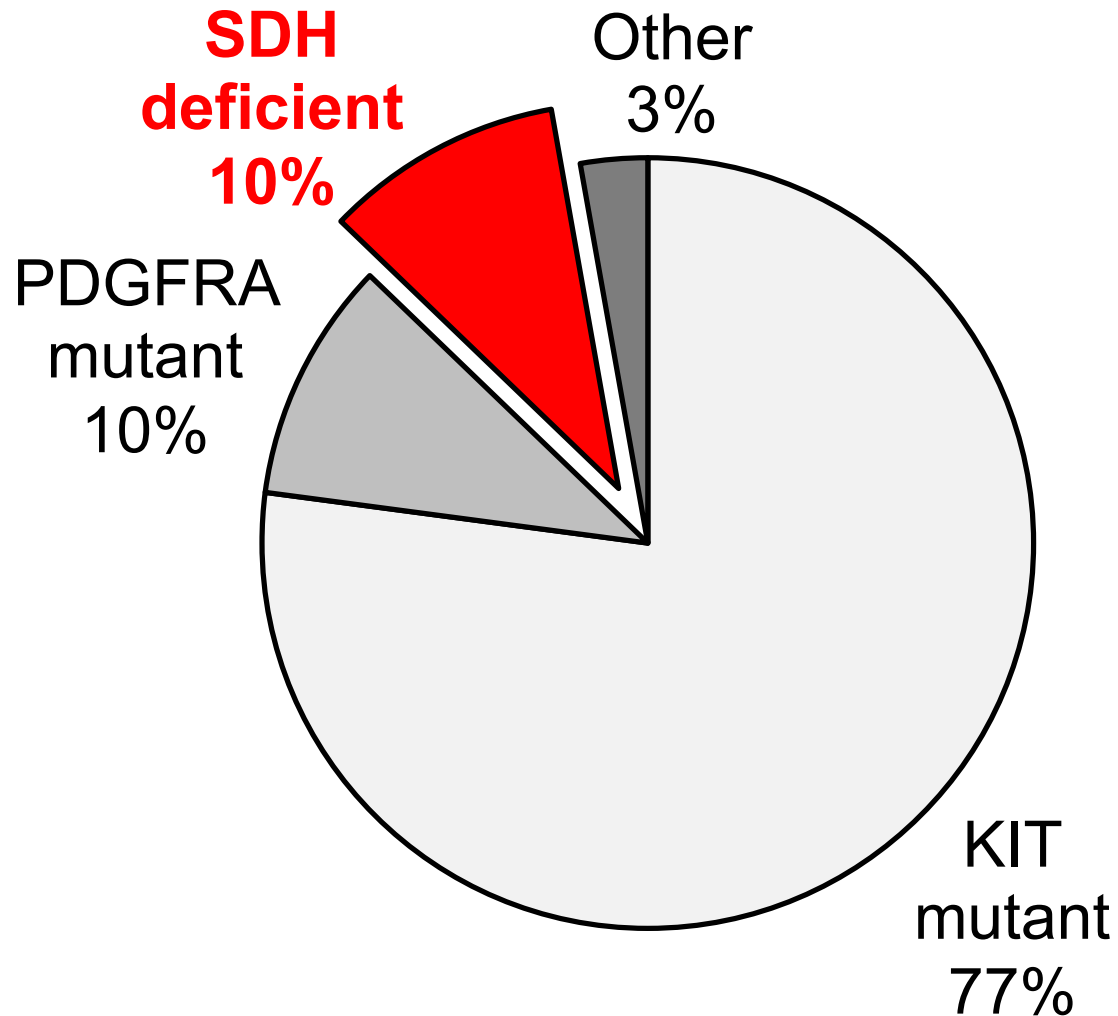


Succinate Dehydrogenase (SDH)

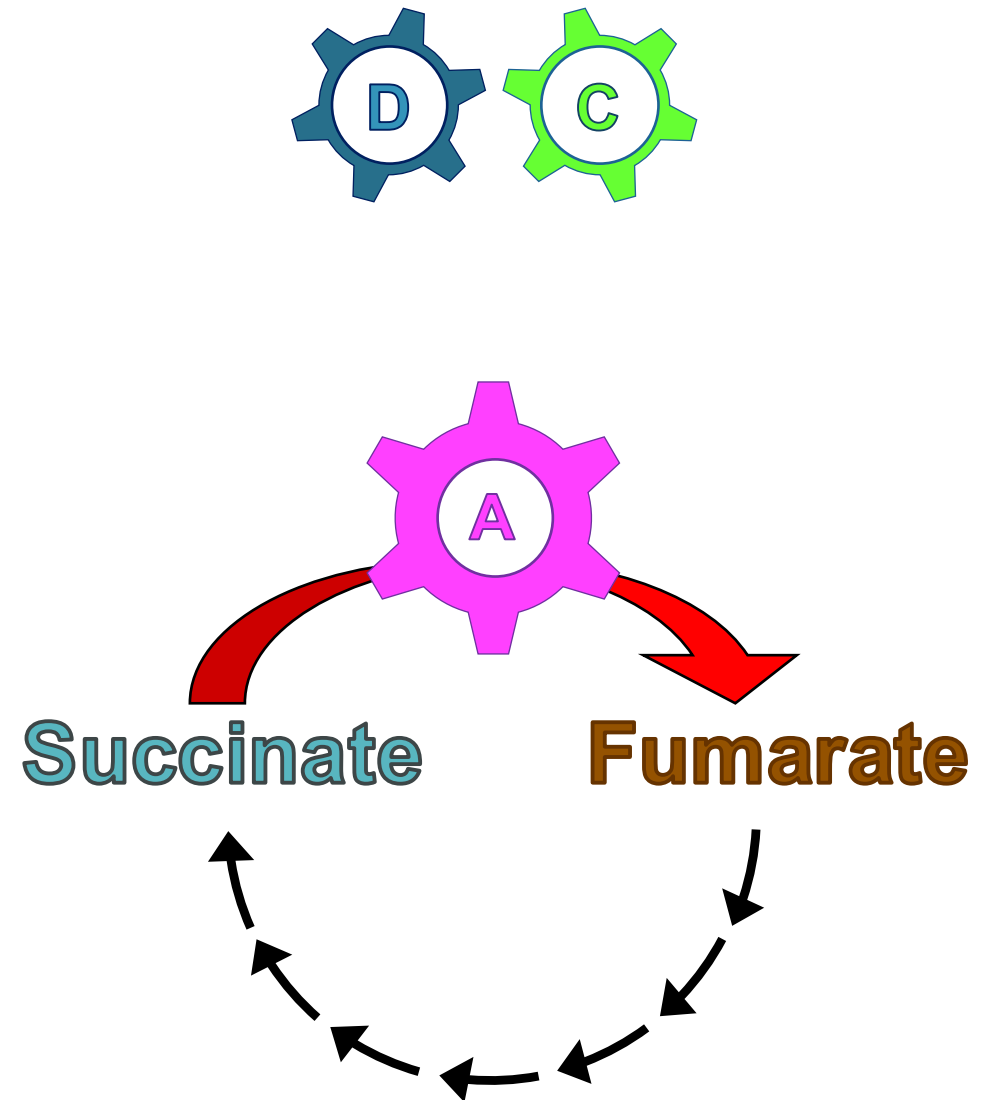
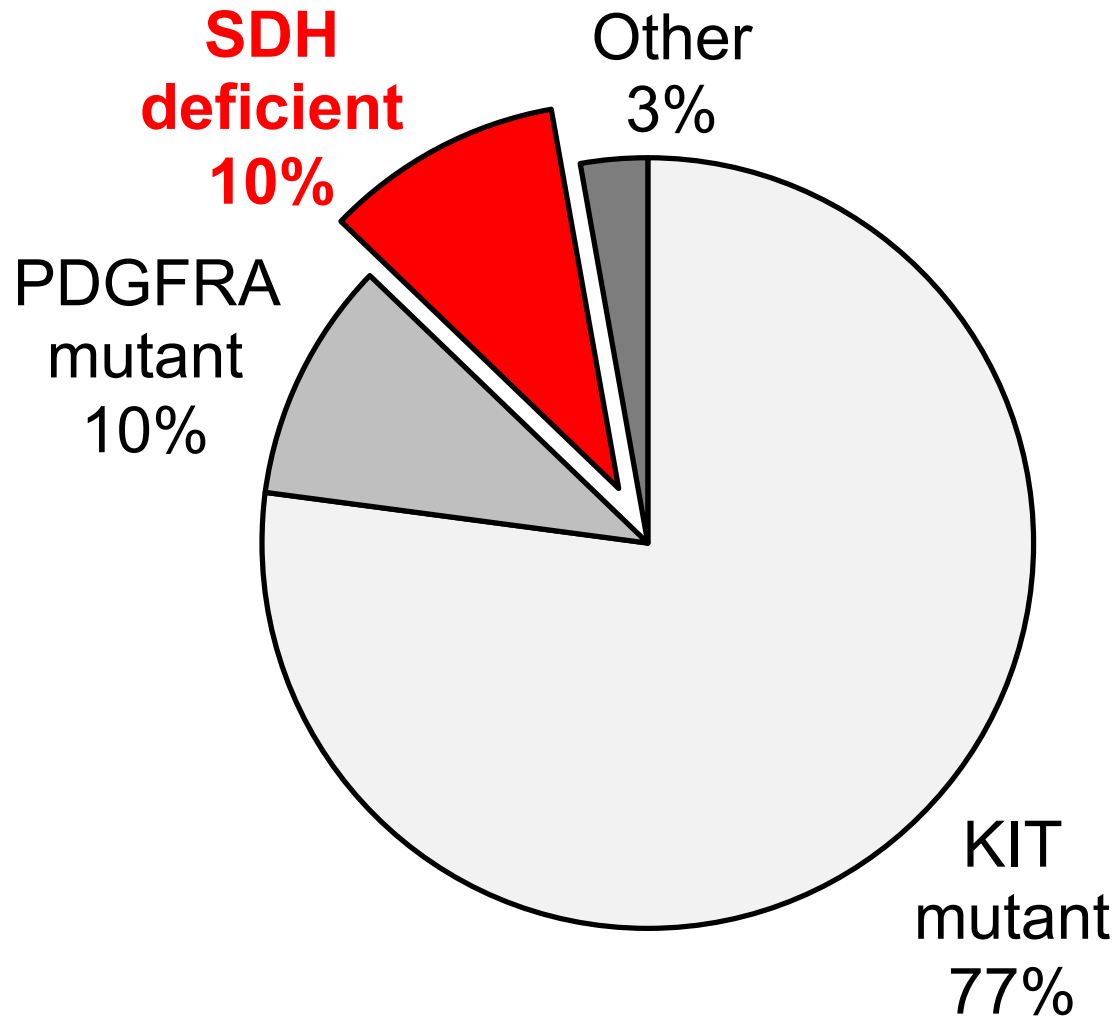
- Enzyme complex made of 4 subunits
- Located in mitochondria
- Important for normal metabolism



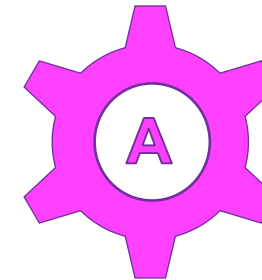
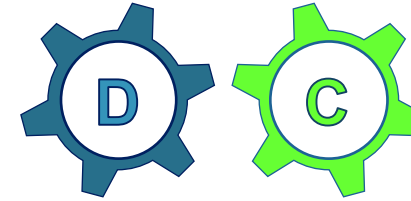
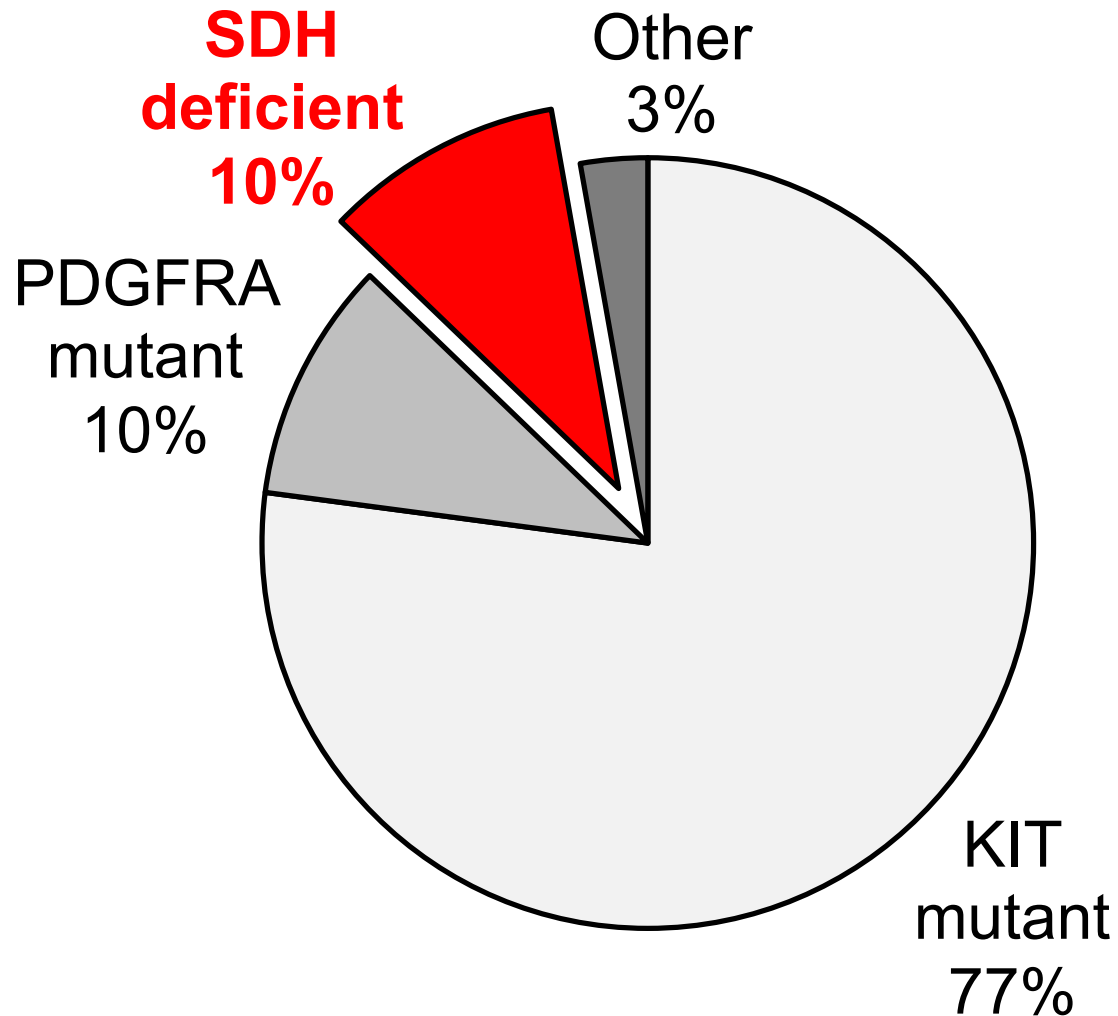
Loss of SDH function is the most common cause of non-KIT/PDGFRα related GIST



Loss of SDH function is the most common cause of non-KIT/PDGFRα related GIST



Loss of SDH function is the most common cause of non-KIT/PDGFRα related GIST



Succinate



Cancer

Mutations in DNA can affect protein function

DNA

Protein

Function

Mutations in DNA can affect protein function

Wild-type

GAG CAG GTA CCG ACG CTA GCT AAT DNA

The cat is fit.

Protein

Function



Mutations in DNA can affect protein function

Wild-type

GAG CAG GTA CCG ACG CTA GCT AAT

DNA

Loss-of-function

GAG CAG GTA CCG ACG CTA G^TT AAT

The cat is fit.

Protein

The cat is ^{fat}.



Function



Mutations in DNA can affect protein function

No-effect

GAG CAG GTA **ACG** ACG CTA GCT AAT

DNA

Loss-of-function

GAG CAG GTA CCG ACG CTA G**T**T AAT

The Cat is fit.

Protein

The cat is **fat**.



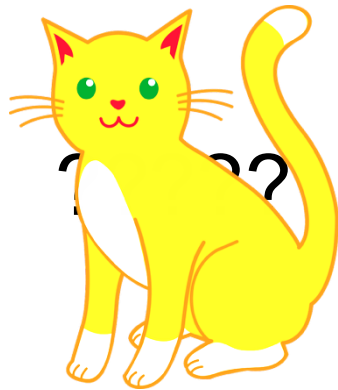
Function



The VUS Problem:

What if we don't know the language?

Pisica este în formă



Pisica este grasă



Romanian translation per Google Translate

Goal: Determine clinical significance of *SDH* VUS by characterizing the impact on *SDH* function

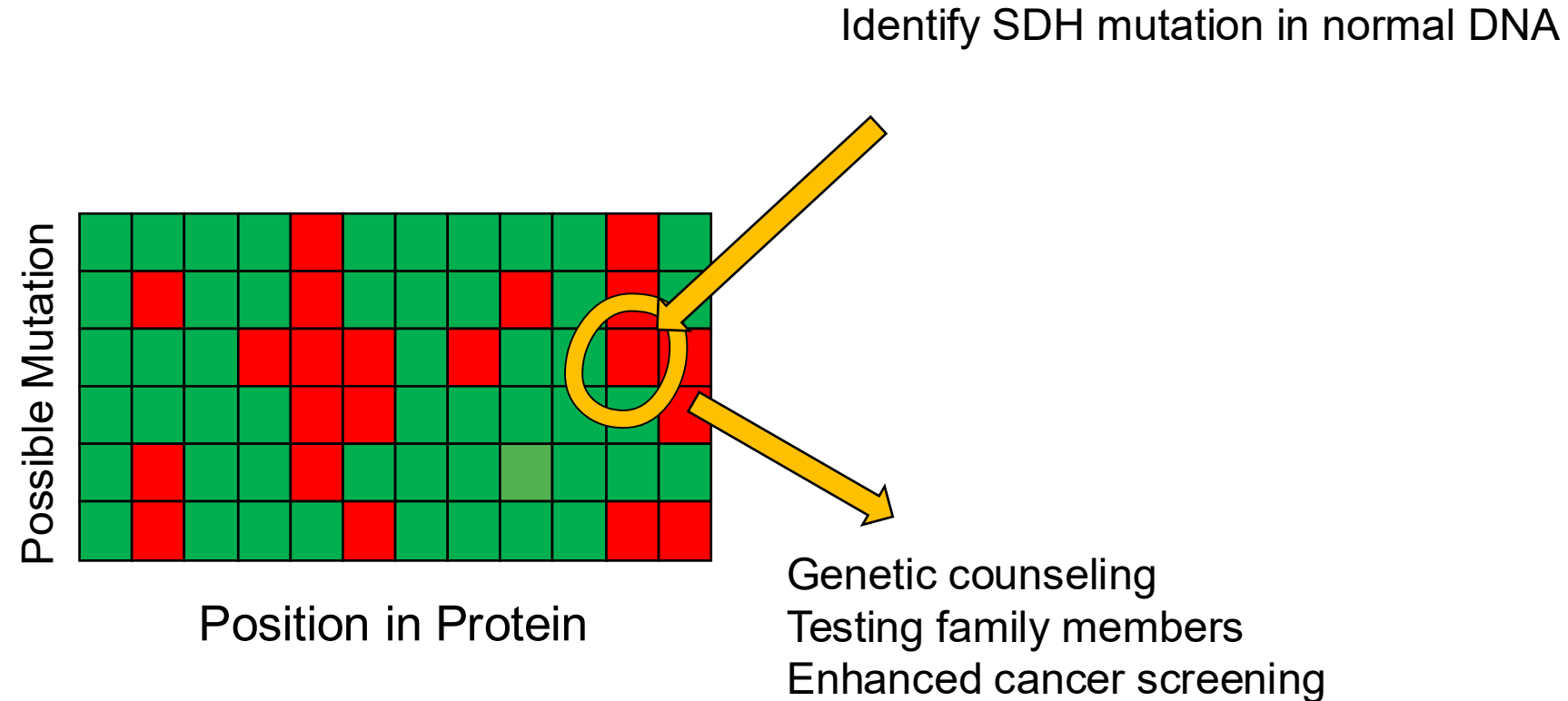
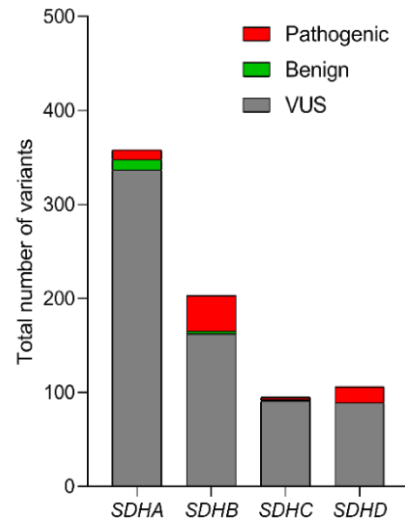
^v all possible



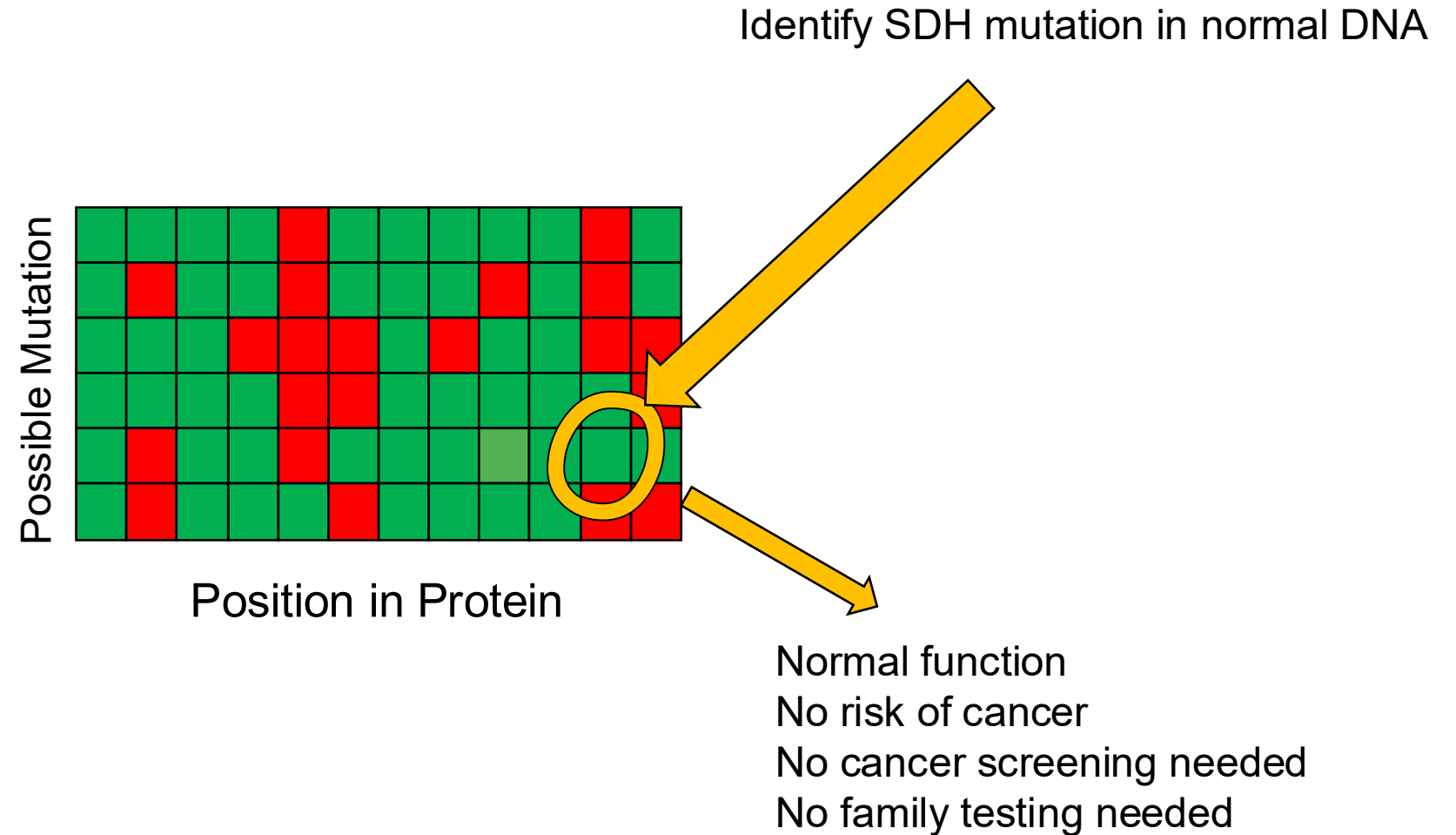
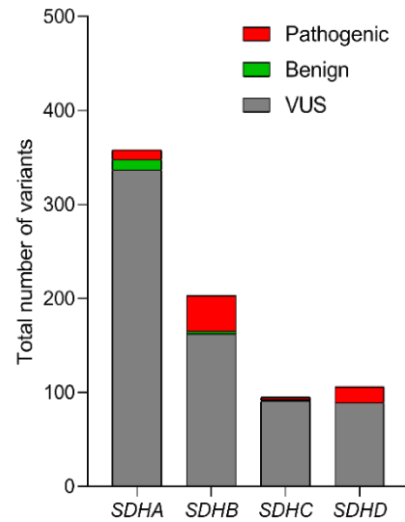
	Amino Acids	Possible Variants
SDHA	664	13,280
SDHB	280	5,600
SDHC	169	3,380
SDHD	159	3,180

Total: **25,440**

Our goal: Create “Encyclopedia” of clinical significance for all SDH mutations



Our goal: Create “Encyclopedia” of clinical significance for all SDH mutations

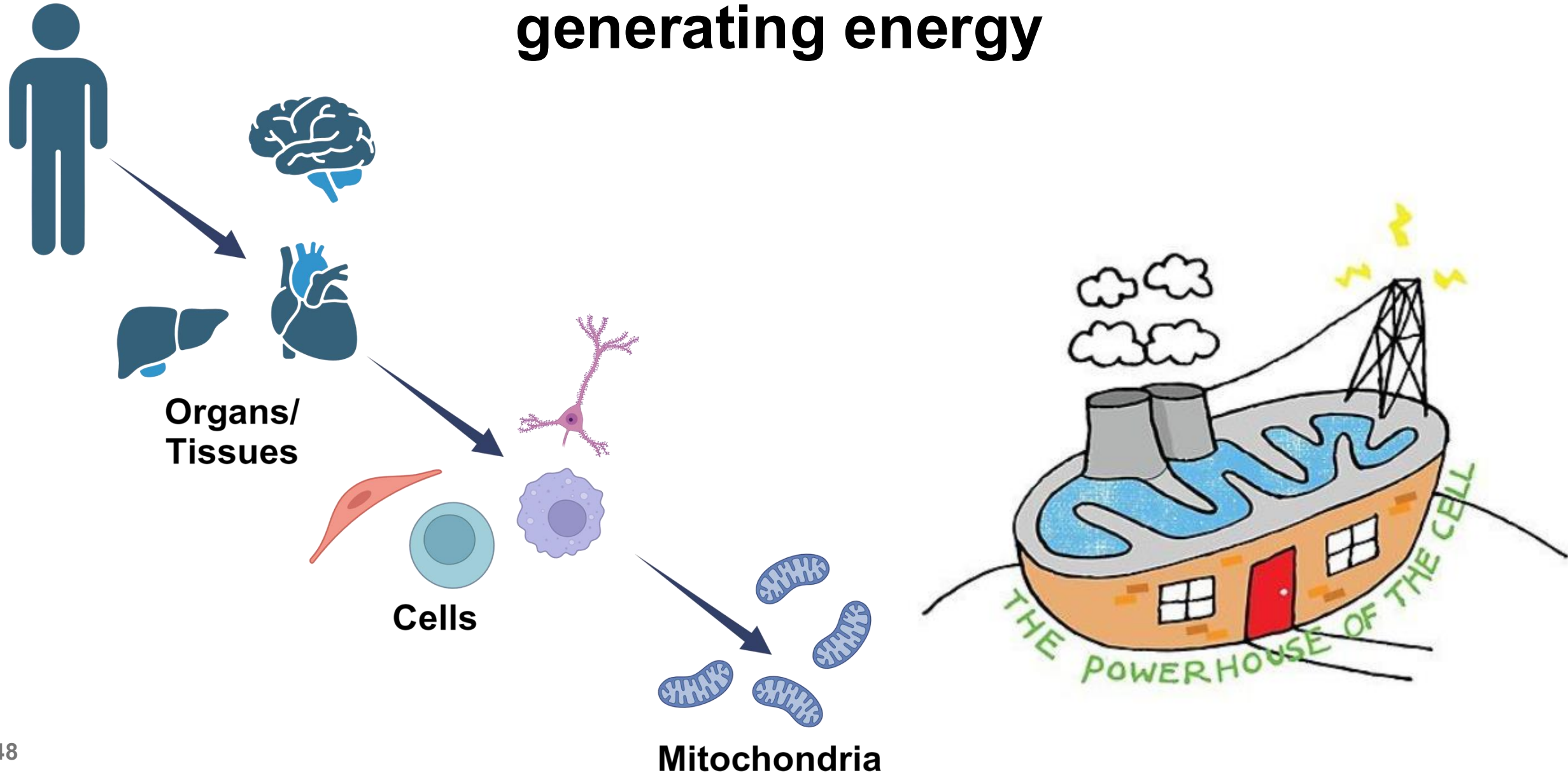


It takes a village, or a small city,

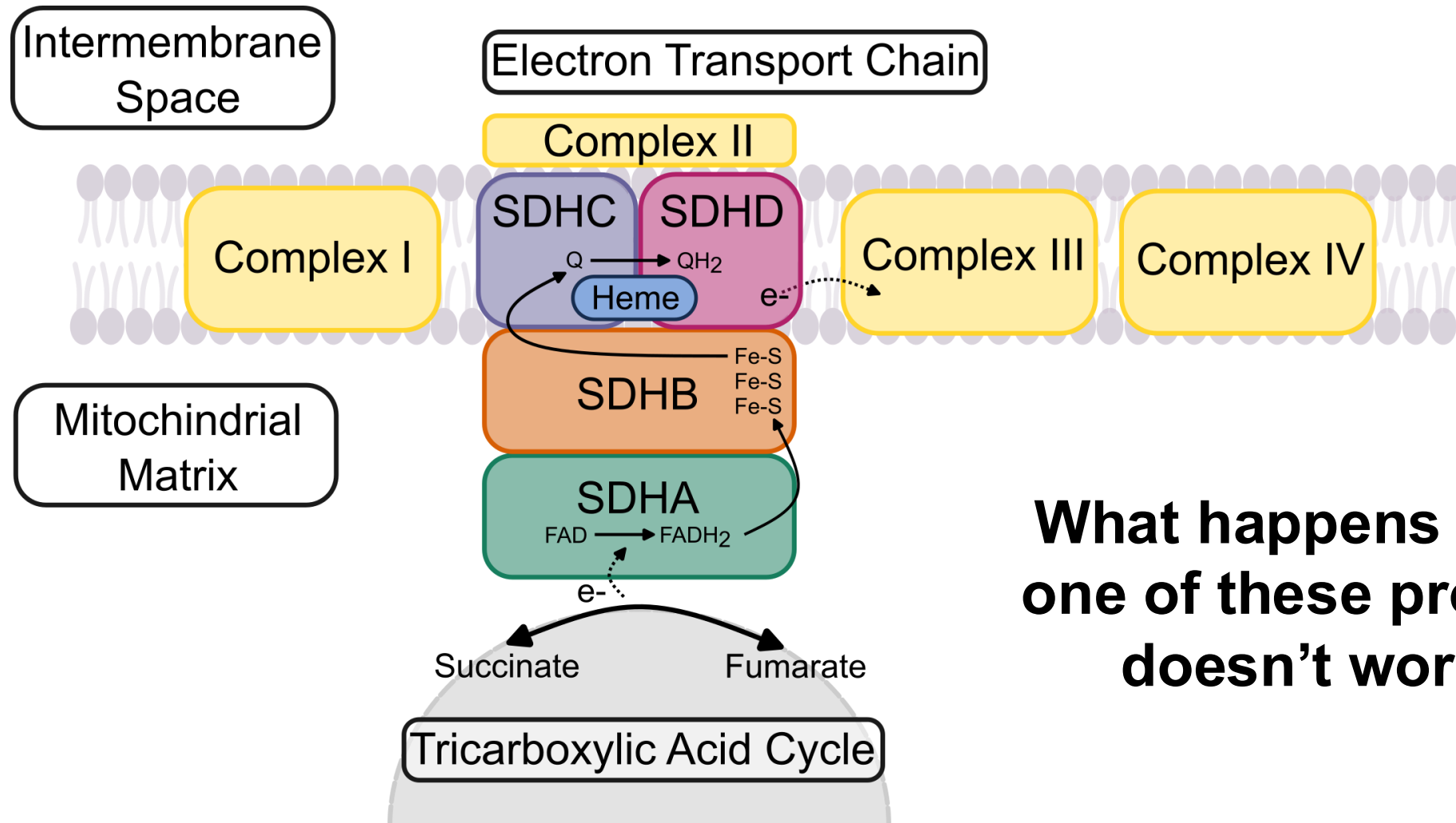


Sally Ison

Succinate DeHydrogenase plays a critical role in generating energy

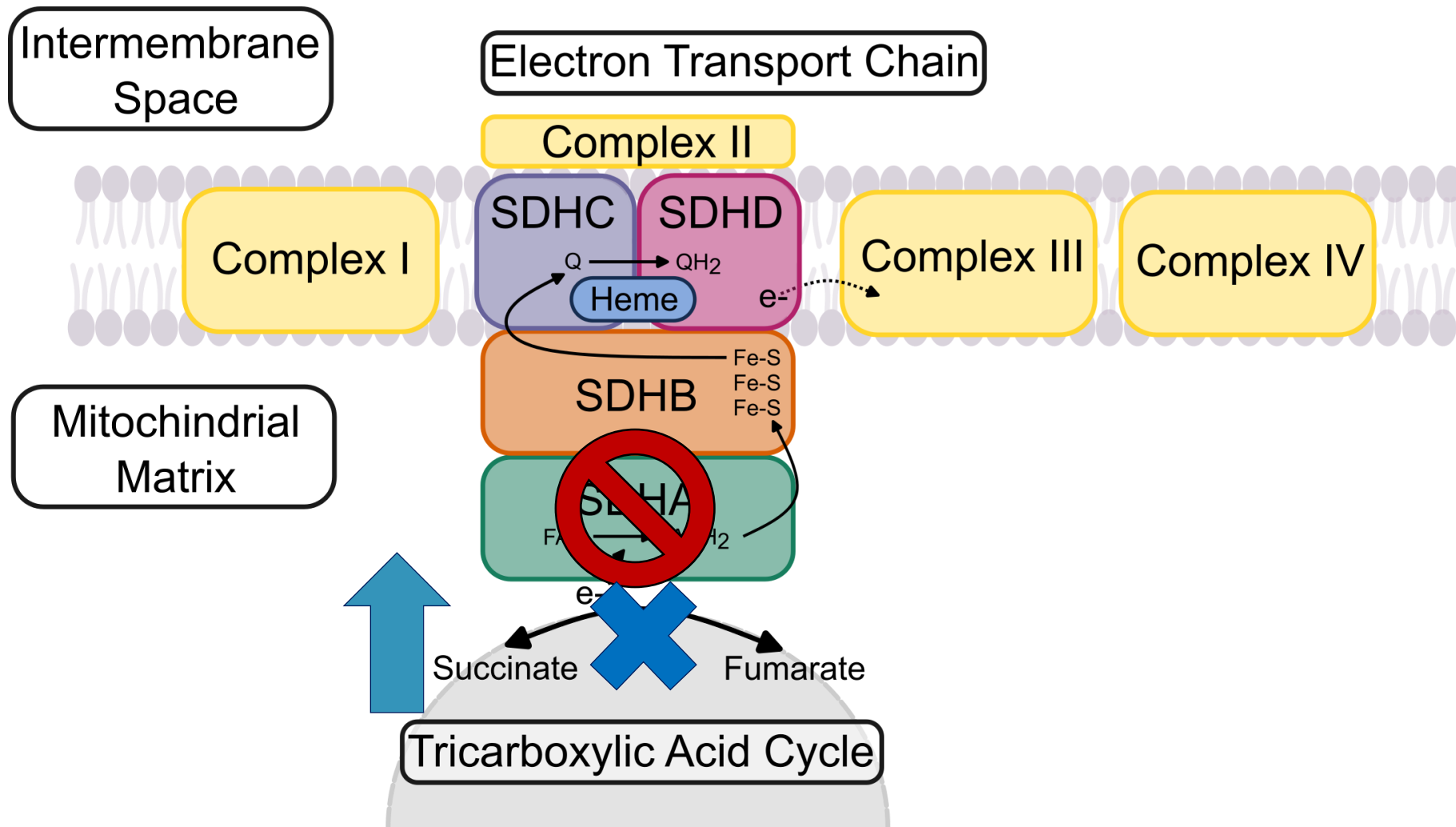


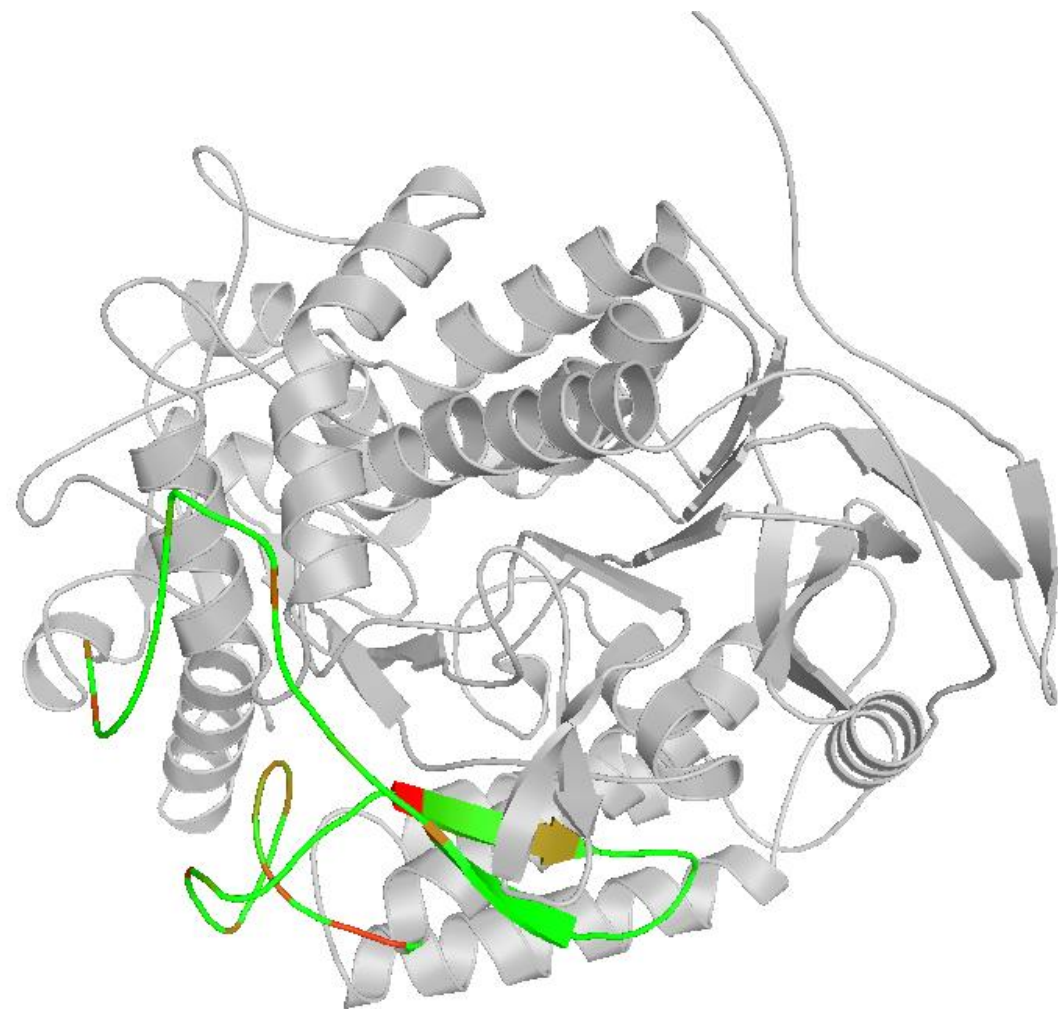
Succinate DeHydrogenase plays a critical role in generating energy and cellular metabolism



What happens when one of these proteins doesn't work?

Mutations in SDH genes can mess up this process





LIFEFEST2026

Nashville



Thank you to our sponsors for supporting our mission to present high-quality education, engagement & support to the GIST community!



SHORLA ONCOLOGY
THE HEART OF INNOVATION

