Polygenic overlap between C-reactive protein, plasma lipids and Alzheimer's disease

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ABSTRACT

Objective: Epidemiological findings suggest a relationship between Alzheimer's disease (AD), inflammation and dyslipidemia, although the nature of this relationship is not well understood. We investigated whether this phenotypic association arises from a shared genetic basis.

Methods and Results: Using summary statistics (p-values and odds ratios) from genome-wide association studies of over 200,000 individuals, we investigated overlap in single nucleotide polymorphisms (SNPs) associated with clinically diagnosed AD and C-reactive protein (CRP), triglycerides (TG), high (HDL) and low-density lipoprotein (LDL) levels. We found up to 50-fold enrichment of AD SNPs for different levels of association with CRP, LDL, HDL and TG SNPs using an FDR threshold < 0.05. By conditioning on polymorphisms associated with the four phenotypes, we identified 55 loci associated with increased AD risk. We then conducted a meta-analysis of these 55 variants across four independent AD cohorts (total n = 29,054 AD cases and 114,824 healthy controls) and discovered two genome-wide significant variants on chromosome 4 (rs13113697, closest gene *HS3ST1*, odds ratio (OR) = 1.07, 95% confidence interval (CI) = 1.05-1.11, $p = 2.86 \times 10^{-8}$) and chromosome 10 (rs7920721, closest gene *ECHDC3*, OR = 1.07, 95% CI = 1.04-1.11, $p = 3.38 \times 10^{-8}$). We also found that gene expression of *HS3ST1* and *ECHDC3* was altered in AD brains compared with control brains.

Conclusions: We demonstrate genetic overlap between AD, CRP, and plasma lipids. By conditioning on the genetic association with the cardiovascular phenotypes, we identify novel AD susceptibility loci including two genome-wide significant variants conferring increased risk for Alzheimer's disease.

Keywords: Alzheimer's disease, inflammation, plasma lipids, GWAS

INTRODUCTION

Late-onset Alzheimer's disease (AD) is the most common form of dementia with an estimated prevalence of 30 million people worldwide, a number that is expected to quadruple in the next 40 years.[1] Given the absence of disease-modifying therapies and increasing awareness that symptoms develop over many years, there is significant interest in identifying effective strategies for AD prevention. Delaying dementia onset by a modest 2 years could potentially lower the worldwide prevalence of AD by more than 22 million cases over the next 40 years, resulting in significant societal savings.[1]

A growing body of evidence suggests an association between AD and potentially modifiable processes including dyslipidemia and inflammation. In observational studies, high serum cholesterol levels have been associated with increased risk of AD [2,3] and molecular [4] and biomarker findings [5] suggest that phospholipids may play an integral role in modulating AD-associated pathogenesis. Complement factors and activated microglia are established histopathologic features in brains of AD patients [6] and epidemiological studies in older individuals indicate that high serum levels of inflammatory proteins are associated with cognitive decline [7] and may predict dementia risk. [8] Genome-wide association studies (GWAS) in late-onset AD have replicated the established association with apolipoprotein E (*APOE*) and identified single nucleotide polymorphisms (SNPs) implicated in lipid metabolism, such as *CLU* and *ABCA7* and inflammatory processes, such as *CR1* and *HLA-DRB5*. [9,10] In addition, a rare sequence variant in *TREM-2* with known anti-inflammatory function has recently been identified as conferring increased risk for AD. [11,12] Taken together, these findings suggest that processes involved with lipid metabolism and inflammation may also impact Alzheimer's pathogenesis.

Combining GWAS from multiple disorders and phenotypes provides insights into genetic pleiotropy (defined as a single gene or variant being associated with more than one distinct phenotype) and could elucidate shared pathobiology. Using this approach, we have recently reported genetic overlap between a number of diseases and phenotypes and identified novel common variants associated with schizophrenia, [13,14] bipolar disorder,[13] prostate cancer,[15] hypertension, [16] and primary sclerosing cholangitis. [17] Here, we applied this method to AD, taking advantage of several large GWASs, [18-20] to identify SNPs associating with clinically diagnosed AD, C-reactive protein (CRP) levels, and plasma lipid levels (specifically triglycerides (TG), high- (HDL) and low-density lipoproteins (LDL)).

METHODS

Participant Samples

We evaluated complete GWAS results in the form of summary statistics (p-values and odds ratios) for clinically diagnosed AD, [18] CRP levels, [19] and plasma lipid levels (TG, HDL and LDL [20] (see Table 1). The CRP GWAS summary statistic data consisted of 82,725 individuals drawn from 25 studies with genotyped or imputed data at 2,671,742 SNPs (for additional details see reference 19). The plasma lipids GWAS summary statistic data consisted of 188,577 individuals with genotyped or imputed data at 2,508,375 SNPs (for additional details see reference 20). We obtained publicly available AD GWAS summary statistic data from the International Genomics of Alzheimer's Disease Project (IGAP Stage 1 + 2, for additional details see Supplemental Information and reference 18). We used IGAP Stage 1 as our discovery cohort, which consisted of 17,008 AD cases (mean age = 74.7 ± 7.7 years; 59.4% female) and 37,154 controls (mean age = 76.3 ± 8.1 years; 58.6% female) drawn from four different consortia across North America and Europe with genotyped or imputed data at

7,055,881 SNPs (for a description of the AD cases and controls within the IGAP Stage 1 sub-studies, please see reference 18). To confirm our findings from IGAP Stage 1, we assessed the p-values of pleiotropic SNPs (conditional FDR < 0.05; see Statistical analysis below) from the discovery analyses in three independent AD cohorts, namely the IGAP Stage 2 sample, a cohort of AD cases and controls drawn from the population of Iceland (deCODE), and a cohort of AD cases and controls drawn from the population of Norway (DemGene). The IGAP Stage 2 sample consisted of 8,572 AD cases (mean age = 72.5 ± 8.1 years; 61% female) and 11,312 controls (mean age = 65.5 ± 8.0 years; 43.3% female) of European ancestry with genotyped data at 11,632 SNPs (for additional details see reference 18). Clinical diagnosis of probable AD within the IGAP Stage 2 cohort was established according to the DSM-III-R and NINCDS-ADRDA criteria. [21] The deCODE dataset was drawn from the Icelandic population and included 2,470 genotyped AD cases (age = 84.9 ± 7.2 years; 65.8 % female) and 65,347 genotyped controls (age = 68.8 ± 13.7 years; 57.8% females) (for additional details see reference 12). As previously described, [12] patients from Iceland were diagnosed with definite, probable or possible Alzheimer's disease based on the NINCDS-ADRDA criteria [21] or according to guidelines for ICD-10 F00, and were compared to population controls. The Norwegian sample (DemGene) included 1,004 cases (age = 74.1 ± 9.6 years; 60.2 % female) and 1,011 controls (age = 74.6 ± 9.3 years; 57.7 % female) with genotyped data at 693,377 SNPs. Clinical diagnosis of AD and dementia within the DemGene sample was established using ICD-10 research criteria [22], the recommendations from the National Institute on Aging-Alzheimer's Association (NIA/AA) [23] or the NINCDS-ADRDA criteria [21] (Supplemental Information). The relevant institutional review boards or ethics committees approved the research protocol of the individual GWAS used in the current analysis, and all human participants gave written informed consent.

For gene expression analyses, we used publicly available total RNA expression data from

1647 autopsied brain tissues (from dorsolateral prefrontal cortex, visual cortex and cerebellum) in 549 brains of 376 AD patients and 173 non-demented healthy controls from the Gene Expression Omnibus (GEO) data set GSE44772. [24] As described previously, [24] all subjects were diagnosed at intake and each brain underwent extensive neuropathology examination. Tissues were profiled on a custom-made Agilent 44K array of 40,638 DNA probes.

Statistical analysis

Using recently developed statistical methods to evaluate pleiotropic effects, [13-17] we evaluated SNPs associating with AD (discovery cohort - IGAP Stage 1) and CRP levels as well as AD and plasma lipid levels. For given associated phenotypes A and B, pleiotropic 'enrichment' of phenotype A with phenotype B exists if the proportion of SNPs or genes associated with phenotype A increases as a function of increased association with phenotype B. To assess for enrichment, we constructed fold-enrichment plots of nominal $-\log_{10}(p)$ values for all AD SNPs and for subsets of SNPs determined by the significance of their association with CRP and plasma lipids. We also utilized conditional quantile-quantile (Q-Q) plots, which are complementary to fold-enrichment plots and provide visualization of polygenic enrichment (for additional details see Supplemental Information). In fold-enrichment plots, the presence of enrichment is reflected as an upward deflection of the curve for phenotype A if the degree of deflection from the expected null line is dependent on the degree of association with phenotype B. To assess for polygenic effects below the standard GWAS significance threshold, we focused the fold-enrichment plots on SNPs with nominal $-\log_{10}(p) < 7.3$ (corresponding to $p > 5x10^{-8}$). The enrichment seen can be directly interpreted in terms of true discovery rate (TDR = 1 – False Discovery Rate (FDR)) (for additional details see Supplemental Information).

To identify specific loci we computed conditional FDRs. [13,14] The standard FDR framework derives from a model that assumes the distribution of test statistics in a GWAS can be formulated as a mixture of null and non-null effects, with true associations (non-null effects) having more extreme test statistics, on average, than false associations (null effects). The FDR can be interpreted, as the probability that a SNP is null given its p-value is as small or smaller than its observed p-value. The conditional FDR is an extension of the standard FDR, which incorporates information from GWAS summary statistics of a second phenotype to adjust its significance level. The conditional FDR is defined as the probability that a SNP is null in the first phenotype given that the p-values in the first and second phenotypes are as small as or smaller than the observed ones. It is important to note that ranking SNPs by standard FDR or by p-values both give the same ordering of SNPs. In contrast, if the primary and secondary phenotypes are related genetically, conditional FDR re-orders SNPs, and results in a different ranking than that based on p-values alone. We used an overall FDR threshold of < 0.05, which means 5 expected false discovery per hundred reported. Additionally, we constructed Manhattan plots based on the ranking of conditional FDR to illustrate the genomic location. In all analyses, we controlled for the effects of genomic inflation by using intergenic SNPs (see Supplemental Information). Detailed information on fold enrichment and conditional Q-Q plots, Manhattan plots, and conditional FDR can be found in the Supplemental Information and prior reports. [13-17]

For loci with conditional FDR < 0.05, we performed a fixed effects, inverse variance weighted meta-analysis[25] across all available AD cohorts (IGAP Stage 1 + 2, deCODE, and DemGene, total n = 29,054 AD cases and 114,824 healthy controls) using the R package *meta* (http://CRAN.R-project.org/package=meta). Briefly, the fixed effects, inverse variance weighted meta-analysis summarizes the combined the statistical support across independent studies under the assumption of

homogeneity of effects. Individual study β estimates (log odds ratios) are averaged, weighted by the estimated standard error. [26] The IGAP Stage 1+2 β estimates and standard errors were obtained from the publicly available summary statistics (for additional details, Online Methods and Supplementary Note within reference18). For the DeCODE and DemGene cohorts, β estimates and standard errors were estimated via logistic regression implemented predicting AD case/control status from SNP risk alleles count.

For the gene expression analyses, we focused on transcript expression (total RNA levels) of genes closest (within 500 kB) to the SNPs reaching genome-wide significance in our meta-analysis. Using logistic regression, we examined whether transcript expression of these genes significantly differed between AD cases and controls.

RESULTS

We observed SNP enrichment for AD (IGAP Stage 1 – discovery cohort) across different levels of significance with CRP, TG, HDL and LDL levels indicating a genetic association between AD and the four cardiovascular phenotypes (Figure 1). For progressively stringent p-value thresholds for AD SNPs (i.e. increasing values of nominal $-\log_{10}(p)$), we found at least 50-fold enrichment using CRP, 30-fold enrichment using TG, 20-fold enrichment using HDL and 40-fold enrichment using LDL (Figure 1). Conditional Q-Q plots similarly demonstrated polygenic enrichment in AD as a function of CRP and plasma lipids (Supplemental Figure 1).

To identify AD-associated polymorphisms that are more likely to replicate, we ranked IGAP Stage 1 AD SNPs conditional on their genetic association with CRP and plasma lipids (conditional FDR). We restricted our analyses to SNPs found in both IGAP Stage 1 and 2 and focused on those AD variants that have not been previously described at a genome-wide significance. At a conditional

253 FDR < 0.05, we found 55 AD susceptibility loci from IGAP Stage 1 (Figure 2, Supplemental Table 1).
254 For these 55 loci, we performed a meta-analysis across all available AD cohorts and found two novel
255 genome-wide significant ($p < 5 \times 10^{-8}$) loci associated with increased risk for AD (Table 2). These
256 two variants are: 1) rs13113697 (chromosome 4, closest gene *HS3ST1*, conditioning trait = TG,
257 reference allele = T, OR = 1.07, 95% CI = 1.05-1.11, $p = 2.86 \times 10^{-8}$) (Figures 3a and 4a) and 2)
258 rs7920721 (chromosome 10, closest gene *ECHDC3*, conditioning trait = TG, risk allele = G, OR =
259 1.07, 95% CI = 1.04-1.11, $p = 3.38 \times 10^{-8}$) (Figures 3b and 4b).
260 The meta-analysis also revealed three suggestive AD susceptibility loci with p-values < $1 \times$
261 10^{-6} (Table 3). These three loci are rs7396366 (on chromosome 11, closest gene *AP2A2*, conditioning
262 trait = CRP, reference allele = C, OR = 0.94, 95% CI = 0.92-0.96, $p = 6.8 \times 10^{-7}$), rs3131609 (on
263 chromosome 15, closest gene *USP50*, conditioning trait = CRP, reference allele = C, OR = 0.93, 95%
264 CI = 0.91-0.96, $p = 7.21 \times 10^{-7}$) and rs2526378 (on chromosome 17, closest gene *BZRAP1*,
265 conditioning trait = TG, risk allele = G, OR = 0.94, 95% CI = 0.92-0.96, $p = 2.73 \times 10^{-7}$).
266 We additionally evaluated the directionality of allelic effects in SNPs associated with AD and
267 the four cardiovascular phenotypes (SNPs with conditional FDR < 0.05). Across all 55 shared loci,
268 we found the same direction of effect between SNPs associated with AD and 1) CRP in 72% (18 out
269 of 25, p-value = 0.02) 2) HDL in 40% (4 out of 10, p-value = 0.62), 3) LDL in 20% (1 out of 5, p-
270 value = 0.81), and 4) TG in 40% (6 out of 15, p-value = 0.69) (Supplemental Table 1). For *HS3ST1*
271 and *ECHD3* variants, we found an opposite direction of allelic effect between increased AD risk and
272 TG levels (Supplemental Table 1).
273 We assessed whether *HS3ST1* and *ECHD3* transcript levels are altered in AD brains compared
274 with control brains (GEO dataset GSE 4472). We found significantly decreased *HS3ST1* transcript
275 expression (standardized β-coefficient = -0.09201, standard error (SE) = 0.01864, $p = 9.99 \times 10^{-7}$) and

significantly increased *ECHDC3* transcript expression (standardized β-coefficient = 0.12715, SE = 0.01829, $p = 8.32 \times 10^{-12}$) in AD brains compared with control brains.

DISCUSSION

In this study, we show that polymorphisms associated with CRP and plasma lipids (TG, HDL and LDL) are also associated with increased risk for AD (genetic pleiotropy). We found that genetic enrichment in AD based on SNP association with cardiovascular phenotypes results in improved statistical power for gene discovery. By conditioning on polymorphisms associated with CRP and plasma lipid levels, we identified 55 AD susceptibility loci. In meta-analyses across 4 independent cohorts, we found that two of these risk variants, namely rs13113697 (on chromosome 4, closest gene *HS3ST1*) and rs7920721 (on chromosome 10, closest gene *ECHDC3),* were genome-wide significant. We additionally observed that *HS3ST1* and *ECHDC3* transcript expression was different in AD brains compared with control brains.

Our findings provide novel insights into the relationship between AD pathogenesis, inflammation and dyslipidemia, beyond the known loci associated with AD. We found a consistent direction of allelic effect between SNPs associated with AD risk and CRP levels indicating overlapping pathobiology between AD and inflammation. These results are consistent with the hypothesis that inflammatory mechanisms influence Alzheimer's pathogenesis [9,27-28] and may have implications for treatment and prevention strategies in AD. On the other hand, we did not find a consistent direction of allelic effect between SNPs associated with AD risk and plasma lipid levels (LDL, HDL and TG). Additionally, for *HS3ST1* and *ECHD3* variants, we found an opposite direction of allelic effect between increased AD risk and TG levels. One hypothesis for these findings is that the observed pleiotropy between AD and plasma lipids could be due to different haplotypes/gene

299 alleles involving the same SNPs. Another equally plausible hypothesis is that the same
300 haplotypes/gene alleles are involved for both AD and plasma lipids but the underlying biologic
301 mechanisms are distinct. Based on these findings, it seems less likely the pleiotropic SNPs detected in
302 this study influence AD pathogenesis via cholesterol mediated pathways.

303 Unlike epidemiological studies, co-heritability analyses, [29] or bivariate GWAS methods, [30]
304 one strength of our current approach is the ability to detect genetic pleiotropy even when there is no
305 correlation of the signed effects (mixed directionality of effect); the conditional FDR method can
306 detect SNPs that have a non-null effect in one trait and that also tend to have a non-null effect in
307 another trait, independent of directionality. Another strength of this framework is leveraging genetic
308 signal in one phenotype to identify variants in a second phenotype that would otherwise not be
309 detected using a single phenotype approach. We note that the conditional FDR approach allows for
310 re-ordering (and re-ranking) of SNPs based on p-value significance in the second phenotype (e.g.
311 CRP or TG) thus enabling identification of novel SNPs in the primary phenotype (e.g. AD). In
312 addition, as previously demonstrated, these genetic analysis methods result in improved sensitivity
313 for a given specificity. [13] Using this 'pleiotropic' approach, we detected 55 novel variants indicating
314 that genetic enrichment improves statistical power for gene discovery.

315 In meta-analyses, we discovered two GWAS significant AD susceptibility loci. The closest
316 genes associated with the two risk variants showed altered RNA levels in postmortem AD brains
317 compared with control brains suggesting a functional role. The first variant (rs13113697) is closest to
318 the *HS3ST1* gene on chromosome 4 (Figure 4a), which encodes heparan sulfate glucosaminyl 3-O-
319 sulfotransferase, an intraluminal Golgi protein enzyme with multiple biological activities. [31] The
320 second variant (rs7920721) is closest to the *ECHDC3* gene on chromosome 10 (Figure 4b), which
321 encodes an enzyme called enoyl CoA hydratase domain containing 3. [32] We note that by conditioning

on cardiovascular traits and evaluating additional AD cohorts (deCODE and DemGene), we were able to find genome-wide significant evidence for previously[18] suggested signal within *HS3ST1* and *ECHDC3.* At p-value < 1.0×10^{-6}, we additionally found three suggestive variants on chromosome 11 (rs7396366, closest gene *APA2A*), chromosome 15 (rs3131609, closest gene *USP50*) and chromosome 17 (rs2526378, closest gene *BZRAP1*).

It is important to note that in this study the diagnosis of AD was established clinically. Post-mortem evidence from community and population based cohorts indicates that vascular brain injury often presents concomitantly with Alzheimer's pathology and correlates with cognitive impairment above and beyond AD neuropathology. [33] It is feasible that the clinically diagnosed AD individuals from the IGAP, deCODE and DemGene cohorts may have concomitant vascular brain disease, which may further contribute to their cognitive decline and dementia. As such, an alternative interpretation of our findings is that the susceptibility loci identified in this study may increase brain vulnerability to vascular and/or inflammatory insults, which in turn may exacerbate the clinical consequences of AD pathological changes.

In conclusion, we found polygenic overlap between AD, CRP and plasma lipids, and leveraged this association to identify three novel genome-wide significant variants associated with increased AD risk. Careful and considerable effort will be required to further characterize the novel candidate genes detected in this study and to detect the functional variants responsible for the association of these loci with Alzheimer's risk. Although no single common variant maybe informative clinically, a combination of variants involved with inflammation or lipid metabolism may help identify older individuals at increased risk for AD. Our findings may also have implications for Alzheimer's prevention trials involving anti-inflammatory agents.

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DISCLOSURES

None

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FIGURE LEGENDS

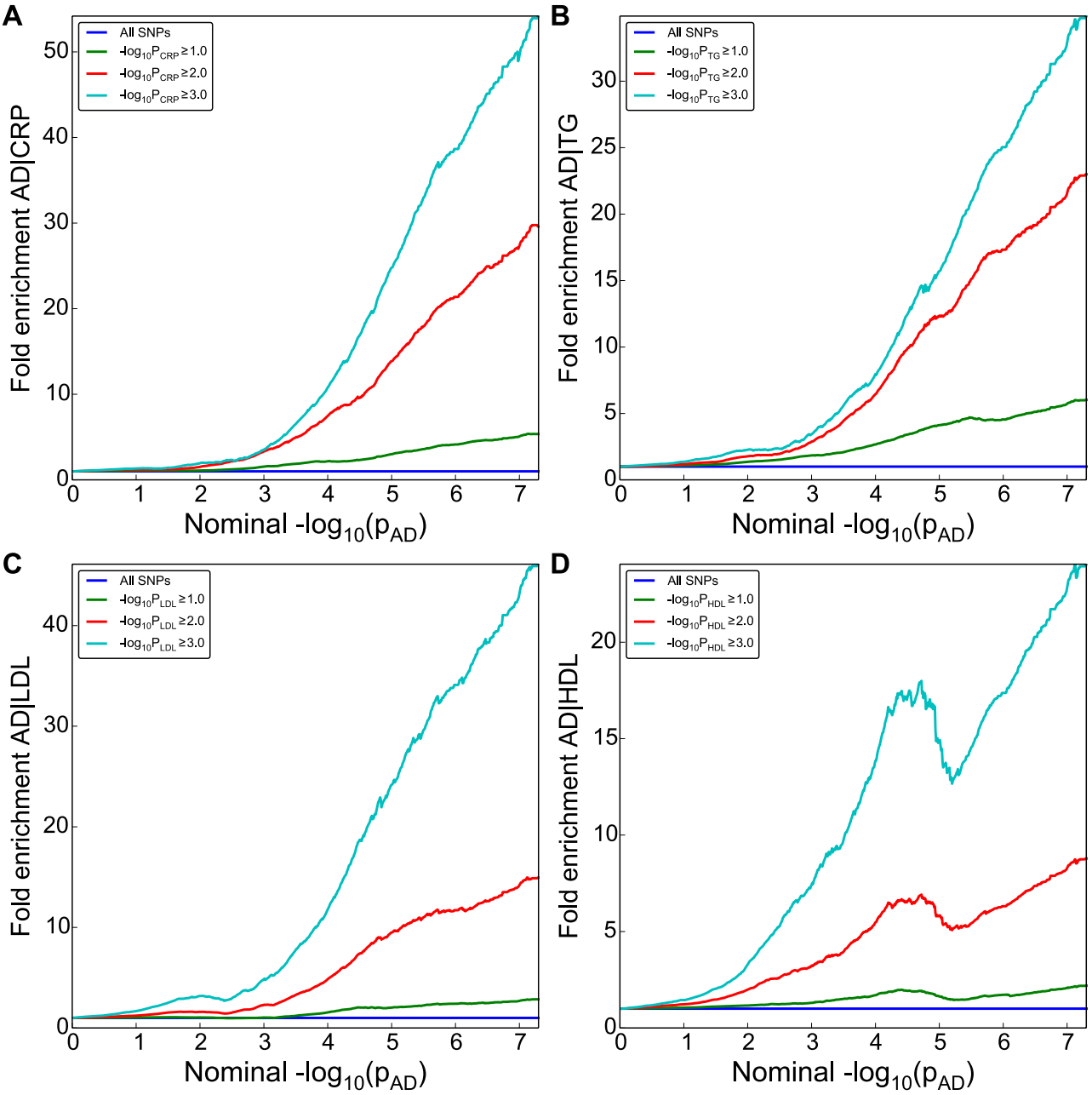
Figure 1. Fold enrichment plots of enrichment versus nominal -$\log_{10}$ p-values (corrected for inflation) in Alzheimer's disease (AD) below the standard GWAS threshold of $p < 5x10^{-8}$ as a function of significance of association with C-reactive protein (CRP) (panel A), high-density lipoprotein (HDL) (panel B), low-density lipoprotein (LDL) (panel C), and triglycerides (TG) (panel D) at the level of $-\log_{10}(p) \geq 0$, $-\log_{10}(p) \geq 1$, $-\log_{10}(p) \geq 2$ corresponding to $p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, respectively. Blue line indicates all SNPs.

Figure 2. 'Conditional Manhattan plot' of conditional $-\log_{10}$ (FDR) values for Alzheimer's disease (AD) alone (IGAP Stage 1 AD cohort) (black) and AD given C-reactive protein (CRP; AD|CRP, green), triglycerides (TG; AD|TG, acquamarine), high-density lipoprotein (HDL, AD|HDL orange), and low-density lipoprotein (LDL; AD|LDL, red). SNPs with conditional $-\log_{10}$ FDR > 1.3 (i.e. FDR < 0.03) are shown with large points. A black line around the large points indicates the most significant SNP in each LD block and this SNP was annotated with the closest gene, which is listed above the symbols in each locus. For additional details, see Supplemental Information.

Figure 3. Forest plots for a) rs13113697 on chromosome 4 and (b) rs7920721 on chromosome 10.

Figure 4. Regional association plots for (a) rs13113697 on chromosome 4, and (b) rs7920721 on chromosome 10. Linkage Disequilibrium measured in the 1000 genomes European Populations using plink v1.07.

580 **Figure 1**



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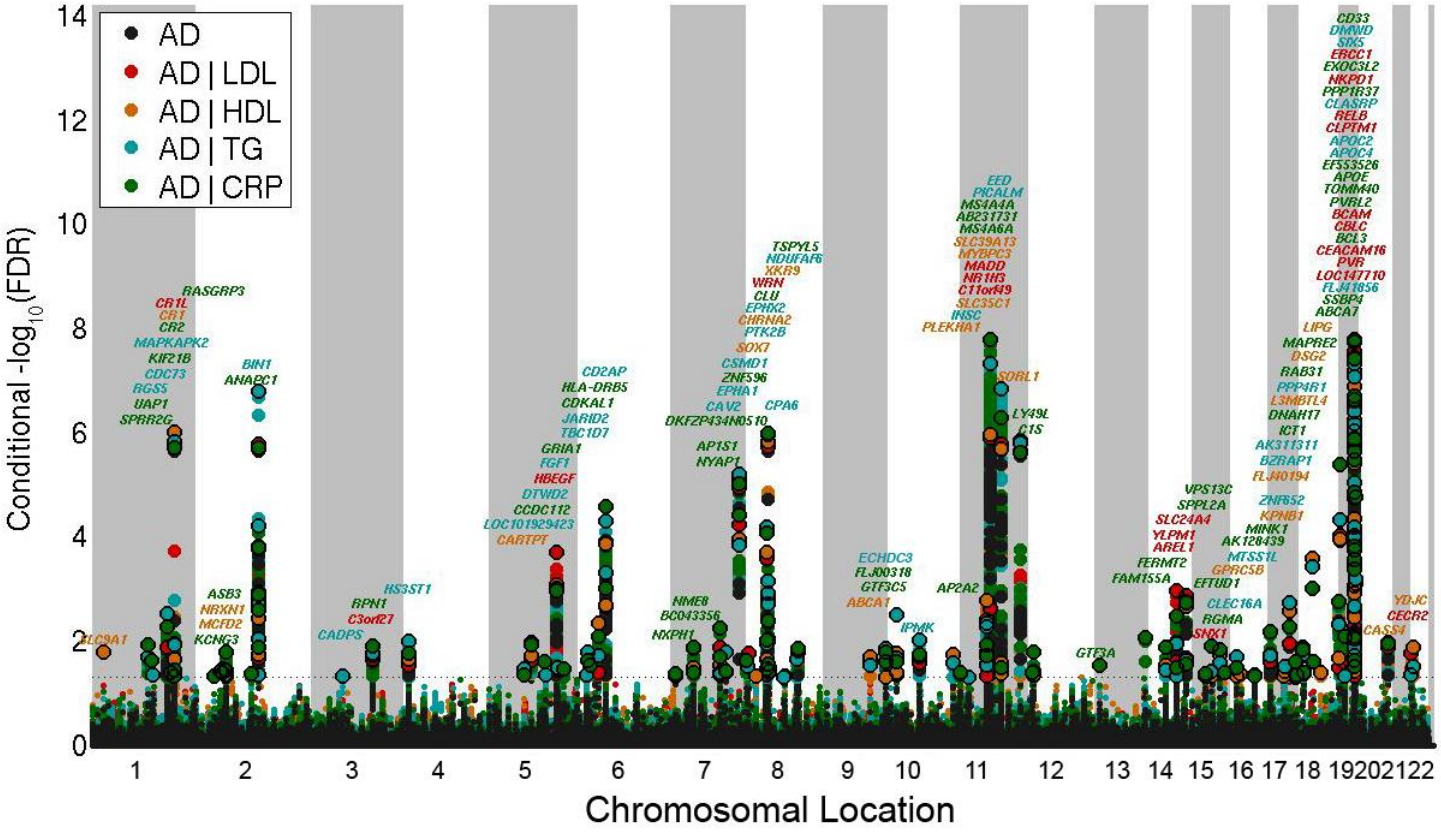
586 **Figure 2**



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589 **Figure 3a**

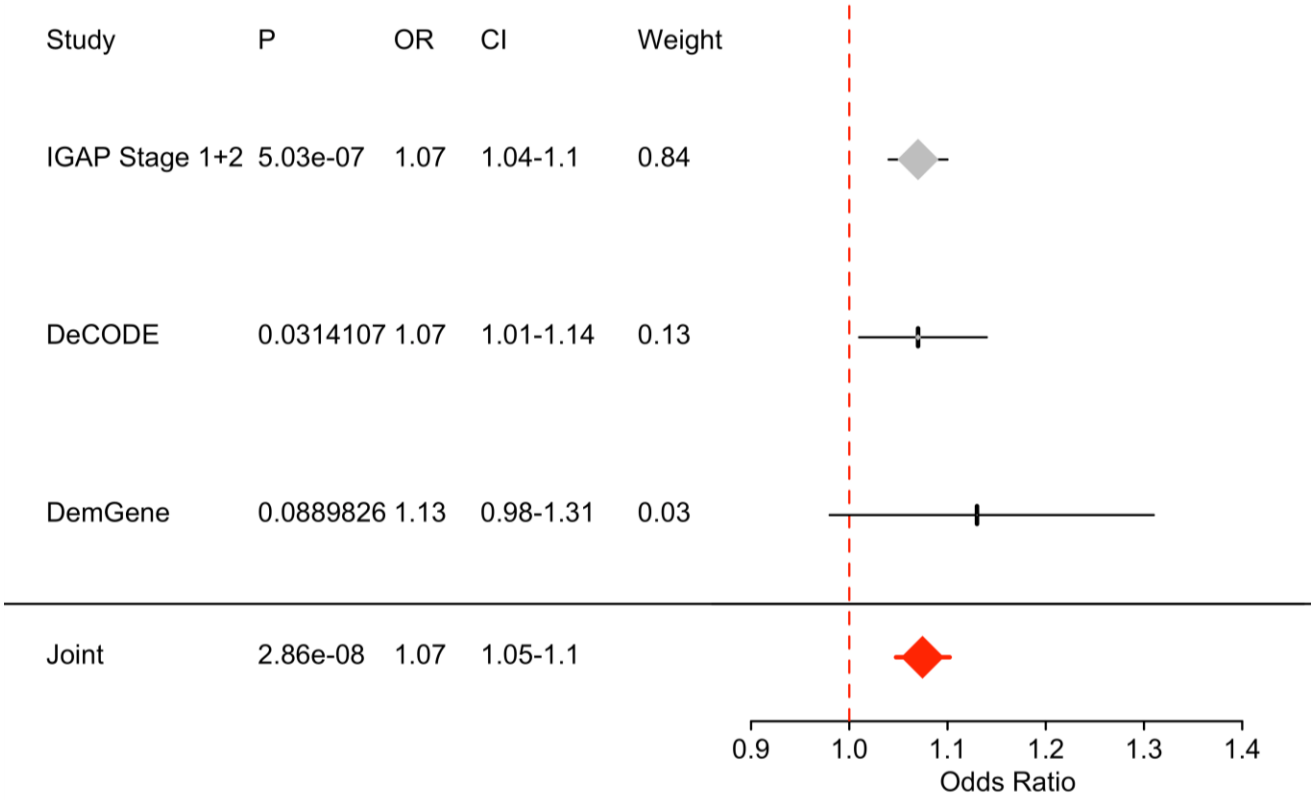

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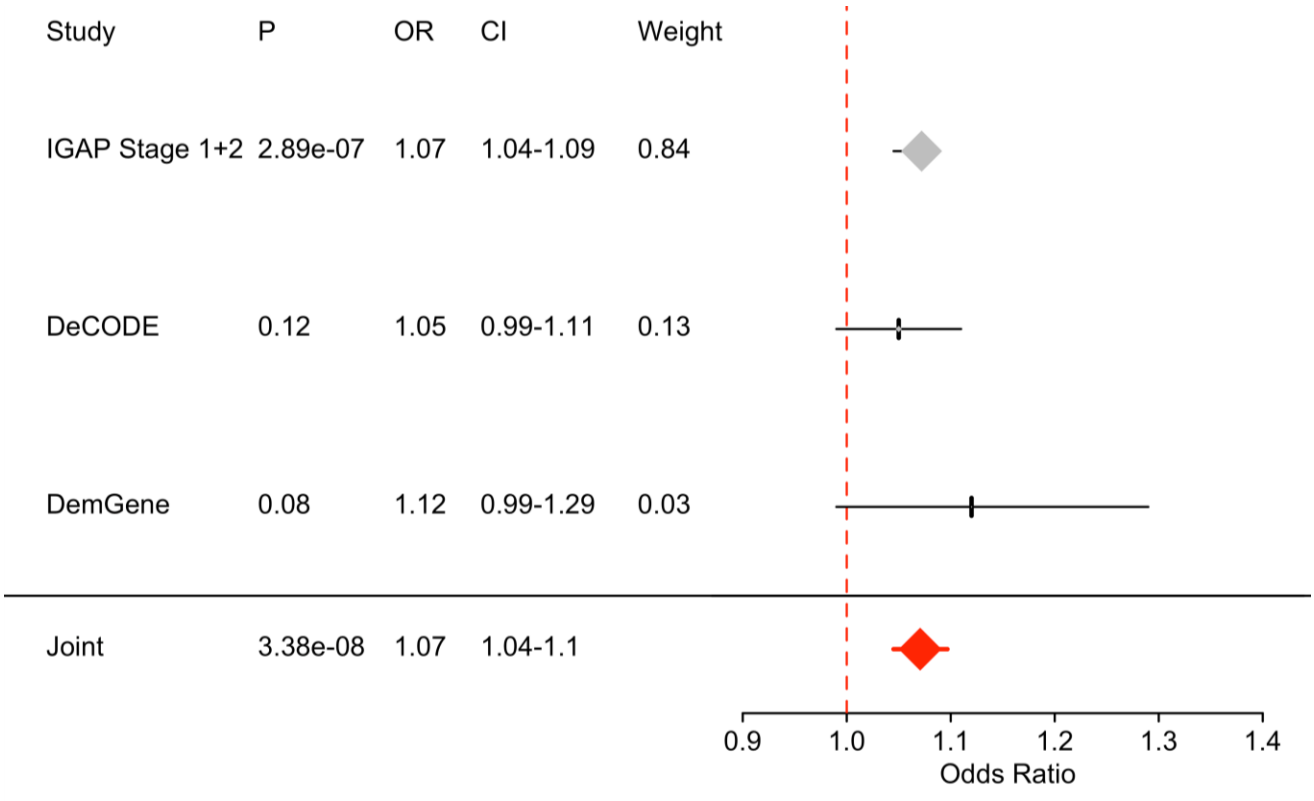
Figure 3b


Study
P
OR
CI
Weight
IGAP Stage 1+2
2.89e-07
1.07
1.04-1.09
0.84
DeCODE
0.12
1.05
0.99-1.11
0.13
DemGene
0.08
1.12
0.99-1.29
0.03
Joint
3.38e-08
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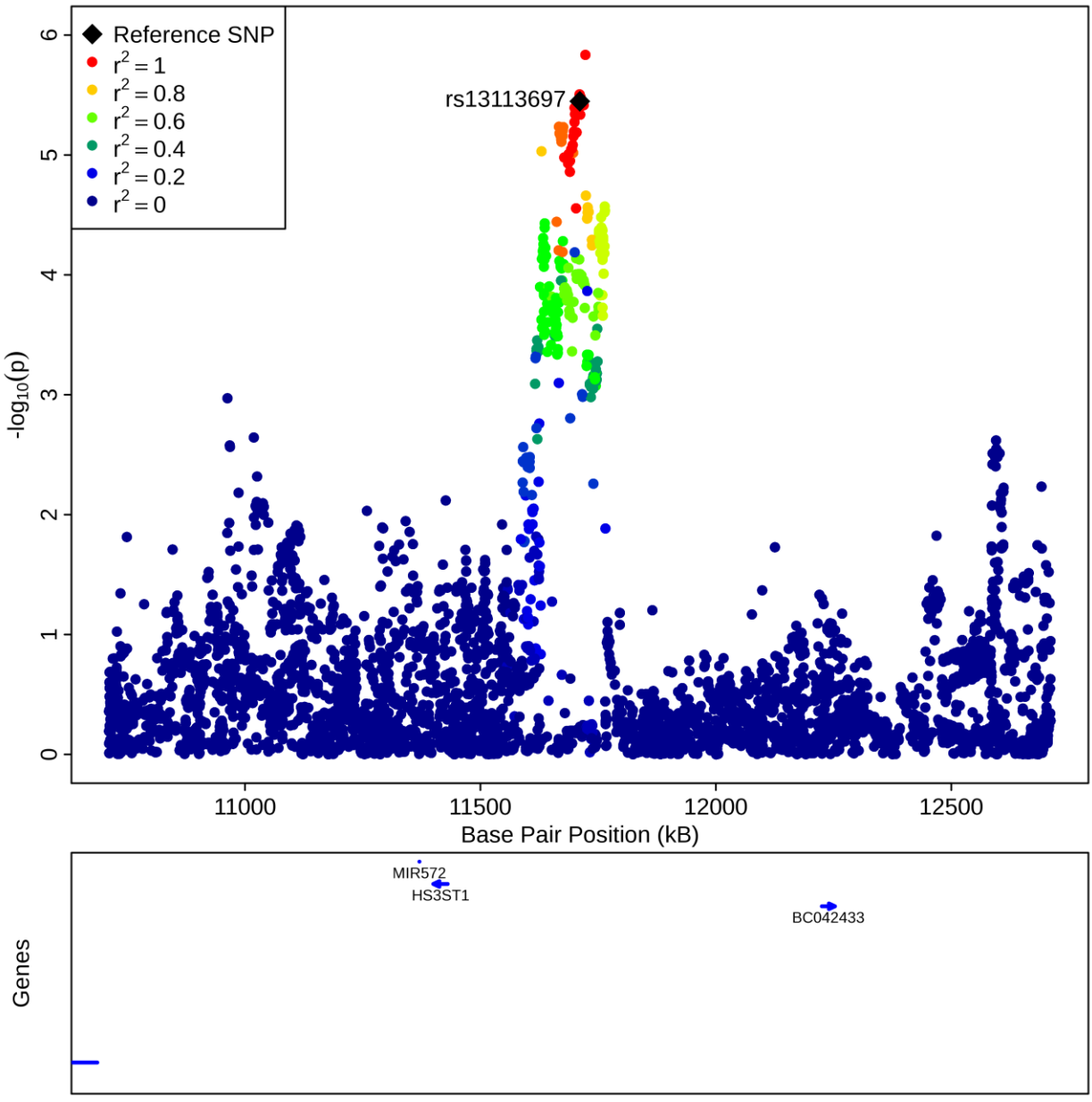
1.04-1.1
0.9
1.0
1.1
1.2
1.3
1.4
Odds Ratio

Figure 4a


Reference SNP
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r2 = 0.6
r2 = 0.4
r2 = 0.2
r2 = 0
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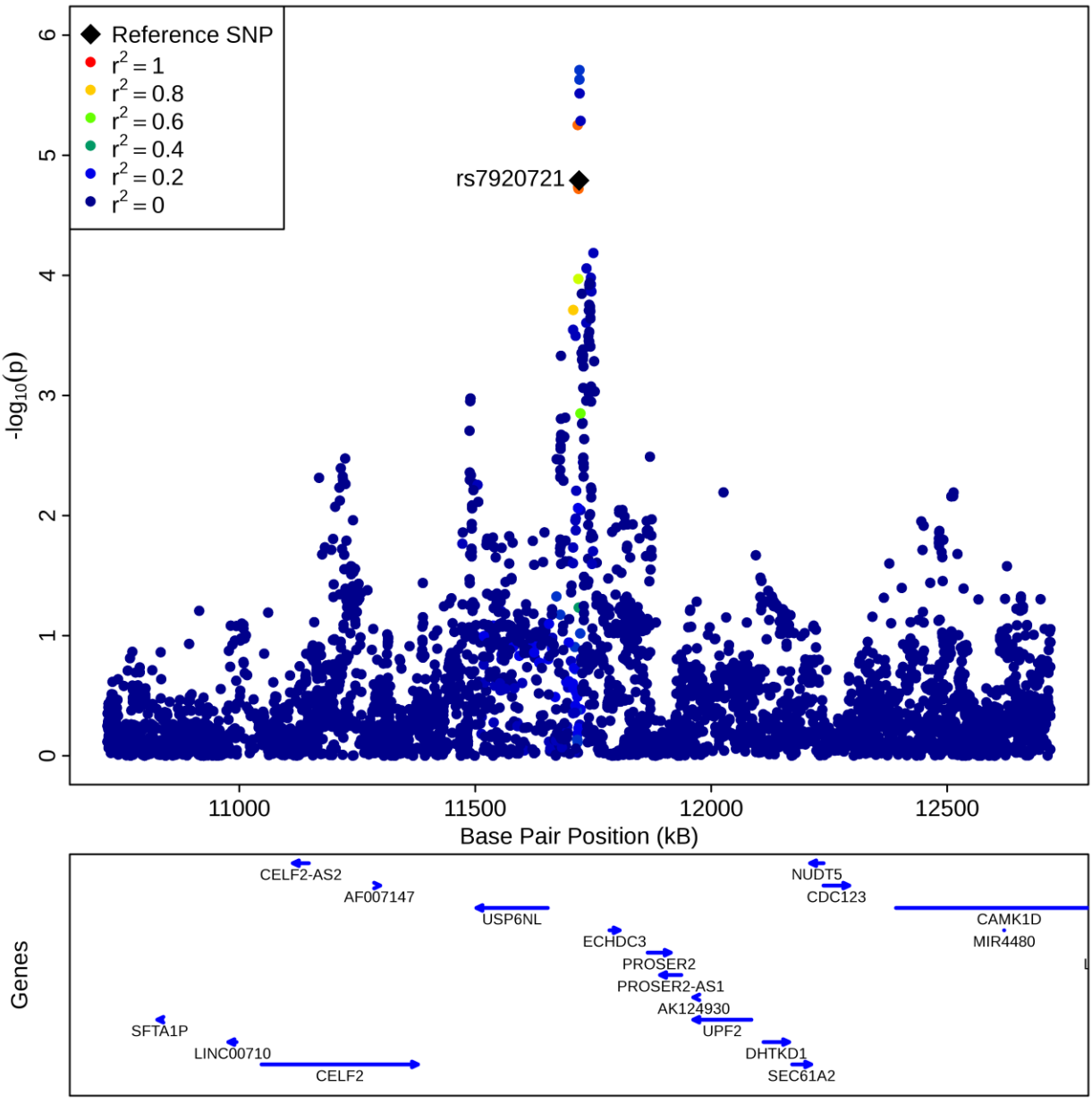
-log10(p)
0
1
2
3
4
5
6
11000
11500
12000
12500
Base Pair Position (kB)
Genes
MIR572
HS3ST1
BC042433

604 **Figure 4b**



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610 **Table 1. Summary data from all GWAS used in the current study**

Disease/Trait	N	# SNPs	Reference
Alzheimer's disease (AD) – IGAP Stage 1+2	74,046 (25,580 AD cases + 48,466 controls)	7,055,881 (Stage 1) 11,632 (Stage 2)	Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013;45:1452-8.
Alzheimer's disease (AD) – deCODE	67,817 (2,470 cases + 65,357 controls)	Whole-genome sequencing	Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. N Eng J Med 2013;368:107-16.
Alzheimer's disease (AD) – DemGene	2,015 (1,004 cases + 1,011 controls)	693,377	N/A
Triglycerides (TG)	188,577	2,508,369	Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010;466:707-13.
Low Density Lipoprotein (LDL)	188,577	2,508,375	
High Density Lipoprotein (HDL)	188,577	2,508,370	
C-Reactive Protein (CRP)	82,725	2,671,742	Dehgan A, Dupuis J, Barbalic M, et al. Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. Circulation. 2011;123:731-8.

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616 **Table 2** New loci reaching genome-wide significance at conditional FDR < 0.05. Odds ratios provided for the major allele.
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SNP	Position	Chr	Nearest Gene	Reference Allele	Associated phenotype	Min Cond FDR	IGAP Stage 1+2 p-value	IGAP Stage 1+2 OR (95% CI)	deCODE p-value	deCODE OR (95% CI)	DemGene p-value	DemGene OR (95% CI)	Meta-analysis p-value	Meta-analysis OR (95% CI)
rs13113697	11711232	4	*HS3ST1*	T	TG	9.56 E-03	5.03E -07	1.07 (1.04-1.10)	0.031	1.07 (1.01-1.14)	0.088	1.13 (0.98-1.31)	2.86E-08	1.07 (1.05-1.11)
rs7920721	11720308	10	*ECHDC3*	G	TG	4.49 E-02	2.89E -07	1.07 (1.04-1.09)	0.12	1.05 (0.99-1.11)	0.08	1.12 (0.99-1.29)	3.38E-08	1.07 (1.04-1.11)

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619 **Table 3**. SNPs showing suggestive association with AD at conditional FDR < 0.05. Odds ratios provided for the major allele.
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SNP	Position	Chr	Nearest Gene	Reference Allele	Associated phenotype	Min Cond FDR	IGAP Stage 1+2 p-value	IGAP Stage 1+2 OR (95% CI)	deCODE p-value	deCODE OR (95% CI)	DemGene p-value	DemGene OR (95% CI)	Meta-analysis p-value	Meta-analysis OR (95% CI)
rs7396366	11711232	11	*AP2A2*	C	CRP	3.91 E-02	2.89E-06	0.93 (0.91-0.96)	0.22	0.96 (0.91-1.02)	0.21	0.92 (0.91-0.96)	6.80E-07	0.94 (0.92-0.96)
rs3131609	11720308	15	*USP50*	C	CRP	4.49 E-02	3.90E-07	0.93 (0.90-0.96)	0.94	1.0 (0.93-1.08)	0.95	0.99 (0.86-1.15)	7.21E-07	0.93 (0.91-0.96)
rs2526378	47336320	17	*BZRAP1*	G	TG	1.83 E-03	8.34E-07	0.94 (0.91-0.96)	0.50	0.98 (0.93-1.03)	9.20E-04	0.80 (0.70-0.91)	2.73E-07	0.94 (0.92-0.96)

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

IGAP Cohort

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

DemGene Cohort

Patients were recruited from research cohorts in Norway as part of the nationwide DemGene Study, including samples from the HUKLI, DemVest, TrønderBrain, and AHUS case-control cohorts. Selection criteria and diagnostic procedures have been published for all cohorts. These three studies had received approval from the relevant regional IRB, and all subjects provided written informed consent. The patients include in this study were all classified as mild cognitive impairment[1] or AD according to the ICD-

10 criteria, the recommendations from the National Institute on Aging-Alzheimer's Association (NIA/AA) or the 1984 NINDS-ADRDA-criteria.

Patients were diagnosed by trained specialists in neurology, geriatric medicine or psychiatry, all trained and experienced in diagnosing dementia. The diagnostic procedures differed slightly among centers, but all patients underwent a standardized comprehensive assessment program, which consisted of a medical history from the patient as well as a close family member, neuropsychological testing, a physical and psychiatric examination with the use of standardized assessment scales, blood sample analyses, and brain imaging. Cognitive assessment consisted of the MMSE global screening scale and a comprehensive battery of neuropsychological battery for memory, attention, executive and visuospatial functions and language. Standardized tests of depression and other neuropsychiatric symptoms were administered. Routine blood sample analysis and brain imaging was performed. In the different cohorts, either all or subgroups of patients had CSF Ab42, T-tau and P-tau AD biomarkers all analyzed at the same certified lab.

Fold enrichment plots

To assess genetic enrichment, we used fold enrichment plots conditional by 'pleiotropic' effects. For a given associated phenotype, enrichment for pleiotropic signals is present if the degree of deflection from the expected null line is dependent on SNP associations with the second phenotype. We constructed fold-enrichment plots of empirical quantiles of nominal $-\log_{10}(p)$ values for SNP association with AD for all SNPs, and for subsets (strata) of SNPs determined by the nominal p-values of their association with CRP, TG,

HDL and LDL. Specifically, we computed the empirical cumulative distribution of nominal p-values for a given phenotype for all SNPs and for SNPs with significance levels below the indicated cut-offs for the other phenotypes ($-\log_{10}(p) \geq 0$, $-\log_{10}(p) \geq 1$, $-\log_{10}(p) \geq 2$ corresponding to $p < 1$, $p < 0.1$, $p < 0.01$ respectively). The nominal p-values ($-\log_{10}(p)$) are plotted on the x-axis, and fold enrichment in the first phenotype as a function of the second phenotype is plotted on the x-axis (Figure 1). To assess for polygenic effects below the standard GWAS significance threshold, we focused the fold enrichment plots on SNPs with nominal $-\log_{10}(p) < 7.3$ (corresponding to $p > 5x10^{-8}$).

Conditional Q-Q plots

Q-Q plots compare a nominal probability distribution against an empirical distribution. In the presence of all null relationships, nominal p-values form a straight line on a Q-Q plot when plotted against the empirical distribution. For AD, CRP, TG, HDL and LDL SNPs and for each categorical subset (strata), $-\log_{10}$ nominal p-values were plotted against $-\log_{10}$ empirical p-values (conditional Q-Q plots, see Supplemental Figure 1). Deflections of the observed distribution from the projected null line reflect increased tail probabilities in the distribution of test statistics (z-scores) and consequently an over-abundance of low p-values compared to that expected by chance (enrichment).

Under large-scale testing paradigms, such as GWAS, quantitative estimates of likely true associations can be estimated from the distributions of summary statistics.[2,3] One common method for visualizing the enrichment of statistical association relative to that expected under the global null hypothesis is through Q-Q plots of nominal p-values obtained from GWAS summary statistics. The usual Q-Q curve has as the y-ordinate the

nominal p-value, denoted by "p", and as the x-ordinate the corresponding value of the empirical cdf, denoted by "q". Under the global null hypothesis the theoretical distribution is uniform on the interval [0,1]. As is common in GWAS, we instead plot $-\log_{10}$ p against $-\log_{10}$ q to emphasize tail probabilities of the theoretical and empirical distributions. Therefore, genetic enrichment results in a leftward shift in the Q-Q curve, corresponding to a larger fraction of SNPs with nominal $-\log_{10}$ p-value greater than or equal to a given threshold. *Conditional* Q-Q plots are constructed by creating subsets of SNPs based on levels of an auxiliary measure for each SNP, and computing Q-Q plots separately for each level. If SNP enrichment is captured by variation in the auxiliary measure, this is expressed as successive leftward deflections in a conditional Q-Q plot as levels of the auxiliary measure increase.

We constructed conditional Q-Q plots of empirical quantiles of nominal $-\log_{10}(p)$ values for SNP association with AD for all SNPs, and for subsets (strata) of SNPs determined by the nominal p-values of their association with CRP, TG, HDL and LDL. Specifically, we computed the empirical cumulative distribution of nominal p-values for a given phenotype for all SNPs and for SNPs with significance levels below the indicated cut-offs for the other phenotypes ($-\log_{10}(p) \geq 0$, $-\log_{10}(p) \geq 1$, $-\log_{10}(p) \geq 2$ corresponding to $p < 1$, $p < 0.1$, $p < 0.01$ respectively). The nominal p-values ($-\log_{10}(p)$) are plotted on the y-axis, and the empirical quantiles ($-\log_{10}(q)$, where q=1-cdf(p)) are plotted on the x-axis (Supplemental Figure 1). To assess for polygenic effects below the standard GWAS significance threshold, we focused the conditional Q-Q plots on SNPs with nominal $-\log_{10}(p) < 7.3$ (corresponding to $p > 5x10^{-8}$).

Genomic Control

The empirical null distribution in GWAS is affected by global variance inflation due to population stratification and cryptic relatedness [4] and deflation due to over-correction of test statistics for polygenic traits by standard genomic control methods. [5] We applied a control method leveraging only intergenic SNPs, which are likely depleted for true associations. [6] First, we annotated the SNPs to genic (5'UTR, exon, intron, 3'UTR) and intergenic regions using information from the 1KGP. We used intergenic SNPs because their relative depletion of associations suggests that they provide a robust estimate of true null effects and thus seem a better category for genomic control than all SNPs. We converted all p-values to z-scores and for all phenotypes we estimated the genomic inflation factor λ_{GC} for intergenic SNPs. We computed the inflation factor, λ_{GC} as the median z-score squared divided by the expected median of a chi-square distribution with one degree of freedom and divided all test statistics by λ_{GC}.

Conditional True Discovery Rate (TDR)

Enrichment seen in the fold enrichment plots can be directly interpreted in terms of TDR (equivalent to one minus the False Discovery Rate (FDR)). [7] We applied the conditional FDR method, [8] previously used for enrichment of GWAS based on linkage information. [9] Specifically, for a given p-value cutoff, the FDR is defined as

$$FDR(p) = \pi_0 F_0(p) / F(p), \qquad [1]$$

where π_0 is the proportion of null SNPs, F_0 is the null cdf, and F is the cdf of all SNPs, both null and non-null. Under the null hypothesis, F_0 is the cdf of the uniform distribution on the unit interval [0,1], so that Eq. [1] reduces to

$$FDR(p) = \pi_0 p / F(p), \qquad [2]$$

The cdf F can be estimated by the empirical cdf q =□ □$_p$ / □, where □$_p$ is the number of SNPs with p-values less than or equal to p, and N is the total number of SNPs. Replacing F by q in Eq. [2], we get

$$\text{Estimated } FDR(p) = \pi_0 p / q, \qquad [3]$$

which is biased upwards as an estimate of the FDR. [10] Replacing π_0 in Equation [3] with unity gives an estimated FDR that is further biased upward;

$$q^* = p/q \qquad [4]$$

If π_0 is close to one, as is likely true for most GWAS, the increase in bias from Eq. [3] is minimal. The quantity 1 – p/q, is therefore biased downward, and hence is a conservative estimate of the TDR.

Referring to the formulation of the Q-Q plots, we see that q* is equivalent to the nominal p-value divided by the empirical quantile, as defined earlier. Given the $-\log_{10}$ of the Q-Q plots we can easily obtain

$$-\log_{10}(q^*) = \log_{10}(q) - \log_{10}(p) \qquad [5]$$

demonstrating that the (conservatively) estimated FDR is directly related to the horizontal shift of the curves in the conditional Q-Q plots from the expected line x = y, with a larger shift corresponding to a smaller FDR, as illustrated in Supplemental Figure 1. As before, the estimated TDR can be obtained as 1-FDR.

Conditional statistics – test of association with AD

To improve detection of SNPs associated with AD, we used a conditional FDR approach. Specifically, we conditioned AD SNPs based on p-values in a pleiotropic phenotype (e.g. CRP). We then assigned a conditional FDR value (denoted as $FDR_{AD|CRP}$) for AD to each SNP, based on the combination of p-value for the SNP in AD and the pleiotropic trait (CRP), by interpolation into a 2-D look-up table. All SNPs with FDR < 0.01 ($-\log_{10}(FDR) > 2$) in AD given CRP, TG, HDL and LDL are listed in Table 2 after 'pruning' (removing all SNPs with $r^2 > 0.2$ based on 1KGP linkage disequilibrium (LD) structure). A significance threshold of FDR < 0.01 corresponds to 1 false positive per 100 reported associations. Pruned SNPs with FDR < 0.05 ($-\log_{10}(FDR) > 1.3$) in AD given CRP, TG, HDL and LDL are listed in Supplemental Table 1.

Conditional FDR Manhattan plots

To illustrate the localization of the genetic markers associated with AD given CRP, TG, HDL and LDL we used a 'Conditional FDR Manhattan plot', plotting all SNPs within an LD block in relation to their chromosomal location. As illustrated in Figure 2 within the main manuscript, the large points represent the SNPs with FDR < 0.05, whereas the small points represent the non-significant SNPs. All SNPs before 'pruning' (removing all SNPs with $r^2 > 0.2$ based on 1KGP LD structure) are shown. The strongest signal in each LD block is illustrated with a black line around the circles. This was identified by ranking all SNPs in increasing order, based on the conditional FDR value for AD, and then removing SNPs in LD $r^2 > 0.2$ with any higher ranked SNP. Thus, the selected locus was the most

significantly associated with AD in each LD block (Figure 2). Supplemental Figure 2 additionally presents AD associated loci with $-\log_{10}$ FDR > 1.3 (i.e. FDR < 0.05).

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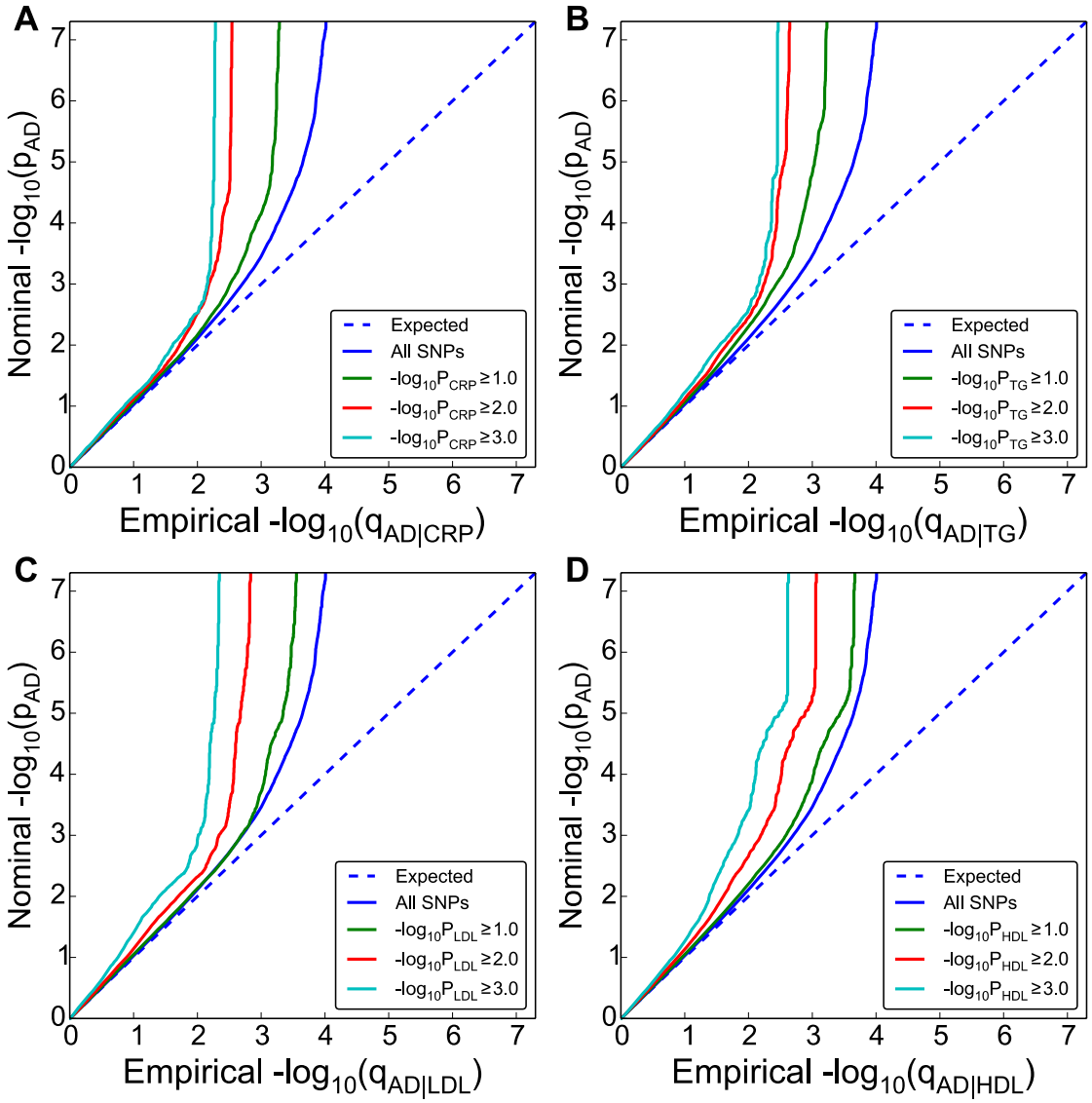
SUPPLEMENTAL FIGURE LEGENDS

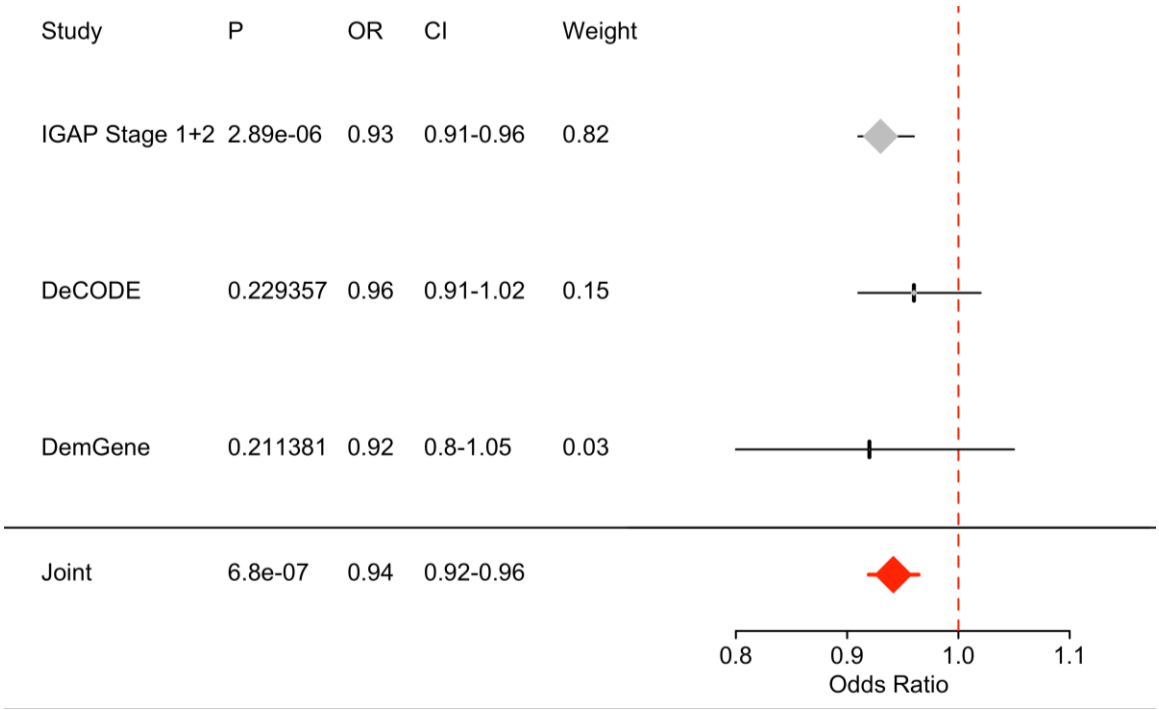
Supplemental Figure 1. Conditional Q-Q plots of nominal versus empirical $-\log_{10}$ p-values (corrected for inflation) in Alzheimer's disease (AD) using IGAP Stage 1 data below the standard GWAS threshold of $p < 5x10^{-8}$ as a function of significance of association with C-reactive protein (CRP) (panel A), high-density lipoprotein (HDL) (panel B), low-density lipoprotein (LDL) (panel C), and triglycerides (TG) (panel D) at the level of $-\log_{10}(p) \geq 0$, $-\log_{10}(p) \geq 1$, $-\log_{10}(p) \geq 2$ corresponding to $p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, respectively. Dotted lines in the conditional Q-Q plots indicate the null hypothesis.

Supplemental Figure 2. Forest plots for the three suggestive AD susceptibility loci. These are a) rs7396366 on chromosome 11, (b) rs3131609 on chromosome 15, and (c) rs2526378 on chromosome 17.

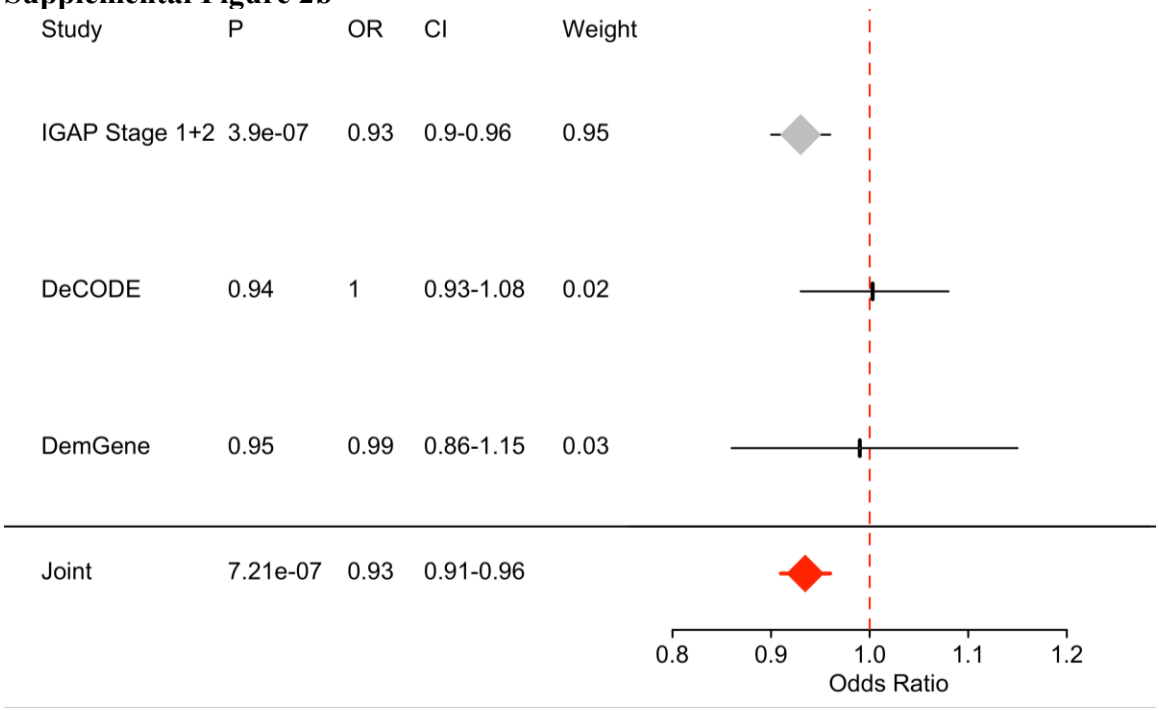
Supplemental Figure 1



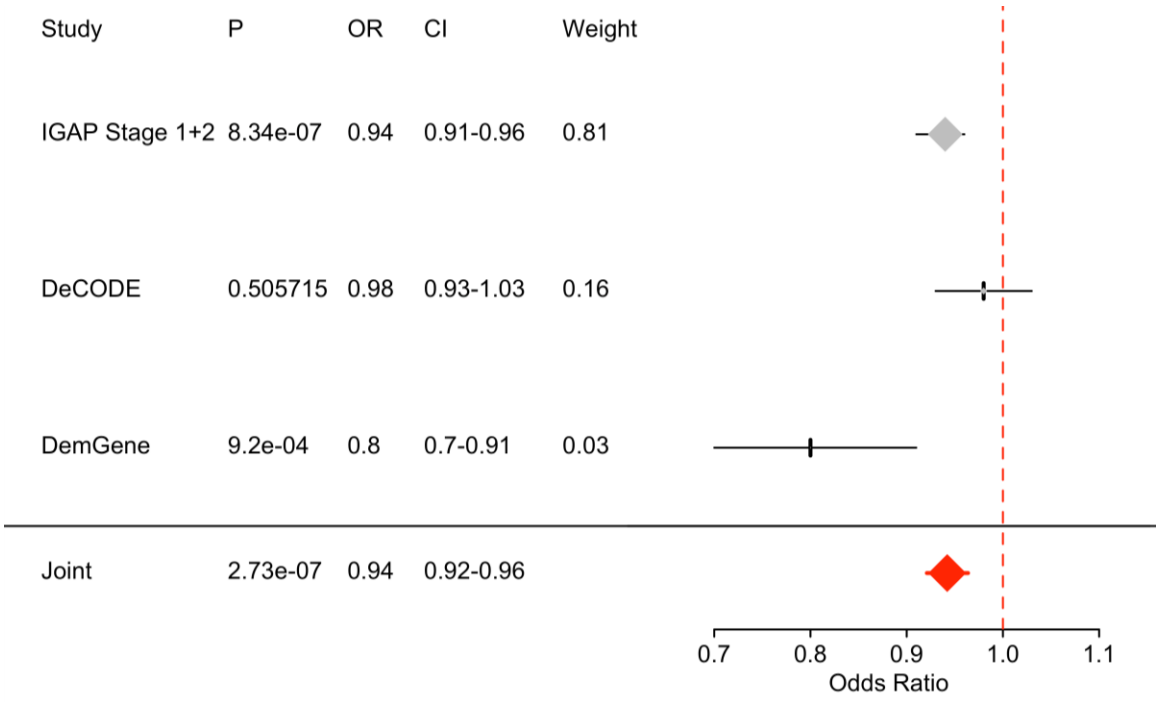
Supplemental Figure 2a



Supplemental Figure 2b



Supplemental Figure 2c



Supplemental Table 1 All 65 novel AD susceptibility loci at conditional FDR < 0.05. Odds ratios provided for the major allele.

SNP	Gene	Chr	Reference Allele	Min Cond FDR	Associated trait	Direction of Effect	IGAP Stage 1+2 p-value	IGAP Stage 1+2 OR	IGAP Stage1+2 95% CI	deCODE p-value	deCODE OR	deCODE 95% CI	DemGene p-value	DemGene OR	DemGene 95% CI	Meta p-value	Meta OR	Meta 95%CI
rs16847470	*KIF21B*	1	G	4.01E-02	CRP	Same	5.46E-05	0.9210877	0.8811037-0.9610717	0.0241721	0.902	0.8246-0.9866	0.788879	1.02298	0.8662-1.2081	8.96E-06	0.9224723	0.8901951-0.9559198
rs12065199	*SPRR2G*	1	G	1.21E-02	CRP	Same	1.86E-06	1.205266	1.128434-1.282098	0.0881917	0.873	0.75-1.0205	0.681216	0.923219	0.6306-1.3516	0.000374895	1.131027	1.056841-1.21042
rs6668320	*UAP1*	1	G	2.31E-02	CRP	Same	0.0004846	1.056646	1.025678-1.087614	0.910853	1.004	0.9362-1.0767	0.109385	1.134588	0.9721-1.324328	0.000517735	1.050566	1.021711-1.080237
rs12410656	*SLC9A1*	1	T	1.61E-02	HDL	Same	0.02356	0.92	0.85-0.99	0.149766	1.079	0.9729-1.1966	0.822626	1.02751	0.8105-1.3027	0.007537913	1.078561	1.020336-1.140082
rs6540582	*MAPKAPK2*	1	C	4.64E-02	TG	Same	0.0001528	1.215068	1.114324-1.315812	0.265066	0.874	0.6897-1.1076	0.784294	1.077427	0.6316321-1.837897	0.002381245	1.152083	1.051521-1.262262
rs11807823	*RGS5*	1	G	4.47E-02	TG	Different	0.0002802	1.094174	1.045566-1.142782	0.019628	0.866	0.7674-0.9772	0.231384	1.18836	0.8958-1.5765	0.007335995	1.062826	1.016525-1.111236
rs1410397	*CDC73*	1	C	2.99E-03	TG	Different	1.62E-06	1.07961	1.04825-1.11097	0.794604	1.008	0.9493-1.0703	0.326269	1.067294	0.9371-1.2155	7.75E-06	1.06397	1.035444-1.093281
rs1399665	*ANAPC1*	2	A	4.27E-02	CRP	Same	0.01049	0.9662816	0.9400176-0.9925456	0.0451093	0.941	0.8867-0.9987	0.535729	0.9575151	0.8345852-1.098539	0.001333334	0.9619857	0.9394801-0.9850305
rs10200743	*RASGRP3*	2	C	4.60E-02	CRP	Same	2.76E-05	1.065559	1.035963-1.095155	0.0413414	1.07	1.0027-1.1419	0.703532	1.02863	0.8894-1.1896	3.12E-06	1.065044	1.037203-1.093632

rs17044055	*ASB3*	2	A	3.57E-02	CRP	Same	0.001283	1.051902	1.02113-1.082674	0.44701	1.028	0.9574-1.1038	0.0420914	0.845863	0.7198-0.994	0.004225559	1.041443	1.012869-1.070823
rs222482	*KCNG3*	2	T	3.81E-02	CRP	Different	5.15E-05	1.054641	1.028769-1.080513	0.665892	1.013	0.9553-1.0742	0.192991	1.09157	0.9567-1.2455	6.58E-05	1.048581	1.024435-1.073296
rs9289330	*C3orf27*	3	G	2.20E-02	LDL	Different	8.66E-06	0.9429896	0.9171176-0.9688616	0.249935	0.963	0.9031-1.0269	0.413234	1.05928	0.9228-1.216	1.21E-05	0.9486108	0.9264541-0.9712974
rs1148828	*CADPS*	3	C	4.74E-02	TG	Different	0.001769	1.05	1.02-1.09	0.896116	1.005	0.9325-1.0831	0.0888352	1.17666	0.9756-1.4192	1.71E-03	1.05	1.02-1.08
rs13113697	*HS3ST1*	4	T	9.56E-03	TG	Different	5.03E-07	1.0732	1.0439-1.1032	0.0314107	1.07	1.006-1.138	0.0889826	1.13291	0.9811617-1.13291	2.86E-08	1.074538	1.047598-1.10217
rs4958667	*GRIA1*	5	G	3.39E-02	CRP	Same	0.008062	0.9658951	0.9402191-0.9915711	0.118991	1.048	0.988-1.1116	0.716889	1.025449	0.895175-1.174674	0.08565268	0.9798631	0.9573949-1.002858
rs1990895	*CCDC112*	5	A	2.50E-02	CRP	Different	0.003893	1.039459	1.013195-1.065723	0.182205	1.04	0.9818-1.1017	0.761345	1.02109	0.8924-1.1683	0.001445672	1.038983	1.014821-1.063721
rs11575893	*CARTPT*	5	T	3.34E-02	HDL	Same	0.002321	0.9217327	0.8692047-0.9742607	0.594436	0.972	0.8755-1.0791	0.420488	1.10742	0.864-1.4195	0.005865835	0.9372351	0.8949987-0.9814648
rs11168036	*HBEGF*	5	T	1.56E-04	LDL	Different	9.87E-06	1.058338	1.03325-1.083426	0.0244499	1.068	1.0085-1.131	0.899574	0.9915127	0.8685833-1.131862	1.01E-06	1.058083	1.034408-1.082301
rs413524	*DTWD2*	5	A	4.49E-02	TG	Same	0.02088	1.039459	1.006035-1.065619	0.1128	1.055	0.9874-1.1272	0.385421	0.9353574	0.8043111-1.087666	0.01034106	1.035604	1.008278-1.06367
rs17612068	*FGF1*	5	G	3.27E-02	TG	Different	3.10E-05	1.076807	1.041919-1.111695	0.105291	0.936	0.864-1.014	0.081021	0.850849	0.7097-1.0201	0.00433872	1.046897	1.014443-1.08039

rs9465770	*CDKAL1*	6	C	2.90E-02	CRP	Different	0.001659	1.161834	1.068342-1.255326	0.921568	1.009	0.8442-1.206	0.914925	1.02544	0.6468-1.6259	0.005028481	1.123722	1.035772-1.219139
rs764650	*JARID2*	6	C	1.60E-02	TG	Same	0.001127	0.9482852	0.9163372-0.9802332	0.903198	1.005	0.9274-1.0891	0.899237	0.9904324	0.8534608-1.149293	0.004307928	0.9584826	0.9309801-0.9867976
rs293188	*NXPH1*	7	A	4.25E-02	CRP	Different	0.0005676	1.077345	1.035009-1.119681	0.042471	0.882	0.7977-0.9753	0.690657	1.04274	0.8485-1.2814	0.000333419	0.9515838	0.9261325-0.9777346
rs1180296	*CAV2*	7	T	1.65E-02	TG	Different	0.0001831	1.106277	1.053357-1.159197	0.770644	0.982	0.8691-1.1095	0.175931	0.81852	0.6125-1.0939	0.002309404	1.077297	1.026922-1.130142
rs7812391	*WRN*	8	T	3.90E-02	CRP	Same	0.00227	1.047493	1.017701-1.077285	0.491454	1.023	0.9588-1.0915	0.574636	1.04348	0.8994-1.2107	0.001859189	1.043195	1.015777-1.071354
rs888577	*ZNF596*	8	T	2.34E-02	CRP	Different	3.91E-06	1.14855	1.08975-1.20735	0.177354	0.912	0.7978-1.0426	0.548658	0.9077952	0.6617696-1.24533	0.0004348	1.099935	1.043087-1.159882
rs7014168	*SOX7*	8	A	4.62E-02	HDL	Same	0.0001387	0.9421413	0.9115653-0.9727173	0.452848	1.026	0.9595-1.0971	0.964695	1.00369	0.8526-1.1815	0.001858053	0.9573933	0.9314962-0.9840104
rs11995526	*XKR9*	8	A	4.83E-02	HDL	Different	0.003551	1.072615	1.025575-1.119655	0.762267	1.015	0.9217-1.1178	0.072 2377	0.804799	0.6351-1.0198	0.016442 48	1.05226	1.009365-1.096979
rs11986035	*CSMD1*	8	T	3.09E-02	TG	Same	4.65E-05	1.058762	1.031322-1.086202	0.764596	0.99	0.927-1.0573	0.784484	0.981017	0.8551-1.1255	0.000400554	1.046013	1.02028-1.072395
rs7818382	*NDUFAF6*	8	T	2.19E-02	TG	Different	8.00E-08	1.071329	1.046241-1.096417	0.428602	0.977	0.9223-1.0349	0.469902	1.05006	0.9198-1.1988	2.94E-06	1.055544	1.031891-1.079739
rs689266	*GTF3C5*	9	T	1.67E-02	CRP	Same	0.0002007	1.052428	1.025576-1.07928	0.564322	0.982	0.9232-1.0446	0.332122	0.934313	0.8144-1.0718	0.002985776	1.037399	1.012558-1.0628

																		5
rs1883025	*ABCA1*	9	T	1.96E-02	HDL	Different	0.000476	1.05327	1.024262-1.082278	0.446452	1.026	0.9604-1.0961	0.205457	0.90744	0.7808-1.0547	0.001182236	1.044227	1.01727-1.071898
rs984668	*PLEKHA1*	10	A	1.94E-02	HDL	Different	0.0004876	0.954337	0.9281097-0.9806377	0.39767	0.975	0.9194-1.0339	0.0948008	1.12378	0.98-1.2887	0.001443893	0.9623548	0.9399018-0.9853441
rs7920721	*ECHDC3*	10	G	4.49E-02	TG	Different	2.89E-07	1.072	1.045-1.09	0.123968	1.05	0.99-1.11	0.08	1.12	0.99-1.29	3.38E-08	1.070587	1.044974-1.096827
rs7396366	*AP2A2*	11	C	3.91E-02	CRP	Same	2.89E-06	0.939113	0.9128673-0.9653953	0.229357	0.963	0.9056-1.0241	0.211381	0.9162879	0.7989135-1.050972	6.80E-07	0.9415092	0.9193811-0.9641699
rs10766249	*INSC*	11	C	3.36E-02	TG	Same	0.0005024	1.052112	1.023496-1.080728	0.909386	0.996	0.9296-1.0672	0.0848683	0.877618	0.7565-1.0181	0.004812693	1.038142	1.011475-1.065512
rs2682484	*LY49L*	12	A	1.62E-02	CRP	Same	0.0001493	0.940792	0.9091732-0.9722852	0.555065	0.98	0.9164-1.048	0.0428516	0.8433054	0.7150518-0.9945301	6.99E-05	0.944522	0.9183212-0.9714704
rs1218788	*GTF3A*	13	A	2.97E-02	CRP	Same	0.004498	1.051271	1.016775-1.085767	0.328863	0.962	0.89-1.0398	0.999751	1.00003	0.8283-1.2074	0.02989411	1.03506	1.003362-1.067759
rs9520713	*FAM155A*	13	A	8.48E-03	CRP	Same	0.002504	0.955424	0.9258281-0.9850201	0.154781	0.951	0.8874-1.0191	0.0972928	0.881116	0.7587-1.0233	0.000432391	0.9523293	0.9267742-0.9785891
rs10483861	*YLPM1*	14	C	3.52E-03	LDL	Same	6.45E-06	1.116613	1.068789-1.164437	0.397863	0.957	0.8643-1.0597	0.556751	1.07327	0.8478-1.3587	0.000887862	1.070457	1.028332-1.114309
rs3131609	*USP50/SPPL2A*	15	C	4.38E-02	CRP	Same	3.90E-07	0.931368	0.9039288-0.9588088	0.936898	1.003	0.9313-1.0802	0.955001	0.995807	0.8606-1.1523	7.21E-07	0.93461	0.9099473-0.9599411
rs17526269	*RGMA*	15	T	3.91E-02	CRP	Same	7.87E-05	0.945917	0.9182814-0.9735534	0.295085	1.033	0.9721-1.0977	0.512346	0.953982	0.8286-	0.001273793	0.9601096	0.9366252-

															1.0984			0.9841828
rs905450	*EFTUD1*	15	A	1.43E-02	CRP	Different	8.72E-06	0.933902	0.9037962-0.9641642	0.595034	0.981	0.914-1.0529	0.735151	0.9730466	0.8305648-1.139991	1.85E-05	0.9420084	0.9165977-0.9681237
rs1802376	*SNX1*	15	A	4.54E-02	LDL	Different	6.08E-06	1.22986	1.140288-1.319432	0.35514	1.103	0.896-1.3578	0.570693	0.869693	0.5368-1.4091	1.28E-05	1.197857	1.104565-1.299028
rs4985560	*AK128439*	16	A	4.60E-02	CRP	Same	6.06E-05	1.052954	1.02767-1.078238	0.227454	1.036	0.9782-1.0972	0.245491	0.9249667	0.8108985-1.055075	0.000102973	1.046192	1.022619-1.070309
rs9941245	*GPRC5B*	16	G	4.20E-02	HDL	Different	9.42E-05	0.936973 8	0.9042418-0.9697058	0.086832	0.931	0.8578-1.0104	0.620198	0.955316	0.7973-1.1446	8.37E-06	0.9361159	0.9093211-0.9637002
rs4781031	*CLEC16A*	16	T	1.99E-02	TG	Same	4.76E-05	1.059079	1.031443-1.086715	0.642469	1.016	0.9501-1.0864	0.50617	1.04969	0.9098-1.211	6.44E-05	1.052616	1.026471-1.079426
rs12150370	*MINK1*	17	C	6.43E-03	CRP	Same	7.01E-07	1.12	1.08-1.16	0.199014	1.06	0.97-1.16	0.130555	0.85	0.68-1.05	1.21E-06	1.08853	1.051883-1.126455
rs2526378	*BZRAP1*	17	G	1.83E-03	TG	Different	8.34E-07	0.94	0.91-0.96	0.505715	0.98	0.93-1.03	0.00092041	0.8	0.7-0.91	2.73E-07	0.9421268	0.9209578-0.9637824
rs614793	*MAPRE2*	18	T	2.49E-02	CRP	Same	0.002772	0.947053 2	0.9113812-0.9827252	0.881478	1.006	0.9299-1.0883	0.668054	1.040545	0.867679-1.247816	0.01098647	0.9593599	0.9291694-0.9905313
rs1015228	*RAB31*	18	A	3.91E-02	CRP	Different	5.39E-05	1.054219	1.028543-1.079895	0.935651	0.998	0.9507-1.0477	0.798735	1.017196	0.8922198-1.159689	0.001109608	1.037922	1.014962-1.061402
rs3745091	*L3MBTL4*	18	C	1.30E-02	HDL	Different	3.11E-06	1.217622	1.13491-1.300334	0.895863	1.02	0.7583-1.3721	0.630884	0.919787	0.654-1.2936	1.70E-05	1.185615	1.097112-1.281258
rs17656498	*LIPG*	18	C	3.97E-02	HDL	Diffe	0.001431	0.95829	0.9320306-	0.6050	1.017	0.9541-	0.164	1.10123	0.9612	0.00975	0.9682	0.9447

						rent		46	0.9845586	08		1.0841	513		-1.2616	6426	09	744-0.9922249
rs2298428	*YDJC*	22	T	1.32E-02	HDL	Same	0.0005042	0.94	0.91-0.98	0.101258	0.94	0.87-1.01	0.301784	0.92	0.79-1.08	8.59E-06	0.95	0.92-0.97
rs4819996	*CECR2*	22	A	1.72E-02	LDL	Different	4.67E-05	0.9436499	0.9158179-0.9714819	0.312624	0.97	0.9143-1.0291	0.512027	0.9552102	0.8329169-1.09541	0.000140153	0.9530137	0.9296966-0.9769155