Vertebrate animal model updates

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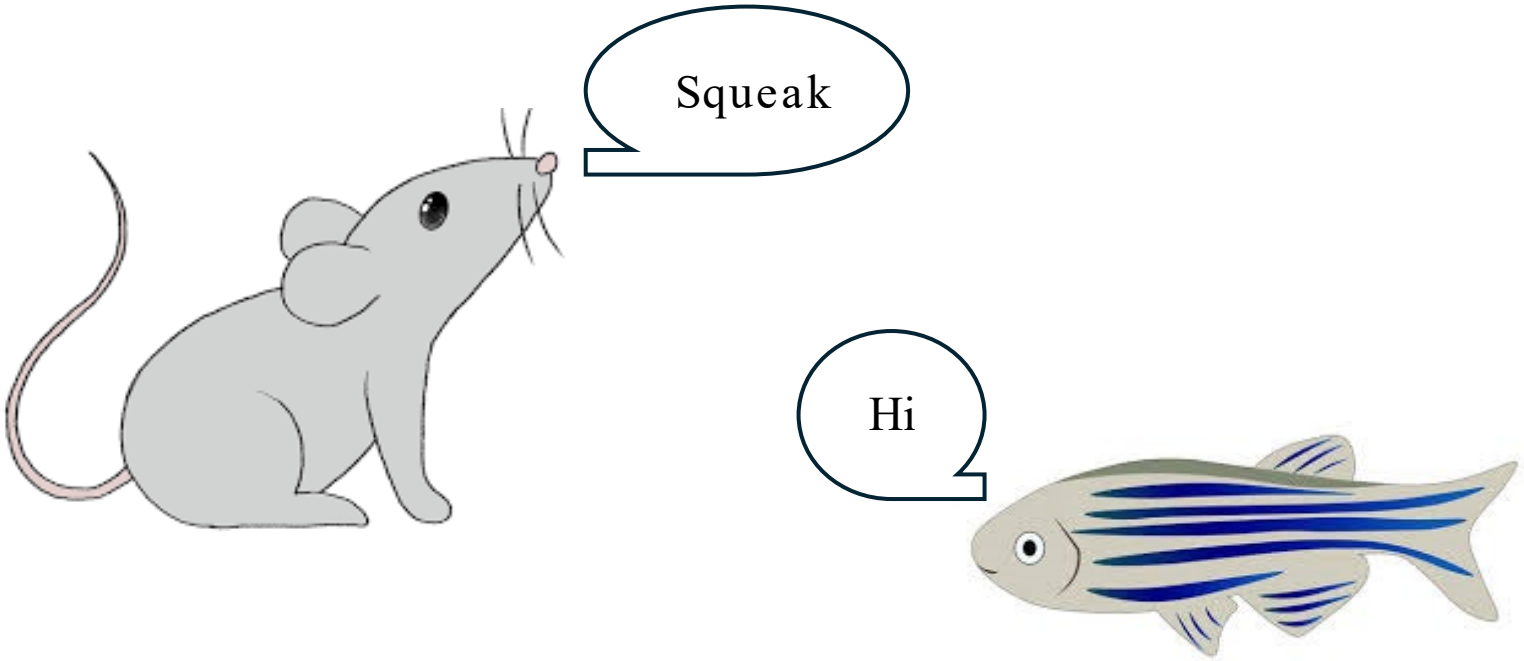
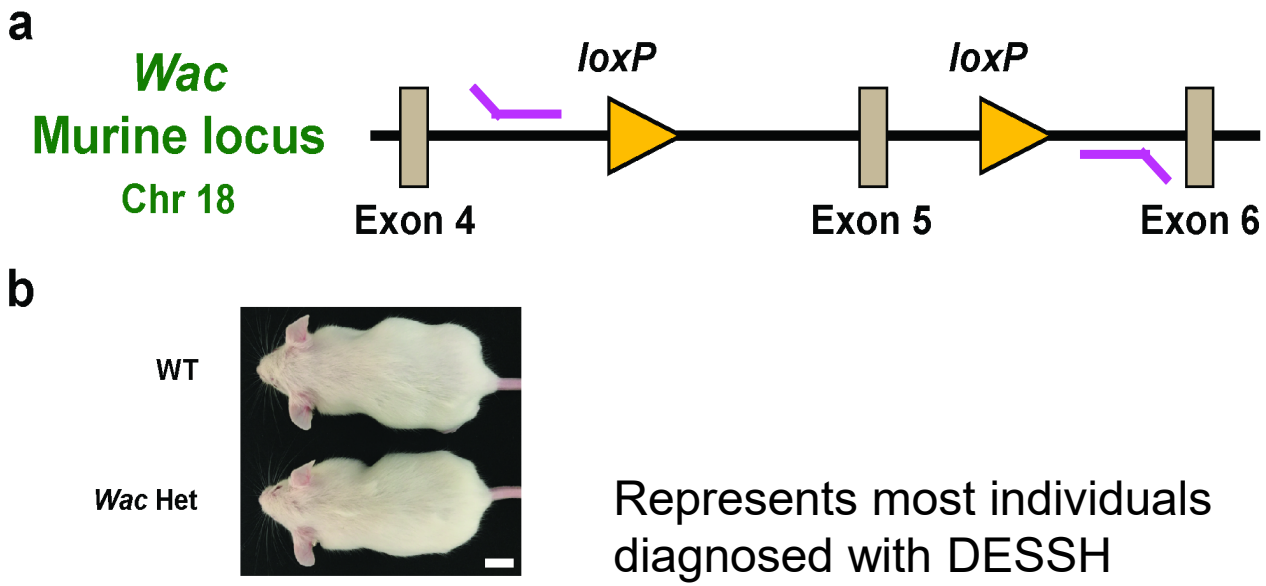


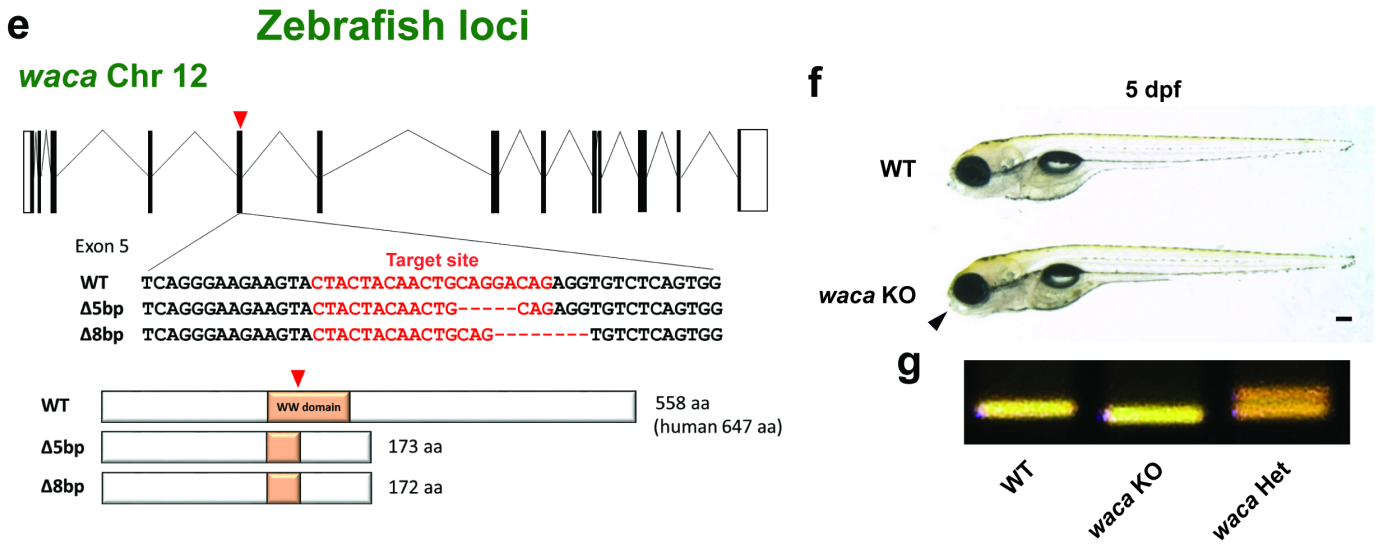
Two existing models being studied

Constitutive heterozygous *Wac* mouse model



Represents most individuals diagnosed with DESSH

waca, *wacb* and double knockout zebrafish

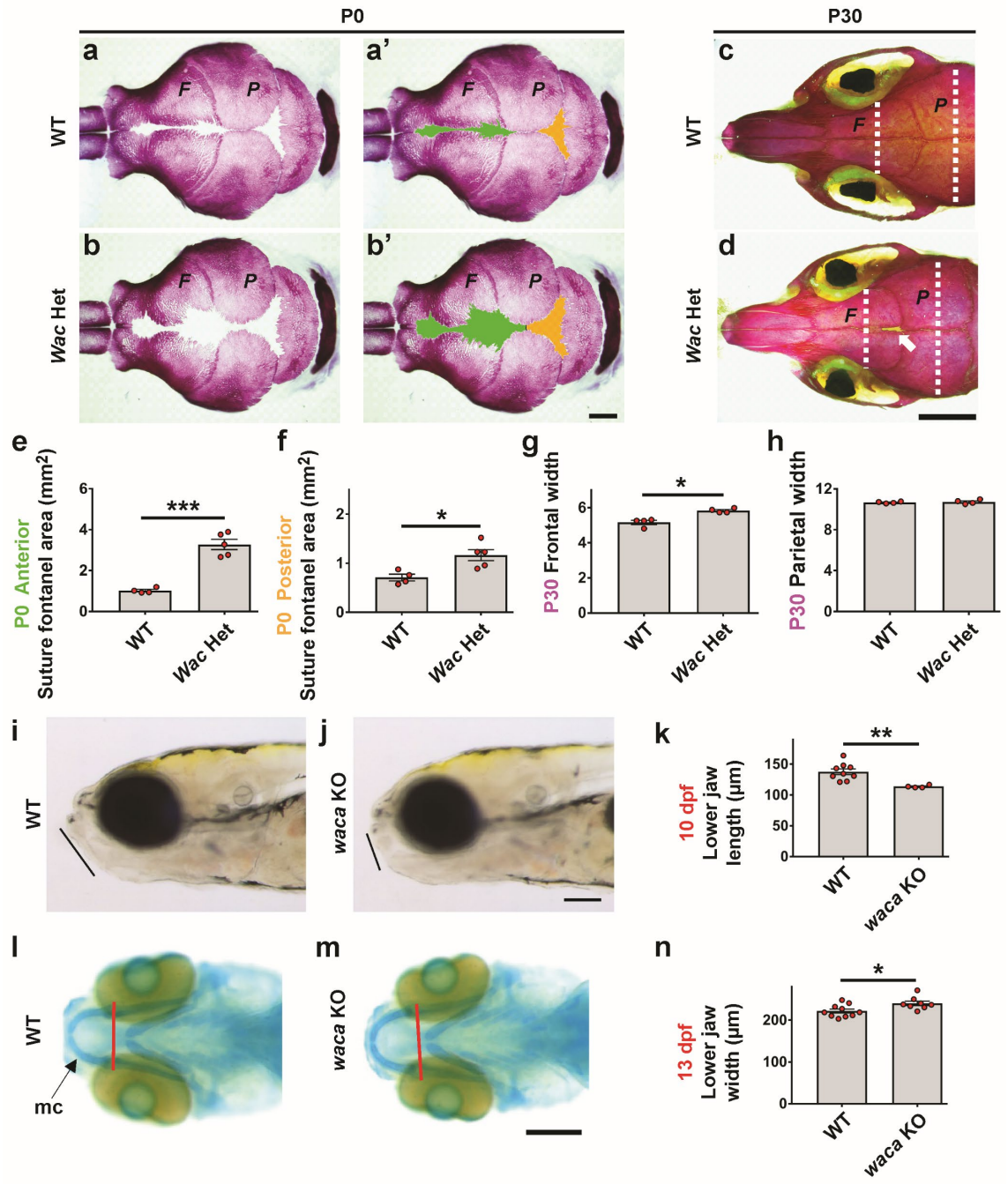


Craniofacial

Both models exhibit changes in craniofacial features

Mouse: larger frontal skull that fails to fully close

Zebrafish: Altered jaw length



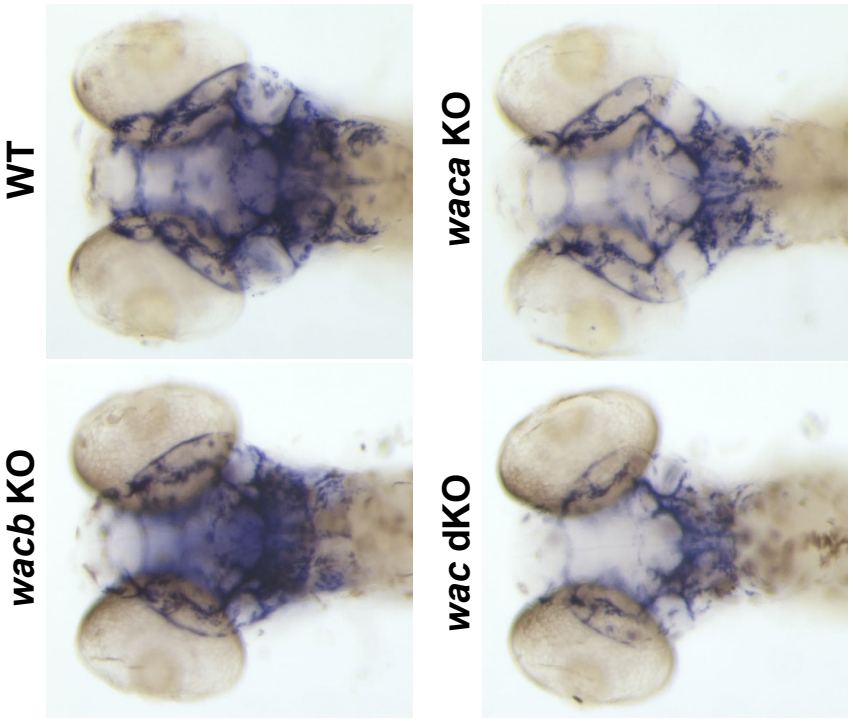
More recent *wac* KO zebrafish show additional craniofacial changes

ependymin (epd) gene expression decreased in wac KO zebrafish

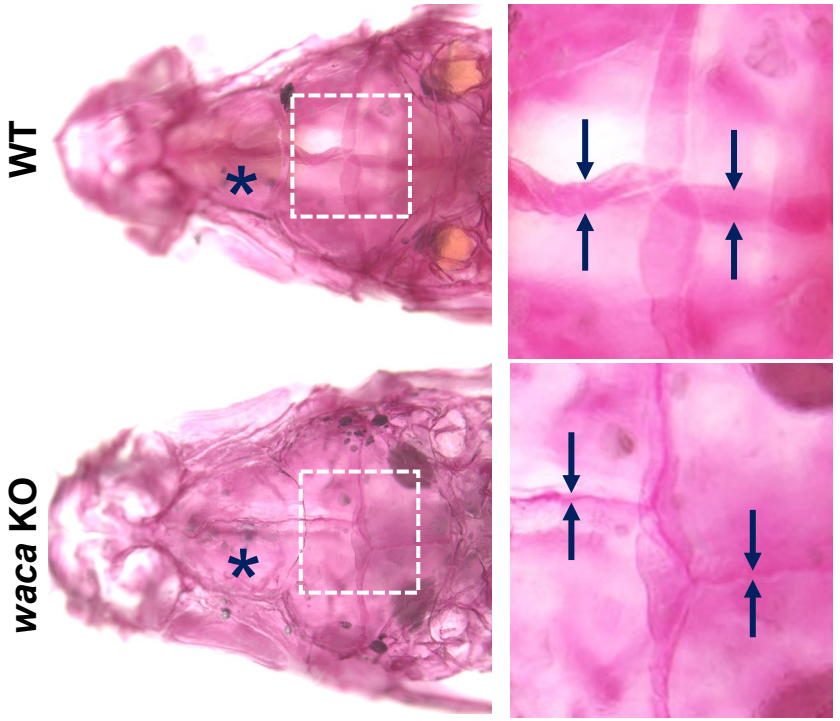
Skull enlarged in forebrain area (asterisks)

Alterations to where skull sutures overlap (arrows)

1. *epd* mRNA (larva at day 5)



2. Skull bone staining (adult head)



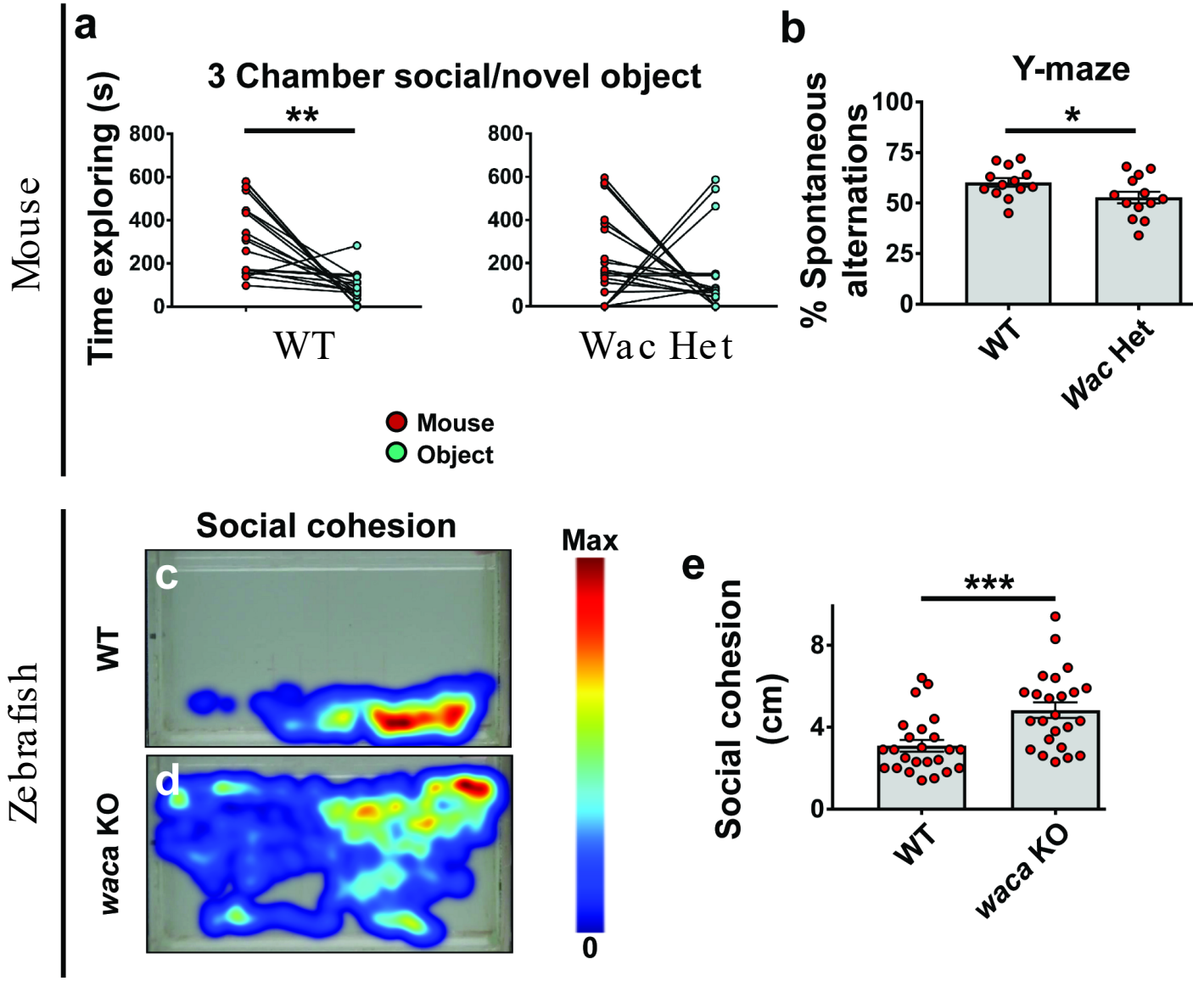
Relevant behaviors

Social behaviors are observed and some short-term memory deficits

Mice:
Spend less time with another mouse

Less times choosing a novel route

Zebrafish:
Spend less time in a tight group



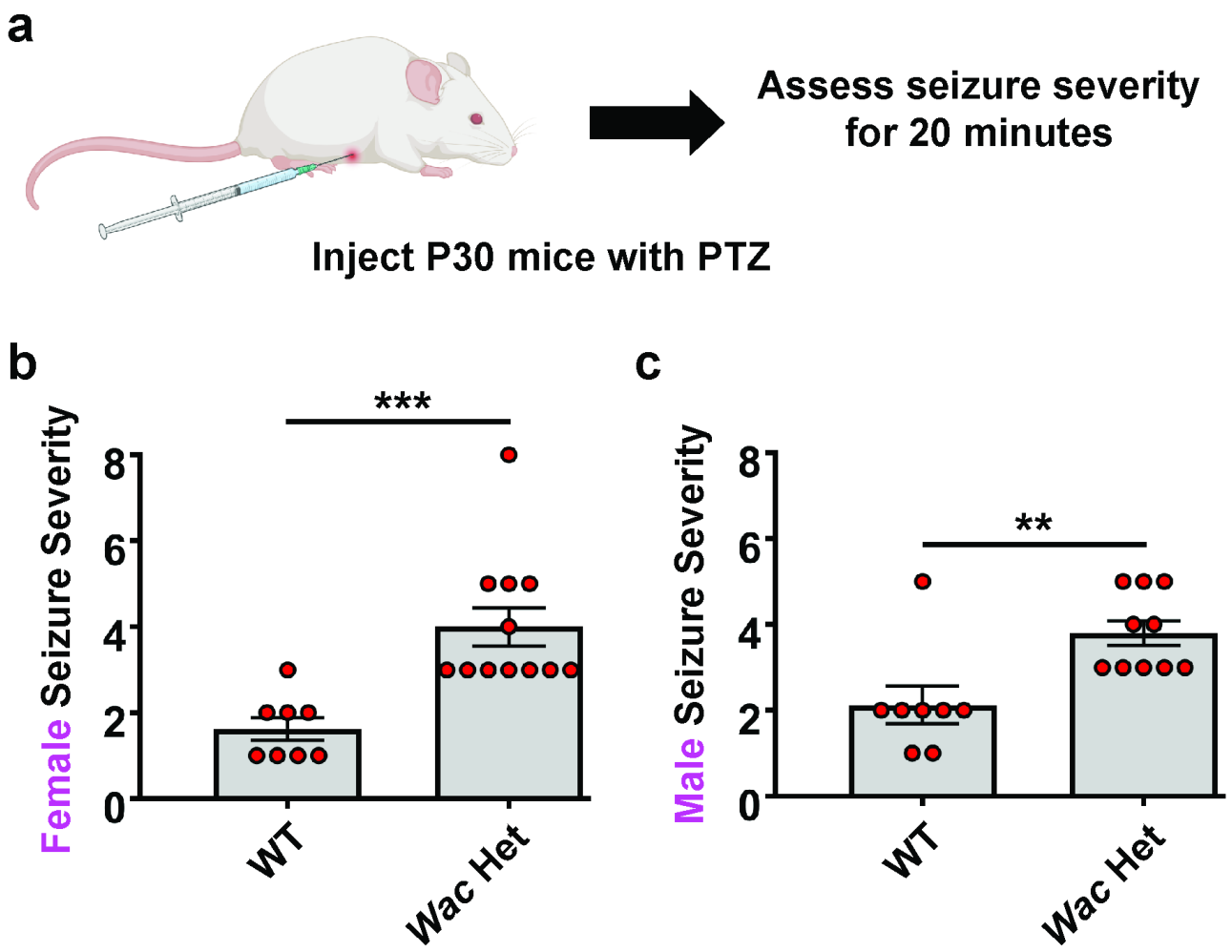
Seizures

Wac Het mice are more susceptible to seizures

Used a drug to lower brain inhibition (PTZ)

Rated seizure behavior from 1-8

- 8 is most severe
- 5 is a tonic-clonic seizure
- 1 is freezing in their cage

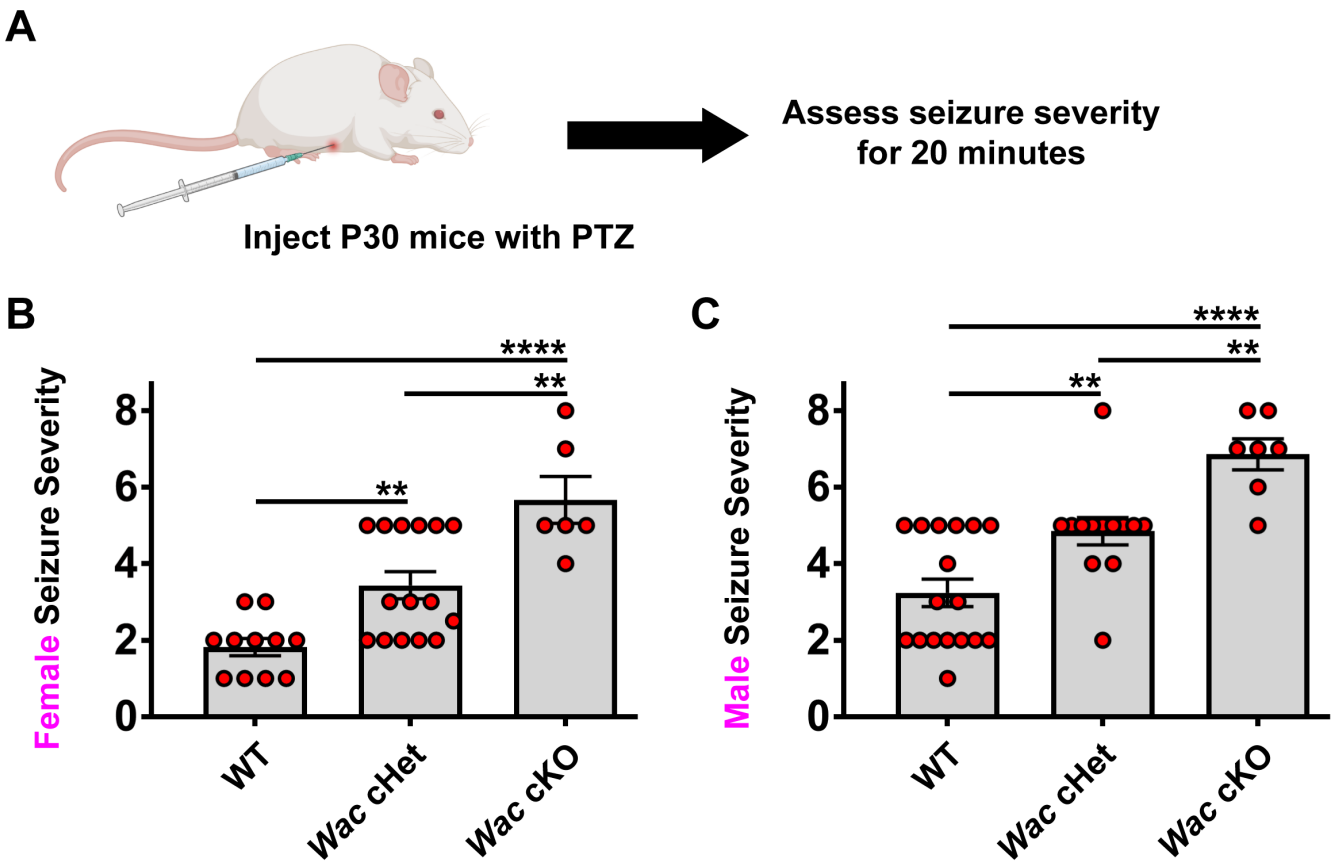


Certain brain cell types may underlie seizures

Loss of *Wac* in GABAergic inhibitory neurons = increased seizures

The *Wac* cHets are most similar to our previous mice

Loss of *Wac* in glutamatergic excitatory neurons = no change



Using these new Wac mouse models to determine what other changes could be due to specific cell types

What’s new

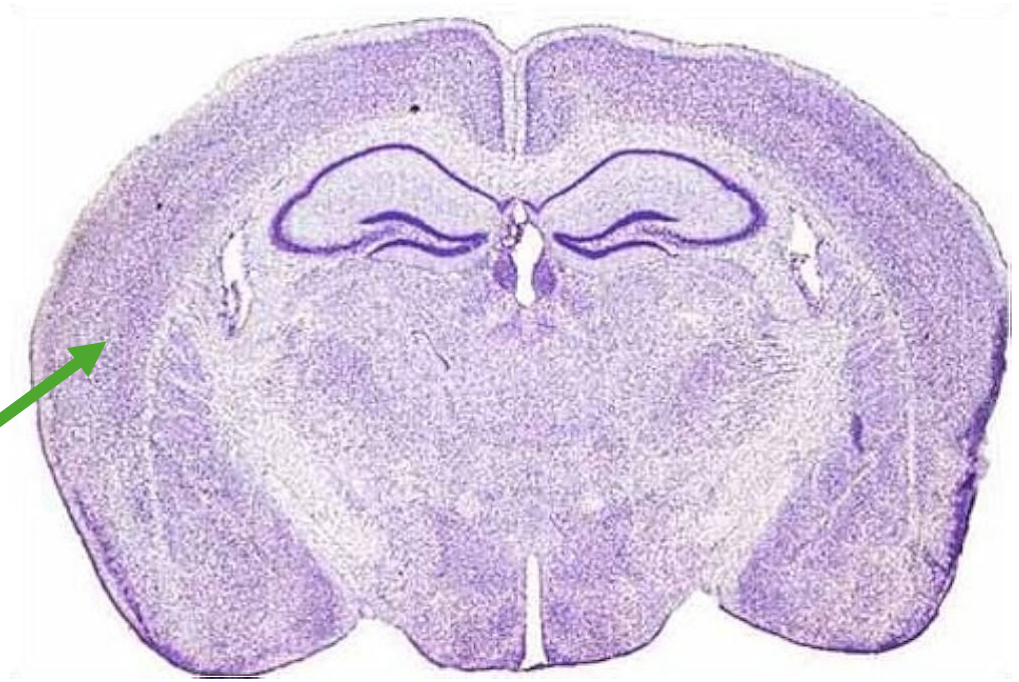
Are there changes in brain volume and/or specific regions?

Worked with UC Irvine imaging core to perform magnetic resonance imaging (MRI) on adult mice

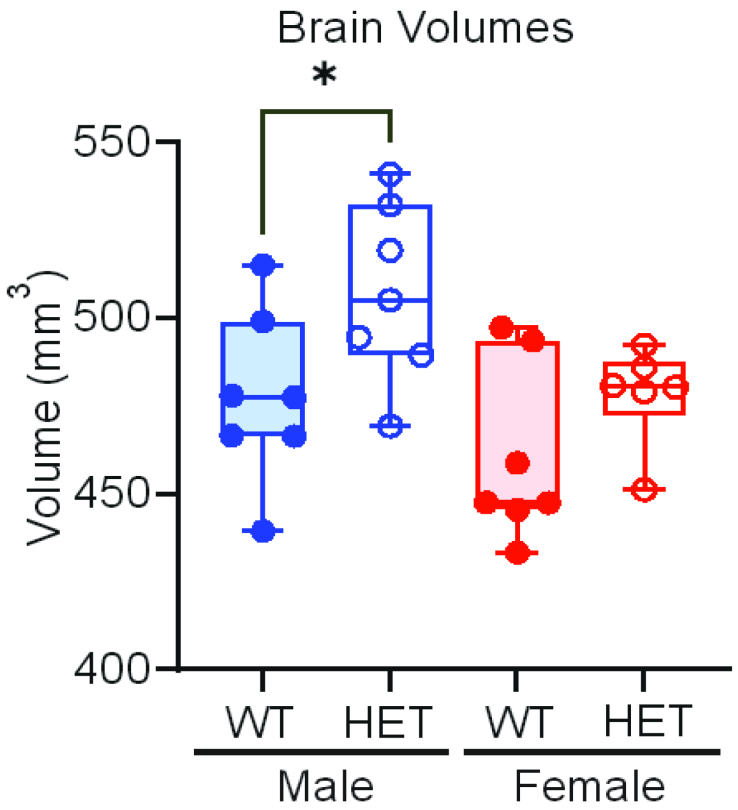
Whole brain volume

and

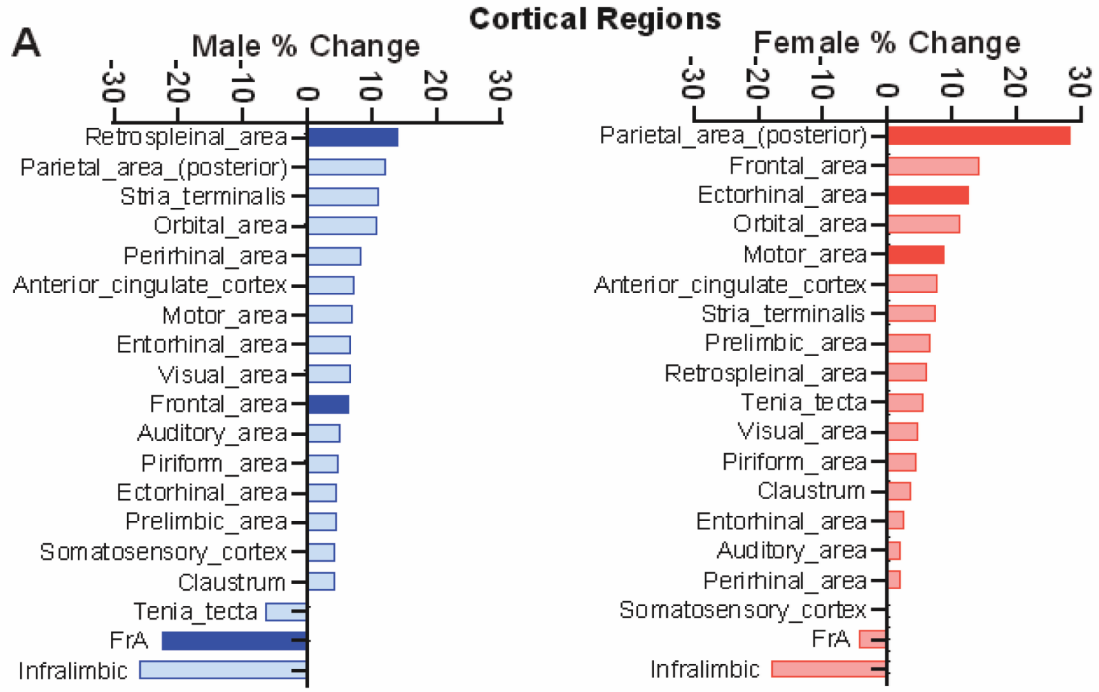
Specific domains, like cortex analyzed

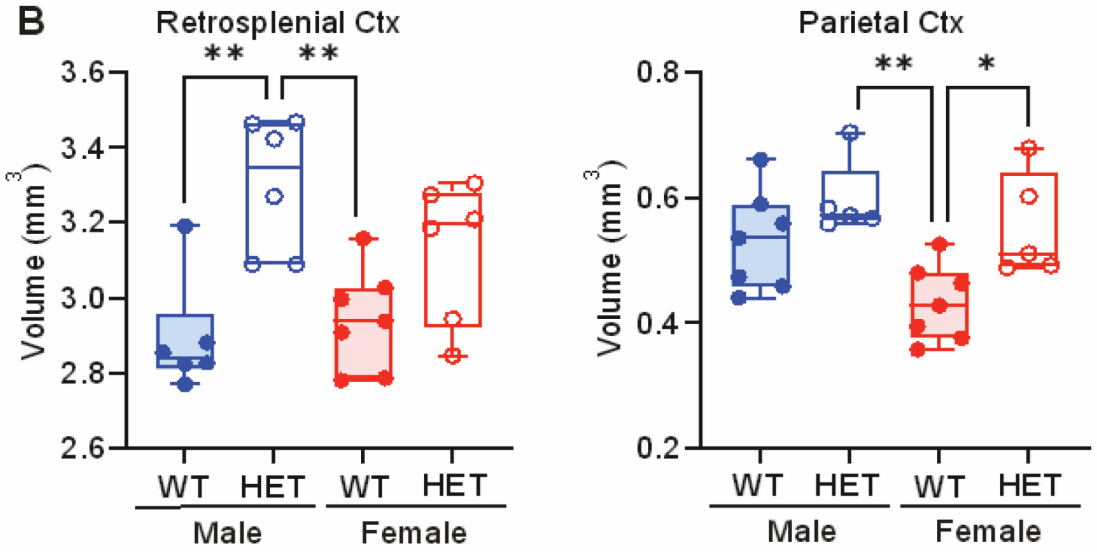


New data reveal alterations in brain volume that bias toward males



All measure were made in adult mice





Vertebrate model studies summary so far…

Vogt and Kim labs still looking into each model

Recapitulate relevant craniofacial, behavior and seizure changes
Both labs have gene expression changes to follow up on

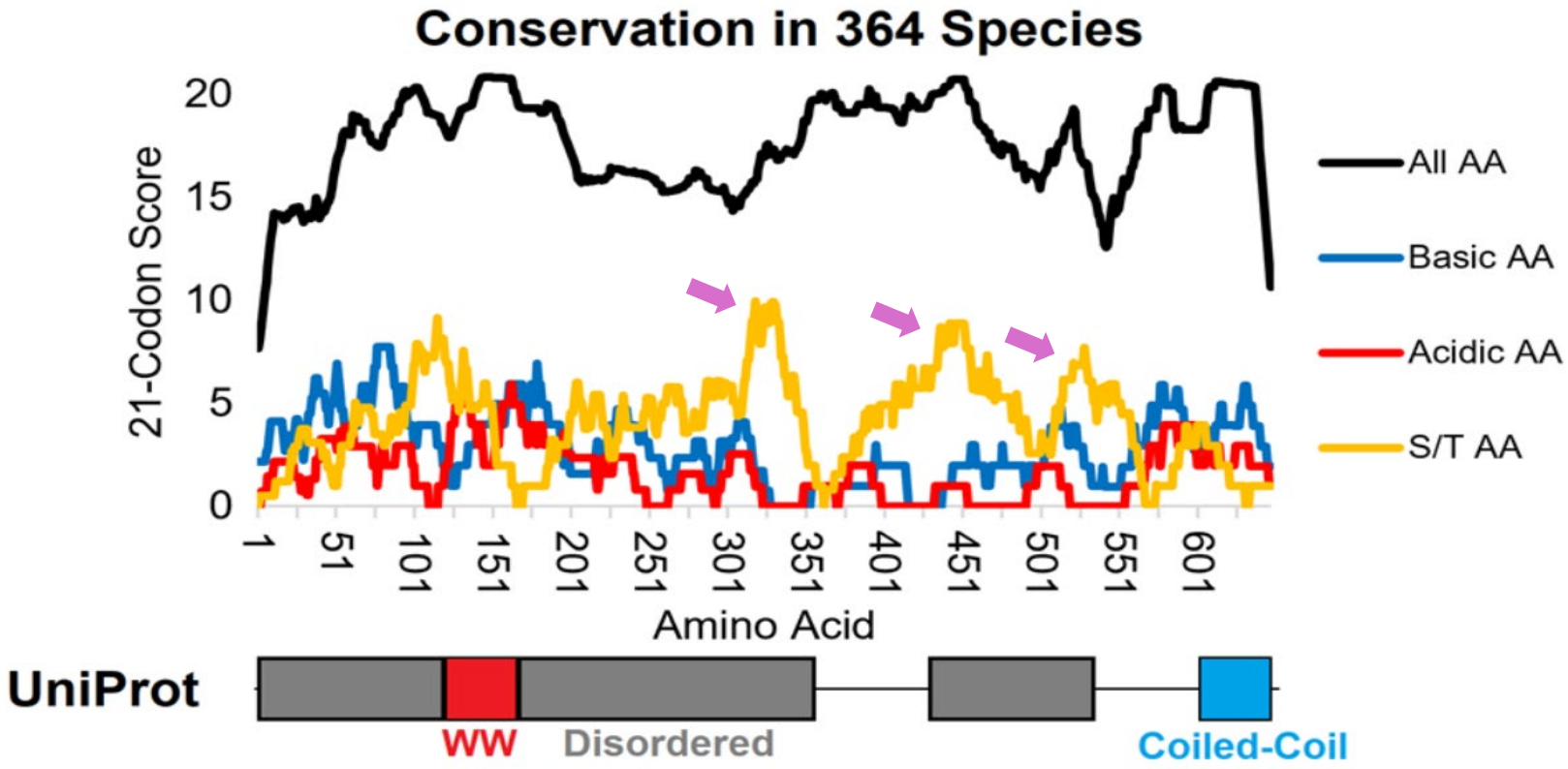
New findings include finding specific brain cell types and areas that should be more focused on in future studies

- GABAergic neurons and seizures
- Brain regions that are different in size when mice are adults

Finally, we are trying to go after how human genetic variants could impact Wac function

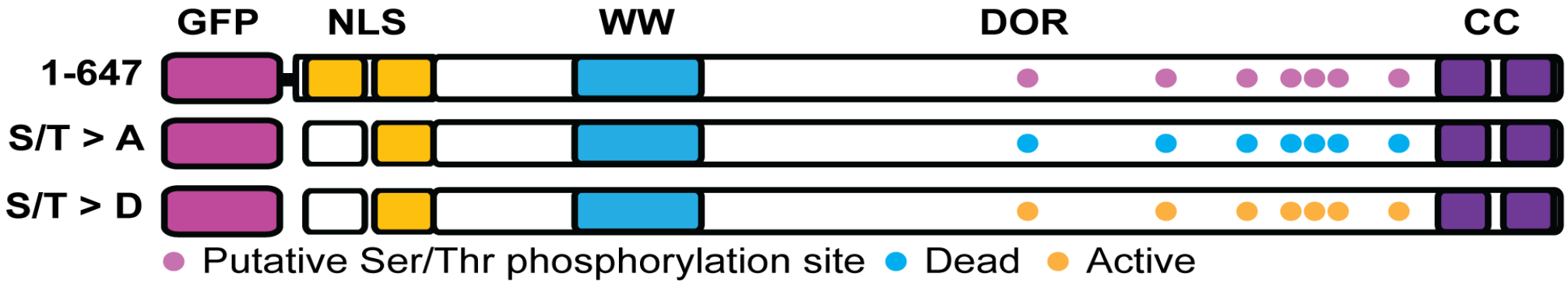
Human genetic variants enriched in the *WAC* gene

Many are found in an unstudied region that contains predicted "on/off switches"



Rudolph et al., 2023. Biology.

Many human genetic variants resemble phosphorylation sites

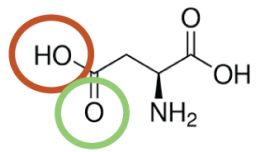


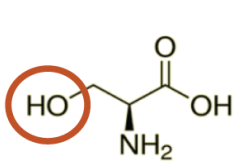
Rudolph et al., 2023. Biology.

Human variants

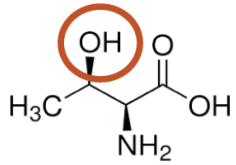
P347 > S next to S346
S449
S511
S520
S523
S525
T556

Aspartic acid (active)

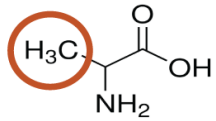




Serine

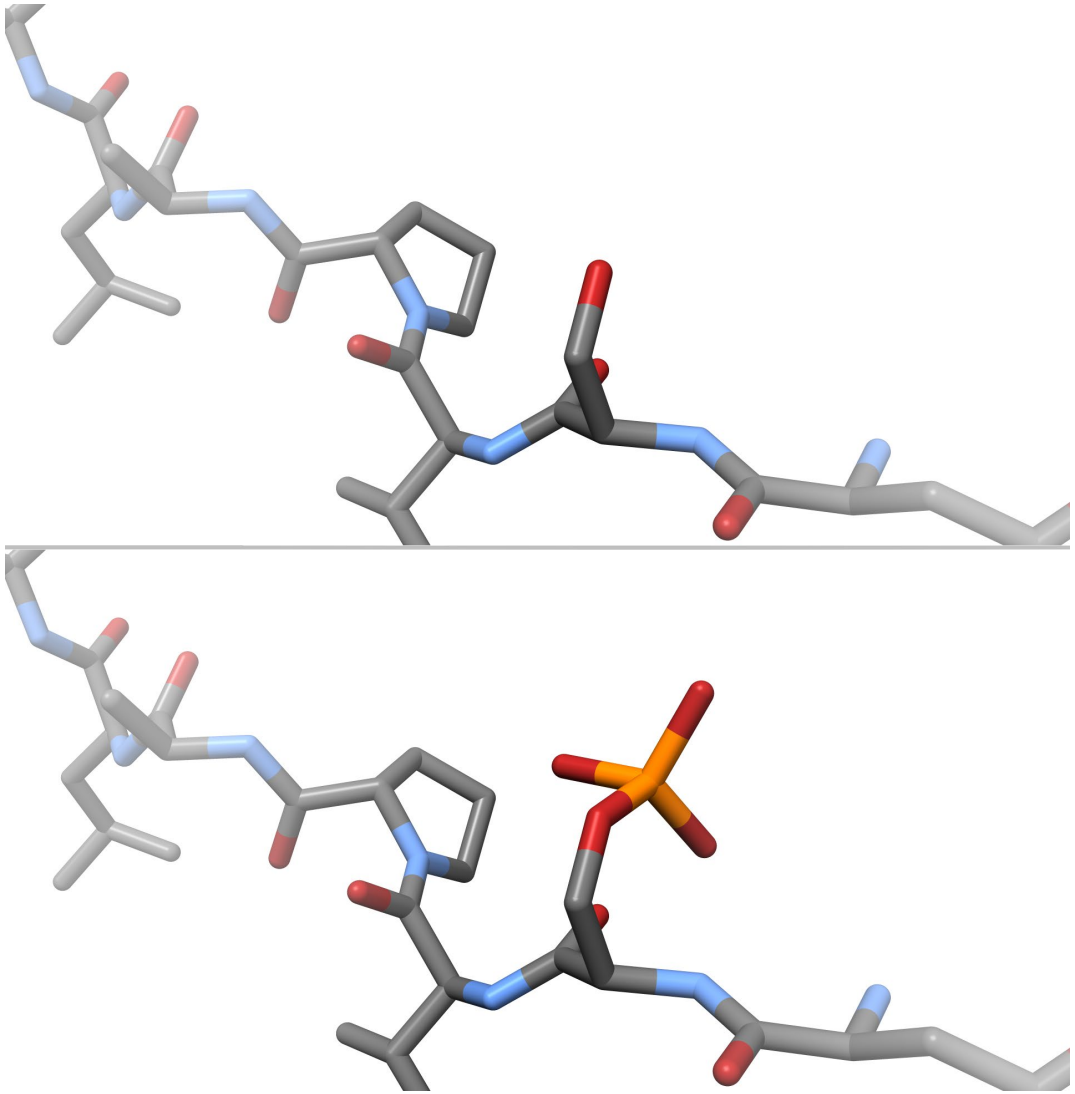


Threonine



Alanine (dead)

Adding a phospho group to a protein changes its shape/function



Sometimes thought of as on/off switches

Regulated by Kinases (proteins that add these groups to proteins)

Several kinases have FDA approved drugs

So, do these amino acids in WAC do anything?

Serine/Threonine amino acids crucial for WAC protein abundance

ST>> A = dead/no phosphorylation

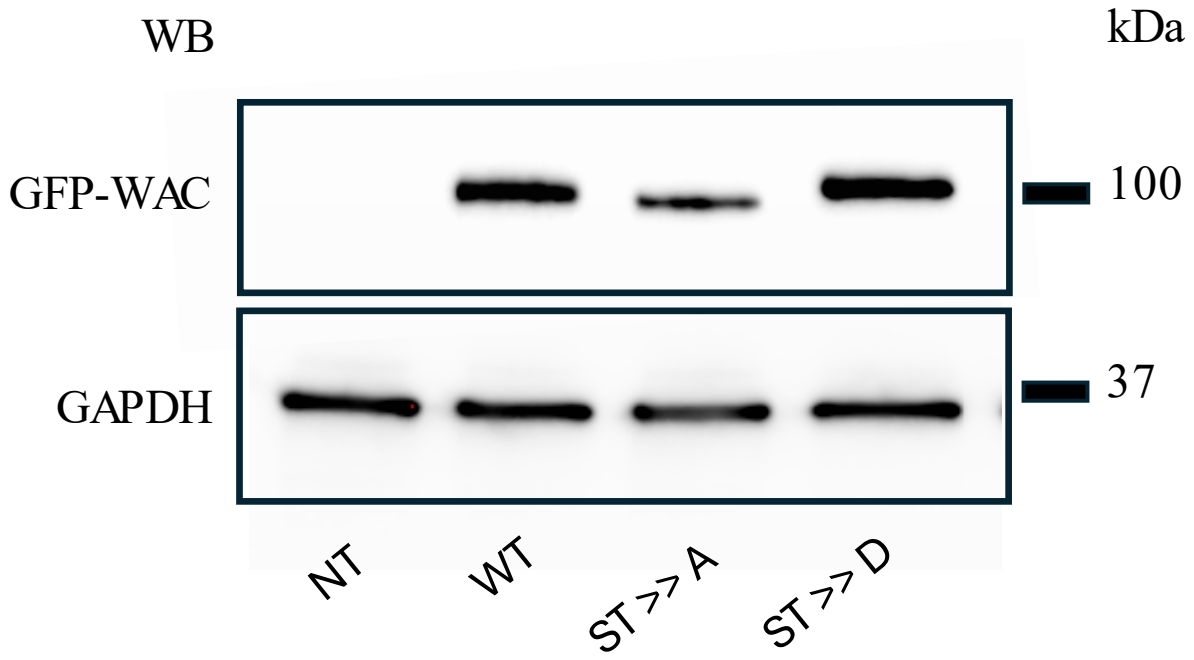
ST>> D = always active/constant phosphorylation

ST>> A smaller (expected) and less protein present

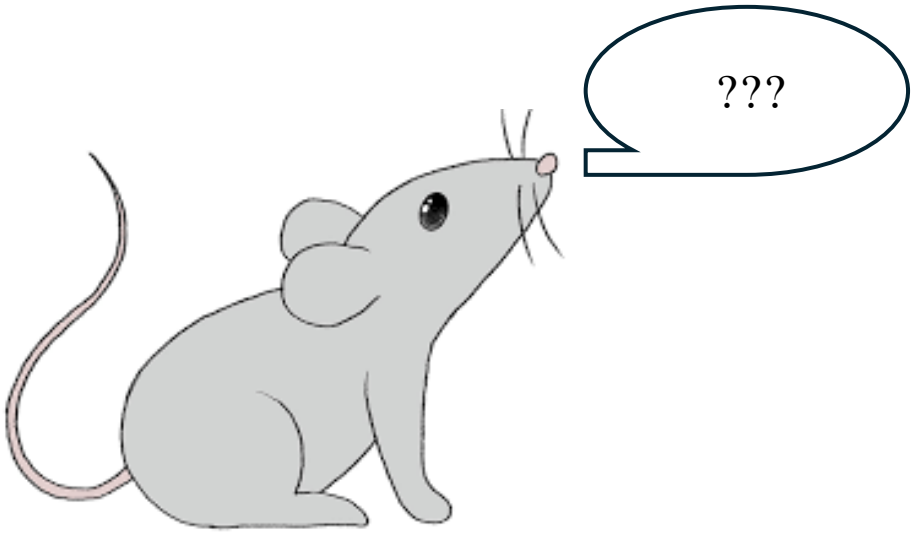
ST>> D larger and more protein present

1 or more of these genetic variants is critical for WAC protein abundance

Since DESSH individuals likely have a reduction in total WAC protein, any therapeutic that could take advantage of this could be a future inroad…



Thank you and acknowledgements



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