

G9 α METHYLTRANSFERASE

FROM TRANSGENERATIONAL EPIGENETIC INHERITANCE TO THE DISCOVERY OF NEW G9 α INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

FACULTY OF PHARMACY AND FOOD SCIENCES

UNIVERSITAT DE BARCELONA

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JUNE 9TH, 2021



Institut de Neurociències
UNIVERSITAT DE BARCELONA



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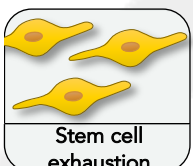
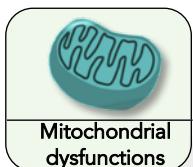
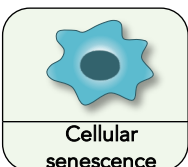
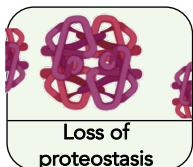
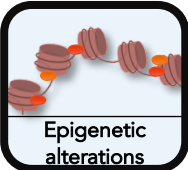
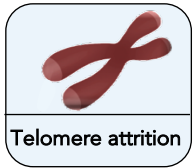
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ALZHEIMER'S DISEASE

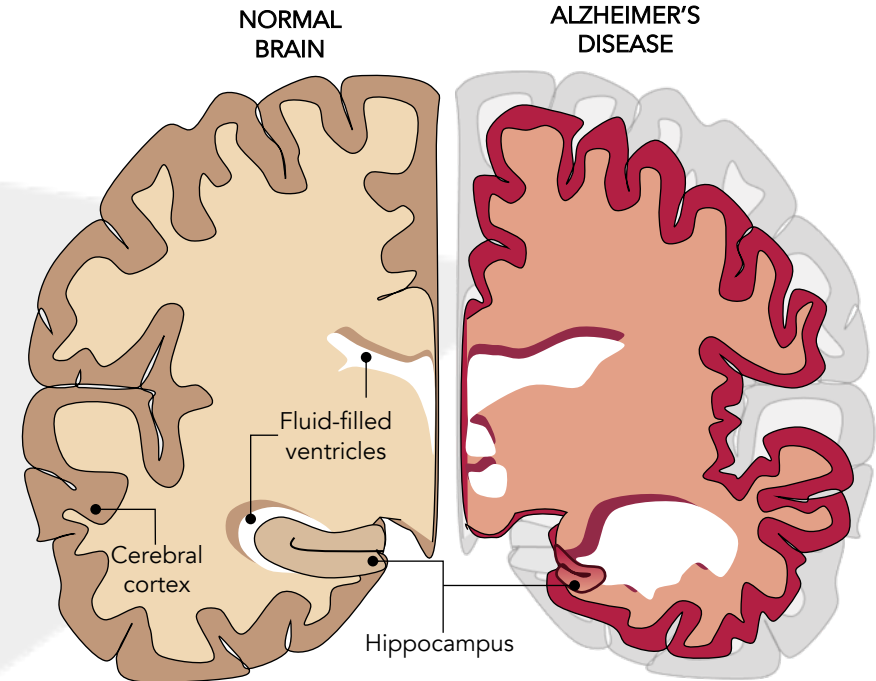
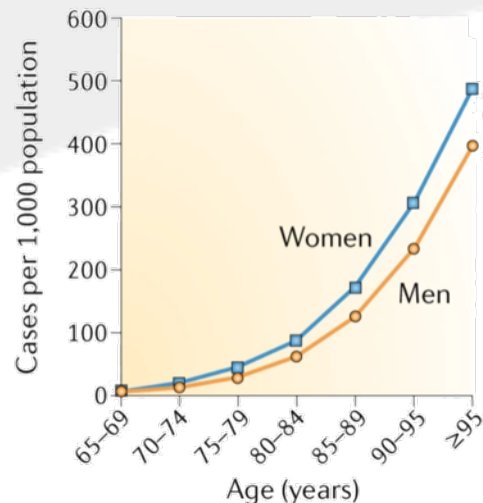
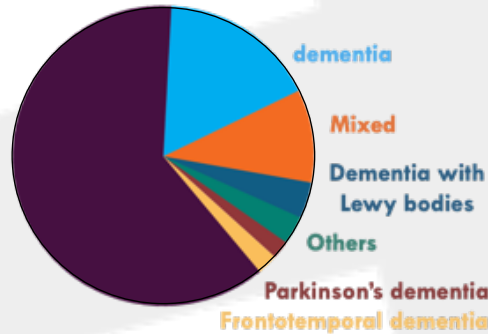


Ageing as a risk factor for neurodegenerative disease

Yujun Hou¹, Xiuli Dan¹, Mansi Babbar¹, Yong Wei¹, Steen G. Hasselbalch², Deborah L. Croteau¹ and Vilhelm A. Bohr^{1,3*}



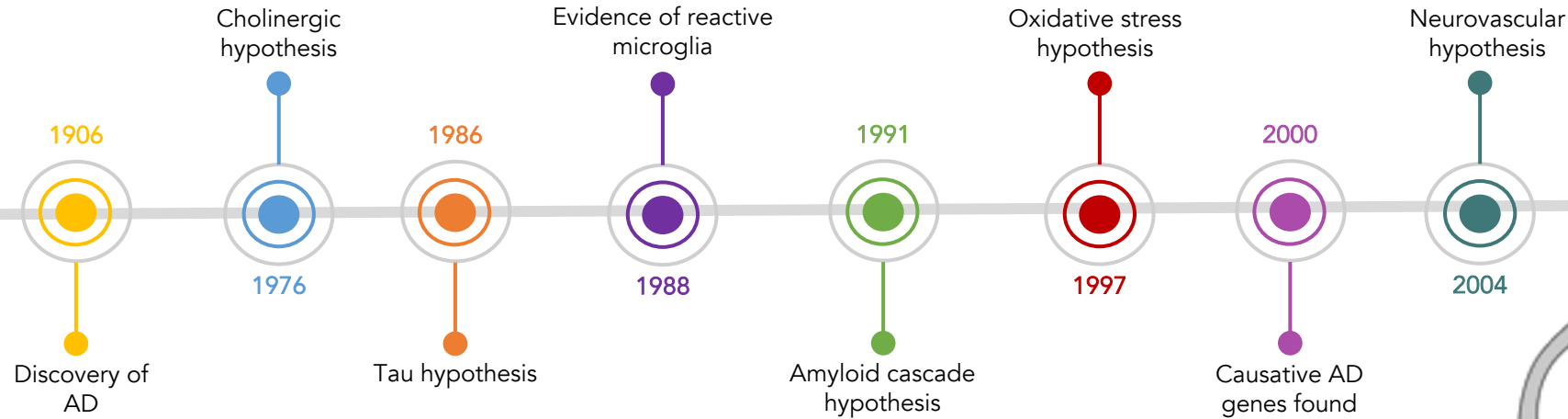
ALZHEIMER'S DISEASE
60-80%



The most common cause of dementia.

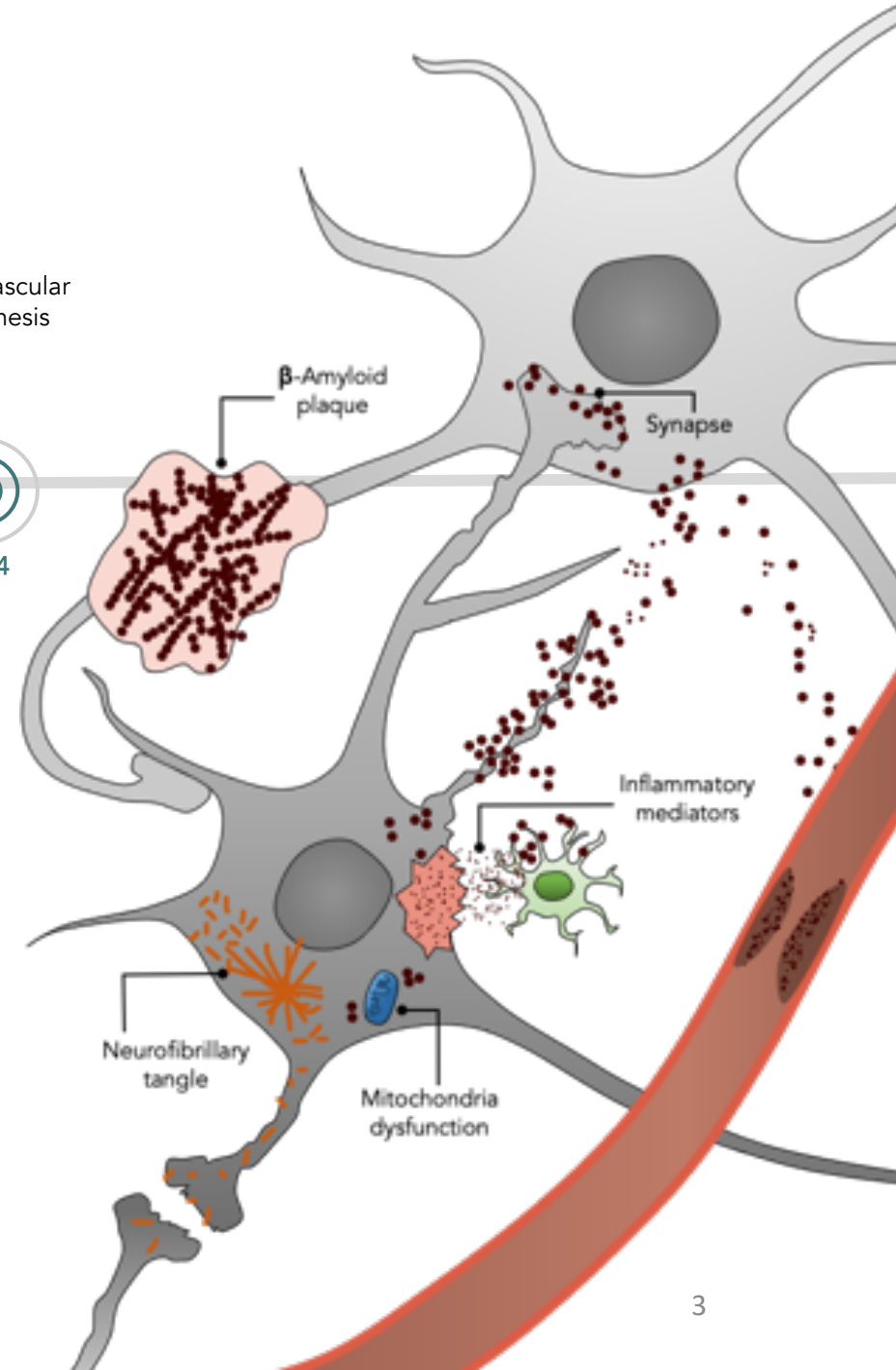
A progressive and irreversible age-dependent neurodegenerative diseases characterized by cognitive decline and memory loss.

ALZHEIMER'S DISEASE

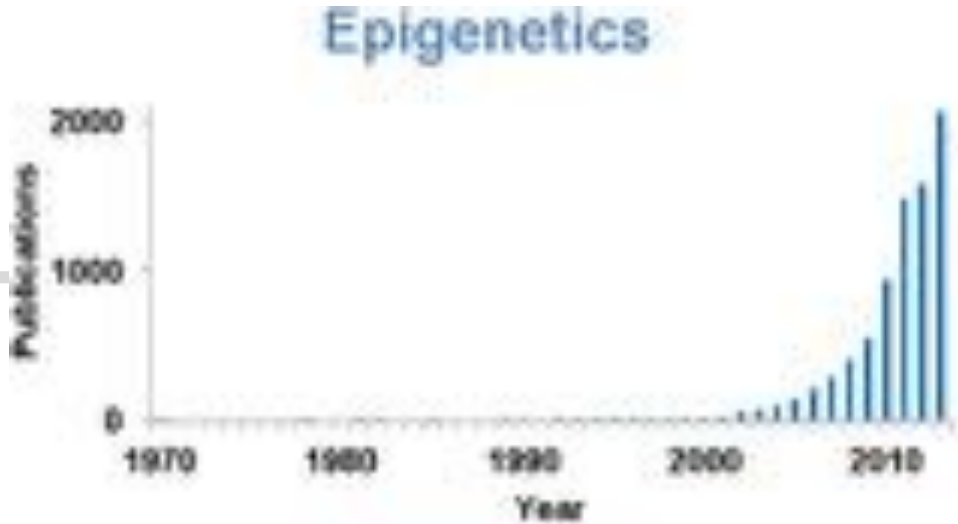
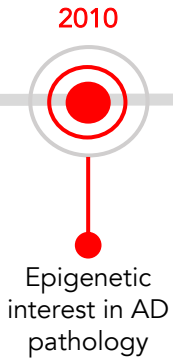


The aetiology of Alzheimer's disease is **multifactorial**.

Drug	Donepezil (1996)	Rivastigmine (2000)	Galantamine (2001)	Memantine (2003)	Aducanumab (2021)
Primary mechanism	AchE inh	AchE inh	AchE inh	NMDA antagonist	Monoclonal antibody



EPIGENETICS IN ALZHEIMER'S DISEASE



Epigenetic Alterations in Alzheimer's Disease

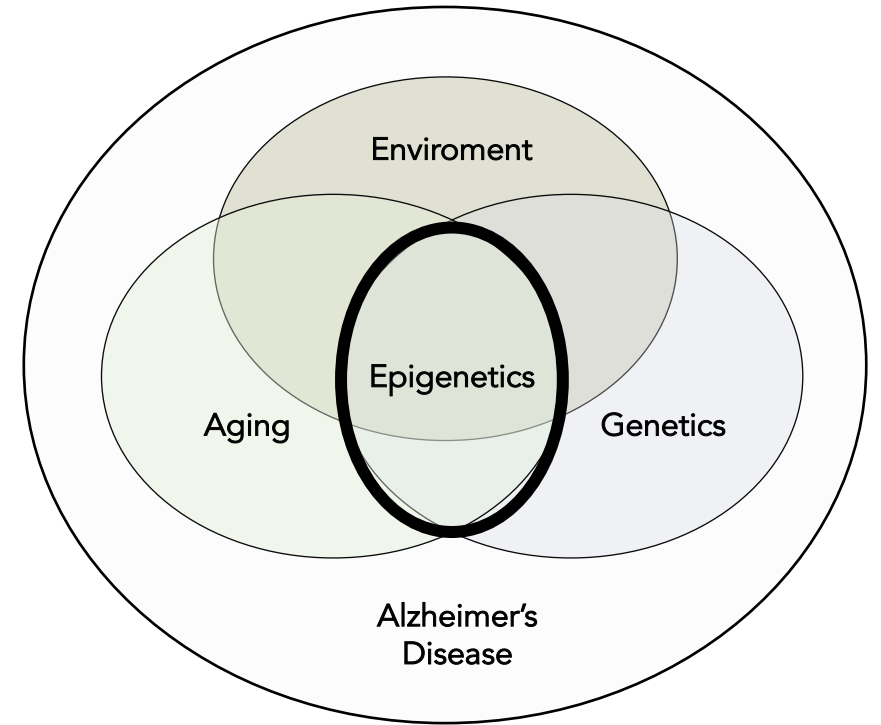
*Jose V. Sanchez-Mut and Johannes Gräff**

Epigenetic mechanisms in Alzheimer's disease: Implications for pathogenesis and therapy

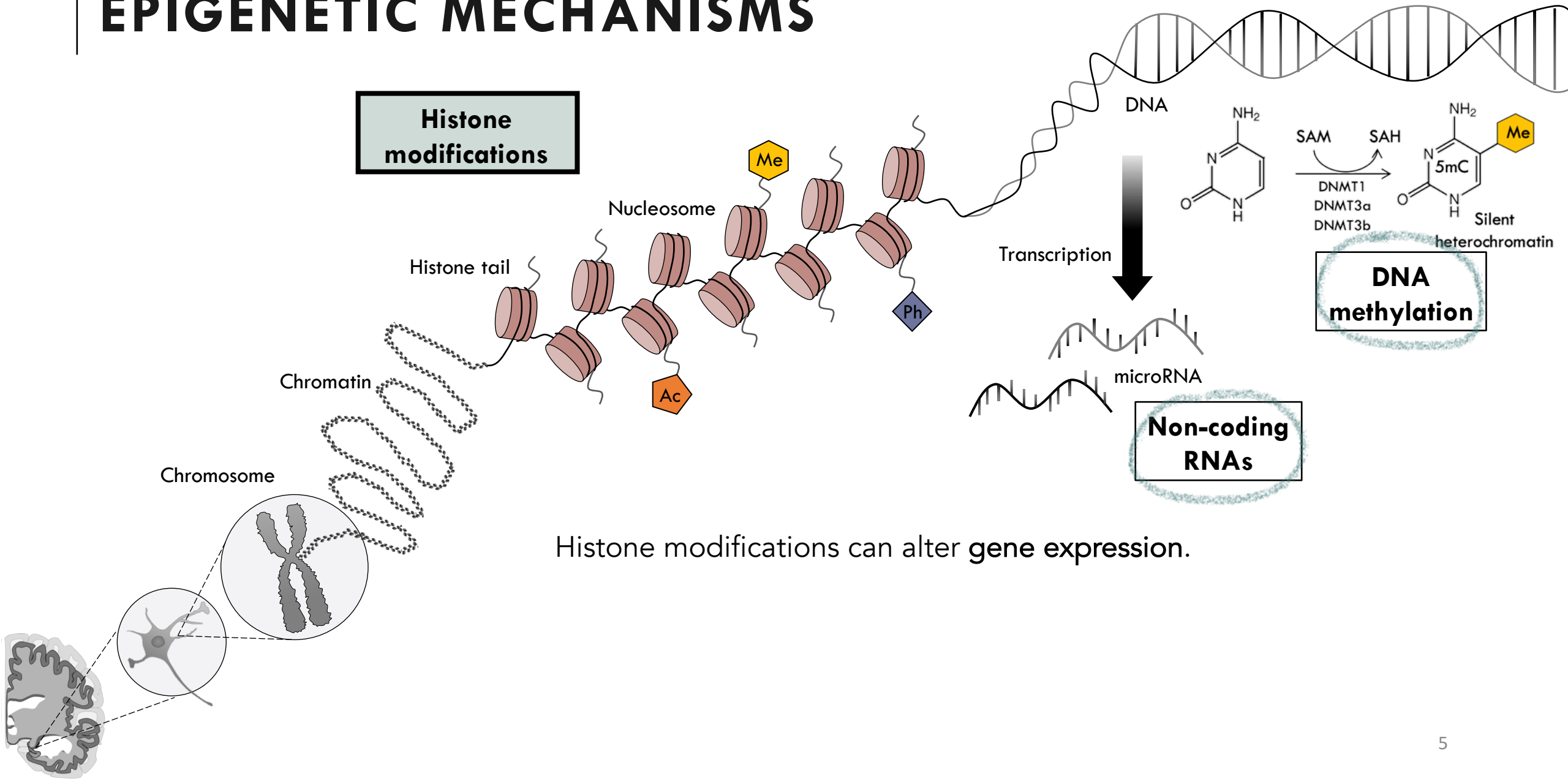
*Jun Wang^a, Jin-Tai Yu^{a,b,c,**}, Meng-Shan Tan^b, Teng Jiang^c, Lan Tan^{a,b,c,*}*

Role of Genes and Environments for Explaining Alzheimer Disease

Margaret Gatz, PhD; Chandra A. Reynolds, PhD; Laura Fratiglioni, MD, PhD; Boo Johansson, PhD; James A. Mortimer, PhD; Stig Berg, PhD; Amy Fiske, PhD; Nancy L. Pedersen, PhD

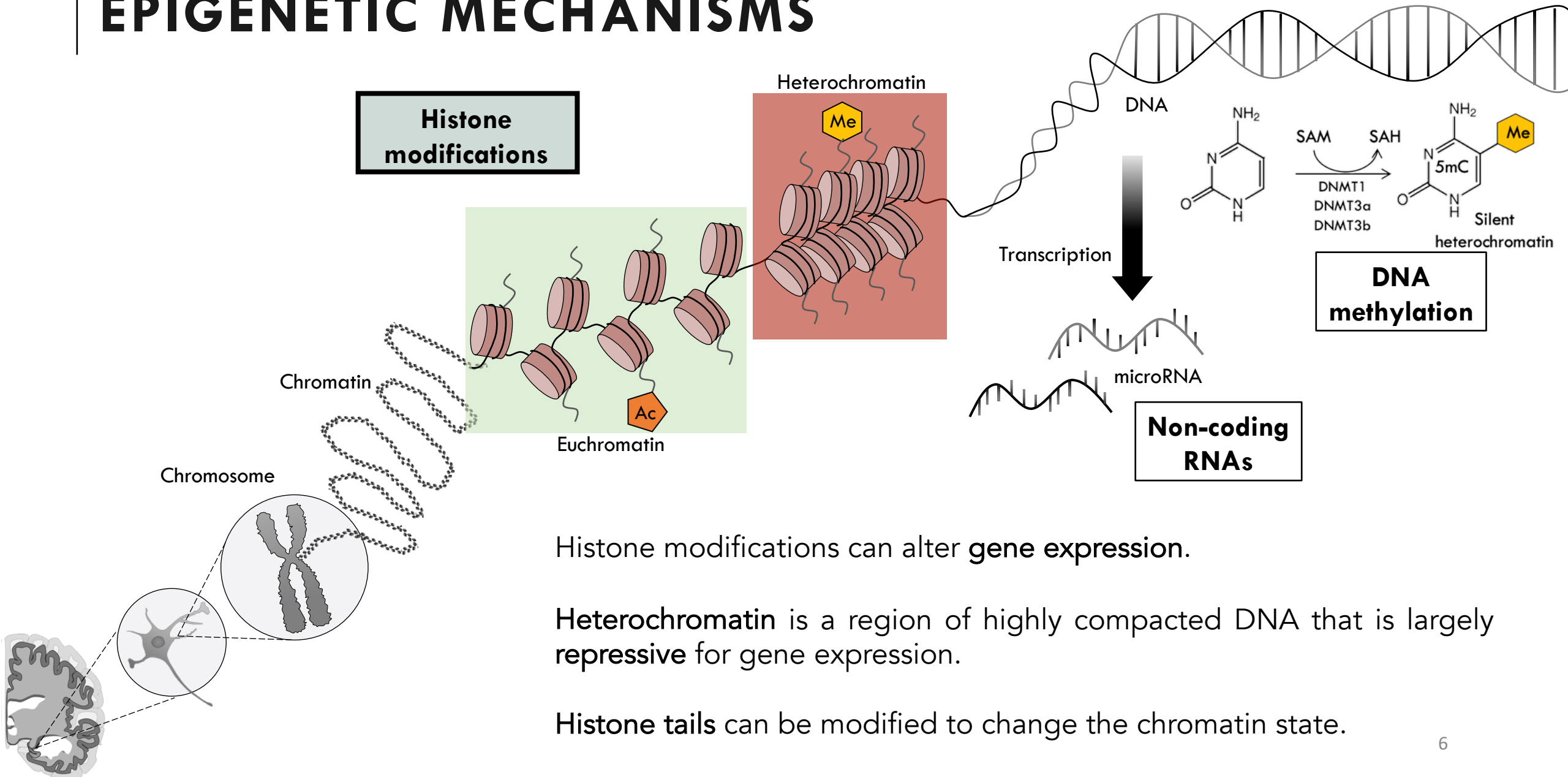


EPIGENETIC MECHANISMS



Histone modifications can alter gene expression.

EPIGENETIC MECHANISMS

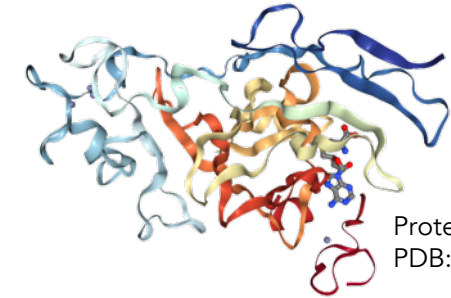
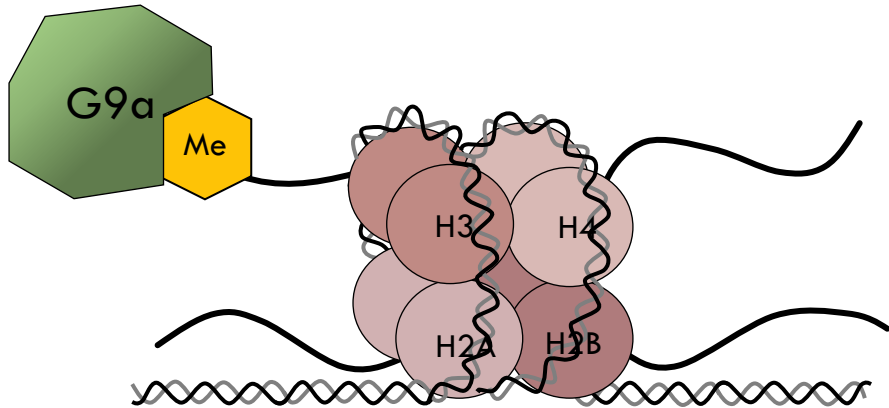


Histone modifications can alter gene expression.

Heterochromatin is a region of highly compacted DNA that is largely repressive for gene expression.

Histone tails can be modified to change the chromatin state.

G9a METHYLTRANSFERASE



Protein Data Bank
PDB: 2O8J

Lysine methyltransferase.

H3K9me and H3K9me2 are repressive marks.

Its inhibition restores the neuropathological hallmarks of AD.

2019

Inhibition of EHMT1/2 rescues synaptic and cognitive functions for Alzheimer's disease

Yan Zheng,^{1,2,*} Aiyi Liu,^{1,3,*} Zi-Jun Wang,^{1,4,*} Qing Cao,¹ Wei Wang,¹ Lin Lin,¹ Kaijie Ma,^{1,4} Freddy Zhang,¹ Jing Wei,^{1,4} Emmanuel Matas,¹ Jia Cheng,¹ Guo-Jun Chen,³ Xiaomin Wang² and Zhen Yan^{1,4}

2019

Epigenetics and memory: Emerging role of histone lysine methyltransferase G9a/GLP complex as bidirectional regulator of synaptic plasticity

Karen Ka Lam Pang^{a,b}, Mahima Sharma^{a,b,c}, Sreedharan Sajikumar^{a,b,*}

Epigenetic regulation by G9a/GLP complex ameliorates amyloid-beta 1-42 induced deficits in long-term plasticity and synaptic tagging/capture in hippocampal pyramidal neurons

Mahima Sharma,^{1,2} Tobias Dierkes^{1,3,4} and Sreedharan Sajikumar^{1,2}

2017

Pharmacological inhibition of G9a/GLP restores cognition and reduces oxidative stress, neuroinflammation and β -Amyloid plaques in an early-onset Alzheimer's disease mouse model

Christian Griñán-Ferré¹, Laura Marsal-García¹, Aina Bellver-Sanchis¹, Shukkoor Muhammed Kondengaden², Ravi Chakra Turga³, Santiago Vázquez⁴, Mercè Pallàs¹

2019 – First study in vivo in AD transgenic mice model

EPIGENETICS IN 5XFAD

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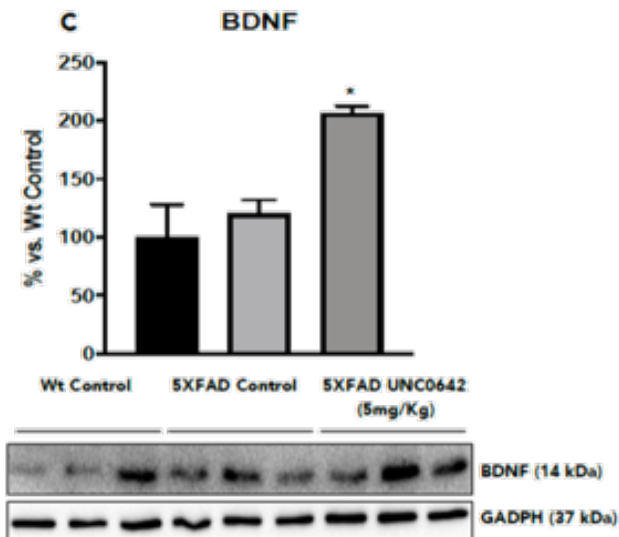
AGING 2019, Vol. 11, Advance

Research Paper

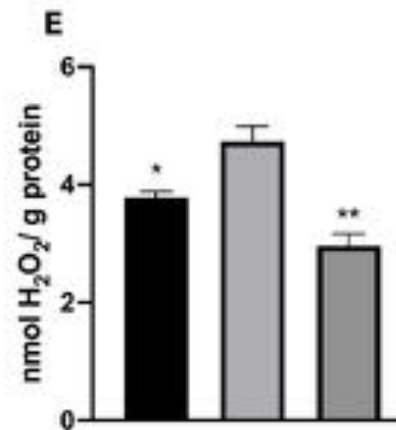
Pharmacological inhibition of G9a/GLP restores cognition and reduces oxidative stress, neuroinflammation and β -Amyloid plaques in an early-onset Alzheimer's disease mouse model

Christian Griñán-Ferré¹, Laura Marsal-García¹, Aina Bellver-Sanchis¹, Shukkoor Muhammed Kondengaden², Ravi Chakra Turga³, Santiago Vázquez⁴, Mercè Pallàs¹

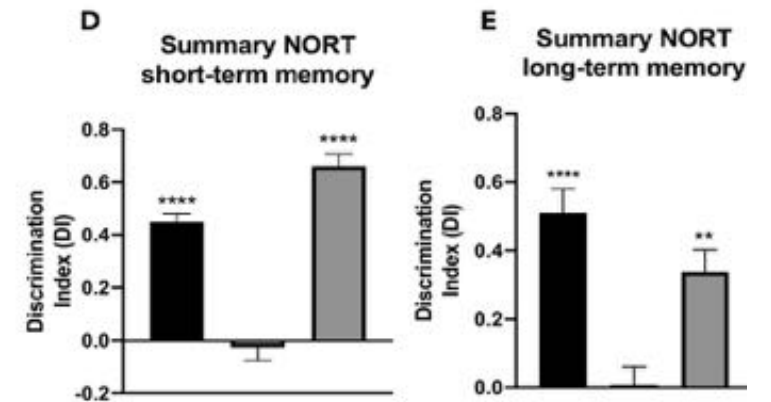
Synaptic plasticity



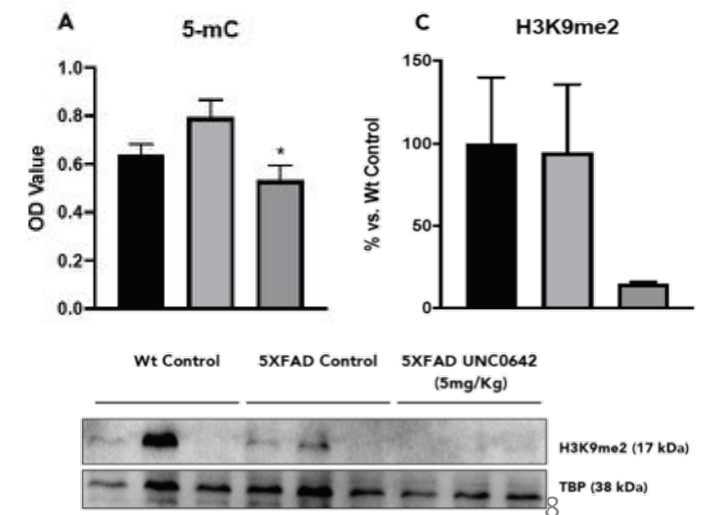
Oxidative stress



Better cognitive performance



Epigenetic modifications



Values represented are mean \pm Standard error of the mean (SEM); (n = 24 (SAMP8 Control = 12, SAMP8 UNC0642 (5mg/Kg) n = 12)). *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

EPIGENETICS IN 5XFAD

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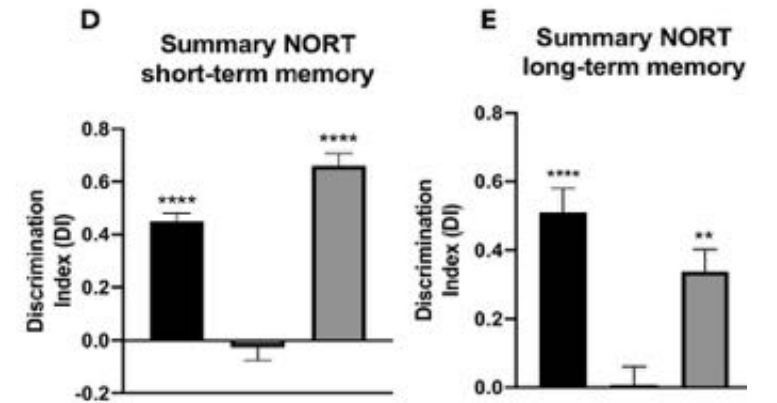
Research Paper

Pharmacological inhibition of G9a/GLP restores cognition and reduces oxidative stress, neuroinflammation and β -Amyloid plaques in an early-onset Alzheimer's disease mouse model

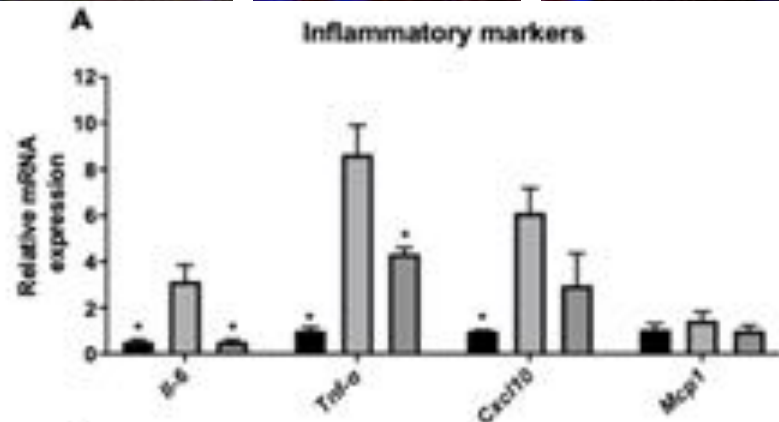
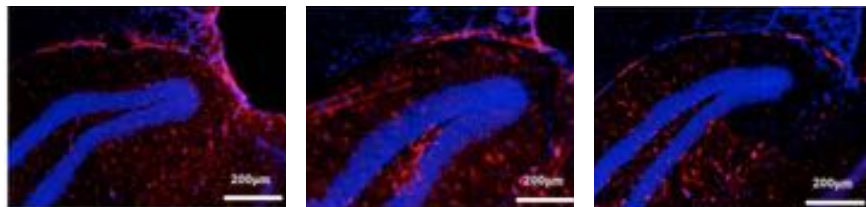
Christian Griñán-Ferré¹, Laura Marsal-García¹, Aina Bellver-Sanchis¹, Shukkoor Muhammed Kondengaden², Ravi Chakra Turga³, Santiago Vázquez⁴, Mercè Pallàs¹

- Wt Control
- 5XFAD Control
- 5XFAD UNC0642 (5mg/Kg)

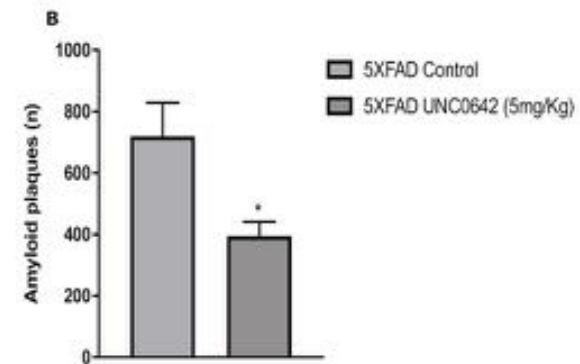
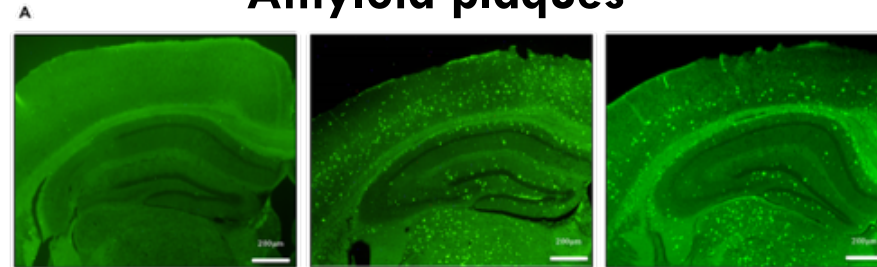
Better cognitive performance



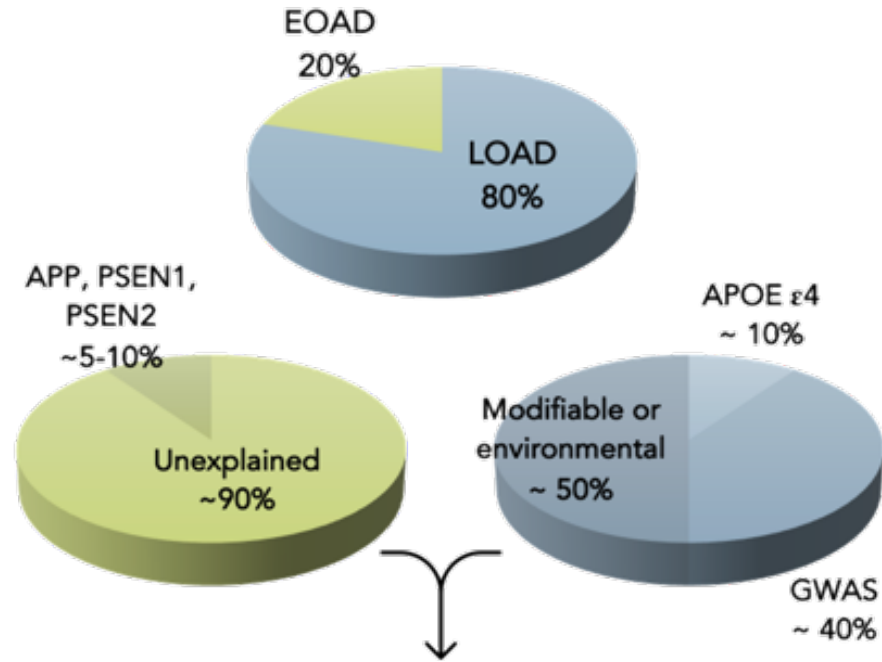
Inflammation



Amyloid plaques



MISSING HERITABILITY



Most disease heritability remains unaccounted

**EPIGENETIC
DYSREGULATION?**

Epigenetic differences arise during the lifetime of monozygotic twins

Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar*, Damia Heine-Suñer†, Juan C. Cigudosa‡, Miguel Urioste§, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling‡, Emma Carlsson‡, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§



Review

The Contribution of Epigenetic Inheritance Processes on Age-Related Cognitive Decline and Alzheimer's Disease

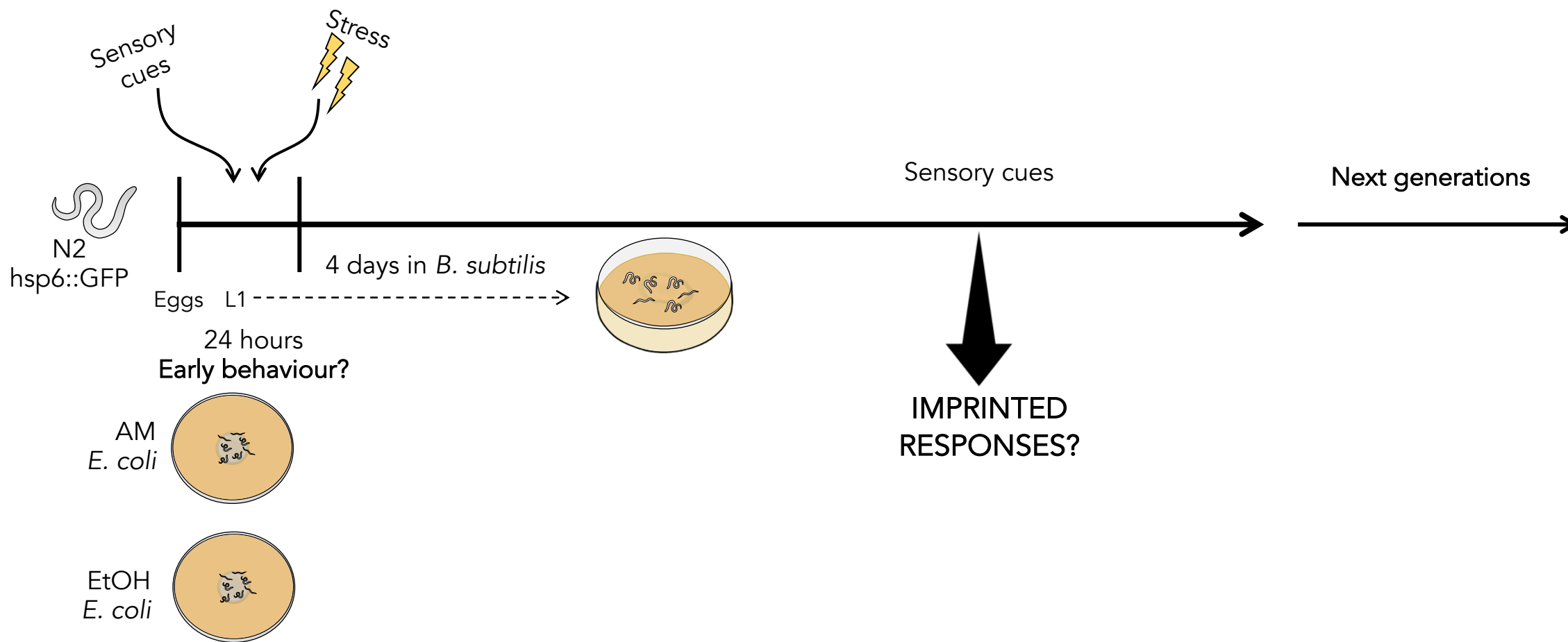
Aina Bellver-Sanchis ¹, Mercè Pallàs ¹ and Christian Griñán-Ferré ^{1*}

Does **set-25** play an important role in **epigenetic inheritance** in cognitive impairment after environmental harmful insults?

EXPERIMENTAL PARADIGM

Imprinting: a phase-specific long-term memory

Design experiment



CONCLUSIONS

- The potential reversibility of epigenetics allows **predicting future disease risk** and **validating new therapeutic targets**, as epigenetic intervention can modify the hippocampal transcriptome, potentially reversing age-related cognitive dysfunction. **Epigenetics**, therefore, is of **considerable translational importance** in the field of **neuroprotection**.
- UNC0642 prevented **A β** plaques accumulation, increased **synaptic plasticity** and neuronal markers that are characteristically loss in AD. Moreover, UNC0642 was able to reduce **OS** and **neuroinflammation**.



Dra Mercè Pallàs
Dr Christian Griñán Ferré
Dra Anna M. Canudas

Foteini Vasilopoulou
Vanessa Izquierdo
Júlia Companys
Júlia Jané

TAKE HOME MESSAGE

Our work reports a new finding that pharmacological inhibition of G9a might be a promising target for AD therapy, promoting neuroprotection through reduction of its repressive chromatin mark

Thank you
Gràcies



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