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Supplementary Data

Genetic Study of Neurexin and Neuroligin Genes in Alzheimer's Disease

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Description of genome-wide association study (GWAS) datasets employed in the study

The Murcia study was designed as a new case-control GWAS in the Spanish population. In this study, 1,128 individuals were genotyped using Affymetrix NspI 250K chip. A sample of 327 sporadic Alzheimer's disease (AD) patients diagnosed as possible or probable AD in accordance with NINCDS-ADRDA criteria by neurologists at the Virgen de Arrixaca University Hospital in Murcia (Spain) and 801 controls with unknown cognitive status from the Spanish general population were included.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) longitudinal study was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the

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[1] Some data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Supplementary Table 1
Primers and probes employed for real-time detection of rs17757879 marker.

PCR primers	Forward	5′ CTTCCCTAAAATAATCCTTGAGG 3′
	Reverse	5′ AGGGTTACAACTTCAGCAGC 3′
FRET probes	Sensor	5′ GTTTATCTCATCCTCCTTGAC-Fluorescein 3′
	Anchor	5′ Cy5-CTCCACATCTCTAAGTAGGAAGTTA–Phosphate 3′

Supplementary Table 2
Top results ($p < 0.01$) in the meta-analysis of five GWAS

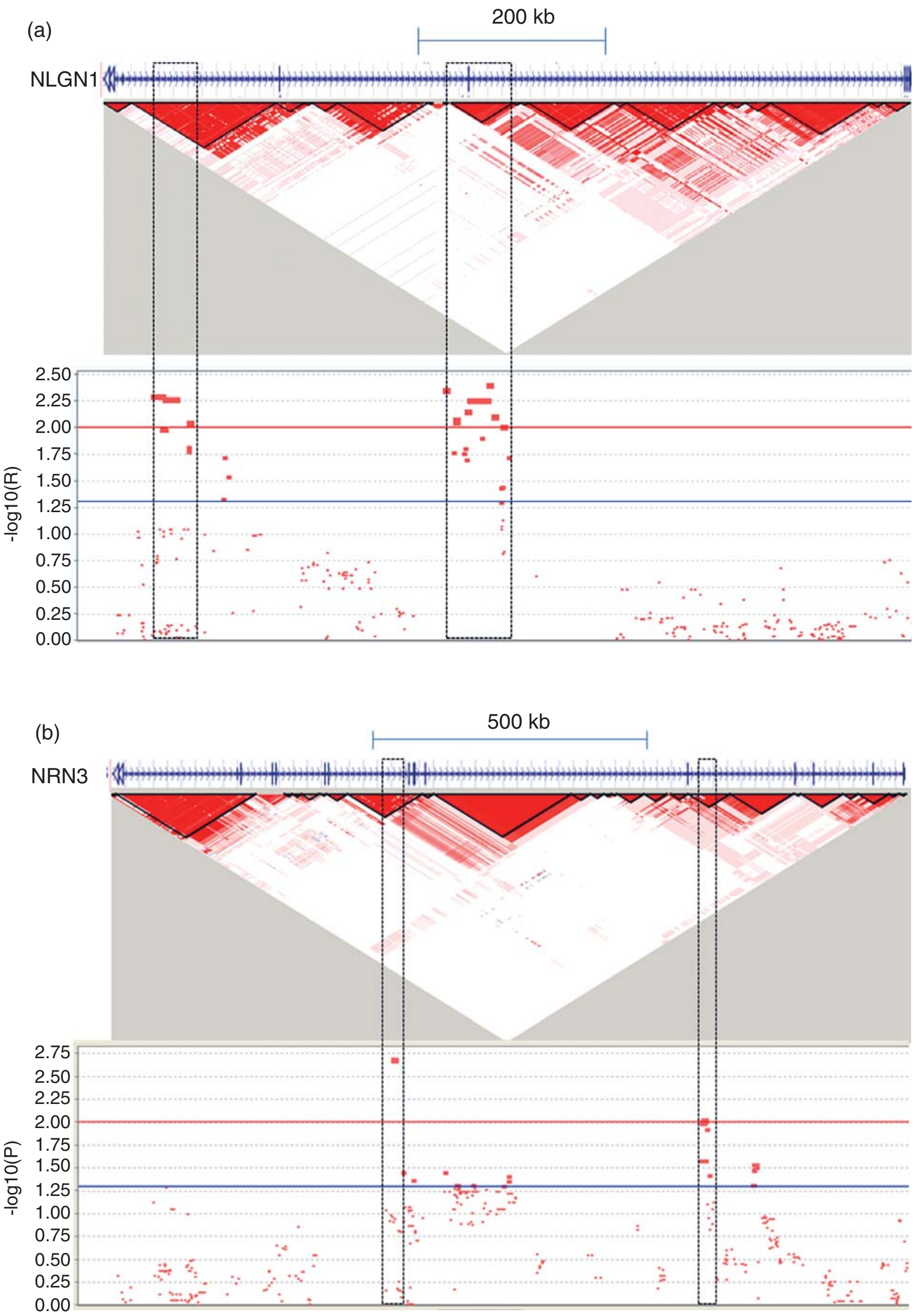
CHR	BP	SNP	A1	A2	*p*	*p* (R)	OR	OR (R)	Q	I	ADNI	Murcia	GenADA	TGEN	NIA
3	174653917	rs247983	T	C	0.004919	0.004919	0.8495	0.8495	0.5105	0.00	1.0700	0.7321	0.7706	0.9188	0.8999
3	174657727	rs247969	G	T	0.004919	0.004919	0.8495	0.8495	0.5105	0.00	1.0700	0.7321	0.7706	0.9188	0.8999
3	174662837	rs34255	C	T	0.004919	0.004919	0.8495	0.8495	0.5105	0.00	1.0700	0.7321	0.7706	0.9188	0.8999
3	174663475	rs665913	C	A	0.009955	0.009955	0.8616	0.8616	0.4204	0.00	1.0730	0.7321	0.7706	0.9234	0.9348
3	174666040	rs623616	C	G	0.005203	0.005203	0.8504	0.8504	0.5026	0.00	1.0700	0.7321	0.7706	0.9234	0.8999
3	174668986	rs522816	G	A	0.005203	0.005203	0.8504	0.8504	0.5026	0.00	1.0700	0.7321	0.7706	0.9234	0.8999
3	174669852	rs247972	A	T	0.005203	0.005203	0.8504	0.8504	0.5026	0.00	1.0700	0.7321	0.7706	0.9234	0.8999
3	174678125	rs546707	A	C	0.005203	0.005203	0.8504	0.8504	0.5026	0.00	1.0700	0.7321	0.7706	0.9234	0.8999
3	174693746	rs550495	G	A	0.008733	0.008733	0.8589	0.8589	0.4955	0.00	1.0700	0.7503	0.7695	0.9492	0.8999
3	174972148	rs9879266	C	T	0.004341	0.004341	1.1201	1.1201	0.8623	0.00	1.0310	1.2260	1.1120	1.1230	1.0900
3	174982953	rs4377507	G	A	0.00819	0.01682	1.1567	1.1592	0.3011	17.83	1.0920	1.4120	0.9870	1.2350	1.1260
3	174983921	rs9876713	A	G	0.008596	0.008596	1.1575	1.1575	0.4553	0.00	1.0890	1.4150	1.0470	1.1830	1.1020
3	174984586	rs1488549	C	T	0.008079	0.008079	1.1589	1.1589	0.4609	0.00	1.0890	1.4150	1.0470	1.1830	1.1060
3	174993426	rs1352418	T	C	0.007675	0.01744	1.1585	1.1621	0.2829	20.68	1.0890	1.4210	0.9991	1.2590	1.1060
3	174994891	rs9290480	T	C	0.006959	0.01554	1.1613	1.1646	0.2898	19.60	1.0930	1.4210	0.9991	1.2590	1.1120
3	174996115	rs1488551	G	A	0.006889	0.006889	1.1631	1.1631	0.4759	0.00	1.0930	1.4150	1.0470	1.1830	1.1160
3	174996913	rs7640492	A	G	0.008551	0.01963	1.1560	1.1601	0.2762	21.72	1.0890	1.4210	0.9991	1.2590	1.0990
3	174999420	rs1352419	A	G	0.005341	0.005341	1.1585	1.1585	0.4145	0.00	1.0010	1.3420	1.0600	1.3010	1.0930
3	175008425	rs1488548	G	T	0.005341	0.005341	1.1585	1.1585	0.4145	0.00	1.0010	1.3420	1.0600	1.3010	1.0930
3	175013554	rs4894630	A	G	0.005341	0.005341	1.1585	1.1585	0.4145	0.00	1.0010	1.3420	1.0600	1.3010	1.0930
3	175016251	rs6790407	G	A	0.005341	0.005341	1.1585	1.1585	0.4145	0.00	1.0010	1.3420	1.0600	1.3010	1.0930
3	175016771	rs6767217	C	A	0.005341	0.005341	1.1585	1.1585	0.4145	0.00	1.0010	1.3420	1.0600	1.3010	1.0930
3	175017094	rs6791322	G	T	0.005341	0.005341	1.1585	1.1585	0.4145	0.00	1.0010	1.3420	1.0600	1.3010	1.0930
3	175017345	rs6782728	A	G	0.005341	0.005341	1.1585	1.1585	0.4145	0.00	1.0010	1.3420	1.0600	1.3010	1.0930
3	175020335	rs1873038	C	T	0.003869	0.003869	1.1643	1.1643	0.4587	0.00	1.0300	1.3420	1.0600	1.3010	1.1050
3	175026145	rs9878812	C	T	0.00767	0.00767	1.1498	1.1498	0.4545	0.00	1.0010	1.3420	1.0510	1.2570	1.0930
3	175035969	rs7652242	A	G	0.00828	0.00947	1.1542	1.1543	0.3896	2.98	1.0480	1.4190	1.0200	1.1460	1.1460
14	78458095	rs17757879	T	C	**0.002009**	**0.002009**	**0.8514**	**0.8514**	**0.9367**	**0.00**	**0.8628**	**0.8446**	**0.7960**	**0.8584**	**0.8980**
14	79023567	rs11845632	A	G	0.009685	0.0633	1.1037	1.1030	0.1308	43.65	1.0220	1.3130	1.0380	0.9762	1.1690
14	79027729	rs8017761	T	C	0.009258	0.05975	1.1044	1.1040	0.1338	43.17	1.0320	1.3130	1.0380	0.9762	1.1690

CHR, chromosome; BP, basepair position; SNP, single nucleotide polymorphism; A1, reference allele; A2, alternative allele; *p*, fixed-effects *p*-value; *p* (R), random-effects *p*-value; OR, fixed-effects odds ratio; OR (R), random-effects odds ratio; Q, *p*-value for heterogeneity of OR; I, effect size for heterogeneity of OR. The last five columns show the OR for each GWAS. Bold values represent the most interesting results.

progression of mild cognitive impairment (MCI) and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

The GenADA study included 801 cases meeting the NINCDS-ADRDA and DSM-IV criteria for probable AD, and 776 control subjects without family history of dementia, that were genotyped using Affymetrix 500K GeneChip Array set.

The NIA Genetic Consortium for Late Onset Alzheimer's Disease (LOAD) Study originally included 1,985 cases and 2,059 controls genotyped



Supplementary Figure 1. *NLGN1* (a) and *NRXN3* (b) gene regions. Gene structure, linkage disequilibrium map, and representation of the genetic association results for each SNP within a) the *NLGN1* gene and b) *NRXN3* gene (dots symbolize the negative logarithm of the *p*-value at each marker).

with Illumina Human 610Quad platform. Using family trees provided in the study, we excluded all related controls and kept one case per family. A total of 1,077 cases and 876 unrelated controls were eligible for our study

The TGEN GWAS study included 643 LOAD cases and 404 controls from a neuropathological cohort and 197 LOAD cases and 114 controls from a clinical cohort, all genotyped with Affymetrix 500K GeneChip Array set.

Supplementary Table 3
Haplotypic meta-analysis in four LD regions from *NLGN1* and *NRXN3* genes

Gene	LD block number	Tag SNPs	Haplotypes	OR (95% CI)	*p*
NLGN1	2	rs583173, rs1248807, rs11709498	ACA	0.988 (0.887–1.102)	0.834
			ATA	1.135 (0.994–1.267)	0.061
			GTA	0.915 (0.822–1.018)	0.102
			ATC	1.012 (0.865–1.182)	0.885
			GTC	1.005 (0.932–1.083)	0.902
	9	rs987613, rs187038, rs1948158	ACA	1.192 (1.063–1.336)	0.002
			GCA	0.960 (0.679–1.357)	0.816
			GTA	0.965 (0.863–1.080)	0.539
			ACC	1.077 (0.769–1.510)	0.665
			GTC	0.925 (0.851–1.005)	0.065
NRXN3	8	rs154323, rs154378, rs150774, rs17108405	ACGG	1.033 (0.921–1.157)	0.579
			ACGA	0.980 (0.788–0.1220)	0.858
			CCAA	0.794 (0.620–1.018)*	0.068*
			CTAA	1.073 (0.980–1.176)	0.128
	16	rs11845632, rs8020593	AT	1.059 (0.987–1.137)	0.112
			AC	1.369 (0.911–2.058)*	0.1304*
			GC	0.912 (0.848–0.981)	0.0129

*Data from random model.