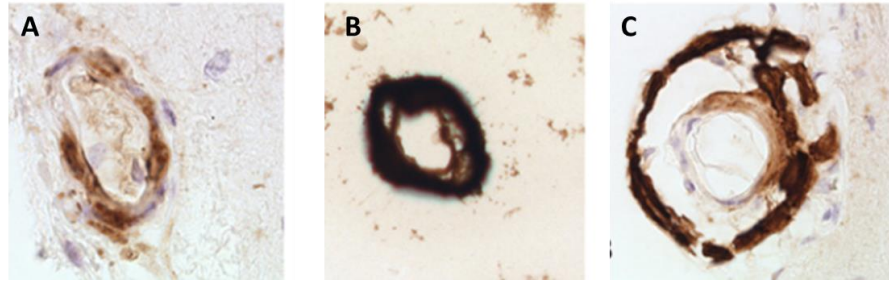# Asociación de variantes genéticas y niveles circulantes de ApoE/ApoJ con características de neuroimagen de la Angiopatía Amiloide Cerebral

ANNA BONATERRA PASTRA

Neurovascular Research Lab
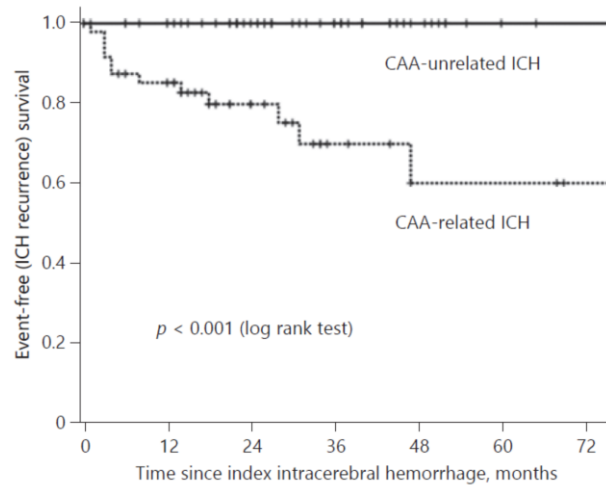Vall d'Hebron Institut de Recerca (VHIR),
Barcelona

08/05/2023 - RICORS

Angiopatía Amiloide Cerebral (AAC)

Charidimou et al., 2012

Depósitos de Aβ en las paredes de los vasos sanguíneos del SNC.

Hemorragia Intracerebral (HIC) lobar / subaracnoidea

Pinho et al., 2021

Recurrencia de HIC

Episodios neurológicos focales transitorios

Motores

Somatosensoriales

Visuales

Del lenguaje

Deterioro cognitivo / Demencia

Pérdida de función cognitiva

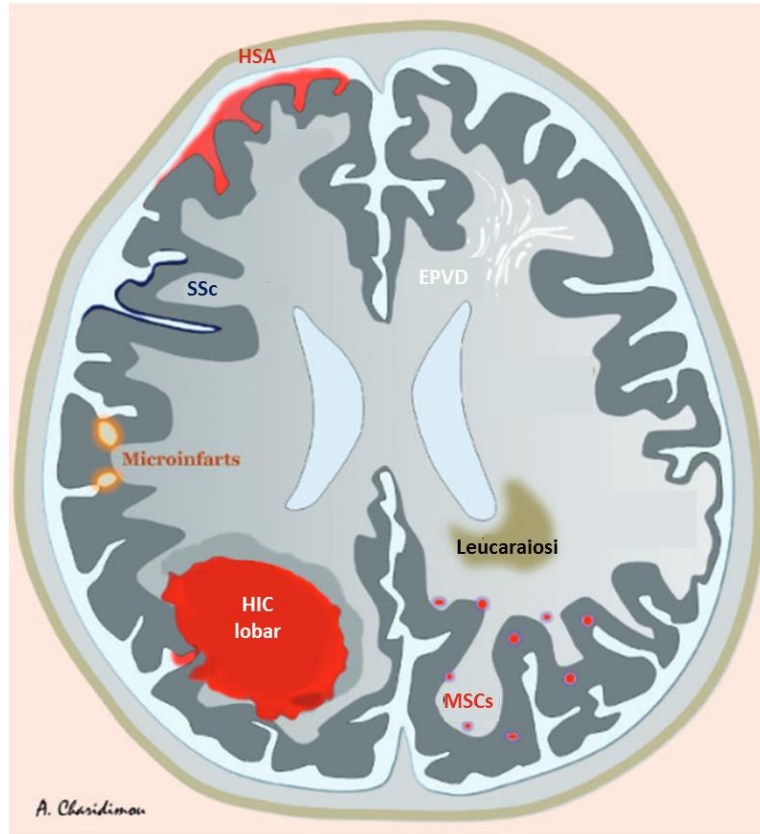Deterioro de memoria episódica

Menor velocidad de percepción

Charidimou et al., 2017

Smith et al., 2021

Boyle et al., 2015

Marcadores de resonancia magnética de la AAC

Charidimou et al., 2017

CAA-SVDB

Escala 0-6 puntos:

...ORES HEMORRÁGICOS

- **Microsangrados lobares:**

  1 punto : 2-4

  ...angrados corticales (MSCs) o lobares
  2 punto >5

  ...sis superficial cortical (SSc)

- **Siderosis superficial cortical (SSc):**

  1 punto : focal

  2 puntos: diseminada

...ORES NO HEMORRÁGICOS

...raiosis o lesiones de substancia blanca

- **Espacios perivasculares dilatados (EPVD) en el Centrum Semiovale (CSO)**

  ...ios perivasculares dilatados (EPVD) en
  1 punto : >20

  ...trum Semiovale (CSO)

- **Lesiones de la substancia blanca (LSB) o leucaraiosis:**

  1 punto: profundas (Fazekas 2-3)
  o periventriculares (Fazekas 3)
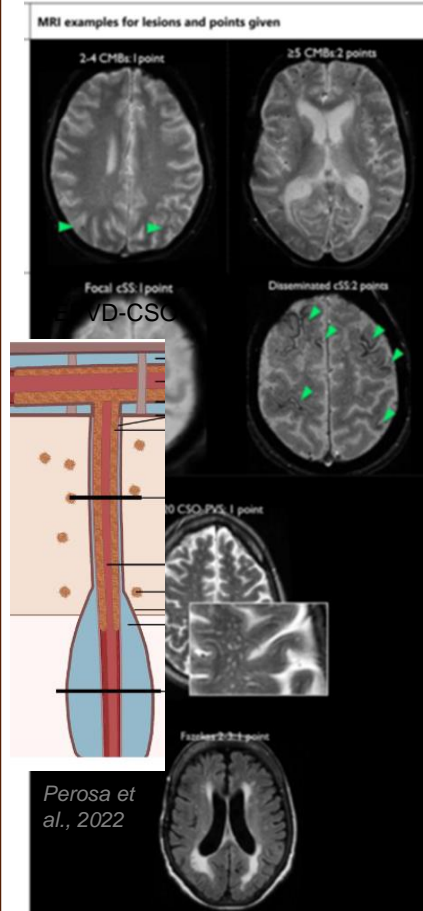
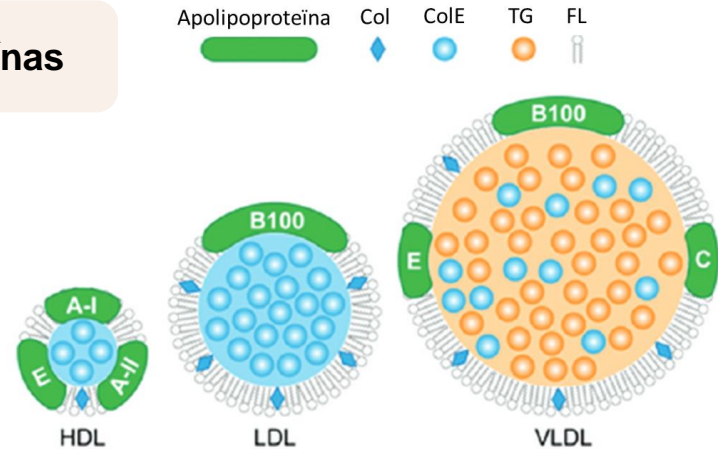*Charidimou et al., 2016*

Metabolismo lipídico

Lipoproteínas

Apolipoproteïna   Col   ColE   TG   FL

Bricarello et al., 2011

Hemorragia intracerebral

↓ colesterol

↓ colesterol LDL

↑ cholesterol HDL

Apolipoproteínas

ApoE

APOEε2 — Protector para la **Enfermedad de Alzheimer (EA)** y de riesgo para una HIC asociada a la **AAC** *Corder et al., 1994; Greenberg et al., 1998.*

APOEε3

APOEε4 — Principal factor de riesgo genético para la **EA** y la **AAC** esporádica *Schmechel et al., 1193; Greenberg et al., 1996*

Zhu et al., 2019   Reed et al., 2014   Button et al., 2019   Pezzini et al., 2016   Rodriguez-Luna et al., 2011
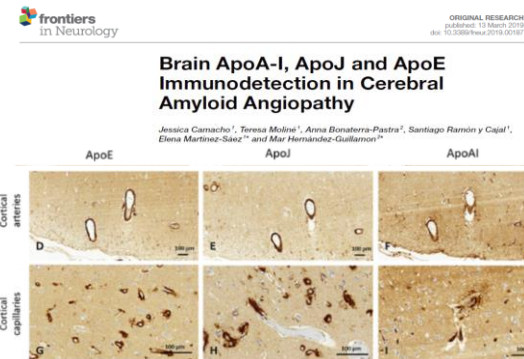
Apolipoproteínas

ApoE

o Involucrada en la agregación y aclaramiento de Aβ *DeMattos et al., 2004; Bales et al., 1997, Holtzman et al., 1999; Deane et al., 2008.*

o Codeposita con Aβ cerebrovascular y parenquimatoso *Hondius et al., 2018.*

Otras apolipoproteínas involucradas en la β-amiloidosis cerebral

Camacho et al., 2019

ApoJ

o Codeposita con Aβ cerebrovascular y parenquimatoso *Matsubara et al., 1996, Lidstrom et al., 1998; Howlett et al., 2013; Manousopoulou et al., 2017; Miners et al., 2017; Hondius et al., 2018; Camacho et al., 2019.*

o Variantes genéticas de CLU son factores de riesgo o protectores para la Enfermedad de Alzheimer *Harold et al., 2009; Lambert, 2013.*

o Chaperona que puede prevenir la fibrilogénesis de Aβ y su toxicidad in vitro *Beef et al., 2016; Yerbury et al., 2007.*

o Aumentar los niveles de ApoJ *in vivo* tiene un efecto modulador de los niveles de Aβ *Wojtas et al., 2020; Qi et al., 2018; Montoliu-Gaya et al., 2018; Chen et al., 2012; Fernandez-de retana et al., 2018.*

frontiers

Association of candidate genetic variants and circulating levels of ApoE/ApoJ with common neuroimaging features of Cerebral Amyloid Angiopathy

Anna Bonaterra-Pastra[1], Sònia Benítez[2,3], Olalla Pancorbo[4], David Rodríguez-Luna[4], Carla Vert[5], Alex Rovira[5], M. Mar Freijo[6], Silvia Tur[7], Maite Martínez-Zabaleta[8], Pere Cardona Portela[9], Rocío Vera[10], Lucia Lebrato-Hernández[11], Juan F. Arenillas[12,13], Soledad Pérez-Sánchez[14], Ana Domínguez-Mayoral[14], Joan Martí Fàbregas[15], Gerard Mauri[16], Joan Montaner[1,17,18], Jose Luis Sánchez-Quesada[2,3]* and Mar Hernández-Guillamon[1]*

Objetivo

Identificar posibles asociaciones entre marcadores genéticos candidatos y la distribución de ApoJ y ApoE en lipoproteínas plasmáticas con características radiológicas características de la AAC detectadas por RM en una cohorte de pacientes con HIC lobar.

Hipótesis: Variantes genéticas asociadas con la **Enfermedad de Alzheimer** podrían estar asociadas con marcadores de AAC

HIC-AAC

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

*Nat Genet*. 2011 May ; 43(5): 429–435. doi:10.1038/ng.803.

Common variants in *MS4A4/MS4A6E, CD2uAP, CD33*, and *EPHA1* are associated with late-onset Alzheimer's disease

Nat Genet. 2011 May ; 43(5): 436–441. doi:10.1038/ng.801.

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

Nat Genet. 2013 December ; 45(12): 1452–1458. doi:10.1038/ng.2802.

SNPs a 15 genes
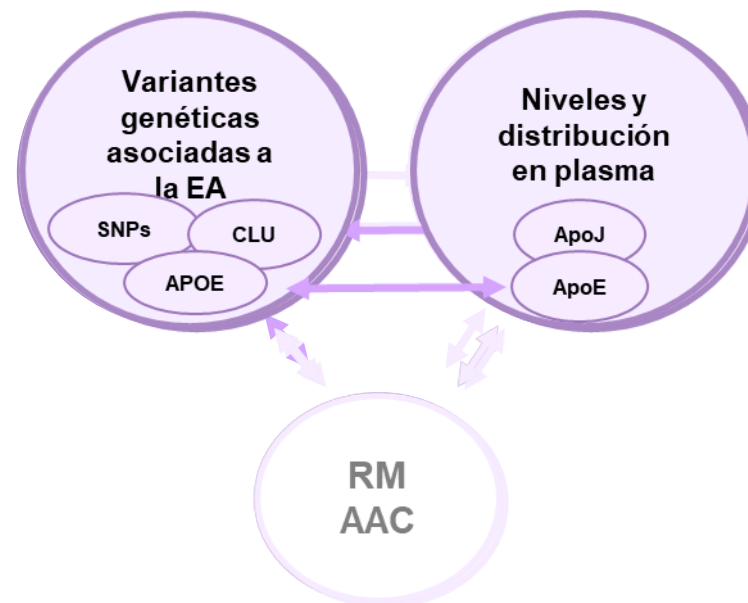
Población de estudio

HIC-AAC

Criterios de inclusión

o ≥ 55 años

o Al menos 1 HIC lobar

o Disponibilidad de RM o muestra histopatológica cerebral

o Consentimiento informado

Criterios de exclusión

o HIC profunda

o Tratamiento anticoagulante

o Hospital Universitari Vall d'Hebron, Barcelona

o Hospital Universitari Son Espasses, Iles Balears

o Hospital Universitario Donostia, Guipúscoa

o Hospital Universitario de Cruces. Bizkaia

o Hospital Universitari de Bellvitge, Barcelona

o Hospital Universitario Ramón y Cajal, Madrid

o Hospital Universitario Virgen del Rocío, Sevilla

o Hopital Clínico Universitario, Valladolid

o Hospital Universitario Virgen Macarena, Sevilla

o Hospital de la Santa Creu i Sant Pau, Barcelona

o Hospital Universitari Arnau de Vilanova de Lleida, Lleida

Instituto de Salud Carlos III

ICH-CAA patients (n=126)

Age, years	76.21 ± 7.110
Sex (Females)	68 (54%)
HTA	72 (60%)
DM	18 (15.7%)
DL	38 (37.6%)
Cognitive impairment	56 (49.6%)
Corticosubcortical ICH	125 (99.2%)
>2	13 (10.4%)
>3	6 (4.8%)
ICH Recurrence	20 (17.7 %)

Table 1. Demographic and clinical characteristics. Data are expressed as n (%). ICH: Intracerebral Hemorrhage; HT: Hypertension; DM: Diabetes Mellitus; DL: Dyslipidemia.
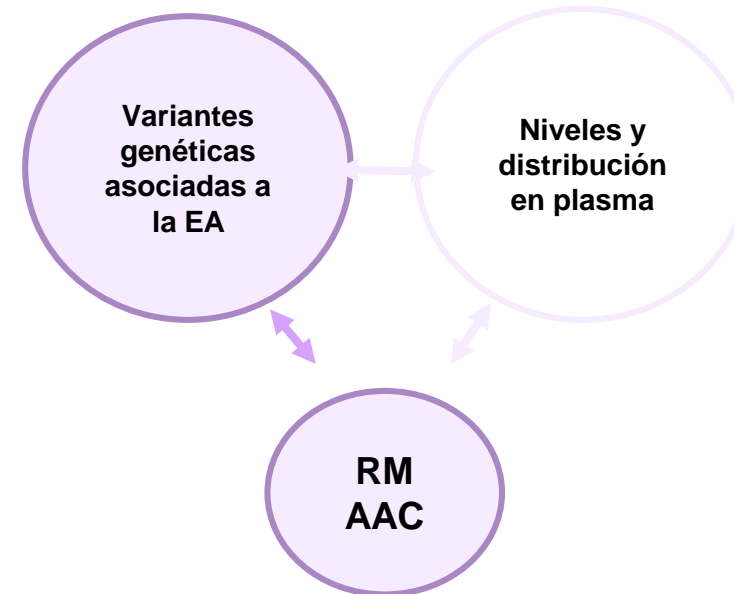
10.42 ± 16.77 meses
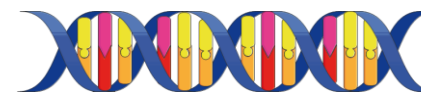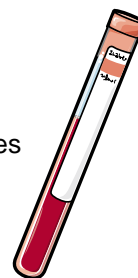
6.70 ± 16.79 meses

Características radiológicas

HIC-AAC

RMN (n=118)	
cSS	50 (42.4%)
Focal	15 (30%)
Disseminated	35 (70%)
EPVS	109 (92.4%)
BG-EPVS	106 (97.25%)
Low degree (1-20)	85 (80.2%)
High degree (21->40)	21 (19.8%)
CSO-EPVS	88 (80.7%)
Low degree (1-20)	45 (51.1%)
High degree (21->40)	43 (48.9%)
CMB	73 (61.9%)
Lobar CMB	69 (94.52%)
1-5	25 (36.23%)
6-10	12 (17.39%)
11-20	7 (10.14%)
>20	25 (36.23%)
Deep CMB	14 (19.18%)
1 - 5	12 (85.7%)
6 - 10	1 (7.1%)
11 - 20	1 (7.1%)
>20	0 (0%)
Cerebellum CMB	15 (20.5%)
1 - 5	12 (80%)
6 - 10	3 (20%)
11 - 20	0 (0%)
>20	0 (0%)
WMH	108 (91.5%)
Periventricular	97 (89.8%)
Caps or pencil/thin lining (1)	24 (24.7%)
Smooth halo or irregular periventricular (2-3)	73 (75.3%)
Deep	98 (90.7%)
Punctate foci (1)	43 (43.9%)
Beginning or large confluent areas (2-3)	55 (56.1%)
Cortico-subcortical atrophy	44 (37.3%)
Mild	29 (65.9%)
Moderate	13 (29.5%)
Severe	2 (4.5%)

Variantes genéticas asociadas a la EA

Niveles y distribución en plasma

RM AAC

MRI-imaging characteristics of a lobar ICH cohort with clinical suspicion of CAA (N = 118). The percentages displayed are within each category. cSS: cortical superficial siderosis; EPVS: Enlarged perivascular spaces; BG: Basal ganglia; CSO: Centrum semiovale; CMB: Cerebral microbleeds; WMH: White matter hyperintensity. Data are expressed as n (%).

Asociaciones genéticas

HIC-AAC

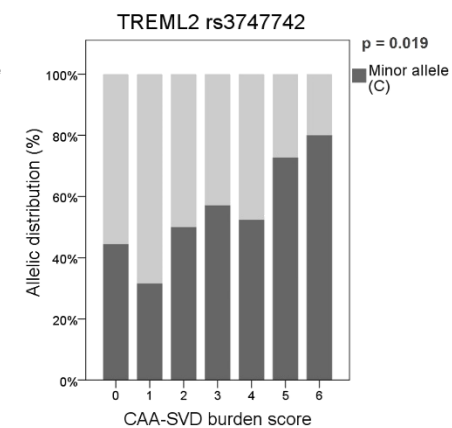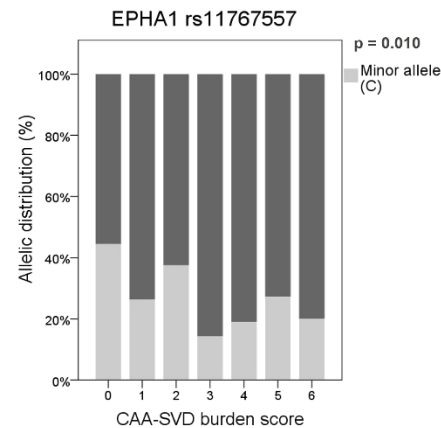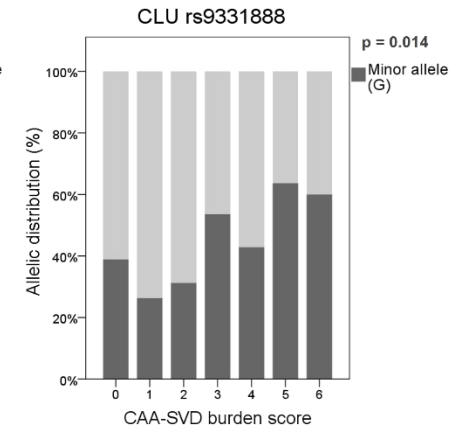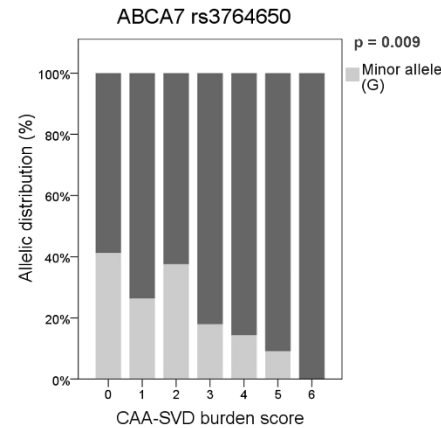|	Genetic and clinical variables	Common dominant model		Additive model	
		OR (95% CI)	p-value	OR (95% CI)	p-value
cSS	**CLU** rs9331888 (G allele, MA)	**2.490 (1.175 – 5.278)**	**0.017**	**1.889 (1.033 – 3.454)**	**0.039**
cSS extent	**CD2AP** rs10948363 (G allele, MA)	**0.188 (0.042 – 0.836)**	**0.028**	–	–
	CD2AP rs9349407 (C allele, MA)	–	–	0.150 (0.039 – 0.581)	0.006
	CLU rs11136000 (T allele, MA)	**6.722 (1.500 – 30.127)**	**0.013**	**8.264 (1.698 – 40.000)**	**0.009**
CSO-EPVS	–	–	–	–	–
High degree CSO-EPVS	CLU rs7012010 (C allele, MA)	2.370 (1.073 – 5.237)	0.033	1.935 (1.082 – 3.462)	0.026
BG-EPVS	–	–	–	–	–
High degree BG-EPVS	CD33 rs3865444 (A allele, MA)	–	–	3.333 (1.437 – 7.752)	0.005
Lobar CMB	**ABCA7** rs3764650 (G allele, MA)	**0.313 (0.126 – 0.778)**	**0.012**	**0.290 (0.115 – 0.728)**	**0.008**
	CLU rs7012010 (C allele, MA)	2.185 (1.006 – 4.749)	0.048	1.853 (1.016 – 3.378)	0.044
Lobar CMB >5	ABCA7 rs3764650 (G allele, MA)	0.323 (0.110 – 0.945)	0.039	–	–
	CLU rs11136000 (T allele, MA)	–	–	0.503 (0.278 – 0.911)	0.023
	TREML2 rs3747742 (C allele, MA)	2.306 (1.44 – 5.092)	0.039	1.918 (1.095 – 3.362)	0.023
High deep WMH burden	**CR1** rs6701713 (A allele, MA)	0.420 (0.177 – 0.994)	0.048	0.419 (0.191 – 0.919)	0.030
	CLU rs9331888 (G allele, MA)	3.054 (1.404 – 6.642)	0.005	2.351 (1.234 – 4.478)	0.009
High periventricular WMH burden	CLU rs9331888 (G allele, MA)	2.673 (1.211 – 5.897)	0.015	–	–
	CLU rs9331896 (C allele, MA)	–	–	0.478 (0.270 – 0.848)	0.012
Atrophy	BIN1 rs6733839 (T allele, MA)	0.307 (0.132 – 0.715)	0.002	0.457 (0.237 – 0.881)	0.019
	CD2AP rs10948363 (G allele, MA)	0.257 (0.111 – 0.595)	0.006	0.359 (0.170 –0.755)	0.007
	CLU rs7012010 (C allele, MA)	–	–	2.101 (1.125 – 3.924)	0.020
CAA-Small vessel disease burden score	ABCA7 rs3764650 (G allele, MA)	0.261 (0.096 – 0.711)	0.009	0.284 (0.105 – 0.764)	0.013
	CLU rs9331896 (C allele, MA)	–	–	0.470 (0.251 – 0.879)	0.018
	CLU rs9331888 (G allele, MA)	2.921 (1.246 – 6.851)	0.014	–	–
	EPHA1 rs11767557 (C allele, MA)	0.285 (0.109 – 0.744)	0.010	0.288 (0.118 – 0.698)	0.006
	TREML2 rs3747742 (C allele, MA)	2.787 (1.184 – 6.650)	0.019	1.963 (1.055 – 3.652)	0.033

Binary logistic regression for CAA MRI markers with SNPs minor alleles adjusting by sex and age. cSS: cortical Superficial Siderosis; EPVS: Enlarged Perivascular Spaces; CSO: Centrum Semiovale; CMB: Cerebral Microbleeds; WMH: White Matter Hyperintensity. OR: Odds Ratio. CI: Confidence Interval. MA: Minor allele.

CAA-SVDB

HIC-AAC

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CAA-Small vessel disease burden score

CAA-SVDB	n (%)
0	18 (15.3%)
1	19 (16.1%)
2	16 (13.6%)
3	28 (23.7%)
4	21 (17.8%)
5	11 (9.3%)
6	5 (4.2%)

Alelo protector

Alelo de riesgo

Asociaciones genéticas

HIC-AAC

| Genetic and clinical variables	Common dominant model		Additive model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
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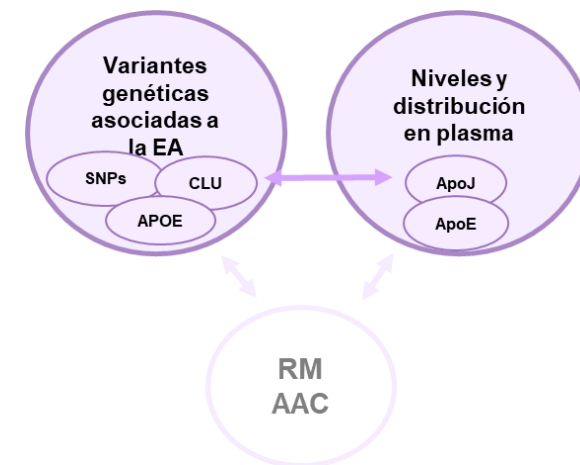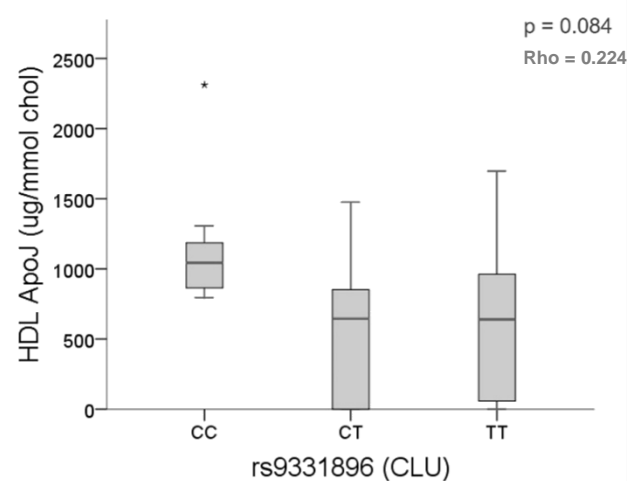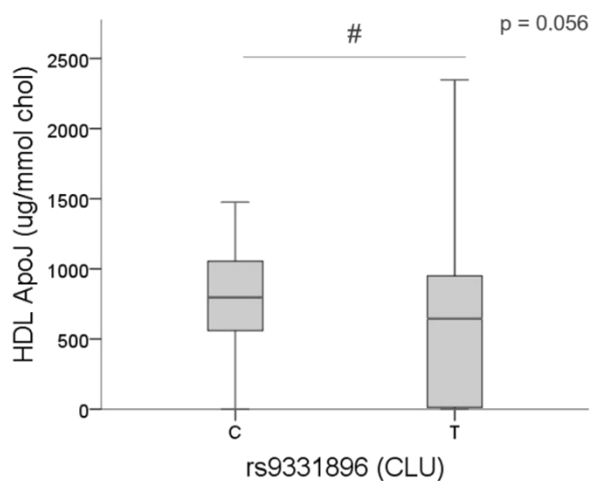
HIC-AAC

Relación entre CLU y niveles y distribución de ApoJ en plasma

HIC-AAC
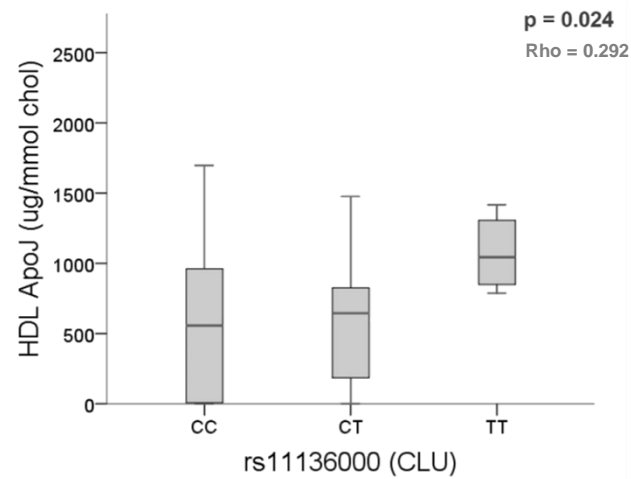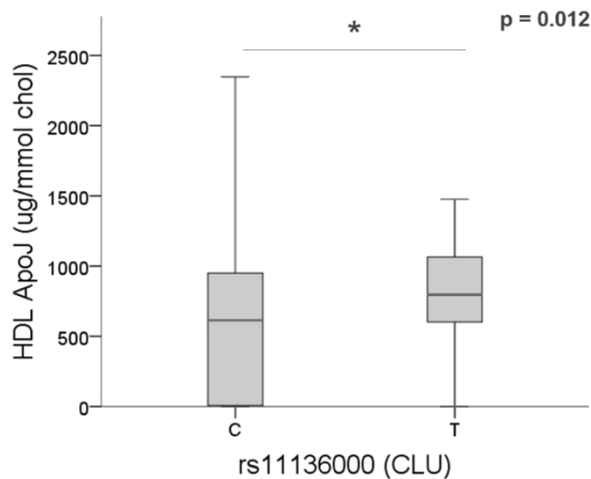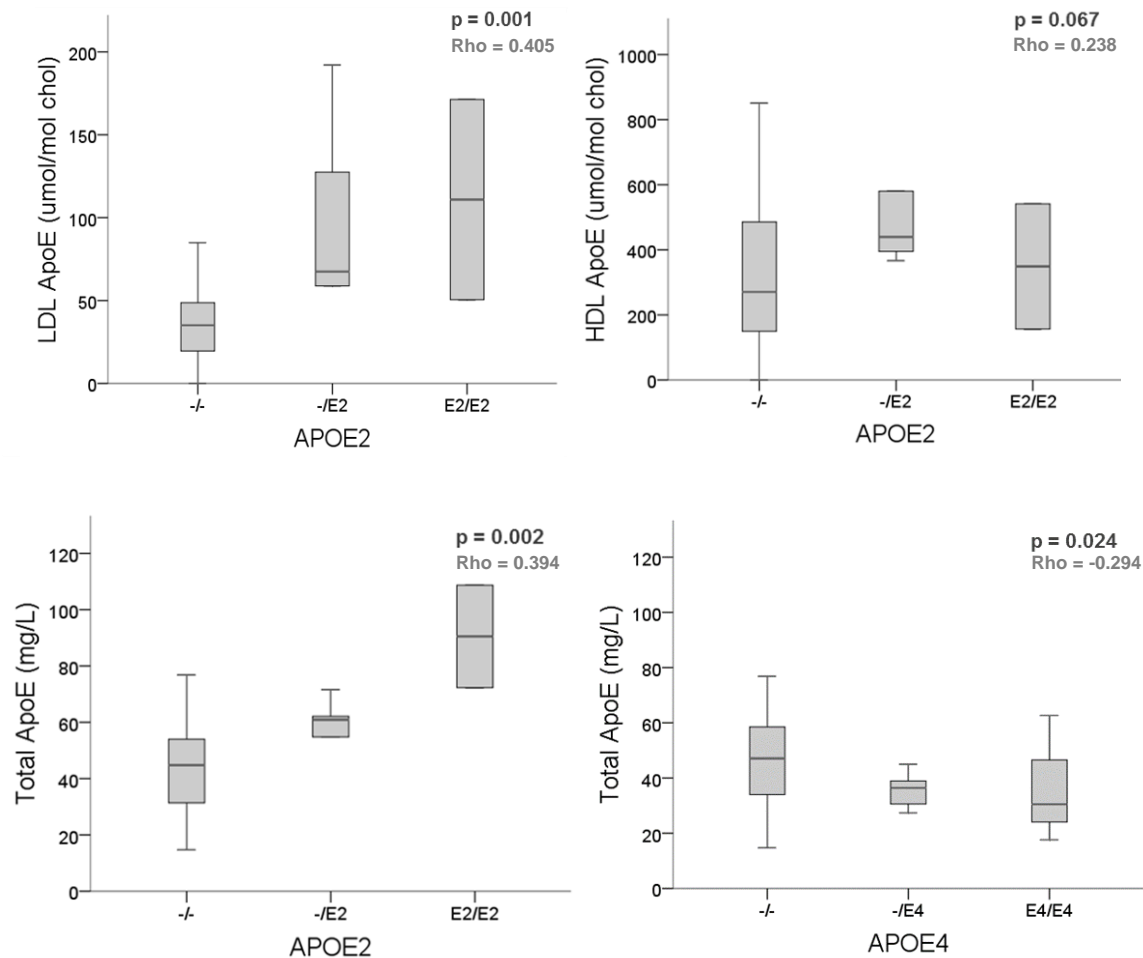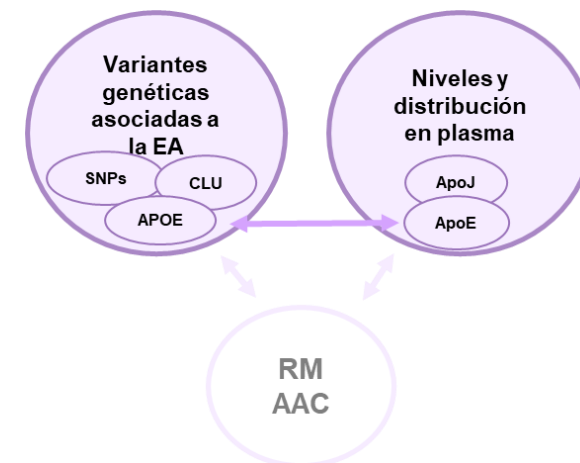
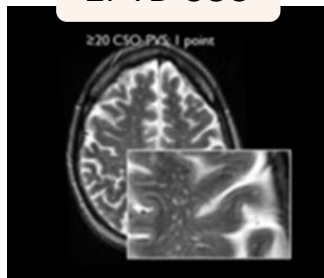# Relación entre APOE y niveles y distribución de ApoE en plasma

Niveles de ApoJ circulante y marcadores de RM

HIC-AAC

EPVD-CSO

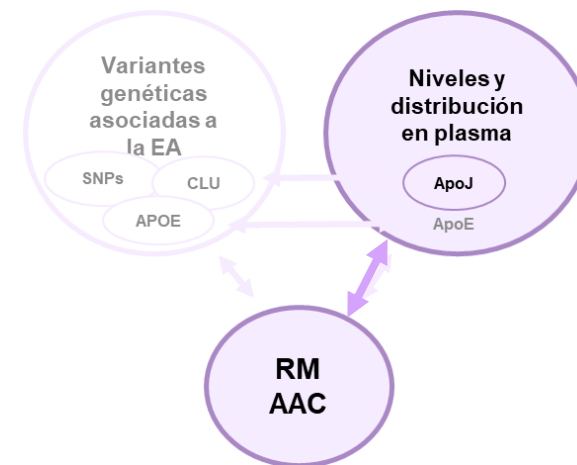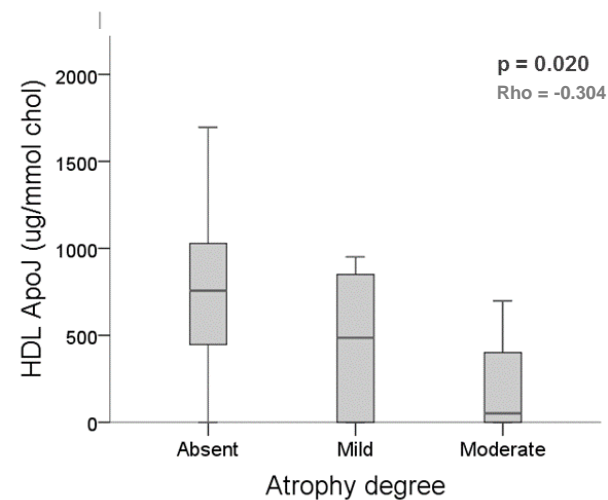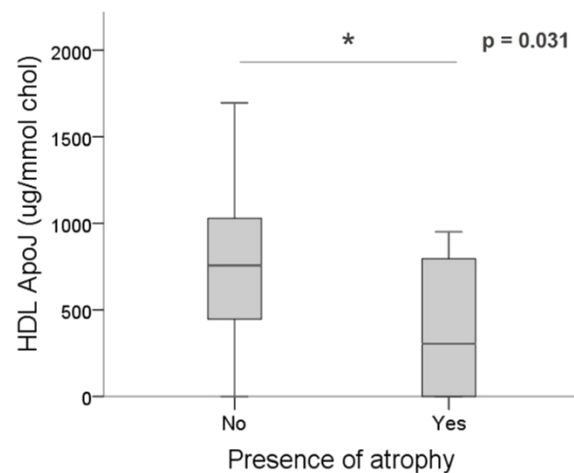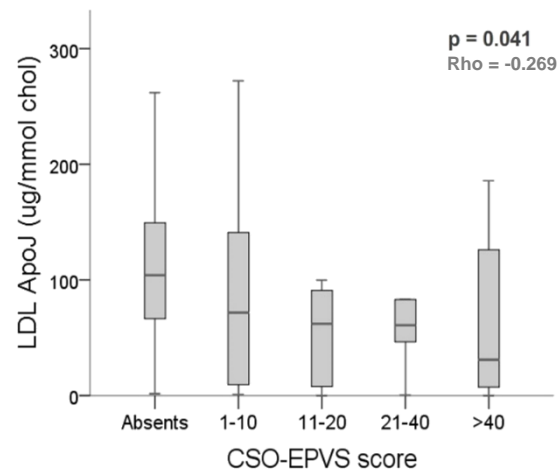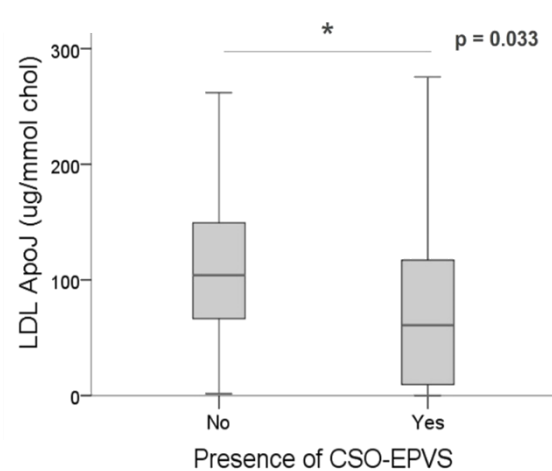*Charidimou et al., 2016*

Atrofia
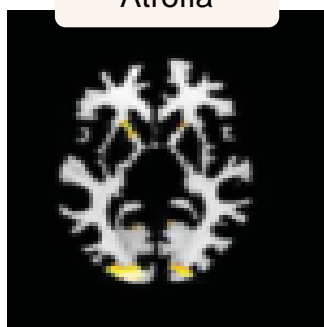
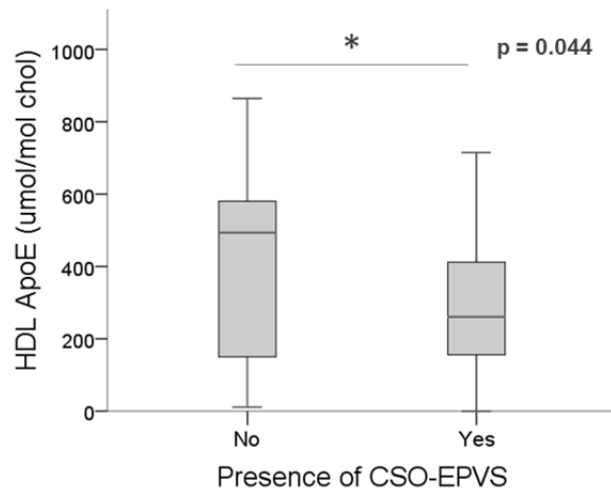*Fotiadis et al., 2020*

Niveles de ApoE circulante y marcadores de RM

HIC-AAC

EPVD-CSO
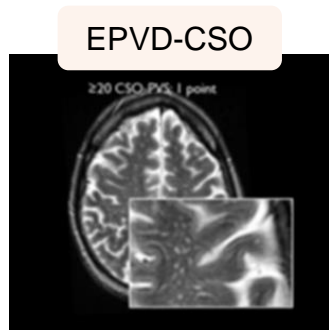
Charidimou et al., 2016

Conclusiones

HIC-AAC
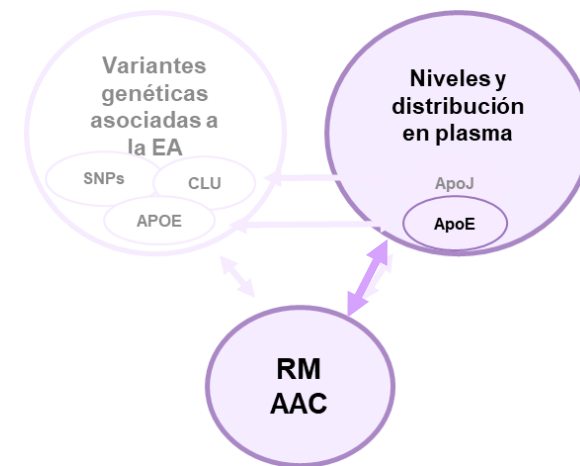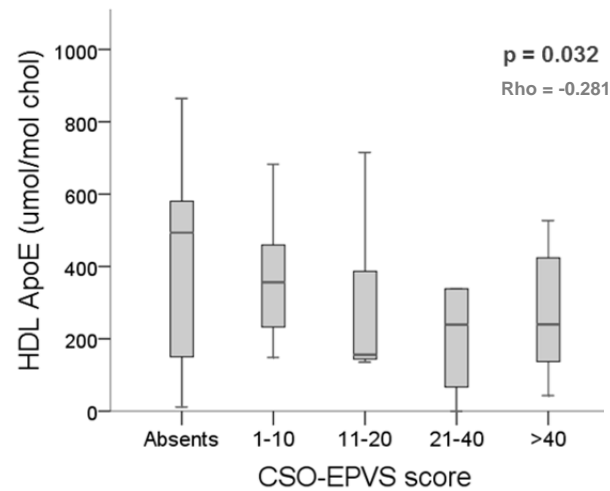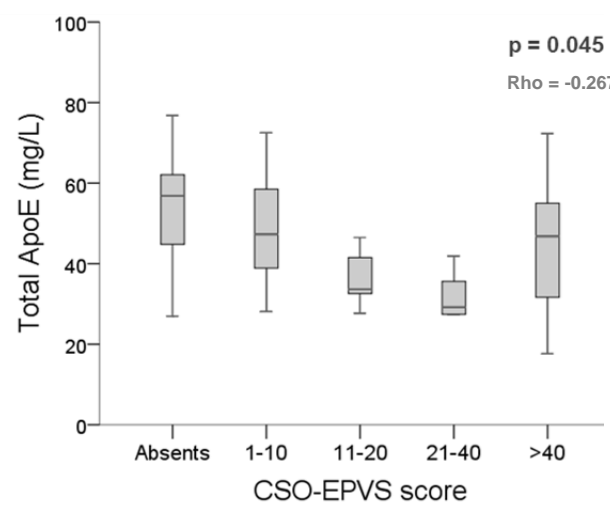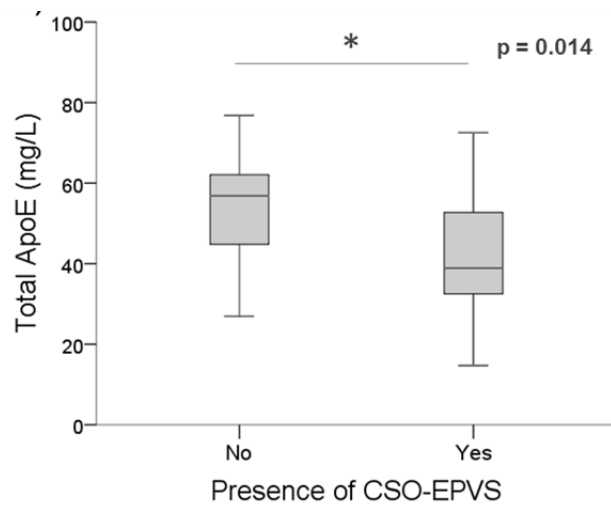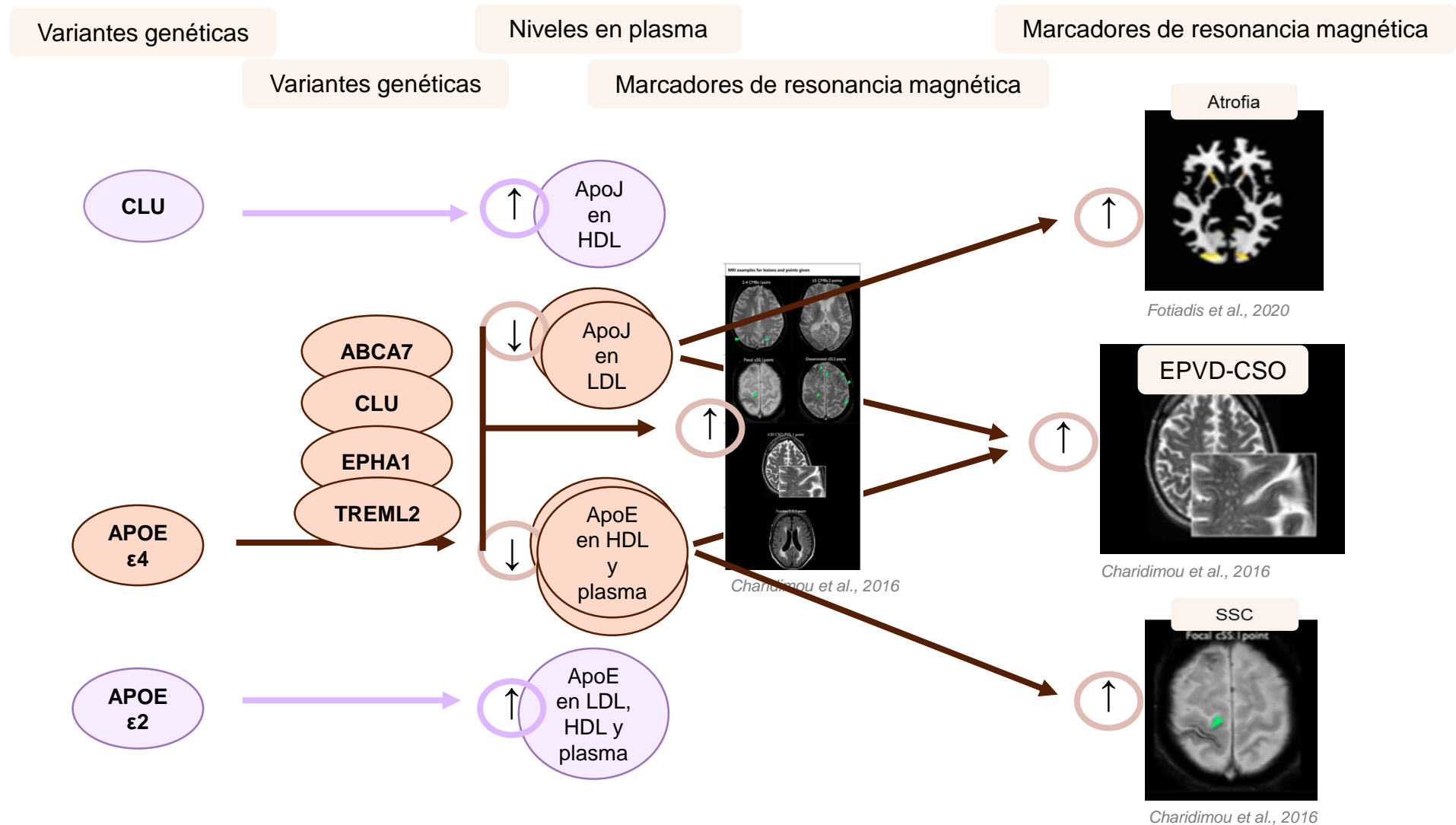
Este estudio refuerza la relevancia del metabolismo lipídico periférico en la AAC y la funcionalidad cerebrovascular.

MUCHAS GRACIAS!!

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