

# Alcohol Intolerance

ALDH2 deficiency  
and liver cancer



Chris Stein



**WISCONSIN**  
UNIVERSITY OF WISCONSIN-MADISON

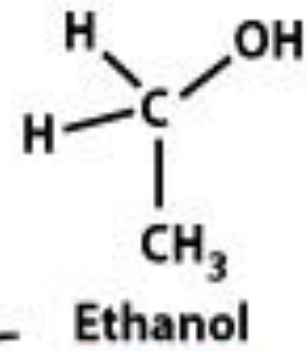


# What is Alcohol Intolerance?

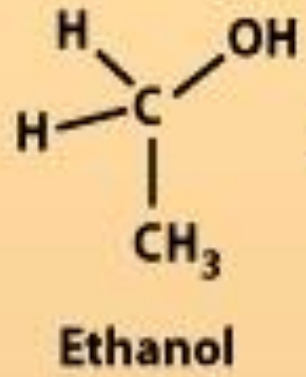


# Alcohol metabolism

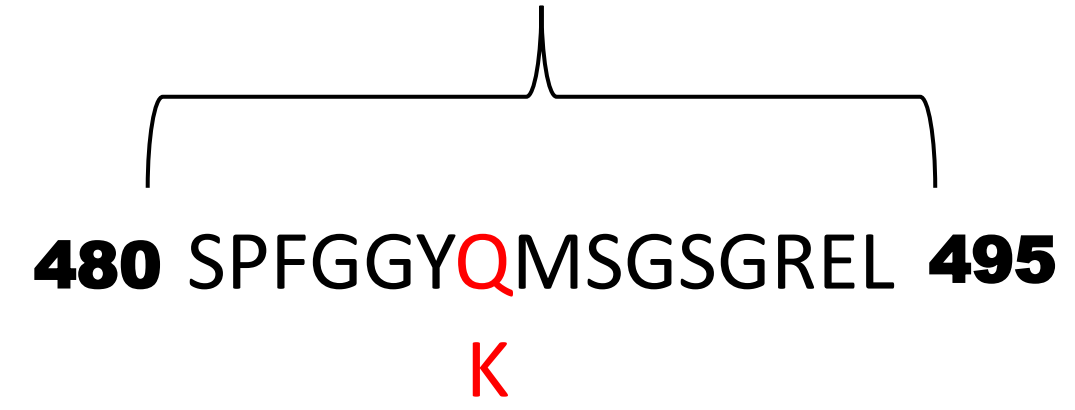
Bloodstream



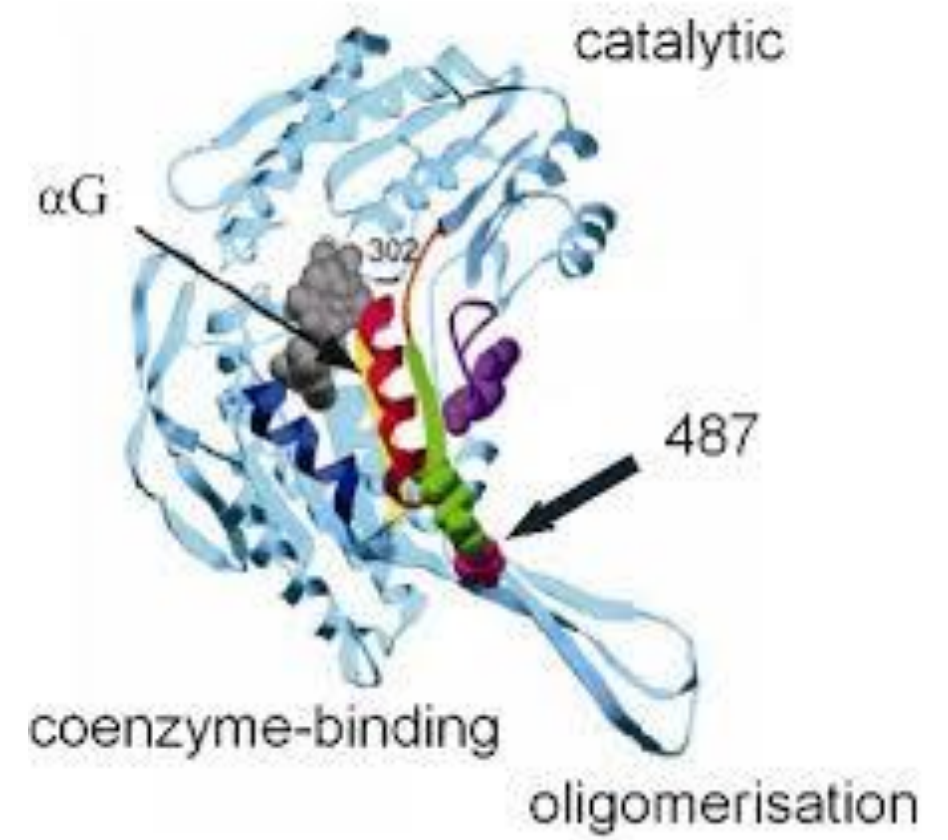
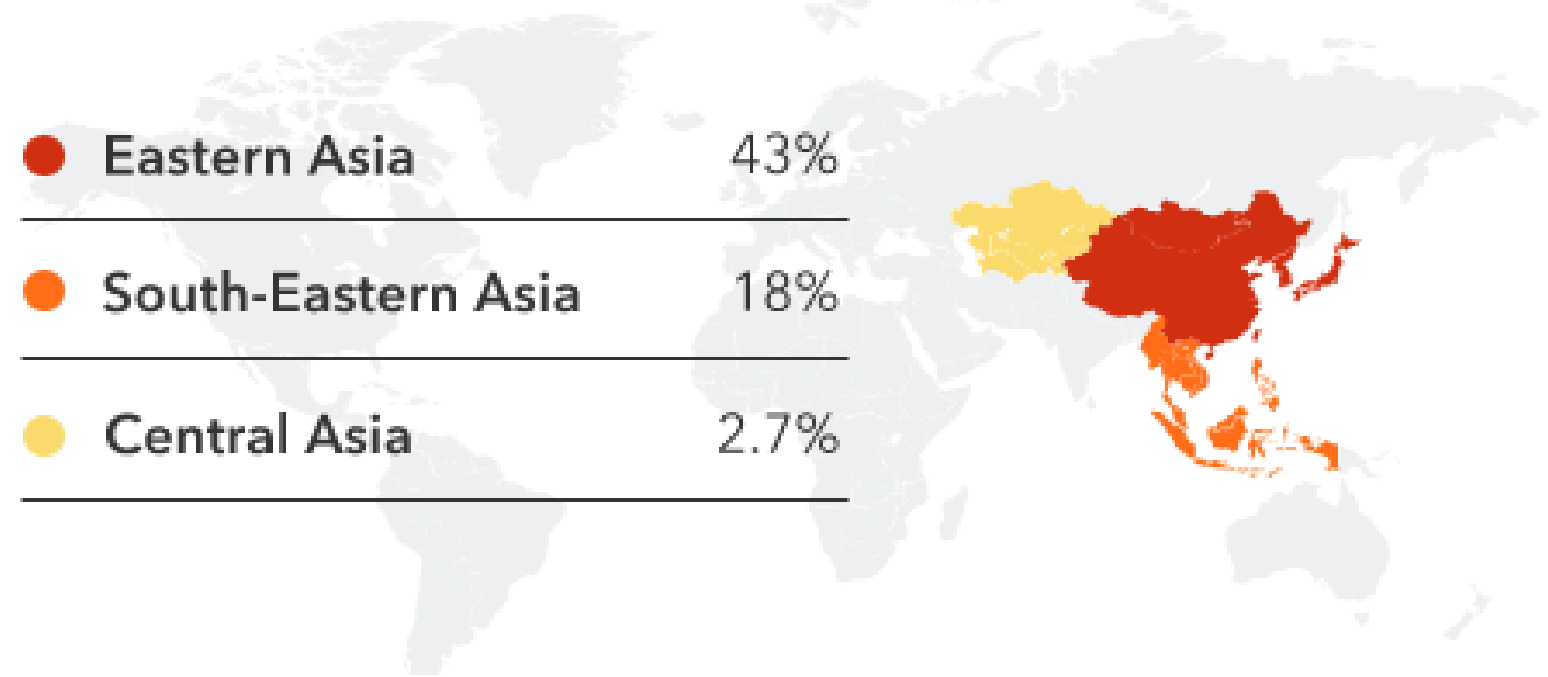
Liver



# Mutation in **ALDH2**



Where is the alcohol flush variant most common?





# Role of ALDH2

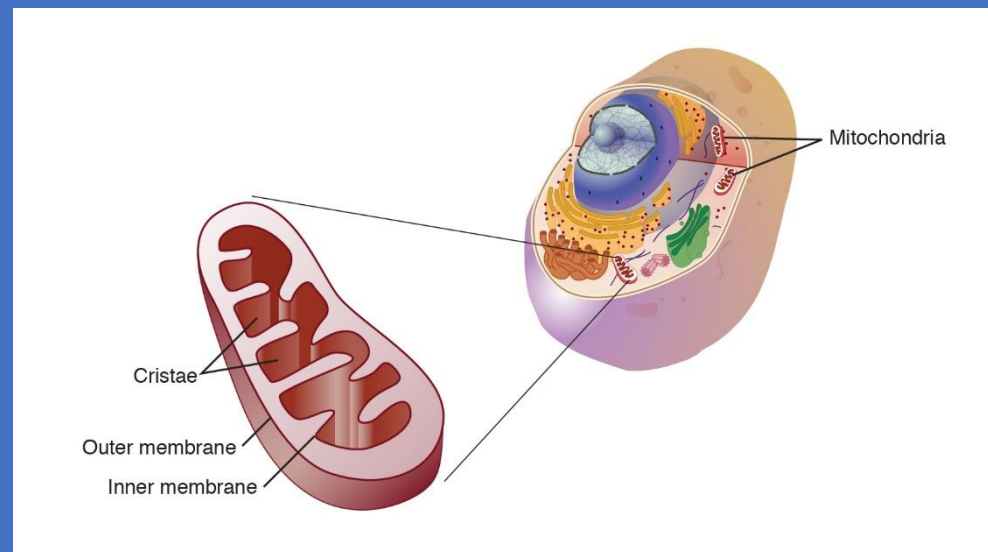
45

Aldedh

508

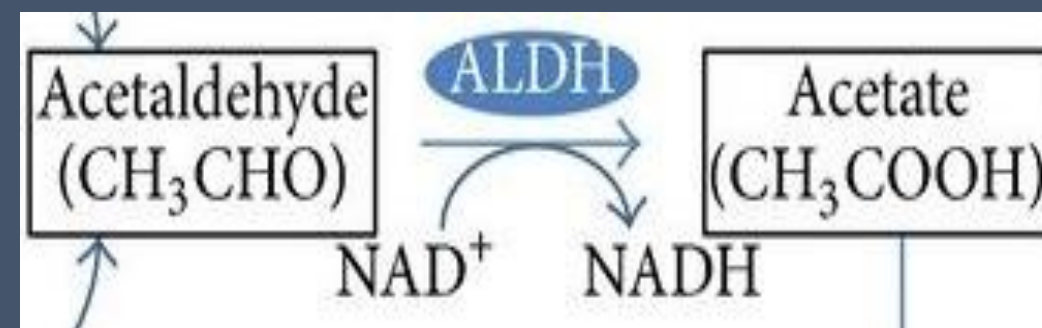
517 AA

## Cellular Component:



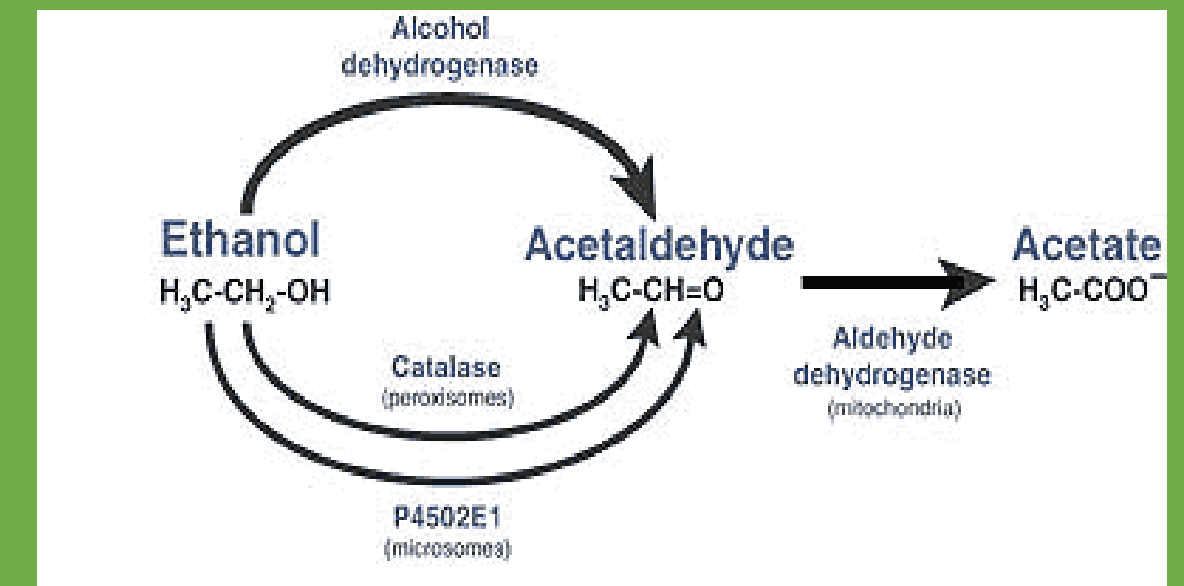
Localizes to the mitochondrial matrix

## Molecular Function:



ALDH2 reduces aldehydes, mostly works on acetaldehyde

## Biological Process:



ALDH2 assists in the alcohol degradation pathway

# Symptoms of Alcohol Intolerance

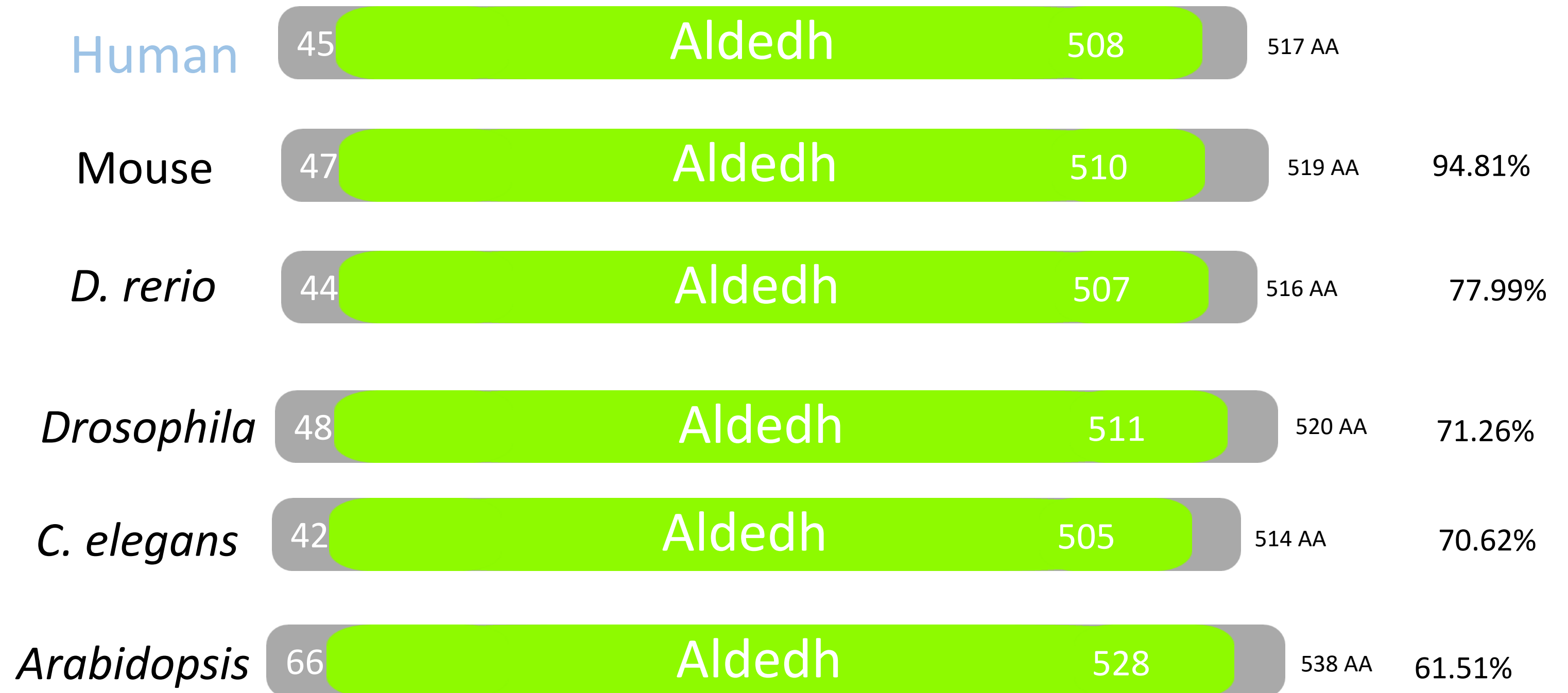
Immediate immune response



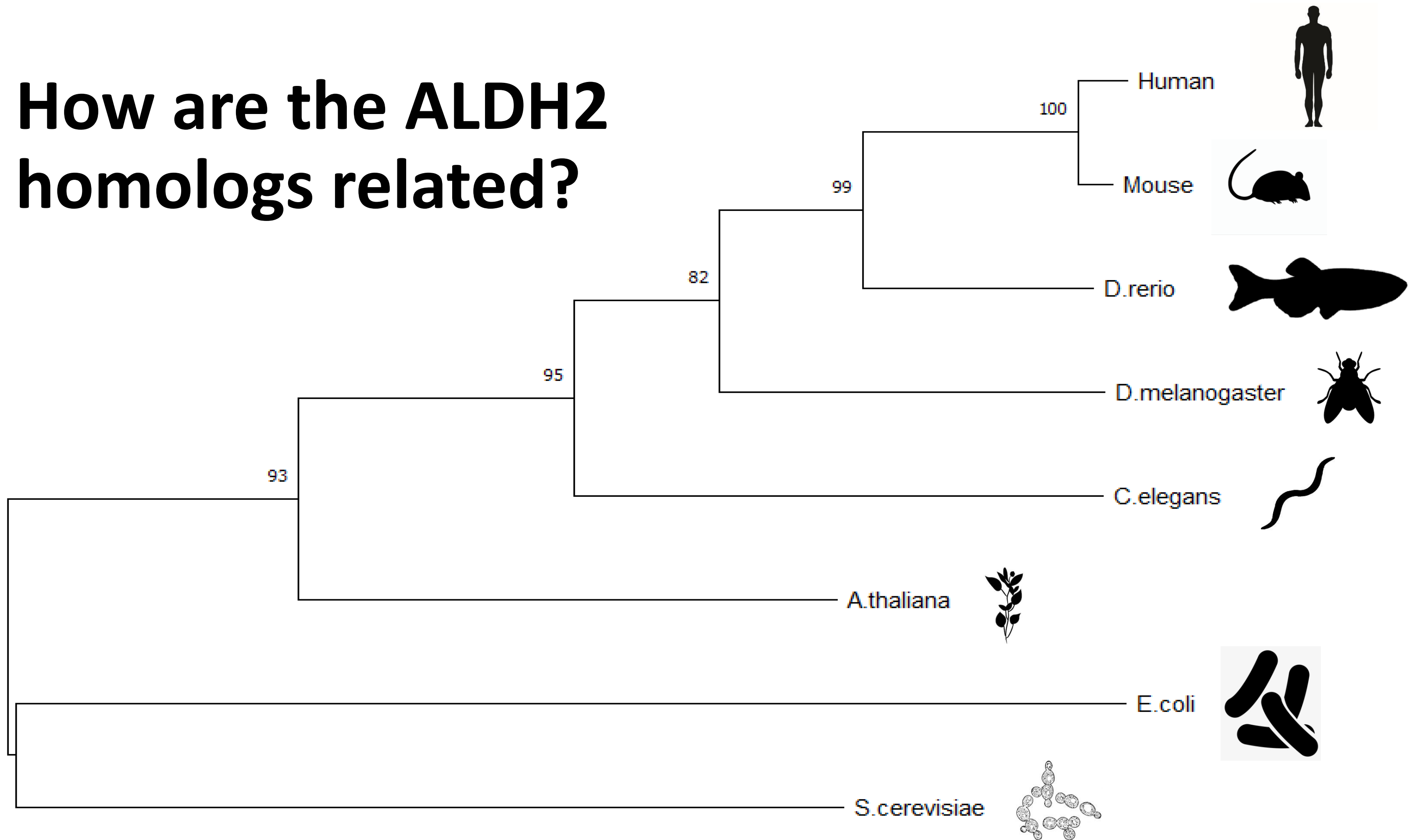
Cancer



# ALDH2 has one domain that assists with its main function of aldehyde dehydrogenase



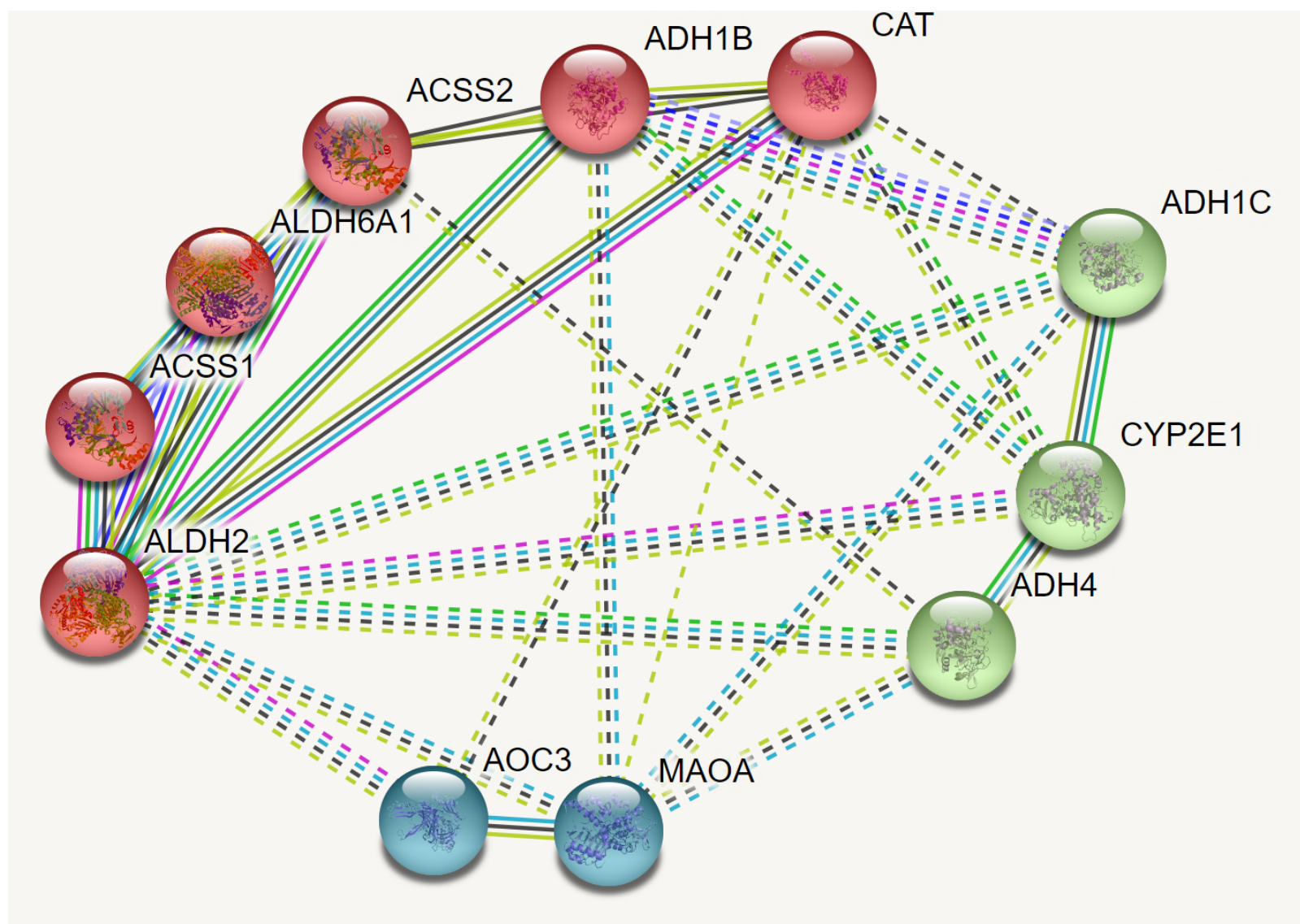
# How are the ALDH2 homologs related?



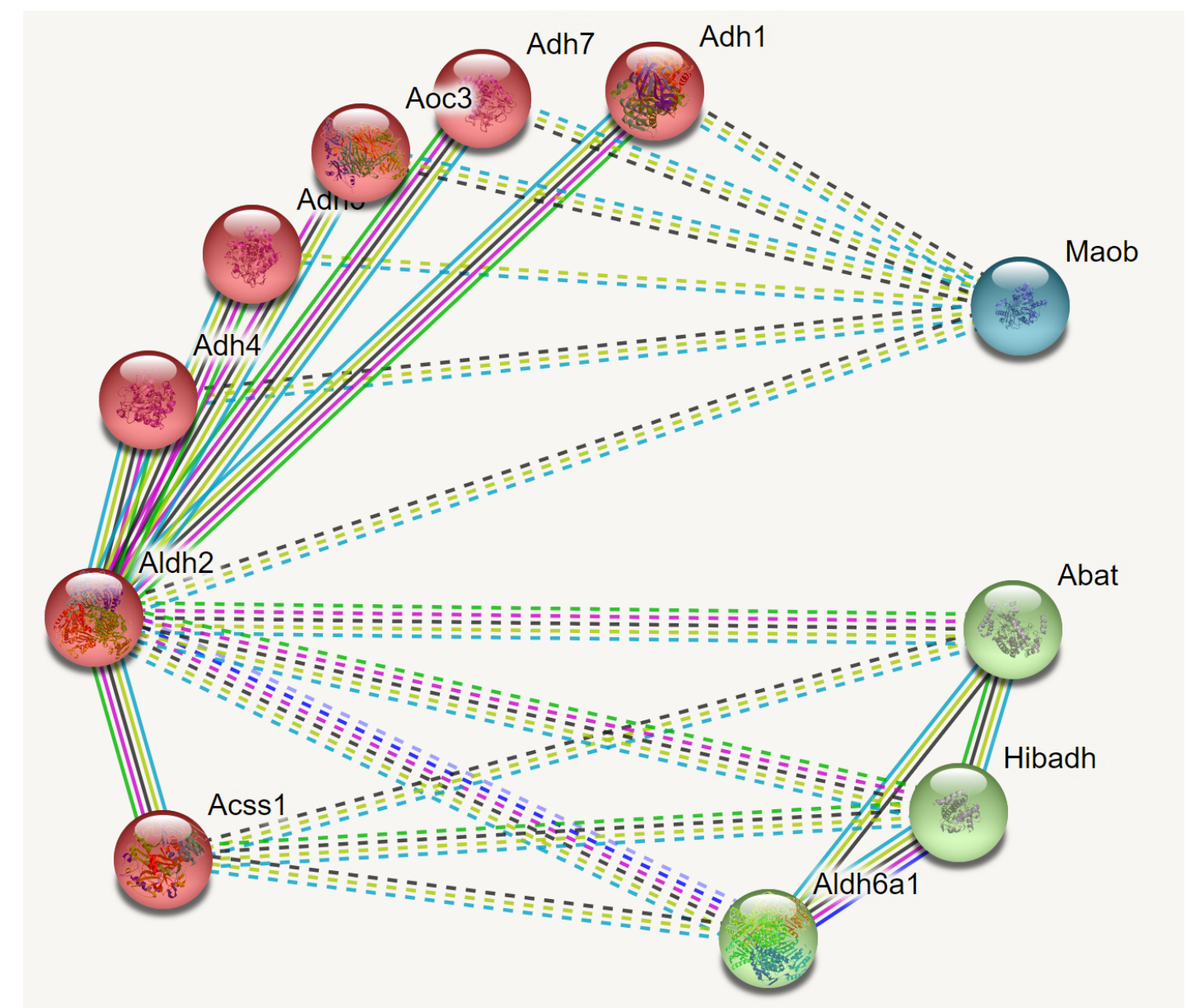


# ALDH2 interactions

## Human

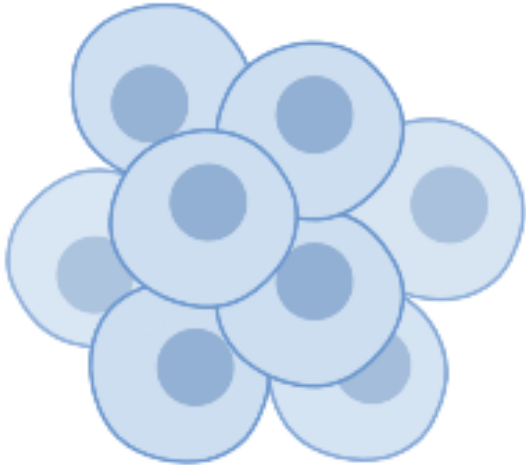


## Mouse



# Gap in knowledge

Normal Growth



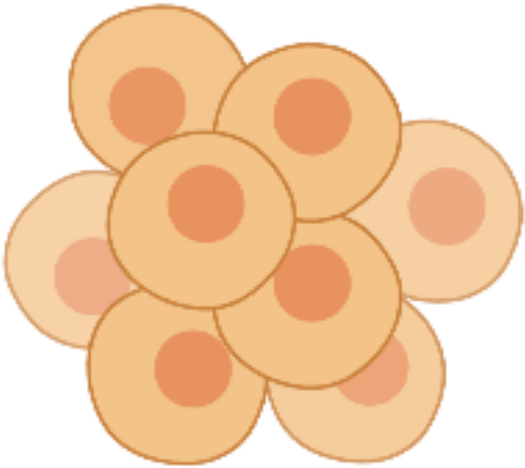
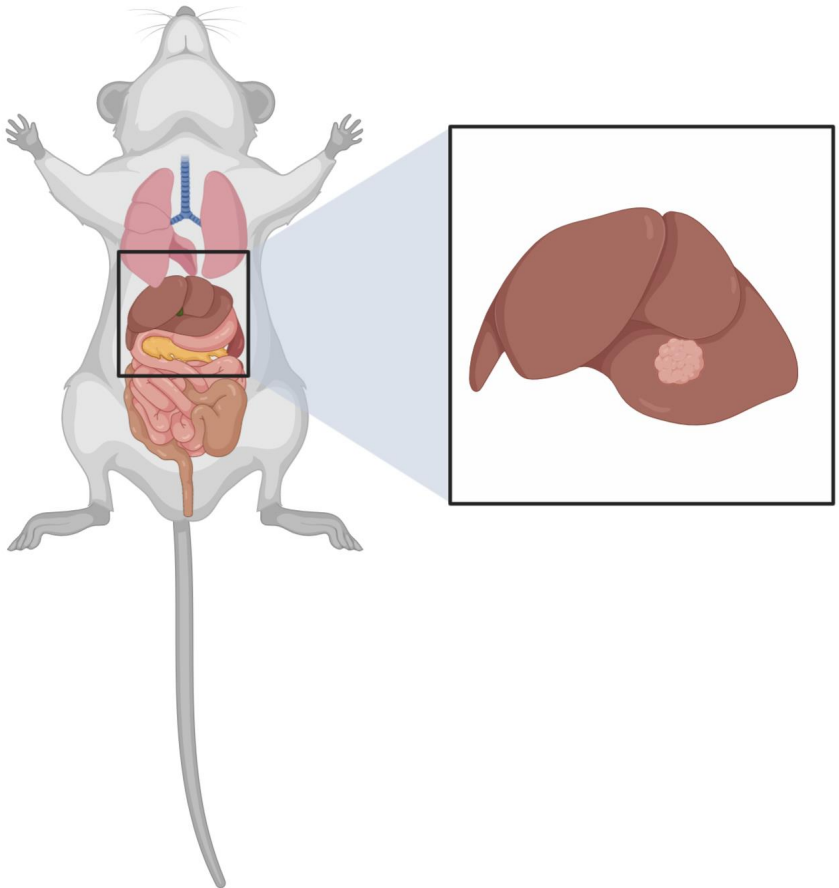
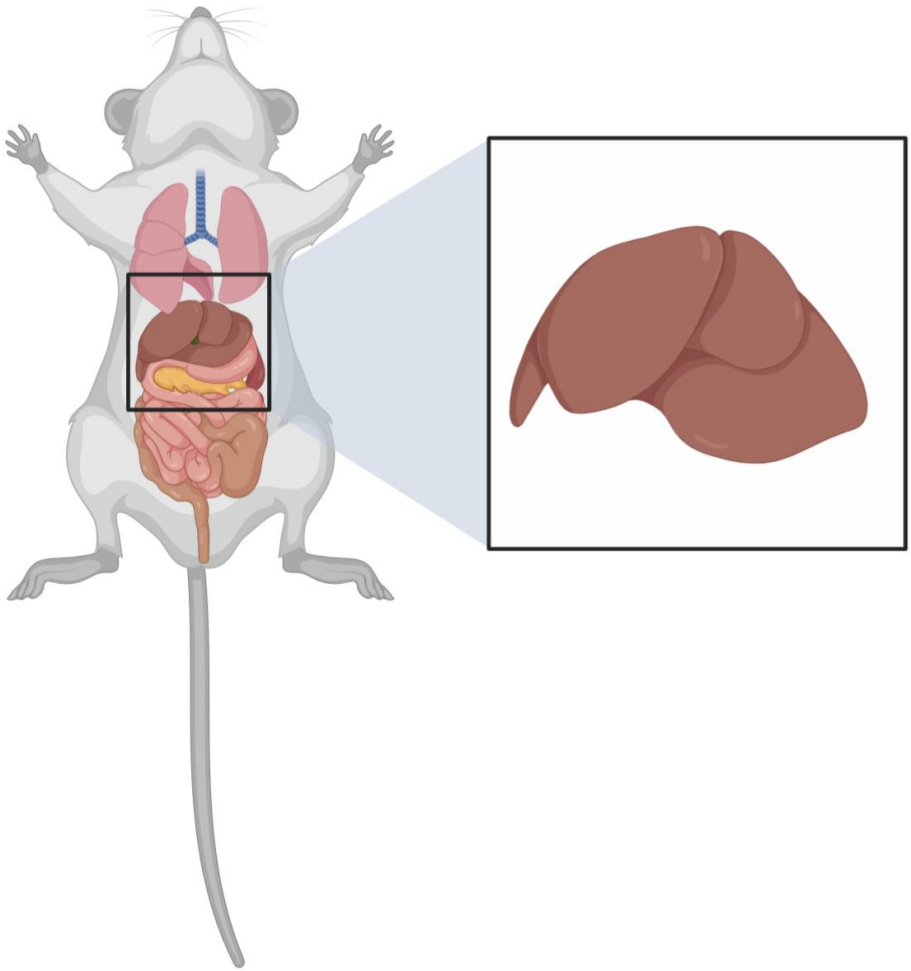
Normal ALDH2



Mutant ALDH2

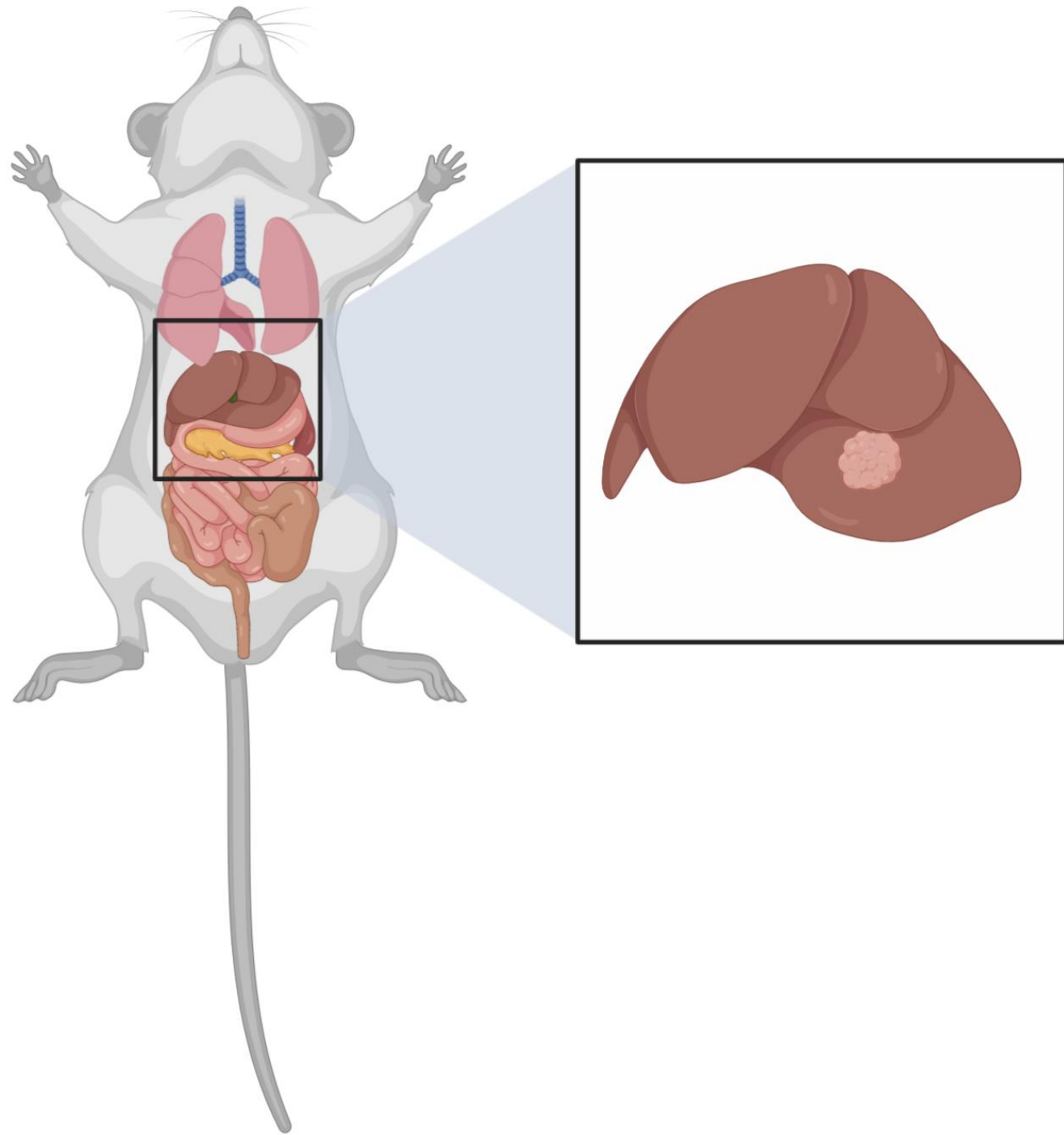


Autophagy





# What model organism should be used?



# Primary goal

To determine how ALDH2 causes cell proliferation in mice hepatocytes.

## Aim 1:

Determine how mutations in aldedh domain affect ALDH2 activity.

## Aim 2:

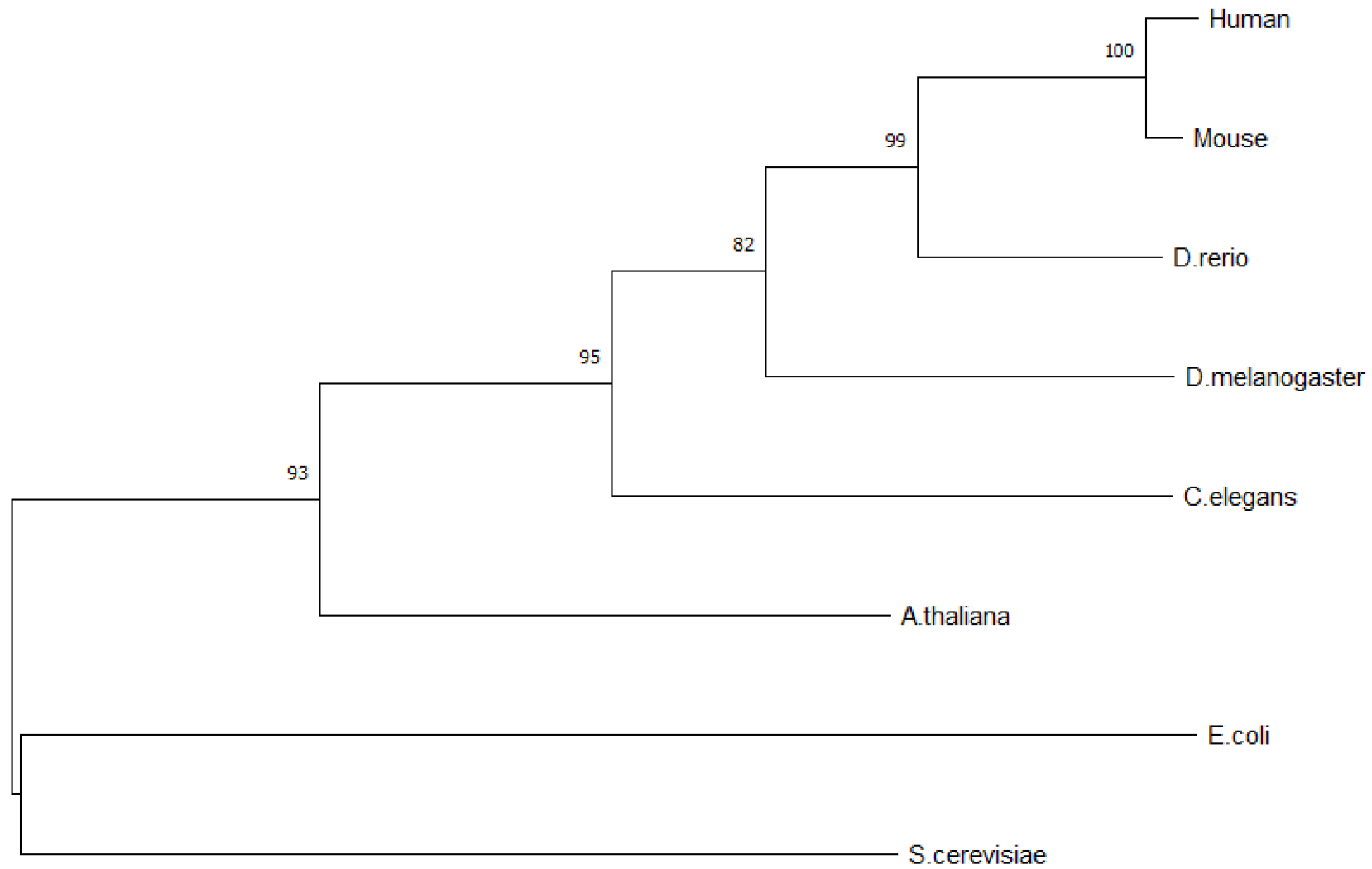
Identify differentially expressed genes across liver development in mice.

## Aim 3:

Characterize novel protein interactions important for liver development



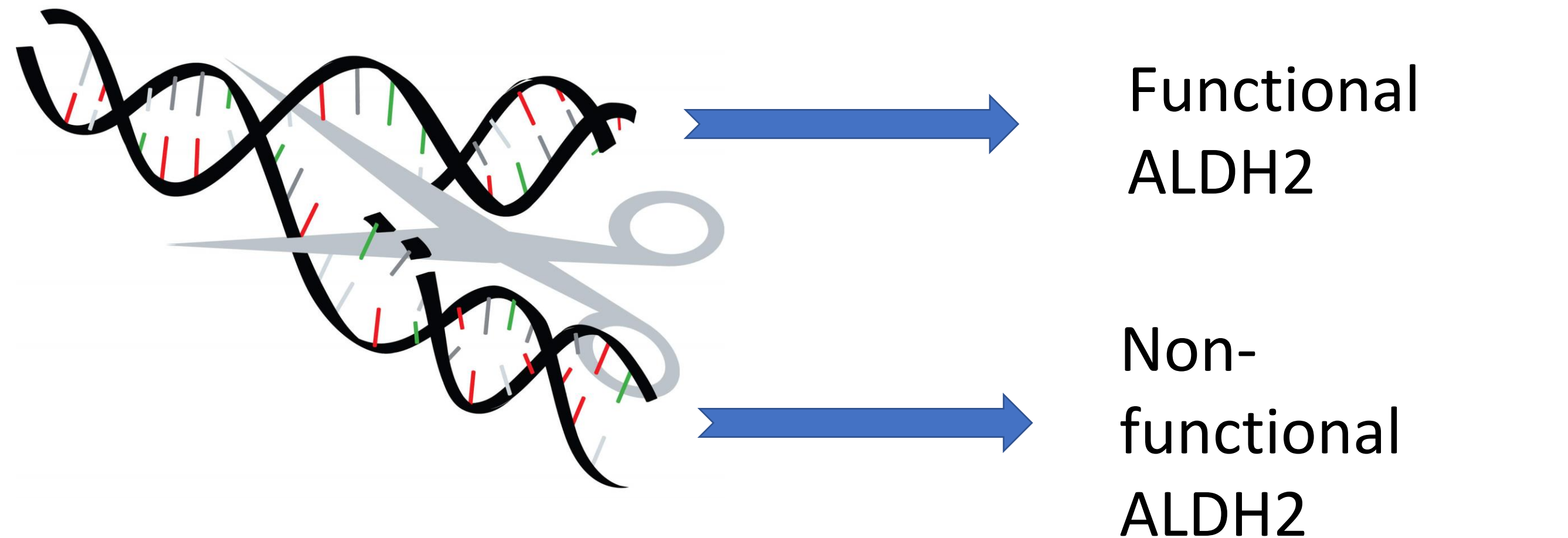
# Aim 1: Determine conserved amino acids essential for ALDH2 function



Species/Abbrv		*							*	*	*		*	*	*	*									
1. E.coli	R	R	I	A	S	L	I	R	D	R	Q	Q	A	L	A	A	L	E	V	R	D	N	G	K	P
2. S.cerevisiae	F	N	L	A	D	L	V	E	K	H	Q	E	T	L	A	A	I	E	S	M	D	N	G	K	S
3. A.thaliana	L	R	F	A	D	L	V	E	K	H	S	E	E	L	A	S	L	E	T	W	D	N	G	K	P
4. C.elegans	N	R	L	A	D	L	M	E	R	D	R	V	I	L	A	S	L	E	S	L	D	N	G	K	P
5. D.melanogaster	Y	R	L	A	D	L	M	E	R	D	Q	V	Y	L	A	S	L	E	T	L	D	N	G	K	P
6. D.rerio	N	R	L	A	D	C	I	E	R	D	A	A	Y	L	A	E	L	E	T	L	D	N	G	K	P
7. Human	N	R	L	A	D	L	I	E	R	D	R	T	Y	L	A	A	L	E	T	L	D	N	G	K	P
8. Mouse	Y	R	L	A	D	L	I	E	R	D	R	T	Y	L	A	A	L	E	T	L	D	N	G	K	P



# Aim 1: Determine conserved amino acids essential for ALDH2 function





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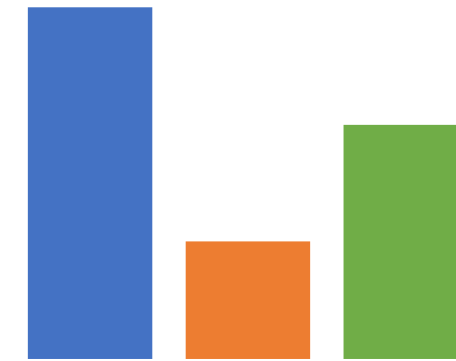
Clustal  
Omega

CRISPR/  
Cas 9

Screening

# Aim 2: What genes are differentially expressed in ALDH2 mutants?

WT



ALDH2 mutant



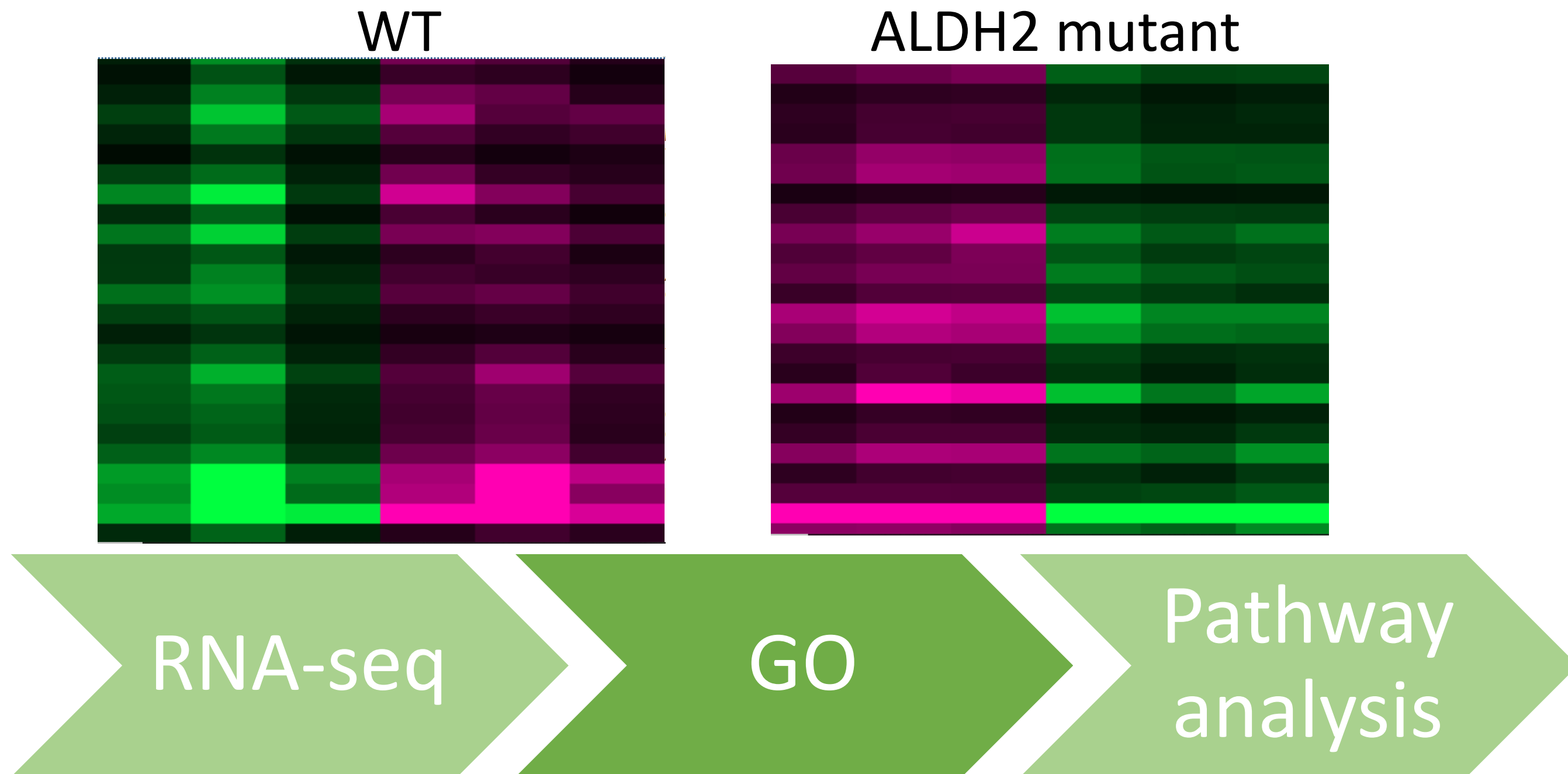
RNA-seq

GO

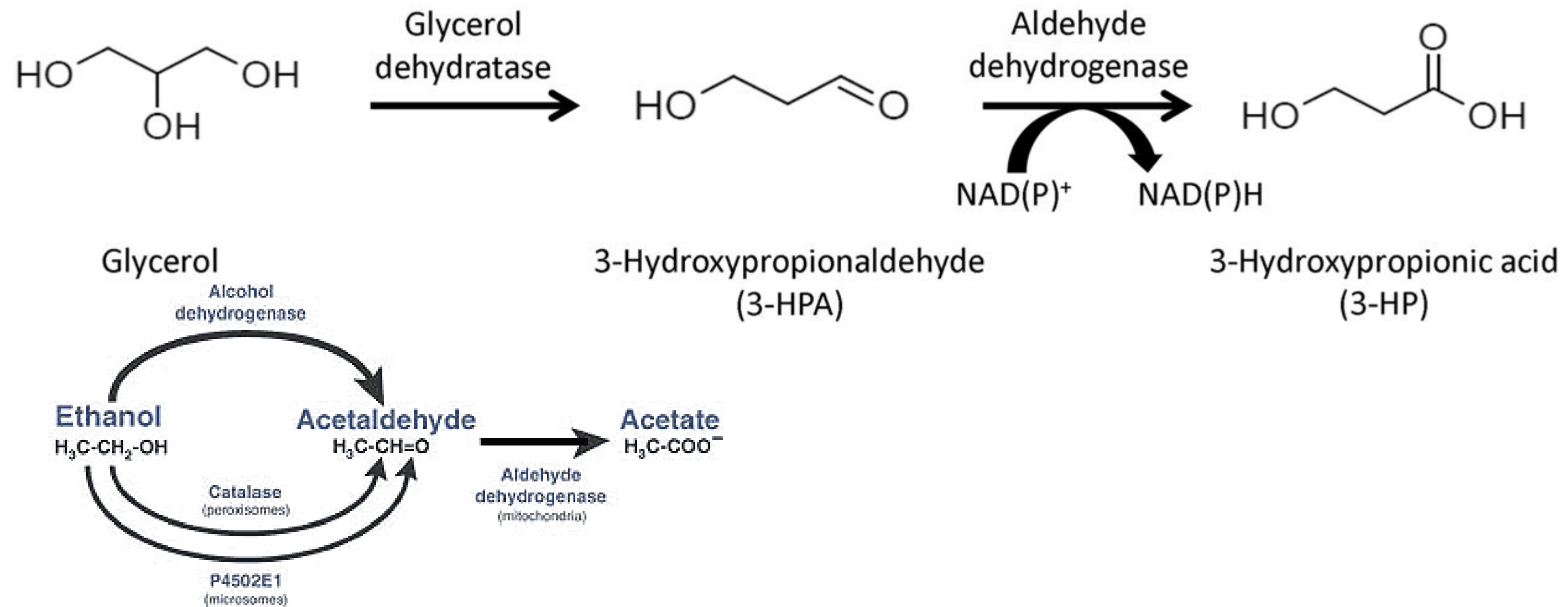
Pathway analysis



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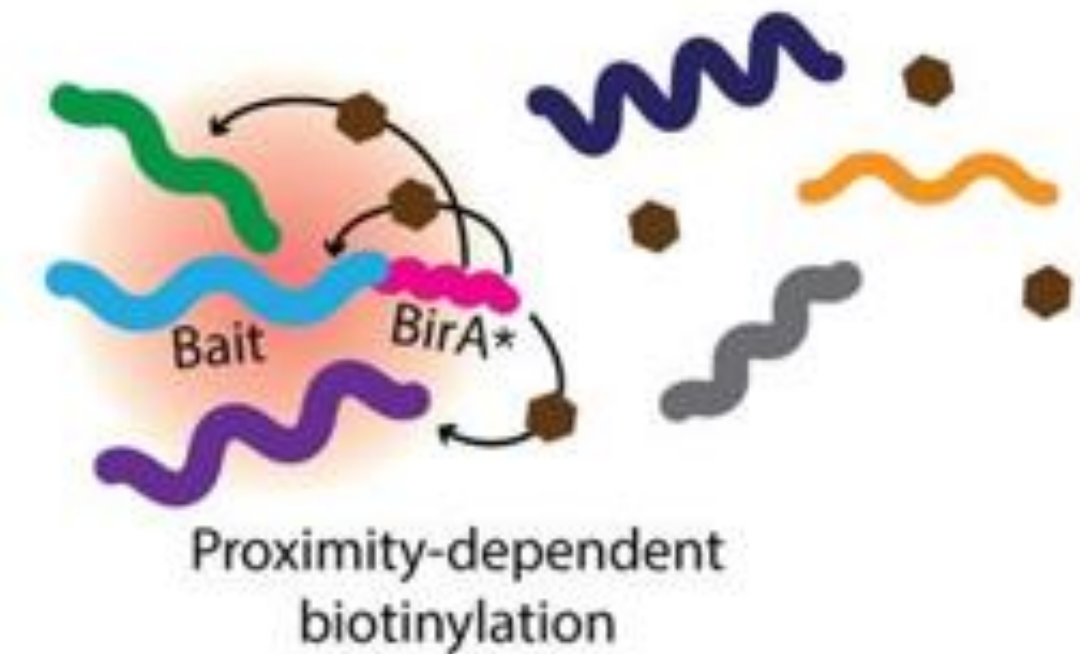
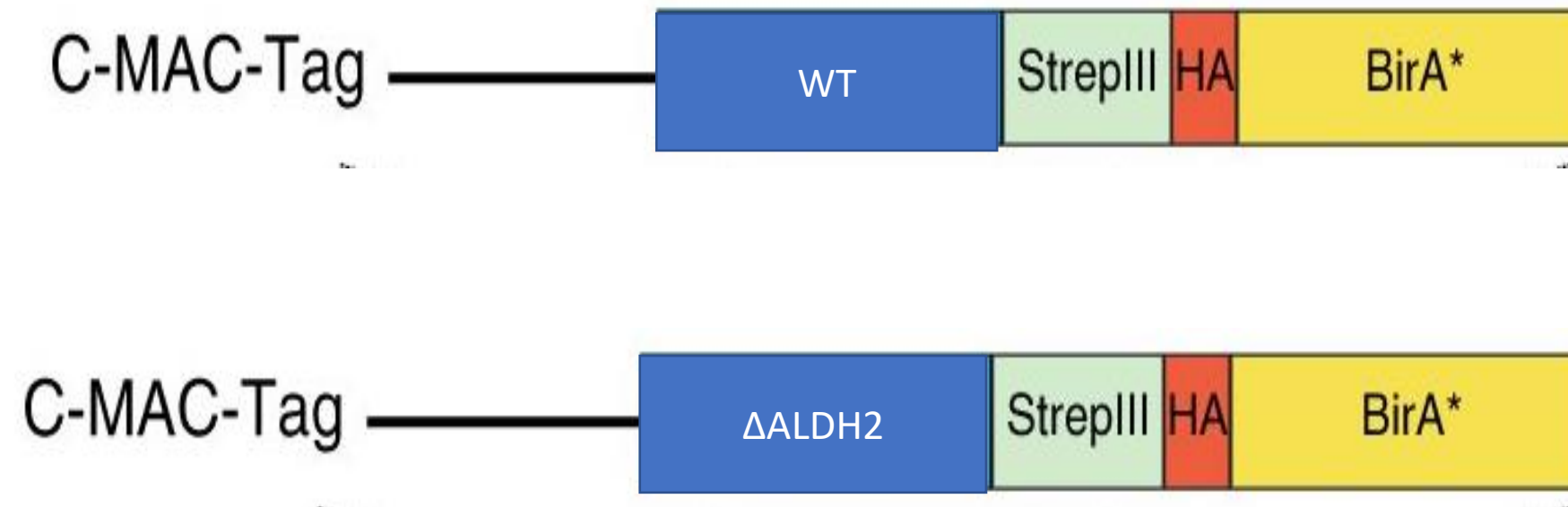


RNA-seq

GO

Pathway  
analysis

# Aim 3: What other proteins interact with ALDH2?



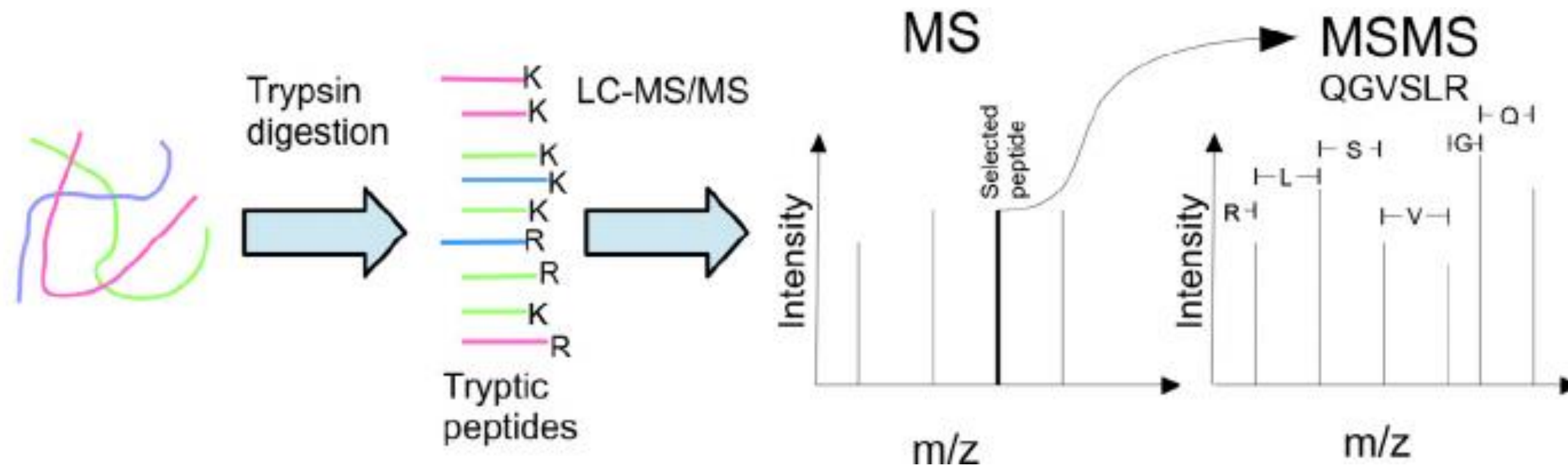
Bio-ID

IP and MS

Compare interactions



# Aim 3: What other proteins interact with ALDH2?

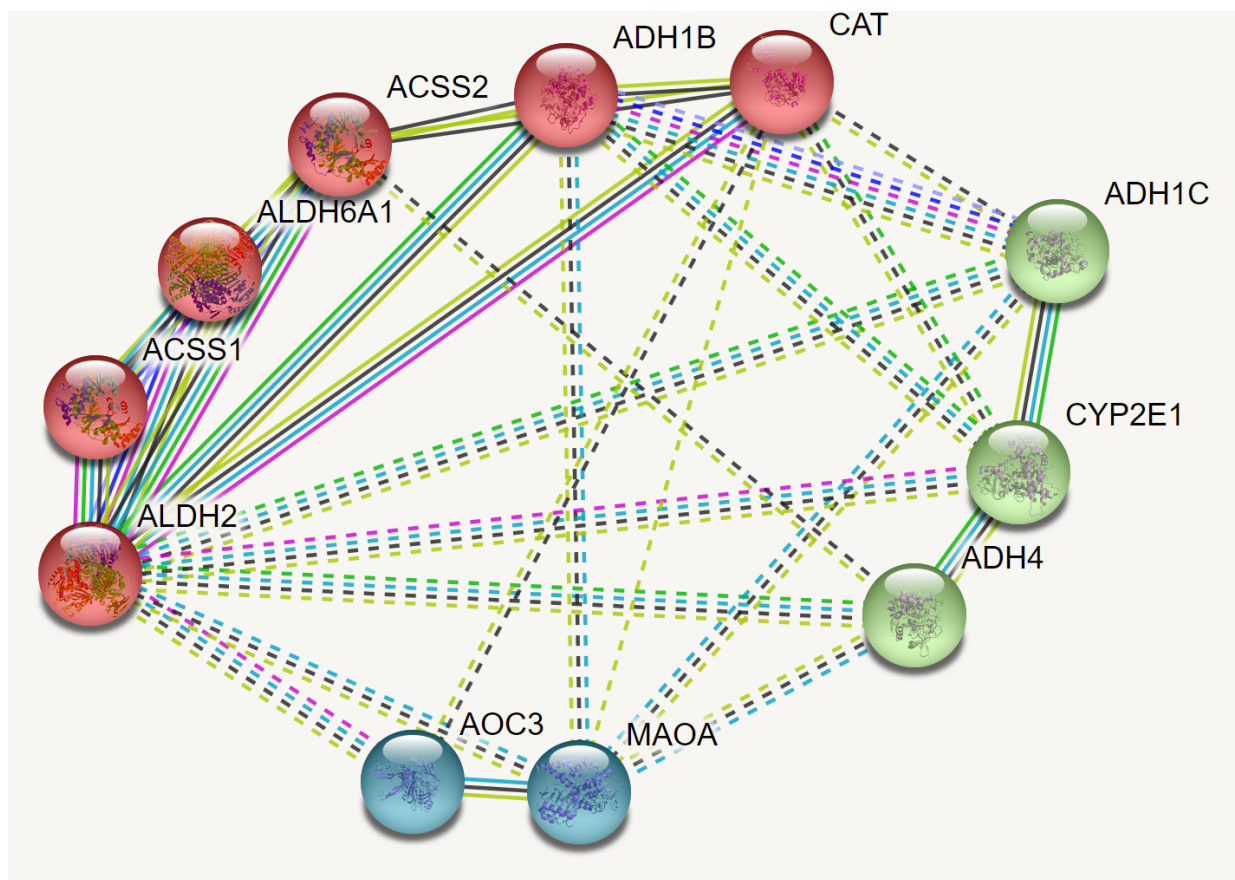


Bio-ID

Digestion  
and MS

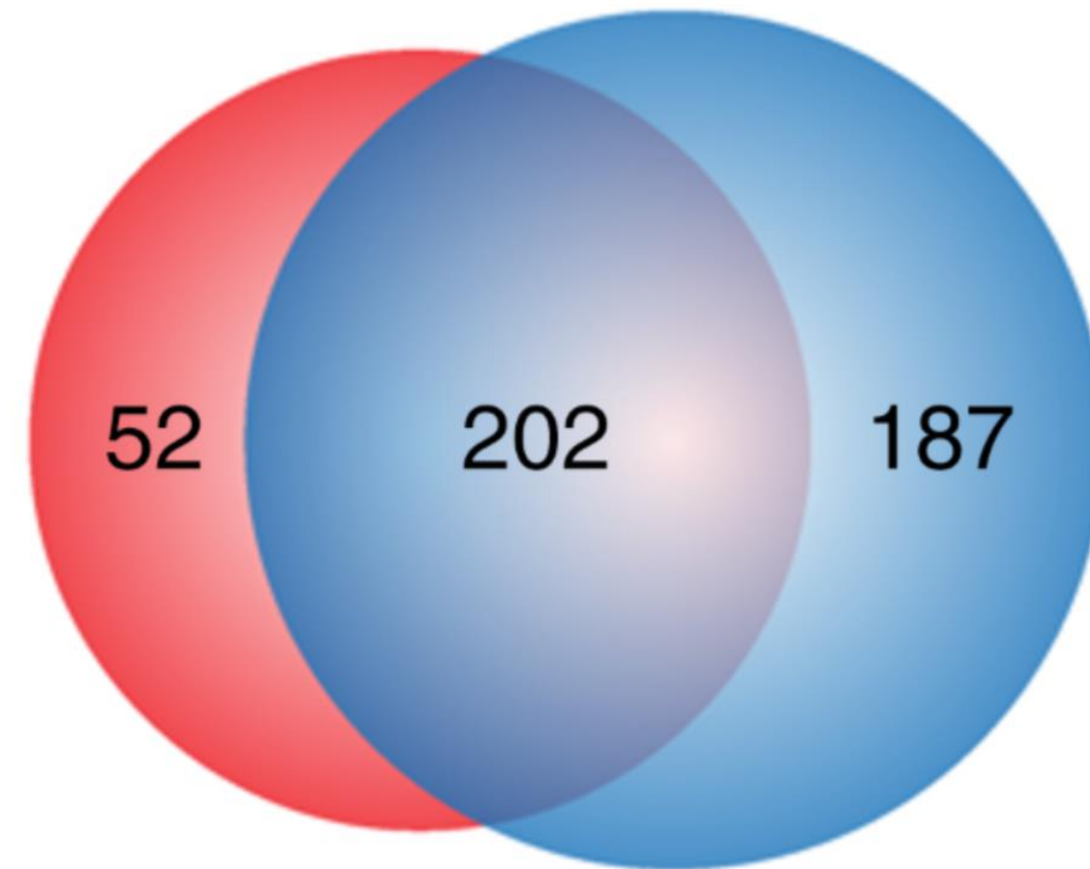
Compare  
interactions

# Aim 3: What other proteins interact with ALDH2?



WT

$\Delta$ ALDH2



Bio-ID

IP and MS

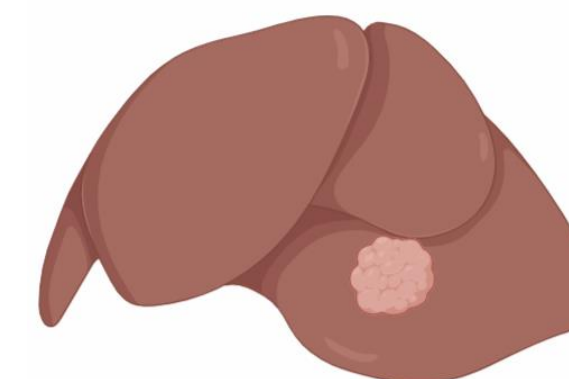
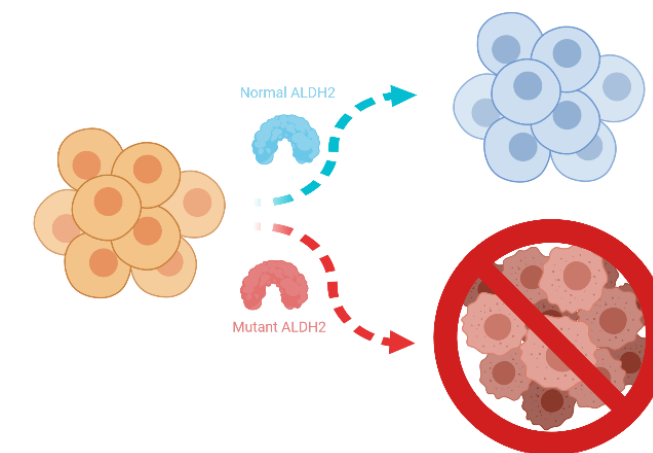
Compare interactions

# Conclusions

ALDH2 deficiency usually results in autophagy but most mutants have a higher incidence of cancer

The alcohol pathway of mice is very similar to that of humans

The proliferative genes may be similar in other cancer types caused by this disease





# References

- 1) Wang, W., Sheikh, S., Saigal, D., Robinson, L., Weiner, H., (December 1996). Heterotetramers of Human Liver Mitochondrial (Class 2) Aldehyde Dehydrogenase Expressed in Escherichia coli. Retrieved from: <https://www.jbc.org/content/271/49/31172.long>
- 2) Zuo, W., Zhan, Z., Ma, L., Bai, W., Zeng, S. (March 2019). Effect of ALDH2 polymorphism on cancer risk in Asians. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6456109/>
- 3) Nene, A., Chen, C.H., Disatnik, M.H., Cruz, L., Mochly-Rosen, D. (2017). Aldehyde dehydrogenase 2 activation and coevolution of its  $\epsilon$ PKC-mediated phosphorylation sites. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5217657/>
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- 5) Tamura, M., Ito, H., Matsui, H., Hyodo, I. (July 2014). Acetaldehyde is an oxidative stressor for gastric epithelial cells. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4078068/#:~:text=>
- 6) Chang, J.S., Hsiao, J. & Chen, C. ALDH2 polymorphism and alcohol-related cancers in Asians: a public health perspective. *J Biomed Sci* **24**, 19 (2017). <https://doi.org/10.1186/s12929-017-0327-y>
- 7) Zuo, W., Zhan, Z., Ma, L., Bai, W., & Zeng, S. (2019). Effect of ALDH2 polymorphism on cancer risk in Asians: A meta-analysis. *Medicine*, 98(13), e14855. <https://doi.org/10.1097/MD.00000000000014855>