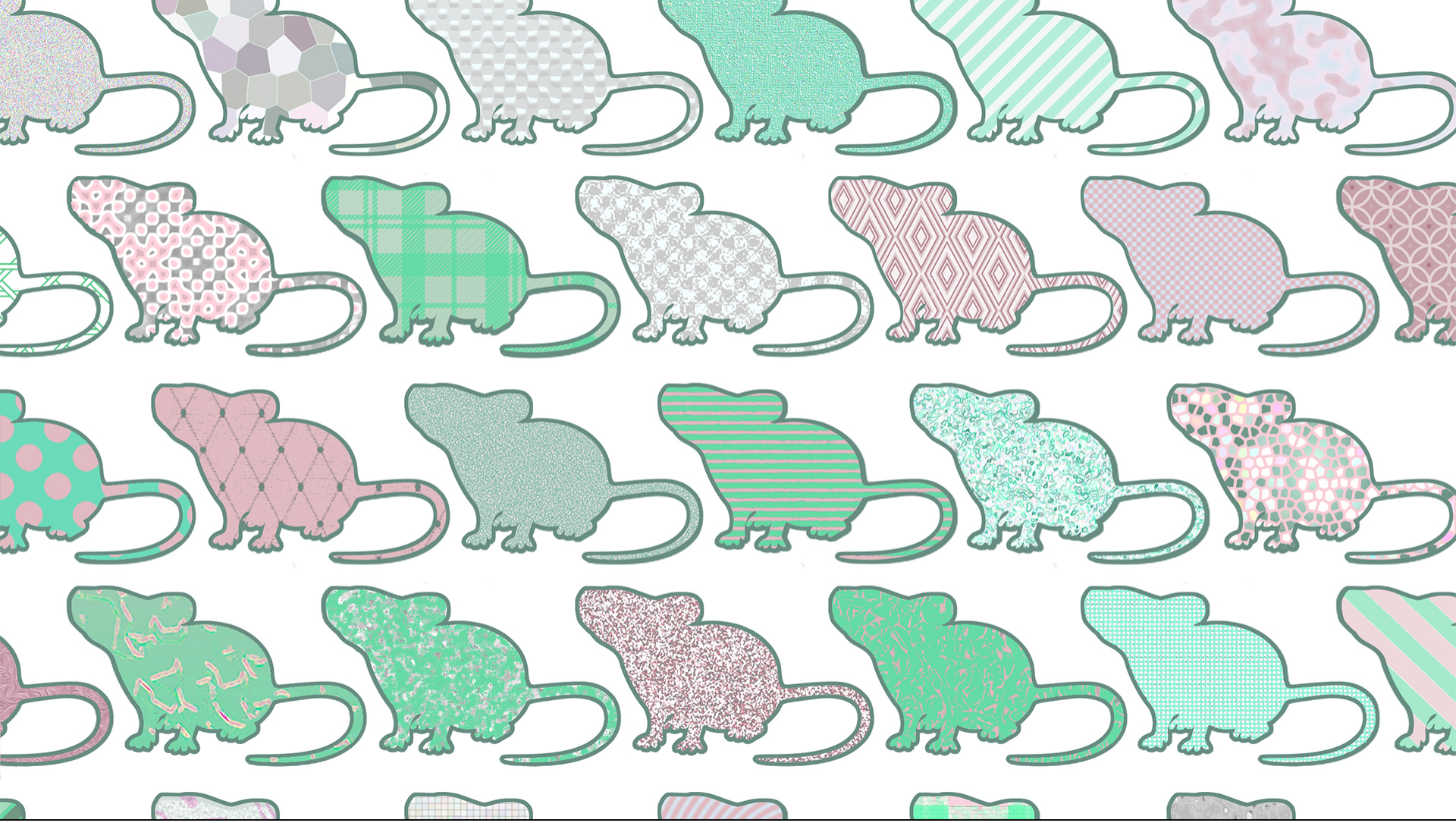

Concept for reproducible animal models for complex human disease: implications for personalized medicine

Catherine Kaczorowski | Associate Professor and Evnin Chair | The Jackson Laboratory

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Paul Robson, PhD (Director, Single-cell)
Michael Samuels, PhD (Scientist)
Sarah M. Neuner, PhD
Amy Dunn, Ph.D. (Scientist)
Andrew Ouellette (Grad student)
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Judy and Tony Evnin

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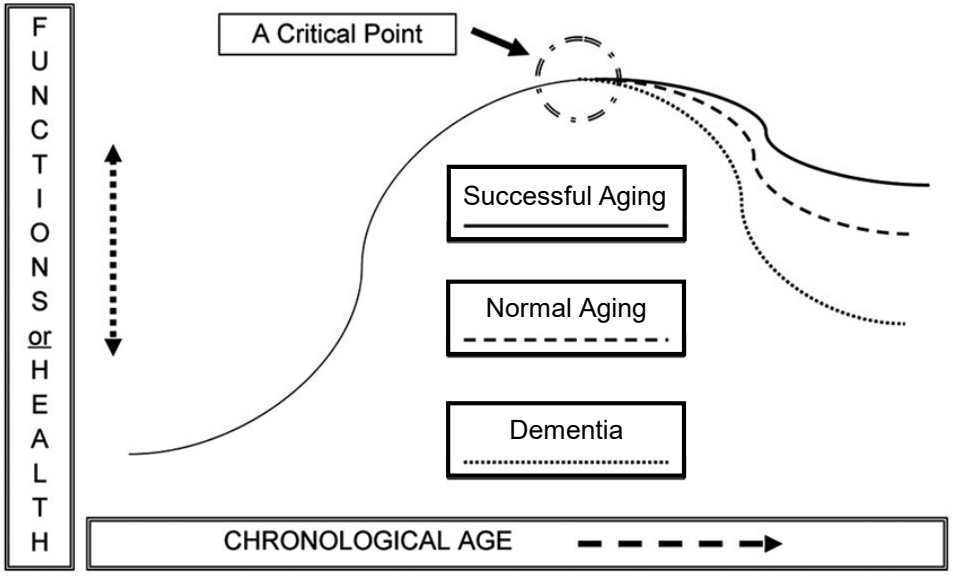
Optimizing the relevance to human biology and disease

- Creation of a polygenic model of human aging and AD
  - Traditional models (single inbred strain) not well validated models of the human disease
- Characterization of cognitive and pathological variation
  - Optimal study design and application of statistical analyses
- Validation of the resource as a model of human late-onset AD
  - Genotype-phenotype validation of a complex disease: PRS
- The quantitation of genetic and environmental interactions
  - Reporting the residual unexplained variance

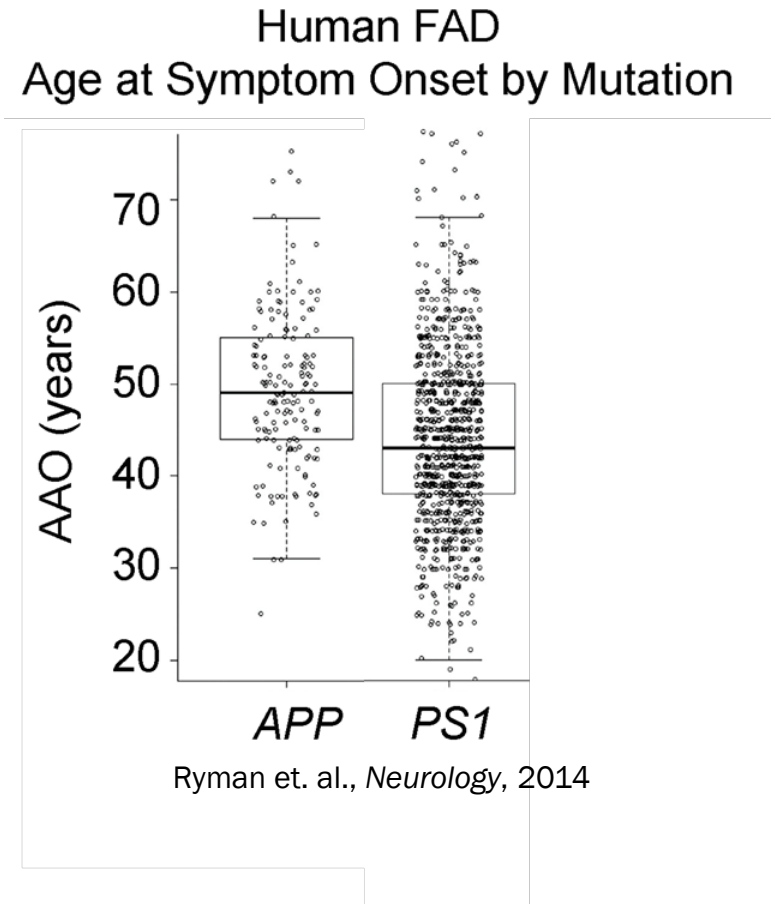
Aging is complex and different for everyone

- Aging is a leading risk factor for many diseases, particularly dementia
- Genetic makeup plays an important role in determining susceptibility
- Identifying specific genes involved in regulating trajectory is critical for:
  - Understanding cause
  - Developing treatments



Cai et al, *Trends in Aging Neuroscience,* 2014

Even among FAD patients, AAO varies widely



Ryman et. al., *Neurology*, 2014

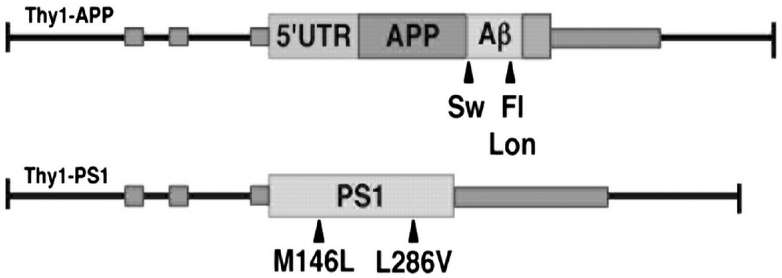
- Variation not explained by sex or *APOE* genotype
- Protective genetic factors exist in humans that delay onset of FAD
- Asymptomatic AD/resilience difficult to study in human populations

The solution: Build a pre-clinical model of AD that better aligns with human disease

Hypothesis: The creation of a genetically diverse panel of mice that carry human mutations that cause AD would better model complex genetics in human AD, and enable identification of modifiers of AD dementia

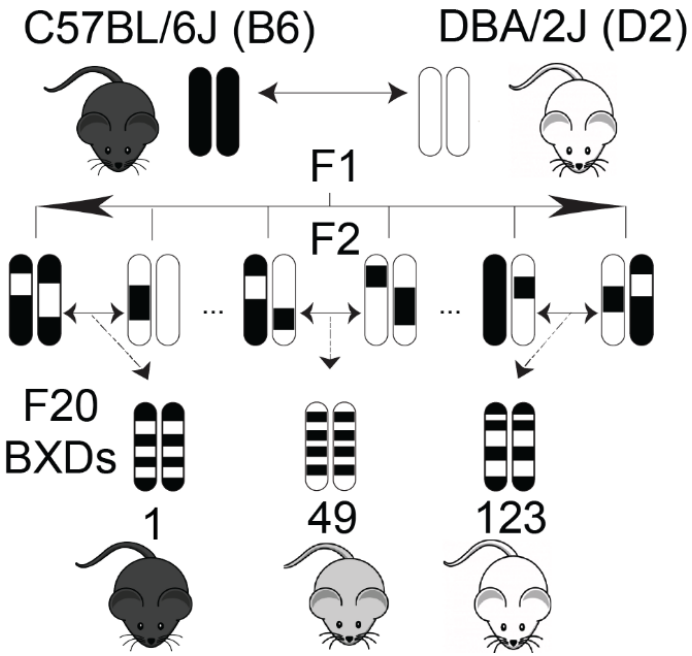
AD-BXD panel to identify modifiers of AD

- Combines two well-established resources:
  - 5XFAD transgenic mouse
  - BXD genetic reference panel is a recombinant inbred (RI) strain

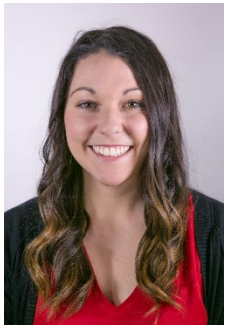


Oakley et al, 2006

X



Peirce et al., 2004

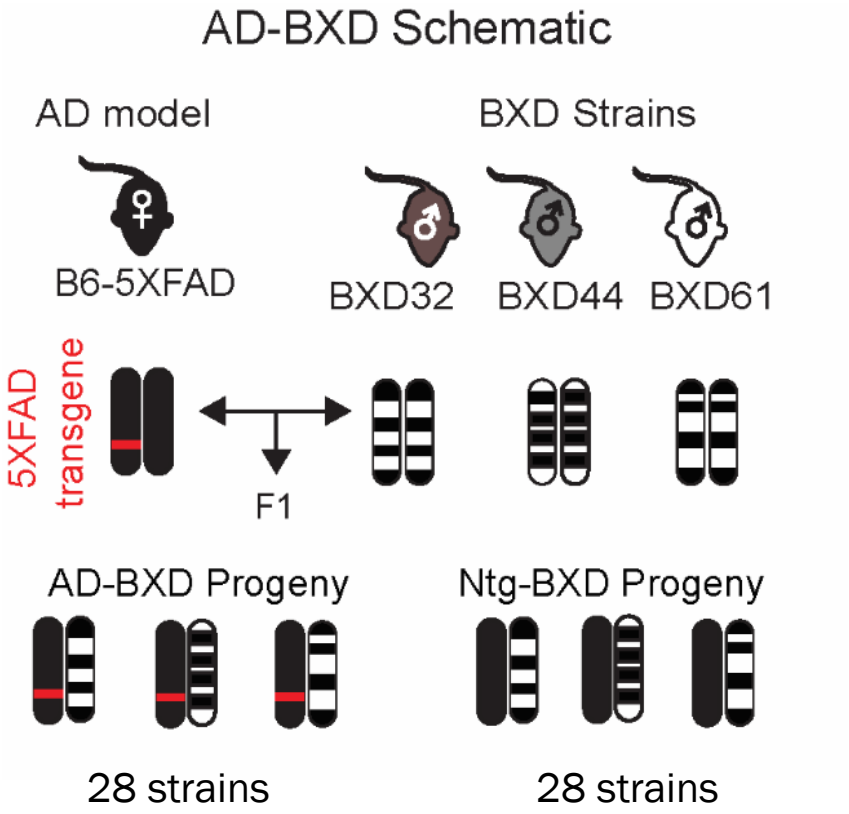


Sarah Neuner, PhD
(current, postdoc Goate lab)

Neuner et al., *Neuron*, 2019

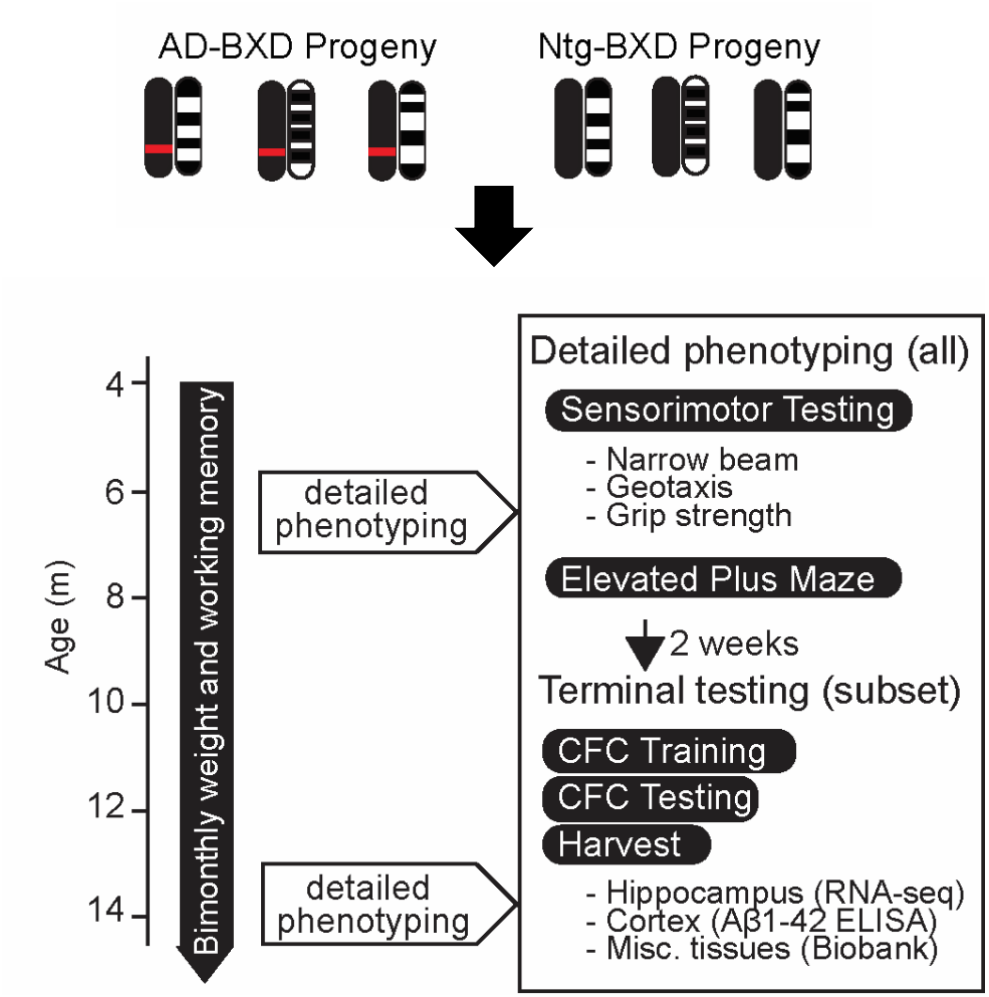
AD-BXD panel to identify modifiers of AD

- Panel of ‘high-risk’ carriers and nontransgenic (Ntg) age-matched littermates
- Replicable across time and laboratories



Neuner et al., *Neuron*, 2019

Phenotyping pipeline to identify modifiers of AD

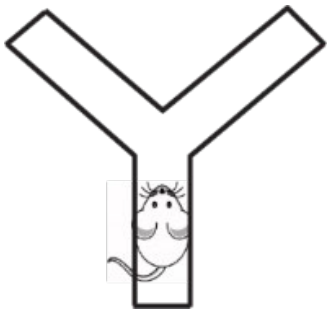


Heritability (h^2) range from 0.5-0.8

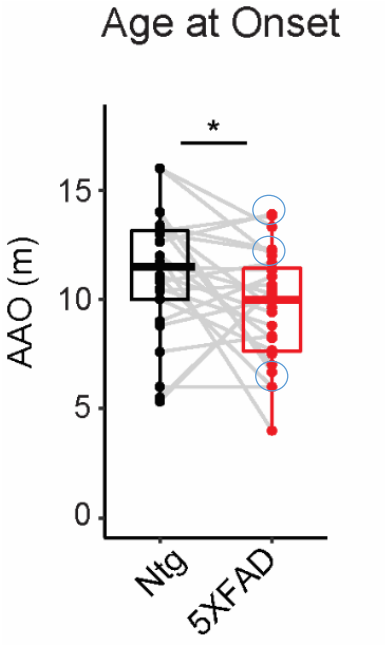
Neuner et al., *Neuron*, 2019

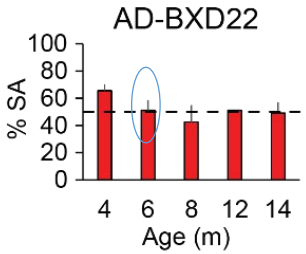
Genetic background modifies age at onset (AAO) of working memory deficits

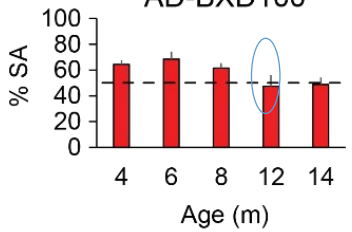
Y-maze test

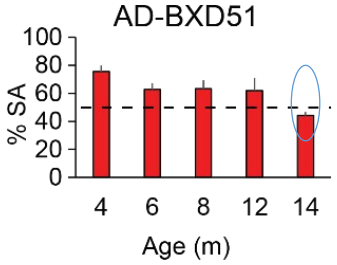


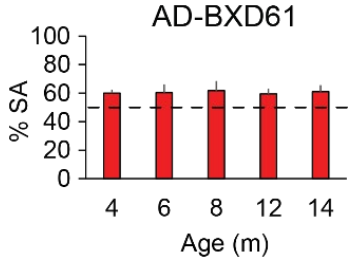
Animal classified as 'impaired' when alternation % reached chance levels (50%)











Neuner et al., *Neuron*, 2019

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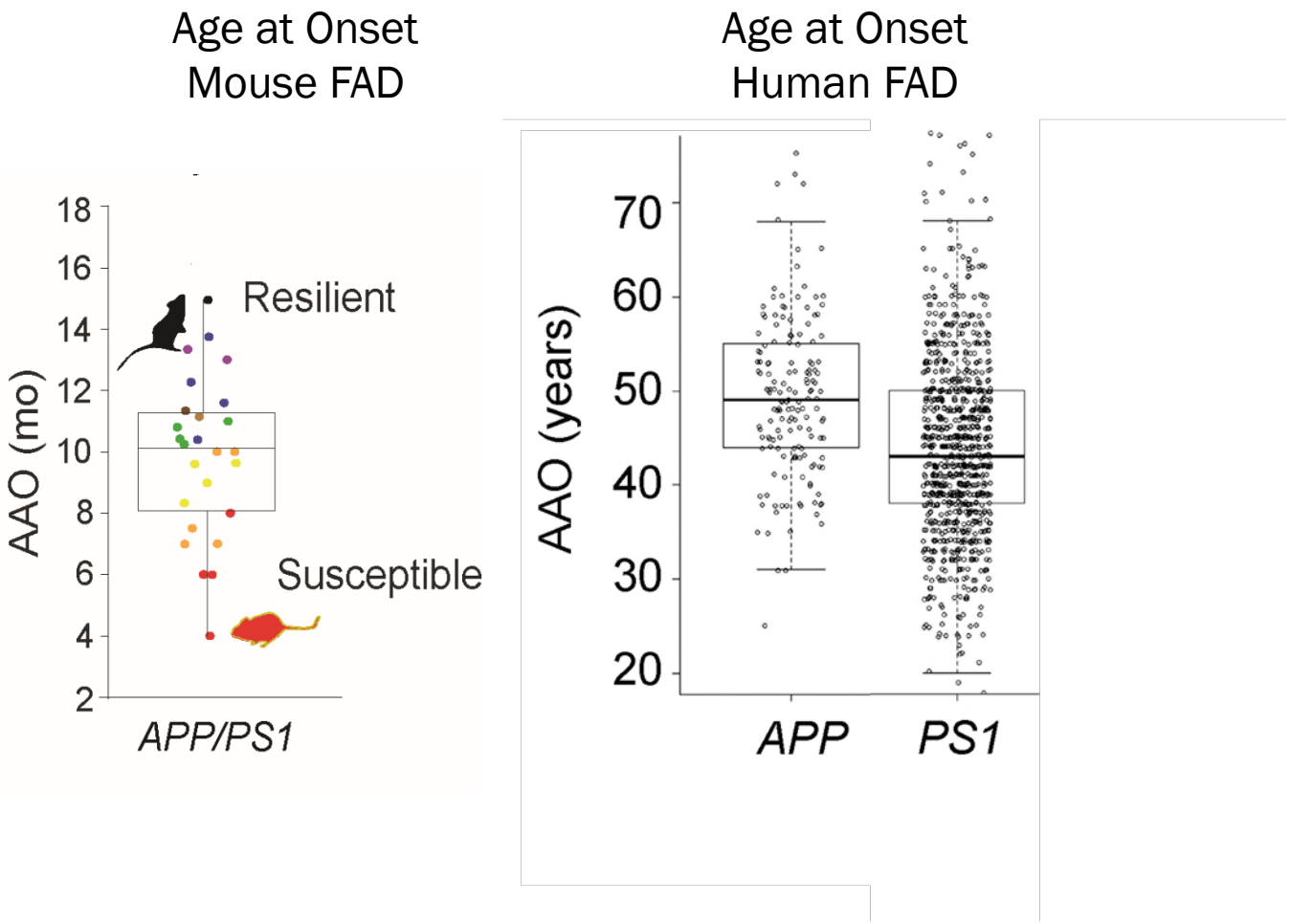
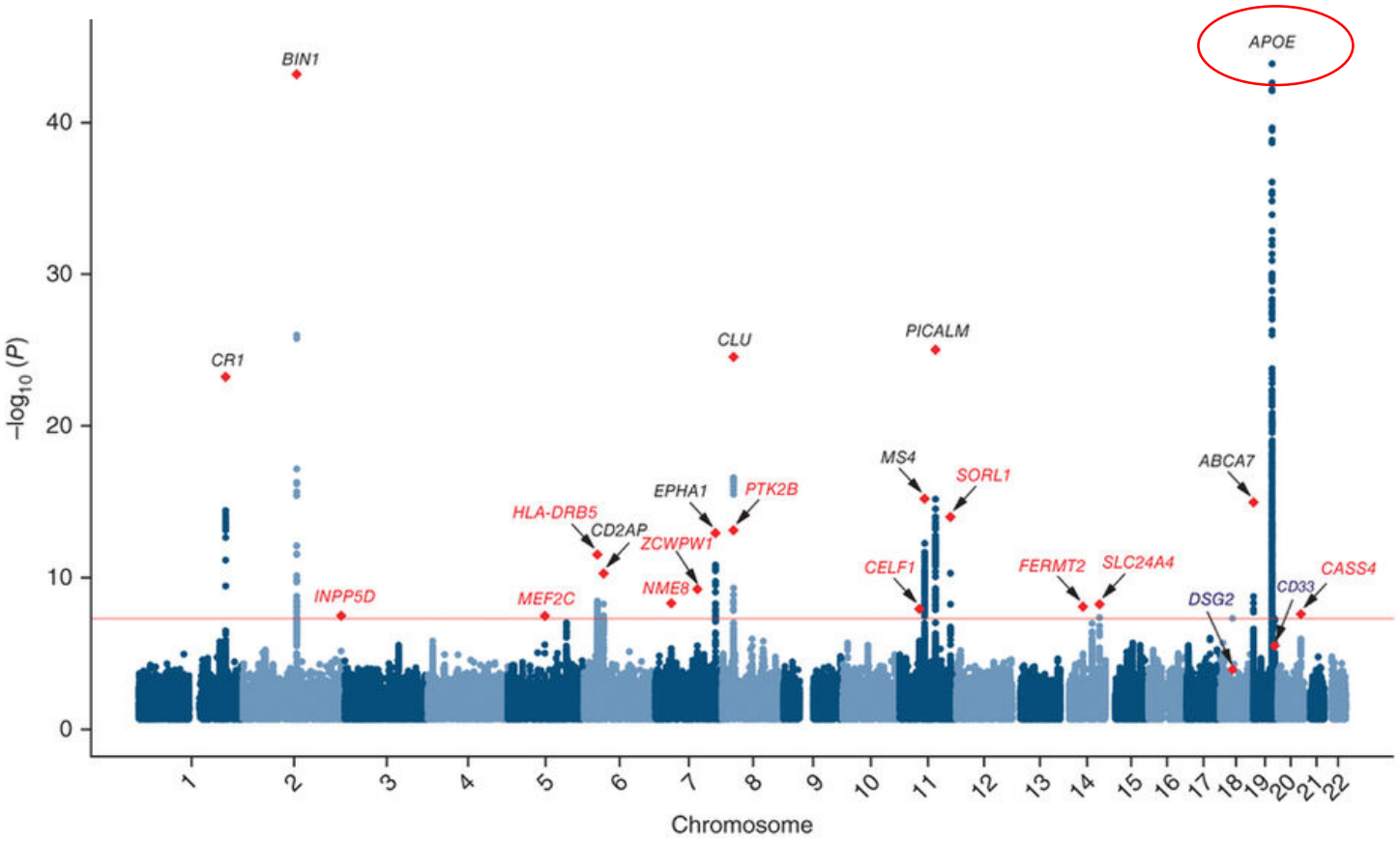


Neuner et al., *Neuron*, 2019

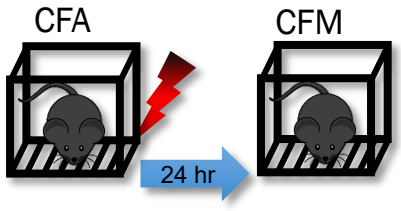
Is susceptibility to AD across our panel sensitive to variation in known human AD risk loci?

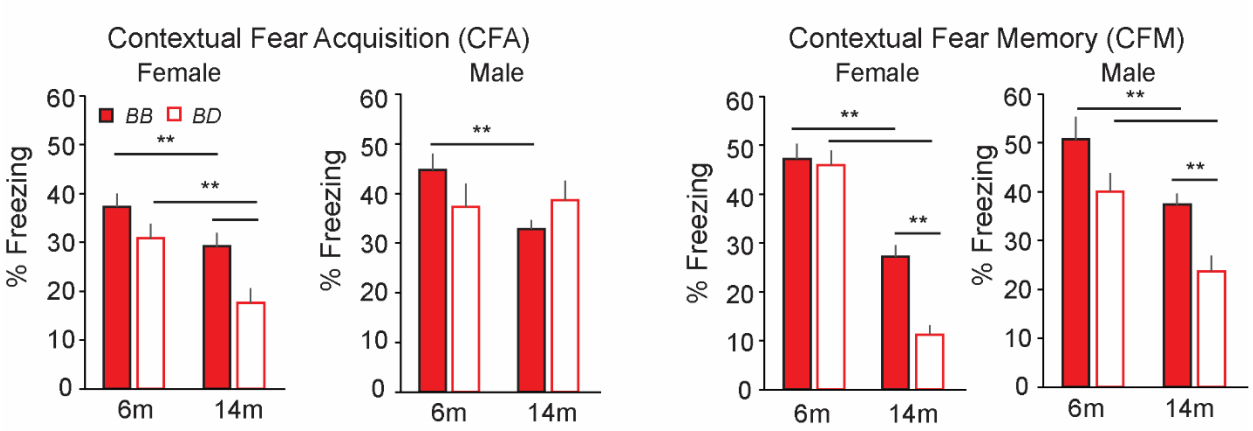


Lambert et al., 2013

Cognitive function in AD-BXDs is sensitive to variation in *Apoe*

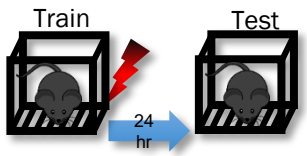
human position	118																			153	158
Apoe ε2	R	L	G	A	D	M	E	D	V	C	G	R	L	V	Q	Y	R	G	E	V	Q	A	M	L	G	Q	S	T	E	E	L	R	V	R	L	A	S	H	L	R	K	L	R	K	R	L	L	R	D	A	D	D	L	Q	K	C	L	A	V	Y
Apoe ε3	R	L	G	A	D	M	E	D	V	C	G	R	L	V	Q	Y	R	G	E	V	Q	A	M	L	G	Q	S	T	E	E	L	R	V	R	L	A	S	H	L	R	K	L	R	K	R	L	L	R	D	A	D	D	L	Q	K	R	L	A	V	Y
Apoe ε4	R	L	G	A	D	M	E	D	V	R	G	R	L	V	Q	Y	R	G	E	V	Q	A	M	L	G	Q	S	T	E	E	L	R	V	R	L	A	S	H	L	R	K	L	R	K	R	L	L	R	D	A	D	D	L	Q	K	R	L	A	V	Y
Apoe B6	R	L	G	A	D	M	E	D	L	R	N	R	L	G	Q	Y	R	N	E	V	H	T	M	L	G	Q	S	T	E	E	I	R	A	R	L	S	T	H	L	R	K	M	R	K	R	L	M	R	D	A	E	D	L	Q	K	R	L	A	V	Y
Apoe D2	R	L	G	A	D	M	E	D	L	R	N	R	L	G	Q	Y	R	N	E	V	H	T	M	L	G	Q	S	T	E	E	I	R	A	R	L	S	T	H	L	R	K	M	R	K	R	L	M	R	D	A	D	D	L	Q	K	R	L	A	V	Y
mouse position	122																			163	168

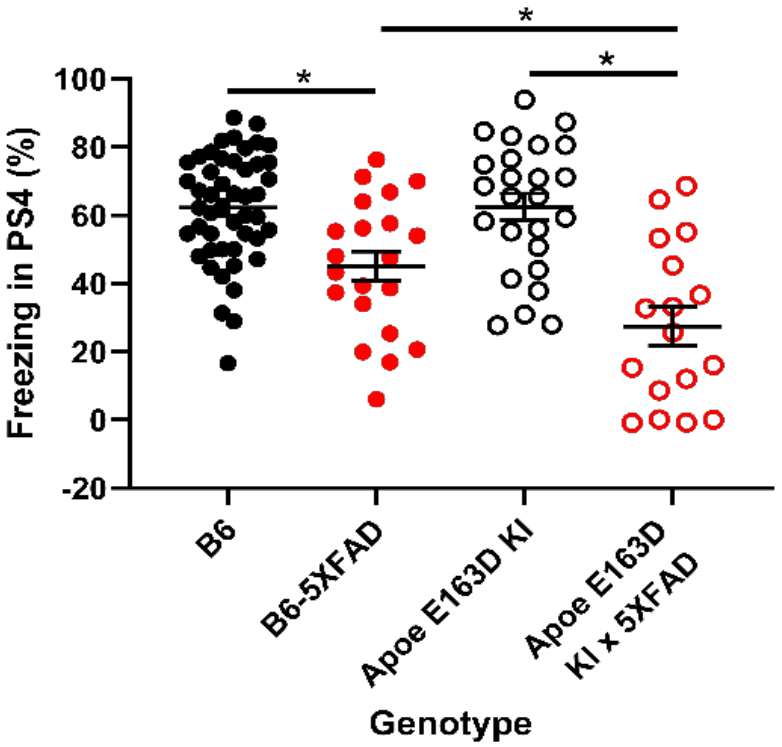




Naturally occurring genetic variants at *Apoe* locus in mice protect against cognitive decline in FAD mutation carriers

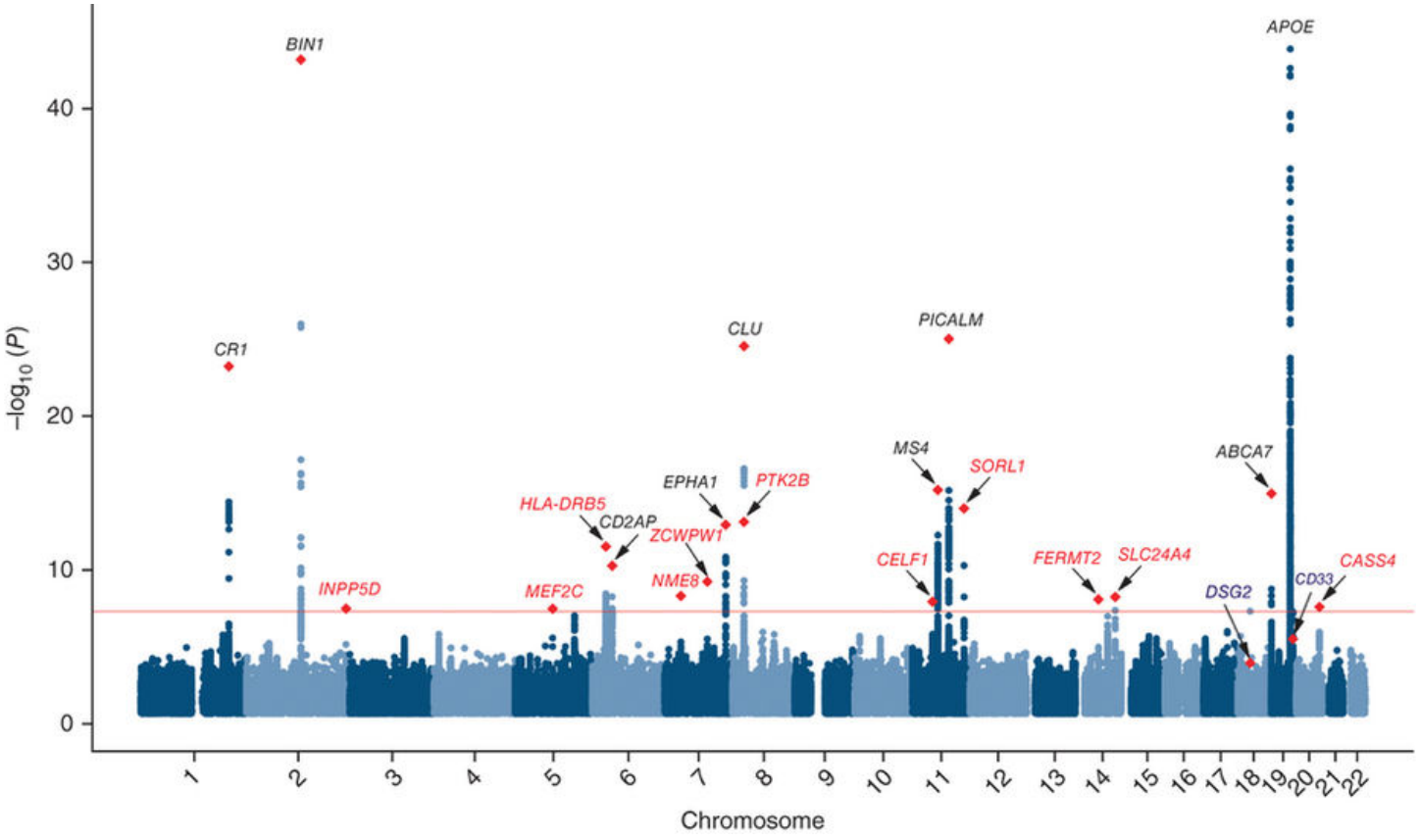
Apoe B6	RLGADMEDLRNRLGQYRNEVHTMLGQSTEEIRARLSTHLRKMRKRLMRDAEDLQKRLAVY			
Apoe D2	RLGADMEDLRNRLGQYRNEVHTMLGQSTEEIRARLSTHLRKMRKRLMRDADDLQKRLAVY			
mouse position		122	163	168





David Anderson, unpublished data

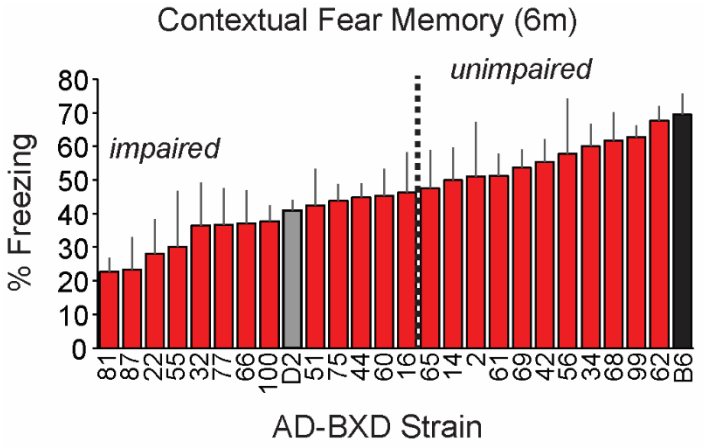
Is susceptibility to AD across our panel sensitive to variation in known human AD risk loci?

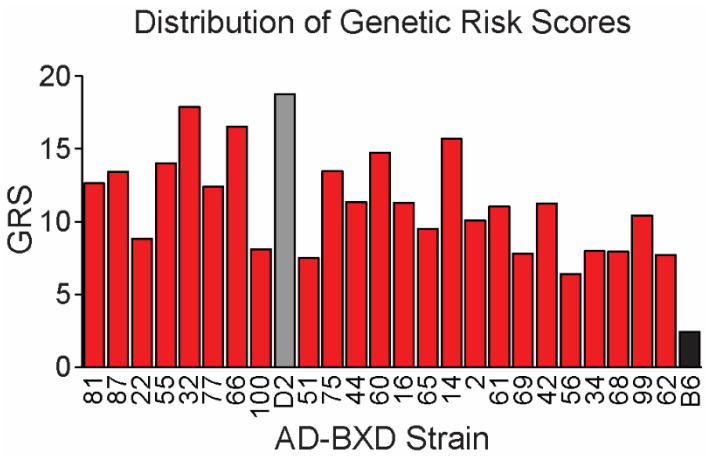


Lambert et al., 2013

Definition of a genetic risk score to assess sensitivity to variation in AD risk loci

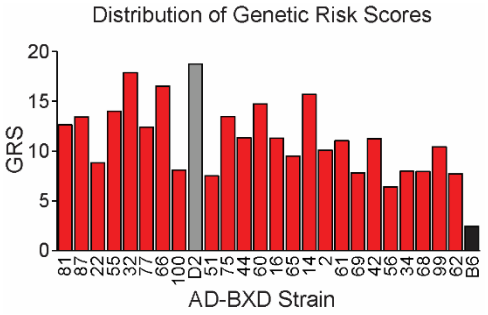
- Stratify ‘impaired’ vs ‘unimpaired’ based on 6m CFM
- Determine each strain’s genotype at 21 loci known to confer risk for LOAD
- Designate risk allele & calculate odds ratio
- Combine into overall genetic risk score

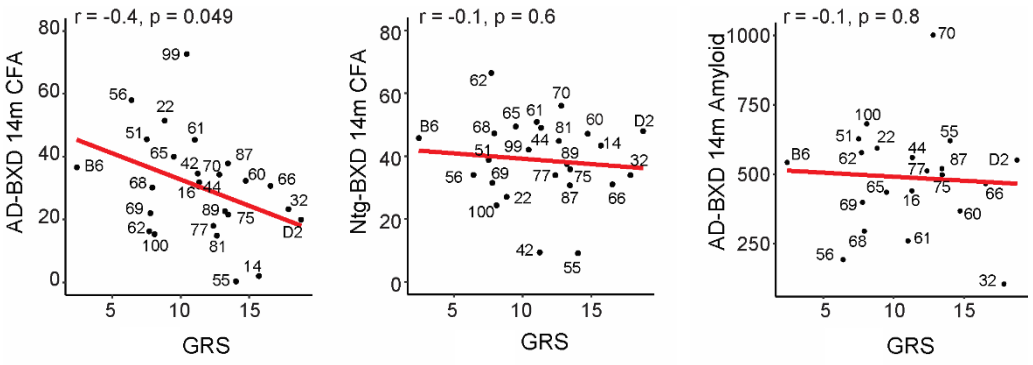




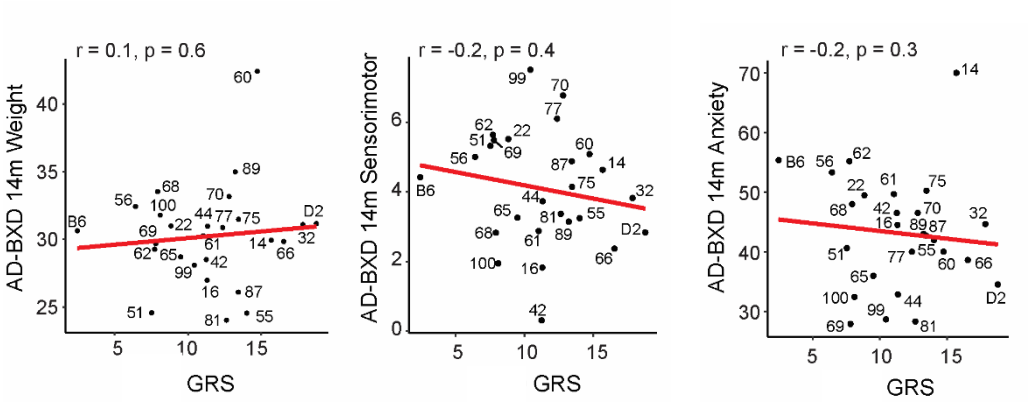
Neuner et al., *Neuron*, 2019

Genetic risk score predicts AD-related cognitive decline





- No association with Ntg-BXD CFA
- Association specific to cognitive traits



Neuner et al., *Neuron*, 2019

Conclusions

- Naturally occurring mouse genetic diversity can be utilized to understand susceptibility to age- and AD-related cognitive decline.
- Use of genetic diversity across model systems is likely to greatly enhance translational relevance of preclinical findings
- Reproducible nature of the BXDs and CCs (with or without the 5XFAD transgene) facilitates future studies to investigate hypotheses regarding mechanism
- Wide array of mouse models of polygenetic diseases will likely be improved by inclusion of genetic diversity and translationally relevant environmental exposures.

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Judy and Tony Evnin

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AMP-AD single-cell working group
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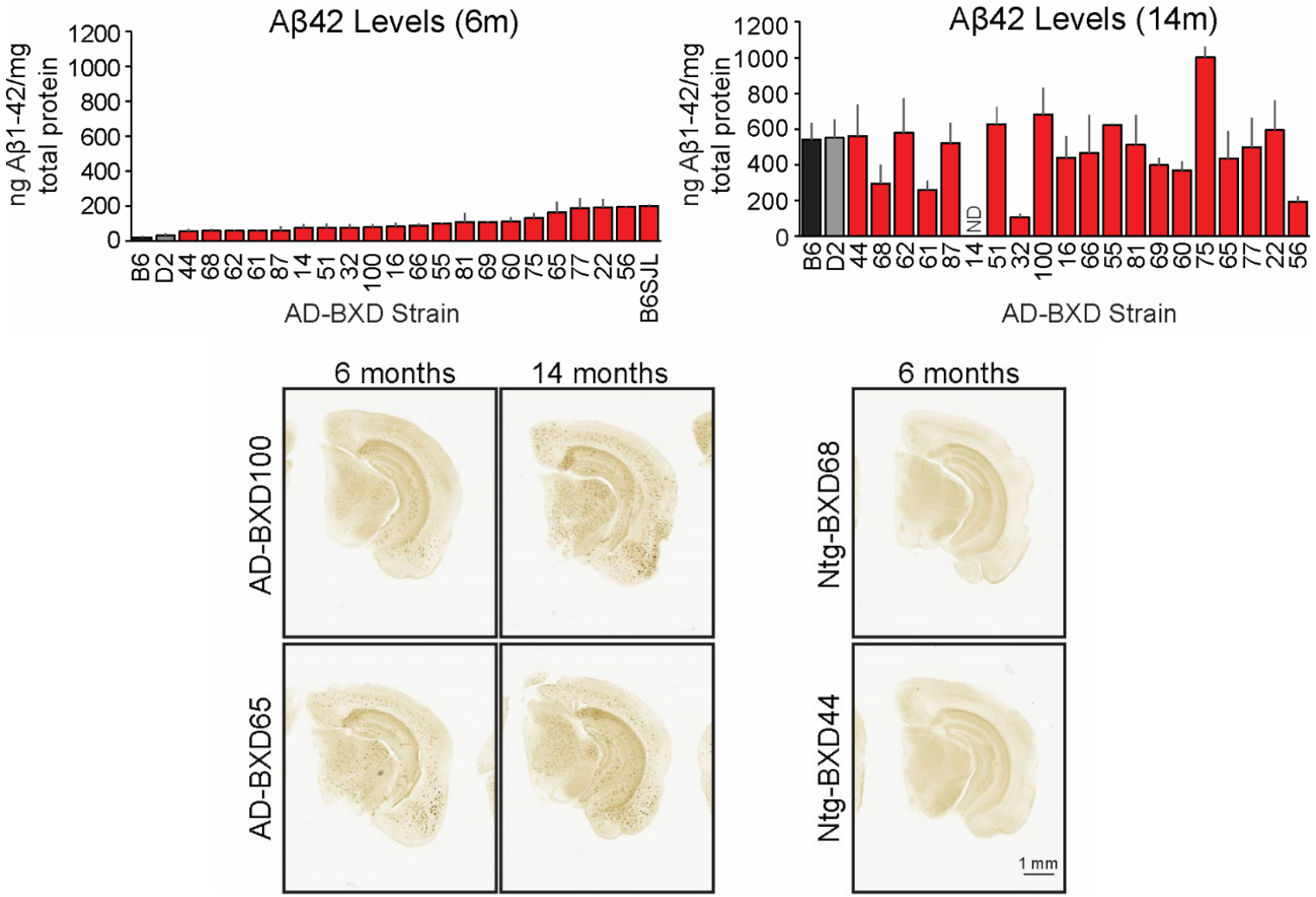
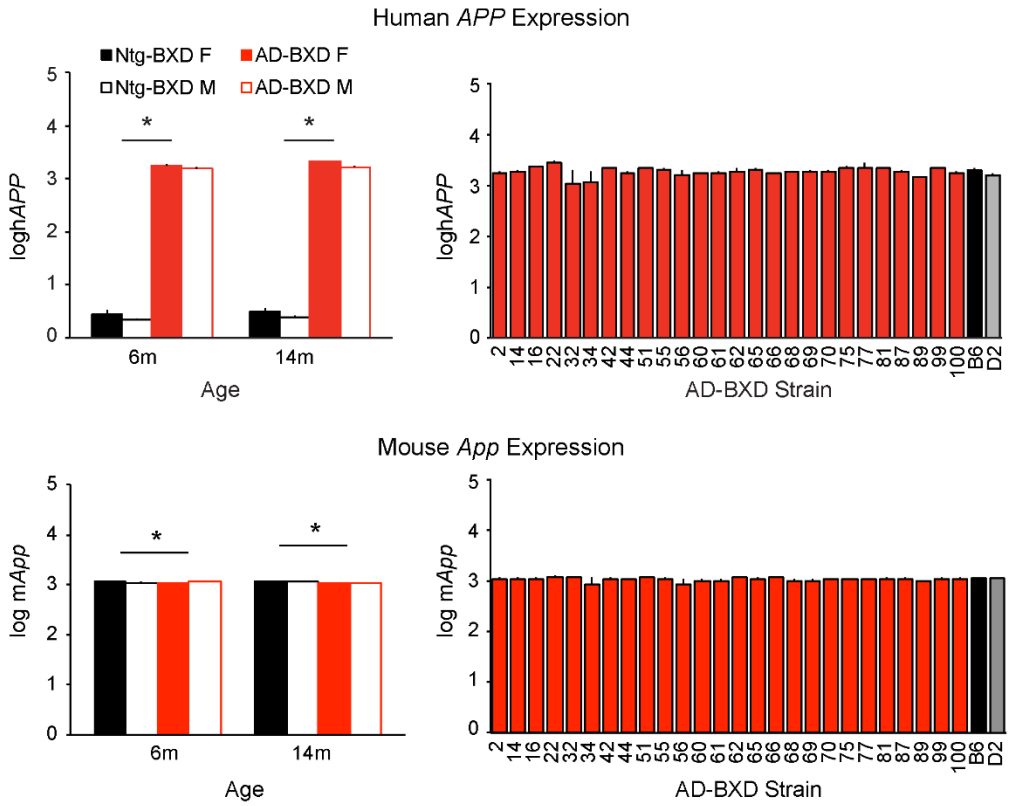
Genetic background modifies human amyloid-beta 1-42 accumulation



Neuner et al., *Neuron*, 2019

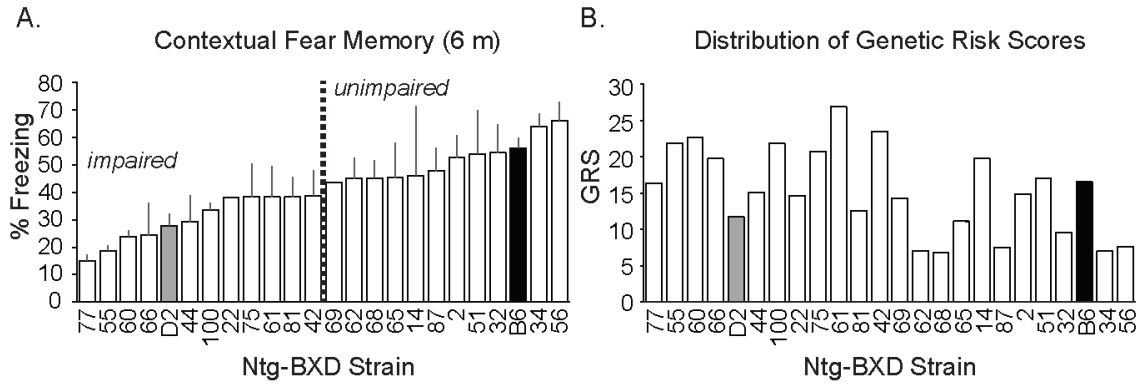
Genetic background does not modify the expression of human or endogenous mouse *APP* mRNA (or *Psen1*, *not shown)



Neuner et al., *Neuron*, 2019

Ntg-based GRS is not associated with cognitive outcomes

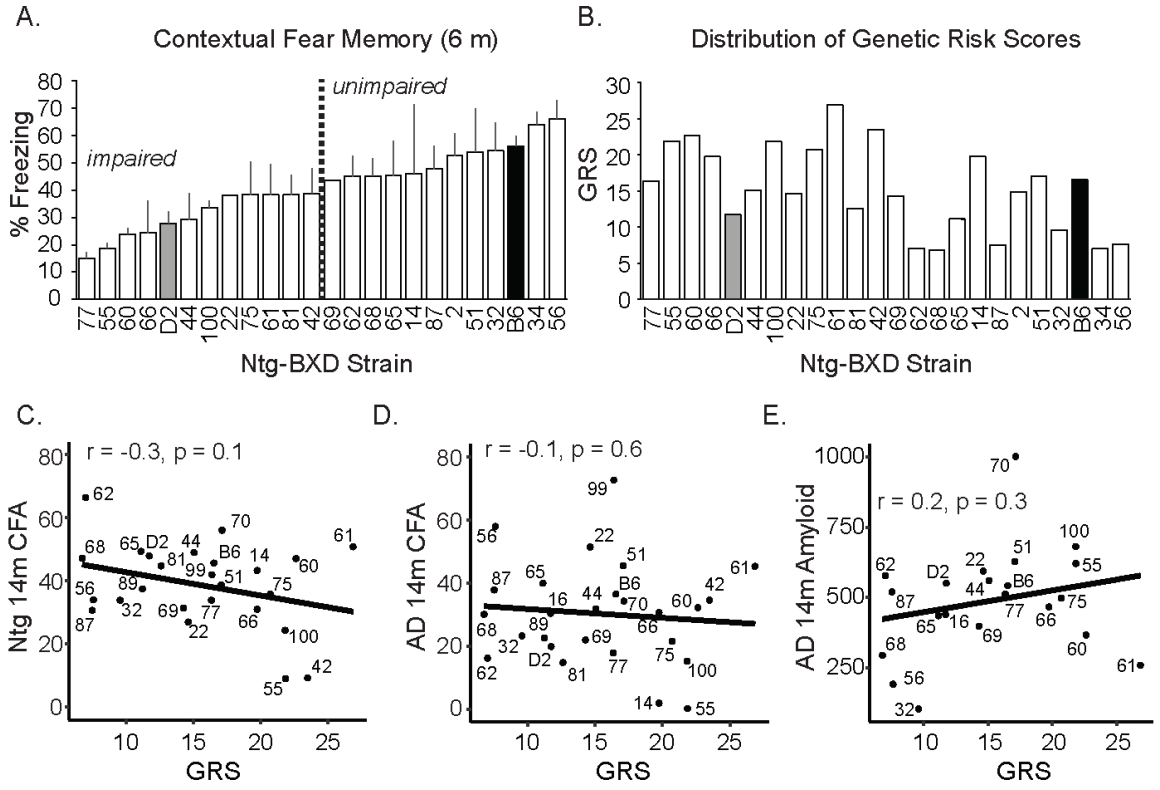
- Hypothesized repeating the process using Ntg-BXDs as baseline would produce uninformative GRS



Neuner et al., *Neuron*, 2019

Ntg-based GRS is not associated with cognitive outcomes

- Hypothesized repeating the process using Ntg-BXDs as baseline would produce uninformative GRS
- No correlation with cognitive or non-cognitive outcomes



Neuner et al., *Neuron*, 2019