

Supplementary information online

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Supplemental Table 5: Association of the main haplotypes derived from rs2395760, rs991762 and rs4711652 in Chr. 6p21 in the EADI1 dataset.

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Supplementary Table 7: individual and meta-analysed association of rs7081208, rs2446581 and rs17314229 with AD risk (adjusted for age and gender).

Supplementary Figure 1: Association of SNP with AD risk in the FRMD4A locus under an additive model adjusted for age and gender using the French GWA data set. SNPs in red and blue, are respectively genotyped (n=304) and imputed (n=2,538).

Supplementary Figure 2: Association of rs7921545 and rs2446581 with $A\beta_{1-42}/A\beta_{1-40}$ level following meta-analyses of Z-score β coefficients under an additive model adjusted for age and gender using three independent healthy populations.

Supplementary Figure 3: Association of SNP in the *FRMD4A* locus with plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ levels following meta-analyses of Z-score β coefficients under an additive model adjusted for age and gender using three independent healthy populations. SNPs in red are nominally associated with A β peptide levels. SNPs in are the three markers defining the AAC haplotype assocated with AD risk.

DESCRIPTION OF THE POPULATIONS USED FOR THE GWHA STUDY

The stage 1 population:

The French GWA study (2,032 AD cases and 5,328 controls) has been described in detail elsewhere. Briefly, AD cases were ascertained by neurologists at Bordeaux, Dijon, Lille, Montpellier, Paris and Rouen university hospitals and were identified as French Caucasian¹. A clinical diagnosis of probable AD was established according to the DSM-III-R and NINCDS-ADRDA criteria². Controls were selected from the 3C Study³. The 3C Study is a population-based, prospective study of the relationship between vascular factors and dementia. It has been carried out in three French cities: Bordeaux (southwest France), Montpellier (south France) and Dijon (central eastern France). A sample of noninstitutionalised, over-65 subjects was randomly selected from the electoral rolls of each city. Between January 1999 and March 2001, 9686 subjects meeting the inclusion criteria agreed to participate. Following recruitment, 392 subjects withdrew from the study. Thus, 9294 subjects entered the study (2104 in Bordeaux, 4931 in Dijon and 2259 in Montpellier). At the baseline clinical examination, blood samples were obtained from 8414 individuals who were representative of the source population. Trained psychologists administered a battery of neuropsychological tests, including the Mini Mental State Examination (MMSE). All the participants in Bordeaux and Montpellier were examined by a neurologist at baseline. All control participants were monitored for 4 years and did not develop dementia during this time period.

The stage 2 population

The GERAD1 sample comprised up to 3,941 AD cases and 7,848 controls⁴. It notably included 4113 cases and 1602 screened, elderly controls genotyped at the Sanger Institute. These samples were recruited by the Medical Research Council (MRC) Genetic Resource for AD (Cardiff University; Institute of Psychiatry, London; Cambridge University; Trinity College Dublin), the Alzheimer's Research Trust (ART) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen's University Belfast; the Oxford Project to Investigate Memory and Ageing (OPTIMA), Oxford University; Washington University, St Louis, United States; the MRC PRION Unit, University College London; London and the South East Region AD project (LASER-AD), University College London; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany and the National Institute of Mental Health (NIMH) AD Genetics Initiative. These data were combined with data from 844 AD cases and 1255 elderly screened controls ascertained by the Mayo Clinic, Jacksonville, Florida, the Mayo Clinic, Rochester, Minnesota, and the Mayo Brain Bank (Mayo1 dataset). All AD cases met

the criteria for either probable AD (NINCDS-ADRDA², DSM-IV) or definite AD (CERAD⁵). All elderly controls were screened for dementia using the MMSE or the Alzheimer's Disease Assessment Scale-cognitive subscale and were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or below. A total of 6,825 unscreened population controls were included in GERAD1. These were drawn from large, existing cohorts with available GWA study datasets, including the 1958 British Birth Cohort (1958BC) (http://www.b58cgene.sgul.ac.uk), the NINDS-funded neurogenetics collection at Coriell Cell Repositories (Coriell) (see http://ccr.coriell.org/), the KORA F4 Study⁶, the Heinz Nixdorf Recall Study^{7,8} and ALS Controls.

The stage 3 populations

European Alzheimer's Disease Initiative case-control samples were obtained from centres in Finland (1 centre)⁹, Flanders-Belgium (1centre)¹⁰, Spain (4 centres)¹¹⁻¹⁴, Italy (10 centres)¹⁵⁻²³, Germany (1 centre)²⁴, Sweden (3 centres)^{25,26}. All clinical diagnoses of probable AD were established according to the DSM-III-R and NINCDS-ADRDA criteria². Controls were defined as subjects not meeting the DMS-III-R criteria for dementia and with unaffected cognitive functions (MMSE score >25). The cases and controls gave their written, informed consent to participation and the study protocols for all populations were reviewed and approved by the appropriate independent ethics committees.

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DESCRIPTION OF THE POPULATIONS USED FOR THE A β plasma study

Fasting plasma samples at inclusion were collected in tubes containing sodium EDTA as an anticoagulant. Following centrifugation, plasma samples were aliquoted into polypropylene tubes, stored at -80° C and only thawed immediately prior to A β quantification. In the 3C study, the plasma A β peptide assay was performed using the INNO-BIA plasma A β forms assay (Innogenetics, Ghent, Belgium) based on the multiplex xMAP technique with a LABScan-100 system (Luminex BV, The Netherlands).¹ In the Rotterdam study, plasma A β concentrations were determined by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) method.^{2,3}

The 3C study.¹ In the present work, the study population was based on a sub-cohort of 1254 subjects randomly selected from the source sample totalling 8,414 individuals (i.e. a sampling ratio of 15%) stratified by centre, 5-year age class and gender. A β plasma concentrations were measured in the whole sample [18]. Non-demented Individuals for whom at least one A β plasma concentration or co-variable measurement was missing were excluded, together with individuals exhibiting at least one aberrant A β plasma concentration measurement (Exclusion of values outside twice the 95% confidence interval values). These selection steps allowed us to define a sample of 840 individuals.

*The Rotterdam study.*² In this study the source population consisted of 6713 individuals who were followed up from baseline (1990–93) until the end of 2004 for incident dementia. From this source population a random subcohort of non-demented 1756 people was drawn Individuals for whom at least one aberrant A β plasma concentration measurement, at least one A β plasma concentration or co-variable measurement was missing were excluded, leading to define a sample of 1465 individuals.

The CHS study.³ This study includes 274 non-demented subjects recruited in 1998-1999 and no individuals were excluded according to the criteria used in the 3C and Rotterdam study. The main characteristics of the populations are described in Supplementary Table 2.

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	N	Controls Age ± sd	% Homme		N	Cases Age ± sd	% Homme
FADI1	5328	73.8 + 5.4	38.7	•	2025	73.6 + 8.9	34.6
GERAD1	6356	53.2 ± 13.4	46.3		2820	78.6 ± 8.3	35.0
Belgium	489	66.2 ± 13.6	41.9		842	78.7 ± 8.1	34.7
Finland	623	69.1± 6.2	40.3		560	71.4 ± 7.3	32.9
Germany	961	47.9 ± 12.4	52.0		728	72.5 ± 8.9	44.2
Italy	904	69.4 ± 11.0	46.0		1846	75.4 ± 8.3	32.8
Spain	1084	74.0 ± 10.8	42.9		1117	78.0 ± 8.2	35.0

	3C study	Rotterdam study	CHS study
Ν	840	1465	274
Age (mean ± SD) Gender (%)	74.0 ± 5.3 61.0	68.6 ± 8.6 59.9	78.6 ± 3.6 58.1
$A\beta_{1.40}$ (mean ± SD)	77.66 ± 18.00	198.83 ± 54.14	142.1 ± 59.7
A β_{1-42} (mean ± SD) A $\beta_{1-42/Ab1-40}$ (mean ± SD)	12.90 ± 3.81 0.170 ± 0.046	19.04 ± 7.12 0.095 ± 0.021	17.3 ± 13.4 0.110 ± 0.060

Popu	lation	Minor Allele Frequency (in bold) rs4711652 Rs2395760 rs991762							
		(G /A)	(A /G)	(T /C)					
EADI1	Controls	0,443	0,103	0,199					
GERAD1	Controls Cases	0,437 0,45	0,098 0,104	0,199 0,203					
Belgium	Controls Cases	0,448 0,452	0,108 0,105	0,197 0,182					
Finland	Controls Cases	0,404 0,41	0,151 0,142	0,23 0,224					
Germany	Controls Cases	0,434 0,424	0,11 0,107	0,177 0,186					
Italy	Controls Cases	0,405 0,396	0,118 0,109	0,212 0,195					
Spain	Controls Cases	0,438 0,427	0,104 0,097	0,187 0,205					

Popu	lation	Genotype distribution										
i opu			rs4711652			rs2395760			rs991762			
		AA	AG	GG	AA	AG	GG	CC	СТ	TT		
	Controls	1655	2607	1051	58	982	4277	3411	1702	211		
EADI1	Cases	621	1013	388	28	427	1565	1237	694	93		
	Controls	1987	3150	1193	53	1135	5167	4076	2033	245		
GERADI	Cases	849	1403	568	18	552	2245	1796	901	123		
Delaium	Controls	156	228	105	10	86	393	317	151	21		
Belgium	Cases	256	410	176	10	156	676	564	250	28		
Finland	Controls	213	317	93	17	154	452	373	214	36		
Filliallu	Cases	198	265	97	16	127	417	338	193	29		
Cormony	Controls	304	462	179	13	186	762	650	277	31		
Germany	Cases	239	353	129	11	134	583	478	227	22		
Italy	Controls	322	431	151	11	192	701	556	313	35		
italy	Cases	672	885	289	28	348	1470	1188	595	63		
Spain	Controls	341	536	207	8	210	866	708	347	29		
Spain	Cases	385	511	221	16	185	916	702	372	43		

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	Poni	lation	Minor Allele Frequency (in bold)						
	i opc		rs7081208 (A /G)	rs2446581 (A /G)	rs17314229 (T /C)				
		Controls	0,235	0,11	0,057				
	EADH	Cases	0,254	0,132	0,067				
G	ERAD1	Controls	0,272	0,101	0,069				
		Cases	0,271	0,11	0,068				
	olaium	Controls	0,275	0,125	0,058				
	eigium	Cases	0,281	0,122	0,066				
	Finland	Controls	0,2	0,152	0,091				
'	manu	Cases	0,215	0,159	0,091				
G	ermany	Controls	0,301	0,109	0,081				
0	ermany	Cases	0,286	0,131	0,068				
	Italy	Controls	0,215	0,129	0,039				
	itary	Cases	0,21	0,128	0,047				
	Snain	Controls	0,199	0,113	0,052				
	Opani	Cases	0,207	0,124	0,049				

						Ger	otype distribu	ution				
3	Popu	lation										
\sum	rs7081						rs2446581		rs17314229			
2			AA	AG	GG	AA	AG	GG	CC	СТ	TT	
<u> </u>												
Ø	FADI1	Controls	297	1912	3113	68	1034	4214	4722	569	16	
5	LADIT	Cases	129	770	1125	32	469	1524	1755	258	7	
S		Controls	450	2556	3350	84	1110	5162	5504	820	29	
\sim	GERADI	Cases	233	1062	1525	28	566	2226	2443	366	10	
1	Dolaium	Controls	35	199	255	7	108	374	432	57	0	
	Beigium	Cases	70	333	439	12	182	648	732	109	1	
	Finland	Controls	23	203	397	15	160	448	513	106	4	
.0	Finiand	Cases	20	201	339	17	144	399	462	94	4	
S	Cormoni	Controls	73	433	455	14	181	765	814	139	8	
é	Germany	Cases	65	287	376	11	169	548	563	87	1	
~	ltoly/	Controls	47	294	563	10	214	680	836	66	2	
\sim	italy	Cases	98	581	1167	27	418	1401	1679	162	5	
33	Chain	Controls	49	334	701	13	220	851	974	107	3	
8	Spain	Cases	38	386	693	11	255	851	1012	101	4	
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		Haplotype frequencies														
	Polymorphis	ms	E	ADI1	GERAD1		Be	Belgium		nland	Ge	rmany	I	taly	Spain	
r	s4711652 rs2395760	rs991762	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases
			(n=5330)	(n=2019)	(n=6356)	(n=2820)	(n=489)	(n=842)	(n=623)	(n=560)	(n=942)	(n=720)	(n=904)	(n=1846)	(n=1084)	(n=1117)
А	G	С	0.393	0.379	0.388	0.375	0.377	0.376	0.374	0.373	0.411	0.411	0.447	0.453	0.435	0.418
А	G	Т	0.122	0.121	0.127	0.120	0.119	0.115	0.137	0.138	0.103	0.118	0.115	0.119	0.099	0.121
А	A	С	0.038	0.054	0.045	0.053	0.057	0.057	0.083	0.077	0.051	0.048	0.030	0.030	0.025	0.031
G	G G	С	0.335	0.312	0.337	0.338	0.343	0.358	0.265	0.269	0.325	0.318	0.272	0.282	0.307	0.310
G	G G	Т	0.047	0.069	0.050	0.063	0.053	0.047	0.073	0.077	0.050	0.047	0.047	0.040	0.055	0.054
G	6 A	С	0.034	0.037	0.031	0.031	0.026	0.028	0.049	0.056	0.036	0.036	0.039	0.040	0.047	0.036
G	a A	Т	0.028	0.025	0.019	0.018	0.026	0.020	0.017	0.007	0.024	0.023	0.048	0.038	0.029	0.027
	Test of haplotypic as	sociation	Chi2=33 P=7	.63 with 6df 7.9e-06	Chi2=16 P=	.48 with 6df =0.01	Chi2=2. P:	84 with 6df =0.83	Chi2=2. P:	91 with 6df =0.82	Chi2=2. P:	70 with 6df =0.84	Chi2=6. P:	73 with 6df =0.34	Chi2=7. P=	09 with 6df =0.31

		Haplotype frequencies														
2	Polymorph	isms	EA	DI1	GER	AD1	Belg	ium	Finl	and	Gern	nany	lta	aly	Sp	ain
\$67	081208 rs24465	81rs17314229	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases
			(n=5330)	(n=2019)	(n=6356)	(n=2820)	(n=489)	(n=842)	(n=623)	(n=560)	(n=961)	(n=651)	(n=904)	(n=1846)	(n=1084)	(n=1117)
5	G A	С	0.085	0.090	0.072	0.073	0.092	0.085	0.140	0.135	0.086	0.099	0.107	0.097	0.091	0.089
)	G G	С	0.637	0.604	0.610	0.605	0.592	0.591	0.607	0.592	0.570	0.597	0.648	0.656	0.670	0.669
1	G G	Т	0.042	0.052	0.045	0.051	0.042	0.043	0.053	0.058	0.042	0.037	0.031	0.036	0.040	0.036
-	A A	С	0.025	0.041	0.028	0.037	0.033	0.037	0.013	0.024	0.023	0.034	0.023	0.031	0.023	0.035
_	A G	С	0.196	0.197	0.220	0.216	0.225	0.221	0.149	0.158	0.239	0.222	0.184	0.170	0.165	0.159
5	A G	Т	0.015	0.015	0.024	0.018	0.017	0.023	0.038	0.033	0.039	0.031	0.008	0.010	0.012	0.013
, T	est of haplotypic	association	Chi2=32.8 P=4.1	32 with 5df 1e-06	Chi2=15.8 P=0	81 with 5df .007	Chi2=3.90 P=0	6 with 5df 9.55	Chi2=2.56 P=0	6 with 5df 0.76	Chi2=6.39 P=0) with 5df .27	Chi2=3.9 P=(4 with 4df).41	Chi2=5.69 P=(9 with 5df).33

RS number	OR	CI, 95%	P value	P value for heterogeinity
rs2446581	1.15	1.08-1.24	2,10E-05	5,18E-01
rs7081208	1.06	1.01-1.12	2,02E-02	8,12E-01
rs17314229	1.09	1.00-1.20	4,94E-02	3,79E-01

Supplementary Figure 1





position on chr10 (Mb)



Z-score Beta Coefficient

rs244658_{hal-00778632,} version 1 - 25 Jan 2013

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