Supplementary Materials

3C-study

Dementia was diagnosed using a three-step procedure (1). Trained psychologists administered a battery of neuropsychological tests. Next, all the participants in Bordeaux and Montpellier were examined by a neurologist at baseline, whereas in Dijon, only those who screened positive for dementia underwent further examination (because of the large number of participants in that centre). During follow-up, participants with suspected incident dementia (on the basis of their neuropsychological test results) were examined by a neurologist. Lastly, an independent committee of neurologists reviewed all potential prevalent and incident cases of dementia in order to validate the diagnosis, according to the criteria given in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). Dementia classification was based on the National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for AD and the National Institute of Neurologic Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for vascular dementia (2, 3). Subjects with a typical history of AD (progressive worsening of memory or other cognitive functions) and documented stroke were classified as having mixed dementia.

Age, gender, centre, educational level, hypertension, body mass index (BMI), diabetes, history of vascular disease and apolipoprotein E (APOE) genotype were systematically used as adjusting factors. Educational level was defined as a six-level variable: no school attendance, primary education without a diploma, primary education with a diploma, secondary education without a baccalaureate degree, secondary education with a baccalaureate degree and a university-level degree. Body-mass Index was defined according to the Quetelet equation. Hypertension was defined as a systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$90 mm Hg or administration of antihypertensives. Subjects were considered as suffering from type 2 diabetes if the fasting glycemia was $\geq$ 126 mg/dL or if they used anti-diabetic treatments. A history of vascular disease was defined as a self-reported history of myocardial infarction, angina pectoris, arteritis and/or stroke.

To limit genetic heterogeneity, subjects whose mother language was not French and those born abroad were removed from the study (n=1181). Individuals for whom information on their dementia status during the 4-year follow-up was missing were withdrawn (n=854; refusal or lost to follow-up and death), together with individuals for whom at least one IL33 or APOE genotyping result was missing (n=710). Baseline characteristics of the remaining population sample (n=6549) are reported in Table 1. Three hundred and fifty individuals were demented, with 143 prevalent cases (91 cases of AD, 39 cases of mixed/vascular dementia, 3 cases of Parkinsonian dementia and 10 cases of other types of dementia) and 207 incident cases (135 cases of AD, 40 cases of mixed/vascular dementia, 15 cases of Parkinsonian dementia and 17 cases of other types of dementia).

Brain samples

AD brains were obtained at autopsy from 114 patients with early- and late-onset sporadic AD accessioned from the Greater Manchester region of United Kingdom during years 1986-2001 (mean age at death = 73.1 ± 9.1 years old; mean age at onset = 65.9 ± 10.3 years old; 51% male) (4). All patients were of Caucasian ethnic origin. Pathological diagnoses were made in accordance with CERAD Neuropathological Criteria for AD. All patients were at Braak stages 5 or 6 at time of death. The proportion of tissue area occupied by $A\beta_{40}$ and $A\beta_{42}$ was quantified in immunohistochemically stained section from Brodmann area 8/9 of the frontal cortex, as previously reported. The extent of cerebral amyloid angiopathy (CAA) in leptomeningeal and intraparenchymal arteries was rated semiquantitatively in 91/114 patients (80%). The severity of CAA was assessed semi-quantitatively on a five –point scale (grades 0-4). Briefly, CAA was rated according to: 0 = no blood vessels (small arteries, arterioles and capillaries) are stained; 1= a few leptomeningeal vessels only involved; 2 = a few leptomeningeal vessels only were affected, mild intracortical vascular involvement; 3 = many leptomeningeal and intracortical vessels affected; 4 = many leptomingeal and intracortical vessels affected with dyshoric angiopathy associated with intracortical vessels.

Control brains were obtained from an initial set of 167 brains recruited from routine autopsies carried out at the Hospices Civils de Strasbourg (France) (5). Recruitment was designed to exclude cases of dementia (individuals were not recruited from medical institutions where the majority of patients presented with dementia, but from a general hospital). Most subjects were admitted less than 48 hours before death via emergency services and were living at home prior to their admission. Cases referred to autopsy for neurological pathologies were excluded. The neuropathological diagnosis for Alzheimer's disease followed CERAD Neuropathological criteria. In addition, Braak stages were assessed in the whole series. Again, all control subjects were Caucasian.

SNPs densification in IL-33, genotyping and SNPs selection

Besides the 4 Tag-SNPs selected using the HapMap website, thirteen SNPs (frequency>10%) were randomly selected along the gene using NCBI website and dHPLC results. All exons, intron/exon boundaries and proximal promoter of the *IL-33* gene were screened in 24 AD cases from the French population for sequence variation using denaturing high-performance liquid chromatography (dHPLC) in Table S2 (supplemental material). All variants identified by dHPLC were confirmed by sequencing. When already referenced, the name of the SNP was indicated in Table S2 (supplemental material).

Eleven SNPs were randomly selected across the *IL-33* gene and correlation coefficients (r^2) between all the SNPs were estimated in the French control sub-population using the Haploview software (supplemental material**,** Figure S1). In addition of the 4 tag-SNPs previously analysed in the Affymetrix GeneChip, 8 SNPs were finally selected (r^2<0**.**8). These 8 SNPs were then genotyped in the French and American sub-populations.

Genotyping of rs1157505 (SNP3), rs1891385 (SNP4), rs10975511 (SNP9), rs7035413 (SNP10), rs11792633 (SNP11), rs7044343 (SNP12), rs1048274 (SNP13), rs8172 (SNP14) were realised by enzymatic digestion following PCR amplification as referenced in Table S3 (supplementary material). Genotyping of rs992969 (SNP1), rs7848215 (SNP2), rs16924144 (SNP5), rs96029 (SNP6), rs16924159 (SNP7), rs16924161 (SNP8), rs10815398 (SNP15) were determined by TaqMan assays using the Biosystems Prism 7900HT system as described by the supplier (supplementary material, Table S16).

For extension of the rs1157505, rs11792633 and rs7044343 analyses in the different case-control populations, the three SNPs were independently genotyped in Lille (complete French and UK populations), in Pittsburgh (complete American case-control study). The two French and American sub-populations were genotyped twice using two different technologies and 6 genotype discordances were observed. The corresponding individuals were removed from the analyses.

In the 3C-study, the rs1157505, rs11792633 and rs7044343 polymorphisms were genotyped using KASPar assays, as described by the supplier (Kbiosciences, Hoddesdon, UK). APOE genotyping was performed using a fluorogenic 5'-nuclease assay with TaqMan chemistry, as previously described (1).

Immunohistochimistry

Brain tissue from the temporal anterior cortex (Brodmann area 38) from nine Alzheimer patients and twelve controls was investigated. Rehydrated, 5 µm thick sections of formalin-fixed, paraffin-embedded brain tissue were heated in a pressure cooker, in pH 6.0 citrate buffer, prior to labelling. The IL-33 immunostaining was performed according to manufacturers' instructions (IL-33 monoclonal antibody IL33305B from Alexis Biochemicals, Vectastain Elite ABC kit from Vector laboratories, diaminobenzidin as chromogen). Positive controls of the staining steps were human tonsils and the colon mucosa from a patient with Crohn's disease. In several cases, an additionnal slide was processed, replacing IL33 by non immune serum, showing any labelling as expected.

IL-33 mRNA quantification

Total RNA was extracted from frozen frontal cortex brain tissue from the 114 AD and 167 control samples using phenol/chloroform protocol (Trizol® reagent, Invitrogen). The quality of total RNA was assessed using Agilent 2100 bionalyser and the ratio of ribosomal RNA 28S/18S systematically estimated using the Agilent 2100 bionalyser bio-sizing software. Total RNA samples from 45 controls and 43 AD cases were randomly selected for *IL33* quantification as described by the supplier

(Quantigene®, Panomics) (6). The quantigene technology is well adapted to our purpose for several reasons: (i) this one allows for the direct quantification of a target mRNA without retro-transcription step and PCR amplification; (ii) it limits biases due to RNA degradation.

Briefly, capture and label extender probe sets specific for *IL-33* and *β-actin* mRNA (as furnished by the supplier) were combined and diluted to 100 fmol/µl in a lysis buffer supplied in the QuantiGene bDNA Signal Amplification Kit (Bayer Diagnostics, East Walpole, MA). Total RNA (0.8 µg for *IL33* and 0.2 µg for *β-actin* in a final volume of 10 µl) was added to each well of a 96-well plate with 40 µl of capture buffer, 40 µl of lysis buffer and 10 µl of each diluted probe set. RNA was allowed to hybridize for at least 16 h at 53°C. Plates were then washed at room temperature (600 µl of a wash buffer). Samples were then hybridized for 60 min at 46°C with the bDNA amplifier molecules (100 µl/well) diluted in a amplifier/label probe buffer (1:100). At room temperature, plates were then rinsed with the wash Buffer. Label probe (1:100 in a amplifier/label probe buffer) was added to each well (100 µl/well) and hybridized to the bDNA-RNA complex for 60 min at 46°C. Plates were again rinsed with wash buffer at room temperature. Alkaline phosphatase-mediated luminescence was triggered by the addition of a dioxetane substrate solution (100 µl /well). The enzymatic reaction was allowed to proceed for 30 min at 46°C, and luminescence was measured with the 1420 Victor light luminometer (Perkin Elmer).

Immunofluorescence (IF)

The SY5Y-APP^{WT} and COS-7 cell line was cultured on poly l-Lys-coated glass coverslips (Chamber Slide System 2 wells (Lab-Tek; Nunc, Rosckilde, Denmark)) for 24 hours. For IL-33 IF, cells were tranfected with IL-33 cDNA. After 48 hours, cells were fixed in PBS containing 4% paraformaldehyde for 20 min at room temperature and further permeabilized with 0.25% (v/v) Triton X-100 in PBS. After blocking in 5% (w/v) bovine serum albumin (BSA), fixed materials were incubated for 1h30 at room temperature (for IL-33 IF) or overnight at 4°C (for ST2 IF) with primary antibodies 1/100 (respectively, PAb to IL-33 (human) (Alexis®, Apotech, Switzerland) or anti-ST2 (2A5)) in PBS added with 5% (w/v) BSA and 0.25% Triton X-100. After washing, secondary antibodies (respectively, anti-rabbit IgG-TRITC or anti-mouse IgG-TRITC (Santa Cruz Biotechnology, USA)) diluted to 1/400 was used. Coverslips were mounted to slides with Vectashield® with DAPI (Vector Laboratories, France). The microscopy platform of the Pasteur Institute of Lille was used for slide reading.

Statistical analyses

The SAS software release 8.02 was used for statistical analyses (SAS Institute, Cary, NC). The association of the 1,156 SNPs with the risk of AD was estimated by multiple logistic regression models, adjusted for age, gender, *APOE* status and centre. Three models were systematically analysed:

recessive, co-dominant and dominant. Following Bonferroni corrections, the significant *P*-value threshold was set at $4.3x10^{-5}$ (0.05/1,156).

In the case-control studies, we used Akaike Information Criterion (AIC) to determine the best-fitting genetic model (dominant, co-dominant or recessive) for rs1157505, rs11792633 and rs7044343 in *IL-33*. The model with the lowest AIC reflects the best balance of goodness-of-fit and parsimony (7, 8). We consequently coded the genotypes of the three polymorphism as a dummy variable according to the hypothesis of a dominant model, i.e., at least one minor allele. Before pooled analyses, homogeneity between populations was tested using Breslow-day computation (9). The association of the 3 SNPs with the risk of AD was then estimated by multiple logistic regression models, adjusted for age, gender, *APOE* status and centre when necessary. Interactions between *IL-33*, *APOE*, gender or age variables were tested in logistic regression models. Haplotypes were estimated using the Haploview software then the Thesias one for confirmation. Permutation tests (1,000) were performed to assess the strength of the observed association. The objective of the Thesias software is to perform haplotype-based association analysis in unrelated individuals. This program is based on the maximum likelihood model described in[7] and is linked to the SEM algorithm (10).

The association of rs1157505, rs11792633 and rs7044343 with age at onset was analysed using a general linear model adjusted for gender and centre following *APOE* stratification. Haplotype associations with age at onset were estimated using the Thesias software.

Comparison of IL-33 mRNA amounts between AD cases and controls was performed using a non parametric Wilcoxon test. However, an analysis of covariance using a general linear model for comparison of IL-33 mRNA amounts between AD cases and controls was also performed (mRNA level data was log transformed to normalize distributions) adjusted for mRNA degradation (evaluated using ratio of ribosomal RNA 28S/18S measured by the Agilent 2100 bionalyser and bio-sizing software). The results were not modified following this additional analysis (data not shown).

Association study of rs1157505, rs11792633 and rs7044343 with CAA score was performed using a non parametric Wilcoxon test.

References

1 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology 2003; **22:** 316-25.

2 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: APA Press, 1994.

3 McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984; **34:** 939–944.

4 Tian, J., Shi, J., Smallman, R., Iwatsubo, T. and Mann, D.M. Relationships in Alzheimer's disease between the extent of Abeta deposition in cerebral blood vessel walls, as cerebral amyloid angiopathy, and the amount of cerebrovascular smooth muscle cells and collagen. *Neuropathol. Appl. Neurobiol.,* 2006; **32**: 332-340.

5 Berr, C., Lambert, J.C., Sazdovitch, V., Amouyel, P., Chartier-Harlin, M.C., Mohr, M., Heldt, N., Kiesmann, M. and Hauw, J.J. Neuropathological epidemiology of cerebral aging: a study of two genetic polymorphisms. *Neurobiol. Aging,* 2001; **22**: 227-235.

6 Canales, R.D., Luo, Y., Willey, J.C., Austermiller, B., Barbacioru, C.C., Boysen, C., Hunkapiller, K., Jensen, R.V., Knight, C.R., Lee, K.Y., *et al*. Evaluation of DNA microarray results with quantitative gene expression platforms. *Nat. Biotechnol.,* 2006; **24**: 1115-1122.

7 Akaike, H. A Bayesian analysis of the minimum AIC procedure. *Ann. Inst. Statist. Math.,* 1978; **30**: 9-14.

8 Bozdogan, H. Model-selection and Akaike's information criterion (AIC): The general theory and its analytical extensions. *Psychometrika,* 1987; **52**: 345-370.

9 Breslow, N.E., Day, N.E., Halvorsen, K.T., Prentice, R.L. and Sabai, C. Estimation of multiple relative risk functions in matched case-control studies. *Am. J. Epidemiol.,* 1978; **8**: 299-307.

10 Tregouet, D.A. and Tiret, L. Cox proportional Hazards survival regression in haplotype-based association analysis using the stochastic-EM algorithm. *Eur. J. Hum. Genet.,* 2004; **12**: 971-974.

Table S1 SNPs exhibiting a significant association with the risk of developing AD using either a recessive or a dominant or a co-dominant model. *P*-value adjusted on age, gender and *APOE* status.

SNP	Chromosome	Gene	12+22 versus 11	22 versus 12+11	Co-dominant model
rs153202	5	MYO10	0.005	ns	0.01
rs27430	5	MYO10	0.008	0.005	0.002
rs2401987	5	MYO10	0.05	ns	ns
rs26315	5	MYO10	0.05	ns	ns
rs6881621	5	MYO10	ns	0.04	ns
rs1445946	5	MYO10	0.009	ns	0.05
rs13356962	5	MYO10	ns	0.01	ns
rs250339	5	MYO10	0.03	ns	0.04
rs10051929	5	MYO10	ns	ns	0.03
rs12520877	5	MYO10	ns	ns	0.04
rs4702173	5	MYO10	ns	0.04	ns
rs17651023	5	MYO10	0.05	ns	ns
rs6898592	5	MYO10	0.01	ns	ns
rs17707609	5	MYO10	ns	0.007	ns
rs17651165	5	MYO10	0.007	ns	ns
rs31505	5	MYO10	0.02	ns	0.05
rs17614059	5	MYO10	0.01	ns	0.02
rs17651266	5	MYO10	0.05	ns	0.05
rs40985	5	MYO10	0.007	ns	0.007
rs716555	5	MYO10	Ns	0.02	0.03
rs253315	5	MYO10	0.009	0.02	0.002
rs2560852	5	MYO10	0.002	ns	0.001
rs7710976	5	MYO10	0.008	ns	ns
rs153709	5	MYO10	ns	0.04	ns
rs716436	5	ITGA2	ns	0.009	ns
rs4865756	5	ITGA2	0.02	ns	0.03
rs11741738	5	ITGA2	ns	0.02	ns
rs9467731	6	NM_007047	ns	0.01	ns
rs3757142	6	NM_007047	ns	0.009	ns
rs3130285	6	TNXB	0.003	ns	0.009
rs3130286	6	TNXB	0.006	ns	0.01
rs185819	6	TNXB	ns	0.03	ns
rs3130287	6	TNXB	ns	0.002	0.004
rs3134943	6	AGER	ns	0.005	0.007
rs8365	6	AGER	0.03	ns	ns
rs3134940	6	AGER	0.04	ns	ns
rs1800684	6	AGER	0.008	ns	0.01
rs3129876	6	HLA-DRA	ns	0.008	0.009
rs3129881	6	HLA-DRA	0.03	ns	0.05
rs9268658	6	HLA-DRA	0.05	0.01	0.008
rs8084	6	HLA-DRA	ns	0.009	ns
rs7192	6	HLA-DRA	0.004	ns	0.03
rs3116713	6	NM_002636	ns	ns	0.04
rs442745	6	NM_002636	ns	0.007	0.02

rs3106196	6	NM_002636	ns	0.05	0.03
rs3218114	6	CCND3	ns	0.003	0.002
rs9529	6	CCND3	0.05	ns	ns
rs3218086	6	CCND3	ns	0.03	0.02
Rs7848215	9	IL-33	0.01	0.02	0.004
rs7044343	9	IL-33	0.00003	ns	0.0001
rs10757145	9	FLJ20375	ns	0.05	ns
rs1332322	9	FLJ20375	ns	ns	0.04
rs4978111	9	FLJ20375	0.02	ns	0.01
rs7860490	9	FLJ20375	ns	0.04	0.05
rs7033259	9	FLJ20375	0.05	ns	ns
rs6475473	9	FLJ20375	0.002	0.02	0.002
rs6475474	9	FLJ20375	ns	0.02	0.01
rs10811438	9	FLJ20375	ns	ns	0.04
rs10964779	9	FLJ20375	0.03	ns	ns
rs3780491	9	NM_001497	ns	ns	0.03
rs10511909	9	NM_001497	0.01	ns	0.008
rs2774272	9	NM_001497	ns	0.05	0.02
rs10758194	9	NM_001497	ns	0.04	0.02
rs1328898	9	NM_001497	0.05	ns	0.02
rs2274592	9	CNTFR	0.04	ns	0.02
rs2381164	9	CNTFR	0.008	0.02	0.002
rs10972149	9	CNTFR	0.0008	ns	0.04
rs10814123	9	CNTFR	ns	0.001	0.05
rs10758268	9	CNTFR	ns	0.0003	0.001
rs12551429	9	CNTFR	ns	0.05	ns
rs3763613	9	CNTFR	ns	0.03	ns
rs3829078	9	CA9	0.01	ns	0.01
rs6481654	10	KIAA1462	0.02	ns	ns
rs9988732	10	KIAA1462	ns	0.003	0.01
rs2488024	10	KIAA1462	0.006	ns	0.02
rs11000780	10	CAMK2G	ns	0.05	ns
rs10824037	10	CAMK2G	ns	0.05	ns
rs10458656	10	CAMK2G	0.05	ns	ns
rs2633310	10	CAMK2G	0.02	ns	0.02
rs2675662	10	CAMK2G	ns	0.02	0.02
rs2459446	10	CAMK2G	0.01	ns	0.02
rs2688614	10	CAMK2G	ns	0.007	0.005
rs6055551	20	ANGPT4	ns	0.04	ns
rs3787566	20	ANGPT4	ns	0.007	ns
rs4816050	20	ANGPT4	ns	0.002	ns
rs13040505	20	ANGPT4	0.02	ns	0.01
rs730169	20	ANGPT4	ns	0.03	0.04
rs574628	20	ANGPT4	0.04	ns	ns
rs1741296	20	HSPA12B	ns	0.004	0.03
rs6076623	20	HSPA12B	0.01	ns	0.04

Table S2 Primer set used for the characterization of *IL33* polymorphisms by dHPLC.

Name		Primer	SNP detected
IL33-1	Forward	5'-aaggtcacccttctaatctt-3'	no mutation
	Reverse	5'-agagatcagtgtattcttcc-3'	
IL33-2	Forward	5'-attactgataggccaaaggg-3'	no mutation
	Reverse	5'-ccatggttcccaaggtttaa-3'	
IL33-3	Forward	5'-ctagcatgaatgcatagtta-3'	no mutation
	Reverse	5'-agcatgtataaacattggag-3'	
IL33-4	Forward	5'-tgataagatactgtgaacct-3'	no mutation
	Reverse	5'-gcatatttagatgtggtaag-3'	
IL33-5	Forward	5'-caatcactactctcagcaag-3'	no mutation
	Reverse	5'-gcagaagtttctggtacaca-3'	
IL33-6	Forward	5'-ttaatctagccaacagtgac-3'	no mutation
	Reverse	5'-ctgtttgccatgtctaagtt-3'	
IL33-7	Forward	5'-ttcatcagagcatattcgtg-3'	rs10975519
	Reverse	5'-tcctctgagaatctaaggtt-3'	rs10975520
IL33-8	Forward	5'-aagatacctgttagtgaatg-3'	no mutation
	Reverse	5'-gtagtaagtgattgtgcttt-3'	
IL33-9	Forward	5'-tccacaactcactaagcaag-3'	no mutation
	Reverse	5'-agatgcagttatacagaggg-3'	
IL33-10	Forward	5'-cttagcatgtgtggaatgtt-3'	rs1048274
	Reverse	5'-catttatgttacctggcttg-3'	rs1200491
IL33-11	Forward	5'-actcagagcagatctccctt-3'	no mutation
	Reverse	5'-cagtgttatcaggaagctgg-3'	
IL33-12	Forward	5'-gggcaaagtttgcttctaatc-3'	no mutation

Table S3 Genotypic and allelic distribution of the *IL33* SNPs studied in American and French sub-populations.

	SNP		American sub-population											French sub-population										
			Genotypic distribution[a]							Allelic distribution[a]				Genotypic distribution[a]							Allelic distribution[a]			
			11		12		22		Total	1		2		11		12		22		Total	1		2	
			n	freq	*n*	freq	*n*	freq	*n*	*n*	freq	*n*	freq	*n*	freq	*n*	freq	*n*	freq	*n*	*n*	freq	*n*	freq
Tag-SNP	rs7848215	controls	*114*	0.582	*70*	0.357	*12*	0.061	*196*	*298*	0.760	*94*	0.240	*119*	0.548	*86*	0.396	*12*	0.055	*217*	*324*	0.747	*110*	0.253
		cases	*98*	0.500	*82*	0.418	*16*	0.082	*196*	*278*	0.709	*114*	0.291	*129*	0.469	*119*	0.433	*27*	0.098	*275*	*377*	0.685	*173*	0.315
	rs16924144	controls	*78*	0.406	*86*	0.448	*28*	0.146	*192*	*242*	0.630	*142*	0.370	*95*	0.426	*98*	0.439	*30*	0.135	*223*	*288*	0.646	*158*	0.354
		cases	*83*	0.428	*89*	0.459	*22*	0.113	*194*	*255*	0.657	*133*	0.343	*133*	0.478	*118*	0.424	*27*	0.097	*278*	*384*	0.691	*172*	0.309
	rs16924159	controls	*77*	0.391	*93*	0.472	*27*	0.137	*197*	*247*	0.627	*147*	0.373	*101*	0.472	*92*	0.430	*21*	0.098	*214*	*294*	0.687	*134*	0.313
		cases	*89*	0.452	*86*	0.437	*22*	0.112	*197*	*264*	0.670	*130*	0.330	*139*	0.513	*107*	0.395	*25*	0.092	*271*	*385*	0.710	*157*	0.290
	rs7044343	controls	*71*	0.360	*100*	0.508	*26*	0.132	*197*	*242*	0.614	*152*	0.386	*78*	0.335	*122*	0.524	*33*	0.142	*233*	*278*	0.597	*188*	0.403
		cases	*77*	0.387	*98*	0.492	*24*	0.121	*199*	*252*	0.633	*146*	0.367	*136*	0.463	*131*	0.446	*27*	0.092	*294*	*403*	0.685	*185*	0.315
Supplementary SNPs	rs1157505	controls	*103*	0.557	*73*	0.395	*9*	0.049	*185*	*279*	0.754	*91*	0.246	*134*	0.573	*89*	0.380	*11*	0.047	*234*	*357*	0.763	*111*	0.237
		cases	*123*	0.621	*63*	0.318	*12*	0.061	*198*	*309*	0.780	*87*	0.220	*212*	0.709	*76*	0.254	*11*	0.037	*299*	*500*	0.836	*98*	0.164
	rs1891385	controls	*157*	0.826	*30*	0.158	*3*	0.016	*190*	*344*	0.905	*36*	0.095	*158*	0.760	*48*	0.231	*2*	0.010	*208*	*364*	0.875	*52*	0.125
		cases	*149*	0.753	*43*	0.217	*6*	0.030	*198*	*341*	0.861	*55*	0.139	*220*	0.780	*56*	0.199	*6*	0.021	*282*	*496*	0.879	*68*	0.121
	rs996029	controls	*180*	0.918	*16*	0.082	*0*	0.000	*196*	*376*	0.959	*16*	0.041	*192*	0.906	*20*	0.094	*0*	0.000	*212*	*404*	0.953	*20*	0.047
		cases	*182*	0.924	*15*	0.076	*0*	0.000	*197*	*379*	0.962	*15*	0.038	*259*	0.918	*23*	0.082	*0*	0.000	*282*	*541*	0.959	*23*	0.041
	rs16924161	controls	*142*	0.714	*51*	0.256	*6*	0.030	*199*	*335*	0.842	*63*	0.158	*162*	0.733	*55*	0.249	*4*	0.018	*221*	*379*	0.857	*63*	0.143
		cases	*147*	0.739	*49*	0.246	*3*	0.015	*199*	*343*	0.862	*55*	0.138	*218*	0.779	*57*	0.204	*5*	0.018	*280*	*493*	0.880	*67*	0.120
	rs10975511	controls	*93*	0.474	*85*	0.434	*18*	0.092	*196*	*271*	0.691	*121*	0.309	*114*	0.502	*93*	0.410	*20*	0.088	*227*	*321*	0.707	*133*	0.293
		cases	*112*	0.566	*70*	0.354	*16*	0.081	*198*	*294*	0.742	*102*	0.258	*153*	0.524	*115*	0.394	*24*	0.082	*292*	*421*	0.721	*163*	0.279
	rs7035413	controls	*133*	0.672	*55*	0.278	*10*	0.051	*198*	*321*	0.811	*75*	0.189	*135*	0.584	*89*	0.385	*7*	0.030	*231*	*359*	0.777	*103*	0.223
		cases	*119*	0.595	*74*	0.370	*7*	0.035	*200*	*312*	0.780	*88*	0.220	*149*	0.521	*114*	0.399	*23*	0.080	*286*	*412*	0.720	*160*	0.280
	rs11792633	controls	*90*	0.469	*84*	0.438	*18*	0.094	*192*	*264*	0.688	*120*	0.313	*95*	0.420	*107*	0.473	*24*	0.106	*226*	*297*	0.657	*155*	0.343
		cases	*91*	0.457	*85*	0.427	*23*	0.116	*199*	*267*	0.671	*131*	0.329	*142*	0.570	*85*	0.341	*22*	0.088	*249*	*369*	0.741	*129*	0.259
	rs8172	controls	*159*	0.820	*33*	0.170	*2*	0.010	*194*	*351*	0.905	*37*	0.095	*240*	0.828	*49*	0.169	*1*	0.003	*290*	*529*	0.912	*51*	0.088
		cases	*170*	0.876	*23*	0.119	*1*	0.005	*194*	*363*	0.936	*25*	0.064	*195*	0.837	*38*	0.163	*0*	0.000	*233*	*428*	0.918	*38*	0.082

[a] Frequent allele is coded 1 and minor allele is coded 2

Table S4 Association of the rs1157505, rs11792633 and rs7044343 SNPs with the risk of developing AD according **(A)** in the combined case-control study (France, American and English) and **(B)** after stratification on the *APOE* status.

A

	OR (12+22 versus 11)[a] [95%-CI]	P^a	OR (12+22 versus 11)[b] [95%-CI]	P^b	*APOE interaction*
rs1157505	0.88 [0.78-1.01]	0.06	0.80 [0.69-0.93]	0.004	*0.004*
rs11792633	0.88 [0.77-1.01]	0.07	0.78 [0.68-0.91]	0.001	*0.0001*
rs7044343	0.88 [0.77-1.01]	0.07	0.79 [0.68-0.92]	0.002	*0.002*

[a] adjusted for age, gender and centre
[b] adjusted for age, gender, centre and *APOE* status

B

	Non-ε4 bearers		**ε4 bearers**	
	OR (12+22 versus 11)[a] [95%-CI]	*P*	OR (12+22 versus 11)[a] [95%-CI]	*P*
rs1157505	0.67 [0.55-0.82]	$6x10^{-5}$	1.07 [0.82-1.38]	ns
rs11792633	0.63 [0.52-0.76]	$1x10^{-6}$	1.16 [0.90-1.50]	ns
rs7044343	0.67 [0.56-0.81]	$3x10^{-5}$	1.10 [0.85-1.43]	ns

[a] adjusted for age, gender and centre

Table S5 Genotypic and allelic distribution of the rs115505, rs1179633 and rs7044343 SNPs in the whole American, English, French and combined populations.

		Genotype distribution[a]									Allele distribution[a]				
		11		12		22		Total			1		2		
		n	freq	n	freq	n	freq	n	p	p trend	n	freq	n	freq	p
rs1157505															
French	controls	406	0.604	224	0.333	42	0.063	672	0.01	0.007	1036	0.771	308	0.229	0.006
	cases	508	0.658	238	0.308	26	0.034	772			1254	0.812	290	0.188	
American	controls	426	0.584	267	0.366	37	0.051	730	0.47	0.72	1119	0.766	341	0.234	0.72
	cases	439	0.603	246	0.338	43	0.059	728			1124	0.772	332	0.228	
English	controls	111	0.561	75	0.379	12	0.061	198	0.92	0.69	297	0.750	99	0.250	0.69
	cases	202	0.546	143	0.386	25	0.068	370			547	0.739	193	0.261	
Pooled	controls	923	0.590	551	0.352	90	0.058	1564	0.35	0.15	2397	0.766	731	0.234	0.15
	cases	1123	0.613	616	0.336	93	0.051	1832			2862	0.781	802	0.219	
rs1179633															
French	controls	300	0.463	287	0.443	61	0.094	648	0.08	0.02	887	0.684	409	0.316	0.03
	cases	383	0.516	307	0.414	52	0.070	742			1073	0.723	411	0.277	
American	controls	337	0.462	320	0.438	73	0.100	730	0.98	0.88	994	0.681	466	0.319	0.88
	cases	339	0.466	317	0.435	72	0.099	728			995	0.683	461	0.317	
English	controls	87	0.439	94	0.475	17	0.086	198	0.61	0.32	268	0.677	128	0.323	0.34
	cases	178	0.481	165	0.446	27	0.073	370			521	0.704	219	0.296	
Pooled	controls	714	0.457	699	0.447	151	0.097	1564	0.11	0.03	2127	0.680	1001	0.320	0.04
	cases	895	0.489	787	0.430	150	0.082	1832			2577	0.703	1087	0.297	
rs7044343															
French	controls	241	0.370	320	0.492	90	0.138	651	0.01	0.004	802	0.616	500	0.384	0.005
	cases	331	0.434	356	0.467	76	0.100	763			1018	0.667	508	0.333	
American	controls	274	0.375	351	0.481	105	0.144	730	0.99	0.95	899	0.616	561	0.384	0.95
	cases	273	0.375	352	0.484	103	0.141	728			898	0.617	558	0.383	
English	controls	70	0.354	102	0.515	26	0.131	198	0.46	0.23	242	0.611	154	0.389	0.24
	cases	150	0.405	178	0.481	42	0.114	370			478	0.646	262	0.354	
Pooled	controls	582	0.372	764	0.488	218	0.139	1564	0.09	0.03	1928	0.616	1200	0.384	0.03
	cases	739	0.403	872	0.476	221	0.121	1832			2350	0.641	1314	0.359	

[a] Frequent allele is coded 1 and minor allele is coded 2

Table S6 Genotypic and allelic distribution of the rs115505, rs1179633 and rs7044343 SNPs in the American, English, French and combined non-ε4 bearers.

		Genotype distribution in non-ε4 bearers[a]									Allele distribution in non-ε4 bearers[a]				
		11		12		22		Total			1		2		
		n	freq	n	freq	n	freq	n	p	p trend	n	freq	n	freq	p
rs1157505															
French	controls	298	0.596	165	0.330	37	0.074	500	0.04	0.04	761	0.761	239	0.239	0.01
	cases	195	0.675	82	0.284	12	0.042	289			472	0.817	106	0.183	
American	controls	343	0.591	207	0.357	30	0.052	580	0.03	0.01	893	0.770	267	0.230	0.01
	cases	208	0.684	84	0.276	12	0.039	304			500	0.822	108	0.178	
English	controls	86	0.544	60	0.380	12	0.076	158	0.18	0.09	232	0.734	84	0.266	0.09
	cases	78	0.624	43	0.344	4	0.032	125			199	0.796	51	0.204	
Pooled	controls	727	0.587	432	0.349	79	0.064	1238	6.10^{-4}	1.10^{-4}	1886	0.762	590	0.238	9.10^{-5}
	cases	481	0.670	209	0.291	28	0.039	718			1171	0.815	265	0.185	
rs1179633															
French	controls	220	0.440	227	0.454	53	0.106	500	1.10^{-4}	1.10^{-4}	667	0.667	333	0.333	1.10^{-4}
	cases	173	0.599	93	0.322	23	0.080	289			439	0.760	139	0.240	
American	controls	266	0.459	252	0.434	62	0.107	580	0.02	0.005	784	0.676	376	0.324	0.02
	cases	165	0.536	120	0.390	23	0.075	308			450	0.731	166	0.269	
English	controls	69	0.437	73	0.462	16	0.101	158	0.20	0.10	211	0.668	105	0.332	0.12
	cases	63	0.504	56	0.448	6	0.048	125			182	0.728	68	0.272	
Pooled	controls	555	0.448	552	0.446	131	0.106	1238	5.10^{-6}	1.10^{-6}	1662	0.671	814	0.329	1.10^{-6}
	cases	401	0.558	269	0.375	48	0.067	718			1071	0.746	365	0.254	
rs7044343															
French	controls	179	0.358	246	0.492	75	0.150	500	3.10^{-4}	3.10^{-4}	604	0.604	396	0.396	9.10^{-5}
	cases	144	0.498	118	0.408	27	0.093	289			406	0.702	172	0.298	
American	controls	217	0.374	274	0.472	89	0.153	580	0.05	0.02	708	0.610	452	0.390	0.02
	cases	131	0.431	143	0.470	30	0.099	304			405	0.666	203	0.334	
English	controls	57	0.361	80	0.506	21	0.133	158	0.14	0.06	194	0.614	122	0.386	0.07
	cases	56	0.448	60	0.480	9	0.072	125			172	0.688	78	0.312	
Pooled	controls	453	0.366	600	0.485	185	0.149	1238	9.10^{-6}	1.10^{-6}	1506	0.608	970	0.392	2.10^{-6}
	cases	331	0.459	324	0.449	66	0.092	721			986	0.684	456	0.316	

[a] Frequent allele is coded 1 and minor allele is coded 2

Table S7 Genotypic and allelic distribution of the rs115505, rs1179633 and rs7044343 SNPs in the American, English, French and combined ε4 bearers.

		Genotype distribution in ε4 bearers[a]									Allele distribution in ε4 bearers[a]				
		11		12		22		Total			1		2		
		n	freq	n	freq	n	freq	n	p	p trend	n	freq	n	freq	p
rs1157505															
French	controls	94	0.639	48	0.327	5	0.034	147	0.97	0.86	236	0.803	58	0.197	0.85
	cases	301	0.645	152	0.325	14	0.030	467			754	0.807	180	0.193	
American	controls	83	0.553	60	0.400	7	0.047	150	0.53	0.55	226	0.753	74	0.247	0.56
	cases	231	0.545	162	0.382	31	0.073	424			624	0.736	224	0.264	
English	controls	28	0.636	16	0.364	0	0.000	44	0.08	0.04	72	0.818	16	0.182	0.04
	cases	139	0.517	106	0.394	24	0.089	269			384	0.714	154	0.286	
Pooled	controls	205	0.601	124	0.364	12	0.035	341	0.21	0.2	534	0.783	148	0.217	0.2
	cases	671	0.578	420	0.362	69	0.059	1160			1762	0.759	558	0.241	
rs1179633															
French	controls	73	0.525	58	0.417	8	0.058	139	0.43	0.23	204	0.734	74	0.266	0.26
	cases	207	0.462	212	0.473	29	0.065	448			626	0.699	270	0.301	
American	controls	71	0.473	68	0.453	11	0.073	150	0.16	0.07	210	0.700	90	0.300	0.07
	cases	174	0.410	197	0.465	53	0.125	424			545	0.643	303	0.357	
English	controls	18	0.450	21	0.525	1	0.025	40	0.35	0.77	57	0.713	23	0.288	0.78
	cases	122	0.477	113	0.441	21	0.082	256			357	0.697	155	0.303	
Pooled	controls	162	0.492	147	0.447	20	0.061	329	0.12	0.05	471	0.716	187	0.284	0.06
	cases	503	0.446	522	0.463	103	0.091	1128			1528	0.677	728	0.323	
rs7044343															
French	controls	59	0.421	69	0.493	12	0.086	140	0.72	0.43	187	0.668	93	0.332	0.45
	cases	181	0.393	230	0.500	49	0.107	460			592	0.643	328	0.357	
American	controls	57	0.380	77	0.513	16	0.107	150	0.15	0.09	191	0.637	109	0.363	0.09
	cases	142	0.335	209	0.493	73	0.172	424			493	0.581	355	0.419	
English	controls	17	0.378	23	0.511	5	0.111	45	0.67	0.84	57	0.633	33	0.367	0.83
	cases	109	0.396	124	0.451	42	0.153	275			342	0.622	208	0.378	
Pooled	controls	133	0.397	169	0.504	33	0.099	335	0.12	0.11	435	0.649	235	0.351	0.11
	cases	432	0.373	563	0.486	164	0.142	1159			1427	0.616	891	0.384	

[a] Frequent allele is coded 1 and minor allele is coded 2

Table S8 Estimated Haplotype distributions in non-ε4 bearers in the American, French, English and combined populations.

	Controls		Cases		OR [95% C.I.]	P
rs1157505 / rs11792633 / rs7044343[a]	freq.	*n*	freq.	*n*		
American non-ε4 bearers						
111	0.55	*643*	0.62	*379*	ref.	
222	0.18	*204*	0.13	*81*	0.67 [0.50-0.91]	**0.007**
122	0.14	*161*	0.12	*76*	0.80 [0.59-1.09]	0.15
112	0.07	*85*	0.07	*44*	0.88 [0.59-1.31]	0.51
P[b]		**0.04**				
French non-ε4 bearers						
111	0.54	*550*	0.63	*388*	ref.	
222	0.18	*179*	0.12	*76*	0.60 [0.44-0.82]	**8.10^{-4}**
122	0.15	*154*	0.11	*70*	0.64 [0.47-0.89]	**0.005**
112	0.07	*67*	0.07	*41*	0.87 [0.56-1.33]	0.50
P[b]		**0.001**				
English non-ε4 bearers						
111	0.54	*173*	0.64	*161*	ref.	
222	0.20	*65*	0.16	*39*	0.64 [0.40-1.04]	**0.05**
122	0.11	*34*	0.11	*27*	0.85 [0.48-1.53]	0.57
112	0.07	*23*	0.05	*12*	0.56 [0.44-1.22]	0.12
P[b]		0.15				
Combined non-ε4 bearers						
111	0.55	*1366*	0.63	*928*	ref.	
222	0.18	*449*	0.13	*197*	0.65 [0.53-0.78]	**4.10^{-6}**
122	0.14	*350*	0.12	*174*	0.73 [0.60-0.90]	**0.002**
112	0.07	*175*	0.07	*97*	0.82 [0.62-1.07]	0.13
P[b]		**7.10^{-6}**				

[a] Frequent allele is coded 1 and minor allele is coded 2

[b] *P* for global haplotype effect

Table S9 Allele and genotype distributions of the rs1157505, rs11792633 and rs11792343 SNPs in the control cohort and AD case populations.

			p	Genotype distribution (%)			p	p for trend
rs1157505	C	G		CC	CG	GG		
Controls	9858 (0.80)	2540 (0.20)		3932 (0.63)	1994 (0.32)	273 (0.04)		
all AD cases[a]	385 (0.85)	67 (0.15)	0.003 [b]	163 (0.72)	59 (0.26)	4 (0.02)	0.01	0.003
incident AD cases	232 (0.86)	38 (0.14)	0.01 [c]	**100 (0.74)**	32 (0.24)	3 (0.02)	0.03	0.01
rs11792633	C	T		CC	CT	TT		
Controls	8696 (0.70)	3702 (0.30)		3047 (0.49)	2602 (0.42)	550 (0.09)		
all AD cases[a]	352 (0.78)	100 (0.22)	0.0004 [d]	139 (0.61)	74 (0.33)	13 (0.06)	0.001	0.0004
incident AD cases	207 (0.77)	63 (0.23)	0.02 [e]	**80 (0.59)**	47 (0.35)	8 (0.06)	0.05	0.02
rs11792343	T	C		TT	CT	CC		
Controls	7950 (0.64)	4448 (0.36)		2550 (0.41)	2850 (0.46)	799 (0.13)		
all AD cases[a]	321 (0.71)	131 (0.29)	0.003 [f]	118 (0.52)	85 (0.38)	23 (0.10)	0.004	0.003
incident AD cases	189 (0.70)	81 (0.30)	0.05 [g]	**69 (0.51)**	51 (0.38)	15 (0.11)	ns	0.02

[a] all AD cases: prevalent and incident cases
[b] Allelic OR (G versus C) = 0.68, 95% CI [0.51-0.89]
[c] Allelic OR (G versus C) = 0.64, 95% CI [0.44-0.91]
[d] Allelic OR (T versus C) = 0.67, 95% CI [0.53-0.84]
[e] Allelic OR (T versus C) = 0.71, 95% CI [0.53-0.93]
[f] Allelic OR (C versus T) = 0.73, 95% CI [0.59-0.90]
[g] Allelic OR (C versus T) = 0.77, 95% CI [0.58-1.00]

Table S10 Associations between *IL33* SNPs and the risk of AD according to the *APOE* status

		all AD cases[a]		incident AD cases	
		OR (95% CI)	p	HR (95% CI)	p
rs1157505	All	0.64 (0.47-0.89)	0.007	0.72 (0.52-1.00)	0.05
	non-ε4 carriers	0.56 (0.37-0.85)	0.006	0.63 (0.43-0.96)	0.03
	ε4 carriers	0.80 (0.48-1.35)	ns	0.94 (0.55-1.59)	ns
rs11792633	All	0.61 (0.46-0.82)	0.0009	0.67 (0.50-0.90)	0.008
	non-ε4 carriers	0.58 (0.44-0.84)	0.004	0.64 (0.44-0.92)	0.02
	ε4 carriers	0.64 (0.40-1.04)	ns	0.71 (0.42-1.18)	ns
rs7044343	All	0.64 (0.48-0.85)	0.002	0.70 (0.53-0.94)	0.02
	non-ε4 carriers	0.62 (0.43-0.88)	0.008	0.67 (0.47-0.96)	0.05
	ε4 carriers	0.69 (0.42-1.12)	ns	0.74 (0.45-1.22)	ns

[a] all AD cases: prevalent and incident cases
Odds ratio (95% CI) for all AD cases (n=226) and hazard ratio (95% CI) for incident AD cases (n=135)
Adjusted for age, centre, gender, educational level, hypertension, BMI, diabetes, history of vascular disease and apolipoprotein E (APOE) genotype, when necessary.

Table S11 Associations between *IL33* haplotypes and the risk of AD, according to the *APOE* status

rs1157505 / rs11792633 / rs7044343	all AD cases (n=226)[a]				incident AD cases (n=135)			
	AD cases	Controls	OR (95% CI)	p	AD cases	Controls	HR (95% CI)	p
All								
CCT	0.593	0.654	Ref.		0.593	0.656	Ref.	
GTC	0.157	0.094	0.54 (0.38-0.75)	0.0003	0.157	0.103	0.62 (0.42-0.93)	0.01
CTC	0.138	0.123	0.79 (0.58-1.07)	ns	0.138	0.122	0.78 (0.55-1.12)	ns
CCC	0.062	0.071	1.01 (0.67-1.52)	ns	0.062	0.074	1.10 (0.68-1.79)	ns
GCT	0.045	0.052	1.00 (0.62-1.61)	ns	0.045	0.037	0.80 (0.44-1.44)	ns
non-ε4 bearers								
CCT	0.591	0.653	Ref.		0.593	0.634	Ref.	
GTC	0.159	0.070	0.39 (0.23-0.67)	0.0005	0.161	0.070	0.42 (0.22-0.80)	0.009
CTC	0.137	0.142	0.89 (0.62-1.29)	ns	0.136	0.163	1.04 (0.69-1.59)	ns
CCC	0.063	0.073	1.03 (0.61-1.73)	ns	0.062	0.081	1.28 (0.70-2.34)	ns
GCT	0.046	0.056	1.11 (0.62-1.95)	ns	0.044	0.041	0.98 (0.49-1.97)	ns
ε4 bearers								
CCT	0.599	0.652	Ref.		0.602	0.704	Ref.	
GTC	0.149	0.131	0.82 (0.51-1.33)	ns	0.151	0.142	0.85 (0.49-1.49)	ns
CTC	0.142	0.092	0.66 (0.38-1.16)	ns	0.140	0.071	0.51 (0.24-1.05)	ns
CCC	0.058	0.067	1.08 (0.54-2.16)	ns	0.058	0.031	0.45 (0.14-1.49)	ns
GCT	0.043	0.047	0.87 (0.36-2.05)	ns	0.040	0.020	0.46 (0.11-1.98)	ns

[a] all AD cases: prevalent and incident cases

Odds ratio (95% CI) for all AD cases (n=226) and hazard ratio (95% CI) for incident AD cases (n=135).

Adjusted for age, home city, gender.

Table S12. Allele and genotype distributions of the rs1157505, rs11792633 and rs11792343 SNPs in the control cohort and cases suffering from other types of dementia.

rs1157505	C	G		CC	CG	GG		
Controls	9858 (0.80)	2540 (0.20)		3932 (0.63)	1994 (0.32)	273 (0.04)		
all demented cases[a]	196 (0.79)	52 (0.21)	ns [b]	75 (0.60)	46 (0.37)	3 (0.02)	ns	ns
incident demented cases	112 (0.78)	32 (0.22)	ns [c]	42 (0.58)	28 (0.39)	2 (0.03)	ns	ns
rs11792633	C	T		CC	CT	TT		
Controls	8696 (0.70)	3702 (0.30)		3047 (0.49)	2602 (0.42)	550 (0.09)		
all demented cases[a]	176 (0.71)	72 (0.29)	ns [d]	62 (0.50)	52 (0.42)	10 (0.08)	ns	ns
incident demented cases	105 (0.73)	39 (0.27)	ns [e]	38 (0.53)	29 (0.40)	5 (0.07)	ns	ns
rs11792633	T	C		TT	CT	CC		
Controls	7950 (0.64)	4448 (0.36)		2550 (0.41)	2850 (0.46)	799 (0.13)		
all demented cases[a]	321 (0.65)	131 (0.35)	ns [f]	49 (0.40)	63 (0.51)	12 (0.10)	ns	ns
incident demented cases	98 (0.68)	46 (0.32)	ns [g]	32 (0.44)	34 (0.47)	6 (0.08)	ns	ns

[a] all demented cases: prevalent and incident cases
[b] Allelic OR (G versus C) = 1.03, 95% CI [0.75-1.22]
[c] Allelic OR (G versus C) = 1.11, 95% CI [0.73-1.27]
[d] Allelic OR (T versus C) = 0.96, 95% CI [0.72-1.28]
[e] Allelic OR (T versus C) = 0.87, 95% CI [0.59-1.28]
[f] Allelic OR (C versus T) = 0.97, 95% CI [0.74-1.27]
[g] Allelic OR (C versus T) = 0.85, 95% CI [0.58-1.21]

Table S13 Genotypic and allelic distribution of the rs10975519 SNP in the Reiman's study (**A**) and Li's study (**B**).

A

	Genotype distribution[a]								**Allele distribution**[a]				
	11		12		22				1		2		
rs10975519	n	freq	n	freq	n	freq	p	p trend	n	freq	n	freq	p
Controls	214	0.41	261	0.50	51	0.10	0.01	0.05	689	0.65	363	0.34	0.05
Cases	407	0.48	350	0.42	85	0.10			1164	0.69	520	0.31	

[a] Frequent allele is coded 1 and minor allele is coded 2

	Genotype distribution in non-ε4 bearers[a]								**Allele distribution in non-ε4 bearers**[a]				
	11		12		22				1		2		
rs10975519	n	freq	n	freq	n	freq	p	p trend	n	freq	n	freq	p
Controls	168	0.41	203	0.49	40	0.10	0.05	0.04	539	0.66	283	0.34	0.05
Cases	161	0.50	133	0.41	29	0.09			455	0.70	191	0.30	

[a] Frequent allele is coded 1 and minor allele is coded 2

B

	Genotype distribution[a]								**Allele distribution**[a]				
	11		12		22				1		2		
rs10975519	n	freq	n	freq	n	freq	p	p trend	n	freq	n	freq	p
Controls	339	0.49	297	0.43	53	0.08	0.59	0.87	975	0.71	403	0.29	0.58
Cases	339	0.49	292	0.42	64	0.09			970	0.70	420	0.30	

[a] Frequent allele is coded 1 and minor allele is coded 2

Table S14 Main characteristics of the different populations used in this study. **(A)** Complete French, American and English case-control studies. **(B)** French and American case-control sub-populations obtained by drawing lots from the complete French and American case-control studies.

A	French case-control study		American case-control study		English case-control study	
	AD cases	controls	AD cases	controls	AD cases	controls
n	734	636	871	829	370	167
Mean age	73.0 ± 8.4	73.1 ± 8.5	76.2 ± 6.2	73.6 ± 6.4	74.9 ± 7.4	68.2 ± 6.4
Mean age at onset	69.5 ± 7.4	-	72.9 ± 6.3	-	n.a	-
% of men	37	37	42	38	43	38

B	French case-control sub-population		American case-control sub-population	
	AD cases	controls	AD cases	controls
n	307	238	200	200
Mean age	74.1 ± 7.8	73.1 ± 8.5	77.2 ± 6.1	74.3 ± 5.8
Mean age at onset	68.6 ± 8.2	-	72.0 ± 12.3	-
% of men	35	43	42	38

Table S15: Baseline sociodemographic variables and potential confounding vascular risk factors for the control cohort and the prevalent & incident AD cases (for details, see the Materials and Methods section).

	Control cohort (n=6199)	Incident/prevalent AD cases (n=226)	Incident AD cases (n=131)
Age (years)	73.8 ± 5.3	79.6 ± 6.1	78.9 ± 5.7
% women	61.6%	64.8%	60.0%
ε4 allele frequency	10.6%	24.7%	19.6%
Educational level	45.7%	69.7%	55.6%
Body mass index (kg/m^2)	25.7 ± 4.0	25.0 ± 4.9	24.5 ± 4.2
Hypertension	77.0%	86.8%	79.3%
History of vascular disease	8.6%	10.0%	13.3%
Diabetes mellitus	9.1%	15.6%	14.2%

Low Educational level (primary education without a diploma, primary education with a diploma, secondary education without a baccalaureate degree).

Table S16 Methodology for genotyping: **(A)** Listing of primers and enzymes used for RFLP. **(B)** TaqMan: primers and probes (assay on demand). **(C)** TaqMan SNP genotyping assay: design already available.

A

SNP		Primer	Enzyme
(rs1157505)	Forward	5'-gctcactgcagcctccaatt-3'	Nla III
	Reverse	5'-ttgtcttgagtaagcattagg-3'	
(rs1891385)	Forward	5'-tcaagtctggtgttgtgatg-3'	HpyCH4V
	Reverse	5'-aaagaggattagagatgcac-3'	
(rs10975511)	Forward	5'-aaatggtgcacttgtattgg-3'	Mse I
	Reverse	5'-atttagtgtagtctaagtgt-3'	
(rs7035413)	Forward	5'-gaagcaggagaaagaggaga-3'	HpyCH4III
	Reverse	5'-ctttggttggtttggtccca-3'	
(rs11792633)	Forward	5'-acatggcataaggaaagagg-3'	Pae I
	Reverse	5'-tcaacactgttacaatggtg-3'	
(rs7044343)	Forward	5'-ttacatgcagacaggaaagc-3'	BspCNI
	Reverse	5'-agaggcactgataagtagag-3'	
(rs1048274)	Forward	5'-atggaaacctgtgagtcttg-3'	Ssp I
	Reverse	5'-agatgcagttatacagaggg-3'	
(rs8172)	Forward	5'-ctttgtttcattgttctgtc-3'	Rsa I
	Reverse	5'-tcgtgcacatggaccctaga-3'	

B

SNP		Primers (5'- 3')[a]	Probes [b]
(rs992969)	Forward	tgctttcttttcctcggactgg	FAM-accatttcaatt**A**acctatcac
	Reverse	agcagtcagaagcaagaacca	VIC-catttcaatt**G**acctatcac
(rs16924144)	Forward	ctgcacgtgtggtggcattatttt	FAM-catatggctcttga**G**taag
	Reverse	accaccacatactgacaattgtgat	VIC-tggctcttga**A**taag
(rs16924159)	Forward	ctcaaagtatgtgaggcatggga	FAM-cacactaaaact**A**cagagcc
	Reverse	gactttccagctggcctgt	VIC-cactaaaact**G**cagagcc
(rs16924161)	Forward	ccctaatatcagattctggctttgc	FAM-caaaacgtc**G**cataggt
	Reverse	ggatatgattgtctccctttagaagtgaa	VIC-caaaacgtc**A**cataggt

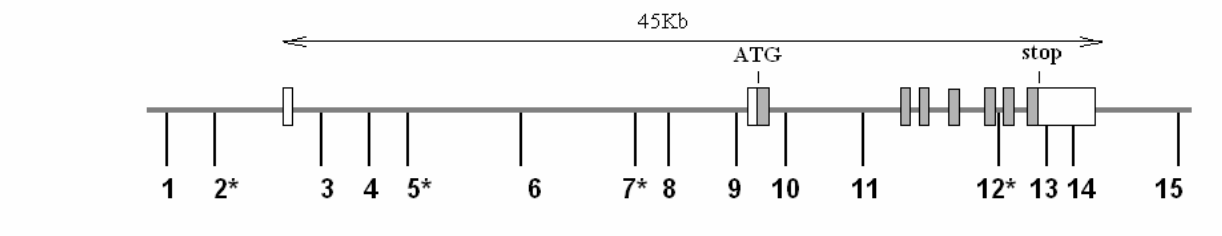
[a] F, forward primer, R reverse primer.
[b] Allelic changes in the probes are shown in boldface.

C

SNP	Reference
(rs7848215)	C_31940459_20
(rs996029)	C_3022646_10
(rs10815398)	C_31940348_20

Figure S1 (A) Location of the 15 SNPs studied in *IL-33*. **(B)** Linkage Disequilibrium between these sixteen polymorphisms using the Haploview software.

A



*TagSNPs selected in HapMap database

B

			D'													
		SNPs	1	2*	3	4	5*	6	7*	8	9	10	11	12*	13	14	15
	1	rs992969		1	0.71	1	0.88	0.93	0.83	0.43	0.05	0.54	0.83	0.82	0.82	0.48	0.87
	2*	rs7848215	**0.97**		0.67	1	0.87	1	0.82	0.48	0.13	0.57	0.81	0.82	0.81	0.62	0.86
	3	rs1157505	0.06	0.06		0.42	0.63	1	0.52	1	0.92	0.15	0.65	0.63	0.68	1	0.68
	4	rs1891385	0.05	0.05	0.01		1	1	1	1	1	1	0.79	1	0.90	1	1
	5*	rs16924144	0.14	0.14	0.26	0.07		1	0.97	1	0.96	0.79	0.38	0.23	0.34	1	0.22
	6	rs996029	0.01	0.02	0.02	0.01	0.03		1	0.19	1	0.93	0.78	1	1	0.93	1
	7*	rs16924159	0.11	0.10	0.18	0.07	**0.89**[a]	0.02		1	1	0.91	0.33	0.16	0.26	1	0.14
r^2	8	rs16924161	0.01	0.01	0.05	0.02	0.09	0.01	0.08		0.93	1	1	1	1	0.02	1
	9	rs10975511	0	0	0.11	0.05	0.20	0.13	0.19	0.37		1	0.77	0.36	0.80	0.88	0.30
	10	rs7035413	0.25	0.29	0	0.05	0.10	0.01	0.11	0.05	0.12		0.78	0.95	0.92	0.21	0.94
	11	rs11792633	0.14	0.13	0.27	0.17	0.13	0.02	0.09	0.09	0.13	0.10		0.91	0.93	0.40	0.93
	12*	rs7044343	0.17	0.17	0.19	0.21	0.04	0.07	0.02	0.11	0.04	0.19	0.64		1	1	1
	13	rs1048274	0.12	0.12	0.31	0.23	0.11	0.03	0.06	0.08	0.13	0.13	**0.81**	0.74		0.50	1
	14	rs8172	0.01	0.01	0.03	0.01	0.05	0.47	0.04	0	0.18	0	0.01	0.13	0.01		1
	15	rs10815398	0.19	0.19	0.23	0.21	0.03	0.07	0.01	0.11	0.02	0.19	0.67	**0.97**	0.75	0.13	

*TagSNPs selected in HapMap database

Bold r^2>0.8

[a] in the Hapmap database, the r^2 between these two polymorphisms was of 0.74. However, we observed in both French and American control populations a r^2 of 0.89 and 0.86, respectively.

Figure S2 Overexpression of IL-33 in the COS-7 cell line cotransfected with APP^{695wt} and IL-33 expression vectors. **(A)** Representative experiment of APP metabolism variations following transfection following IL-33 and APP^{695wt} cDNA transfection; **(B)** Representative experiment of $A\beta_{40}$ secretion following transfection of the IL-33 expression vector; **(C)** Mean variations of the $A\beta_{40}$ secretions from three independent experimentations in duplicates. **(D)** IL-33 accumulates in nucleus (colocalisation with dense regions of DAPI staining, indicating association with heterochromatin). No signal was detected using an empty vector (Mock) (Data not shown).

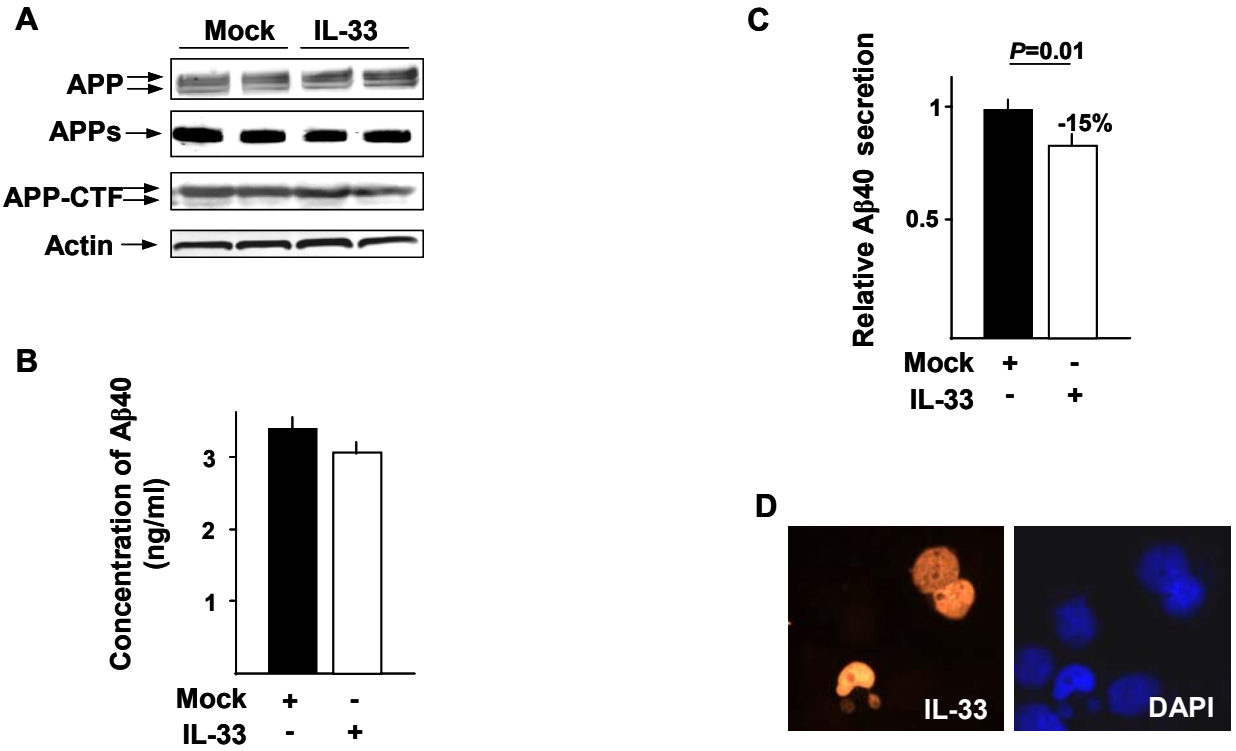


Figure S3 Integrated strategy for the characterization of new AD genetic determinants.