

# **Regulatory mechanisms affecting AD risk**

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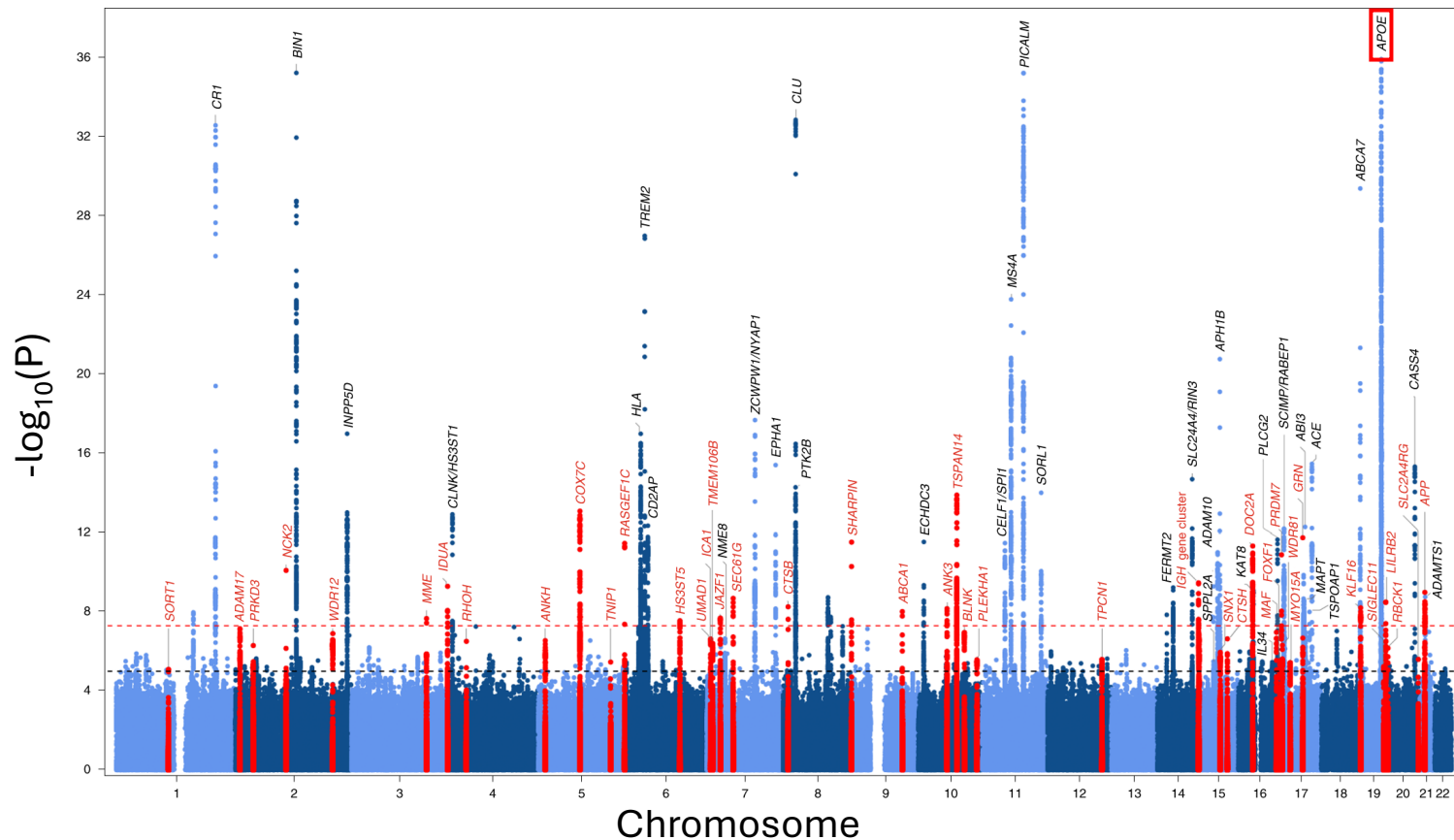
# Disclosures

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- Other financial relationships: NA
- Conflicts of interest: NA


# Genetic Studies in ADRD

Genetic targets are 2X more successful in drug trials than non-genetic targets (Nelson et al Nature Genetics. 2015).

More than 70 genetic risk loci for AD discovered



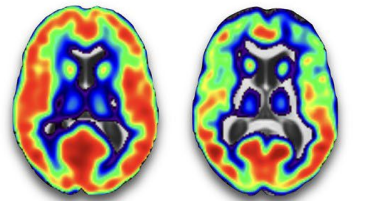
# APOE4 exacerbates age-dependent deficits

 N = 1954 cognitively normal midlife APOE  $\epsilon$ 4 carriers and non-carriers



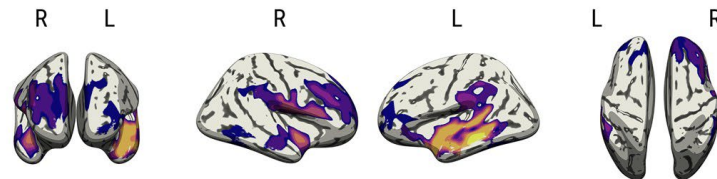
Orientation Dispersion Index (ODI) maps were derived from diffusion weighted imaging data using the NODDI model

ODI maps in 2 subjects



0.14 0.20 0.28 0.35

Is there a significant interaction between APOE status and age?



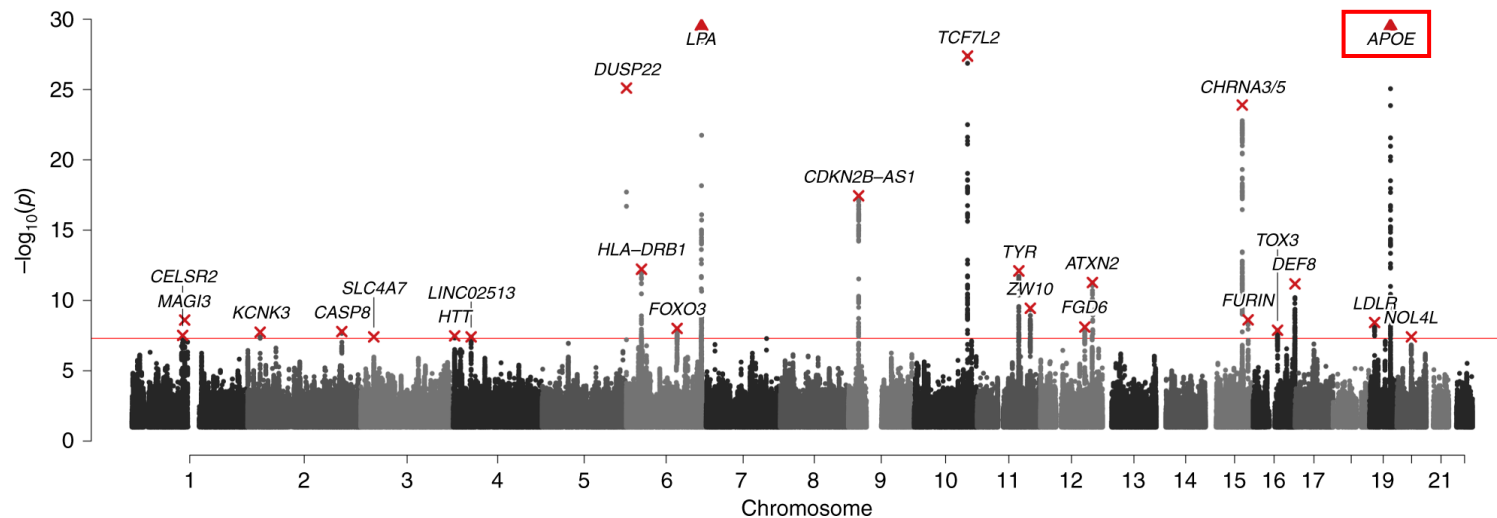
TFCE FWE p

0.05 0.001

The presence of apolipoprotein E  $\epsilon$ 4 may worsen age-related ODI decreases in brain regions typically associated with atrophy patterns of Alzheimer's disease amongst cognitively normal midlife adults.

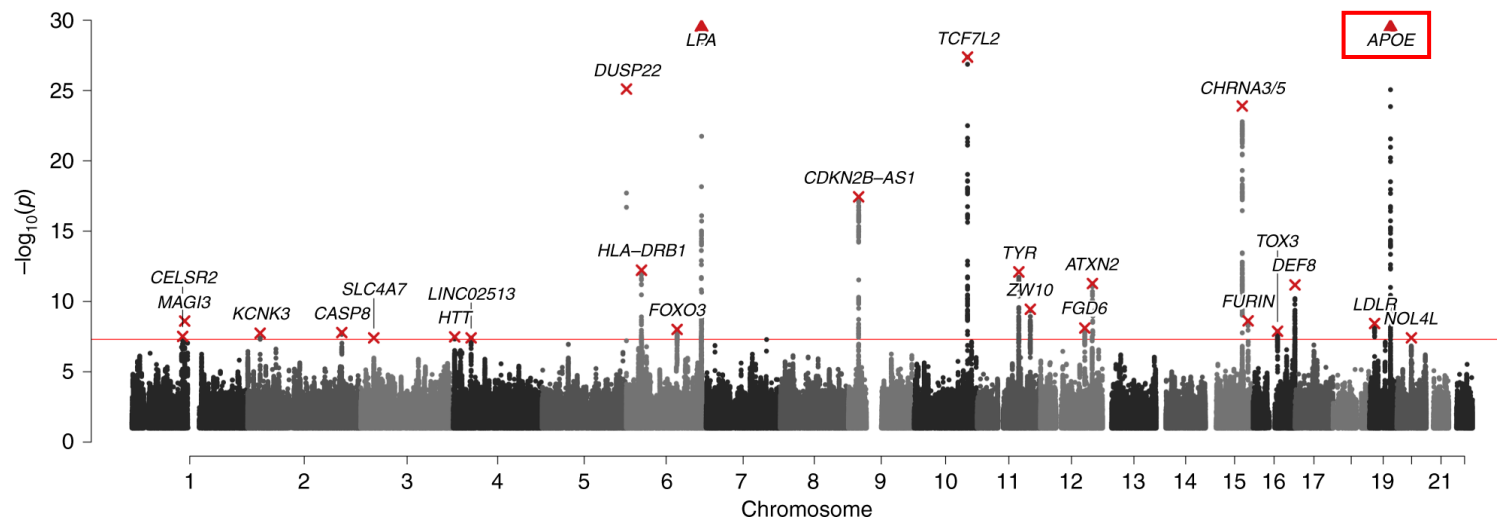
# Genetic longevity determinants

Loci that affect healthspan, parental lifespan, and longevity (meta-analysis of GWAS)



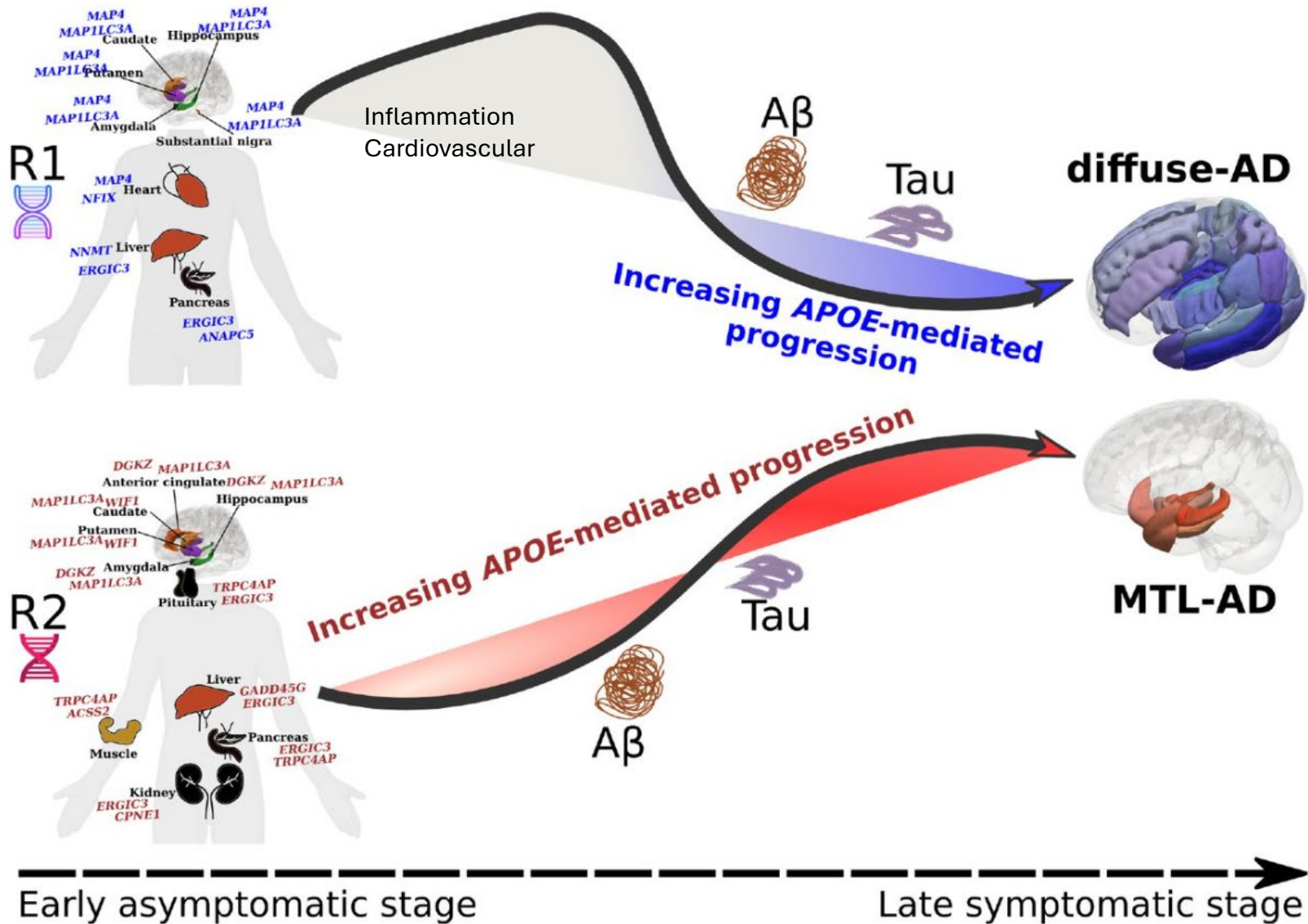
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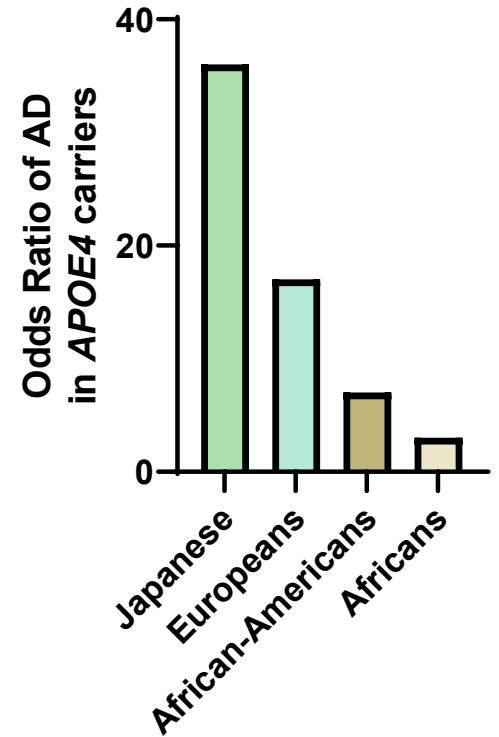
The most important single risk factor for AD is aging, the common driver of multiple chronic diseases and conditions

# Facilitators of the pathogenesis of AD might involve processes outside the brain



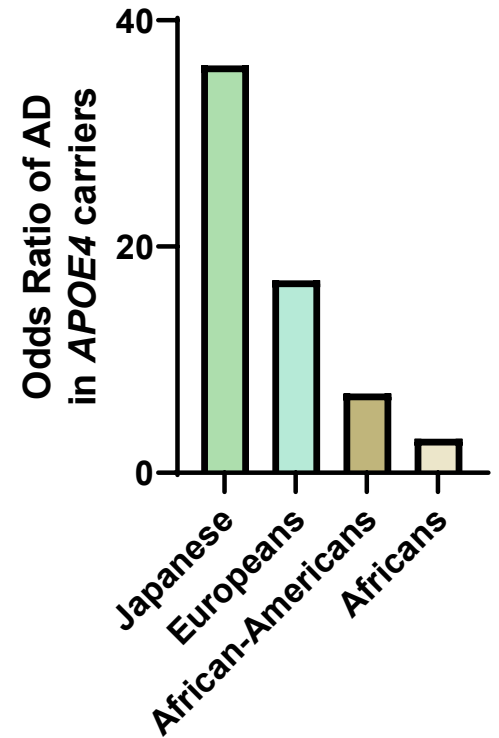
# APOE4-AD risk for different ancestries

- The APOE  $\epsilon$ 4 allele increases the risk for AD in nearly all populations, but the risk differs among ancestries.



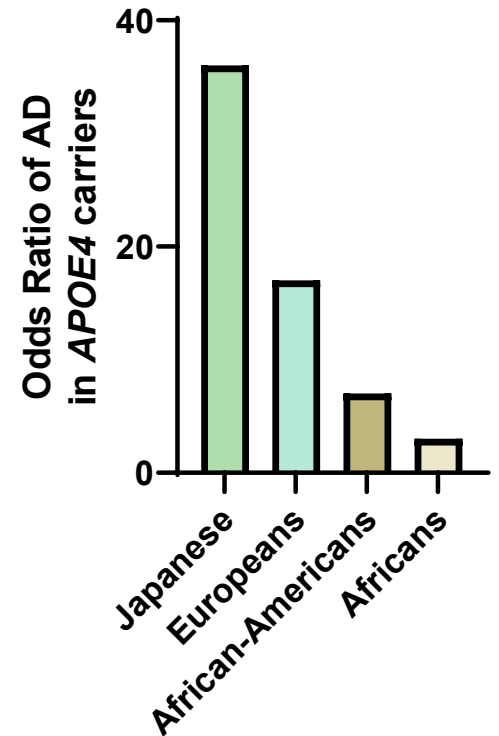
# APOE4-AD risk for different ancestries

- The APOE  $\epsilon$ 4 allele increases the risk for AD in nearly all populations, but the risk differs among ancestries.
- APOE4/4 carriers in European ancestry have higher chromatin accessibility and expression of APOE compared to APOE4/4 carriers in African ancestry (Griswold et al, 2021; Celis et al, 2023).

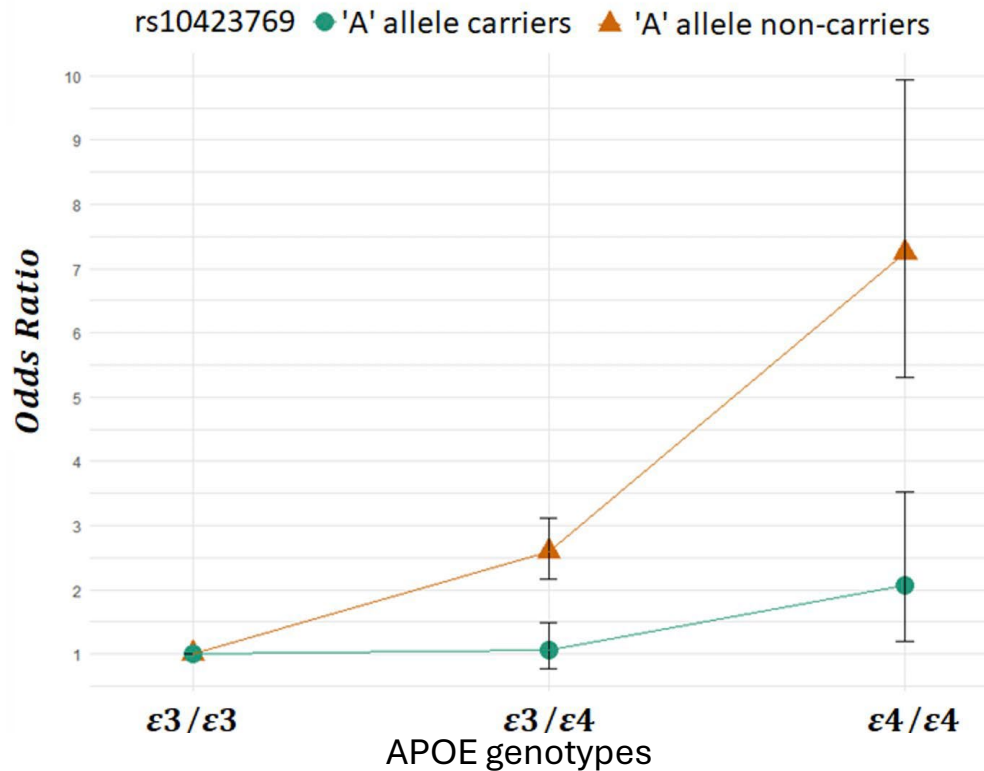
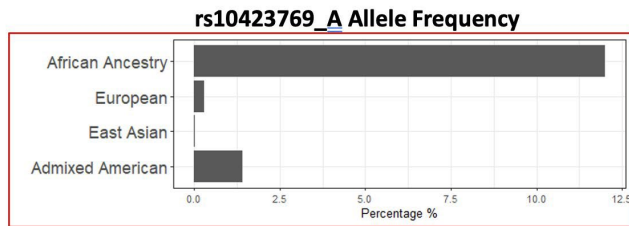
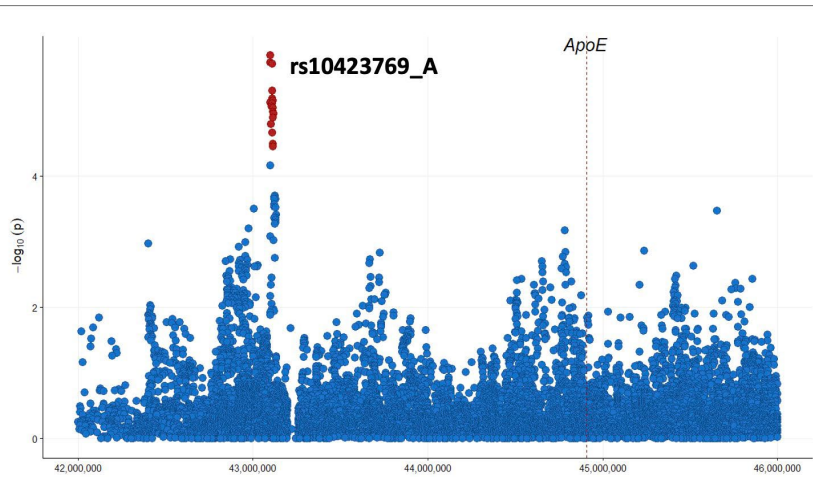


# APOE4-AD risk for different ancestries

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- APOE4/4 carriers in European ancestry have higher chromatin accessibility and expression of APOE compared to APOE4/4 carriers in African ancestry (Griswold et al, 2021; Celis et al, 2023)
- Difference in AD risk is associated with the local ancestry region around APOE (Rajabli et al 2018)

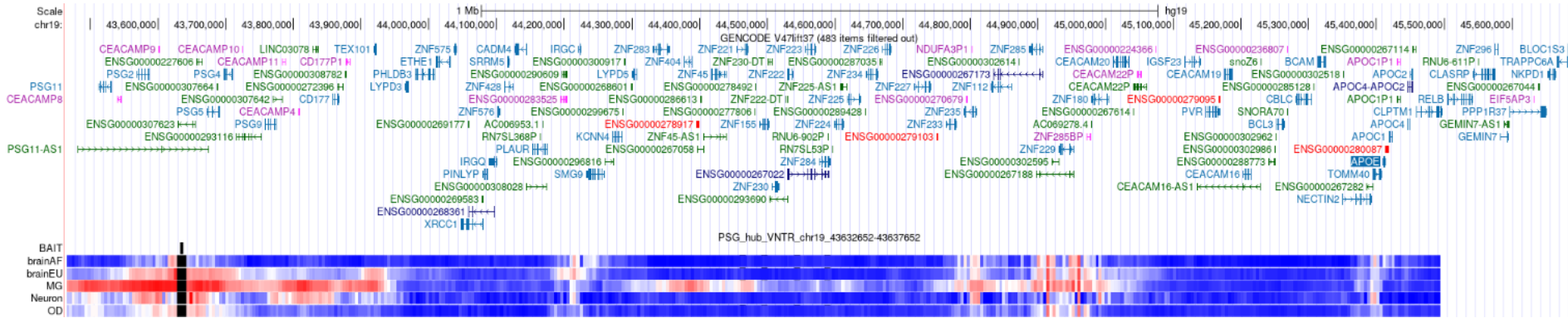


# Protective locus for APOE4

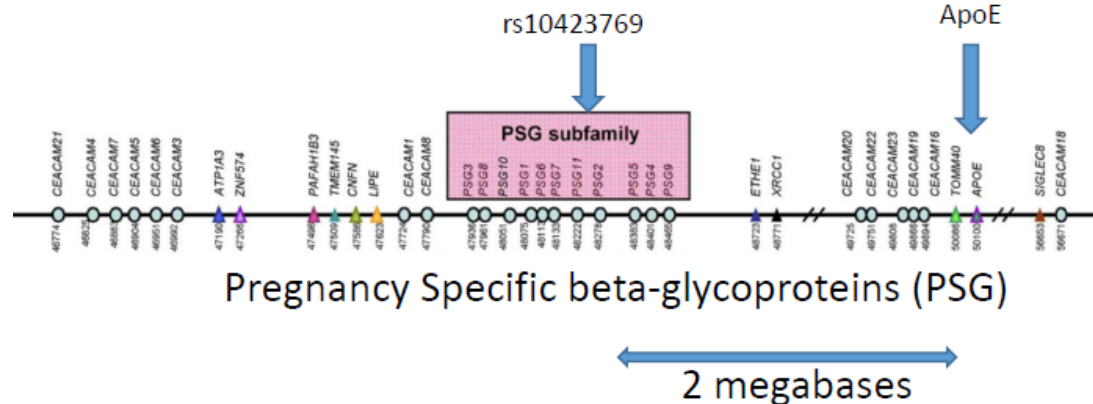


Reduces the AD risk effect of APOE4/4 ~75%

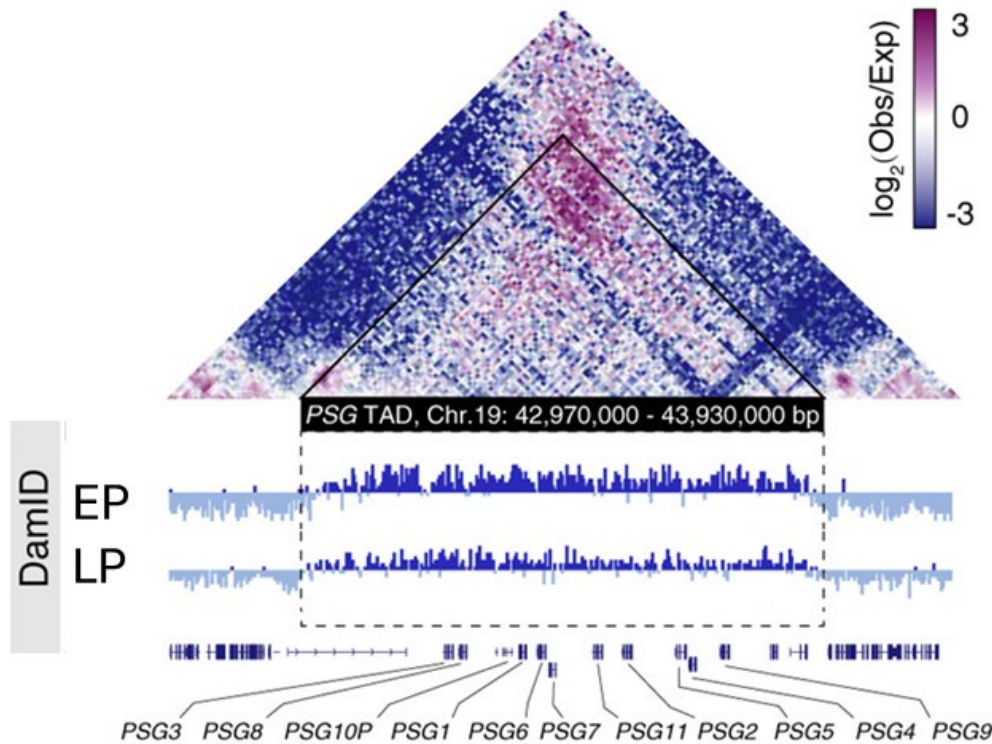
# Protective mechanism?



Chromatin long range interaction between the protective and the APOE loci

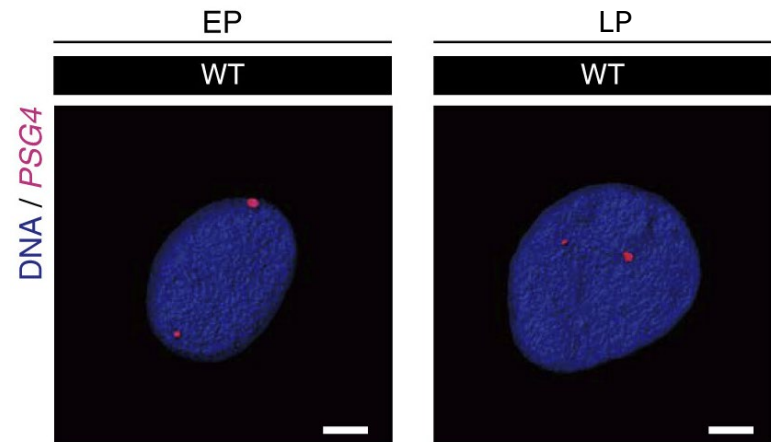


# Age-related chromatin reorganization of the PSG region



## Article Large-scale chromatin reorganization reactivates placenta-specific genes that drive cellular aging

Zunpeng Liu,<sup>1,5,18</sup> Qianzhao Ji,<sup>2,6,18</sup> Jie Ren,<sup>4,5,6,9,17,18</sup> Pengze Yan,<sup>2,5,18</sup> Zeming Wu,<sup>2,5,18</sup> Si Wang,<sup>3,7,17,18</sup> Liang Sun,<sup>12,13,17</sup> Zehua Wang,<sup>1,8</sup> Jiaming Li,<sup>4,5,9</sup> Guoqiang Sun,<sup>1,8</sup> Chuqian Liang,<sup>2,6</sup> Run Sun,<sup>1,8</sup> Xiaoyu Jiang,<sup>2,6</sup> Jianli Hu,<sup>4,9</sup> Yingjie Ding,<sup>4,9</sup> Qiaoran Wang,<sup>4,6,9</sup> Shijia Bi,<sup>1,8</sup> Gang Wei,<sup>14,11</sup> Gang Cao,<sup>15,16,11</sup> Guoguang Zhao,<sup>3,10,17</sup> Hongmei Wang,<sup>1,5,6,17</sup> Qi Zhou,<sup>1,5,6,17</sup> Juan Carlos Izpisua Belmonte,<sup>11,17</sup> Jing Qu,<sup>1,5,6,9</sup> Weiqi Zhang,<sup>1,5,5,9</sup> and Guang-Hui Liu<sup>2,3,5,5,14</sup>\*



Early vs late passage (senescent) hMPCs differ in the extent of interaction between the nuclear lamina and chromatin at the PSG region



# CONCLUSIONS

- Genetic ancestry-aware studies contribute to:

Improved Disease Risk Prediction

Equity in Healthcare

Understanding Disease Mechanisms

**Identification of therapeutic avenues:** Reducing APOE4 in carriers is a therapeutic goal for Alzheimer's disease (Vance et al, 2024)

-Our data suggest that naturally evolved mechanisms of protection for APOE4 AD risk involve long term chromatin interactions that in turn affect promoter accessibility and APOE4 expression

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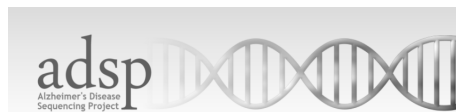
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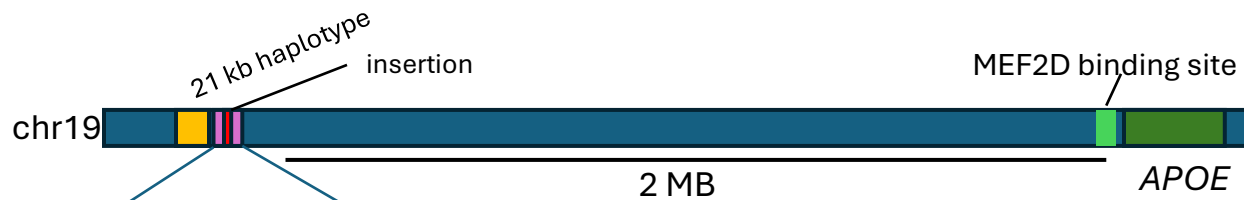
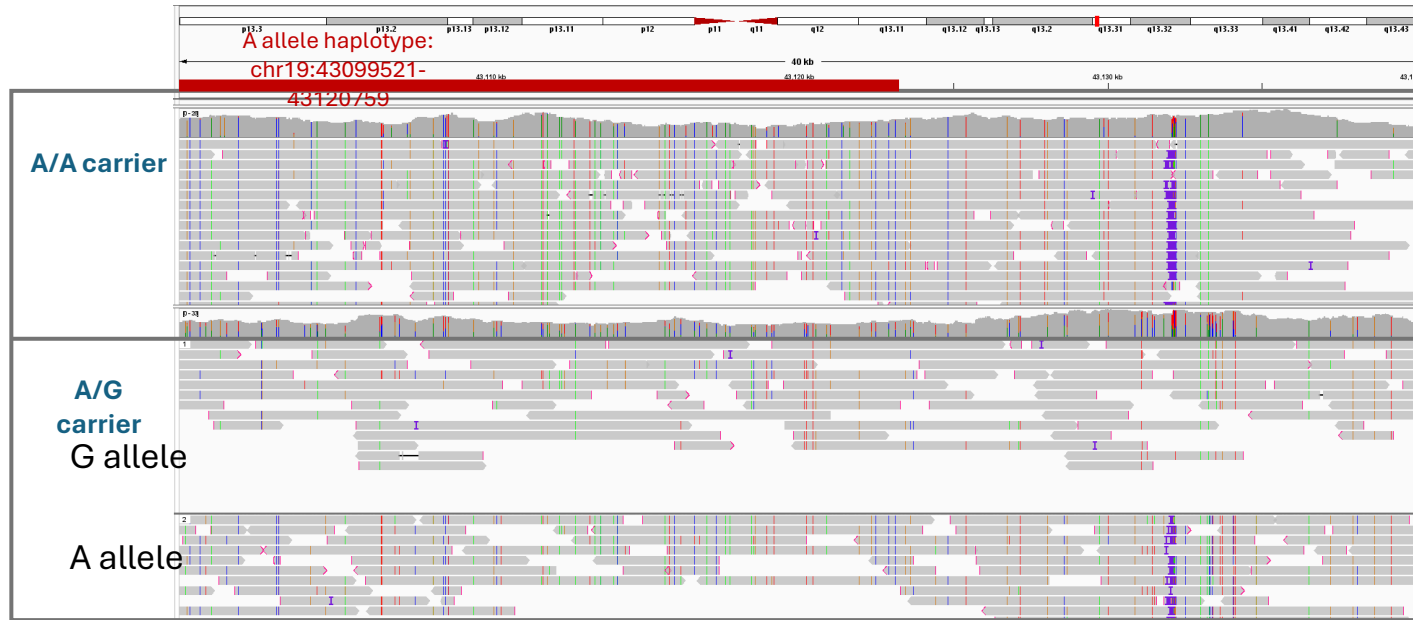


Genomic Services Provided By





# Protective allele is associated with repeat expansion

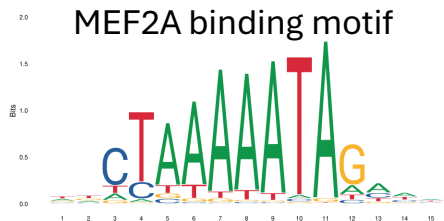
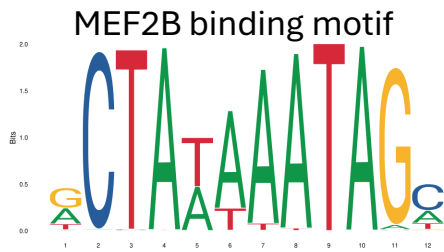
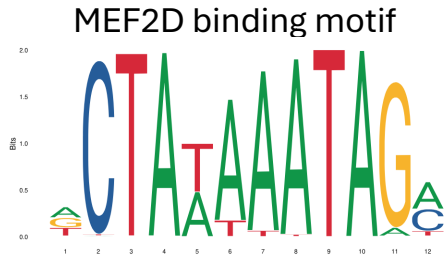


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 TAGTTAT TCTATATATAGA CTATA GACTACATTATAG TCTATATATAGA CTATAGACTACATTATAG TCTATATATAGA CTATAGACTACATTATAG TCTATATAT  
 AGA CTATAGACTACATTATAG TCTATATATAGA CTATAGACTACATTATAG TCTATATATAGA CTATAGACTACATTATAG TCTATATATAGA CTATAGACTAC  
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 AGA CTATAGACTACATTATAG TCTATATATAGA CTATAGACTACATTATAG TCTATATATAGA CTATAGACTACATTATAG TCTATATATAGA CTATAGACTAC  
 ATTATAG TCTATATATAGA CTATAGACTACATTATAG TCTATATATAGA CTATAGACTACAATATAGTCTTATATAGATTATATATAGAATATATATTTCTATA  
 TATAGACTATTTTTCTATATATAGTTTATAGAGATTATACAT

FIMO motif finding



# Structural Variation Determination through LRS



## MEF2 Transcription Factor Family – under investigation

- Role in neuronal survival by controlling the expression of several genes and miRNAs (Lisek, 2023)
- Both in brain development and in mature neurons (Lisek, 2023).
- MEF2C is an AD GWAS risk locus (Lambert, 2013)
- MEF2C has a role in synaptic integrity, plasticity and memory (Udeochu, 2022)

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**Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease**



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<https://doi.org/10.1093/abbs/2021012>  
Advance Access Publication Date: 28 December 2021  
Original Article

Original Article

### MEF2C ameliorates learning, memory, and molecular pathological changes in Alzheimer's disease *in vivo* and *in vitro*

Jiamou Ren<sup>1,2,†</sup>, Shuli Zhang<sup>3,†</sup>, Xiaoling Wang<sup>1</sup>, Yuxin Deng<sup>1</sup>, Yi Zhao<sup>1</sup>, Yan Xiao<sup>1</sup>, Jian Liu<sup>4</sup>, Liangzhao Chu<sup>4,\*</sup>, and Xiaolan Qi<sup>1,3,\*</sup>

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