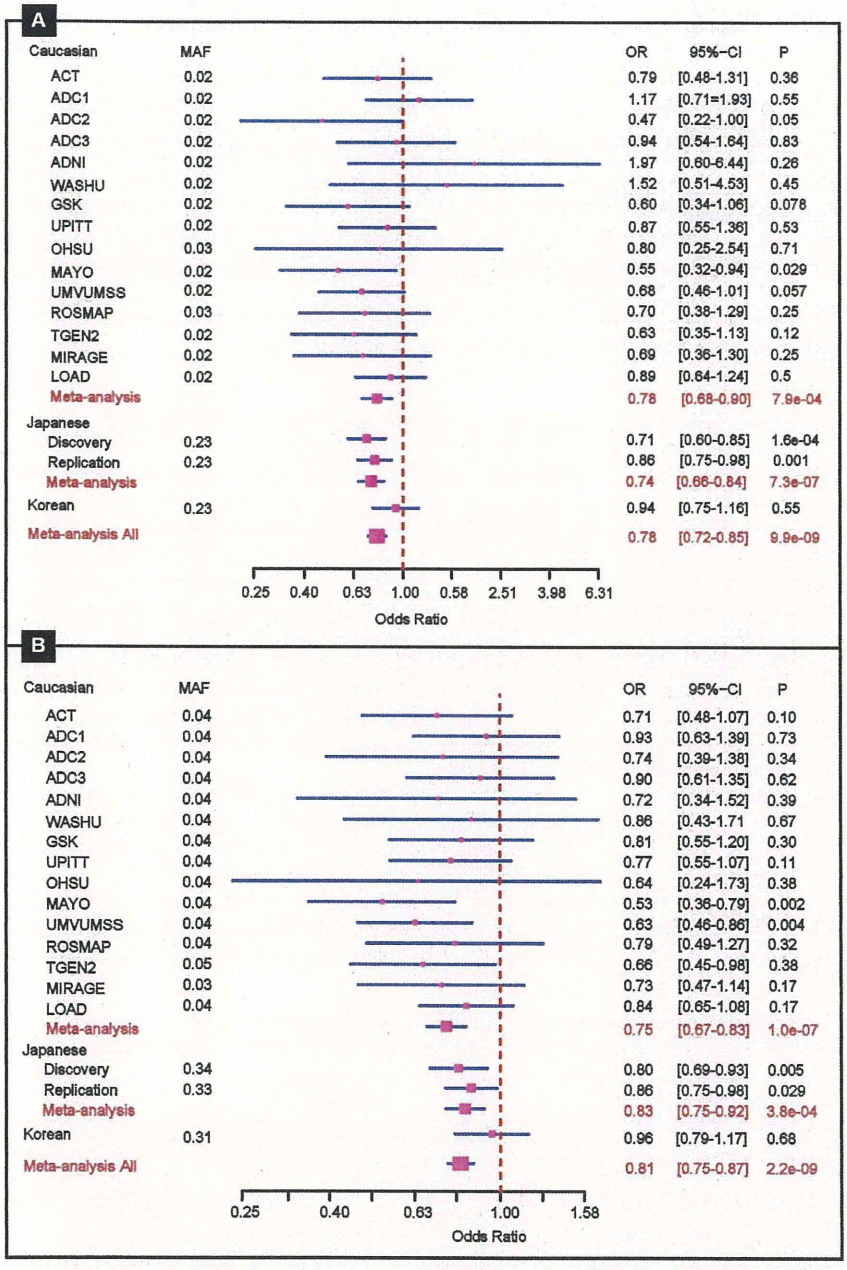

Figure 2. Forest plots of the two most strongly associated SNPs, rs3781834 (A) and rs11218343 (B), in the *SORL1* region showing the strength and pattern of significance in the Japanese discovery and each replication dataset in the model of adjusting for population structure, age, and sex.
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wide significant AD locus in much larger GWAS [4,5]. Given the discovery sample size, effect size (odds ratio [OR] =0.74) and MAF (0.23) of the top *SORL1* SNP (rs3781834) in the Japanese sample, and a significance level of 2×10^{-5} (i.e., threshold for including a SNP in the Stage 2 replication phase), calculation of power *post hoc* using the PAWE-3D program [22] confirmed that the discovery sample had sufficient power (83.7%). By comparison, the Caucasian sample of 22,771 subjects had only 52.8% power to detect association with this SNP at the observed significance level of 7.9×10^{-4} and OR (0.78) and a much lower MAF (0.02) than in Japanese.

The most significant result in the GWAS in Japanese was obtained for *PALM2* SNP rs913360 ($P=1.8\times10^{-7}$), but this SNP was not significant in the Japanese replication sample ($P=0.16$) and the result for the combined Japanese datasets was less significant than in the discovery sample ($P=6.6\times10^{-6}$). There was no evidence in the large Caucasian dataset supporting association for rs913360 ($P=0.38$) or other *PALM2* SNPs.

Table 3. Meta-analysis of top-ranked association results with *SORL1* in Japanese, Korean, and Caucasian datasets.

SNP	MA	Japanese (Stage 1+2)			Korean (Stage 3)			Caucasian (Stage 3)			Meta-Analysis (Stages 1–3)	
		MAF	OR (95% CI)	P	MAF	OR (95% CI)	P	MAF	OR (95% CI)	P	OR (95% CI)	P
rs4598682	G	0.23	0.75 (0.66–0.85)	9.5×10^{-6}		not available		0.02	1.04 (0.85–1.28)	0.68	0.82 (0.72–0.93)	3.6×10^{-3}
rs11218343	C	0.34	0.83 (0.75–0.92)	3.8×10^{-4}	0.31	0.96 (0.79–1.17)	0.68	0.04	0.75 (0.67–0.83)	1.0×10^{-7}	0.81 (0.75–0.87)	2.2×10^{-9}
rs3781834	G	0.23	0.74 (0.66–0.84)	7.3×10^{-7}	0.23	0.94 (0.75–1.16)	0.55	0.02	0.78 (0.68–0.9)	7.9×10^{-4}	0.78 (0.72–0.85)	9.9×10^{-9}
rs17125523	G	0.25	0.77 (0.68–0.86)	5.5×10^{-6}	0.23	0.96 (0.78–1.19)	0.72	0.02	0.85 (0.74–0.99)	0.034	0.82 (0.76–0.89)	3.3×10^{-6}
rs3737529	T	0.25	0.77 (0.68–0.86)	4.1×10^{-6}	0.26	1.04 (0.84–1.29)	0.70	0.02	0.83 (0.71–0.97)	0.016	0.82 (0.76–0.89)	5.1×10^{-6}

CH:MB, chromosome:position (in megabase pairs, build 19); MA, minor allele; MAF, minor allele frequenc; OR, odds ratio; *P* P-value.
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We obtained evidence in Japanese and Korean populations for association of AD with the same SNPs in the *PICALM* and *BIN1* regions that were identified as genome-wide significant in multiple large GWAS in Caucasians [4,5]. There are no previously reported association studies of these loci in Japanese. Several small association studies of *PICALM* in comparatively smaller Chinese samples have yielded conflicting results [23–25]. We also found nominally significant associations in the Japanese sample for previously associated SNPs in *CR1*, *CLU*, and *ABCA7*. Lack of association with *EPHA1*, *CD2AP*, *MS4A6A*, and *CD33* may be due to insufficient power, different linkage disequilibrium structure of these regions than in Caucasisans, locus heterogeneity or intragenic heterogeneity.

In addition, our analyses showed numerous highly significant results for imputed SNPs in the *APOE* region (including *CEACAM/BCL3*, *PVRL2*, *TOMM40*, and *LOC284352)* even after adjustment for the dose of the ε4 allele. However, recognizing that the reliability of imputation is poor for SNPs in this region [13], we genotyped 10 of the significant SNPs in the Japanese discovery and replication datasets. Only one of these results, a *PPP1R37* SNP, was nominally significant after adjustment for dose of ε4. Association of AD with this SNP, which is located approximately 225 kb from *APOE*, has not been observed previously. *PVRL2* and *APOE* are located in a genomic region sandwiched between two recombination hotspots [26], where strong association signals for LOAD have been reproducibly detected in Caucasians [1,5], but dissipate almost completely for all non-*APOE* loci after conditioning on *APOE*, suggesting that no other loci in this region influence LOAD susceptibility [13]. This conclusion is consistent with the observation of moderate linkage disequilibrium between the SNPs determining *APOE* genotype, rs7412 and rs429358 (Fig. S5), SNPs showing genomewide significant evidence for association with LOAD without adjustment for *APOE* genotype, and our prior LOAD association studies with SNPs in this region among Caucasians [13].

SorL1, also known as SorLA and LR11, and APP proteins are co-localized in the endosomal and Golgi compartments [27]. SorL1 through its co-dependent interaction with vps26 regulates the intracellular transport and processing of APP, resulting in reduction of amyloid beta (Aß) peptide production [20,27,28]. *SORL1* knock-out mice carrying both pathogenic mutations in the *PSEN1* (exon 9 deletion) and *APP* (Swedish, K595M/N596L)

Table 4. Association of LOAD in Asians with SNPs showing genome-wide significance in Caucasians.

Gene	CH	BP	SNP	MA	Japanese			Korean		
					MAF	P	OR (95% CI)	MAF	P	OR (95% CI)
CR1	1	207,692,049	rs6656401	A	0.04	***9.02E-03***	1.38 (1.08–1.76)	0.04	3.75E-01	1.24 (0.77–1.99)
CR1	1	207,784,968	rs3818361	A	0.39	2.54E-01	0.94 (0.85–1.04)	0.31	4.08E-01	0.92 (0.76–1.12)
BIN1	2	127,894,615	rs744373	G	0.33	***1.39E-04***	1.25 (1.11–1.4)	0.36	8.05E-01	0.98 (0.81–1.18)
CD2AP	6	47,453,378	rs9349407	G	0.14	3.83E-01	0.94 (0.82–1.08)	NT	–	–
EPHA1	7	143,109,139	rs11767557	C	0.17	6.47E-01	1.03 (0.9–1.17)	NT	–	–
CLU	8	27,456,253	rs2279590	T	0.25	***7.01E-03***	0.85 (0.76–0.96)	0.2	9.70E-02	0.82 (0.65–1.04)
CLU	8	27,464,519	rs11136000	T	0.28	***1.09E-02***	0.87 (0.78–0.97)	0.23	***3.61E-02***	0.79 (0.63–0.98)
CLU	8	27,468,862	rs9331888	G	0.41	6.97E-02	1.1 (0.99–1.22)	0.47	1.92E-01	0.89 (0.74–1.06)
MS4A6A	11	59,939,307	rs610932	T	0.3	7.99E-01	0.99 (0.89–1.1)	NT	–	–
MS4A6A	11	59,971,795	rs670139	T	0.4	8.23E-01	0.99 (0.89–1.09)	NT	–	–
MS4A6A	11	60,034,429	rs4938933	C	0.27	3.23E-01	1.06 (0.95–1.18)	NT	–	–
PICALM	11	85,868,640	rs3851179	T	0.39	***1.71E-05***	0.8 (0.73–0.89)	0.34	***1.99E-02***	0.79 (0.66–0.96)
ABCA7	19	1,046,520	rs3764650	G	0.42	***3.66E-02***	1.13 (1.01–1.27)	NT	–	–
EXOC3L2	19	45,708,888	rs597668	C	0.43	***8.23E-03***	0.88 (0.79–0.97)	0.37	7.31E-01	0.97 (0.8–1.17)
CD33	19	51,727,962	rs3865444	A	0.2	4.92E-01	1.04 (0.92–1.18)	NT	–	–

NT not tested; P<0.05 was italized.
doi:10.1371/journal.pone.0058618.t004

exhibited increased production and accumulation of Aß [29]. *SORL1* variants might influence the CSF Aß42 level in AD patients [30]. Recently, Pottier et al. sequenced the exomes of 29 index cases with autosomal dominant early-onset AD who lacked mutations in *APP*, *PSEN1* and *PSEN2* [2]. Seven of these subjects had private *SORL1* mutations (2 nonsense and 2 missense) that were predicted to have a pathogenic effect. By comparison, the two genome-wide significant SNPs in this study are both intronic. It is expected that future large resequencing studies of *SORL1* will identify the functional variants, thus providing important clues about the mechanisms governing normal and abnormal action of SorL1 on processes leading to LOAD. The emergence of *SORL1* as a genome-wide significant locus for AD confirms existing genetic and functional evidence and elevates the importance of intracellular trafficking involving retromer and the Golgi-to-endosome as a key pathway leading to AD [31,32].

Supporting Information

Figure S1 Quantile-quantile (Q-Q) plot of observed (y-axis) vs. expected (x-axis) *P*-values from tests of association genome-wide (5,877,918 SNPs) adjusted for population structure, age and sex for LOAD in the Japanese discovery sample. Genomic inflation was low ($\lambda = 1.047$).
(TIF)

Figure S2 Manhattan plot of observed $-\log_{10}$ *P*-values for genome-wide SNP association tests for LOAD (y-axis) according to chromosomal location (x-axis) in the Japanese discovery sample adjusted for population structure, age, and sex. All genome-wide significant SNPs (above the horizontal line corresponding to $P = 5 \times 10^{-8}$ on the y-axis) are located in the *APOE* region on chromosome 19.
(TIF)

Figure S3 Linkage disequilibrium (r^2) among SNPs in the *APOE* region genotyped using TaqMan calculated in the Japanese discovery (A) and replication (B) datasets. *APOE* genotype is derived from haplotypes of coding SNPs rs429358 and rs7412.
(TIF)

Figure S4 Linkage disequilibrium (r^2) among SNPs in the *SORL1* region genotyped in the Japanese discovery (A) and replication (B) datasets.
(TIF)

Figure S5 Comparison of *SORL1* association findings in the current study with association signals previously identified by Rogaeva et al. [20]. (**A**) Regional association plot of the *SORL1* region. P-values are expressed as $-\log_{10}$(P) (y-axis) for every tested SNP ordered by chromosomal location (x-axis) and represented as blue rectangles for the Japanese discovery set (J1), light blue diamonds for the ADGC Caucasian set (C), pink circles for meta-analysis of Japanese discovery and Caucasian sets (J1+C), and red circles for meta-analysis of Japanese discovery, Japanese replication (J2), Korean (K), and Caucasian sets (J1+J2+K+C). The numbers below the line showing the orientation of *SORL1* are the designations for associated SNPs in the Rogaeva et al. study: 8 = rs668387, 9 = rs689021, 10 = rs641120, 11 = rs4935775, 19 = rs2070045, 22 = rs1699102, 23 = rs3824968, 24 = rs2282649, and 25 = rs1010159. Recombination hotspots are indicated by the continuous blue line behind the symbols for the SNP P-values. (**B**) Linkage disequilibrium (r^2) of the previously associated SNPs in the *SORL1* region [20] in the HapMap 2 reference Japanese population (JPT). The association signal with rs3781834 (contained in Block 2) appears to be independent of one of the distinct AD-associated haplotypes reported by Rogaeva et al. [20] (including SNPs in Block 1), but not necessarily independent of the other AD-associated haplotype reported by Rogaeva et al which includes rs1699102 in Block 2 and the SNPs in Block 3.
(TIF)

Table S1 Top-ranked GWAS results in the Japanese GWAS dataset ($P<1\times10^{-4}$ and imputation quality ≥0.8) with and withut adjustment for the number of *APOE* ε4 alleles.
(DOCX)

Table S2 Association of individually genotyped SNPs in the *APOE* region in models with and without adjustment for the number of *APOE* ε4 alleles.
(DOCX)

Table S3 Association results for *SORL1* SNPs genotyped in the Japanese replication sample.
(DOCX)

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