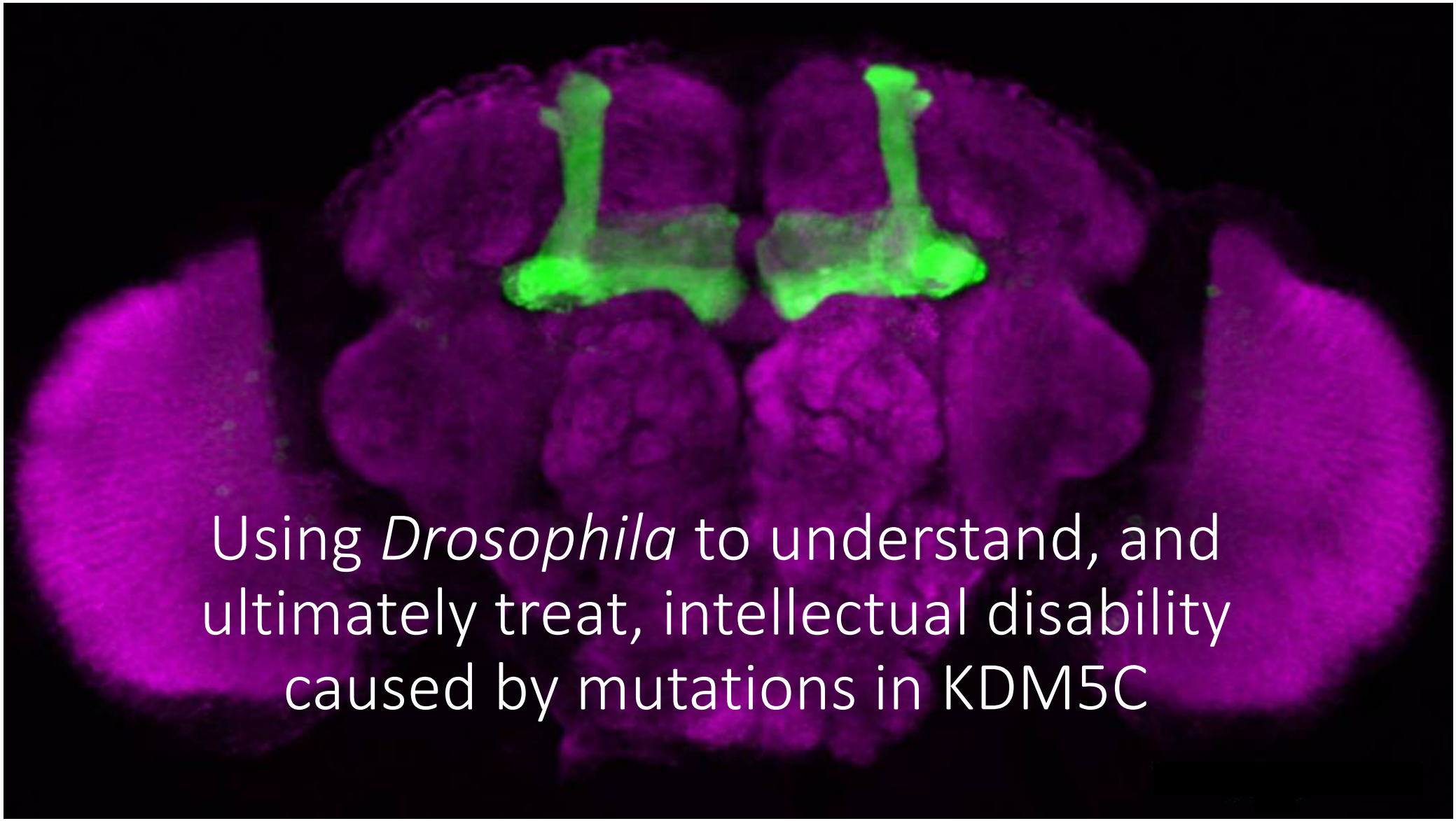
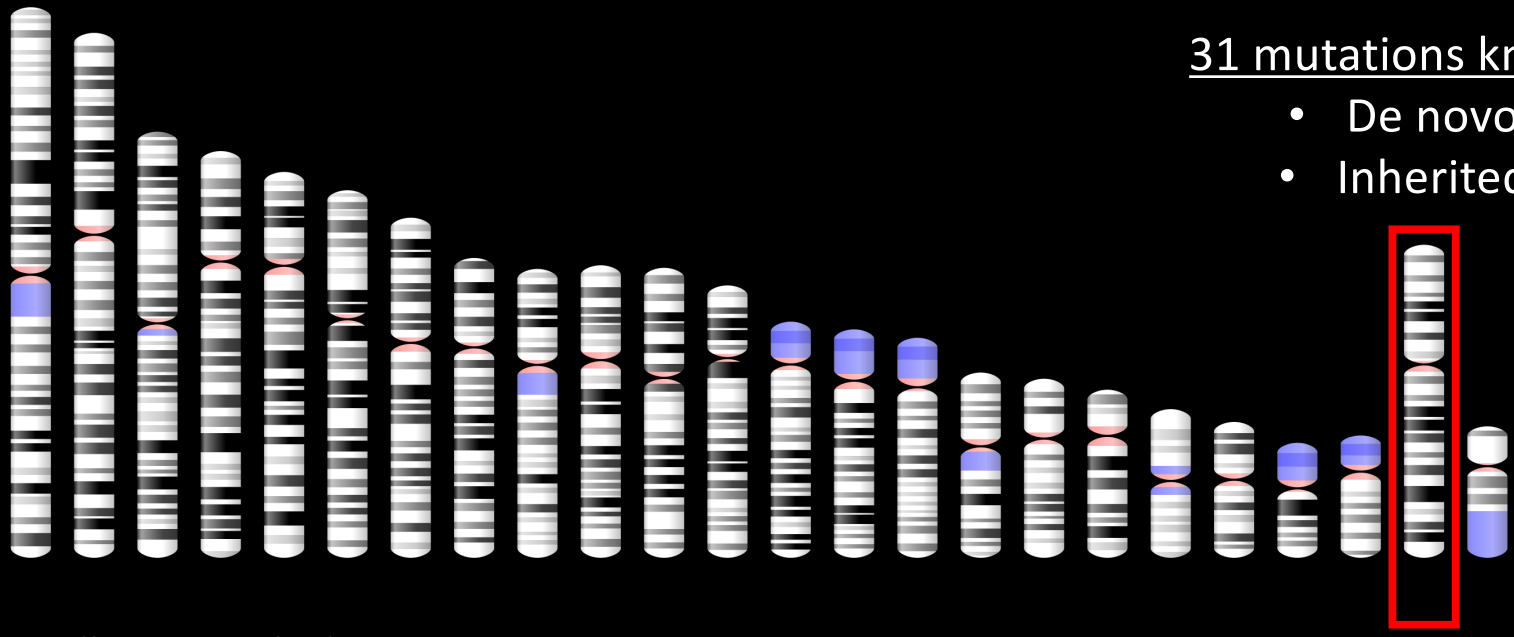

Using *Drosophila* to understand, and
ultimately treat, intellectual disability
caused by mutations in KDM5C

KDM5C is an X-linked gene that is mutated in patients with intellectual disability



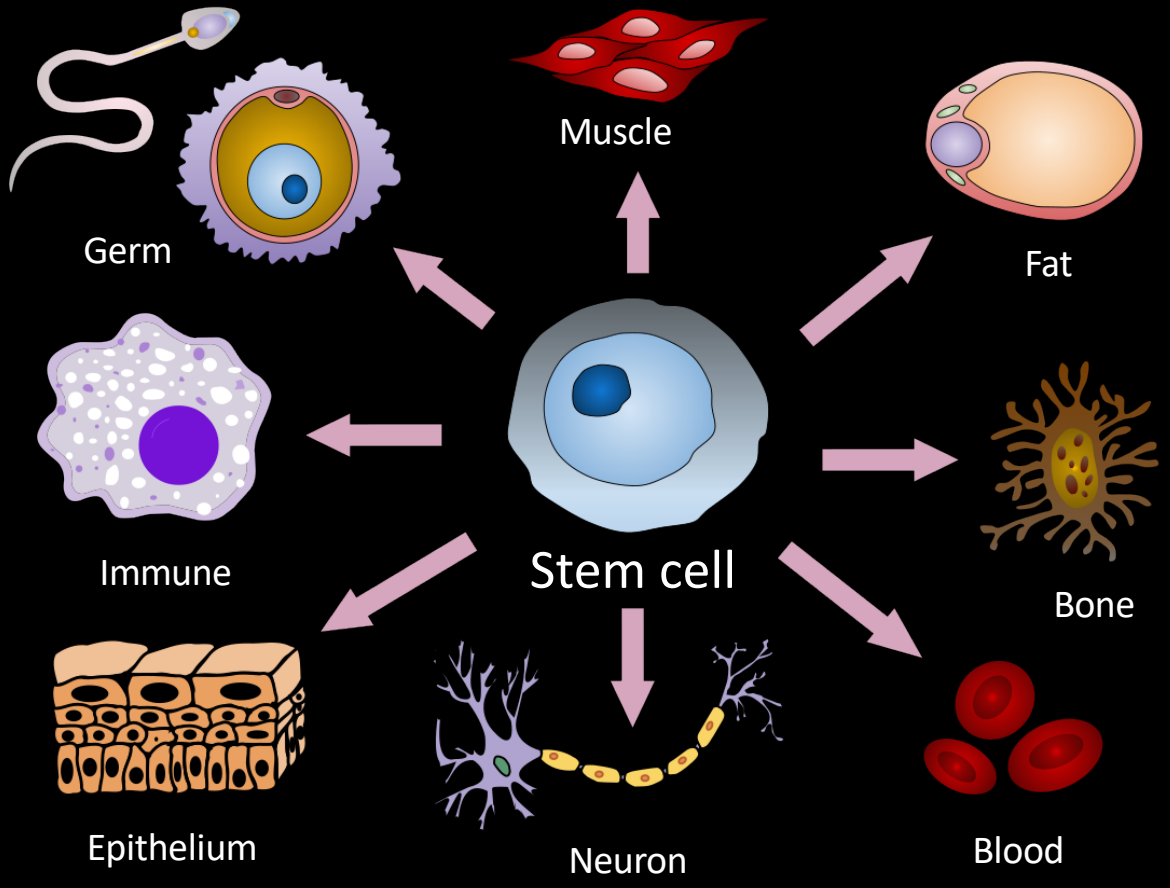
https://en.wikipedia.org/wiki/KDM5C#Function

31 mutations known

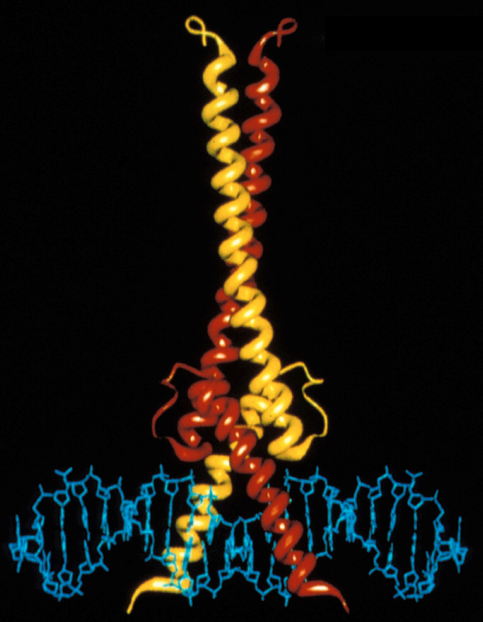
- De novo
- Inherited

Mild to severe intellectual disability, autism, short stature, seizures, hyperreflexia, increased aggression

KDM5C regulates gene expression – which is important for everything

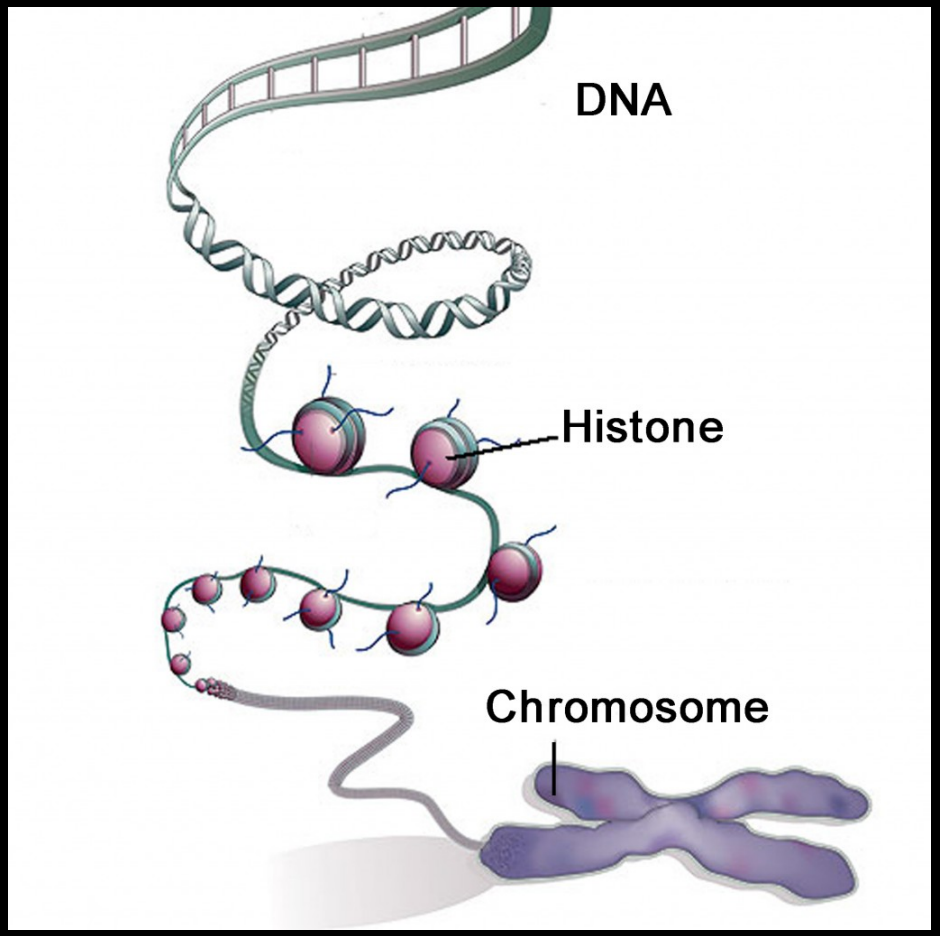


Transcription factors bind DNA



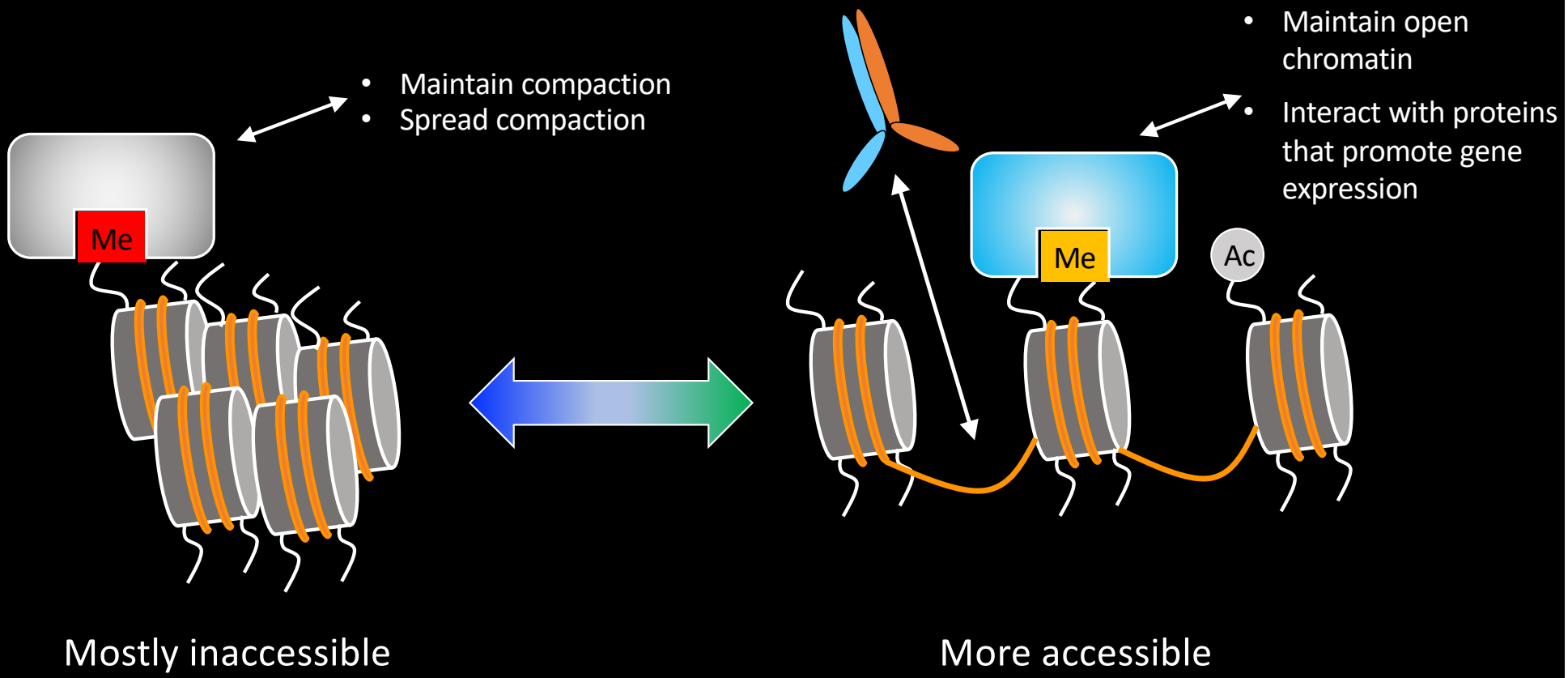
Ferré D'Amaré et al., 1994

In our cells, DNA occurs in the context of chromatin



Gene regulation is important and must occur in the context of chromatin

Chromatin affects gene regulation

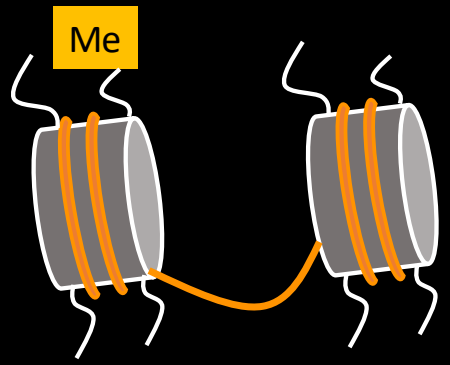


What do we know about how KDM5C functions?

KDM5C protein

JmjN + JmjC

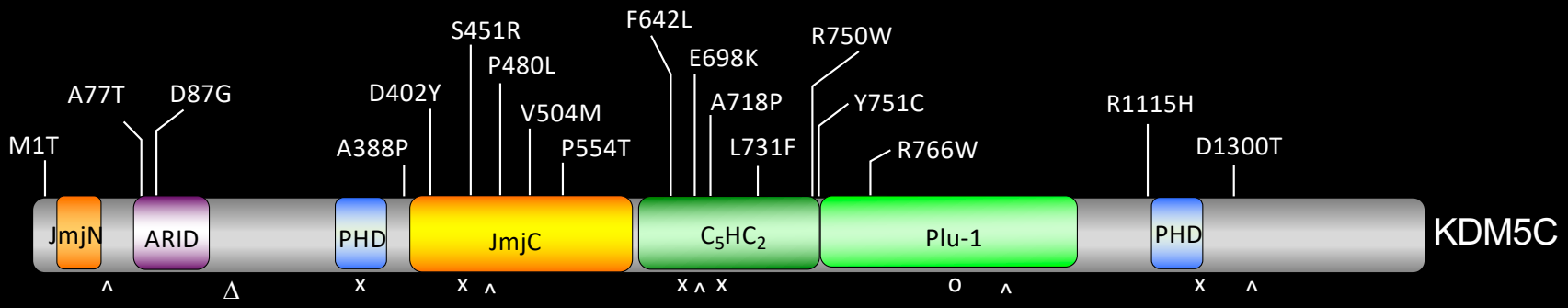
Demethylate Via JmjN/C



ARID Can bind DNA via ARID

- Other functions that remain to be discovered

The link between KDM5C mutations and neuronal function remains largely unknown



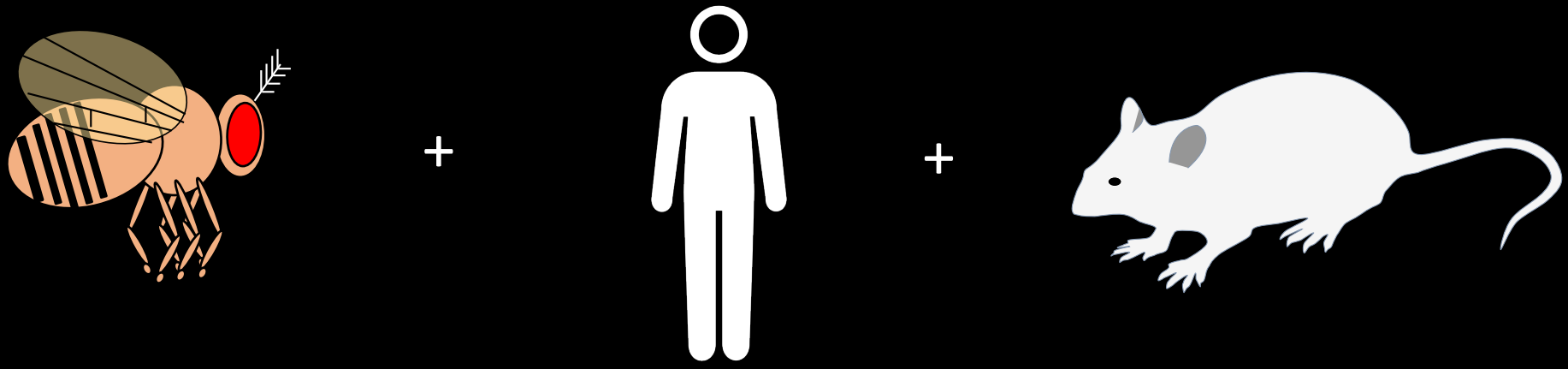
x = stop codon ^ = frameshift Δ splice site

****

Which target genes are affected?
Do all mutations affect the same pathways?
What is the role of demethylase activity?
Which cell types are affected and what happens to them?

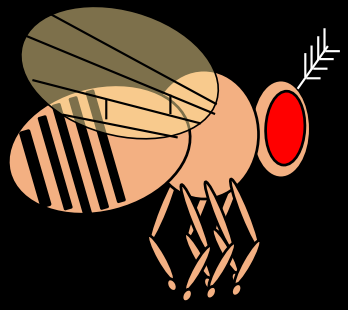
****

Understanding and (ultimately) treating patients with KDM5C mutations is going take a team effort

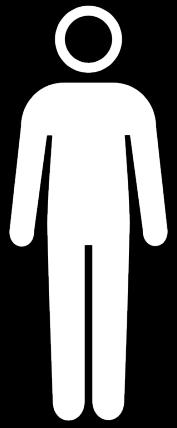


- Difficult to examine neuronal cells in a physiological (normal) setting
- Genetic background of patients very diverse making it difficult to determine which
- Ethical considerations makes testing potential treatments initially difficult

Understanding and (ultimately) treating patients with KDM5C mutations is going take a team effort



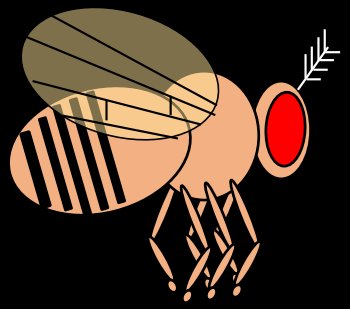
+



+

Dr. Shigeki Iwase

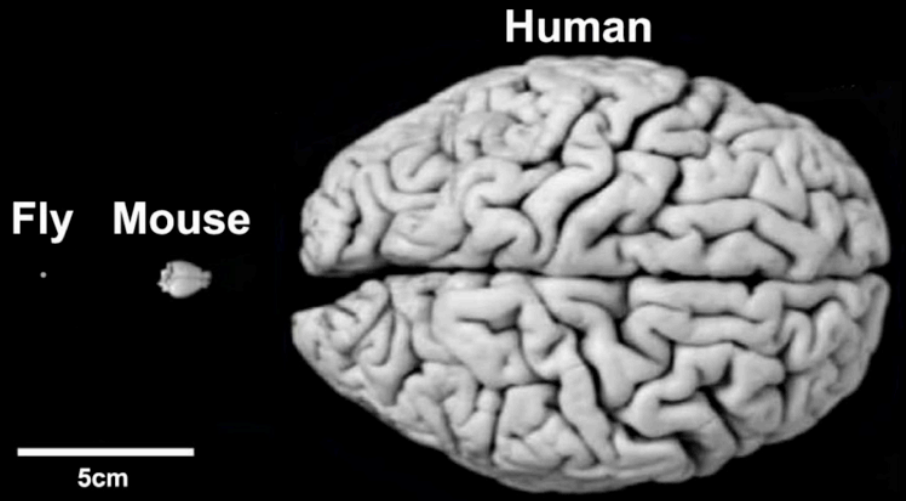
Why did we choose flies?



Drosophila have been used for 100 years to unlock secrets of human physiology and biology

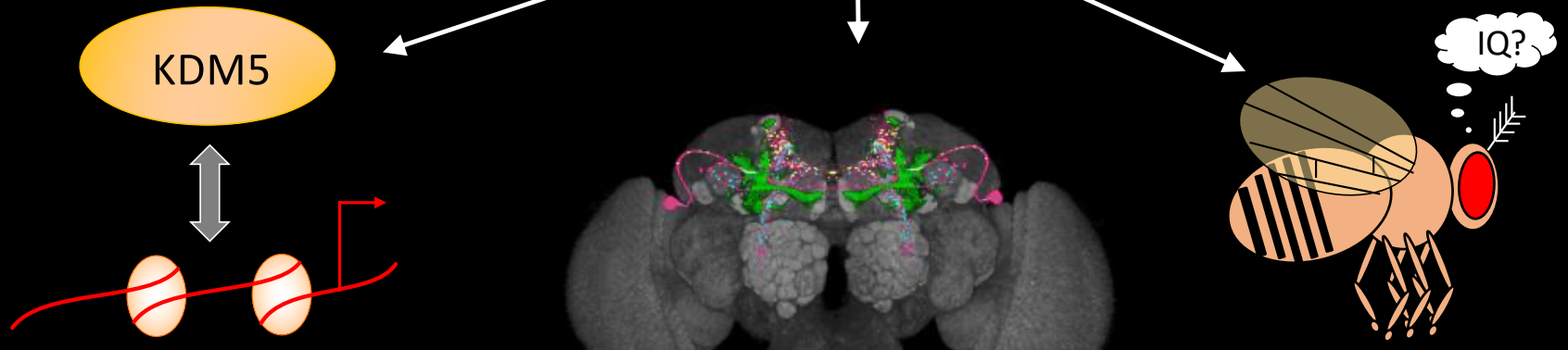
75% of genes associated with human disorders have an equivalent gene in flies

Despite *Drosophila* not being the same size as a human, nor looking much like one, gene function is highly conserved



Drosophila have an unparalleled genetic toolkit

- Loss of KDM5
- 10 strains with point mutations found in patients with intellectual disability
- A strain specifically lacking demethylase activity (not a patient mutation)

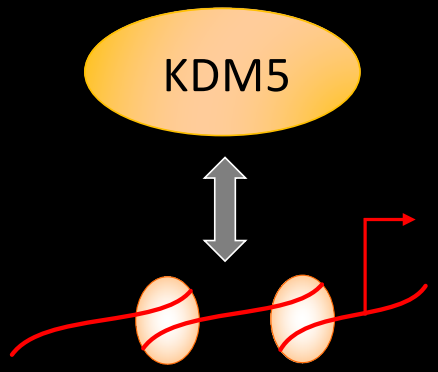


KDM5-mediated changes to transcription

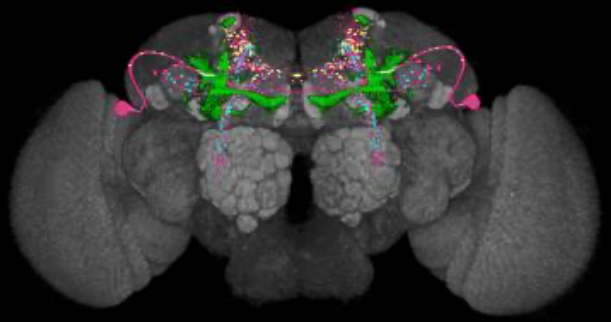
Changes to neuronal morphology

Cognitive and other behavioral defects

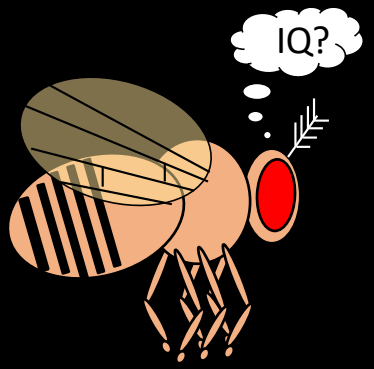
The power of combining multiple approaches



KDM5-mediated changes to transcription



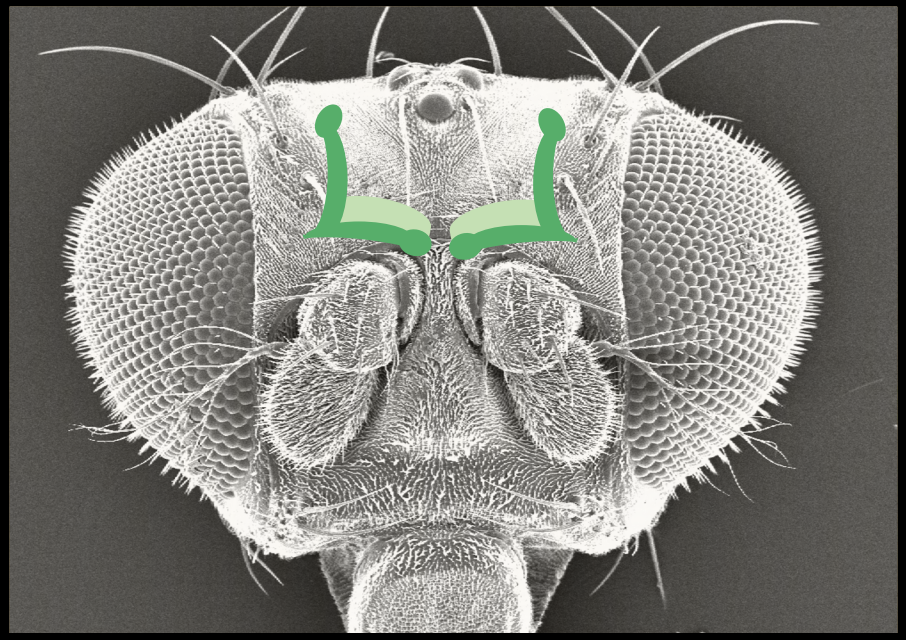
Changes to neuronal morphology



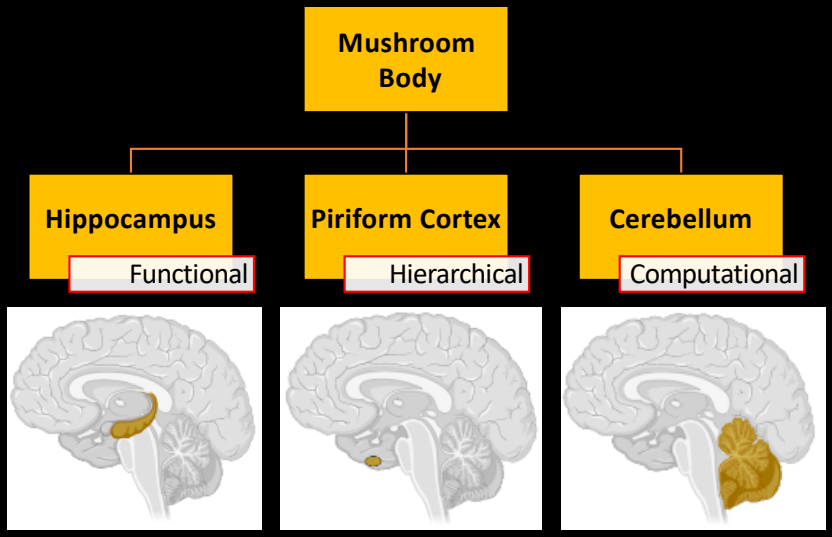
Cognitive and other behavioral defects

- Do mutations affect a core set of target genes? What are they?
- What are the neuronal defects?
- What is the contribution of KDM5's demethylase activity?

The mushroom body is critical for learning and memory in flies

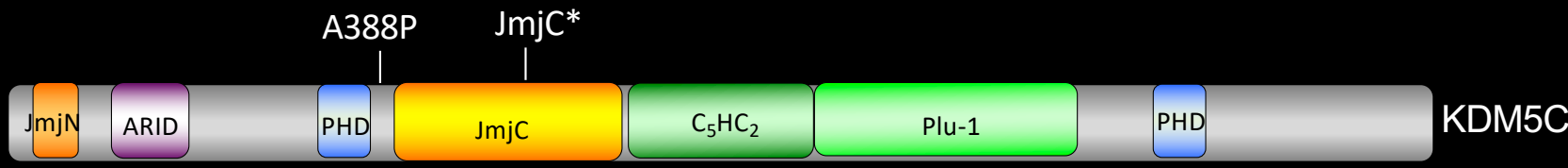


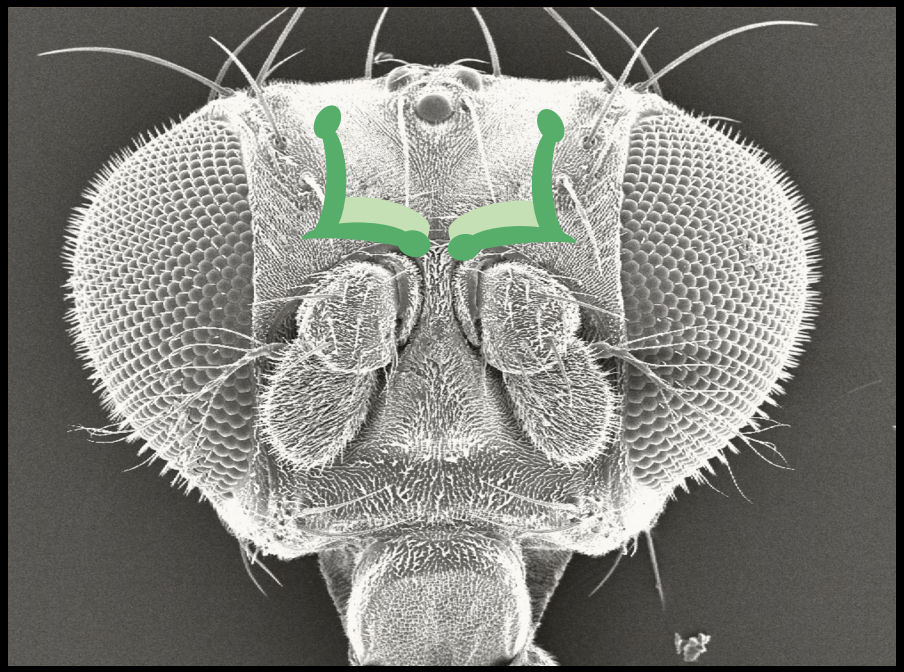
Adult mushroom body neurons



A tale of demethylase-dependent and independent KDM5 functions

Some alleles simply abolish demethylase activity



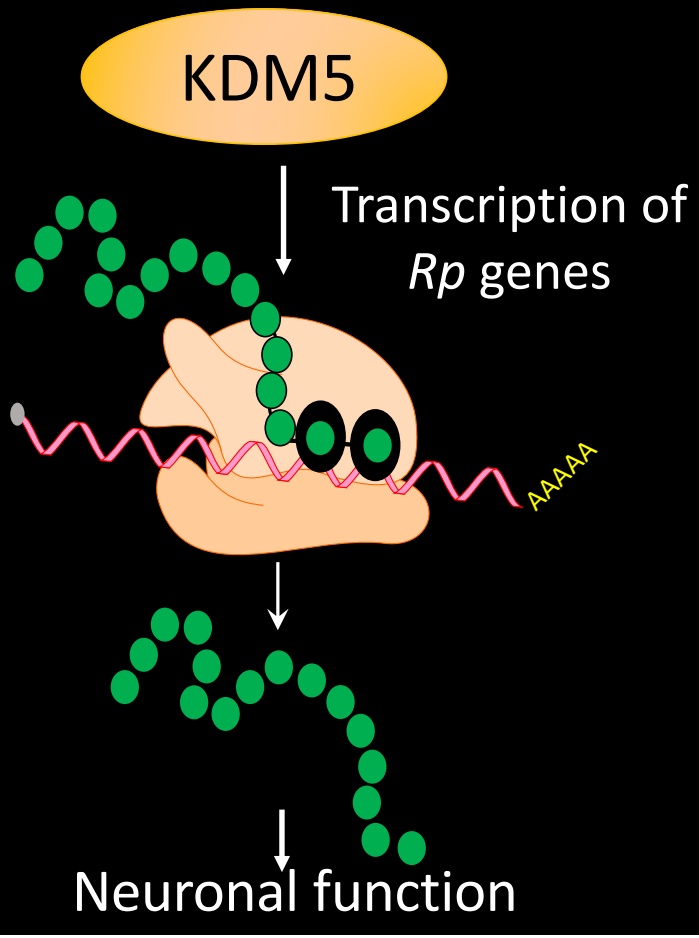


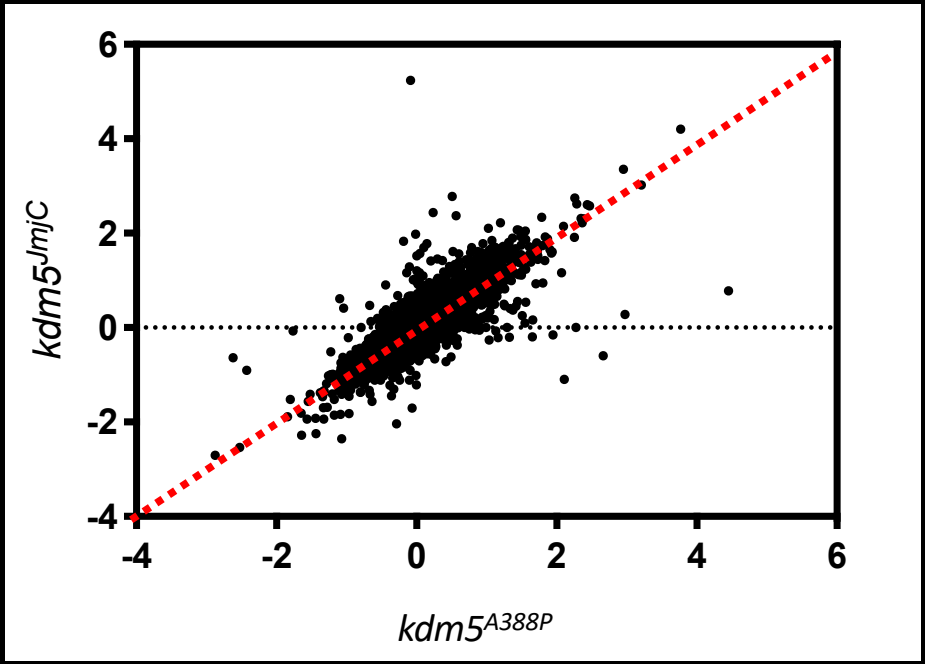
Adult mushroom body neurons

Transcriptome analyses
(examine the expression level of every gene in the genome)

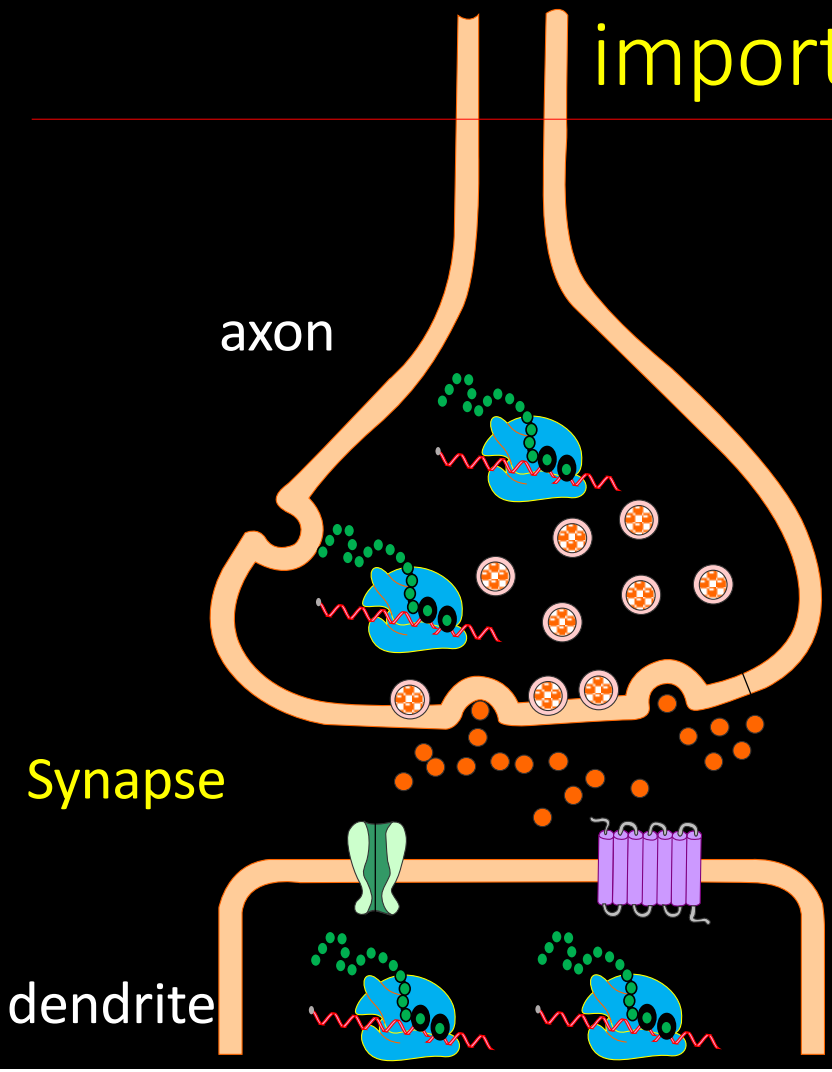
Sumaira Zamurrad

KDM5 is required for the transcription of ribosomal protein genes





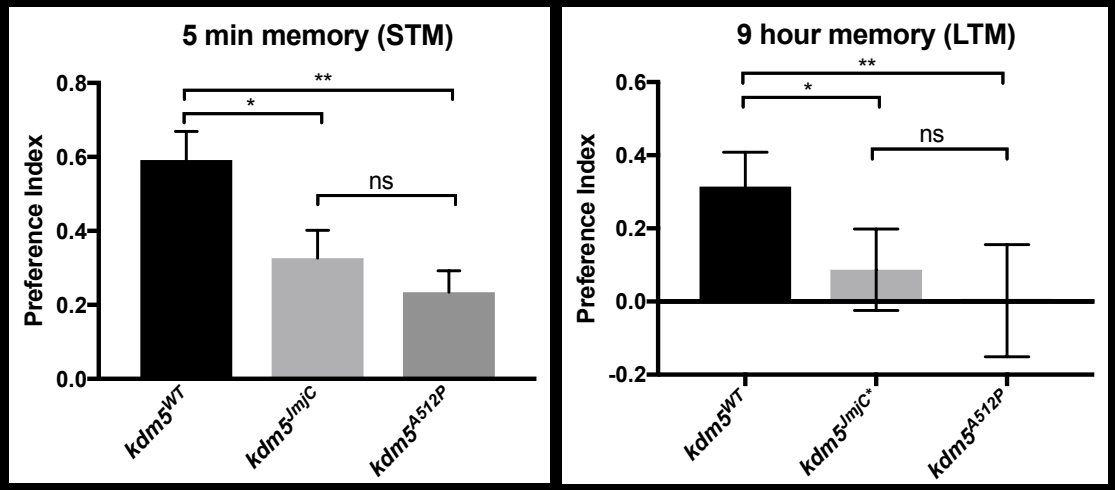
Local translation in neuronal compartments is important for function



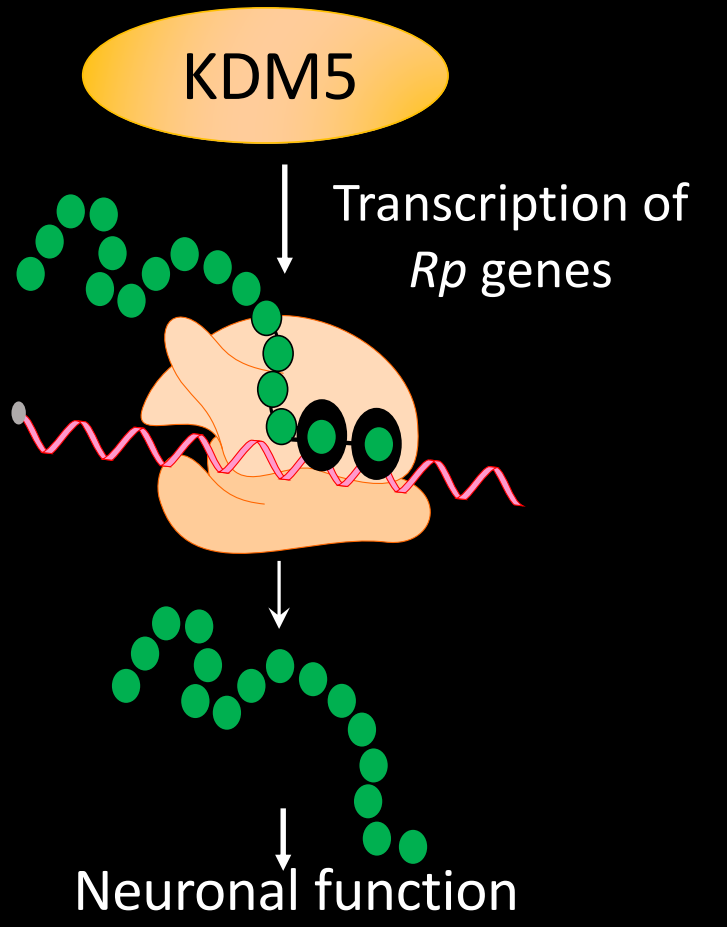
- Mutations in the mTOR pathway are found in ID patients.
- Mutations in the fragile X gene Fmr1 affect translation.
- Alzheimer's Disease patient brains show decreased translation.

The demethylase activity of KDM5 is required for learning and memory

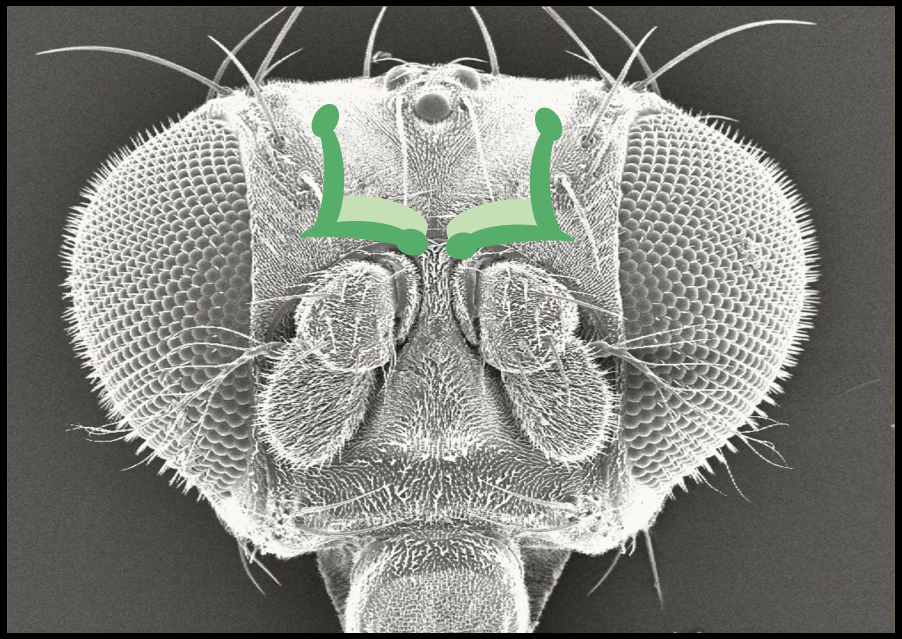
Learning and memory test



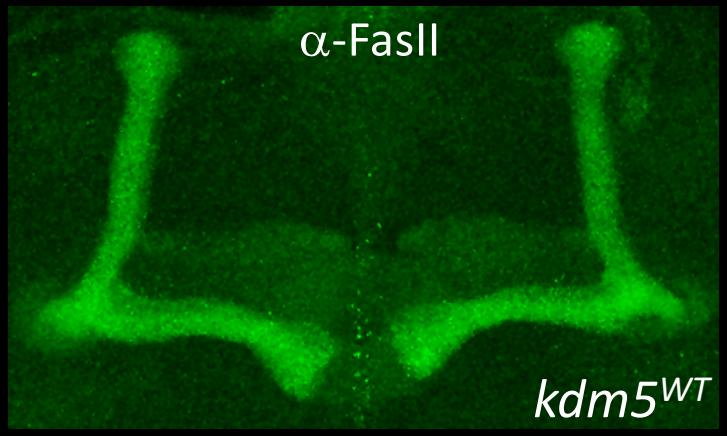
The pathways that mediate short- and long-term memory are evolutionarily conserved

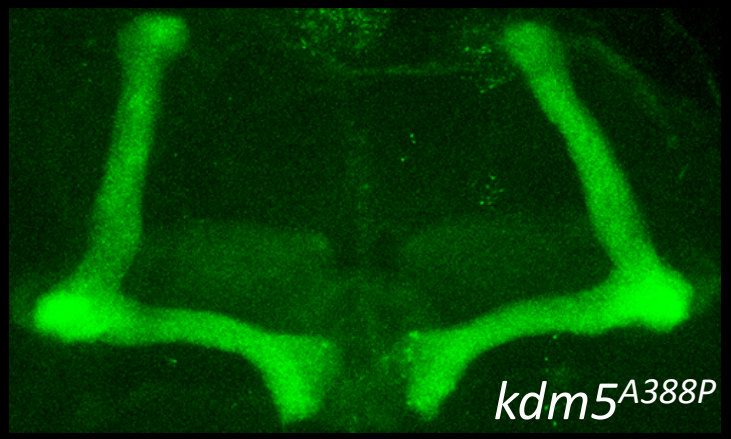


The *kdm5c*^{A388P} mutation does not affect neuronal structure



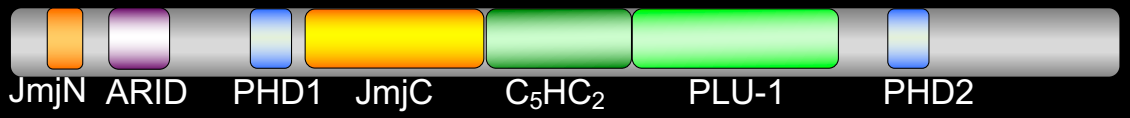
Adult mushroom body neurons





Hayden Hatch

Other *kdm5c* alleles affect neuroanatomy



KDM5C

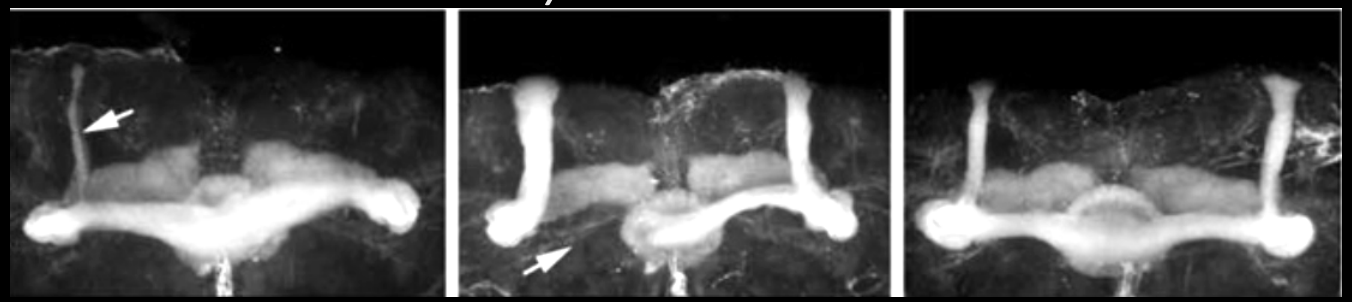
- This slide contained unpublished data that is unable to be made public at this point.

Mushroom body defects are observed in other *Drosophila* models of intellectual disability

fmr1 mutant

Michel et al., 2004

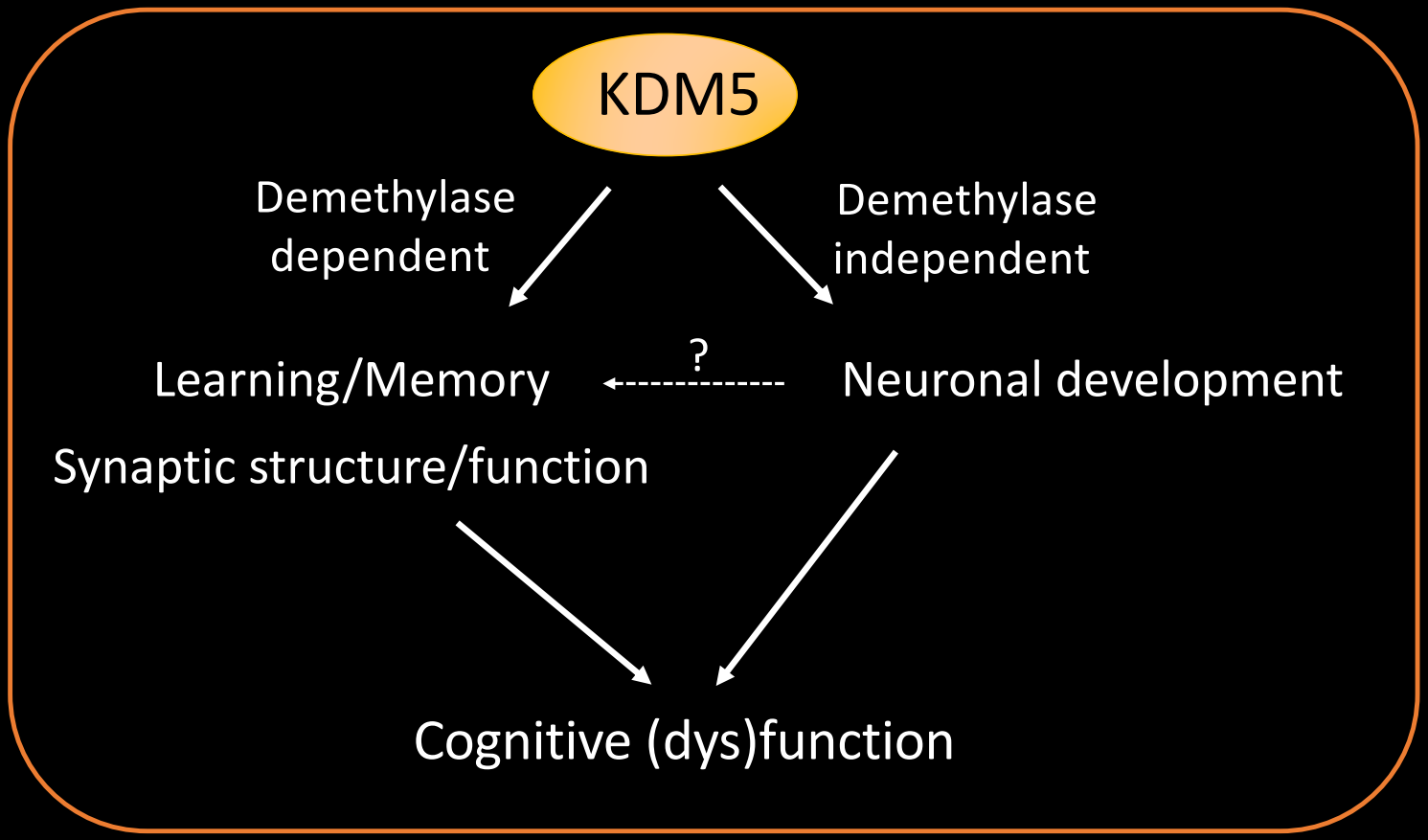
Nab2/ZC3H14 mutant



Kelly et al., 2016

The pathways dysregulated by these mutations are conserved across species

KDM5 functions in neuronal development and function



Understanding the basic biology of KDM5 is the first step to developing treatments for patients.

Thank you

Secombe Lab

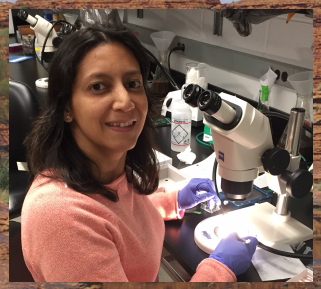
Helen Belalcazar
Hayden Hatch
Michael Rogers
Blair Schneider
Matanel Yheskel

Former lab members

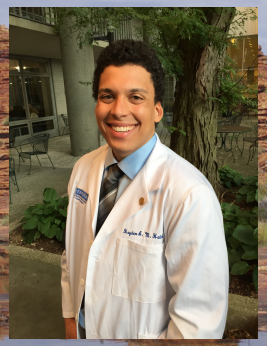
Coralie Drelon
Christina Greer
Shannon Lightcap
Xingyin Liu
Ariel Parker
Sumaira Zamurrad

Collaborators

Dr. Owen Marshall (University of Tasmania)
Dr. Xingyin Liu (Nanjing Medical University)
Dr. Nicola Neretti (Brown University)
Dr. Faith Leibl (Southern Illinois University)



Helen Belalcazar



Hayden Hatch

Mike Rogers

POSTERS ON MAIN STREET

Funding

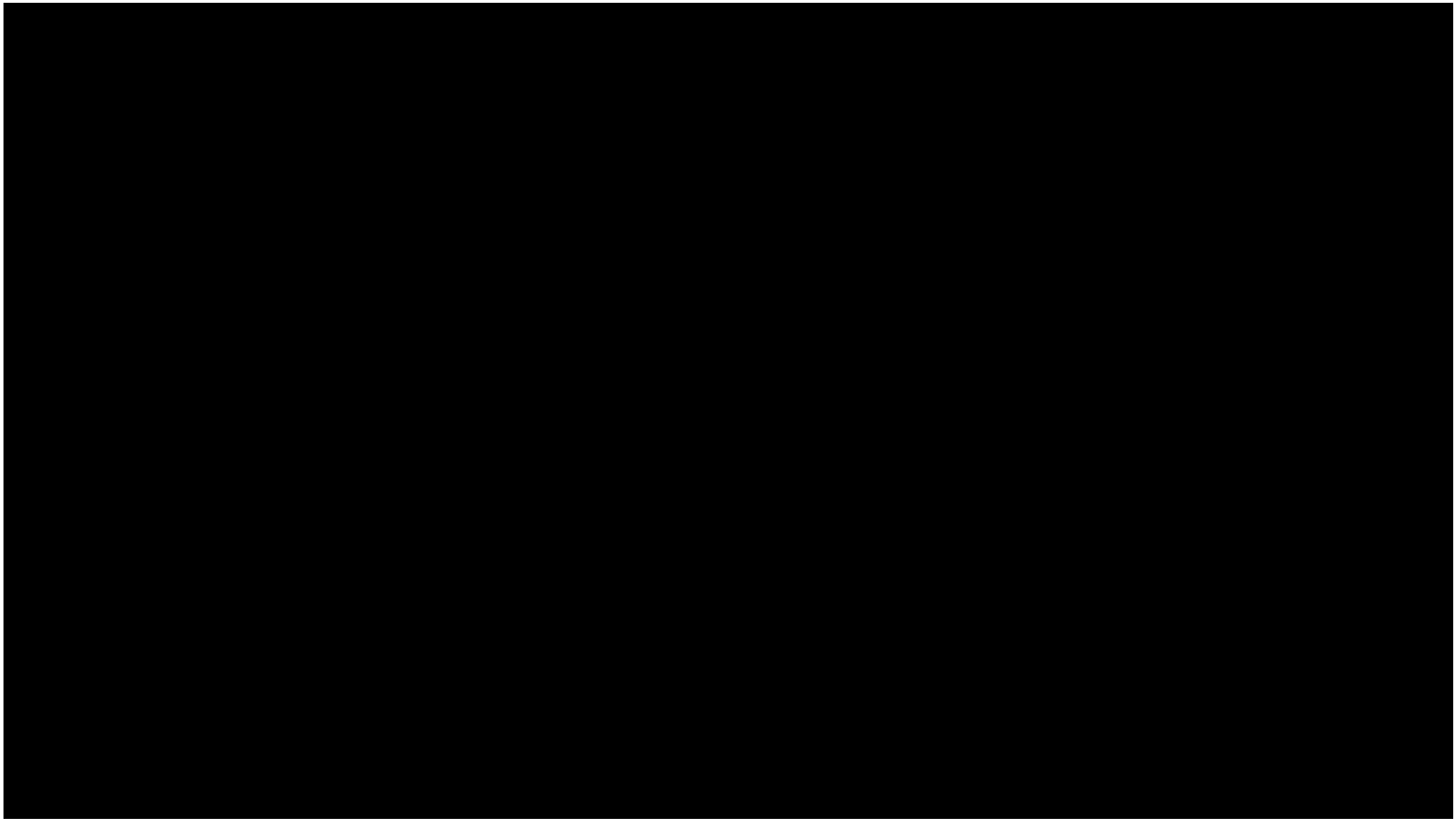
NIGMS

NIH National Institute on Aging

EINSTEIN Albert Einstein College of Medicine

THE IRMA T. HIRSCHL TRUST

march of dimes A FIGHTING CHANCE FOR EVERY BABY



KDM5C Support Group

Home | Create

KDM5C Support Group

Private group

- About
- **Discussion**
- Announcements
- Members
- Events
- Videos
- Photos
- Files
- Watch Party

Search this group

Joined | Notifications | Share | More

Write Post | Photo/Video | Live Video | More

Write something...

Photo/Video | Watch Party | Tag Friends | ...

INVITE MEMBERS

+ Enter name or email address...

MEMBERS 149 Members







Most Improved
KAMIAKIN COUGARS
Gabby Robl
GIRLS BADMINTON






MY FIRST DA
of
My favorite things are:
9
Camping
Pool
when I grow up
I want to be a: