

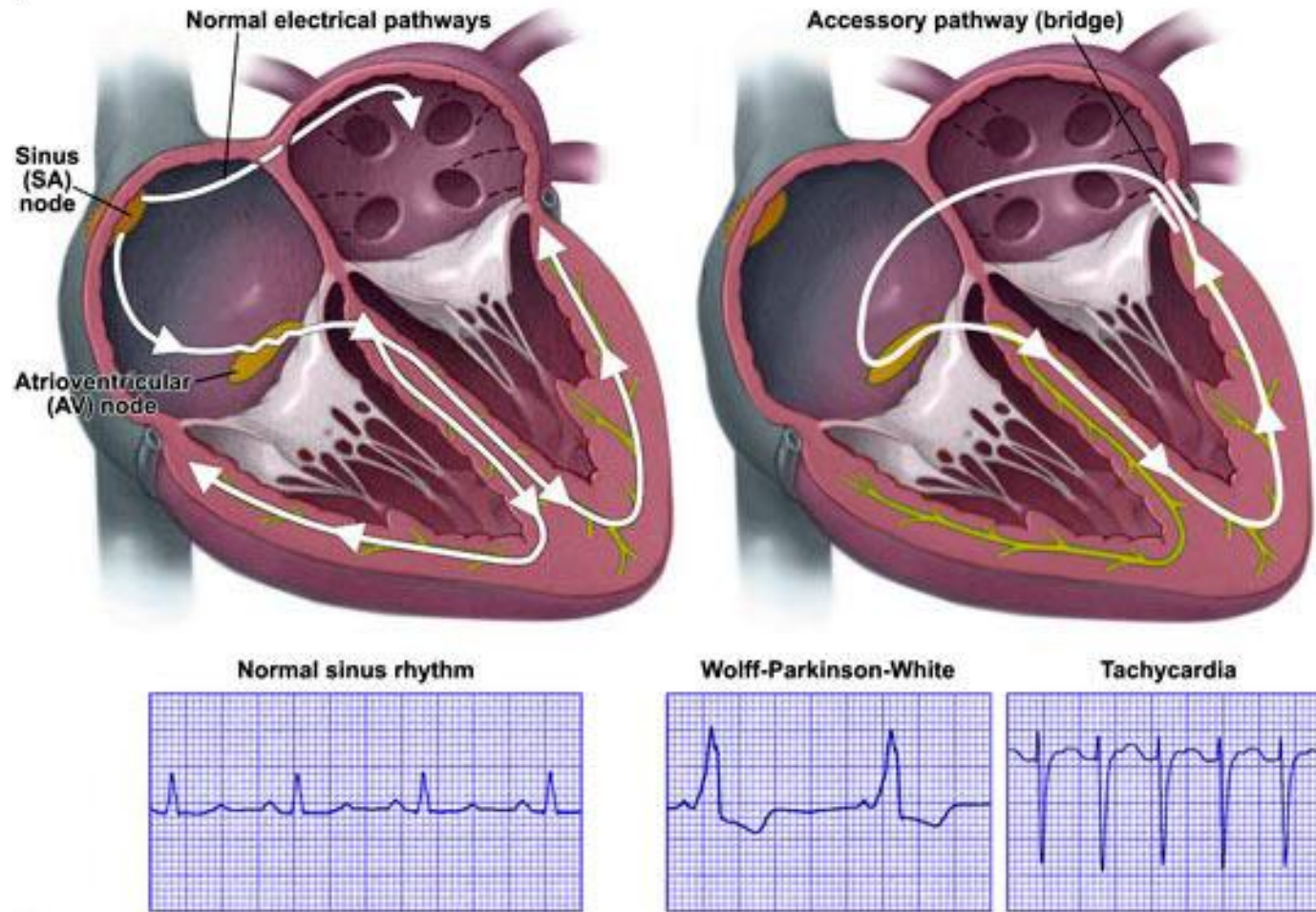


Wolff-Parkinson-White Syndrome and PRKAG2

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What causes Wolff-Parkinson-White?

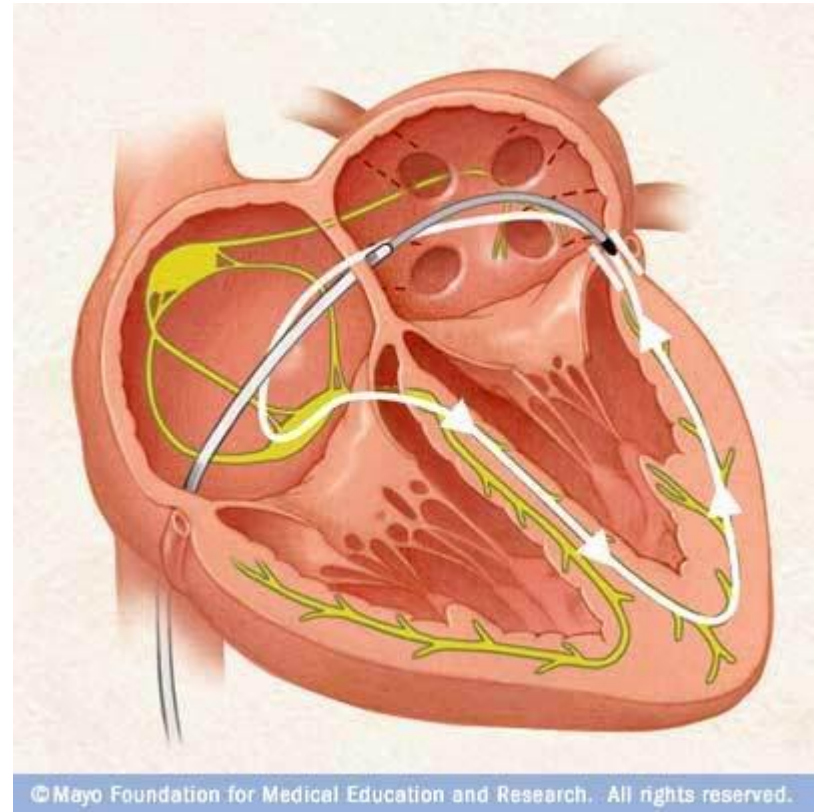


Current Disease Treatment

Medications = Adenosine,
and antiarrhythmic drugs

Electric cardioversion therapy

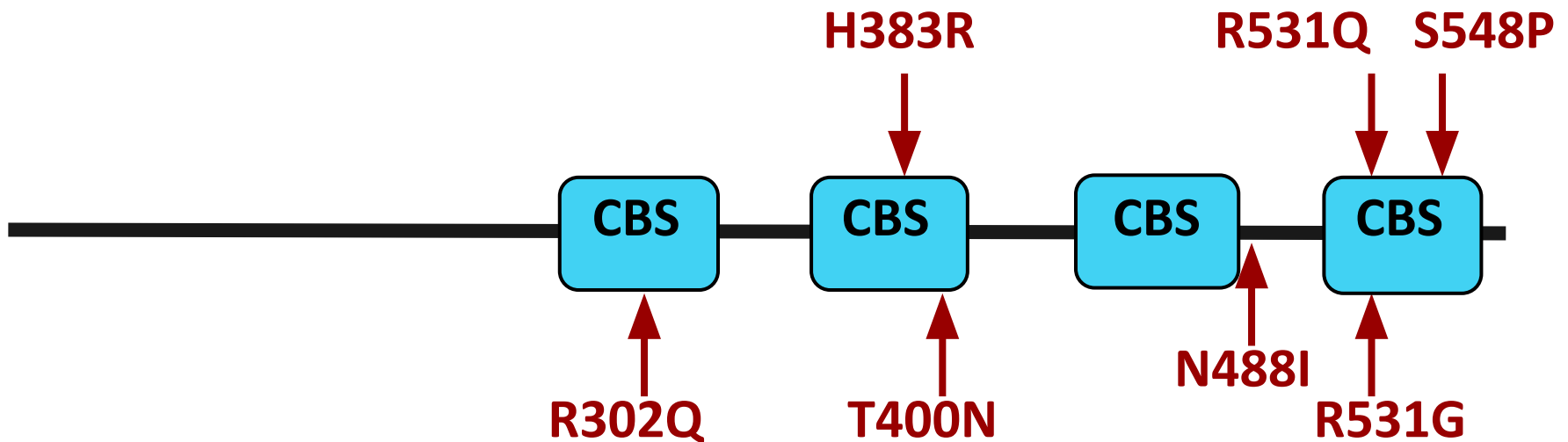
Radiofrequency catheter
ablation



Missense Mutations in PRKAG2

PRKAG2 = Protein Kinase AMP-Activated Gamma 2

Mutation alters activity of 5'-AMP-activated protein kinase subunit gamma 2 protein (**AAKG2**)



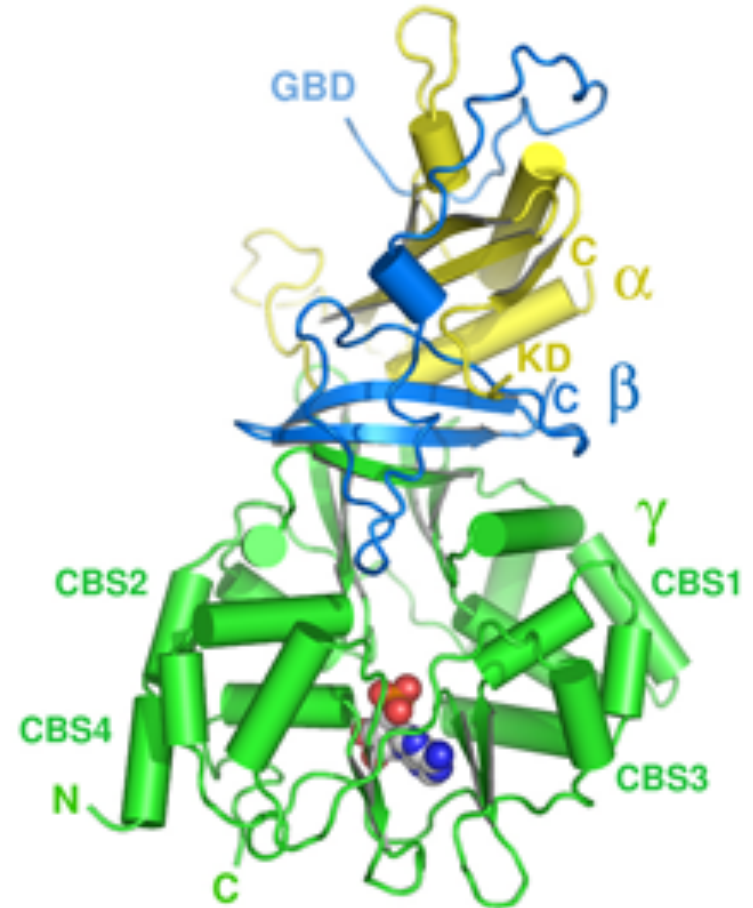
AAKG₂ Protein

Heterotrimeric (AMPK)

- Catalytic subunit = alpha
- Regulatory subunits = beta and gamma

Gamma Subunit

- Contains four CBS domains



PRKAG2 Gene Ontology

Biological Processes

ATP Biosynthesis Process
Carnitine Shuttle
Cell Cycle Arrest
Cellular Lipid Metabolic Process
Fatty Acid Biosynthetic Process
Glycogen Metabolic Process
Insulin Receptor Signaling
Pathway
Intracellular Protein Kinase
Cascade
Regulation of Protein Kinase
Activity
Regulation of Fatty Acid
Oxidation
Regulation of Glucose Import
Regulation of Glycolysis

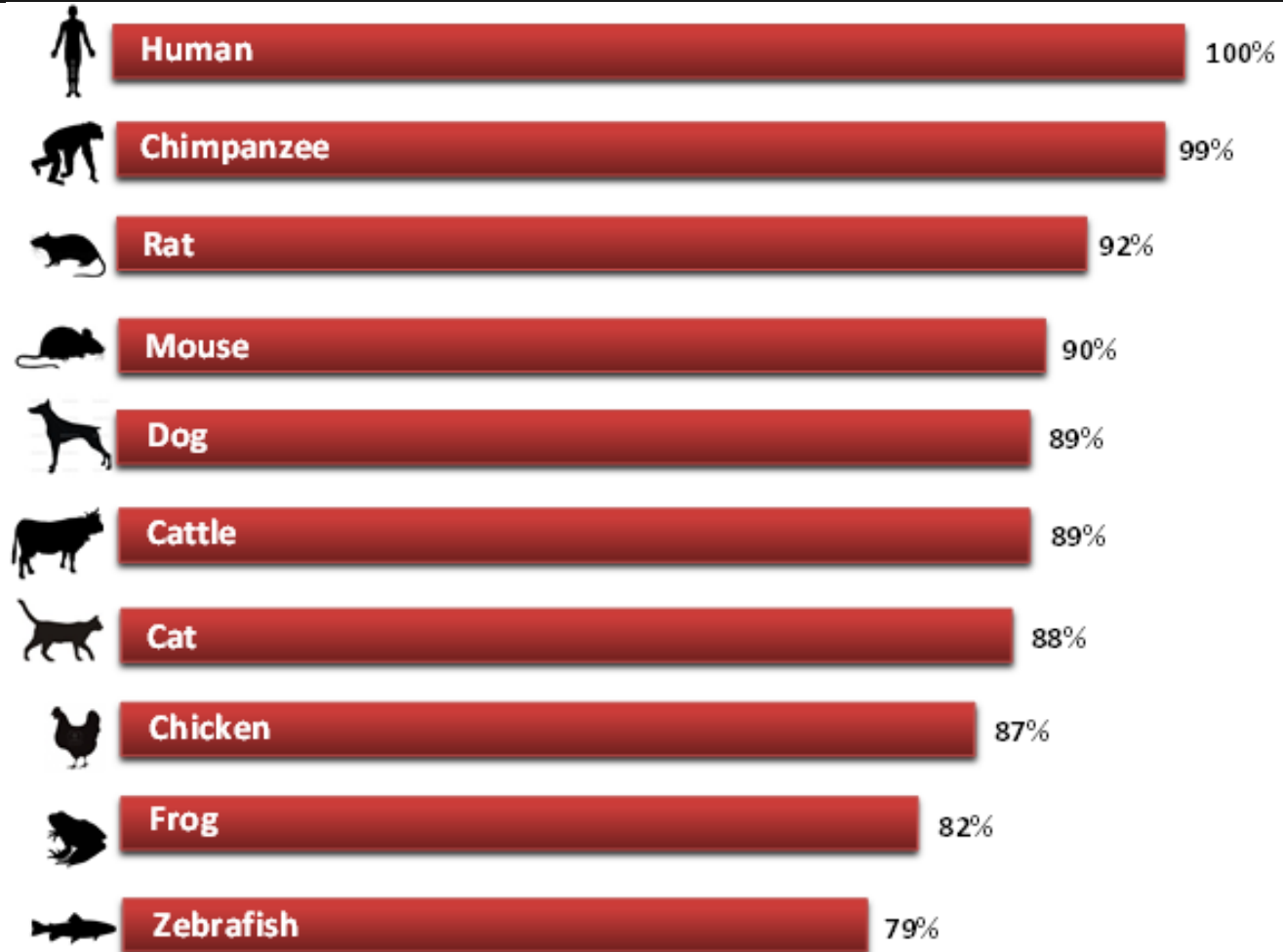
Molecular Function

ADP Binding
ATP Binding
cAMP-Dependent Protein
Kinase Inhibitor Activity
cAMP-Dependent Protein
Kinase Regulator Activity
Phosphorylase Kinase
Regulator Activity
Protein Kinase Activator
Activity
Protein Kinase Binding

Cellular Component

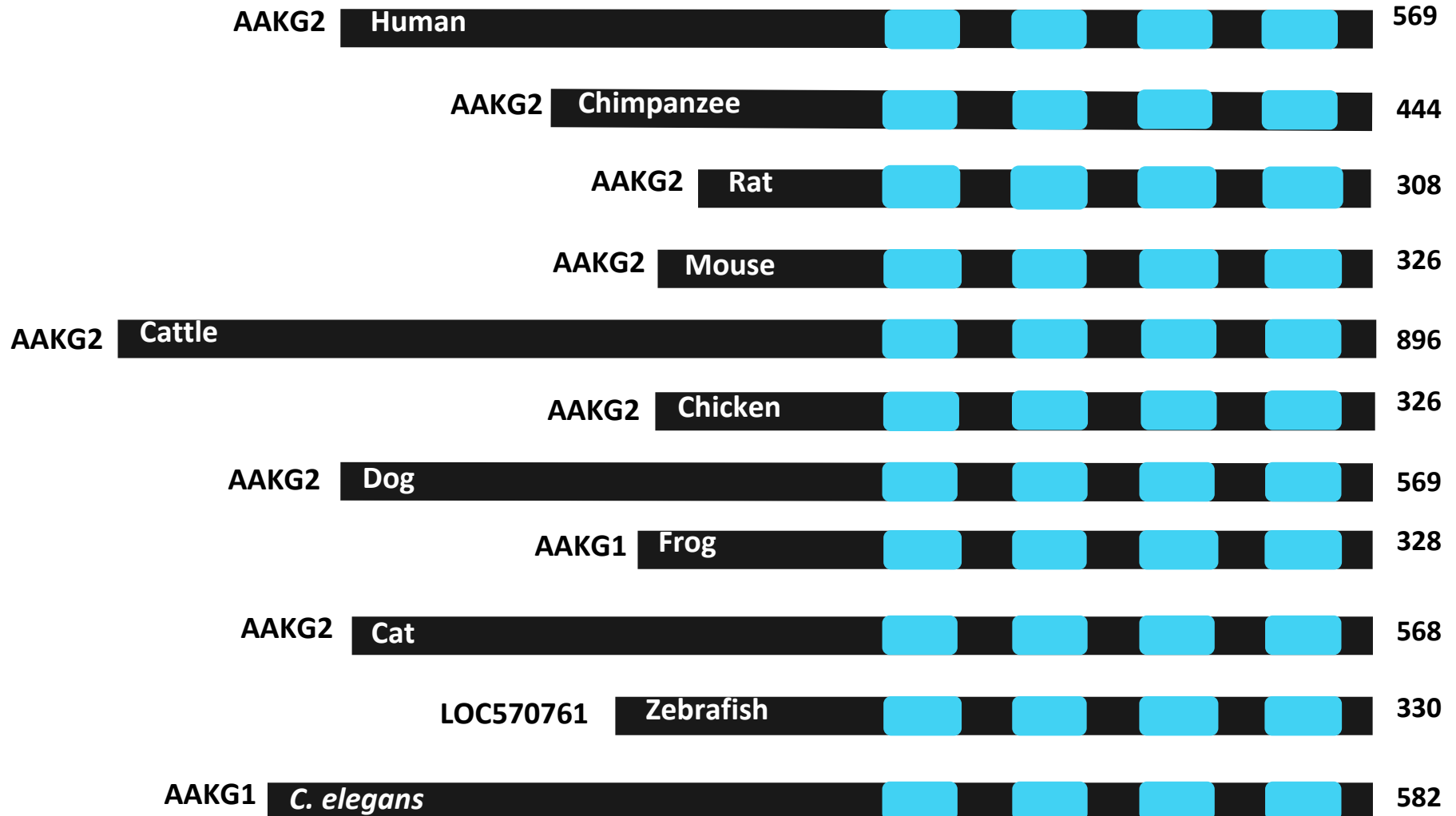
AMP-Activated Protein Kinase
Complex
Cytosol
Nucleoplasm

PRKAG2 Highly Conserved



AAKG2 Protein Homologs

 = CBS



CBS Domains



The diagram consists of a horizontal black bar representing a protein. On the right side of the bar, four light blue rounded rectangular boxes are arranged in a row, each containing the text 'CBS' in black. This represents a tandem array of four CBS domains.

CBS

CBS

CBS

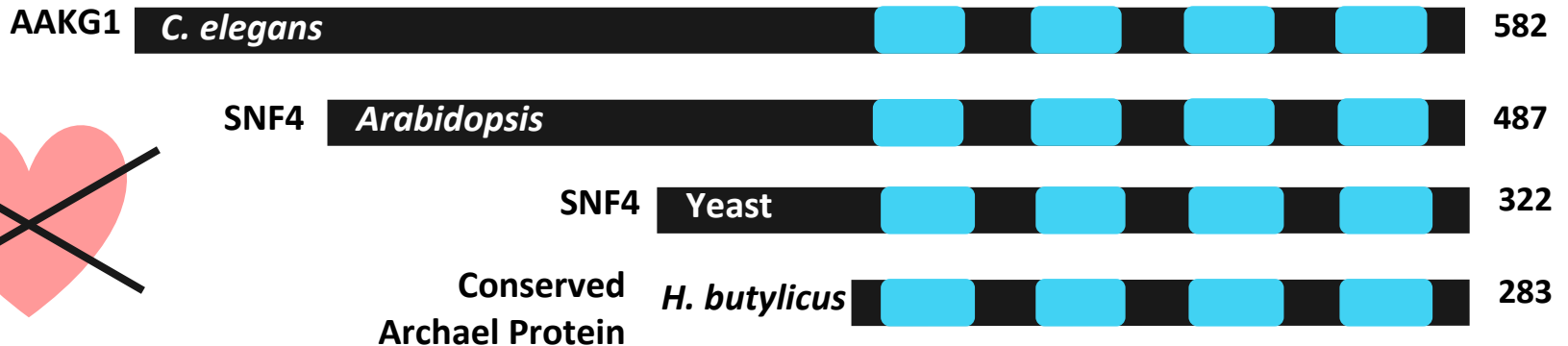
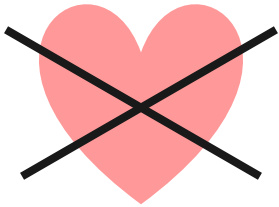
CBS

Highly evolutionarily conserved

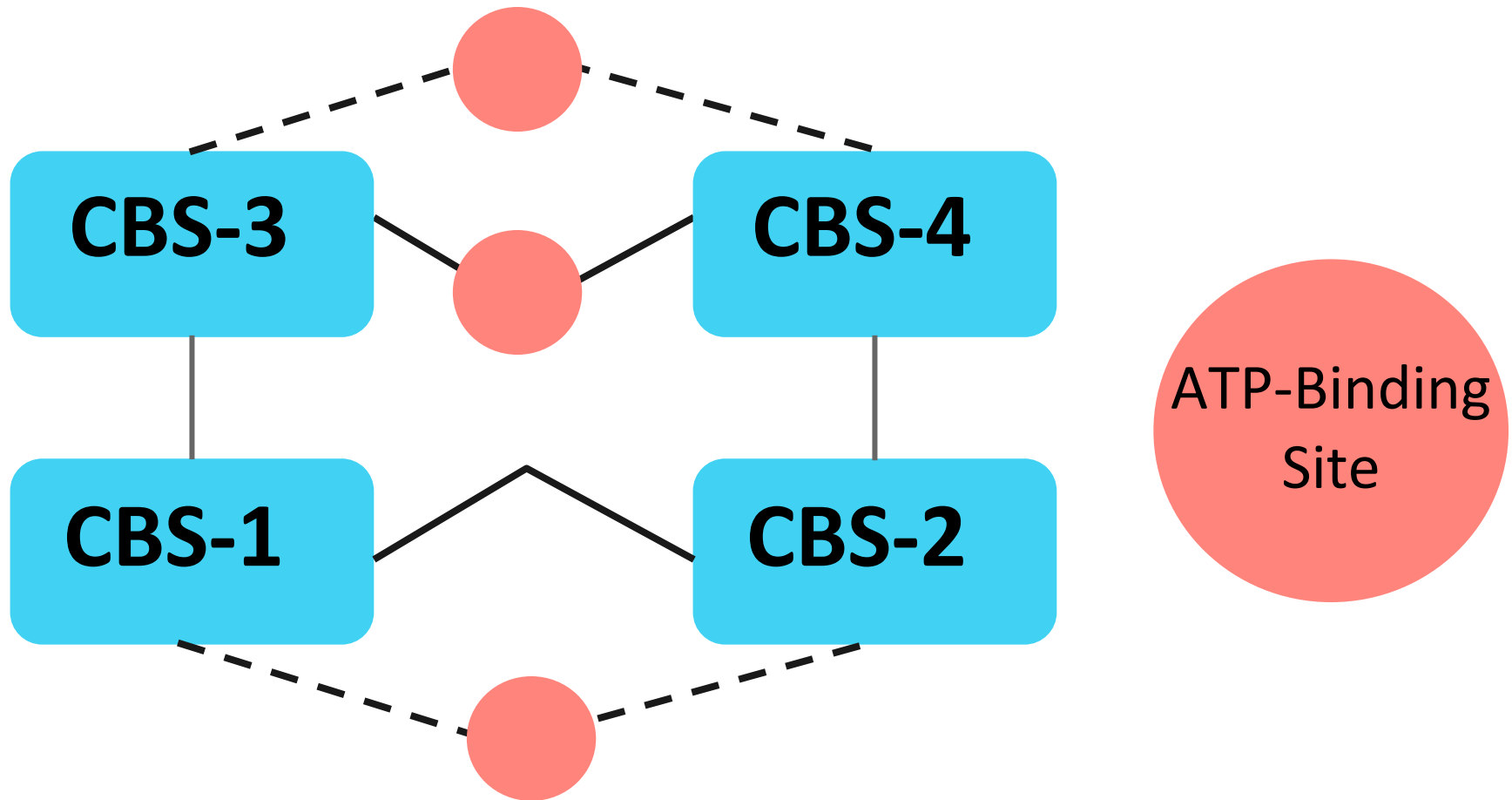
Often come in tandem pairs

Restore cellular **ATP** balance during metabolic stress

Heart vs. No Heart



Where are ATP-binding sites in CBS domains?

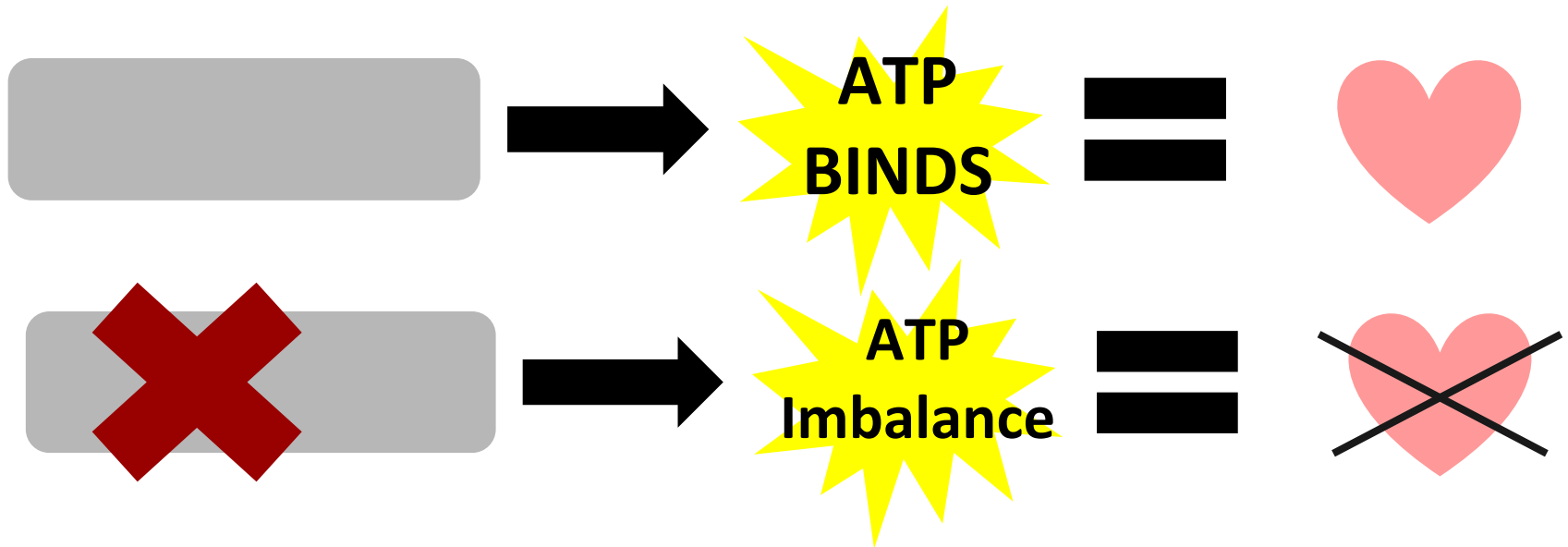


Are these ATP-binding sites important in **PRKAG2** missense mutations?

Human Mutation	Reduce AMP/ATP Binding	Structurally Close (Interacting)
R302Q	YES	YES (YES)
H383R	YES	YES (YES)
T400N	YES	YES (YES)
N488I	NO	NO (NO)
R531Q	YES	YES (YES)
R531G	YES	YES (YES)
S548P	No Data	YES (YES)

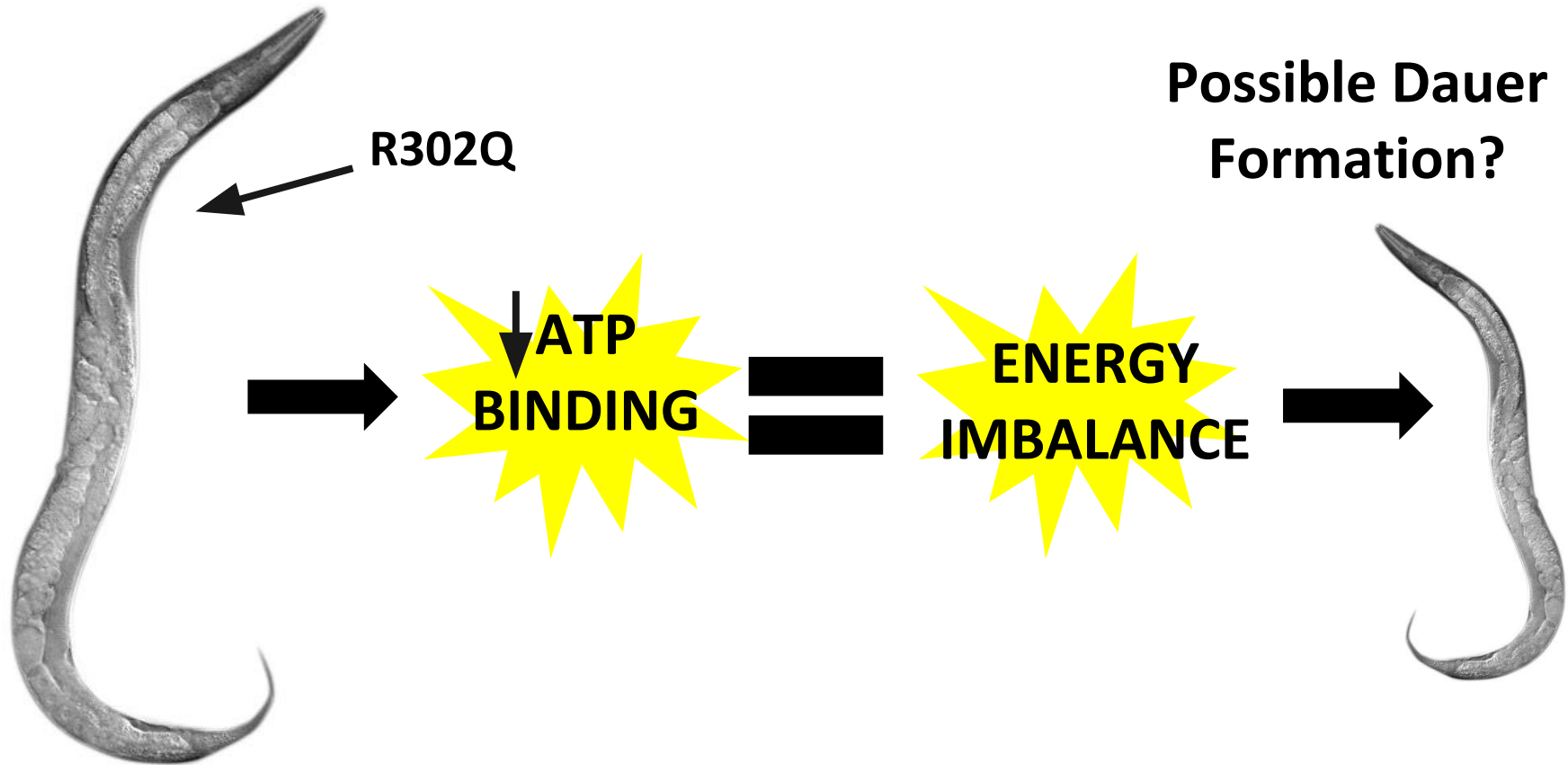
Xiao, B., Heath, R., Saiu, P., et al. (2007) Structural basis for AMP binding to mammalian AMP-activated protein kinase. *Nature* 449, 496- 500

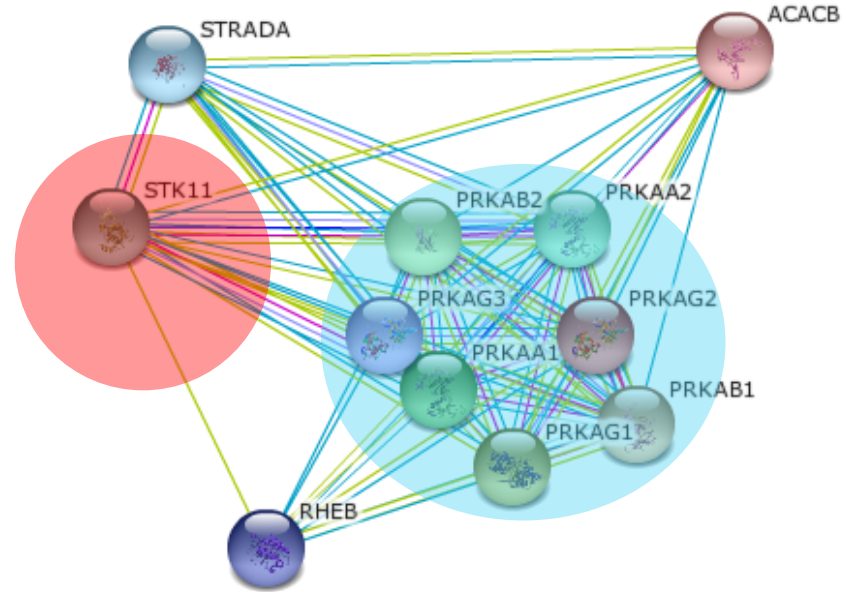
Will these **missense mutations** have the same effect in a model organism without a heart?



Without Heart???

Hypothesis: Dauer formation would be observed if human missense mutation introduced into heartless *C. elegans*.





What is STK11/LKB1?

Protein Kinase

Serine/Threonine 11

Role in G1 cell cycle arrest

Tumor suppressor

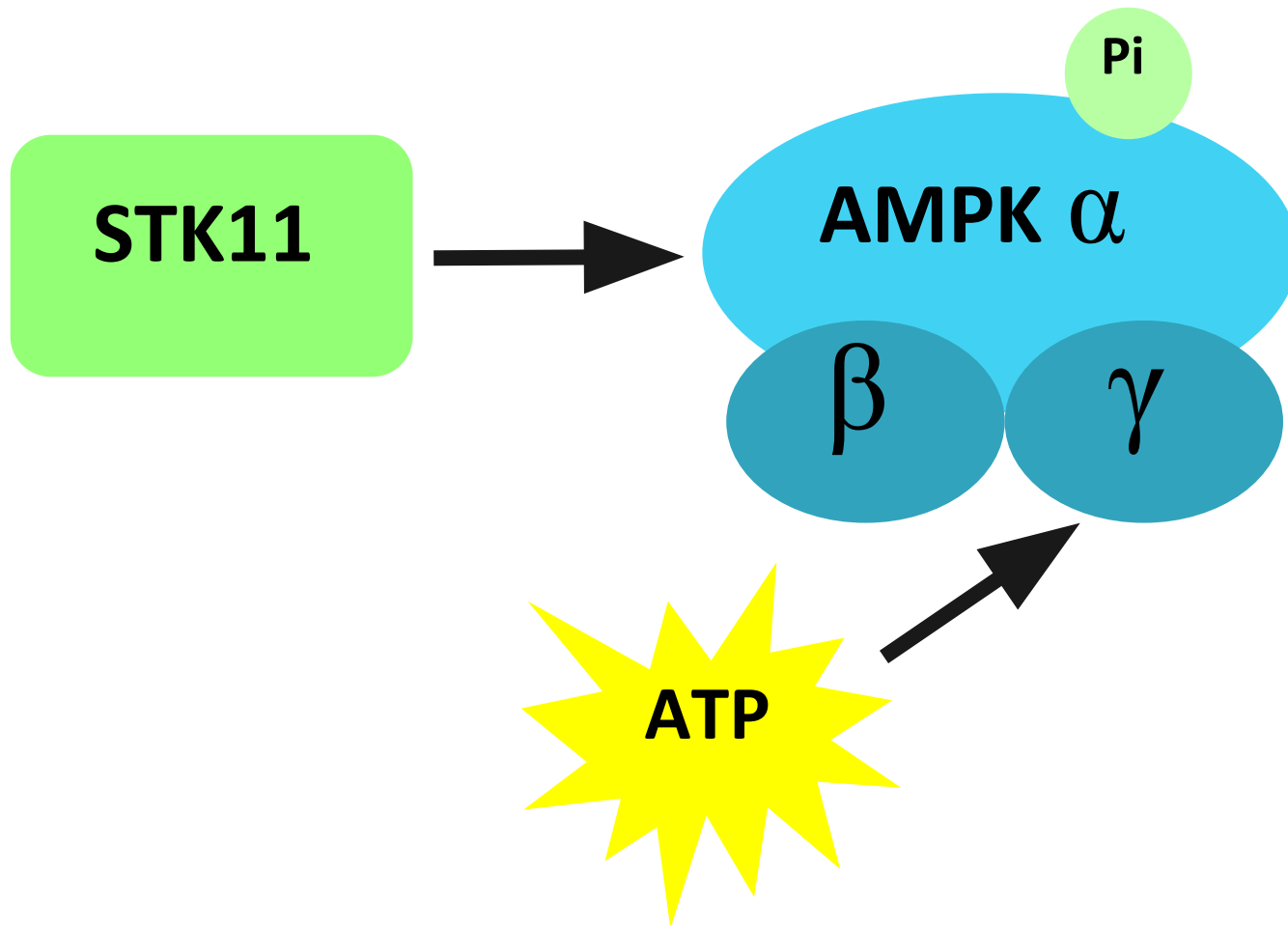
Mutation causes Peutz-Jeghers syndrome

Activates AMPK-related proteins by **phosphorylation**

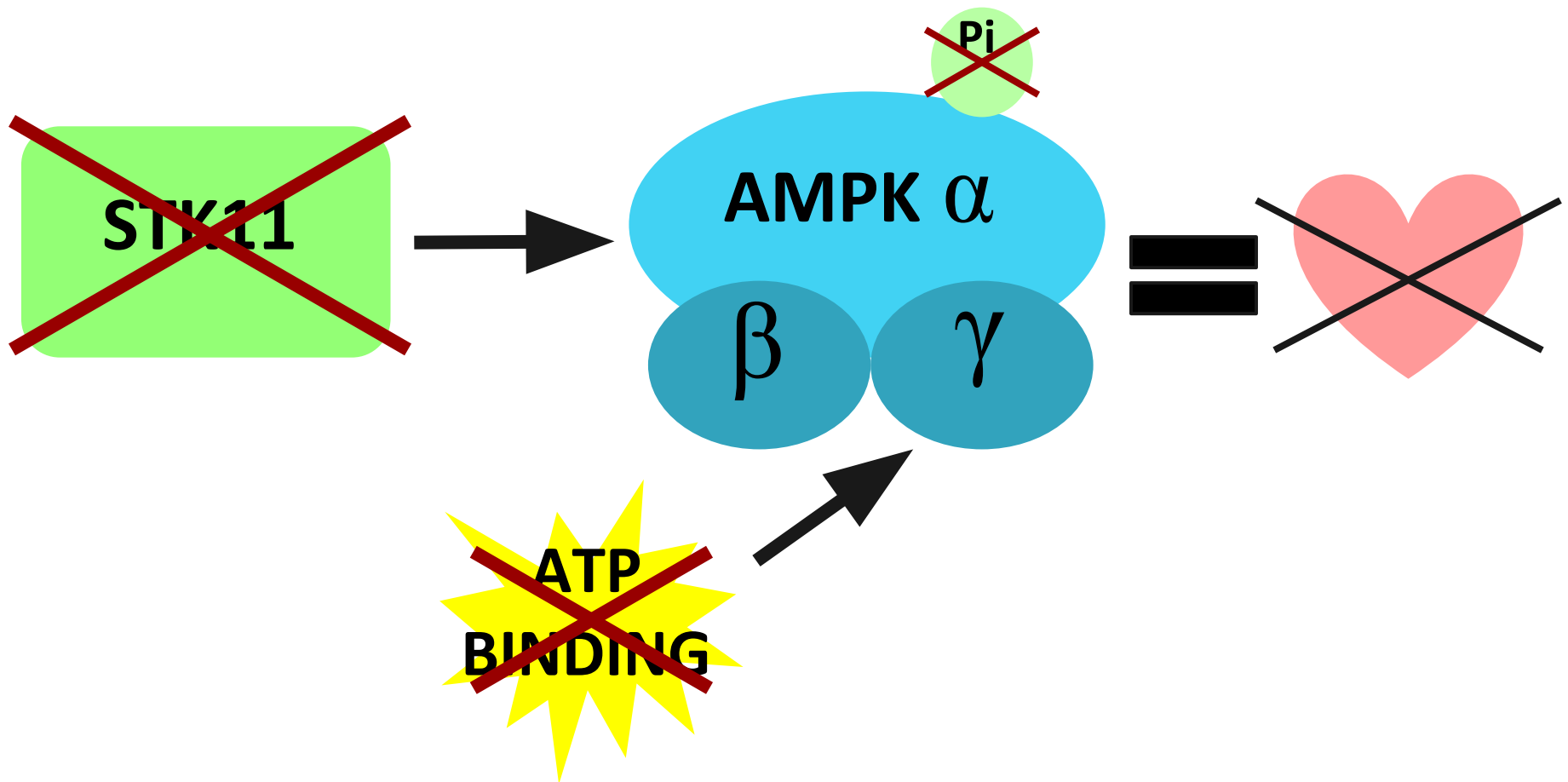
What is the function of
STK11 in ATP regulation?



STK11 activates AMPK



Hypothesis: Mutations in STK11 would inhibit ATP binding and alter development of the heart



How would PRKAG2 be expressed if STK11 were mutated?

PRKAG2 Expression				
Tissue	Cardiac	Skeletal	Brain	Liver
WT	Overexpressed	Overexpressed	Overexpressed	Overexpressed
PRKAG2 Mutant	Underexpressed	Underexpressed	Underexpressed	Underexpressed
STK11 Mutant	Underexpressed	Underexpressed	Underexpressed	Underexpressed

Overexpressed

Underexpressed

Conclusions

PRKAG2 and Wolff-Parkinson-White have been well studied/characterized

CBS domains are found in all three domains of life = **highly conserved**

Mutations in PRKAG2 homologs may still have significant implications in heartless organisms

Future Directions

Highly conserved--where did these CBS domains stem from?

Looking into the AMPK protein in order to potentially develop treatments for STK11 related diseases

Are there any other proteins affected by mutation to PRKAG2 gene?

A 3D anatomical rendering of the human cardiovascular system, showing the heart, lungs, and a network of blood vessels (arteries and veins) in shades of purple and brown, overlaid on a semi-transparent human torso. The word "Questions?" is written in large, bold, black font across the center of the image.

Questions?

References

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