AD Genetics and Post-Genomic Era: What Have We Learned and Where Do We Go? A European Point of View

Jean-Charles Lambert, PhD
INSERM U1167, Institut Pasteur de Lille, France

Common forms of AD

It has been estimated that genetics account for 60-80% of Alzheimer attributable risk

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In 1993, APOE was reported for the first time as a major genetic risk factor for AD

Molecular Psychiatry (2011) 16, 903–907
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www.nature.com/mp

IMMEDIATE COMMUNICATION

APOE and Alzheimer disease: a major gene with semi-dominant inheritance

E Genin[1,2], D Hannequin[3,4], D Wallon[3,4], K Sleegers[5,6], M Hiltunen[7], O Combarros[8], MJ Bullido[9], S Engelborghs[6,10], P De Deyn[6,10], C Berr[11], F Pasquier[12,4], B Dubois[13,4], G Tognoni[14], N Fiévet[15,16], N Brouwers[5,6], K Bettens[5,6], B Arosio[17], E Coto[18], M Del Zompo[19], I Mateo[8], J Epelbaum[20], A Frank-Garcia[21], S Helisalmi[7], E Porcellini[22], A Pilotto[23], P Forti[24], R Ferri[25], E Scarpini[26], G Siciliano[14], V Solfrizzi[27], S Sorbi[28], G Spalletta[29], F Valdivieso[9], S Vepsäläinen[7], V Alvarez[18], P Bosco[25], M Mancuso[14], F Panza[27], B Nacmias[28], P Bossù[29], O Hanon[30], P Piccardi[19], G Annoni[31], D Seripa[23], D Galimberti[26], F Licastro[22], H Soininen[7], J-F Dartigues[32], MI Kamboh[33], C Van Broeckhoven[5,6], JC Lambert[12,15,16], P Amouyel[12,13,15,16] and D Campion[3,4,34]

Life time risk of AD at the age of 85:

- without reference to *APOE* genotype, was 11% in males and 14% in females.

- from 23% for *APOE34* male carriers to 30% for *APOE34* female carriers
- from 51% for *APOE44* male carriers to 60% for *APOE44* female

→ *These risks are similar to those of major genes such as BRCA1 in breast cancer*

Common forms of AD

It has been estimated that genetics account for 60-80% of Alzheimer attributable risk

However

Since the discovery of the *APOE* gene
as a major genetic risk factor,
no consensus was obtained in the genetics
of the late-onset forms of AD from 1993 to 2009

The advent of the genome wide association studies

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7]†

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly. We report a genome-wide screen of 96 cases and 50 controls for polymorphisms associated with AMD. Among 116,204 single-nucleotide polymorphisms genotyped, an intronic and common variant in the complement factor H gene (*CFH*) is strongly associated with AMD (nominal *P* value $<10^{-7}$). In individuals homozygous for the risk allele, the likelihood of AMD is increased by a factor of 7.4 (95% confidence interval 2.9 to 19). Resequencing revealed a polymorphism in linkage disequilibrium with the risk allele representing a tyrosine-histidine change at amino acid 402. This polymorphism is in a region of CFH that binds heparin and C-reactive protein. The *CFH* gene is located on chromosome 1 in a region repeatedly linked to AMD in family-based studies.

Science. 2005 Apr 15;308(5720):385-9.

The advent of the genome wide association studies

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Science. 2005 Apr 15;308(5720):385-9.

GAB2 Alleles Modify Alzheimer's Risk in *APOE* ε4 Carriers

Eric M. Reiman,[1,2,3,17,18,*] Jennifer A. Webster,[1,17,18] Amanda J. Myers,[4,5,18] John Hardy,[5,6] Travis Dunckley,[1,17] Victoria L. Zismann,[1,17] Keta D. Joshipura,[1,17] John V. Pearson,[1,17] Diane Hu-Lince,[1,17] Matthew J. Huentelman,[1,17] David W. Craig,[1,17] Keith D. Coon,[1,7,17] Winnie S. Liang,[1,17] RiLee H. Herbert,[1,17] Thomas Beach,[8,17] Kristen C. Rohrer,[5] Alice S. Zhao,[5] Doris Leung,[5] Leslie Bryden,[5] Lauren Marlowe,[5] Mona Kaleem,[5] Diego Mastroeni,[8] Andrew Grover,[8,17] Christopher B. Heward,[9] Rivka Ravid,[10] Joseph Rogers,[8,17] Michael L. Hutton,[11] Stacey Melquist,[11] Ron C. Petersen,[12] Gene E. Alexander,[13,17] Richard J. Caselli,[14,17] Walter Kukull,[16] Andreas Papassotiropoulos,[1,15] and Dietrich A. Stephan[1,2,17,*]

Neuron juin 2007; GAB2: GRB-associated binding protein 2

REPORT

Genome-wide Association Analysis Reveals Putative Alzheimer's Disease Susceptibility Loci in Addition to *APOE*

Lars Bertram,[1,6] Christoph Lange,[2,6] Kristina Mullin,[1] Michele Parkinson,[1] Monica Hsiao,[1] Meghan F. Hogan,[1] Brit M.M. Schjeide,[1] Basavaraj Hooli,[1] Jason DiVito,[1] Iuliana Ionita,[2] Hongyu Jiang,[2] Nan Laird,[2] Thomas Moscarillo,[4] Kari L. Ohlsen,[5] Kathryn Elliott,[5] Xin Wang,[5] Diane Hu-Lince,[5] Marie Ryder,[5] Amy Murphy,[2] Steven L. Wagner,[5] Deborah Blacker,[3,4] K. David Becker,[5] and Rudolph E. Tanzi[1,*]

Genetic variation in *PCDH11X* is associated with susceptibility to late-onset Alzheimer's disease

Minerva M Carrasquillo[1], Fanggeng Zou[1], V Shane Pankratz[2], Samantha L Wilcox[1], Li Ma[1], Louise P Walker[1], Samuel G Younkin[1], Curtis S Younkin[1], Linda H Younkin[1], Gina D Bisceglio[1], Nilufer Ertekin-Taner[1,3], Julia E Crook[4], Dennis W Dickson[1], Ronald C Petersen[3,5], Neill R Graff-Radford[1,3] & Steven G Younkin[1]

Nature genetics, janvier 2009; PCDH11X: protocadherin 11, linked X

The two first consortia with enough statistical power to detect genuine signals

- EADI ; discovery sample : 2,032 cases and 5,328 controls
- GERAD ; discovery sample : 3,941 cases and 7,848 controls

October 2009

LETTERS

nature genetics

Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease

Jean-Charles Lambert[1–3], Simon Heath[4], Gael Even[1,2], Dominique Campion[5], Kristel Sleegers[6,7], Mikko Hiltunen[8], Onofre Combarros[9], Diana Zelenika[4], Maria J Bullido[10], Béatrice Tavernier[11], Luc Letenneur[12], Karolien Bettens[6,7], Claudine Berr[13], Florence Pasquier[3,14], Nathalie Fiévet[1,2], Pascale Barberger-Gateau[12], Sebastiaan Engelborghs[7,15], Peter De Deyn[7,15], Ignacio Mateo[9], Ana Franck[16], Seppo Helisalmi[8], Elisa Porcellini[17], Olivier Hanon[18], the European Alzheimer's Disease Initiative Investigators[19], Marian M de Pancorbo[20], Corinne Lendon[21], Carole Dufouil[22,23], Céline Jaillard[24], Thierry Leveillard[24], Victoria Alvarez[25], Paolo Bosco[26], Michelangelo Mancuso[27], Francesco Panza[28], Benedetta Nacmias[29], Paola Bossù[30], Paola Piccardi[31], Giorgio Annoni[32], Davide Seripa[33], Daniela Galimberti[34], Didier Hannequin[5], Federico Licastro[17], Hilkka Soininen[8], Karen Ritchie[13], Hélène Blanché[35], Jean-François Dartigues[12], Christophe Tzourio[22,23], Ivo Gut[4], Christine Van Broeckhoven[6,7], Annick Alpérovitch[22,23], Mark Lathrop[4,35] & Philippe Amouyel[1–3,14]

LETTERS

nature genetics

Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease

Denise Harold[1,45*], Richard Abraham[1,45], Paul Hollingworth[1,45], Rebecca Sims[1], Amy Gerrish[1], Marian L Hamshere[1], Jaspreet Singh Pahwa[1], Valentina Moskvina[1], Kimberley Dowzell[1], Amy Williams[1], Nicola Jones[1], Charlene Thomas[1], Alexandra Stretton[1], Angharad R Morgan[1], Simon Lovestone[2], John Powell[3], Petroula Proitsi[3], Michelle K Lupton[3], Carol Brayne[4], David C Rubinsztein[5], Michael Gill[6], Brian Lawlor[6], Aoibhinn Lynch[6], Kevin Morgan[7], Kristelle S Brown[7], Peter A Passmore[8], David Craig[8], Bernadette McGuinness[8], Stephen Todd[8], Clive Holmes[9], David Mann[10], A David Smith[11], Seth Love[12], Patrick G Kehoe[12], John Hardy[13], Simon Mead[14], Nick Fox[15], Martin Rossor[15], John Collinge[14], Wolfgang Maier[16], Frank Jessen[16], Britta Schürmann[16], Hendrik van den Bussche[17], Isabella Heuser[18], Johannes Kornhuber[19], Jens Wiltfang[20], Martin Dichgans[21,22], Lutz Frölich[23], Harald Hampel[24,25], Michael Hüll[26], Dan Rujescu[25], Alison M Goate[27], John S K Kauwe[28], Carlos Cruchaga[27], Petra Nowotny[27], John C Morris[27], Kevin Mayo[27], Kristel Sleegers[29,30], Karolien Bettens[29,30], Sebastiaan Engelborghs[30,31], Peter P De Deyn[30,31], Christine Van Broeckhoven[29,30], Gill Livingston[32], Nicholas J Bass[32], Hugh Gurling[32], Andrew McQuillin[32], Rhian Gwilliam[33], Panagiotis Deloukas[33], Ammar Al-Chalabi[34], Christopher E Shaw[34], Magda Tsolaki[35], Andrew B Singleton[36], Rita Guerreiro[36], Thomas W Mühleisen[37,38], Markus M Nöthen[37,38], Susanne Moebus[39], Karl-Heinz Jöckel[39], Norman Klopp[40], H-Erich Wichmann[40–42], Minerva M Carrasquillo[43], V Shane Pankratz[44], Steven G Younkin[43], Peter A Holmans[1], Michael O'Donovan[1], Michael J Owen[1] & Julie Williams [1]

CLU : rs11136000

OR = 0.86 [0.81-0.90], $p=7.5 \times 10^{-9}$

CR1 : rs665401

OR = 1.21 [1.14-1.29], $p=3.5 \times 10^{-9}$

PICALM : rs3851179

OR = 0.86 [0.82-0.90], p=1.3x10-9

A third player in the GWAS AD field

- CHARGE ; discovery sample : 3,006 cases and 14,642 controls
- EADI and GERAD used as replication samples

May 2010

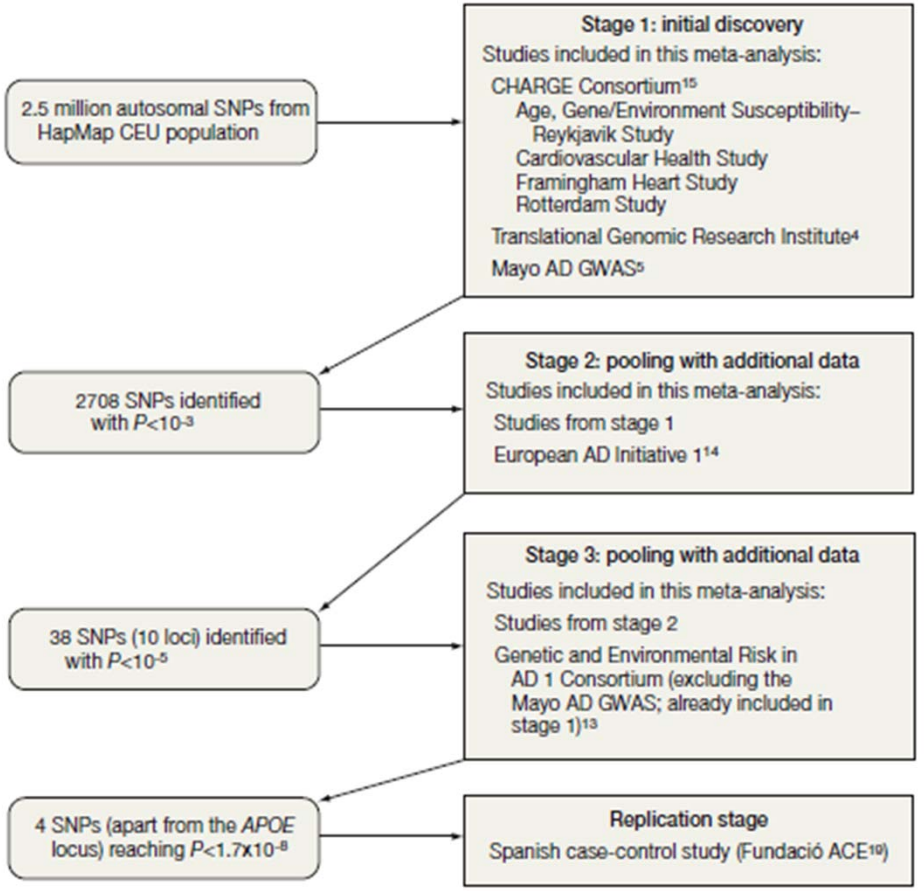
Genome-wide Analysis of Genetic Loci Associated With Alzheimer Disease

Sudha Seshadri, MD; Annette L. Fitzpatrick, PhD; M. Arfan Ikram, MD, PhD; Anita L. DeStefano, PhD; Vilmundur Gudnason, MD, PhD; Merce Boada, MD, PhD; Joshua C. Bis, PhD; Albert V. Smith, PhD; Minerva M. Carassquillo, PhD; Jean Charles Lambert, PhD; Denise Harold, PhD; Elisabeth M. C. Schrijvers, MD; Reposo Ramirez-

Context Genome-wide association studies (GWAS) have recently identified *CLU*, *PICALM*, and *CR1* as novel genes for late-onset Alzheimer disease (AD).

Objectives To identify and strengthen additional loci associated with AD and confirm these in an independent sample and to examine the contribution of recently identified genes to AD risk prediction in a 3-stage analysis of new and previously published GWAS on more than 35 000 persons (8371 AD cases).

JAMA, 2010, 303, 1832-1840.



BIN1 : rs744373

OR= 1.13 [1.06-1.21], $p=1.6 \times 10^{-10}$

A fourth player in the GWAS AD field

- ADGC; discovery sample : 8,309 cases and 7,366 controls

May 2011

LETTERS

nature genetics

Common variants at *MS4A4/MS4A6E*, *CD2AP*, *CD33* and *EPHA1* are associated with late-onset Alzheimer's disease

Naj AC*, Gyungah J*, et al.
* Equally contributed to this work

LETTERS

nature genetics

Common variants at *ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33* and *CD2AP* are associated with Alzheimer's disease

Hollingworth P,* Harold D*, Sims R*, Gerrish A,* Lambert JC,* Carrasquillo MM,* et al., in press
* Equally contributed to this work

EPHA1 : rs11767557
OR= 0.90 [0.85-0.95], $p=6.0x10^{-10}$

CD2AP : rs9349407
OR= 1.11 [1.04-1.18], $p=8.6x10^{-9}$

CD33 : rs386544
OR= 0.89 [0.84-0.95], $p=1.6x10^{-9}$

ABCA7 : rs3764650
OR= 1.23 [1.17-1.28], $p=5.0x10^{-21}$

MS4A6A/MS4A4E : rs610932
OR= 0.91 [0.88-0.93], $p=1.2x10^{-16}$

Lessons from the 5 initial AD GWAS

- No other common variant presented an association with AD risk as strong as *APOE*.

- As observed in most of the GWAS developed in other multifactorial diseases, the new characterised genes in AD have “modest” magnitude of association.

- The functional genetic variants are mainly unknown.

high-throughput approaches involve finding a balance between:

- the risk of observing significant results by chance
- the risk of rejecting biologically valid hypotheses.

Application of a conventional, highly conservative Bonferroni correction led to select only the most statistically significant associations ($p<5x10^{-8}$).

To overcome this limitation, it is possible

(i) to develop more complex statistical approaches

(ii) to increase the statistical power of GWASs by performing larger meta-analyses.

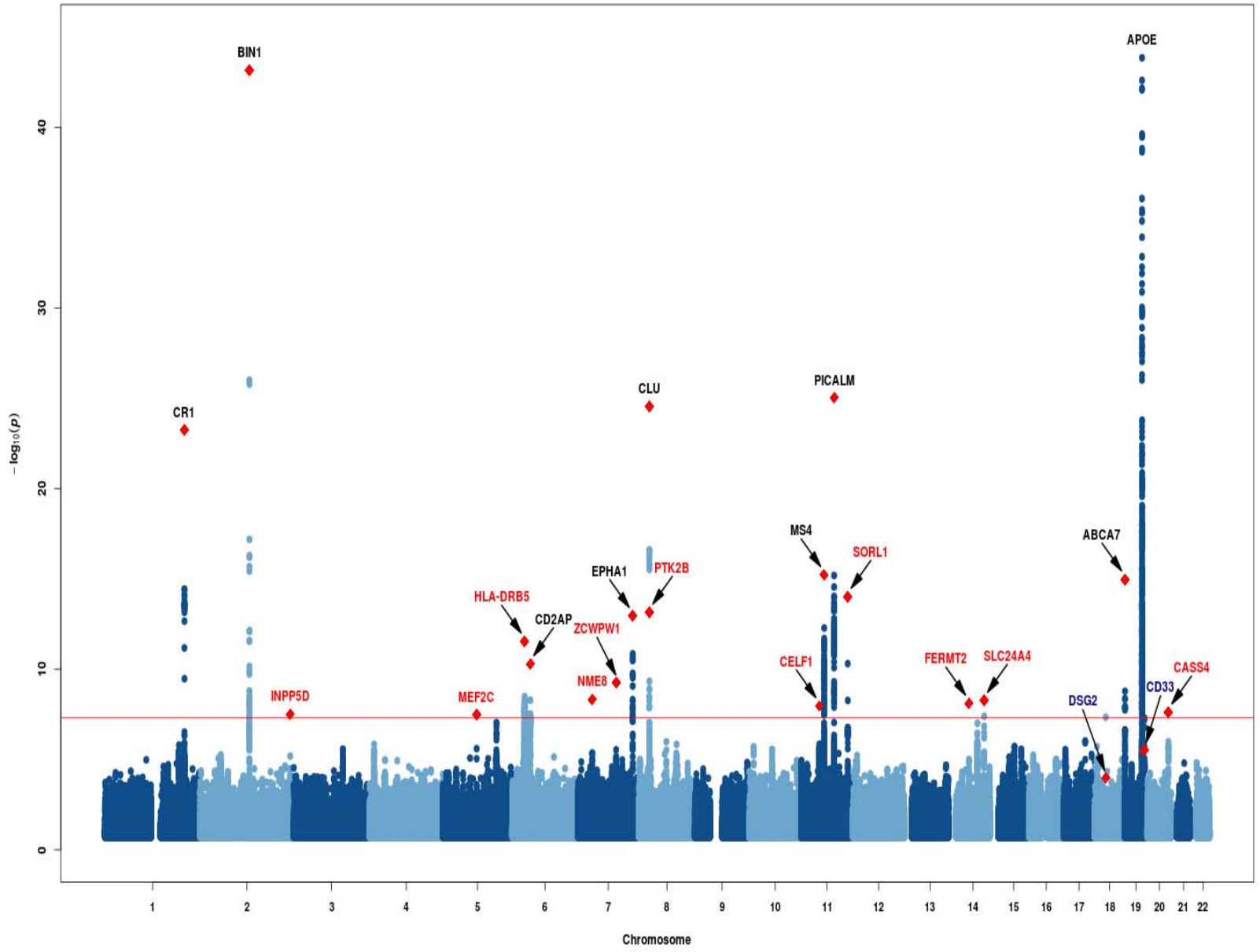
IGAP
INTERNATIONAL
GENOMICS OF ALZHEIMER'S PROJECT

imputation from the 1000 genome project : **7,035,000** millions of SNPs

Step 1 :	EADI 1	2,243 cases	6,017 Controls
	GERAD 1	3,177 cases	7,277 Controls
	CHARGE 1	1,315 cases	10,496 Controls
	ADGC 1	10,507 cases	10,892 Controls
	TOTAL 1	**17,008 cases**	**34,682** Controls

Replication (11,692 SNPs)

Step 2 :	EADI 2	6,967 cases	8,678 Controls
	GERAD 2	1,568 cases	2,520 Controls
	CHARGE 2	500 cases	500 Controls
	TOTAL 2	**8,035 cases**	**11,698** Controls



Lambert et al, Nat Genet, 2013

Exome chip analysis (IGAP)

The main content of the chip comprises protein altering variants (nonsynonymous coding, splice site and stop gain or loss codons).

LETTERS

nature genetics

Rare coding variants in *PLCG2*, *ABI3*, and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease

Sims et al., Nat Genet, 2017

GWAS analysis using age at onset (IGAP)

nature neuroscience

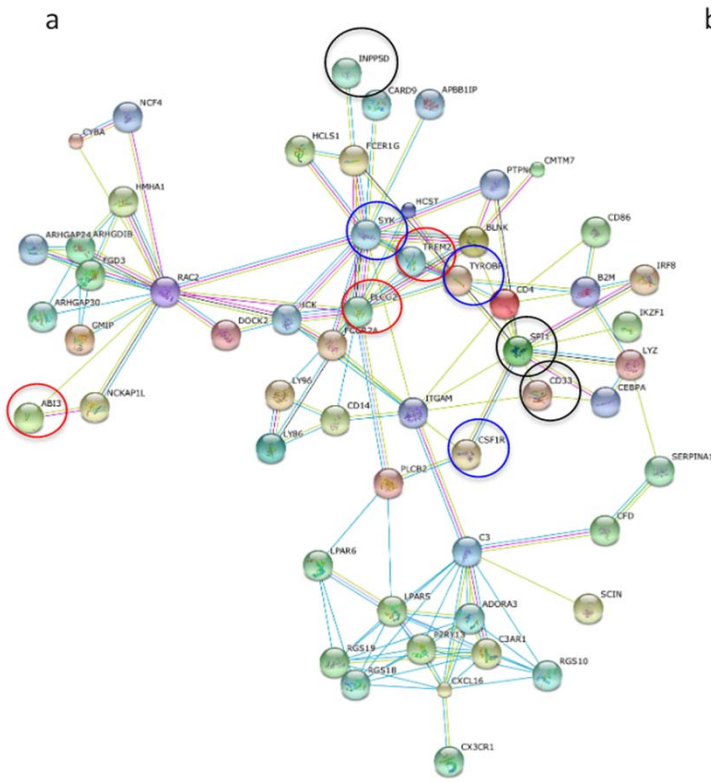
A common haplotype lowers PU.1 expression in myeloid cells and delays onset of Alzheimer's disease

Kuan-lin Huang[1,30], Edoardo Marcora[2,3,30], Anna A Pimenova[3], Antonio F Di Narzo[2], Manav Kapoor[2,3], Sheng Chih Jin[4], Oscar Harari[5], Sarah Bertelsen[3], Benjamin P Fairfax[6], Jake Czajkowski[7], Vincent Chouraki[8], Benjamin Grenier-Boley[9–11], Céline Bellenguez[9–11], Yuetiva Deming[3], Andrew McKenzie[2], Towfique Raj[2,3], Alan E Renton[3], John Budde[5], Albert Smith[12], Annette Fitzpatrick[13], Joshua C Bis[14], Anita DeStefano[15], Hieab H H Adams[16], M Arfan Ikram[16], Sven van der Lee[16], Jorge L Del-Aguila[5], Maria Victoria Fernandez[5], Laura Ibañez[5], The International Genomics of Alzheimer's Project[17], The Alzheimer's Disease Neuroimaging Initiative[18], Rebecca Sims[19], Valentina Escott-Price[19], Richard Mayeux[20], Jonathan L Haines[21], Lindsay A Farrer[15,22–24], Margaret A Pericak-Vance[24,25], Jean Charles Lambert[9–11], Cornelia van Duijn[16], Lenore Launer[26], Sudha Seshadri[8], Julie Williams[19], Philippe Amouyel[9–11,27], Gerard D Schellenberg[28], Bin Zhang[2], Ingrid Boreckí[7], John S K Kauwe[29], Carlos Cruchaga[5], Ke Hao[2] & Alison M Goate[2,3]

Four genetic risk factors of AD:

- ABI3
- TREM2 (two rare variants associated)
- PLCG2
- PU.1

Almost only expressed in microglia



PPI network highlights a specific pathway in microglia potentially deregulated in AD

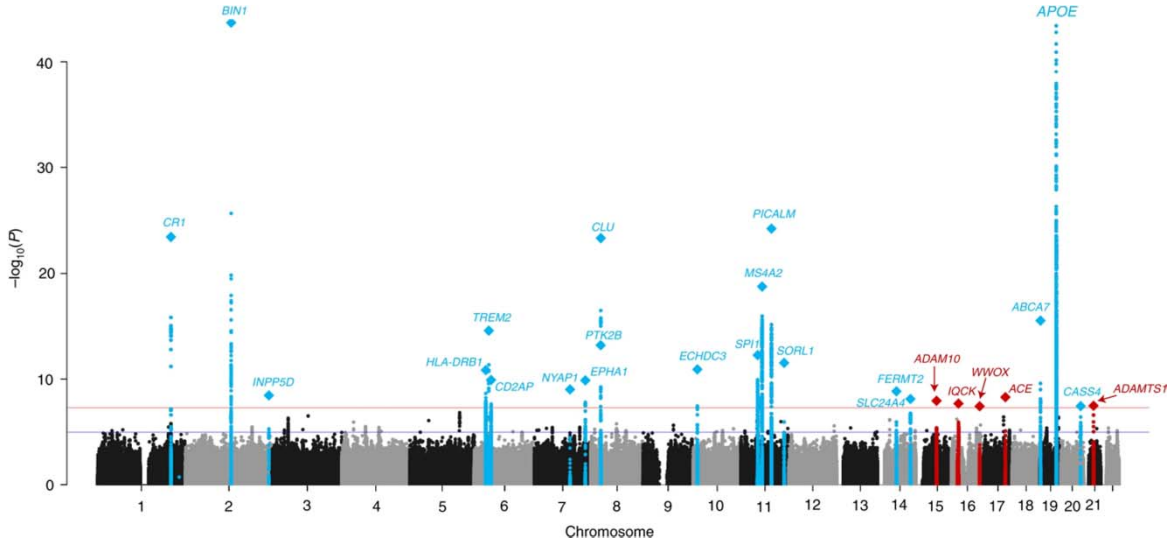
A new IGAP meta-analysis

IGAP 2013	**17,008 cases**	**34,682 controls**
IGAP 2019	**21,982 cases**	**41,944 controls**

+24% in terms of population size for the discovery step

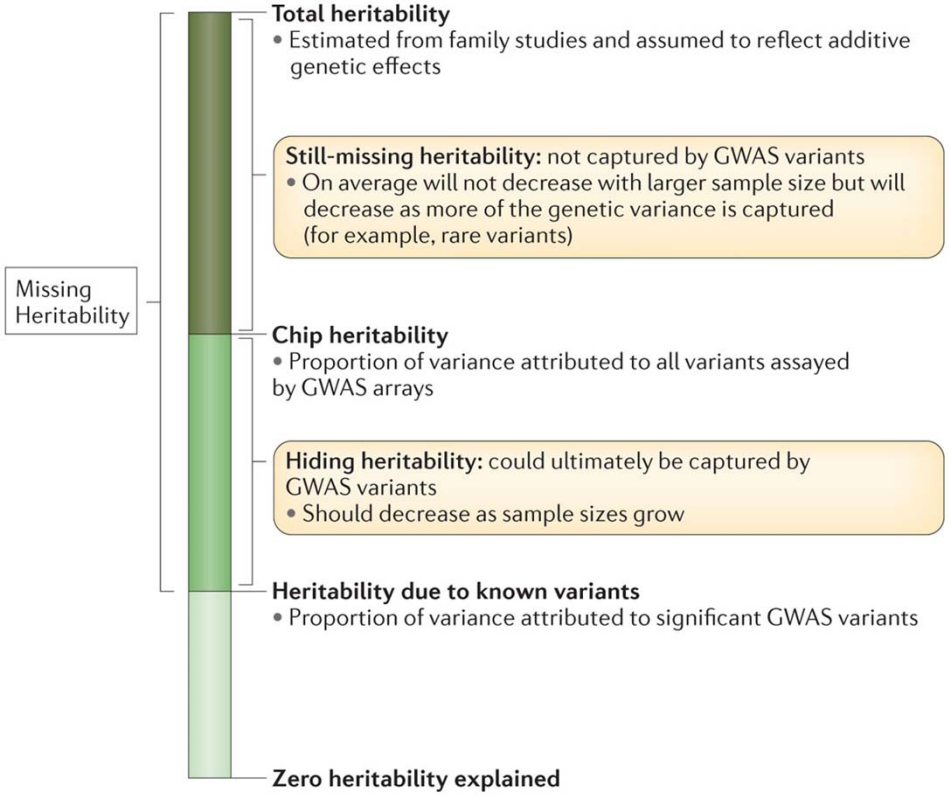
5 new signals reaching genome wide-significance after replication

- ADAM10
- ADAMTS1
- ACE
- IQCK
- WWOX



B. Kunkle, B. Grenier-Boley* et al., Nat Genet, 2019*

The missing heritability is still high in AD : How to characterise it ?



Witte et al, Nat Rev Genet, 2014

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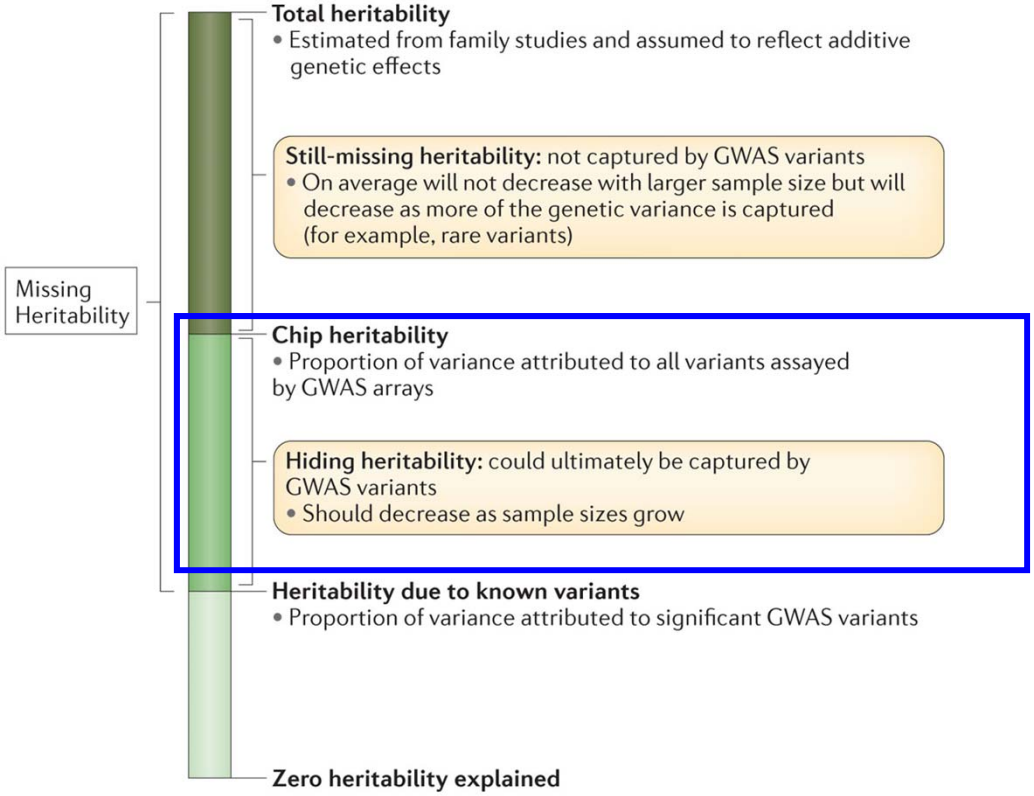

Increasing the population size analyzed by GWAS should allow to characterize new genetic risk factors
Improving imputations should allow to optimize GWAS

Witte et al, Nat Rev Genet, 2014

EADB

European Alzheimer DNA Biobank

Four axes :

- Genetics of Alzheimer disease
- Genetics of MCI - evolution and conversion -
- Genetics of vascular dementia
- Genetics of normal pressure hydrocephalus

<u>16 European countries and more than 60 laboratories/hospital departments:</u>

- Austria (Helena Schmidt)
- Belgium (Kristel Sleegers)
- Czech Republic (Jakub Hort)
- Denmark (Ruth Frikke-Schmidt)
- Finland (Mikko Hiltunen)
- France (Jean-Charles Lambert, PI)
- Germany (Alfredo Ramirez)
- Greece (Magda Tsolaki)
- Italy (Giacomina Rossi)
- Norway (Ole Andreassen)
- Portugal (Alexandre Mendoca)
- The Netherlands (Wiesje van der Flier)
- The UK (Rebecca Sims)
- Spain (Jordi Clarimon)
- Sweden (Martin Ingelson)

- Australia (Karen Mather)

EADB dataset genotyped using the ILLUMINA Global screening array (GSA)

63,049 samples

And available for analyses after QCs

- 19,478 AD cases
- 6,690 MCI cases
- 1,519 VCI cases
- 1,543 other dementia
- 843 NPH cases
- 24,039 controls

- 2,351 missing status

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<u>EADB discovery phase</u>

	Cases	**Controls**
EADB core :	19,478	24,039
Gra@ce/Degesco	6,331	6,055
EADI	2,328	6,661
GERAD	3,332	7,355
Rotterdam Study	1,306	6,700
NORWAY	2,066	7,637
Denmark	403	7,907
Germany	514	416
AddNeuroMed	450	187
NxC	324	754
Total :	**36,532**	**67,711**

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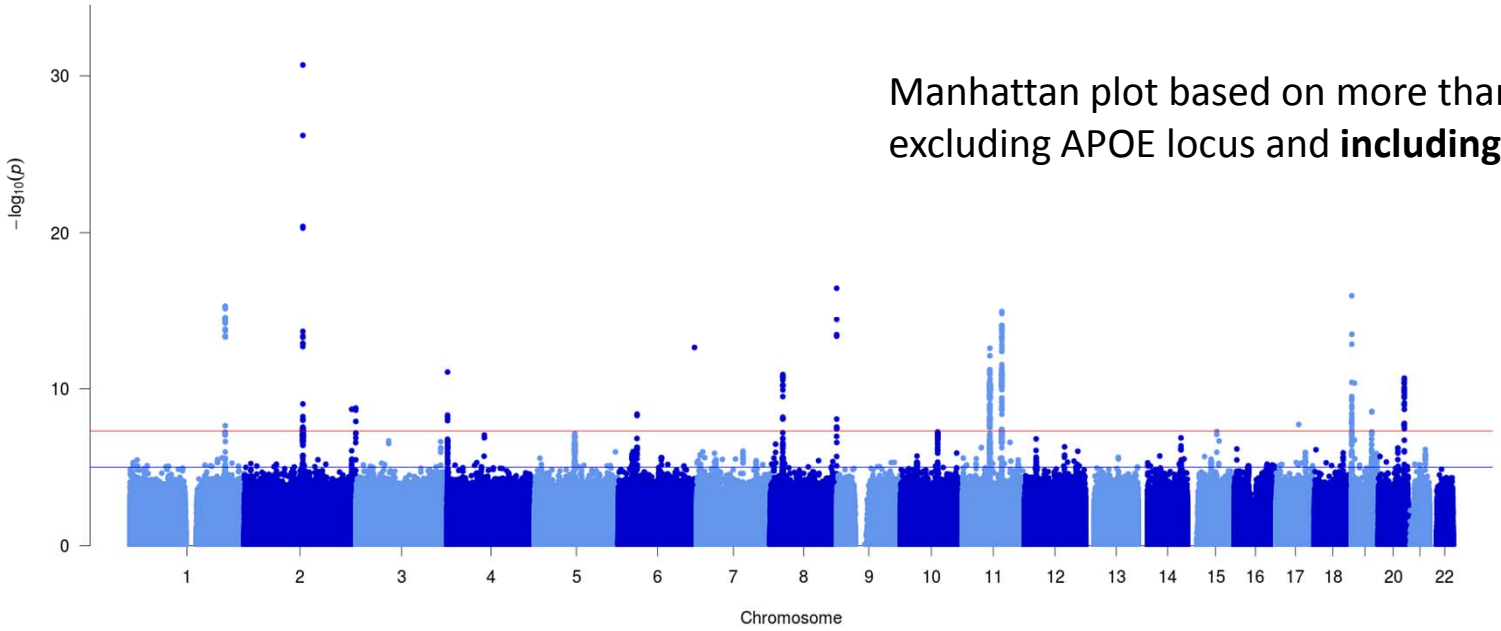
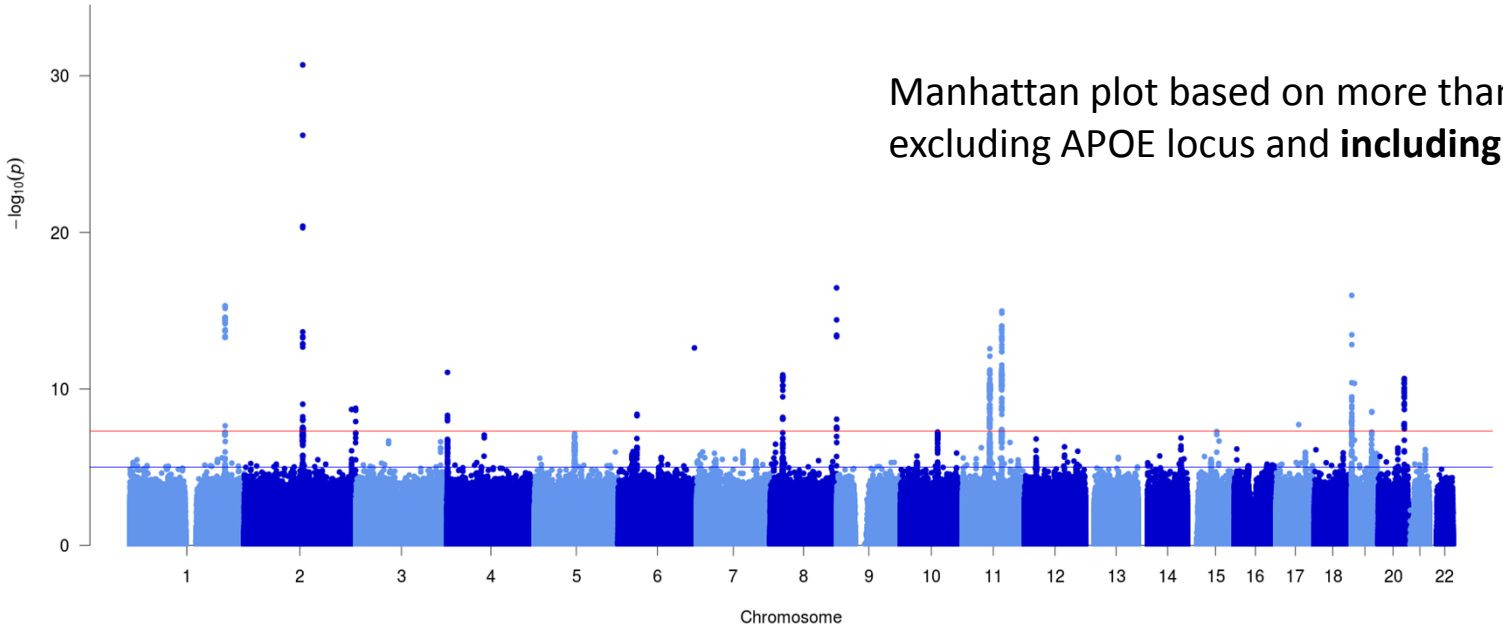
Imputations using the TopMed panel are in progress



Manhattan plot based on more than 65 millions of SNPs excluding APOE locus and **including known GWAS loci**



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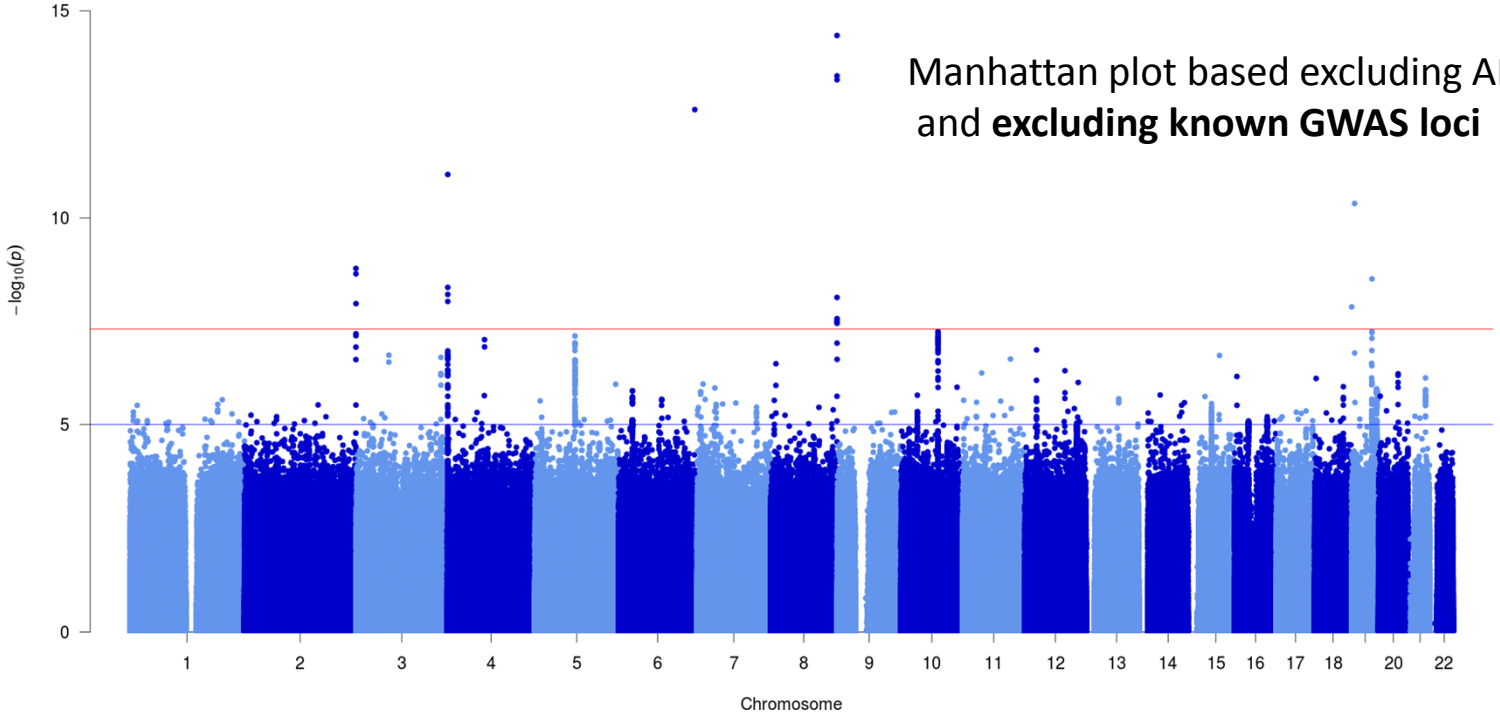
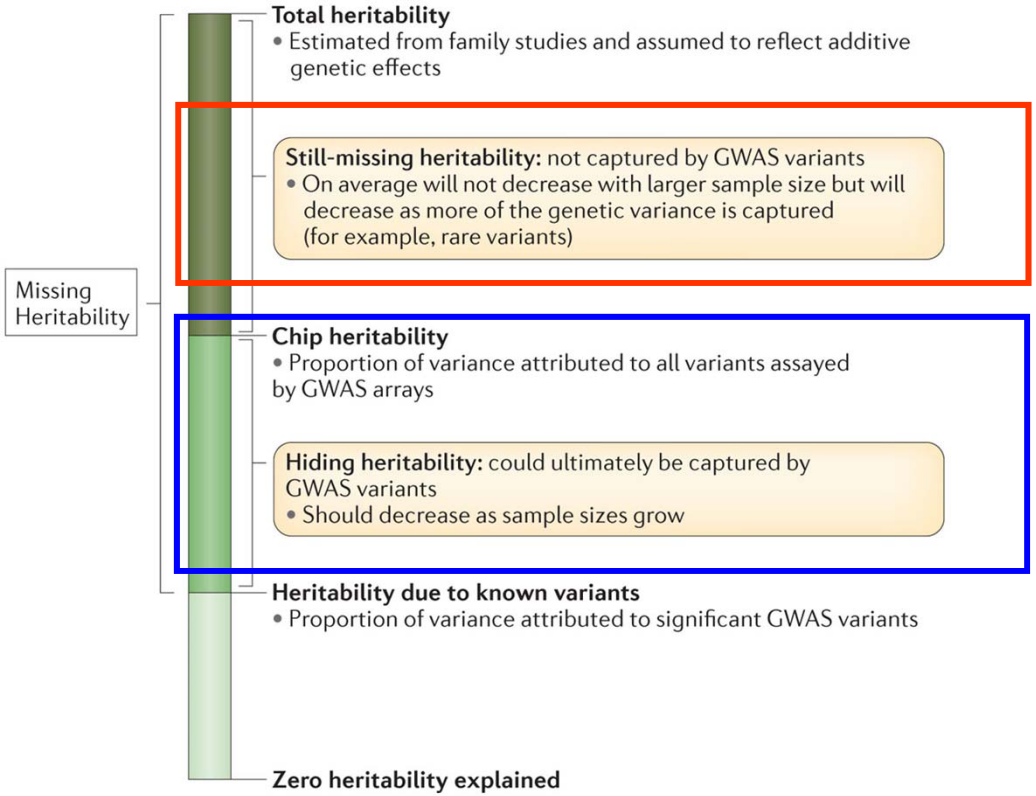


Manhattan plot based excluding APOE locus and **excluding known GWAS loci**

Final results expected first quarter of 2020

Replication in ADGC and CHARGE

The missing heritability is still high in AD : How to characterise it ?



To capture the genetic information carried by the rare or structural variants
Ex: SORL1

Increasing the population size analyzed by GWAS should allow to characterize new genetic risk factors
Improving imputations should allow to optimize GWAS

Witte et al, Nat Rev Genet, 2014

ADES

Alzheimer Disease exome sequencing consortium

- France (Lille and Rouen)
- Germany (Bonn)
- Spain (Barcelona)
- The Netherlands (Rotterdam and Amsterdam)
- The UK (Cardiff and London)

14,756 samples available

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Molecular Psychiatry
https://doi.org/10.1038/s41380-018-0112-7

ARTICLE

Whole exome sequencing study identifies novel rare and common Alzheimer's-Associated variants involved in immune response and transcriptional regulation

Joshua C. Bis[1] et al · Alzheimer's Disease Sequencing Project

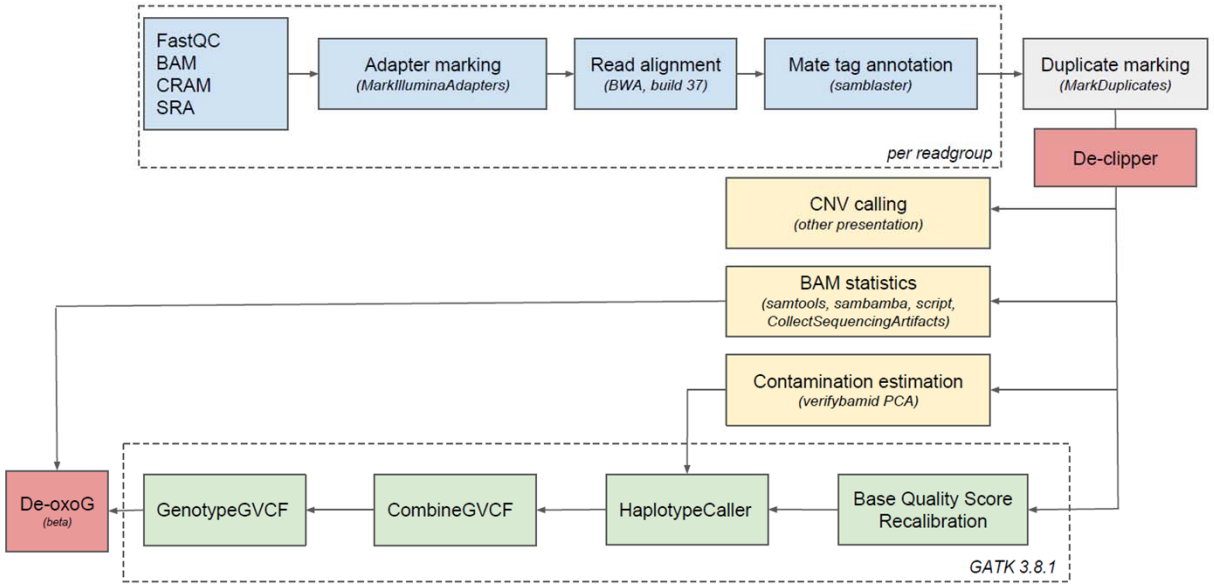
ADSP
11,365 samples

Is it meaningful to analyze ADES and ADSP separately ?

	ADES	ADSP	Combined
Sequences			
N WES	13,787	10,819	24,606
N WGS	969	546	1,515
Total	14,756	11,365	26,121
Batches			
N batches	31	6	37
Capture kits			
N WES kits	13	2	15

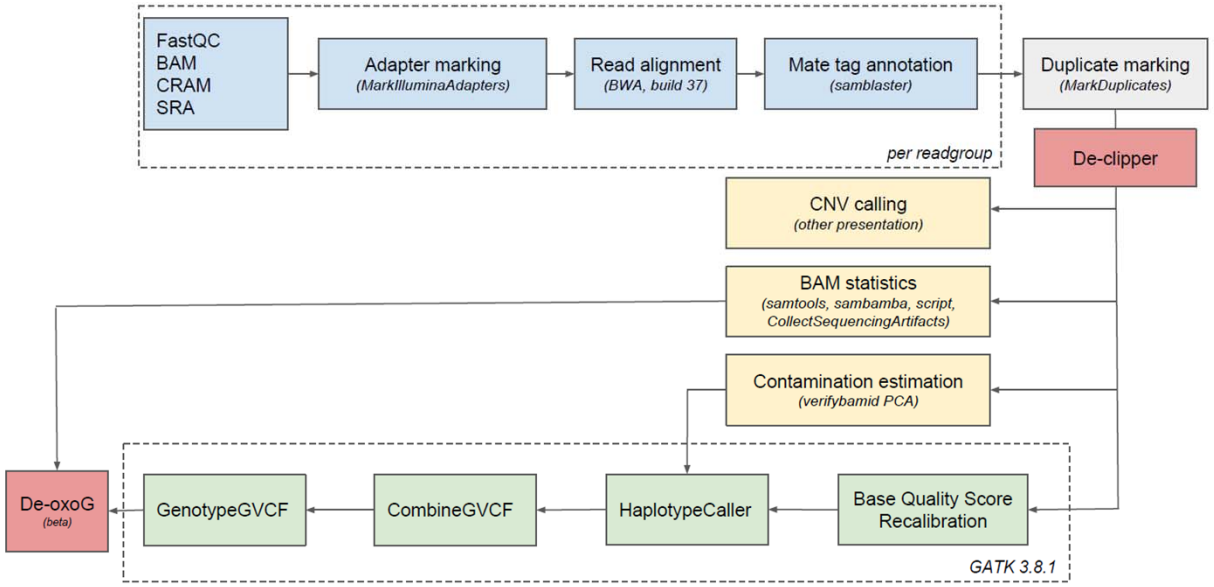
- High number of batches
- High number of different capture kits
- Different coverage

→ Need for a common pipeline (alignment, calling and QC samples/variants) to combine together all these data in the most efficient way



Quality control Steps

1. Missingness / Contamination
2. Basic QC measures
3. Ancestry
4. Relatedness
5. Private variants
6. Population structure



Quality control Steps

1. Missingness / Contamination
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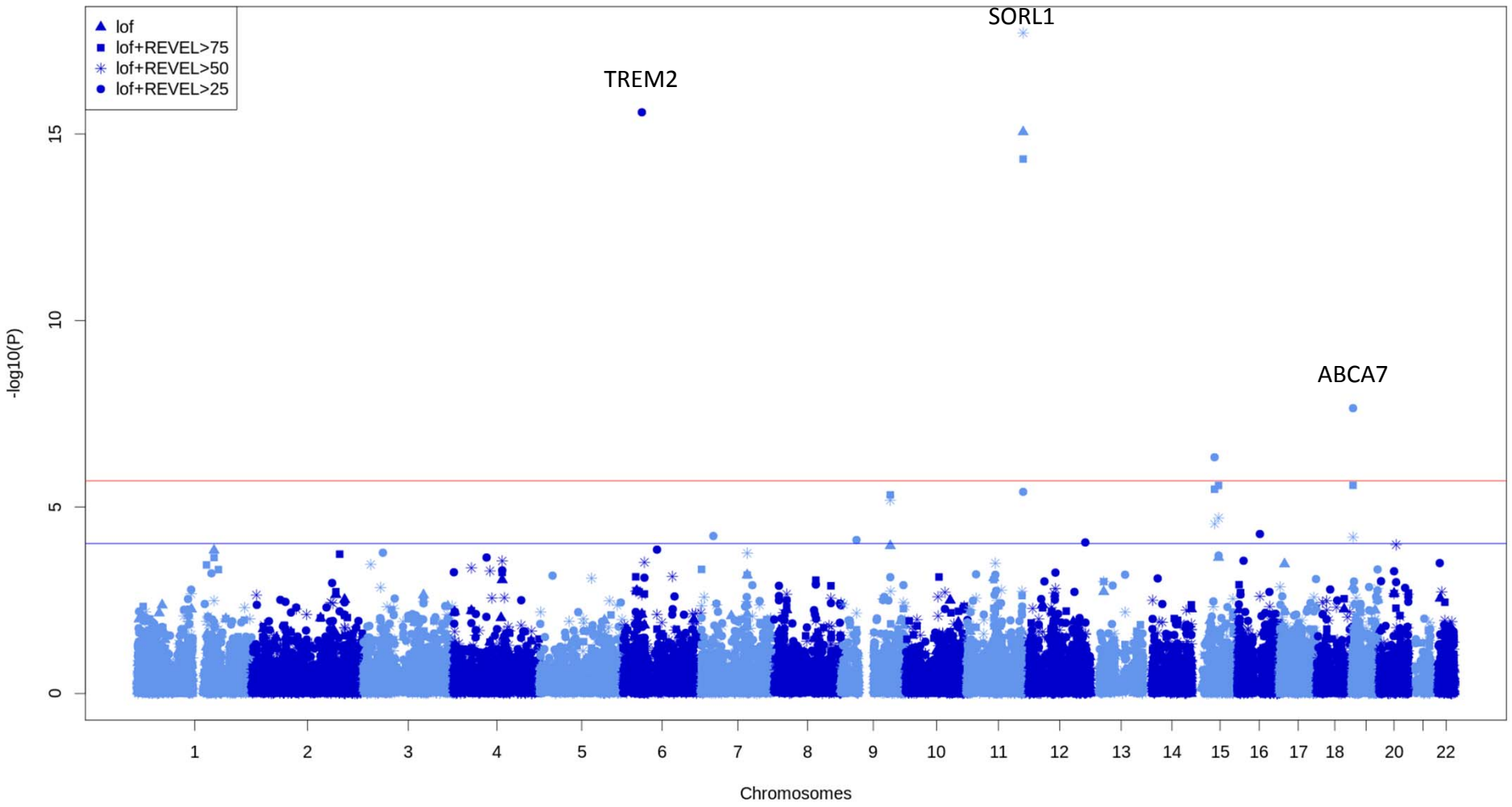
6. Population structure

- Consider both early-onset (EOAD) and late-onset (LOAD) AD cases (age threshold of 65)

	EOAD + LOAD	EOAD	LOAD	Controls
N	12,675	4,060	8,592	8,693
N females (%)	7,494 (59.12)	2,219 (54.66)	5,265 (61.28)	4,996 (57.47)
Mean age (sd)	71.62 (11.44)	58.06 (5.48)	77.89 (7.3)	82.14 (11.98)

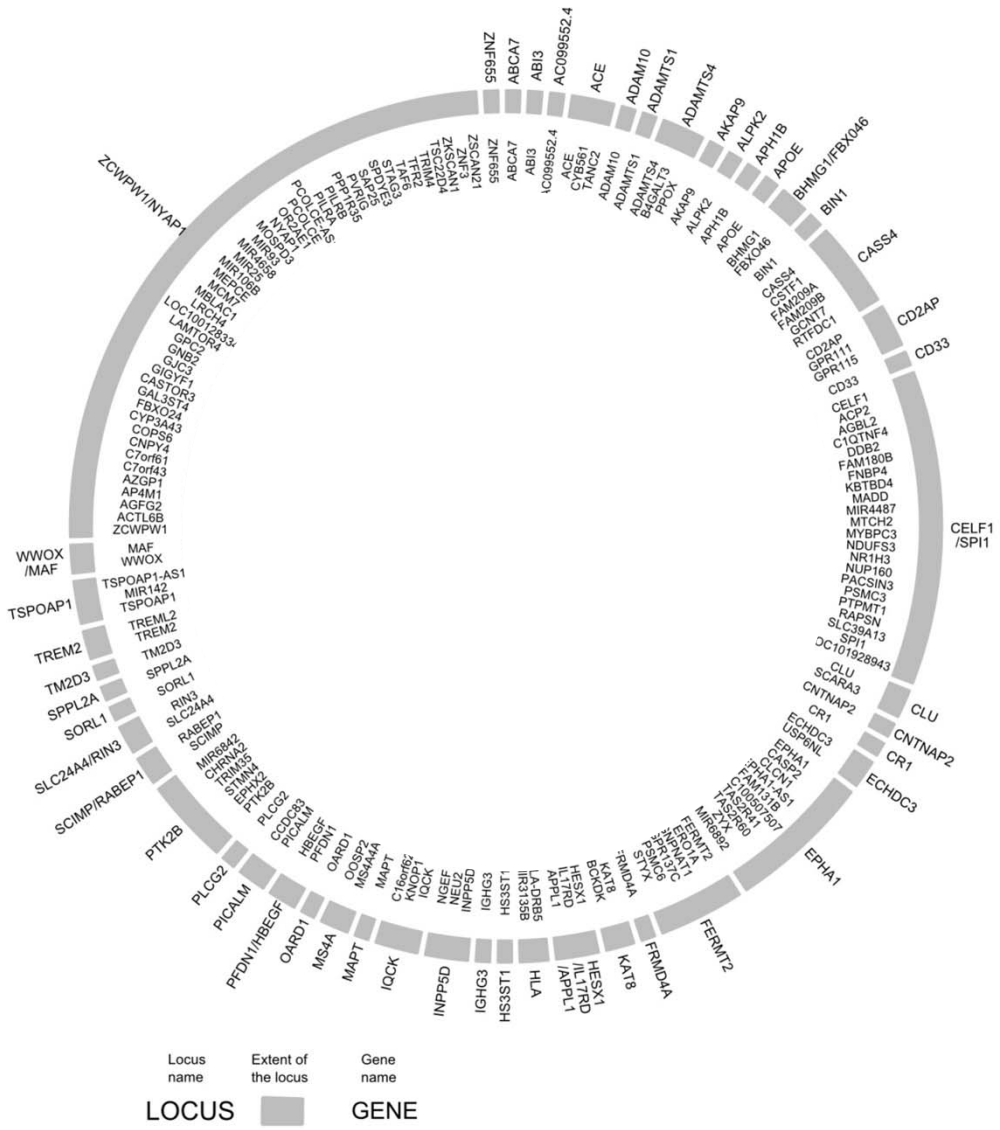

lof
lof+REVEL>75
lof+REVEL>50
lof+REVEL>25
TREM2
SORL1
ABCA7
-log10(P)
0
5
10
15
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
20
22
Chromosomes

Final results expected in the next few weeks

Replication at least in ADSP

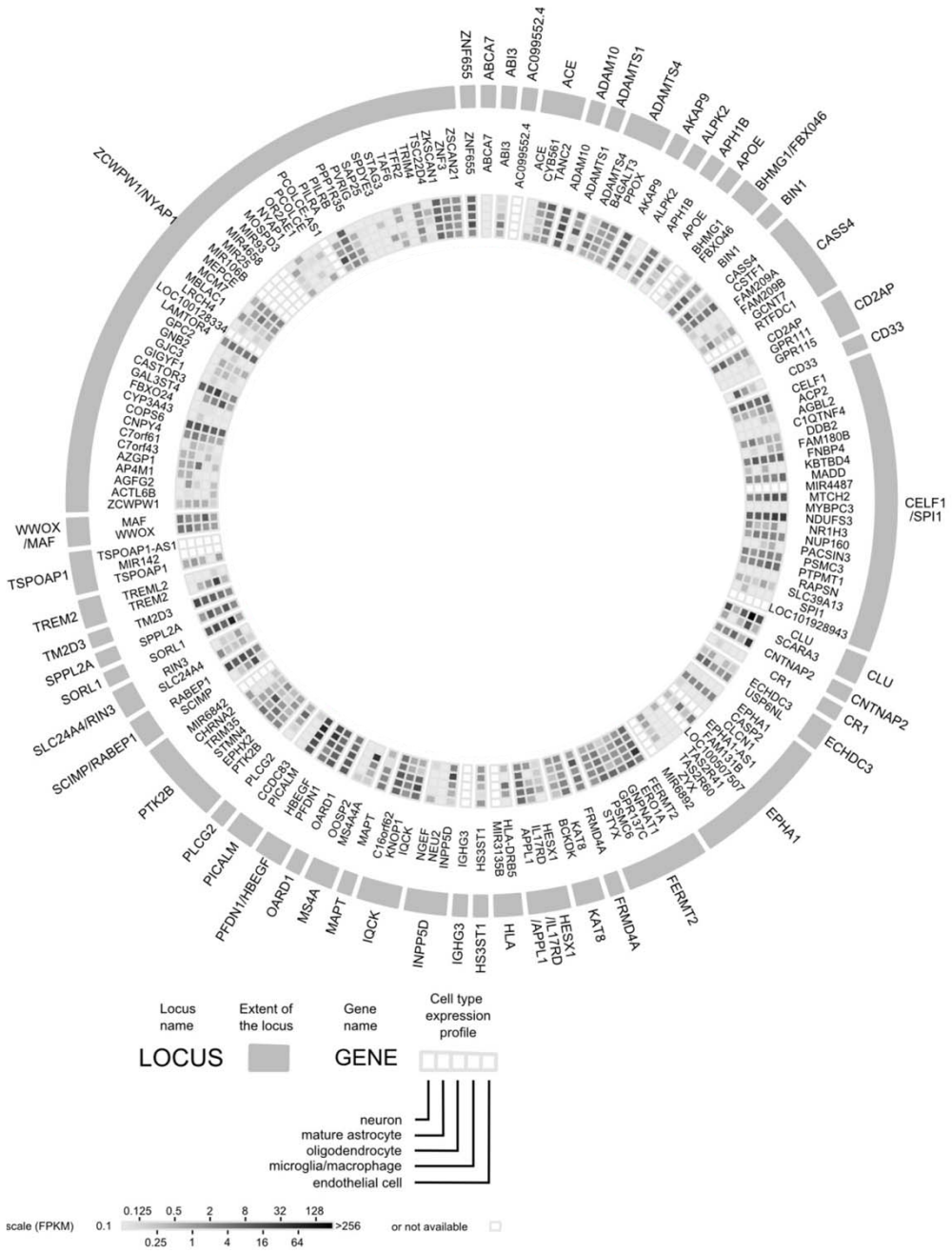
GWASs/ highthroughput approaches have the key advantage of selecting candidate-genes/locus without predetermined ideas about their respective functions.

However, this means that it can be a challenging task to determine the genetic and molecular mechanisms by which the GWAS-defined genes affect AD risk



- Loci can contain numerous genes
- Most of the Functional variants are still not known

Dourlen et al, Acta Neuropathologica, 2019



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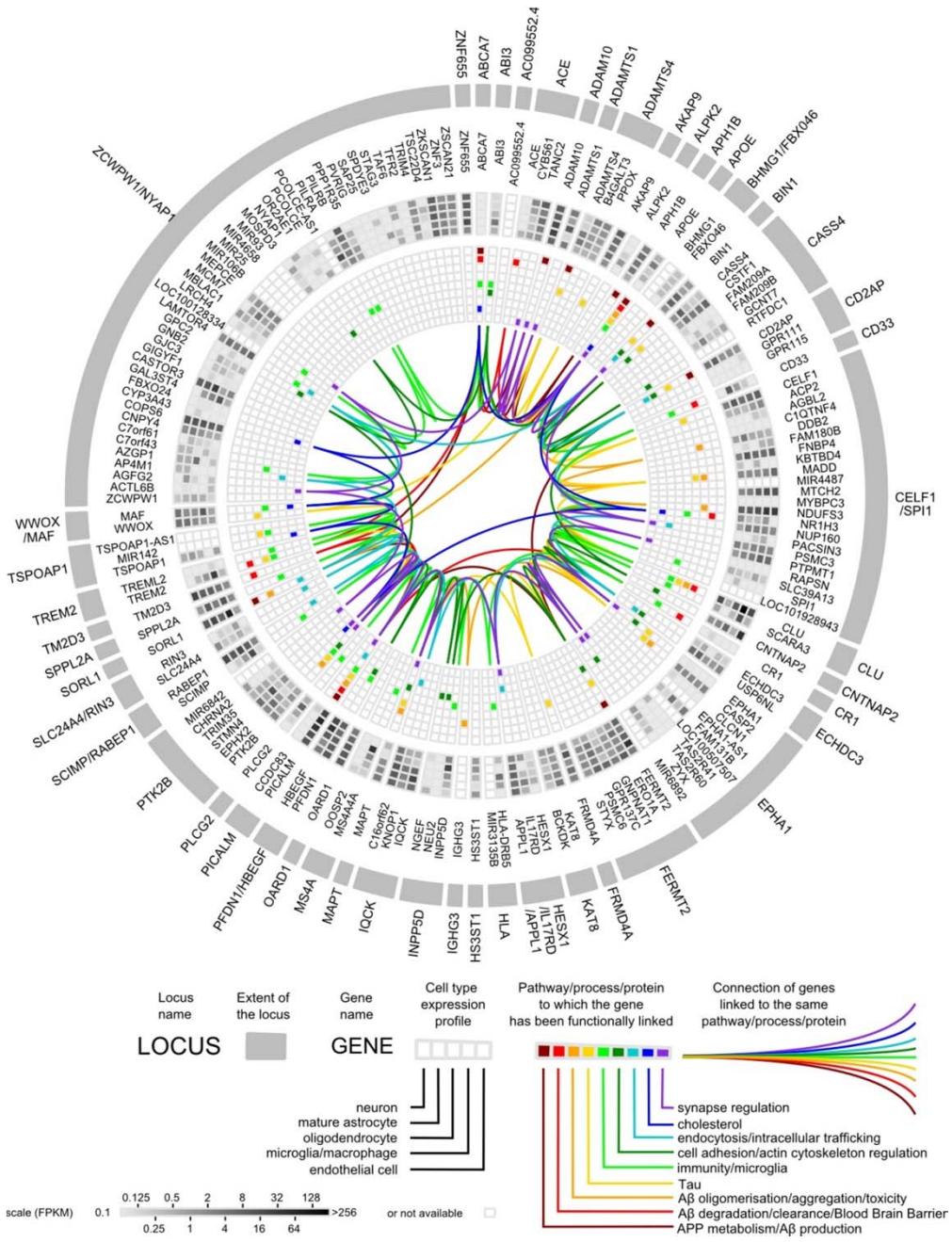

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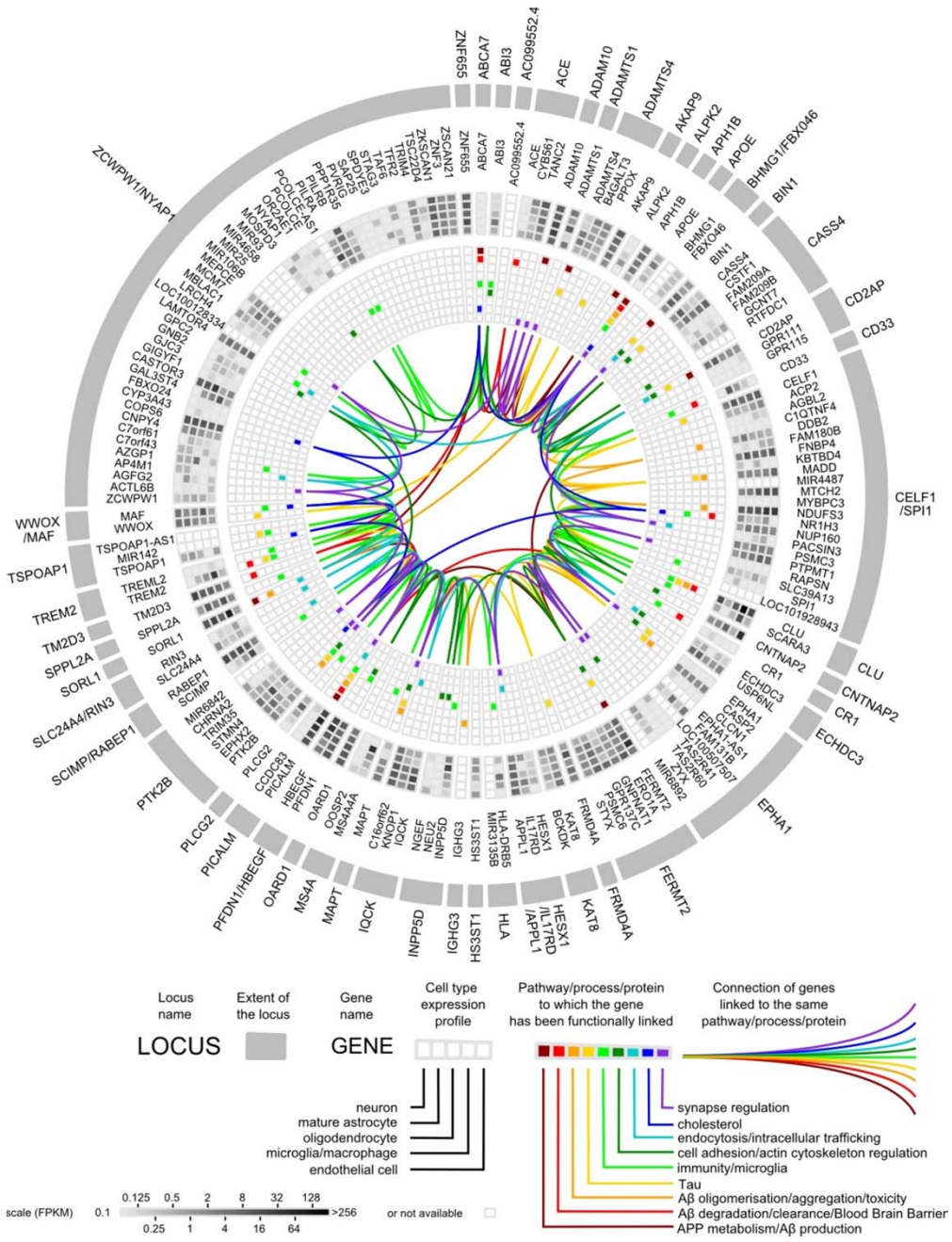
Dourlen et al, Acta Neuropathologica, 2019



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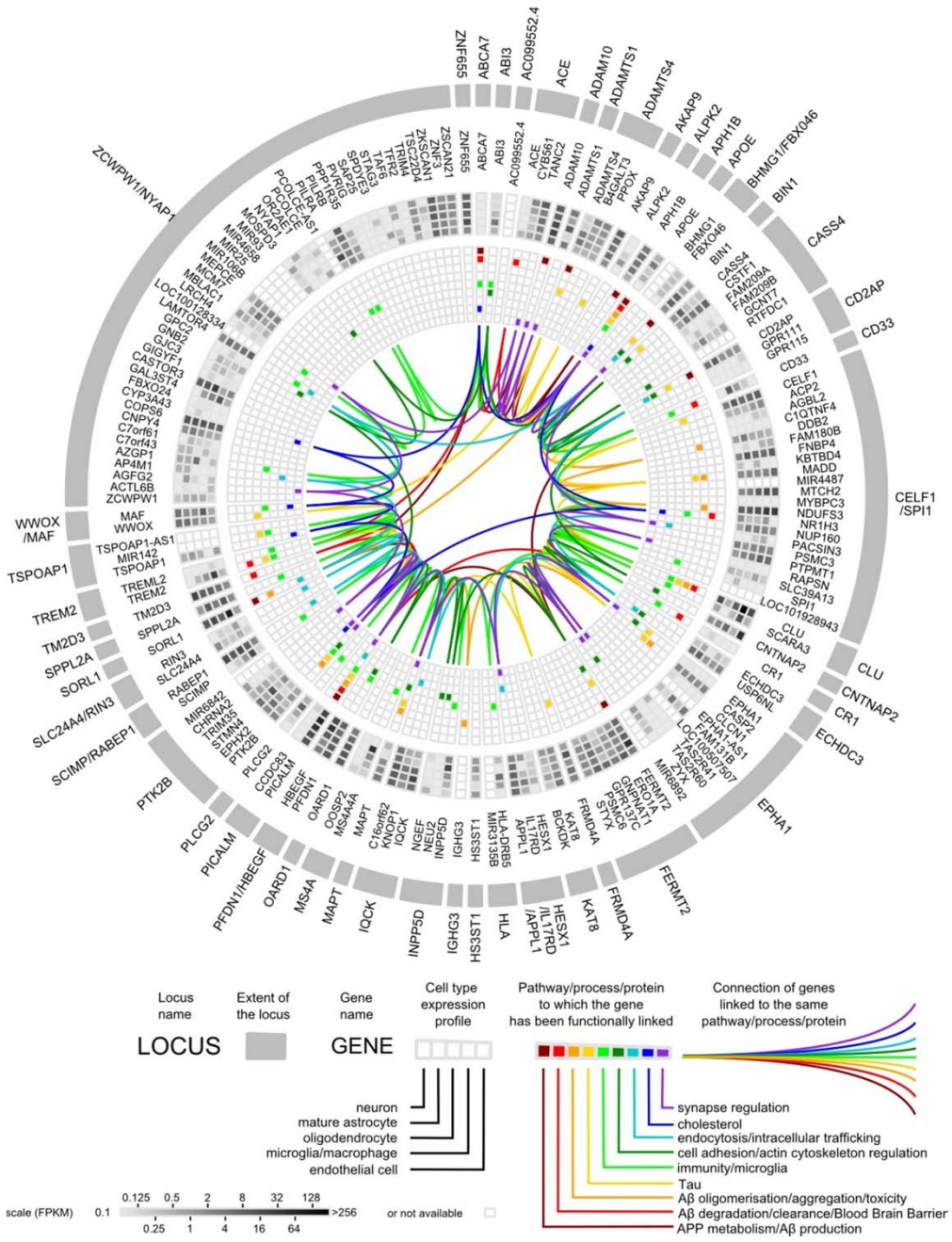
Dourlen et al, Acta Neuropathologica, 2019



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- Most of the Functional variants are still not known
- Genes can be expressed in different cell types
- Genes may have several functions in several pathways

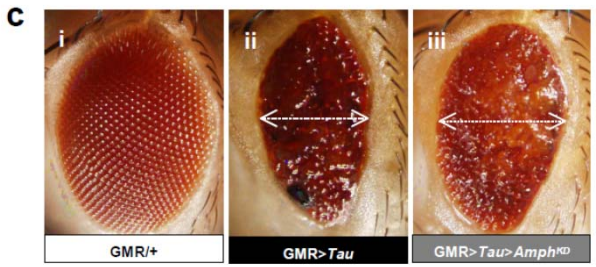
→ *difficult to prioritize a specific physiological and thus pathophysiological process*

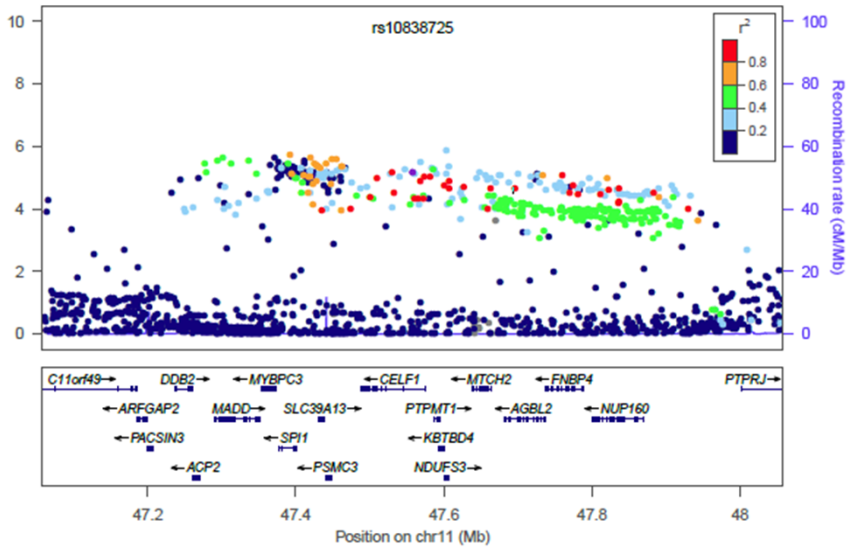
In addition, genome-wide pathway analyses intrinsically favor canonical pathways based on known information.

What about the functions of a gene in the brain if never studied in such a context yet ?

Dourlen et al, Acta Neuropathologica, 2019

THe Fly-IGAP project
to assess how GWAS-defined genes may modulate Tau toxicity in Drosophila





Dourlen et al., Mol Psychiatry, 2017

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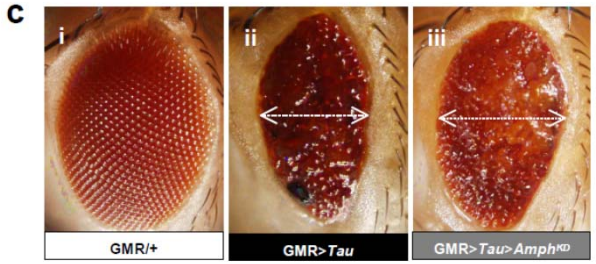
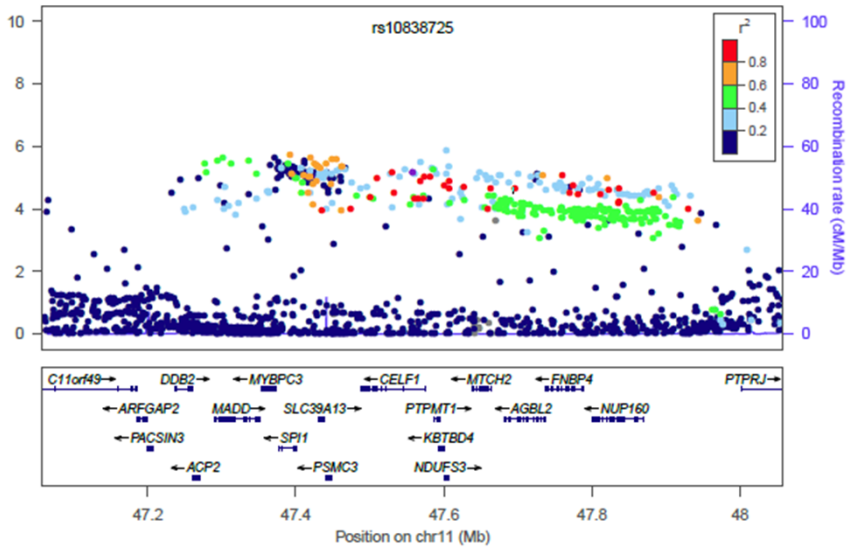
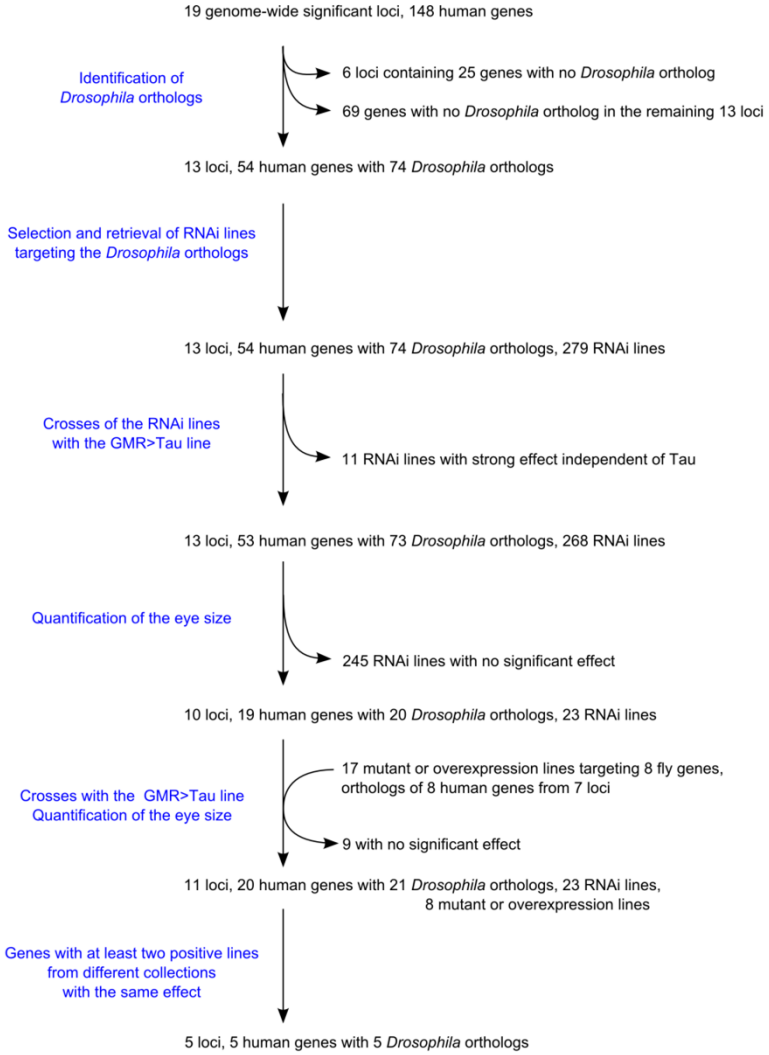




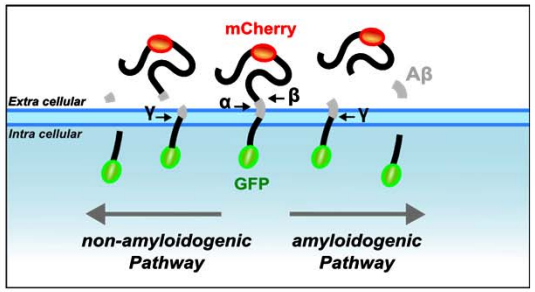


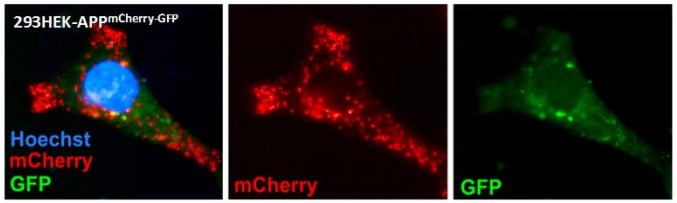
Dourlen et al., Mol Psychiatry, 2017

High-Content Screening for the APP metabolism

Multi-parameter image processing to extract quantitative data from cell populations.

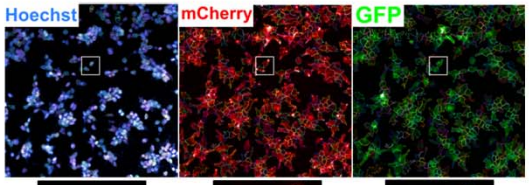
- **Cellular model**





R Sannerud *et al., PNAS.* 2011

- **Images analysis (Number of cells>300)**



nuclei detection → Number of cells

cytoplasm detection → Fluorescence intensity mean / cell

Robotic HCS platform

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Multi-parameter image processing to extract quantitative data from cell populations.

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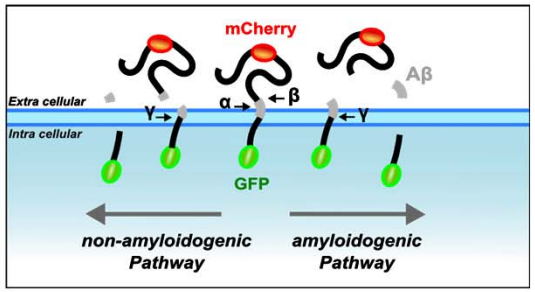

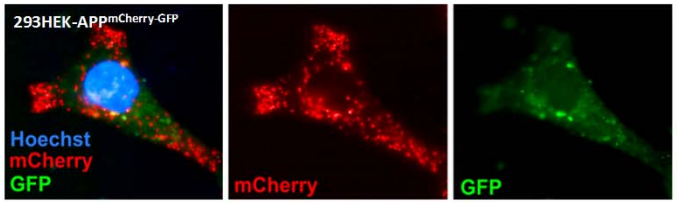

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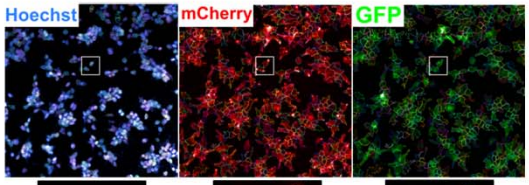

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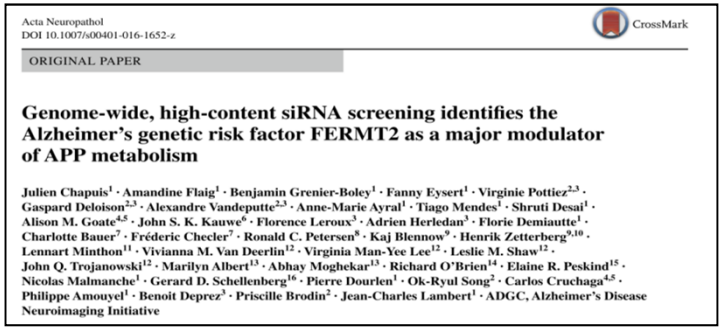

Acta Neuropathol
DOI 10.1007/s00401-016-1652-z

CrossMark

ORIGINAL PAPER

Genome-wide, high-content siRNA screening identifies the Alzheimer's genetic risk factor FERMT2 as a major modulator of APP metabolism

Julien Chapuis[1] · Amandine Flaig[1] · Benjamin Grenier-Boley[1] · Fanny Eysert[1] · Virginie Pottiez[2,3] · Gaspard Deloison[2,3] · Alexandre Vandeputte[2,3] · Anne-Marie Ayral[1] · Tiago Mendes[1] · Shruti Desai[1] · Alison M. Goate[4,5] · John S. K. Kauwe[6] · Florence Leroux[3] · Adrien Herledan[3] · Florie Demiautte[1] · Charlotte Bauer[7] · Fréderic Checler[7] · Ronald C. Petersen[8] · Kaj Blennow[9] · Henrik Zetterberg[9,10] · Lennart Minthon[11] · Vivianna M. Van Deerlin[12] · Virginia Man-Yee Lee[12] · Leslie M. Shaw[12] · John Q. Trojanowski[12] · Marilyn Albert[13] · Abhay Moghekar[13] · Richard O'Brien[14] · Elaine R. Peskind[15] · Nicolas Malmanche[1] · Gerard D. Schellenberg[16] · Pierre Dourlen[1] · Ok-Ryul Song[2] · Carlos Cruchaga[4,5] · Philippe Amouyel[1] · Benoit Deprez[3] · Priscille Brodin[2] · Jean-Charles Lambert[1] · ADGC, Alzheimer's Disease Neuroimaging Initiative

Robotic HCS platform

18,107 siRNA tested

832 genes strongly modify the APP metabolism

What have we learned from these systematic screening ?

Molecular Psychiatry (2017) 22, 874–883
www.nature.com/mp

OPEN

ORIGINAL ARTICLE

Functional screening of Alzheimer risk loci identifies *PTK2B* as an *in vivo* modulator and early marker of Tau pathology

P Dourlen[1,2,3], FJ Fernandez-Gomez[4,5,6], C Dupont[1,2,3], B Grenier-Boley[1,2,3], C Bellenguez[1,2,3], H Obriot[4,5,6], R Caillierez[4,5,6], Y Sottejeau[1,2,3], J Chapuis[1,2,3], A Bretteville[1,2,3], F Abdelfettah[1,2,3], C Delay[1,2,3], N Malmanche[1,2,3], H Soininen[7], M Hiltunen[7,8], M-C Galas[4,5,6], P Amouyel[1,2,3,9], N Sergeant[4,5,6], L Buée[4,5,6], J-C Lambert[1,2,3,11] and B Dermaut[1,2,3,10,11]

Human Molecular Genetics, 2014, Vol. 23, No. 4 **870–877**
doi:10.1093/hmg/ddt478
Advance Access published on September 25, 2013

Functional screening in *Drosophila* identifies Alzheimer's disease susceptibility genes and implicates Tau-mediated mechanisms

Joshua M. Shulman[1,2,3,*], Selina Imboywa[4,5,7,10], Nikolaos Giagtzoglou[1,2,3], Martin P. Powers[1,2,3], Yanhui Hu[8], Danelle Devenport[1,2], Portia Chipendo[4,5,7,10], Lori B. Chibnik[4,5,7,10], Allison Diamond[4,5,7,10], Norbert Perrimon[8,11], Nicholas H. Brown[12], Philip L. De Jager[4,5,7,10,†] and Mel B. Feany[6,9,†]

Acta Neuropathol (2017) 133:955–966
DOI 10.1007/s00401-016-1652-z

ORIGINAL PAPER

Genome-wide, high-content siRNA screening identifies the Alzheimer's genetic risk factor FERMT2 as a major modulator of APP metabolism

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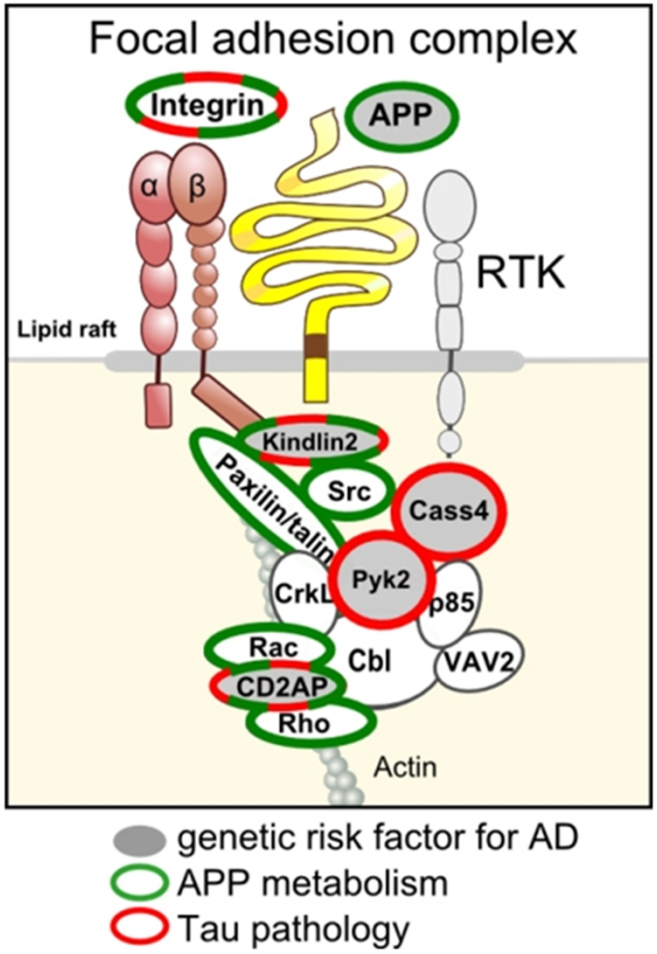
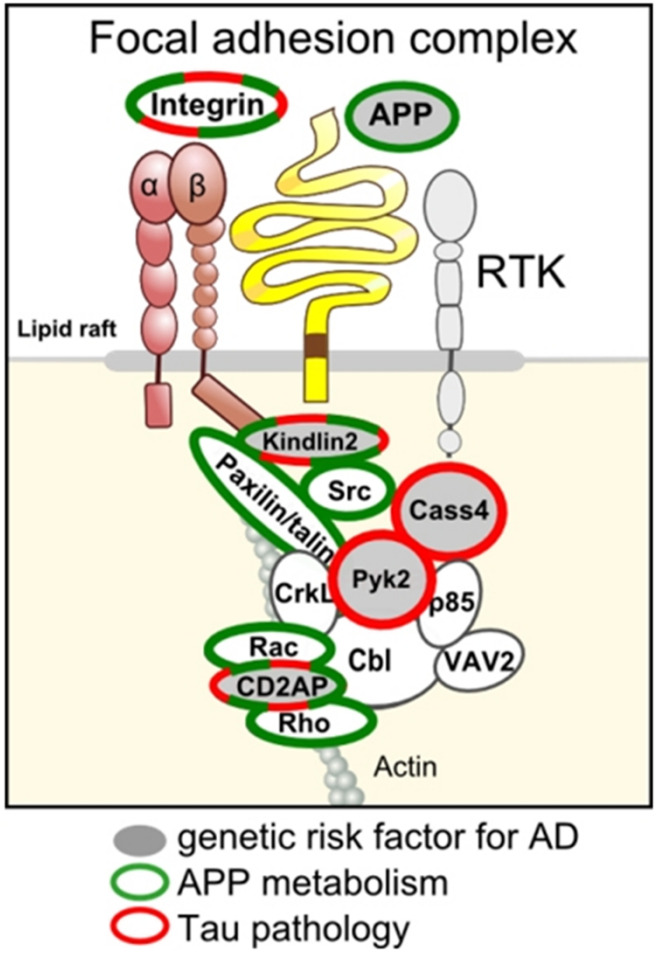
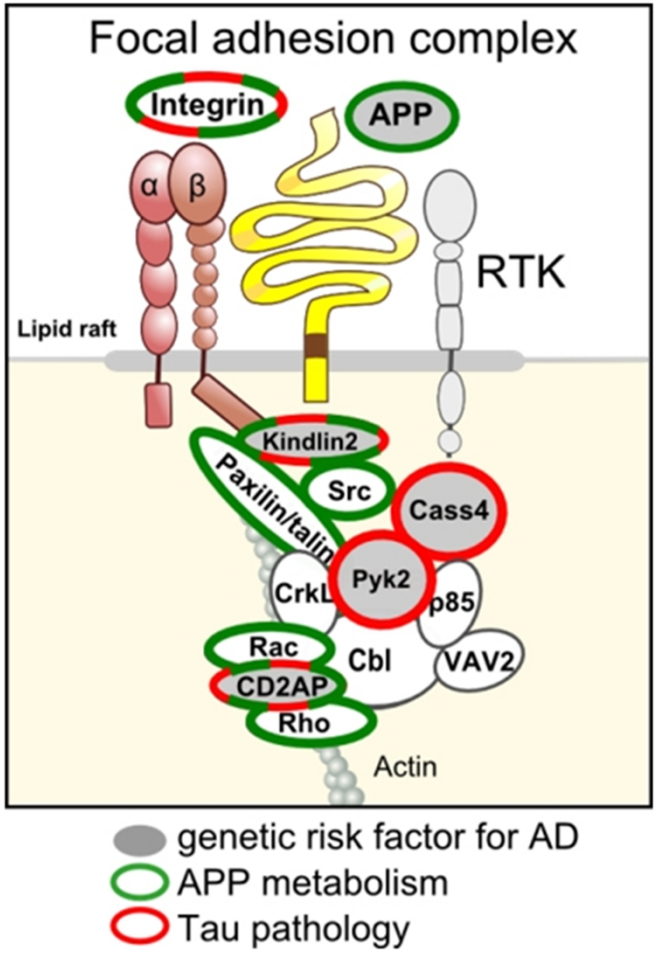


GWAS-defined genes and synapses



Focal adhesions are central for synaptic functions. Evidences indicate that several GWAS-defined genes involved in this core may modulate synaptic functions:

GWAS-defined genes and synapses ?



Focal adhesions are central for synaptic functions. Evidences indicate that several GWAS-defined genes involved in this core may modulate synaptic functions:

- **CD2AP (linked to Tau toxicity and APP metabolism)**

Cell Reports
Article

OPEN ACCESS
CellPress

***cindr*, the *Drosophila* Homolog of the *CD2AP* Alzheimer's Disease Risk Gene, Is Required for Synaptic Transmission and Proteostasis**

Shamsideen A. Ojelade,[1,2] Tom V. Lee,[1,2] Nikolaos Giagtzoglou,[1,2,11] Lei Yu,[3] Berrak Ugur,[4,12] Yarong Li,[1,2] Lita Duraine,[5] Zhongyuan Zuo,[5] Vlad Petyuk,[6] Philip L. De Jager,[7,8] David A. Bennett,[3] Benjamin R. Arenkiel,[2,4,5,9] Hugo J. Bellen,[2,4,5,9,10] and Joshua M. Shulman[1,2,4,5,9,13,*]

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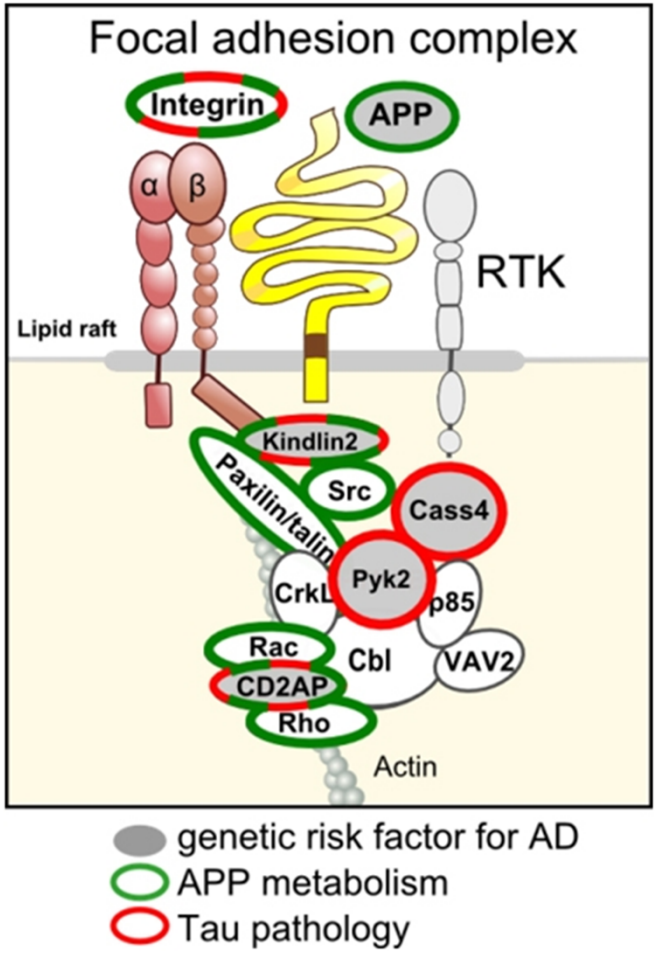

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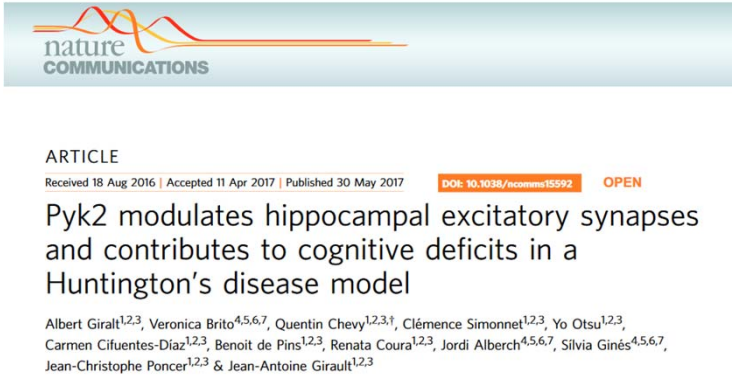

nature COMMUNICATIONS

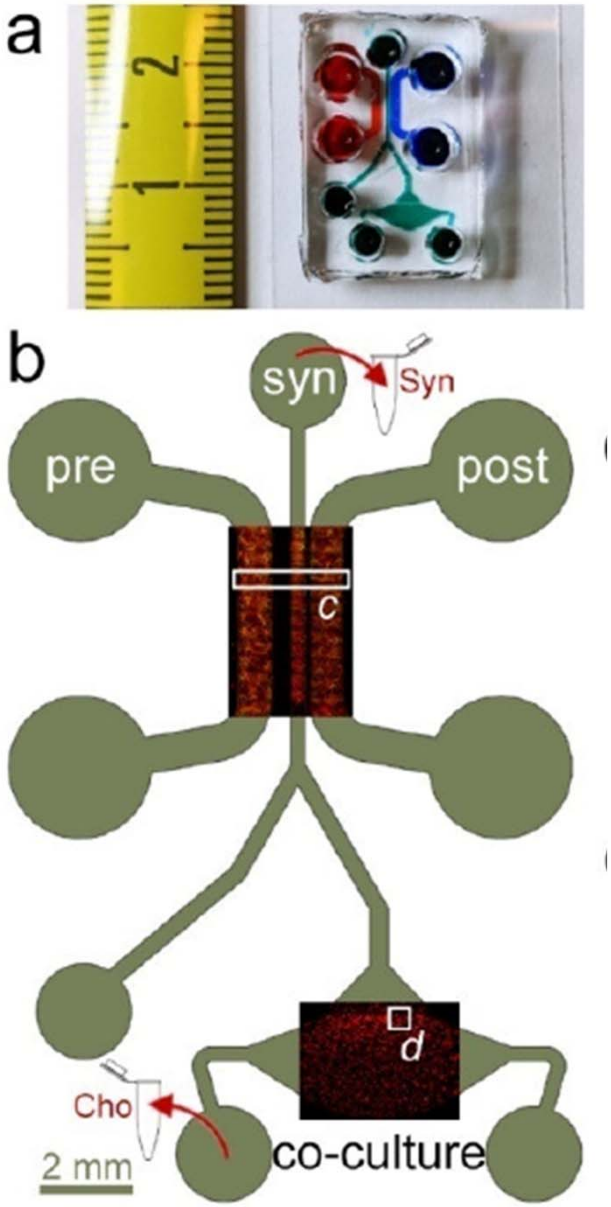
ARTICLE

Received 18 Aug 2016 | Accepted 11 Apr 2017 | Published 30 May 2017 DOI: 10.1038/ncomms15592 OPEN

Pyk2 modulates hippocampal excitatory synapses and contributes to cognitive deficits in a Huntington's disease model

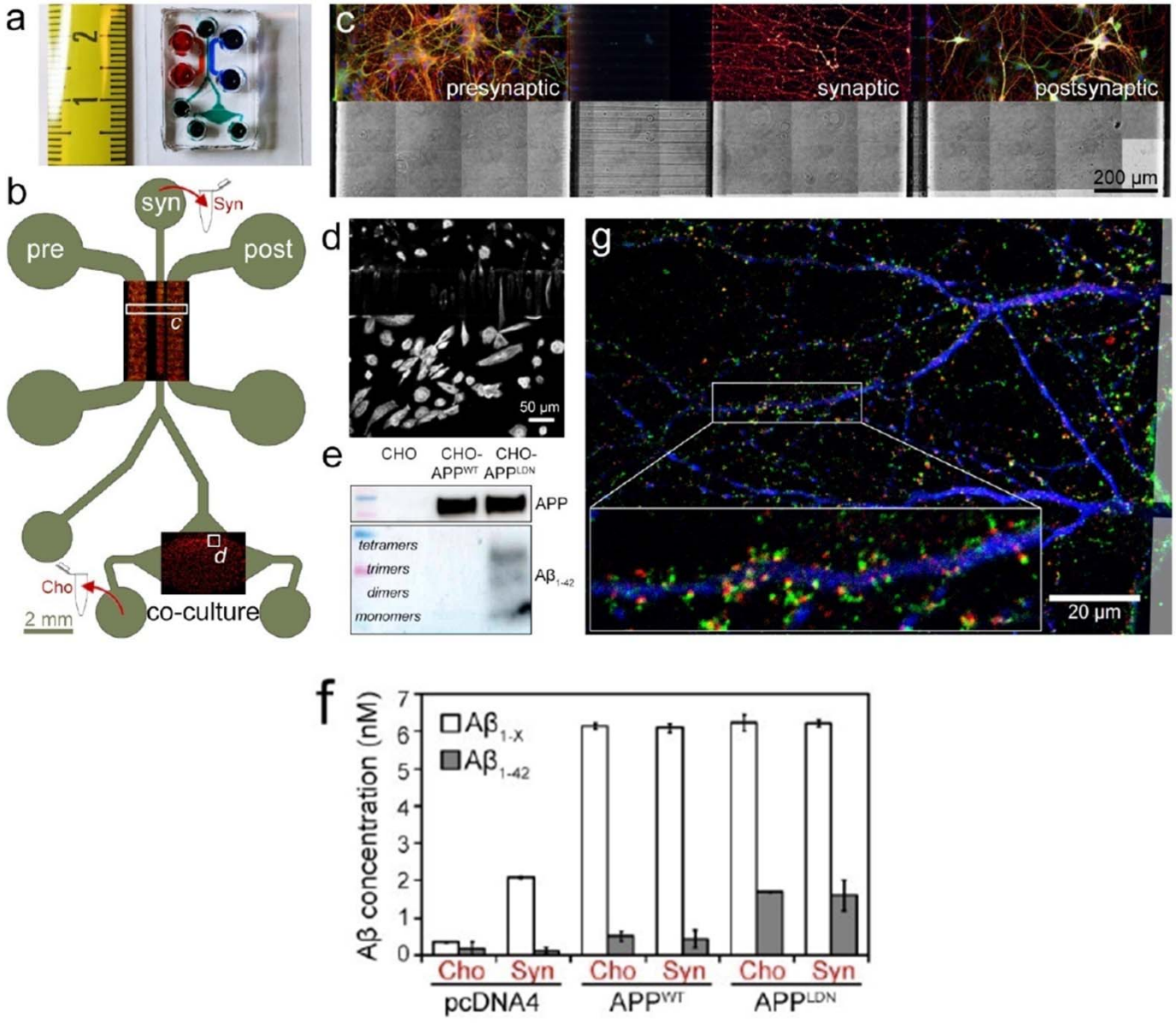
Albert Giralt[1,2,3], Veronica Brito[4,5,6,7], Quentin Chevy[1,2,3,†], Clémence Simonnet[1,2,3], Yo Otsu[1,2,3], Carmen Cifuentes-Díaz[1,2,3], Benoit de Pins[1,2,3], Renata Coura[1,2,3], Jordi Alberch[4,5,6,7], Sílvia Ginés[4,5,6,7], Jean-Christophe Poncer[1,2,3] & Jean-Antoine Girault[1,2,3]

A new co-culture microfluidic device to assess Aβo synaptotoxicity



Kilinc et al, in preparation

A new co-culture microfluidic device to assess Aβo synaptotoxicity



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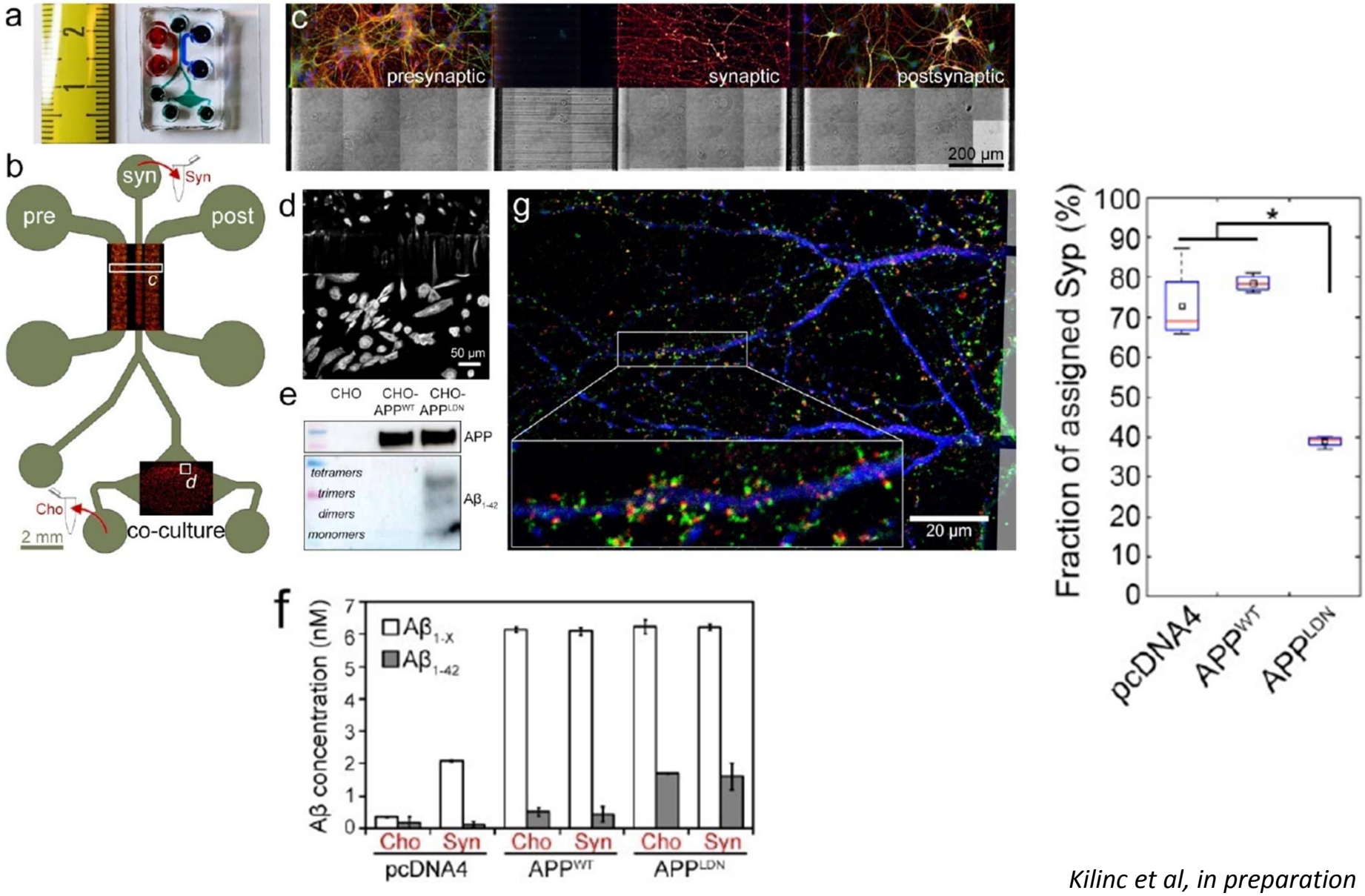
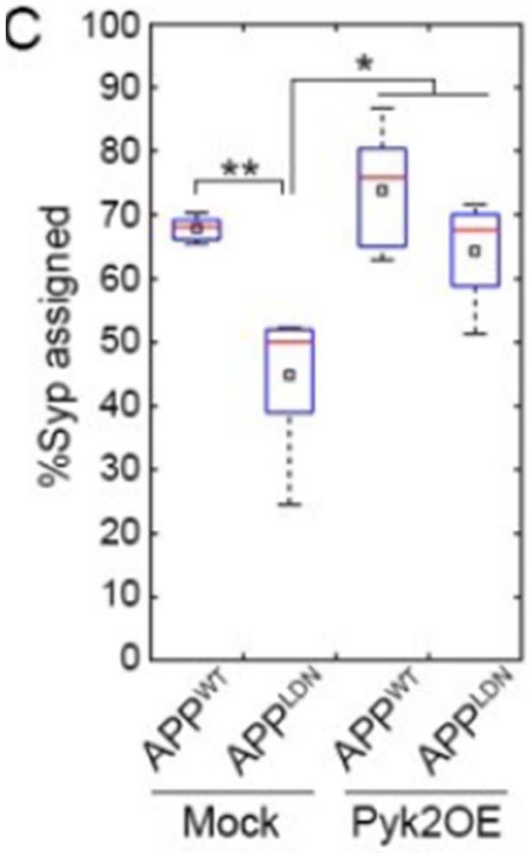


Kilinc et al, in preparation



Pyk2 over-expression in the post-synaptic compartment protects against Aβo-dependent synaptotoxicity

758 • The Journal of Neuroscience, January 23, 2019 • 39(4):758 –772

Neurobiology of Disease

Alzheimer's Disease Risk Factor Pyk2 Mediates Amyloid-β-Induced Synaptic Dysfunction and Loss

Santiago V. Salazar,[1,2] Timothy O. Cox,[1] Suho Lee,[1] A. Harrison Brody,[1] Annabel S. Chyung,[1] Laura T. Haas,[1] and Stephen M. Strittmatter[1]

[1]Cellular Neuroscience, Neurodegeneration, and Repair, Departments of Neurology and Neuroscience, and [2]Department of Genetics, Yale University School of Medicine, New Haven, Connecticut 06536

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

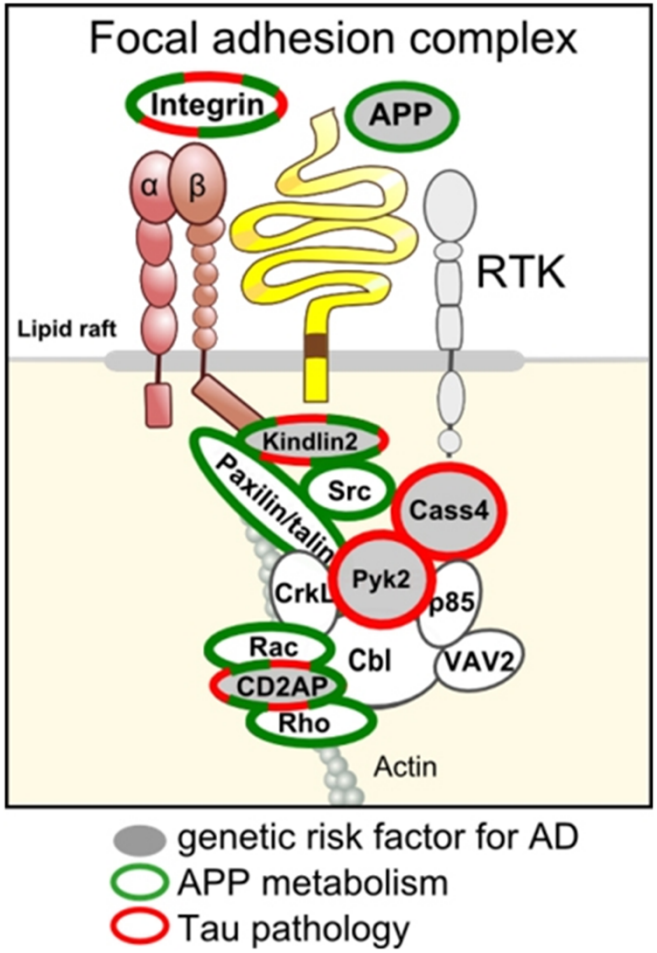
Research Paper

PTK2B/Pyk2 overexpression improves a mouse model of Alzheimer's disease

Albert Giralt[a,b,c,d,e,f], Benoit de Pins[a,b,c], Carmen Cifuentes-Díaz[a,b,c], Laura López-Molina[d,e,f], Amel Thamila Farah[a,b,c,1], Marion Tible[g,h], Vincent Deramecourt[i], Stefan T Arold[j], Silvia Ginés[d,e,f], Jacques Hugon[g,h], Jean-Antoine Girault[a,b,c,*]

Kilinc et al, in preparation

GWAS-defined genes and synapses ?



Focal adhesions are central for synaptic functions. Evidences indicate that several GWAS-defined genes involved in this core may modulate synaptic functions:

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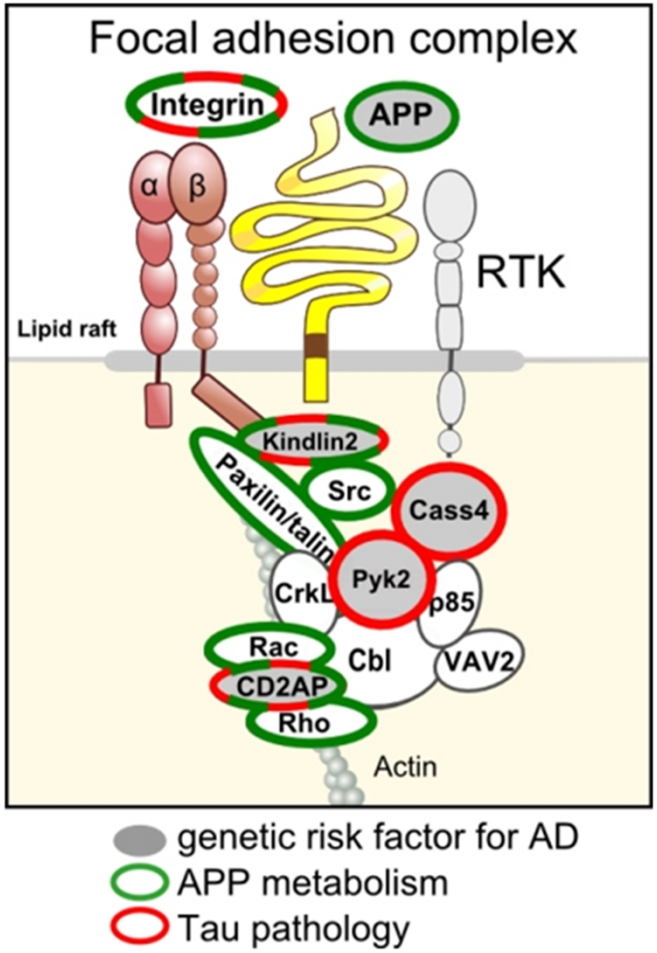

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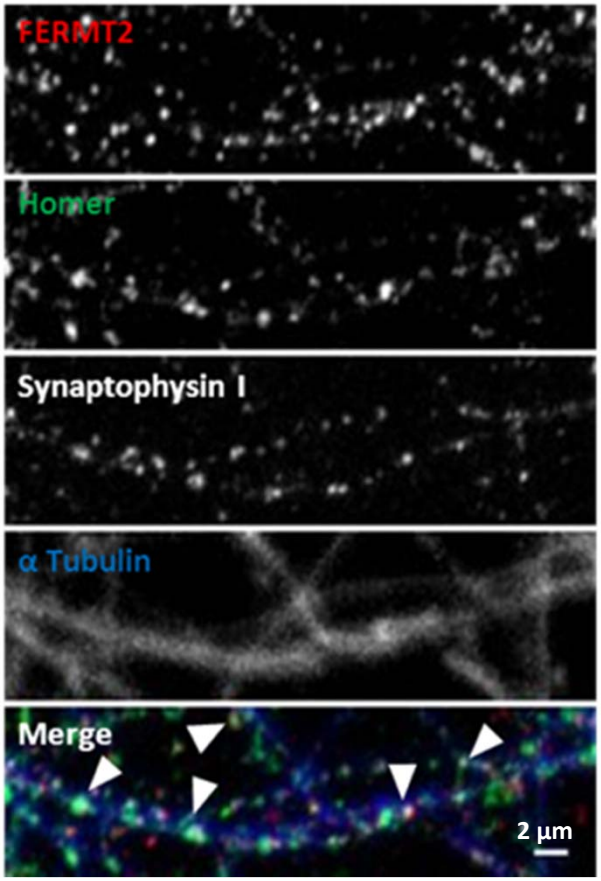
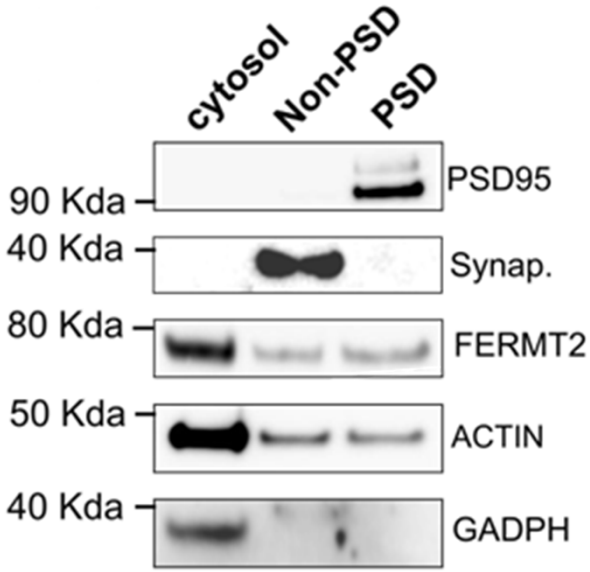
- PTK2B (linked to Tau toxicity and Aβo toxicity)
- **FERMT2 ?**

PNC 21 DIV - Immunofluorescence



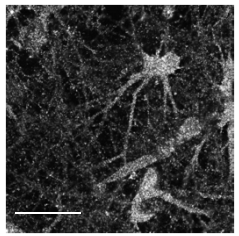
PNC 21 DIV – synaptosome Purification



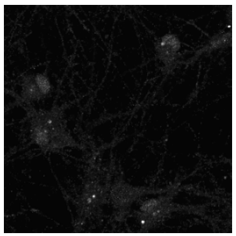
Eysert et al, BioRvix

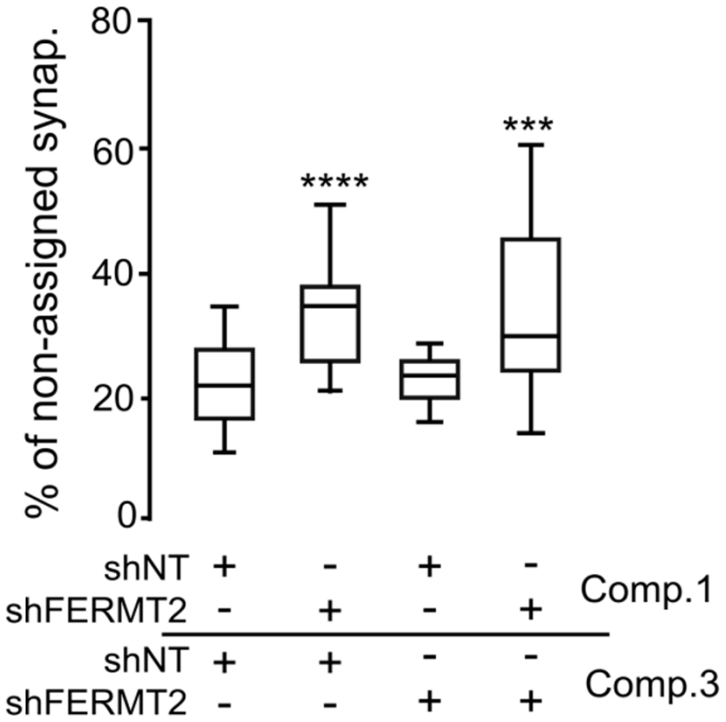
Under-expression of FERMT2 in pre- and/or post synpatic compartments

shNT



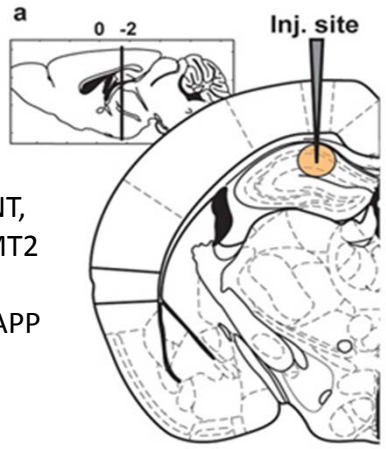
shFERMT2

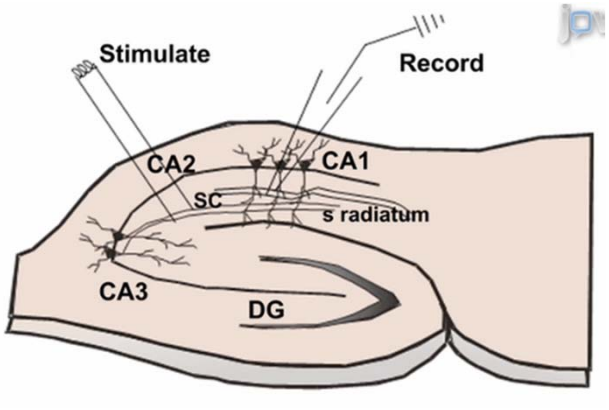




Eysert et al, BioRvix

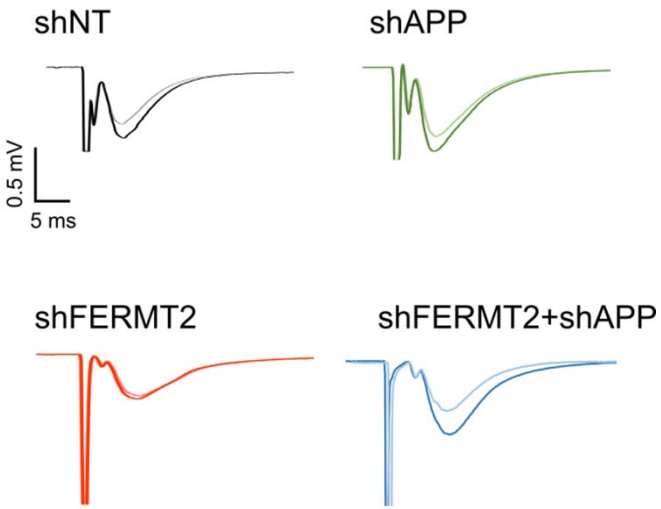
Lentivirus shNT, shAPP, shFERMT2 and shFERMT2+shAPP

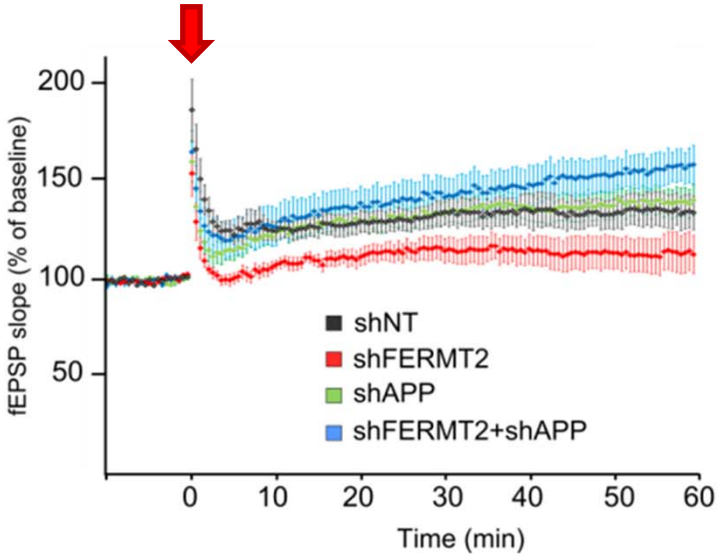


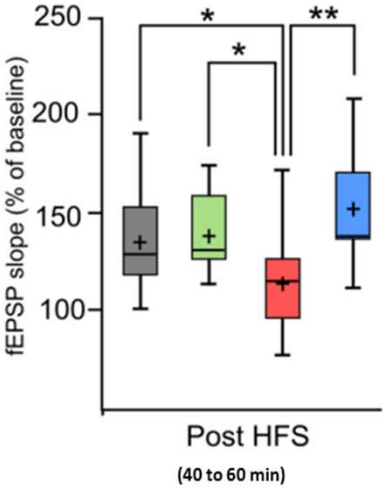


Hippocampus slides - C57bl6 mice (10 weeks old) - Electrophysiology

Collaboration E-PHY-SCIENCE, Sophia Antipolis

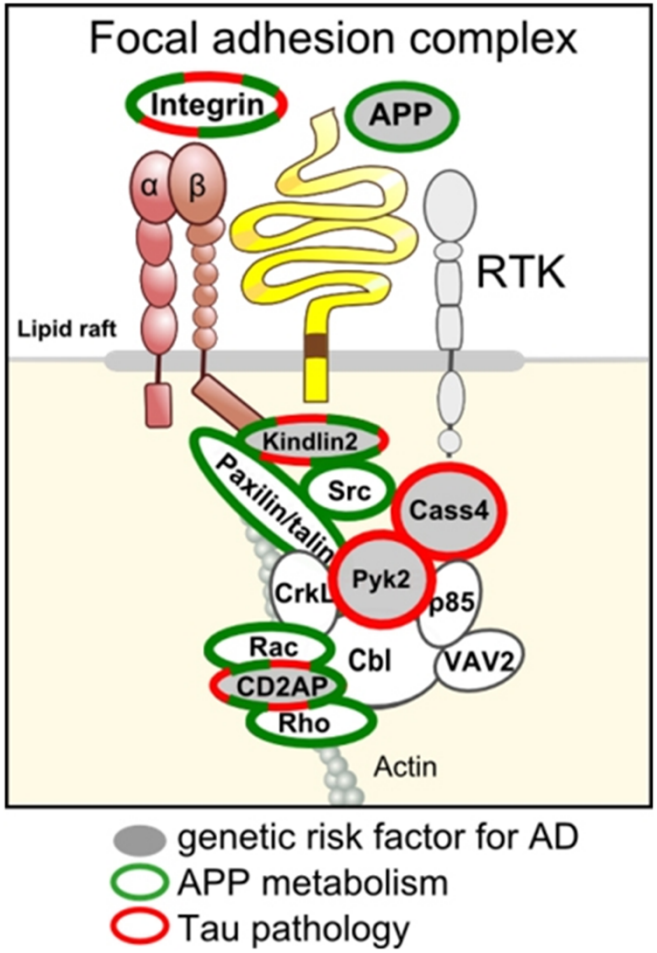






Eysert et al, BioRvix

GWAS-defined genes and synapses



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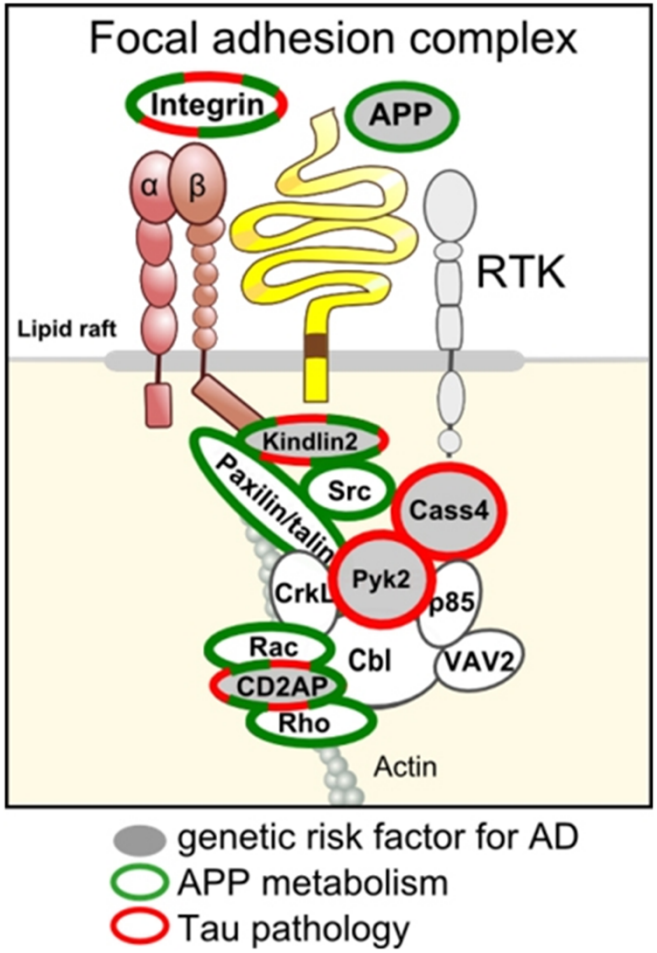
GWAS-defined genes and synapses



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- **BIN1 ?**

Molecular Psychiatry
https://doi.org/10.1038/s41380-019-0407-3

ARTICLE

A novel role for the late-onset Alzheimer's disease (LOAD)-associated protein Bin1 in regulating postsynaptic trafficking and glutamatergic signaling

Britta Schürmann[1,2] · Daniel P. Bermingham[1] · Katherine J. Kopeikina[1] · Kristoffer Myczek[1] · Sehyoun Yoon[1] · Katherine E. Horan[1] · Crystle J. Kelly[1] · Maria Dolores Martin-de-Saavedra[1] · Marc P. Forrest[1] · Jessica M. Fawcett-Patel[1] · Katharine R. Smith[1] · Ruoqi Gao[1] · Anthony Bach[1] · Alain C. Burette[3] · Joshua Z. Rappoport[4] · Richard J. Weinberg[3] · Marco Martina[1] · Peter Penzes[1,5]

BIN1 genetic risk factor for Alzheimer is sufficient to induce early structural tract alterations in entorhinal cortex-dentate gyrus pathway and related hippocampal multi-scale impairments

R Daudin, D Marechal, Q Wang, Y Abe, N Bourg, M Sartori, Y Loe-Mie, J Lipecka, C Guerrera, A McKenzie, B Potier, P Dutar, J Viard, A.M Lepagnol-Bestel, A Winkeler, V Hindié, MC Birling, L Lindner, C Chevalier, G Pavlovic, M Reis, H Kranz, G Dupuis, S Lévêque-Fort, J Diaz, E Davenas, D Dembele, J Laporte, C Thibault-Carpentier, B Malissen, J.C Rain, L Ciobanu, D Le Bihan, B Zhang, Y Herault, M Simonneau

bioRxiv 437228; doi: https://doi.org/10.1101/437228

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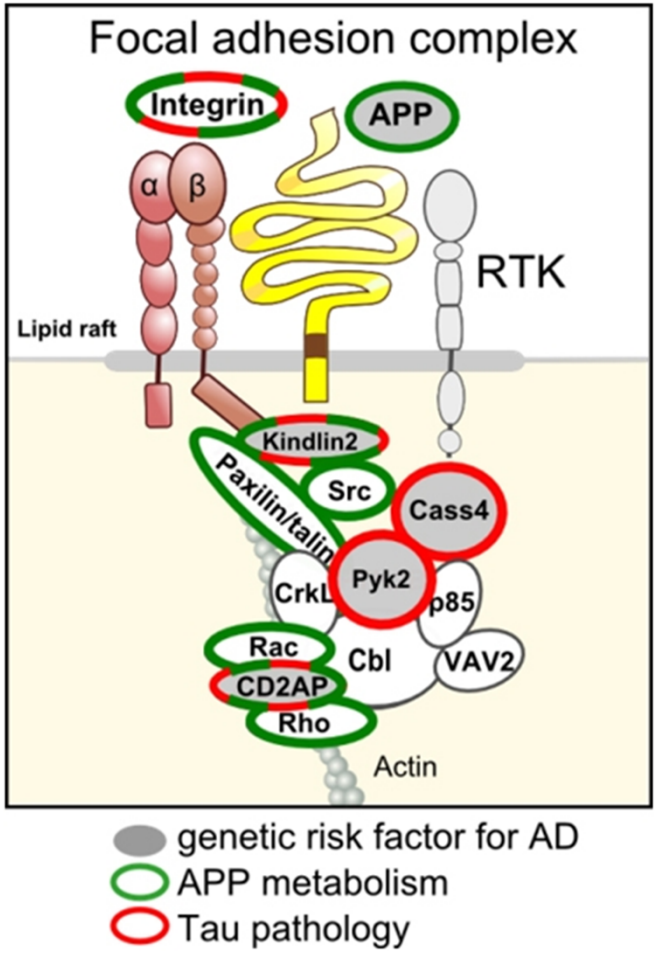
GWAS-defined genes and synapses



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- **BIN1 ?**

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MYOPATHIES

Amphiphysin 2 modulation rescues myotubular myopathy and prevents focal adhesion defects in mice

Valentina M. Lionello[1,2,3,4], Anne-Sophie Nicot[1,2,3,4,5,6], Maxime Sartori[1,2,3,4], Christine Kretz[1,2,3,4], Pascal Kessler[1,2,3,4], Suzie Buono[1,2,3,4]*, Sarah Djerroud[1,2,3,4], Nadia Messaddeq[1,2,3,4], Pascale Koebel[1,2,3,4], Ivana Prokic[1,2,3,4], Yann Hérault[1,2,3,4], Norma B. Romero[7,8,9], Jocelyn Laporte[1,2,3,4†‡], Belinda S. Cowling[1,2,3,4*‡]

Bin1 and Pyk2 interact as shown by co-immunoprecipitation and NMR experiments (unpublished data)

BIN1 and Tau

Sottejeau et al. Acta Neuropathologica Communications (2015) 3:58
DOI 10.1186/s40478-015-0237-8

ACTA NEUROPATHOLOGICA COMMUNICATIONS

RESEARCH Open Access

Tau phosphorylation regulates the interaction between BIN1's SH3 domain and Tau's proline-rich domain

Yoann Sottejeau[1,2,3†], Alexis Bretteville[1,2,3†], François-Xavier Cantrelle[3,4,5], Nicolas Malmanche[1,2,3], Florie Demiaute[1,2,3], Tiago Mendes[1,2,3], Charlotte Delay[1,2,3], Harmony Alves Dos Alves[1,2,3], Amandine Flaig[1,2,3], Peter Davies[6,9], Pierre Dourlen[1,2,3], Bart Dermaut[1,2,3,8], Jocelyn Laporte[7], Philippe Amouyel[1,2,3], Guy Lippens[3,4,5], Julien Chapuis[1,2,3], Isabelle Landrieu[3,4,5*†] and Jean-Charles Lambert[1,2,3*†]

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Regulation of the interaction between the neuronal BIN1 isoform 1 and Tau proteins – role of the SH3 domain

Idir Malki[1], François-Xavier Cantrelle[1], Yoann Sottejeau[2], Guy Lippens[1], Jean-Charles Lambert[2] and Isabelle Landrieu[1]

1 Lille University, CNRS UMR8576, Lille, France
2 Lille University, INSERM UMR1167, Pasteur Institute of Lille, Lille, France

frontiers in Molecular Neuroscience
ORIGINAL RESEARCH
published: 14 November 2018
doi: 10.3389/fnmol.2018.00421

Structural Basis of Tau Interaction With BIN1 and Regulation by Tau Phosphorylation

*Alessia Lasorsa†‡, Idir Malki†‡, François-Xavier Cantrelle‡, Hamida Merzougui‡, Emmanuelle Boll‡, Jean-Charles Lambert‡ and Isabelle Landrieu‡**

Acta Neuropathologica (2019) 138:631–652
https://doi.org/10.1007/s00401-019-02017-9

ORIGINAL PAPER

BIN1 recovers tauopathy-induced long-term memory deficits in mice and interacts with Tau through Thr^{348} phosphorylation

Maxime Sartori[1,2,3,4] · Tiago Mendes[5,6,7,8] · Shruti Desai[5,6,7] · Alessia Lasorsa[7,9] · Adrien Herledan[6,10,11] · Nicolas Malmanche[5,6,7] · Petra Mäkinen[12] · Mikael Marttinen[12] · Idir Malki[7,9] · Julien Chapuis[5,6,7] · Amandine Flaig[5,6,7] · Anaïs-Camille Vreulx[5,6,7] · Marion Ciancia[1,2,3,4] · Philippe Amouyel[5,6,7] · Florence Leroux[6,10,11] · Benoit Déprez[6,10,11] · François-Xavier Cantrelle[7,9] · Damien Maréchal[1,2,3,4] · Laurent Pradier[8] · Mikko Hiltunen[12] · Isabelle Landrieu[7,9] · Devrim Kilinc[5,6,7] · Yann Herault[1,2,3,4] · Jocelyn Laporte[1,2,3,4] · Jean-Charles Lambert[5,6,7]

BIN1 and Tau

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frontiers in Molecular Neuroscience
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ORIGINAL PAPER

The FEBS Journal
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1 Lille University, CNRS UMR8576, Lille, France
2 Lille University, INSERM UMR1167, Pasteur Institute of Lille, Lille, France

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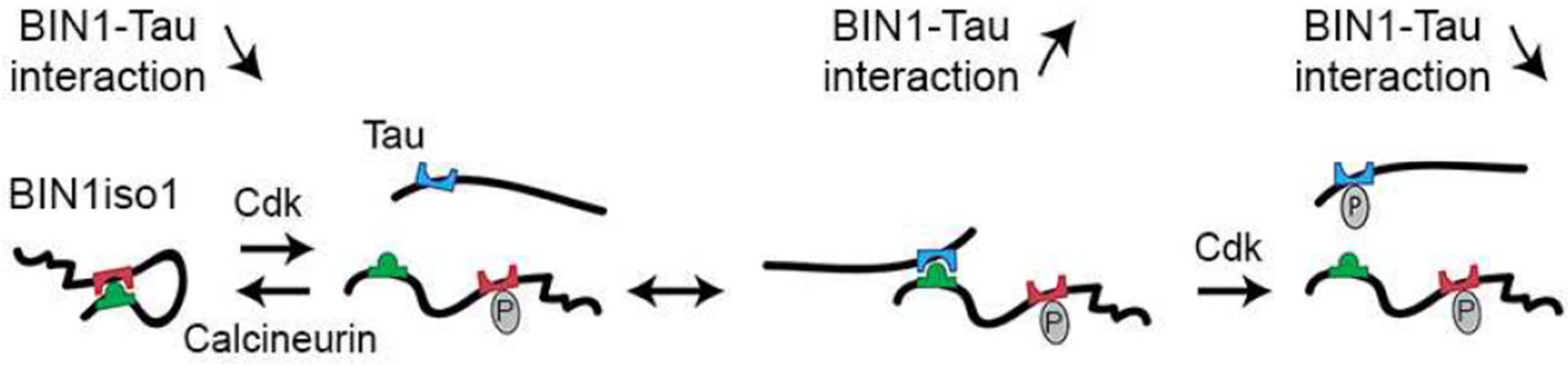
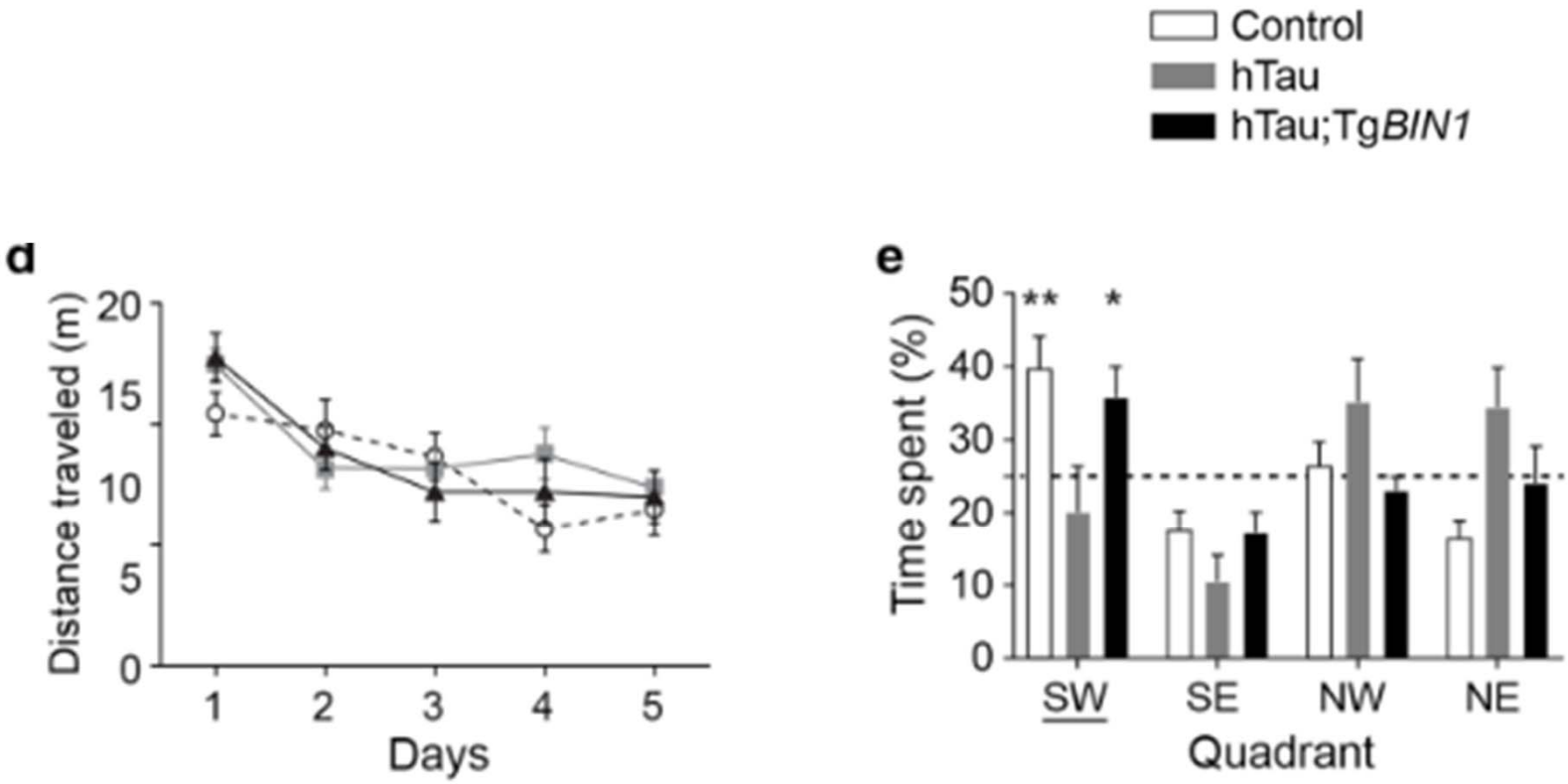


BIN1 and Tau



Over-expression of BIN1 in a model of Tauopathy

- Rescue of long-term memory deficits

Acta Neuropathologica (2019) 138:631–652
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ORIGINAL PAPER

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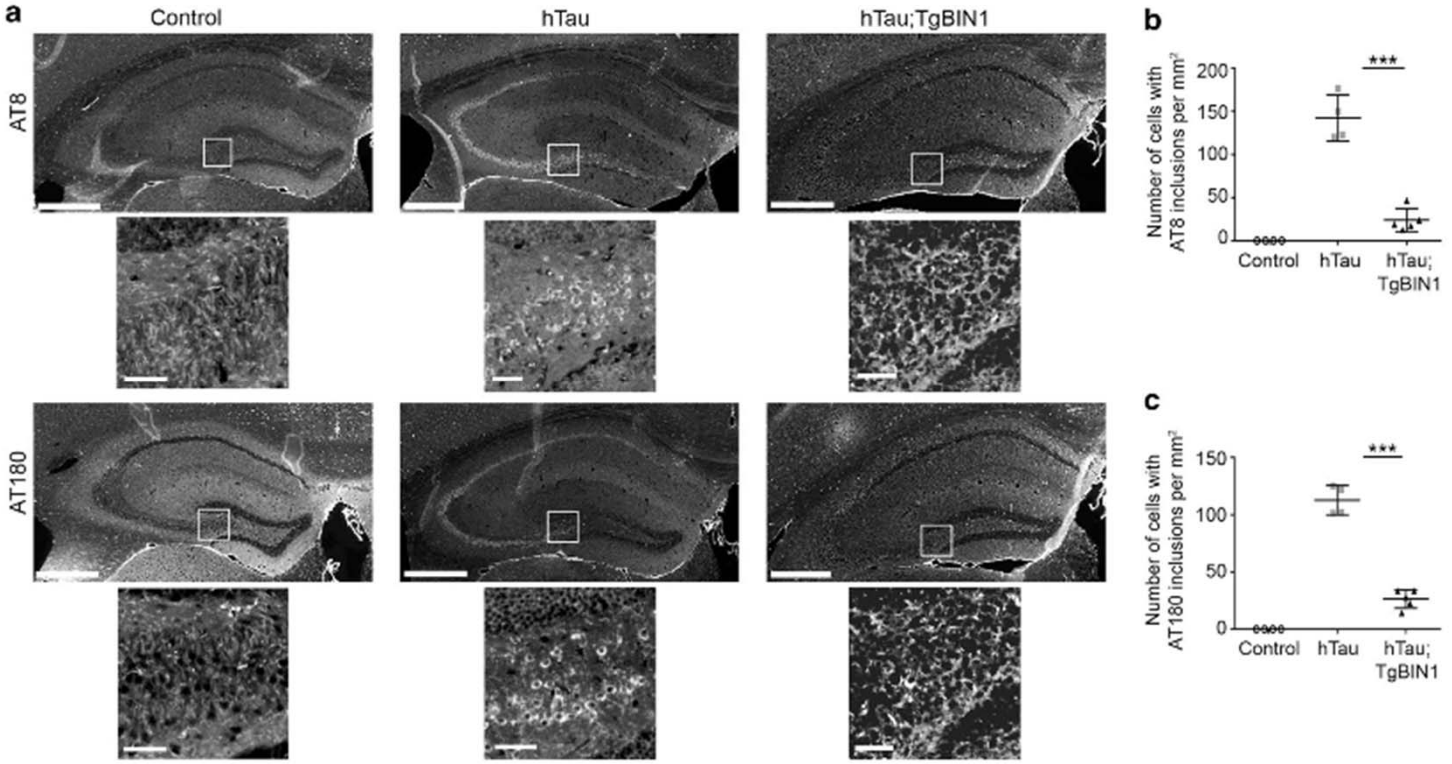
BIN1 and Tau



Over-expression of BIN1 in a model of Tauopathy

- Rescue of long-term memory deficits
- **Decrease in AT8 inclusion in cells**

Acta Neuropathologica (2019) 138:631–652
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ORIGINAL PAPER

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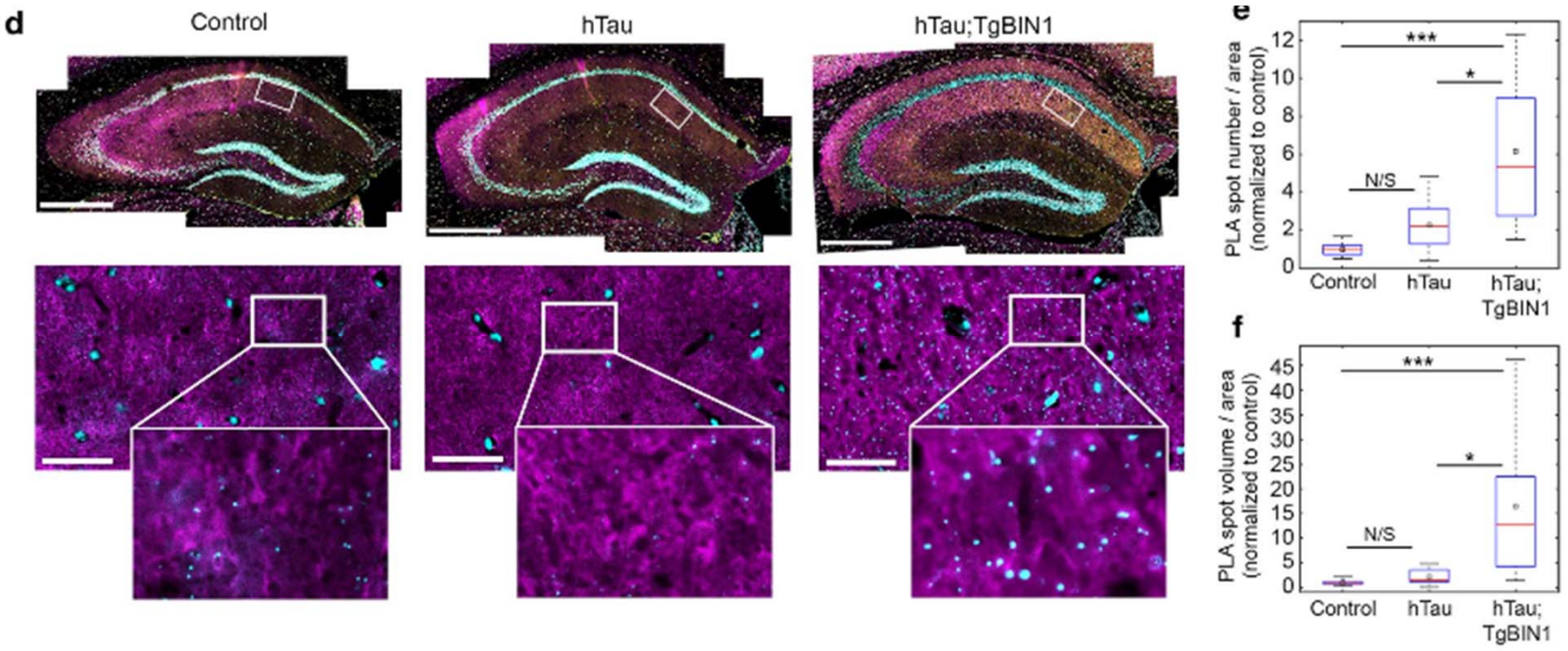
BIN1 and Tau



Over-expression of BIN1 in a model of Tauopathy

- Rescue of long-term memory deficits
- Decrease in AT8 inclusion in cells
- **Increase in Tau-Bin1 interaction**

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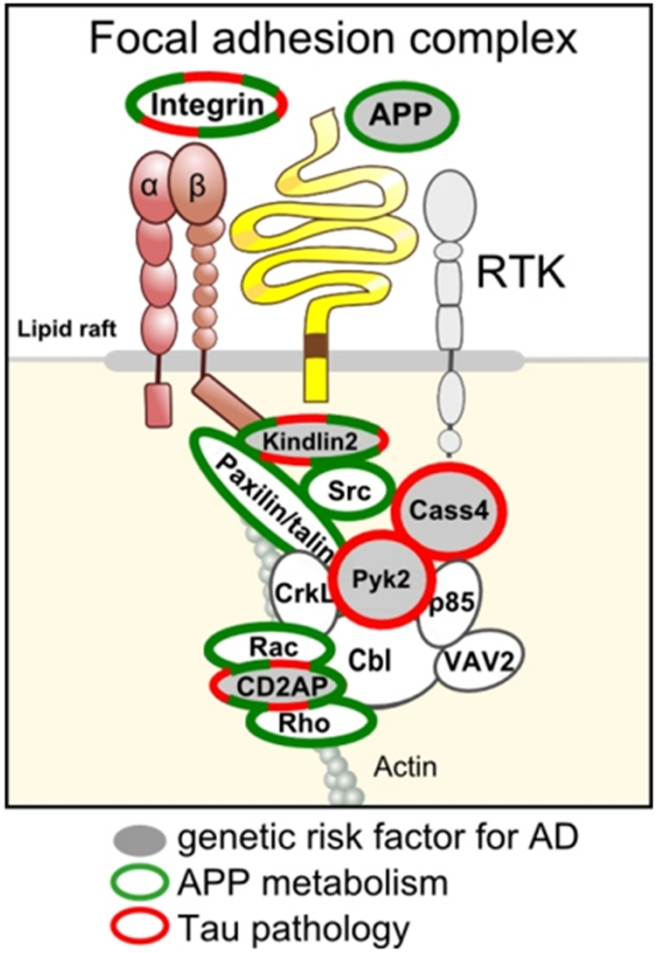
GWAS-defined genes and synapses



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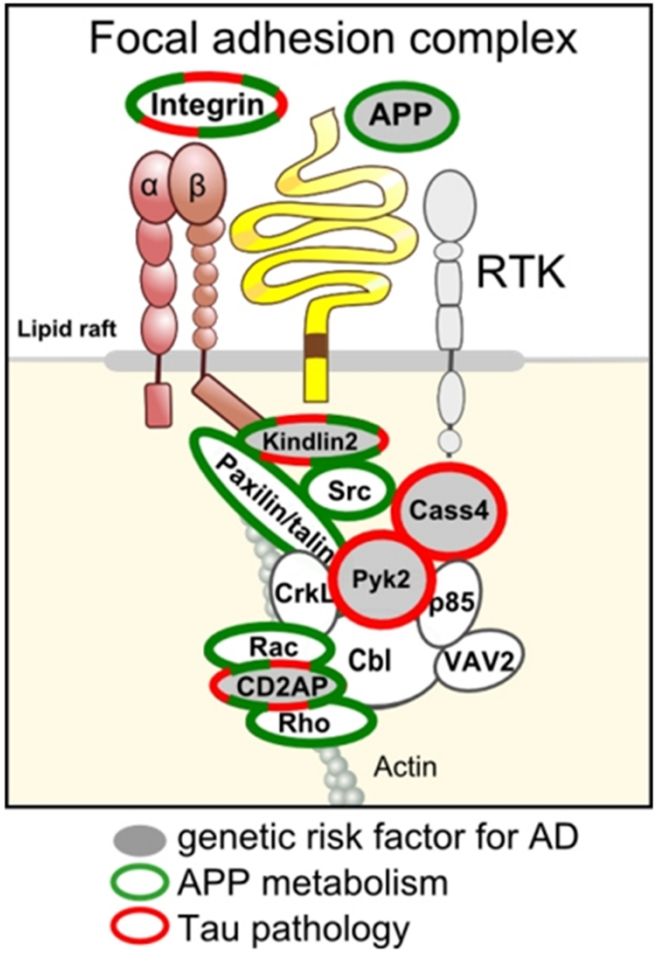

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- **BIN1 (linked to Tau toxicity and APP metabolism)**

- **APP and Tau are also known to be involved in the synaptic functions and plasticity**

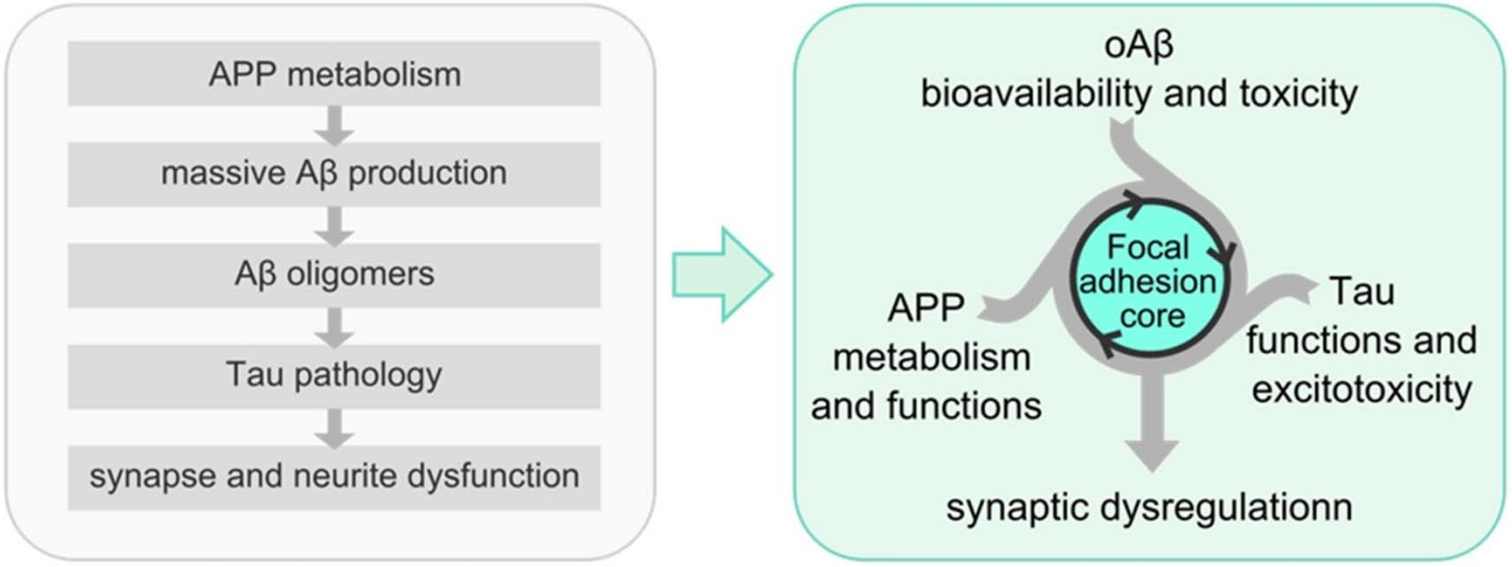
Is the synapse the place making the link between APP, Tau and some of the AD genetic risk factors ?

Acta Neuropathologica (2019) 138:221–236
https://doi.org/10.1007/s00401-019-02004-0

REVIEW

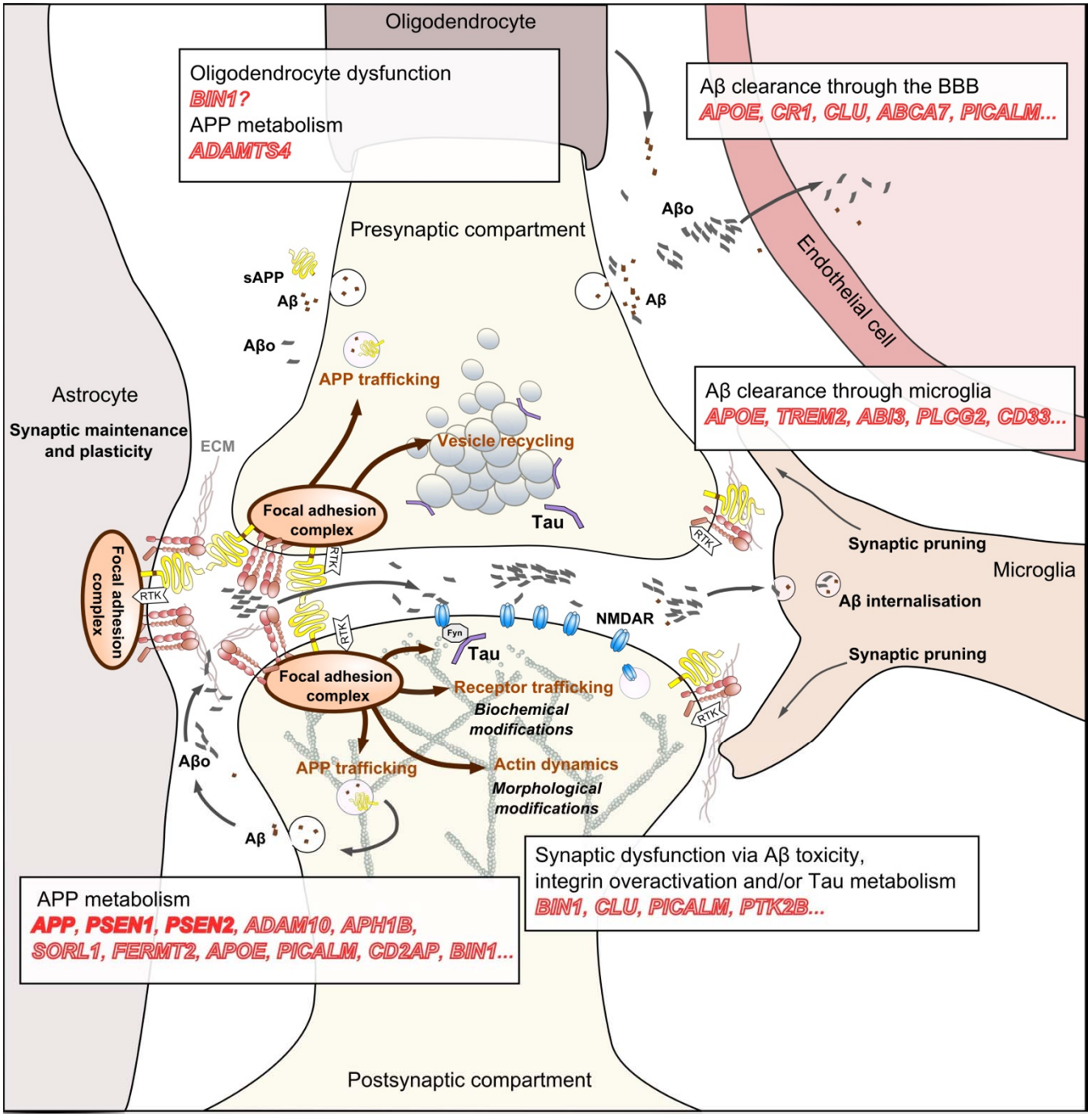
The new genetic landscape of Alzheimer's disease: from amyloid cascade to genetically driven synaptic failure hypothesis?

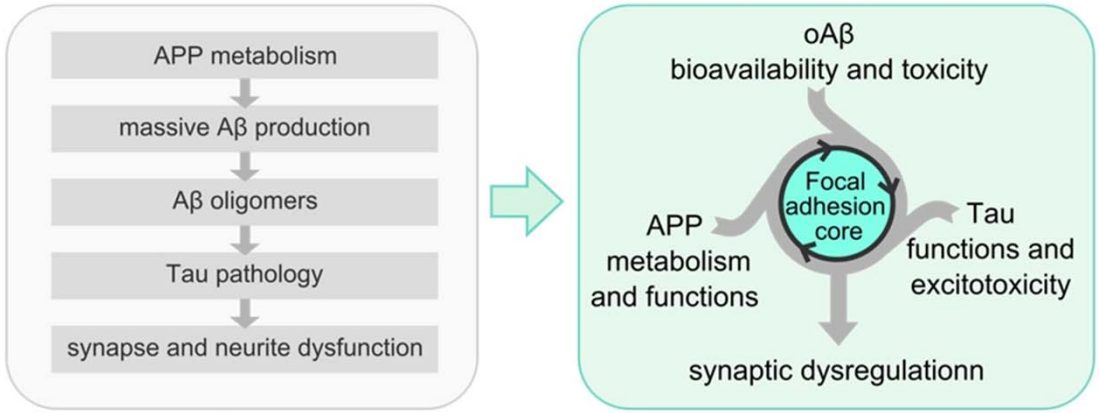
Pierre Dourlen[1] · Devrim Kilinc[1] · Nicolas Malmanche[1] · Julien Chapuis[1] · Jean-Charles Lambert[1]



Current view: linear model of AD

Circular model in which the core of the focal adhesion pathway is central


Oligodendrocyte
Oligodendrocyte dysfunction
BIN1?
APP metabolism
ADAMTS4
Aβ clearance through the BBB
APOE, CR1, CLU, ABCA7, PICALM...
Aβo
Endothelial cell
Presynaptic compartment
sAPP
Aβ
Aβo
Aβ
APP trafficking
Vesicle recycling
Tau
Astrocyte
Synaptic maintenance and plasticity
ECM
Aβ clearance through microglia
APOE, TREM2, ABI3, PLCG2, CD33...
Focal adhesion complex
RTK
Synaptic pruning
Microglia
Aβ internalisation
NMDAR
Fyn
Tau
Receptor trafficking
Biochemical modifications
Actin dynamics
Morphological modifications
APP trafficking
Aβo
Aβ
Synaptic dysfunction via Aβ toxicity, integrin overactivation and/or Tau metabolism
BIN1, CLU, PICALM, PTK2B...
APP metabolism
APP, PSEN1, PSEN2, ADAM10, APH1B, SORL1, FERMT2, APOE, PICALM, CD2AP, BIN1...
Postsynaptic compartment



Current view: linear model of AD

Circular model in which the core of the focal adhesion pathway is central

With the new genetic landscape of AD which will be described in the next years,

Will the hypothesis of the amyloid cascade be strengthened or not?
will our hypothesis be confirmed or rejected?
will new hypotheses emerge?

No matter how, it is likely that from these genetic and biological data, a poly-therapeutic approach will be necessary depending on the point of entry into the disease and its genetic background.

Team 3- UMR1167

Head : Jean-Charles Lambert

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Valérie Buiche

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Marcos Costa

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Shruti Desai

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Amandine Flaig

Benjamin Grenier-Boley

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Erwan Lambert

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