# Alzheimer's Disease Genetics Symposium
# November 12-13, 2019 Philadelphia, PA

## Alzheimer's genetics in diversity populations : The Genome Research at Fundació ACE/Dementia Genetics Spanish Consortium project GR@ACE/DEGESCO


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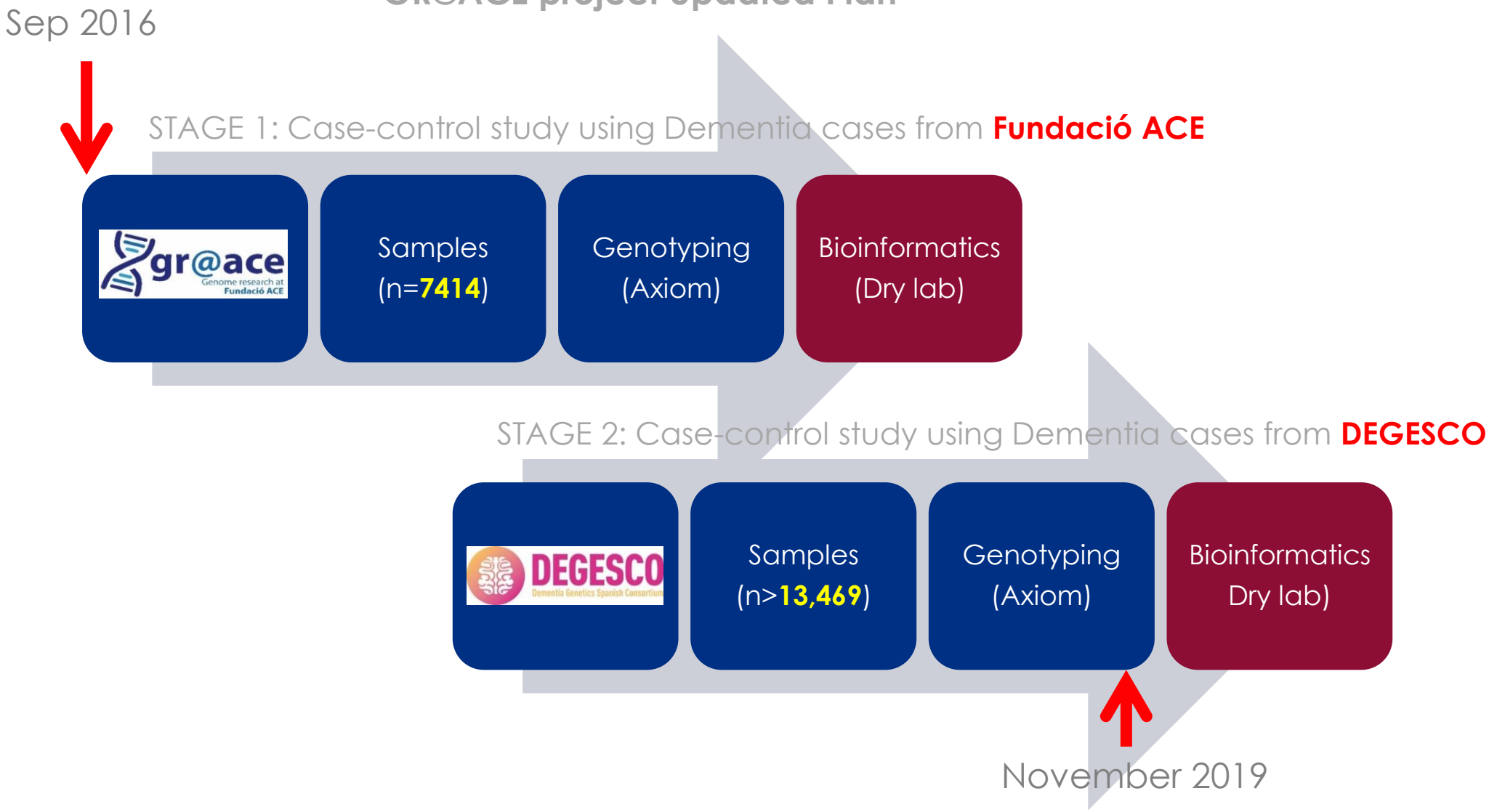
CIBERNED, Instituto de Salud Carlos III, Ministerio de Salud. Spain.

The gr@ace Genome research at Fundació ACE DEGESCO Dementia Genetics Spanish Consortium project


1. A three year multicentric 2-stage research project focused on the etiology of Alzheimer's Dementia and related disorders.
2. The largest GWAS effort in Spain to disentangle any human disease to date.

## GR@ACE project Updated Plan



# Methods: details about Dementia cases included

## Why is the gr@ace Project different?

**4124** dementia cases were evaluated following identical methodology. Each subject was assigned three diagnoses (syndromic, primary and secondary). AD cases were defined as probable or possible AD at every clinical evaluation, either as their primary or secondary label, and clinical comorbidities were identified as well.

| Phenotype | Primary Diagnostic | Secondary Diagnostic | N | Mean Age ± (SD) | Women % | *APOE* ε4 % |
|---|---|---|---|---|---|---|
| Controls | -- | -- | 3.290 | 54.6 ± 14.8 | 48.9 | 21.4 |
| VaD++ | VaD | Pss AD | 373 | 80.1 ± 5.5 | 54.9 | 25.0 |
| VaD+ | VaD/ Pss AD | VaD/ Pss AD | 1.168 | 80.4 ± 6.3 | 65.0 | 32.8 |
| AD | Pr/Pss AD in any moment of the medical history | | 4.124 | 79.1 ± 7.5 | 69.6 | 40.2 |
| AD+ | Pr/Pss AD | Pr/Pss AD | 3. 797 | 79.2 ± 7.5 | 70.6 | 41.2 |
| AD++ | Pr AD | Pr/Pss AD | 2.611 | 78.8 ± 7.9 | 72.8 | 44.6 |
| AD+++ | Pr AD | Pr AD | 1. 852 | 78.5± 7.9 | 74.6 | 46.4 |

Pr AD: Probable AD; Pss AD: Possible AD;

Each patient was assigned:

a) A Syndromic diagnosis: Dementia vs MCI
b) A Primary diagnosis: probable or possible AD, vascular dementia, DLB, FTLD…
c) A Secondary diagnosis: probable or possible AD, vascular dementia, LBD, FTLD…
d) The subject clinical chart is not static - diagnosis might change over time.
e) The **level of certainty** for the clinical diagnosis of AD (probable vs possible) is available for all cases.

Moreno-Grau et al. Alzheimer's & Dementia 2019.

# Classification of known AD markers using sub-clinical categories of AD patients, defined according to level of certainty for AD diagnosis and vascular co-morbility

## Genotyping and GWAS QC

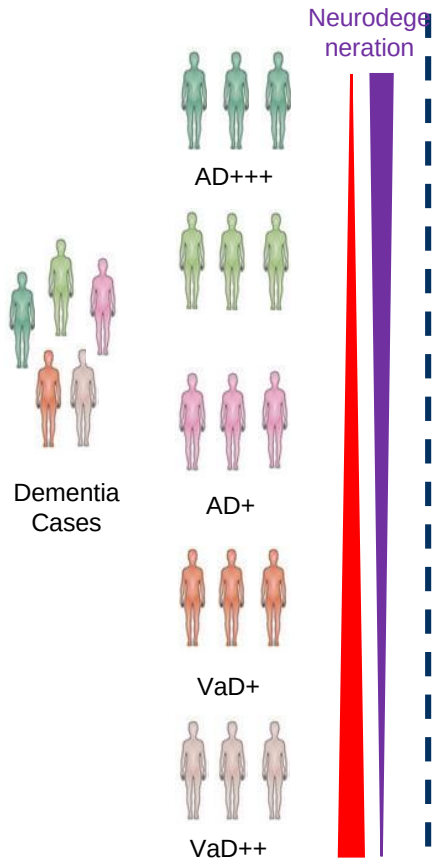
**Lab QC**
- Semi-automated processing
- DNA extraction, Quantification & DNA integrity control
- Cases and controls randomisation across plates

**Genotyping**
- 815K. Axiom Spanish Biobank Array. CEGEN.
- Axiom™ 2.0 Assay Manual Workflow

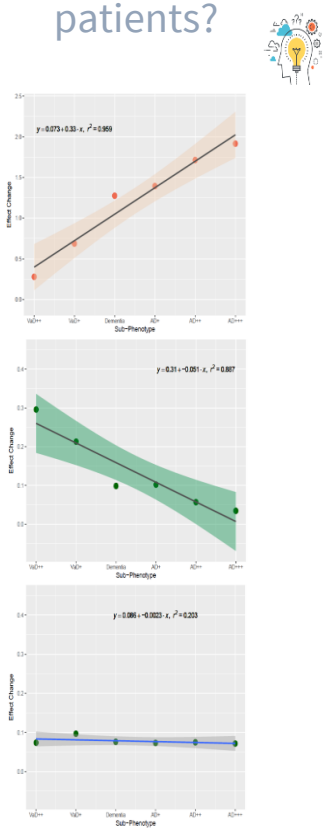
**CEL QC**
APT 1.15.0 software. SNPolisher R package
- Dish QC. Resolution > 0.82
- Call rate per sample > 0.97; per plate > 0.985
- Pre-QC per plate → mind, geno & Heterozygosity rate
- Final SNP calling in a unique batch

**GWAS Analysis**
PLINK 1.9 software
SMARTPCA v.13050 Software
- Data Preparation
- GWAS QC
- Imputation using Michigan Server, HRC reference panel
- Association Analysis

## 1.Clinical Subgroups of AD patients

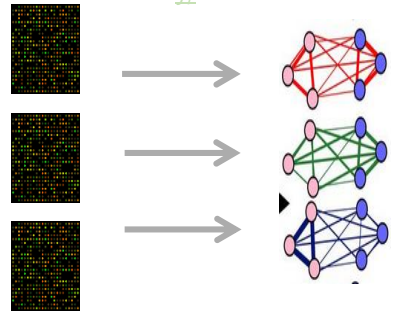



## 2. Are LOAD variants differently associated with a specific subgroup of AD patients?



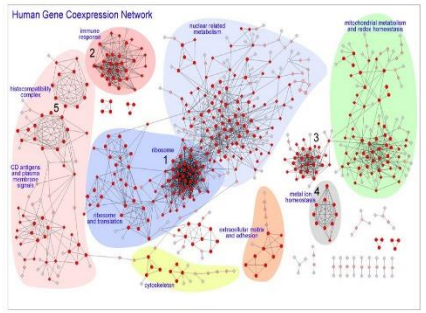
## 3. Co-expression Network

http://www.genefriends.org/microArray/



## 4. Pathway analysis

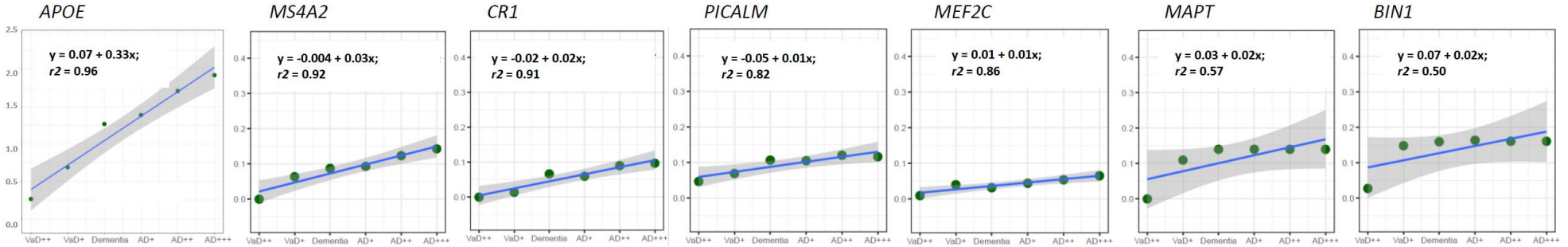
http://www.webgestalt.org/




Sonia Moreno Grau et al. Alzheimer's & Dementia 2019

# Classification of known AD markers using sub-clinical categories of AD patients, defined according to level of certainty for AD diagnosis and vascular co-morbidity

A

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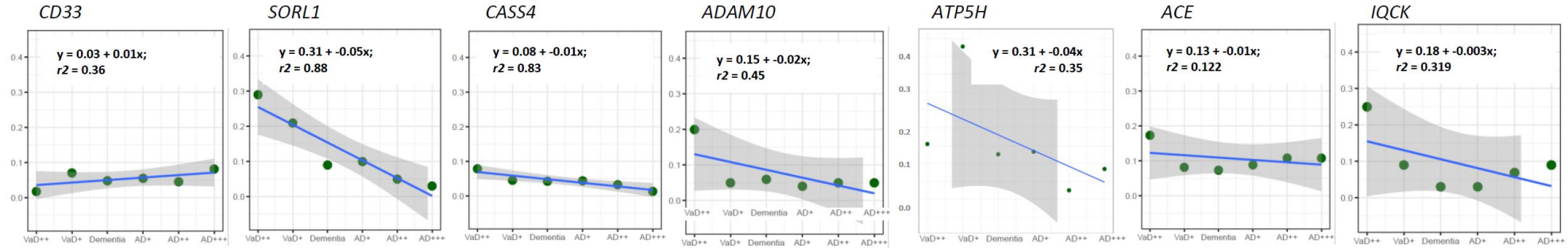
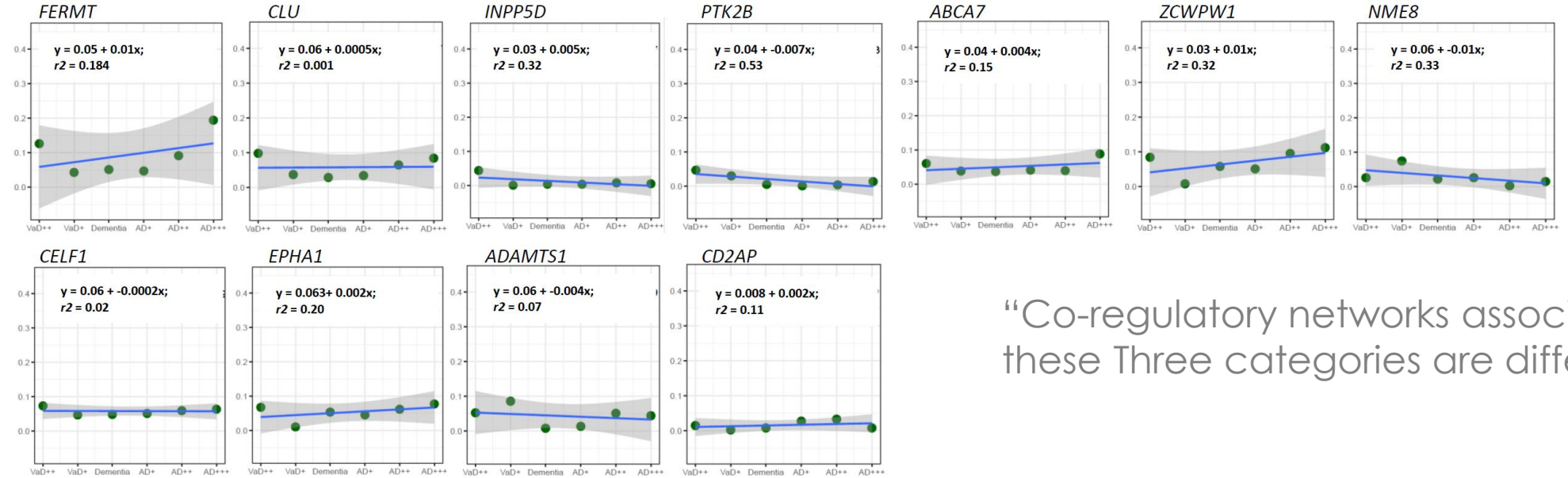



C

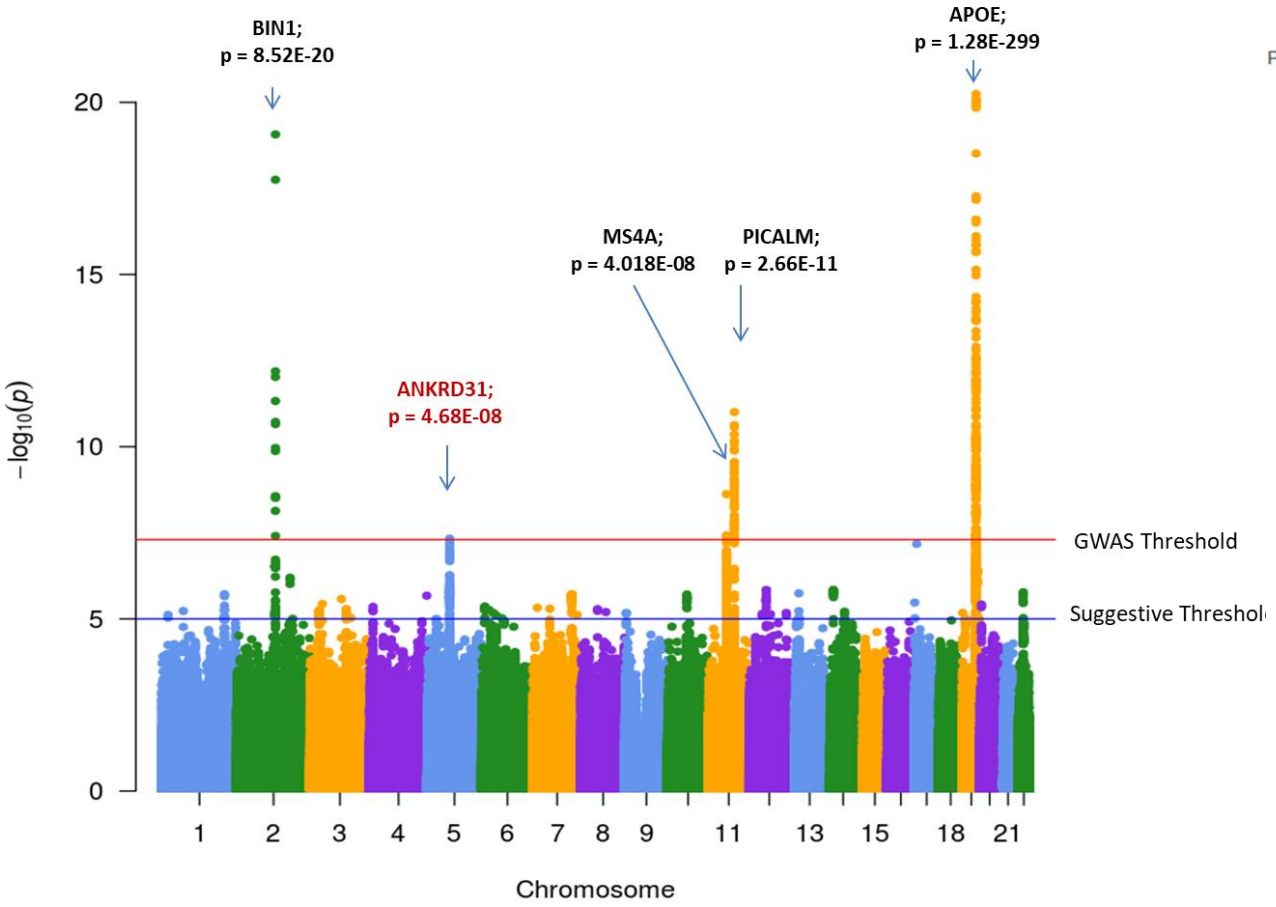


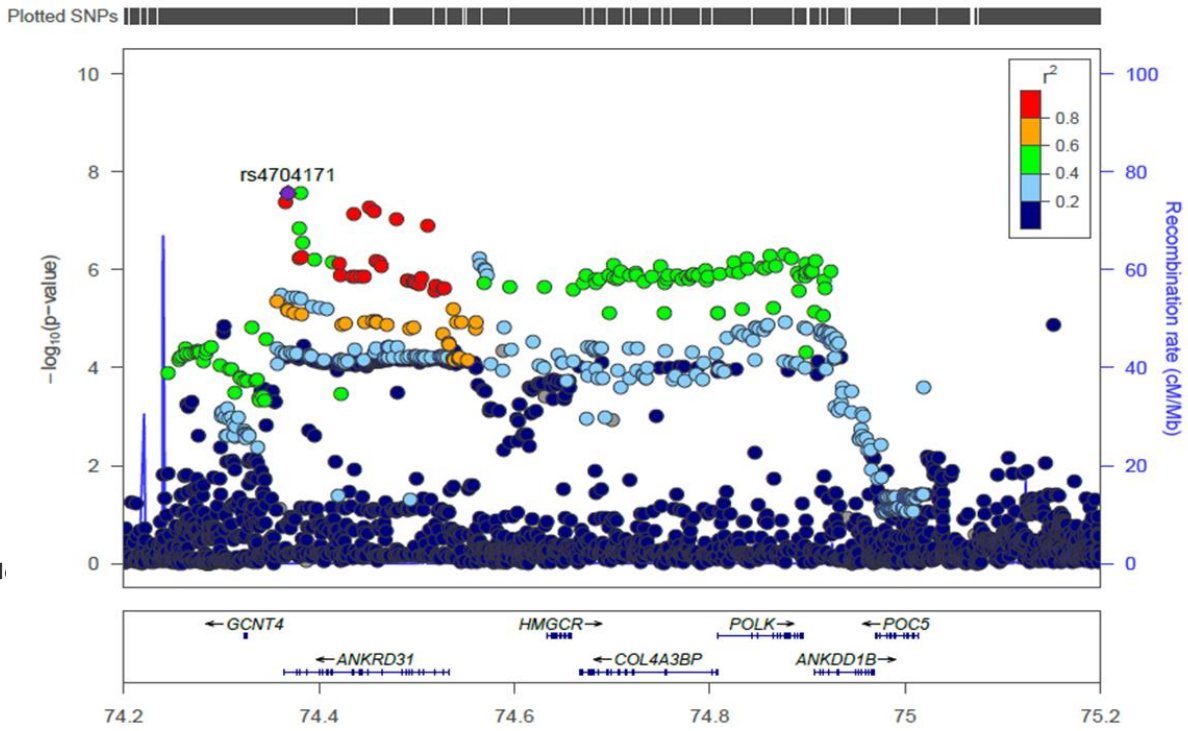

"Co-regulatory networks associated to these Three categories are different"

Sonia Moreno Grau et al. Alzheimer's & Dementia 2019



**A novel genome-wide significant** signal was detected in chromosome 5. This signal is close to the ***HMGR*** locus, which has been previously associated to cardiovascular risk-related phenotypes.




Moreno-Grau et al. Alzheimer's & Dementia 2019.

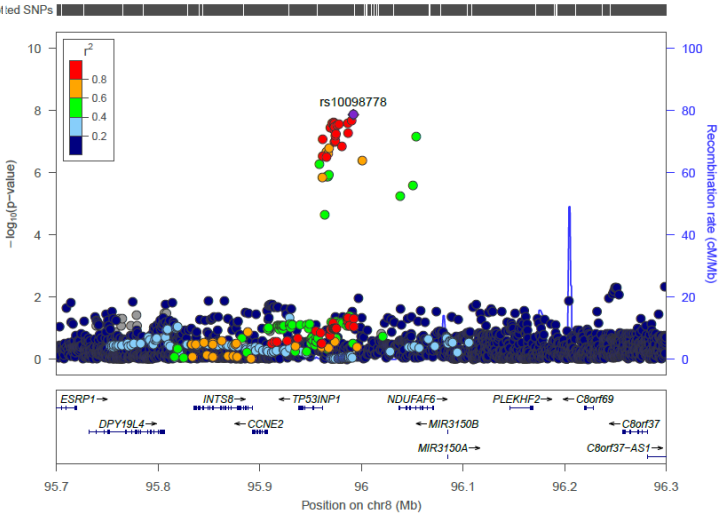
# IGAP (Lambert 2013) grey zone exploration

IGAP I&II 74 046 + GR@ACE 7 414 + NxC 1 078 + AddNeuro 637 = 83 125

13 GWAS signals in NDUFAF6 region

A novel GWAS significant signal was detected in **chromosome 8**. The new locus is close to the *TP53INP1* signal, previously detected by gene-wide analysis (Escott-Price 2014)

| Suggestive signal IGAP* | | | | IGAP Stage1&2 + 4db | | | |
|---|---|---|---|---|---|---|---|
| GENE | CHR | SNP | A1 | OR | P | Q | I |
| ------- | 1 | rs6678275 | C | 1.07 | 6.87E-06 | 0.13 | 43.98 |
| HS3ST1 | 4 | rs6448799 | T | 1.07 | 1.37E-06 | 0.13 | 44.11 |
| SQSTM1 | 5 | rs72807343 | T | 1.29 | 3.32E-06 | 0.40 | 2.25 |
| TREML2 | 6 | rs9381040 | T | 0.95 | 5.70E-05 | 0.02 | 66.91 |
| NDUFAF6 | 8 | rs7818382 | T | 1.06 | 7.26E-08 | 0.76 | 0 |
| **NDUFAF6** | **8** | **rs10098778** | | **0.93** | **1.37E-08** | **0.97** | **0** |
| ECHDC3 | 10 | rs7920721 | G | 1.06 | 2.86E-06 | 0.11 | 47.36 |
| AP2A2 | 11 | rs10751667 | A | 0.95 | 1.37E-05 | 0.01 | 70.65 |
| ADAMTS20 | 12 | rs7295246 | G | 1.06 | 2.44E-06 | 0.30 | 18.24 |
| IGH@ | 14 | rs10134526 | T | 1.07 | 1.04E-06 | 0.26 | 26.16 |
| SPPL2A | 15 | rs8035452 | C | NA | NA | NA | NA |
| TRIP4 | 15 | rs74615166 | C | 1.23 | 3.02E-06 | 0.03 | 63.23 |
| SCIMP | 17 | rs7225151 | A | 1.09 | 3.56E-07 | 0.12 | 44.96 |
| ACE | 17 | rs138190086 | A | 1.25 | 1.37E-05 | 0.06 | 55.8 |




*Suggestive signals published in Lambert et al. Nat. Genet 2013

Moreno-Grau et al. Alzheimer's & Dementia 2019.

# GR@ACE Stage II

| Samples GR@ACE/DEGESCO Stage II | | | | | |
|---|---|---|---|---|---|
| *Center name* | *AD* | *Controls* | *Other* | *Total* | *Status* |
| Fundació ACE | 2624 | 501 | 242 | 3367 | Processed |
| Banco Nacional de ADN | 262 | 2908 | 0 | 3170 | Processed |
| Centro Alzheimer Fundación Reina Sofía (FCIEN) | 290 | 1169 | 0 | 1459 | Ongoing |
| Instituto de Biomedicina de Sevilla (IBiS) | 230 | 1034 | 0 | 1264 | Ongoing |
| IANEC/UMA | 109 | 350 | 0 | 459 | Ongiong |
| Hospital Universitario Central de Asturias | 78 | 285 | 0 | 363 | Ongoing |
| Biobanco Vasco | 350 | 0 | 0 | 350 | Tramited |
| Biobanc Institut Recerca Biomèdica Lleida | 333 | 0 | 0 | 333 | Processed |
| Neurology Service Marqués de Valdecilla University Hospital | 71 | 41 | 204 | 316 | Processed |
| Fundació de Recerca i Docència Mútua de Terrassa | 197 | 118 | 0 | 315 | Processed |
| Hospital Universitario de Valme | 0 | 193 | 0 | 193 | Processed |
| Hospital Ramón y Cajal | 41 | 0 | 0 | 41 | Processed |
| Centro de Biologia Molecular Severo Ochoa (CBM-CSIC) | 18 | 10 | 0 | 28 | Processed |
| **TOTAL** | **4603** | **6609** | **446** | **11658** | |

| *Other projects* | *AD* | *Controls* | *Other* | *Total* | *Status* |
|---|---|---|---|---|---|
| Biomedica Research group (Chile) | 197 | 735 | 0 | 932 | Ongoing |
| Higher Institute of Biotechology Monastir, University of Monastir (Tunisia) | 71 | 232 | 0 | 303 | Processed |
| Biobanco HUP - Down Sindrome (Madrid) | 0 | 0 | 576 | 576 | Ongoing |
| **TOTAL** | **5042** | **7810** | **576** | **13469** | |

# Interim Meta-analysis with IGAP (Kunkle 2019) and UKBiobank proxy-AD

## Meta-GWAS analysis

**Discovery.** *Meta-analysis Case-control + AD-by-proxy*

| GR@ACE[a] | IGAP[b] | UKB[c] |
|---|---|---|
| N=12,386 | N=81,771 | N=548,955 |

Global N= 644,112 (78,709 Cases and 565,403 Controls)

***Sensitivity analysis Case-control AD status***

| GR@ACE[a] | IGAP[b] |
|---|---|
| N= 12,386 | N=81,771 |

**Follow-up.** *Analysis of genome-wide significant loci*

| | | |
|---|---|---|
| EADB<br>N=33,495<br>7 cohorts | PGC<br>N=17,537<br>3 cohorts | Gothenburg<br>N=3,981 |
| GR@ACE<br>N=1,204 | NxC<br>N=1,078 | ADDN<br>N=637<br>2 cohorts |
| | MAS<br>N=258 | |

Global N= 58,190 (19,089 Cases and 39,101 Controls)

## Polygenic Risk Score

Pathological dataset
N=2,062

*Concomitant pathologies* — *Gender effect* — *Age at onset*

GR@ACE[a]
N=12,386

*APOE stratification*

*Age at Onset*

[a] Extended dataset (S.Moreno-Grau et al. 2019)
[b] StageI + StageII (Kunkle et al. 2019)
[c] By proxy AD: Meta-analysis of maternal and paternal history of dementia (Marioni et al. 2018)

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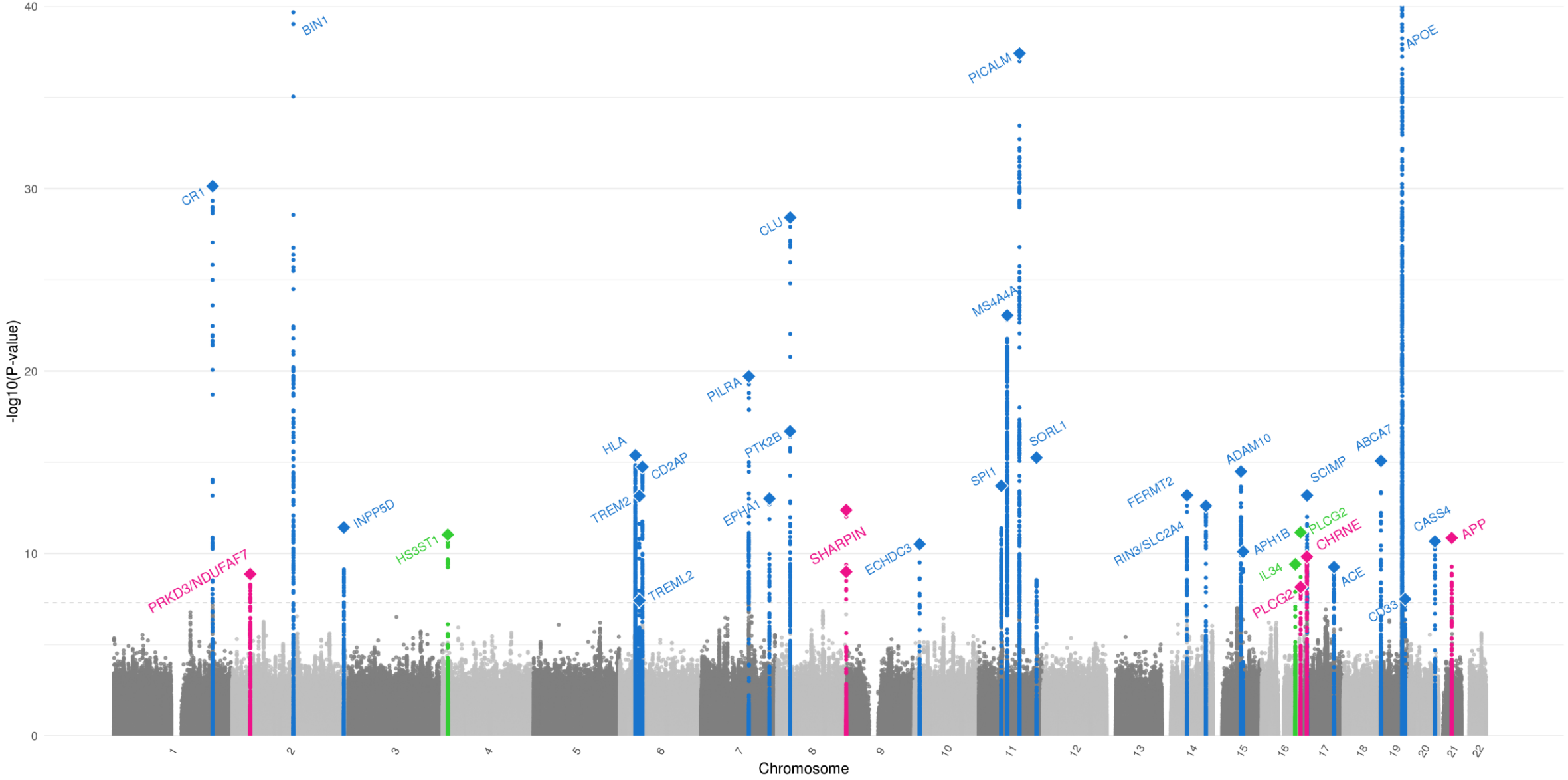
# New Meta-GWAS (GR@ACE-IGAP-UKbiobank)

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# New Meta-GWAS (GR@ACE-IGAP-UKbiobank)

**Table 1. Results for the AD loci selected for follow-up**

*Note: FreqA1 is from GR@ACE discovery dataset. P-value for significance < 5 × 10−8. Effect allele: Allele 1.*

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Discovery meta-analysis | | | | | Follow-up datasets | | Overall | |
| Chr | Closest gene | SNP | BP | Allele 1 | Allele 2 | FreqA1 | OR[CI95%] | P | OR[CI95%] | P | OR[CI95%] | P |
| Variants showing novel genome-wide significant association with AD | | | | | | | | | | | | |
| 2 | *PRKD3/NDUFAF7* | rs876461 | 37515958 | A | G | 0.143 | 1.07[1.04-1.09] | 9.14E-07 | 1.08[1.04-1.13] | 3.07E-04 | 1.07[1.05-1.09] | 1.34E-09 |
| 8 | *SHARPIN* | rs34674752 | 145154222 | A | G | 0.052 | 1.11[1.06-1.16] | 4.02E-06 | 1.20[1.10-1.31] | 1.65E-05 | 1.13[1.09-1.18] | 1.00E-09 |
| 8 | *SHARPIN* | rs34173062 | 145158607 | A | G | 0.085 | 1.16[1.11-1.21] | 1.33E-11 | 1.09[1.02-1.17] | 7.35E-03 | 1.14[1.10-1.18] | 9.62E-13 |
| 16 | *PLCG2* | rs3935877 | 81900853 | C | T | 0.868 | 0.92[0.90-0.95] | 1.12E-07 | 0.92[0.85-0.99] | 1.96E-02 | 0.92[0.90-0.95] | 6.85E-09 |
| 17 | *CHRNE* | rs72835061 | 4805437 | A | C | 0.085 | 1.09[1.06-1.12] | 3.92E-09 | 1.07[1.02-1.12] | 7.83E-03 | 1.09[1.06-1.11] | 1.51E-10 |
| 21 | *APP* | rs2154481 | 27473875 | C | T | 0.483 | 0.95[0.93-0.96] | 9.26E-10 | 0.96[0.93-0.99] | 3.31E-03 | 0.95[0.94-0.96] | 1.39E-11 |
| Previously reported genome-wide significant hits replicating in the follow-up | | | | | | | | | | | | |
| 4 | *HS3ST1* | rs4351014 | 11027619 | C | T | 0.684 | 0.94[0.92-0.96] | 5.37E-10 | 0.93[0.88-0.98] | 4.54E-03 | 0.94[0.92-0.95] | 9.16E-12 |
| 16 | *IL34* | rs4985556 | 70694000 | A | C | 0.111 | 1.08[1.05-1.11] | 2.28E-08 | 1.09[1.03-1.16] | 4.59E-03 | 1.08[1.06-1.11] | 3.91E-10 |
| 16 | *PLCG2* | rs12444183 | 81773209 | A | G | 0.407 | 0.95[0.93-0.97] | 1.48E-08 | 0.92[0.88-0.96] | 3.23E-05 | 0.95[0.93-0.96] | 6.81E-12 |
| Suggestive signals (not replicating) | | | | | | | | | | | | |
| 14 | *ELK2AP* | rs7153315 | 106195719 | C | G | 0.750 | 0.94[0.92-0.96] | 9.80E-08 | 1.16[1.01-1.33] | 0.0412 | 0.94[0.92-0.97] | 9.04E-07 |
| 15 | *SPPL2A* | rs76523702 | 51002342 | C | T | 0.802 | 1.06[1.04-1.08] | 6.86E-08 | 1.02[0.97-1.07] | 0.3501 | 1.05[1.03-1.08] | 1.08E-07 |

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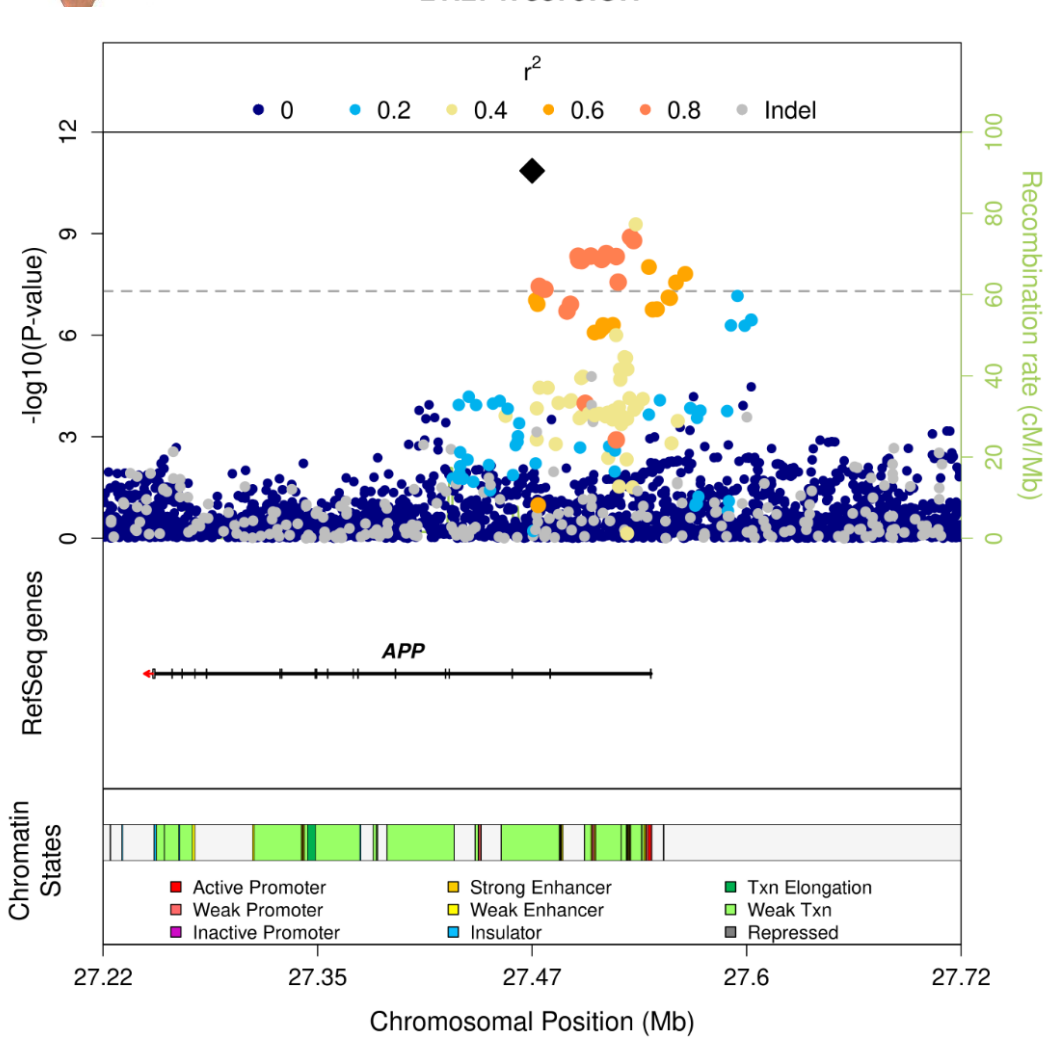
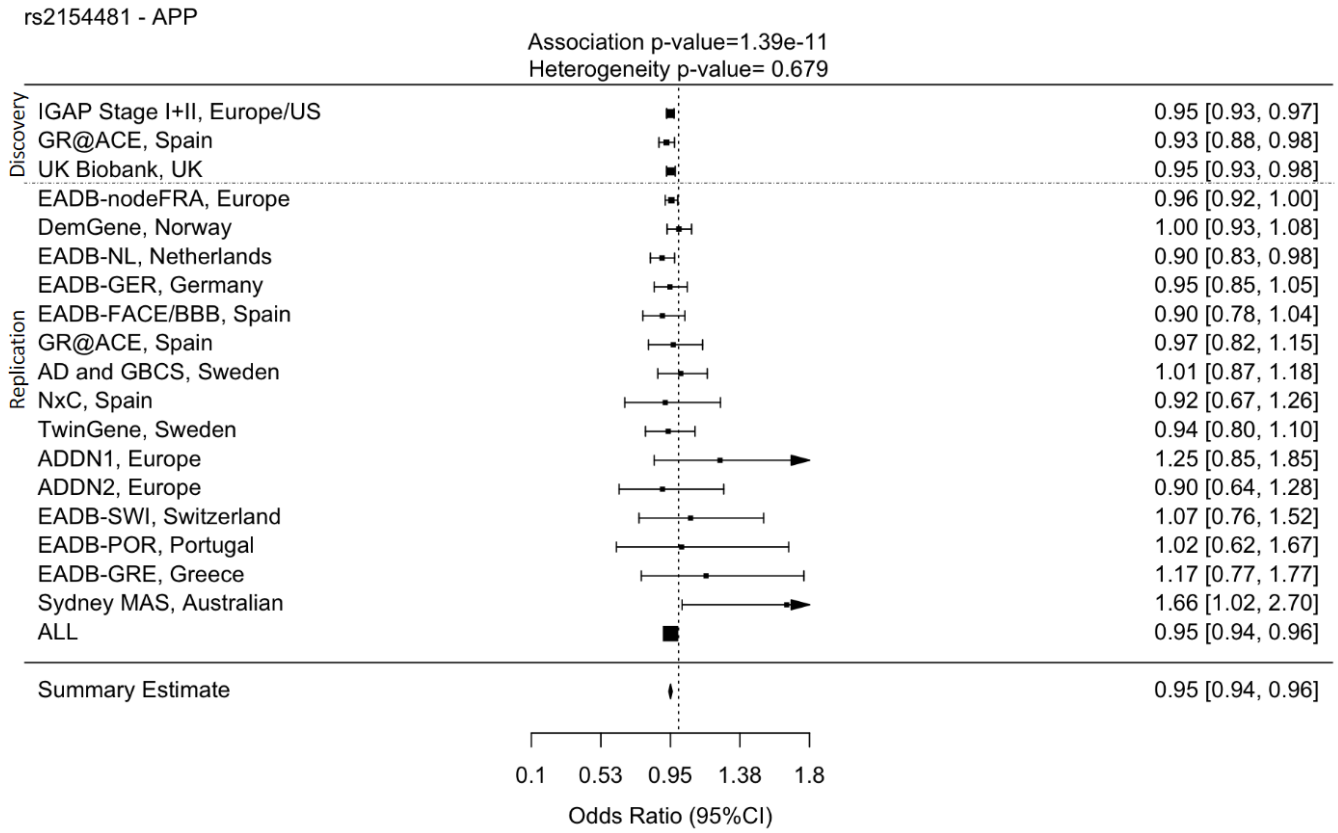
# *APP locus* confirmed for non-mendelian or Sporadic AD

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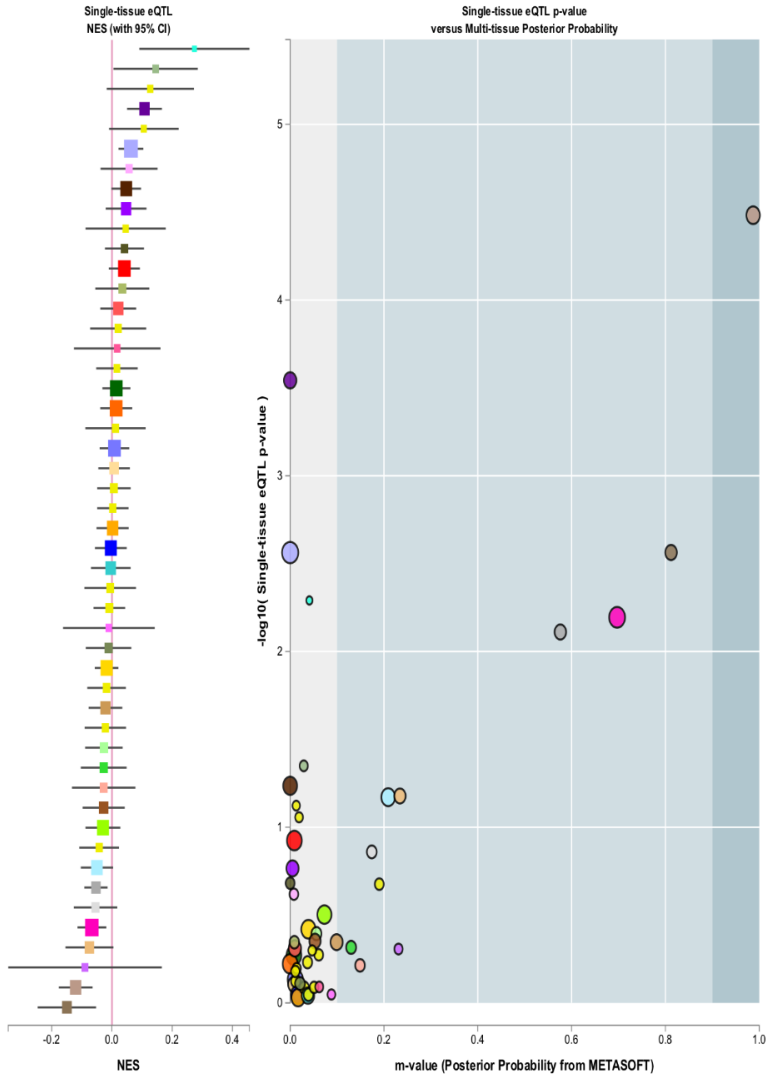
# Identifed *APP* variant is modulating mRNA expression levels

A

| Tissue | Samples | NES | p-value | m-value |
|---|---|---|---|---|
| Kidney - Cortex | 73 | 0.274 | 0.005 | 0.0410 |
| Minor Salivary Gland | 144 | 0.145 | 0.04 | 0.0290 |
| Brain - Spinal cord (cervical c-1) | 126 | 0.127 | 0.09 | 0.0190 |
| Heart - Left Ventricle | 386 | 0.108 | 2.9e-4 | 0.00 |
| Brain - Substantia nigra | 114 | 0.106 | 0.08 | 0.0130 |
| Muscle - Skeletal | 706 | 0.0630 | 2.7e-3 | 0.00 |
| Ovary | 167 | 0.0569 | 0.2 | 0.00800 |
| Esophagus - Mucosa | 497 | 0.0476 | 0.06 | 0.00 |
| Heart - Atrial Appendage | 372 | 0.0472 | 0.2 | 0.00500 |
| Brain - Amygdala | 129 | 0.0456 | 0.5 | 0.0470 |
| Small Intestine - Terminal Ileum | 174 | 0.0417 | 0.2 | 0.00 |
| Artery - Tibial | 584 | 0.0412 | 0.1 | 0.00900 |
| Liver | 208 | 0.0346 | 0.5 | 0.00900 |
| Artery - Aorta | 387 | 0.0210 | 0.5 | 0.0100 |
| Brain - Hippocampus | 165 | 0.0208 | 0.7 | 0.0110 |
| Vagina | 141 | 0.0176 | 0.8 | 0.0620 |
| Brain - Anterior cingulate cortex (BA24) | 147 | 0.0167 | 0.6 | 0.0140 |
| Thyroid | 574 | 0.0147 | 0.5 | 0.00800 |
| Adipose - Subcutaneous | 581 | 0.0142 | 0.6 | 0.00 |
| Brain - Hypothalamus | 170 | 0.0119 | 0.8 | 0.0510 |
| Skin - Sun Exposed (Lower leg) | 605 | 0.00851 | 0.7 | 0.0110 |
| Stomach | 324 | 0.00734 | 0.8 | 0.00800 |
| Brain - Nucleus accumbens (basal ganglia) | 202 | 0.00651 | 0.8 | 0.0300 |
| Brain - Frontal Cortex (BA9) | 175 | 0.00300 | 0.9 | 0.0160 |
| Adipose - Visceral (Omentum) | 469 | 0.00231 | 0.9 | 0.0170 |
| Skin - Not Sun Exposed (Suprapubic) | 517 | -0.00353 | 0.9 | 0.0170 |
| Breast - Mammary Tissue | 396 | -0.00388 | 0.9 | 0.0380 |
| Brain - Cerebellum | 209 | -0.00566 | 0.9 | 0.0390 |
| Brain - Cortex | 205 | -0.00855 | 0.8 | 0.0120 |
| Uterus | 129 | -0.0103 | 0.9 | 0.0880 |
| Spleen | 227 | -0.0110 | 0.8 | 0.0210 |
| Nerve - Tibial | 532 | -0.0175 | 0.4 | 0.0390 |
| Brain - Caudate (basal ganglia) | 194 | -0.0178 | 0.6 | 0.0370 |
| Colon - Transverse | 368 | -0.0215 | 0.5 | 0.0990 |
| Brain - Putamen (basal ganglia) | 170 | -0.0219 | 0.5 | 0.0610 |
| Pituitary | 237 | -0.0266 | 0.4 | 0.0560 |
| Adrenal Gland | 233 | -0.0272 | 0.5 | 0.130 |
| Artery - Coronary | 213 | -0.0274 | 0.6 | 0.149 |
| Pancreas | 305 | -0.0274 | 0.4 | 0.0530 |
| Lung | 515 | -0.0297 | 0.3 | 0.0730 |
| Brain - Cerebellar Hemisphere | 175 | -0.0423 | 0.2 | 0.190 |
| Cells - Cultured fibroblasts | 483 | -0.0499 | 0.07 | 0.209 |
| Testis | 322 | -0.0530 | 0.008 | 0.576 |
| Prostate | 221 | -0.0547 | 0.1 | 0.174 |
| Whole Blood | 670 | -0.0666 | 0.006 | 0.697 |
| Colon - Sigmoid | 318 | -0.0747 | 0.07 | 0.234 |
| Cells - EBV-transformed lymphocytes | 147 | -0.0893 | 0.5 | 0.231 |
| Esophagus - Muscularis | 465 | -0.120 | 3.3e-5 | 0.987 |
| Esophagus - Gastroesophageal Junction | 330 | -0.149 | 2.7e-3 | 0.812 |

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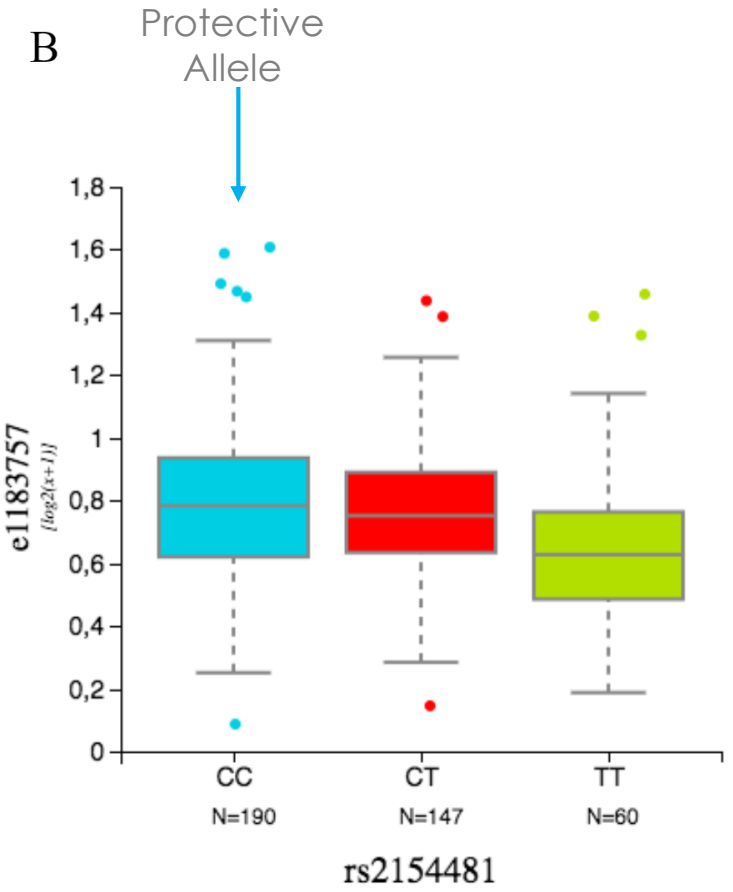


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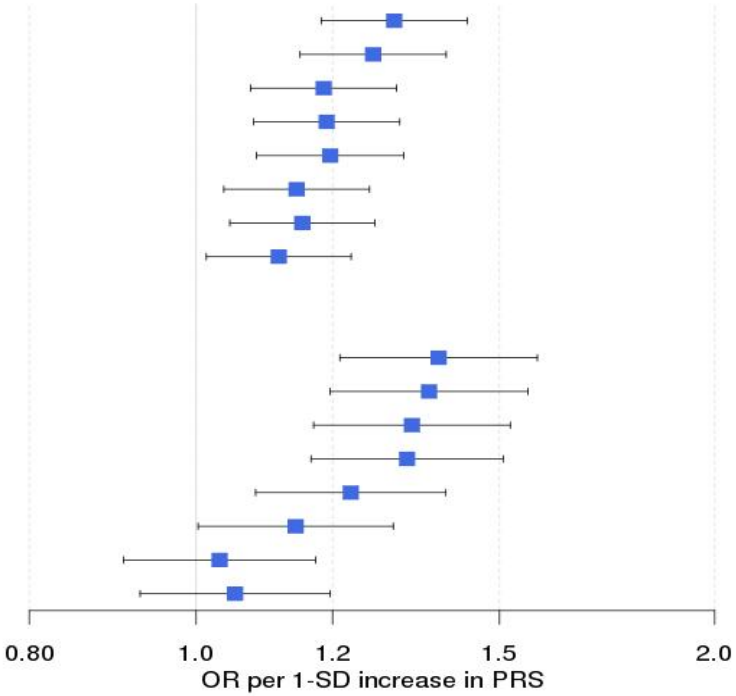
Expression for *APP* eQTL. A) Differential tissue expression for APP eQTL according to GTEx. B) Expression of the APP transcript in the brain according to BrainSeq

# PRS using the 39 common variants valdiated to date

**A**

| Clinical AD | N-variants | OR [95% CI] | P-value |
|---|---|---|---|
| All studies p<5e-8 | 39 | 1.30 [1.18-1.44] | 1.1e-07 |
| Excluding novel | 32 | 1.27 [1.15-1.40] | 2.1e-06 |
| Kunkle 2019 p<1e-7 | 23 | 1.19 [1.08-1.31] | 6.2e-04 |
| Kunkle 2019 p<1e-6 | 33 | 1.19 [1.08-1.31] | 4.7e-04 |
| Kunkle 2019 p<1e-5 | 61 | 1.20 [1.08-1.32] | 3.6e-04 |
| Kunkle 2019 p<1e-4 | 191 | 1.14 [1.04-1.26] | 6.9e-03 |
| Kunkle 2019 p<1e-3 | 540 | 1.15 [1.05-1.27] | 4.1e-03 |
| Kunkle 2019 p<1e-2 | 1085 | 1.12 [1.01-1.23] | 2.5e-02 |

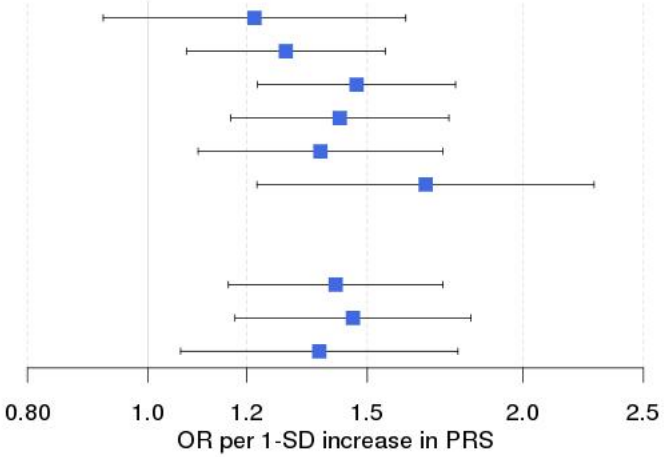
| Pathologic AD | N-variants | OR [95% CI] | P-value |
|---|---|---|---|
| All studies p<5e-8 | 39 | 1.38 [1.21-1.58] | 1.5e-06 |
| Excluding novel | 32 | 1.37 [1.20-1.56] | 4.0e-06 |
| Kunkle 2019 p<1e-7 | 23 | 1.33 [1.17-1.52] | 1.7e-05 |
| Kunkle 2019 p<1e-6 | 33 | 1.33 [1.17-1.51] | 1.7e-05 |
| Kunkle 2019 p<1e-5 | 61 | 1.23 [1.08-1.40] | 1.5e-03 |
| Kunkle 2019 p<1e-4 | 191 | 1.14 [1.00-1.30] | 4.6e-02 |
| Kunkle 2019 p<1e-3 | 540 | 1.03 [0.91-1.17] | 6.3e-01 |
| Kunkle 2019 p<1e-2 | 1085 | 1.05 [0.93-1.20] | 4.2e-01 |




**B**

| Concomitant pathologies: | N-cases | OR [95% CI] | P-value |
|---|---|---|---|
| Only AD pathology | 54 (16%) | 1.22 [0.92-1.61] | 1.7e-01 |
| Cerebrovascular disease | 145 (44%) | 1.29 [1.07-1.55] | 6.6e-03 |
| Lewy body disease | 140 (42%) | 1.47 [1.22-1.77] | 3.7e-05 |
| Microscopic vascular lesions | 118 (36%) | 1.43 [1.17-1.74] | 5.7e-04 |
| TDP43 aggregates | 87 (26%) | 1.38 [1.10-1.72] | 5.8e-03 |
| Hippocampal sclerosis | 43 (13%) | 1.67 [1.22-2.28] | 1.3e-03 |

| Number of concomitant pathologies: | N-cases | OR [95% CI] | P-value |
|---|---|---|---|
| AD + single pathology | 116 (35%) | 1.41 [1.16-1.73] | 6.1e-04 |
| AD + two pathologies | 95 (29%) | 1.46 [1.17-1.82] | 6.7e-04 |
| AD + three and more pathologies | 67 (20%) | 1.37 [1.06-1.77] | 1.6e-02 |

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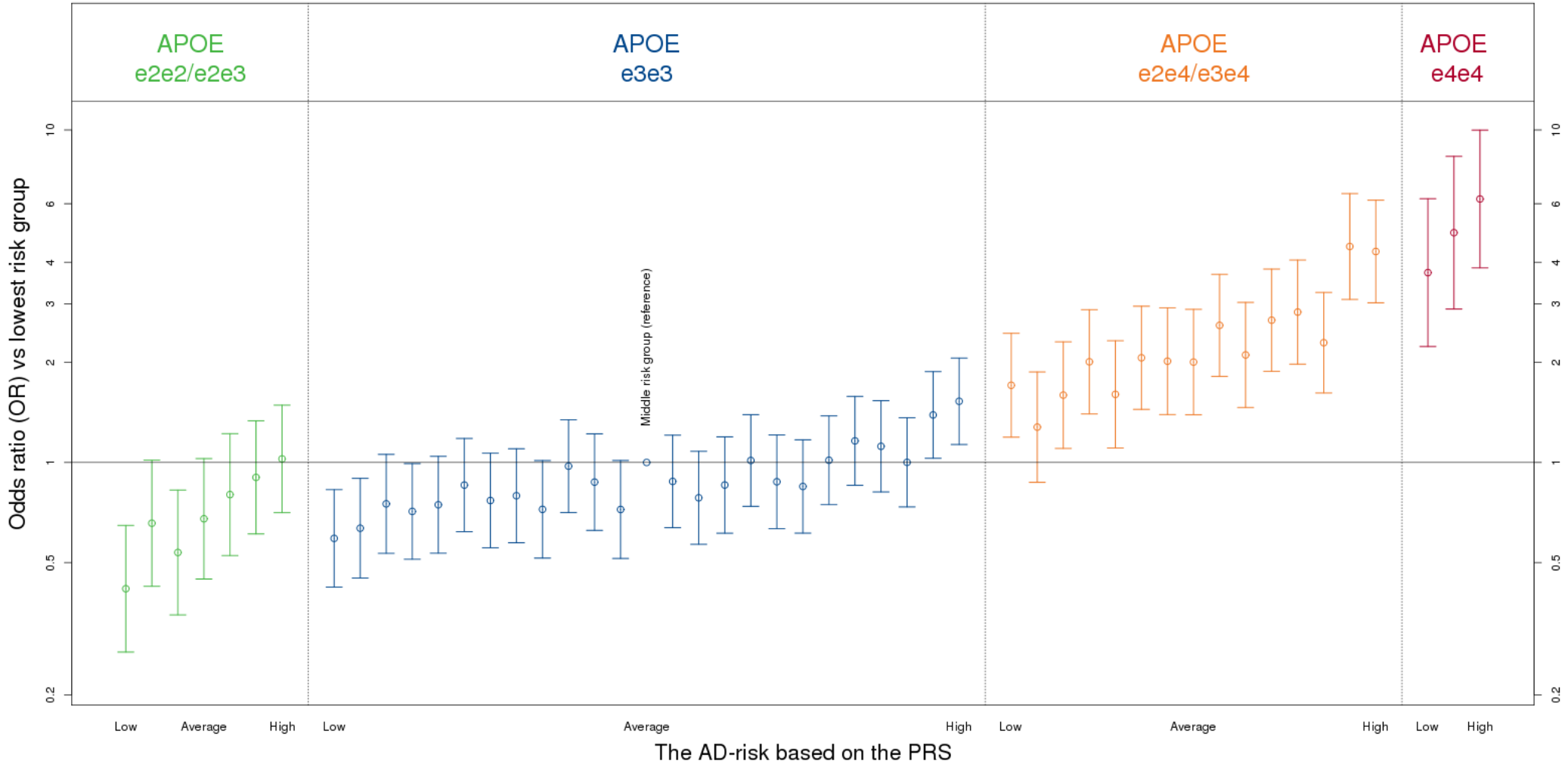
# PRS-39 effect on risk in GR@ACE/DEGESCO dataset stratified by *APOE*

n = 12,386

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DEGESCO
Dementia Genetics Spanish Consortium

gr@ace
Genome research at
Fundació ACE

# Collaborations. What's next?

- EADB collaboration
  - JC Lambert: AD GWAS (case-Control study)
  - A. Ramírez: MCI progression analysis (longitudinal study)
  - P. Kehoe: Vascular Dementia (case-control study)

- Collaboration with Dr. Cruchaga/Dr. Fernández/Dr. Harari (Washington University)
  - arAD loci detection
  - pQTL analyses of CSF proteins & multiomics

- Hispanic meta-GWAS ongoing- Collaboration with Dr. Tosto (Columbia University)

- APOE-stratified studies are underway
  - Collaboration with Dr. Jun and Farrer (Boston University)
  - Collaboration with IMI2-ADAPTED (EU Project)

- AD+P phenotype collaboration with Dr. Robert Sweet (U. Pittsburgh)

- Collaboration with Dr. Seshadri for WGS (Glenn Biggs Institute. Tx. UTHSA)

# Conclusions

- GR@ACE Stage I GWAS identified at least three **different groups of AD loci**. This discovery when confirmed may have an impact on GWAS analysis interpretation, patient classification and drug development.
- dbGAP meta-GWAS detected a new locus close to ***HMGCR.*** It needs independent replication.
- Exploration of IGAP grey zone confirmed ***TP53INP1/NDUFAF6*** **locus** associated with AD.
- **Seven GWAS-significant hits** forAD have been confirmed combining GR@ACE,IGAP,UKBiobank estimates and replication in EADB-PGC cohorts (ms in preparation).
- **PRS** with 39 common SNPs, permitted patient stratification.
- More genotyping (**Stage II still underway**) to increase gene discoveries.
- Multiple collaborations are underway to explore data generated.
- GR@ACE Stage I dataset released to the public domain via **European Genome Phenome Archive (https://www.ebi.ac.uk/ega/home)**

# Anonymous and altruistic patients & families

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## GR@ACE team. People involved

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   - F.ACE Nurse Station
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   - Victor Andrade M.S.
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Hi collabora:

Agustín Ruiz | Fundació ACE