Genetic data and cognitively-defined late-onset Alzheimer's disease subgroups

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Supplemental Materials

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Supplemental Text 1. Psychometric analyses

Supplemental Text 1A. Confirmatory factor analyses in each study

Step 1: Domain assignment: In each of the studies (Adult Changes in Thought [ACT], Alzheimer's Disease Neuroimaging Initiative [ADNI], the Religious Orders Study–Memory and Aging Project (ROS/MAP], and the University of Pittsburgh data set [PITT]), the expert panel (Dr. Trittschuh, Dr. Mez, and Dr. Saykin) assigned items from the neuropsychological battery to one of the four domains (memory, language, executive functioning, and visuospatial ability); other items did not map to any of these domains. The expert panel also assigned each of these items to sub-domains based on the cognitive processes involved in each task. We also noted methods effects where the same stimulus was used in multiple assessments. We also used a data-driven approach looking at patterns of responses among participants to identify alternate possible secondary domain structures.

Step 2: Data quality control: Each of the studies sent their neuropsychological data sets to our team and Ms. Sanders, our data manager, ran an initial quality control on these. Ms. Sanders prepared a data set which included item-level data for individuals at their first Alzheimer's disease diagnosis. Before running psychometric models, we performed additional recoding of the data. Some items such as Trails A and B were reverse coded. We checked each item to make sure lower values represent lower cognitive performance. We considered the distribution of each item among those with non-missing data and combined categories as needed. Our goals were a.) to avoid sparse categories (operationally defined as <5 responses for each study administering each item) and b.) to have a maximum of 10 categories, which is the maximum number of categories handled by Mplus v7.4[1]. We treated each item as an ordinal indicator of the domain—the numerical value assigned to each category is irrelevant beyond its rank, e.g. calling the lowest category 3 points vs. 18 points makes no difference in how the item is treated or what the final score would be.

We also looked at informative missingness in each study and recoded relevant items accordingly. For example, some of the studies include multiple missing codes, where it was possible to identify refusal to respond to an item as opposed to the interviewer ran out of time and the item was never administered. The first of these—refusal—we took as informative missing and assigned that code to the lowest response category, while the second of these—missing due to scheduling etc.—we took as non-informative missing and omitted that item from consideration.

Step 3: Confirmatory factor analyses: We then turned to confirmatory factor analysis modeling with Mplus[2] using a Robust Weighted Least Squares including terms for the mean and the variance (WLSMV) estimator. We ran four models: a.) a single factor model, with no residual structure; b.) A theory-driven cognitive process bifactor model, using the a priori sub-domain assignments; c.) a theory-driven methods effects bifactor model, using the "methods effects" assignments; and d.) a data-driven bifactor model, using hierarchical clustering-assigned sub-domains. We consulted the expert panel on the sub-domain assignment of items in our data-driven approach to make sure these models made sense to our experts. Our overall strategy was that we would choose the single factor model if adding secondary factors did not markedly improve model fit and if adding secondary factors did not markedly impact any individual's score (see below).

Our goal with the three bifactor models (models b, c, and d) was to identify a single candidate bifactor model to compare with the single-factor model (model a). Our criteria for selecting the candidate bifactor model included fit statistics (see below) and concordance of model results with theory, such as all loadings on secondary factors being positive. The fit statistics we considered were the confirmatory fit index (CFI) where higher values indicate better fit; thresholds of 0.90 and 0.95 have been used in other settings as criteria for adequate or good fit[3, 4]; the Tucker-Lewis Index (TLI), which has similar criteria as the CFI; and the root mean squared error of approximation (RMSEA), where lower values indicate better fit, and thresholds of 0.08 and 0.05 have been used in other settings as criteria for adequate or good fit[3, 4].

When comparing the single factor model with the best bifactor model, we a) looked at whether loadings on the primary factor were within 10% of each other across the two models and b) compared the scores for the single factor model vs. scores for the final candidate bifactor model. We used as our threshold a difference of 0.30 units. We chose this value based on the default stopping rule for computerized adaptive testing; this has been used for years as

the default level of tolerable measurement differences in the setting of computerized adaptive tests. While arbitrary, this is a level of ambiguity that has been thought to be tolerable in a variety of situations. If there were a substantial number of people for whom the differences in scores were larger than 0.3 from each other, and if the bifactor model conformed to our theory better and had better fit statistics, we selected the final candidate bifactor model as our choice for modeling a domain.

Supplemental Text 1B. Co-calibration of the domains across ACT, ADNI, and ROS/MAP

Step 1: Identification of anchor items: Co-calibration requires either the same people taking different tests or different tests sharing common items. Here we had common items. We identified candidate anchor items with identical content across tests administered in different studies and ensured that their relationship with the underlying ability tested was the same across studies by performing preliminary confirmatory factor analysis models within each study. These items were then used to anchor the scales in each domain to a common metric**.** We consulted the expert panel (Dr. Trittschuh) to make sure we chose the anchor items correctly.

Step 2: Quality control for anchor items: Anchor items were cleaned and recoded after merging in the items from all the studies making sure that the range of the anchor items were similar in each study. We carefully reviewed documentation from each study to ensure that the stimulus was precisely the same, that the response options were precisely the same or could be re-coded to be the same, and that we were mapping data from each study in a way that the same response would result in the same score regardless of which study the person was enrolled in.

A note regarding response options—in many cases the stimulus is fairly open-ended, such as "can you please draw from memory the figure you copied a while ago", where the participant is handed a blank sheet of paper and a writing implement. The resulting drawing then gets scored based on how similar it was to the initial stimulus figure. The specific scoring applied to such a stimulus could vary across studies. One study could score such an item as correct vs. incorrect, while another could apply points for various aspects of the drawing. We reviewed the scoring documentation from both studies to determine what "correct" meant in the first study, and how many aspects of the drawing would need to be present for a "correct" score in that study. Then we would map all scores from the second study that would have resulted in a "correct" score in the first study to a "correct" score, and all other scores from the second study to an "incorrect" score. In this way, the resulting score is invariant to which study the person is participating in, as each response would be consistently scored regardless of study.

Step 3: Confirmatory factor analyses: We co-calibrated each of the four domains (memory, executive functioning, language, and visuospatial ability) by incorporating the components of the best model in each study (i.e., the final single-factor or bifactor model selected as described above) into one mega-calibration model.

One particularly tricky aspect of co-calibrating scores using bifactor models is how to handle secondary domains. Some anchor items had loadings on the primary domain (e.g. memory) and also on a secondary domain. That structure by itself does not lead to conceptual problems. However, item representation of the secondary domain may vary across studies, with variable numbers of items, and potential missing data and identifiability issues. To address this we used robust maximum likelihood (MLR) estimation that is robust to missing data, and assigned all subdomain indicators across studies to the same subdomain. Unlike running a CFA model with the WLSMV estimator, a CFA model with MLR estimator does not output fit statistics like CFI/TLI/RMSEA. For our purposes, these secondary domains were nuisances. We performed a number of sensitivity analyses to reassure ourselves that scores on the primary domain were minimally impacted by various ways of specifying the mean and variance on secondary domains. In the final models we selected, we specified a mean of 0 and a variance of 1 for each secondary domain factor, regardless of the number of studies that included items that loaded on that factor.

Once we had fit the final mega-calibration model for each domain, we extracted factor scores for the primary factor (e.g. memory). The resulting scores are on the same metric with a mean of 0 and variance of 1. We used all participants with relevant data to fit data for each domain, so different the scale for each domain was based on models that included different specific people, since some people were missing for some domains. We therefore picked a reference population for standardizing scores for each domain. We used ACT for this, as it was a

community-based prospective cohort study, and had a very large sample (n=825) of people with sufficient cognitive data to generate all of our scores. We applied the same standardization to all participants for each study.

Thus, a score of 0, regardless of study, reflects the mean for people with Alzheimer's disease in the ACT study; and a score of -1, regardless of study, reflects 1 SD below the mean for people with Alzheimer's disease in the ACT study.

For future data sets in our pipeline such as University of Pittsburgh (PITT), we used these estimated thresholds and loadings of items from the co-calibration mega-calibration models to obtain scores for individuals. New items (not part of ACT, ADNI, and ROS/MAP) were freely estimated while already seen items will have their parameters fixed based on these mega-calibration models.

Supplemental Text 1C. Confirmatory factor analysis model considerations in co-calibration models

1. For all CFA models, we categorized items to ≤ 10 categories. For co-calibration purpose, we had to re-categorize some of the items even though they already had ≤ 10 categories. This was because some studies had more granular data (more categories) for anchor items compared to other studies. In these cases, after we estimated item parameters from the co-calibration model, we re-estimated parameters of the anchor item(s) in the most granular form in the given study. For example, the item "q20mme" was an anchor item for visuospatial ability administered in ACT, ROS/MAP, and ADNI. The item asks individuals to copy intersecting pentagons. In ROS/MAP and ADNI, this item is coded as 0/1 (incorrect/correct) while in ACT it is coded 0–10 (four points for aspects of the left pentagon, four points for aspects of the right pentagon, two points for aspects of the intersection). For co-calibration purpose, we dichotomized this item to 0/1. We consulted scoring algorithms for each of the studies to determine that only scores of 10/10 from the ACT study would have received scores of 1 from ROS/MAP or ADNI; any drawing receiving a score of 9 or fewer from ACT would have scored a 0 in the other studies.

After using re-coded items for co-calibration, we fixed all of the other items to their values from the co-calibration run and freely estimated parameters for re-coded anchors in their most granular form. This approach enabled us to obtain more precise scores in studies that incorporated more granular scoring rules, while still using all items administered across studies to co-calibrate metrics across studies.

2. The base co-calibration exercise for each of the four domains was performed across ACT, ROS/MAP, and ADNI. PITT data were subsequently added with the following steps. For each domain, we identified anchor items and fixed their item parameters to those estimated previously in the base co-calibration models; unique items administered in the new study that were not administered to people in ACT, ROS/MAP, or ADNI were freely estimated.

In these models,

a) The mean and variance for the primary factor were freely estimated.

b) If every item in a sub-domain in the new data had parameters available from the co-calibration model, we fixed those item parameters to their previously identified values, and allowed the mean and variance to be freely estimated in the new data.

If no item from a sub-domain had parameters available, then we freely estimated each of the sub-domain loadings, fixing the mean and variance of the subdomain factor to 0 and 1.

If there was a mix of previously specified and new items in a subdomain, we fixed the parameters for the previously specified items, and allowed the mean and variance of the factor and the loadings for new items to be freely estimated in the new data.

NOTE: Detailed overview and all code snippets and can be obtained from authors on request.

Supplemental Text 2. Neuropsychological items by domain for each study and fit statistics from CFA models

- **MEMORY**

ACT: Final model was a theory driven methods-effects bifactor model with CFI = 0.923, TLI = 0.914, and RMSEA = 0.052. The following items were included in the CFA analysis (Supplemental Table 1).

Supplemental Table 1. Items and secondary structure for memory for the ACT study

Study	Variable	Description	Secondary Structure
ACT	mat_mem	Mattis Dementia Rating Scale Memory score	
ACT	w_in_c1	Word list learning trial 1 total score	F1
ACT	w_in_c2	Word list learning trial 2 total score	F1
ACT	w_in_c3	Word list learning trial 3 total score	F1
ACT	w_rcl_c	Word List Recall—correct	F1
ACT	w_rcg_t	Word Recognition—total correct	F1
ACT	cp_re_ci	Constructional Praxis Delay—circle	F2
ACT	cp_re_di	Constructional Praxis Delay—diamond	F2
ACT	cp_re_re	Constructional Praxis Delay—rectangles	F2
ACT	cp_re_cu	Constructional Praxis Delay—cube	F2
ACT	w_lm_ima	Logical Mem I—immediate recall total story A	F3
ACT	w_lm_imb	Logical Mem I—immediate recall total story B	F4
ACT	w_lm_dea	Logical Mem II—delayed recall total story A	F3
ACT	w_lm_deb	Logical Mem II—delayed recall total story B	F4
ACT	w_vp_ine	Verbal Paired Associates I easy	F5
ACT	w_vp_inh	Verbal Paired Associates I hard	F6
ACT	w_vp_ree	Verbal Paired Associates II easy	F5
ACT	w_vp_reh	Verbal Paired Associates II hard	F6
ACT-CASI	rgs1	repeat words	F7
ACT-CASI	rc1a	Word recall—something to wear—1	F7
ACT-CASI	rc1b	Word recall—a color—1	F7
ACT-CASI	rc1c	Word recall—personal quality—1	
ACT-CASI	yr	What is today's date?—year	F8
ACT-CASI	mo	What is today's date?—month	F8
ACT-CASI	casi_dat	What is today's date?—day	F8
ACT-CASI	day	What day of week?	F8
ACT-CASI	casi_ssn	What season is it?	F8
ACT-CASI	spa	What state and city?	F8
ACT-CASI	spb	What is this place?	F8
ACT-CASI	rc2a	Word recall—something to wear—2	F7

ACT-CASI	rc2b	Word recall—a color—2	F7
ACT-CASI	rc2c	Word recall—personal quality—2	F7
ACT-CASI	rcobj	Recall of 5 objects	

ADNI: Final model was a data driven bifactor model with CFI = 0.951, TLI = 0.946, and RMSEA = 0.036. The following items were included in the CFA analysis (Supplemental Table 2).

Supplemental Table 2. Items and secondary structure for memory for the ADNI study

Study	Variable	Description	Secondary Structure
ADNI	limmtotal	Logical Memory—Immediate Recall	F1
ADNI	ldeltotal	Logical Memory—Delayed Recall	F1
ADNI	avtot1*	AVLT Trial 1 Total	F2
ADNI	avtot2*	Trial 2 Total	F2
ADNI	avtot3*	Trial 3 Total	F2
ADNI	avtot4*	Trial 4 Total	F2
ADNI	avtot5*	Trial 5 Total	F2
ADNI	avtot6*	Trial 6 Total	F3
ADNI	avtotb*	List B Total	F2
ADNI	avdel30min*	30 Minute Delay Total	F3
ADNI	avdeltot*	Recognition Score	F4
ADNI	q1score	ADAS Word Recall—score	F2
ADNI	q4score	ADAS Delayed Word Recall	F4
ADNI	q7score	ADAS Orientation—score	F5
ADNI	q8score	ADAS Word Recognition—score	
ADNI	mmdate	What is today's date?	F5
ADNI	mmyear	What is the year?	F5
ADNI	mmmonth	What is the month?	F5
ADNI	mmday	What day of the week is today?	F5
ADNI	mmseason	What season is it?	
ADNI	mmhospit	What is the name of this hospital (clinic, place)?	
ADNI	mmfloor	What floor are we on?	
ADNI	mmcity	What town or city are we in?	
ADNI	mmarea	What county (district, borough, area) are we in?	
ADNI	mmstate	What state are we in?	
ADNI	mmball	Ball	F6
ADNI	mmflag	Flag	F6
ADNI	mmtree	Tree	F6
ADNI	mmballdl	Ball delayed	F7
ADNI	mmflagdl	Flag delayed	F7
ADNI	mmtreedl	Tree delayed	F7
ADNI	imm1sum	Immediate recall of the MoCA list (#1)	F2

ADNI	imm2sum	Immediate recall of the MoCA list(#2)	F2
ADNI	delsum	Delayed recall of the MoCA list	

MoCA (blue) items were only administered in ADNI GO/2 while orange items were in all ADNI waves (1/GO/2).

ADNI administered two versions (different word lists) of RAVLT (avtot1–avdeltot) and three different versions of ADAS-Cog items (q*) across waves. We ran the model separately for the two versions. The ADAS-Cog versions were found to be equivalent while the RAVLT versions were not. For determining secondary factor structures and extracting model fit statistics, we considered all RAVLT versions to be equivalent. The different versions of RAVLT were taken into account in the final co-calibration phase.

There were additional MoCA items, which were the same (theoretically) as corresponding items from the Mini-Mental State Examination (MMSE). We excluded MoCA items if those items were already asked as part of the neuropsychological battery.

ROS/MAP: Final model was a data driven bifactor model with CFI = 0.941, TLI = 0.929, and RMSEA = 0.063. The following items were included in the CFA analysis (Supplemental Table 3):

Supplemental Table 3. Items and secondary structure for memory for the ROS and MAP studies

Study	Variable	Description	Comments	Secondary Structure
ROS/MAP	Q1mme	What is the year?		F1
ROS/MAP	Q2mme	What is the season of the year?		
ROS/MAP	Q3mme	What is the date?		F1
ROS/MAP	Q4mme	What is the day of the week?		F1
ROS/MAP	Q5mme	What is the month?		F1
ROS/MAP	Q6mme	What state are we in?		F2
ROS/MAP	Q8mme	What city are we in?		F2
ROS/MAP	Q7mme	What county are we in?		F2
ROS/MAP	Q9mme	What room are we in?		F2
ROS/MAP	Q10amme	What is the address of this place?		F2
ROS/MAP	Q10bmme	Street Name		F2
ROS/MAP	atb1	Apple, table, penny (immediate)	3 items collapsed	
ROS/MAP	story	Logical memory		F3
ROS/MAP	WordT1	Word list learning Trial 1	10 items collapsed	F4
ROS/MAP	WordT2	Word list learning Trial 2	"	F4
ROS/MAP	WordT3	Word list learning Trial 3	"	F4
ROS/MAP	WordRec	Which one of these words is from that list? (Word list recognition)	10 items collapsed	F6
ROS/MAP	Recall	Word list recall	10 items collapsed	F6
ROS/MAP	ebmt	East Boston immediate recall	12 items collapsed	F5
ROS/MAP	atb2	apple, table, penny (delayed)	3 items collapsed	
ROS/MAP	ebdr	East Boston delayed recall	12 items collapsed	F5
ROS/MAP	Delay	Tell me the story again		F3

Supplemental Table 4. Co-calibration of memory across ACT, ADNI, ROS/MAP

Study	Variable	Secondary structure	Comments
ACT, ADNI, ROS/MAP	mmyear	F2	Q1mme in ROS/MAP; yr in ACT
ACT, ADNI, ROS/MAP	mmseason		Q2mme in ROS/MAP; casi_ssn in ACT
ACT, ADNI, ROS/MAP	mmdate	F2	Q3mme in ROS/MAP; casi_dat in ACT
ACT, ADNI, ROS/MAP	mmday	F2	Q4mme in ROS/MAP; day in ACT
ACT, ADNI, ROS/MAP	mmmonth	F2	Q5mme in ROS/MAP; mo in ACT
ACT, ADNI, ROS/MAP	mmctst	F6	Collapsed (Q6mme Q8mme) in ROSMAP and (mmcity mmstate) in ADNI to create a single variable; spa in ACT
ACT, ADNI	limmtotal	F3	limmtotal in ADNI; w_lm_ima in ACT
ACT, ADNI	ldeltotal	F3	limmtotal in ADNI; w_lm_dea in ACT
ROS/MAP	Q7mme	F6	
ROS/MAP	Q9mme	F6	
ROS/MAP	Q10amme	F6	
ROS/MAP	Q10bmme	F6	
ROS/MAP	atb1		
ROS/MAP	story	F9	
ROS/MAP	WordT1	F7	
ROS/MAP	WordT2	F7	
ROS/MAP	WordT3	F7	
ROS/MAP	ebmt	F8	
ROS/MAP	WordRec	F10	
ROS/MAP	atb2		
ROS/MAP	Recall	F10	
ROS/MAP	ebdr	F8	
ROS/MAP	Delay	F9	
ACT	mat_mem		
ACT	w_in_c1	F11	
ACT	w_in_c2	F11	
ACT	w_in_c3	F11	
ACT	w_rcl_c	F11	
ACT	w_rcg_t	F11	
ACT	cp_re_ci	F12	
ACT	cp_re_di	F12	
ACT	cp_re_re	F12	
ACT	cp_re_cu	F12	
ACT	w_lm_imb	F14	
ACT	w_lm_deb	F14	
ACT	w_vp_ine	F15	
ACT	w_vp_inh	F16	

ACT	w_vp_ree	F15	
ACT	w_vp_reh	F16	
ACT-CASI	rgs1		
ACT-CASI	rc1a	F13	
ACT-CASI	rc1b	F13	
ACT-CASI	rc1c	F13	
ACT-CASI	spb	F6	
ACT-CASI	rc2a	F13	
ACT-CASI	rc2b	F13	
ACT-CASI	rc2c	F13	
ACT-CASI	rcobj		
ADNI	avtot1	F1	Each RAVLT item was split into two items to account for two versions of RAVLT used in ADNI at specific waves where both versions of the same item were loaded into the same secondary structure
ADNI	avtot2	F1	
ADNI	avtot3	F1	
ADNI	avtot4	F1	
ADNI	avtot5	F1	
ADNI	avtot6	F5	
ADNI	avtotb	F1	
ADNI	avdel30min	F5	
ADNI	avdeltot	F4	
ADNI	q1score	F1	
ADNI	q4score	F4	
ADNI	q7score	F2	
ADNI	q8score		
ADNI	mmhospit		
ADNI	mmfloor		
ADNI	mmarea		
ADNI	bft1		Immediate—ball, flag, tree collapsed
ADNI	bft2		Delayed—ball, flag, tree collapsed
ADNI	imm1sum	F1	
ADNI	Imm2sum	F1	
ADNI	delsum		

EXECUTIVE FUNCTIONING

ACT: Final model was a data driven bifactor model with CFI = 0.948, TLI = 0.929, and RMSEA = 0.064. The following items were included in the CFA analysis (Supplemental Table 5):

Supplemental Table 5. Items and secondary structure for executive functioning for the ACT study

Study	Variable	Description	Comments	Secondary Structure
ACT	mat_attn	Mattis Dementia Rating Scale, Attention score		
ACT	mat_conc	Mattis Dementia Rating Scale, Concentration score		
ACT	mat_ip	Mattis Dementia Rating Scale, initiation / perseveration score		
ACT	tr_a_tm	Trails A		F1
ACT	tr_b_tm	Trails B		F1
ACT	clockdr	Clock		
ACT-CASI	dbsum	repeat numbers backward 1–3	Repeat numbers backward—3 trials collapsed	F2
ACT-CASI	subtra	Subtraction 1–3	Subtraction—3 trials collapsed	F2
ACT-CASI	sim	similarities		
ACT-CASI	jgmt	judgement		

ADNI: Final model was a theory driven methods-effects bifactor model with CFI = 0.951, TLI = 0.946, and RMSEA = 0.041. The following items were included in the CFA analysis (Supplemental Table 6):

Supplemental Table 6. Items and secondary structure for executive functioning for the ADNI study

Study	Variable	Description	Comments	Secondary Structure
ADNI	clockcirc	Approximately circular face		
ADNI	clocksym	Symmetry of number placement		F2
ADNI	clocknum	Correctness of numbers		F2
ADNI	clockhand	Presence of the two hands		
ADNI	clocktime	Presence of the two hands, set to ten after eleven		
ADNI	dspanbac	Backward Total Correct		F4
ADNI	traascor	Part A Time to Complete		F3
ADNI	trabscor	Part B Time to complete		F3
ADNI	digitscor	Digit Symbol Total Correct		F1
ADNI	dspanfor	Digit Span Forward Total Correct		F4
ADNI	q13score	Number cancellation task		F1
ADNI	absmeas	Abstraction: watch-ruler		

ADNI	abstran	Abstraction: train-bicycle		
ADNI	trails	MoCA Trails		
ADNI	digback	Digits Backward	5 trials collapsed	
ADNI	serial	Serial 7 total		
ADNI	digfor	Digits Forward		
ADNI	letters	List of Letters/Tapping: # Errors		

ROS/MAP: Final model was a theory driven methods-effects model with CFI = 0.975, TLI = 0.960, and RMSEA = 0.064. The following items were included in the CFA analysis (Supplemental Table 7):

Supplemental Table 7. Items and secondary structure for memory for the ROS and MAP studies

Study	Variable	Description	Comments	Secondary structure
ROS/MAP	AA	Which piece would complete the pattern…	4 A patterns merged	
ROS/MAP	BB	Which piece would complete the pattern…	8 B patterns merged	
ROS/MAP	Q12bmme	Spell WORLD backwards		
ROS/MAP	DigBak	digits backward	combined 12 items	
ROS/MAP	cts_sdmt	symbol digits modality (oral)		F1
ROS/MAP	cts_nccrtd	Number comparison		F1
ROS/MAP	DigFor	digits forward	combined 12 items	

Supplemental Table 8. Co-calibration of executive functioning across ACT, ADNI, ROS/MAP

Study	Variable	Description	Secondary structure
ACT, ADNI	traascor	Trails A	F3
ACT, ADNI	trabscor	Trails B	F3
ADNI, ROS/MAP	dspanfor	Digit Span Forward: Total Correct	F4
ADNI, ROS/MAP	dspanbac	Digit Span Backward: Total Correct	F4
ROS/MAP	AA	Which piece would complete the pattern…	
ROS/MAP	BB	Which piece would complete the pattern…	
ROS/MAP	Q12bmme	Spell WORLD backwards	
ROS/MAP	cts_sdmt	symbol digits modality (oral)	F6
ROS/MAP	cts_nccrtd	Number comparison	F6
ACT	mat_attn	Mattis Dementia Rating Scale	
ACT	mat_conc	Mattis Dementia Rating Scale	
ACT	mat_ip	Mattis Dementia Rating Scale	
ACT	clockdr	Clock	
ACT-CASI	dbsum	repeat numbers backward	F5
ACT-CASI	subtra	subtraction	F5
ACT-CASI	sim	similar types	

ACT-CASI	jgmt	judgement	
ADNI	clockcirc	Approximately circular face	
ADNI	clocksym	Symmetry of number placement	F2
ADNI	clocknum	Correctness of numbers	F2
ADNI	clockhand	Presence of the two hands	
ADNI	clocktime	Presence of the two hands, set to 10 after 11	
ADNI	digitscor	Digit Symbol Total Correct	F1
ADNI	q13score	Number cancellation task	F1
ADNI	absmeas	Abstraction: watch–ruler	
ADNI	abstran	Abstraction: train–bicycle	
ADNI	trails	Trails	
ADNI	digback	Digits Backward	
ADNI	serial	Serial 7	
ADNI	digfor	Digits Forward	
ADNI	letters	List of Letters/Tapping: # Errors	

LANGUAGE

ACT: Final model was a data driven bifactor model with CFI = 0.956, TLI = 0.943, and RMSEA = 0.055. The following items were included in the CFA analysis (Supplemental Table 9):

Supplemental Table 9. Items and secondary structure for language for the ACT study

Study	Variable	Description	Secondary Structure
ACT	bnt_adpr*	Boston Naming Test – 10-item version	F1
ACT	bnt_cer *	Boston Naming Test – 15-item version	F1
ACT	v_flu_t	Verbal Fluency	
ACT-CASI	animal	animals with 4 legs	
ACT-CASI	rpta	repeat phrase 1	F2
ACT-CASI	rptb	repeat phrase 2	F2
ACT-CASI	cas_read	read and follow a command	
ACT-CASI	cas_writ	write a sentence	
ACT-CASI	cmd	obey oral commands	
ACT-CASI	body	identify parts of body	
ACT-CASI	obja	identify objects—1	F3
ACT-CASI	objb	identify objects—2	F3

***** ACT administers all 15 items from the CERAD version of the Boston Naming Test (bnt_cer) and another 8 distinct items from a long version of the Boston Naming Test (bnt_adpr).

ADNI: Final model was a theory driven methods-effects bifactor model with CFI = 0.951, TLI = 0.946, and RMSEA = 0.041. The following items were included in the CFA analysis (Supplemental Table 10):

Supplemental Table 10. Items and secondary structure for language for the ADNI study

Study	Variable	Description	Secondary structure
ADNI	catanimsc	Category Fluency (Animals) —Total Correct	F1
ADNI	catvegesc	Category Fluency (VegSupplemental Tables) —Total Correct	
ADNI	bnttotal	Total Number Correct (1+3)	F1
ADNI	q2score	ADAS Commands	
ADNI	q5score	ADAS Naming	F1
ADNI	q6score	Ideational Praxis—score	
ADNI	mmwatch	Show wrist watch, ask: What is this?	
ADNI	mmpencil	Show pencil, ask: What is this?	
ADNI	mmrepeat	Say: Repeat after me: no ifs, ands, or buts.	
ADNI	mmhand	Takes paper in right hand	
ADNI	mmfold	Folds paper in half	
ADNI	mmonflr	Puts paper on floor	

ADNI	mmread	Present the piece of paper which reads—CLOSE YOUR EYES—and say: Read this and	
ADNI	mmwrite	Give the participant a blank piece of paper and say: Write a sentence.	
ADNI	camel	Camel	
ADNI	lion	Lion	
ADNI	rhino	Rhinoceros	
ADNI	repeat1	Repeat Sentence.	
ADNI	repeat2	Repeat Sentence.	
ADNI	ffluency	Letter Fluency—F: Total number of correct words	

ROS/MAP: Final model was a data driven model with CFI = 0.932, TLI = 0.924, and RMSEA = 0.036. The following items were included in the CFA analysis (Supplemental Table 11):

Supplemental Table 11. Items and secondary structure for language for the ROS and MAP studies

Study	Variable	Description	Secondary Structure
ROS/MAP	Q12amme	Spell WORLD forwards	
ROS/MAP	Q14mme	[SHOW WRIST WATCH] What is this called?	
ROS/MAP	Q15mme	[SHOW PENCIL] What is this called?	
ROS/MAP	Q16mme	Repeat a phrase	
ROS/MAP	Q17mme	Read the words on this card, then do what it says	
ROS/MAP	paper	Takes piece of paper	
ROS/MAP	folds	Folds paper in half	
ROS/MAP	places	Places paper in lap	
ROS/MAP	Q19mme	Write any complete sentence	
ROS/MAP	dnaming	What is the name of this object?	
ROS/MAP	clothing	all of the things that belong in that category	
ROS/MAP	animals	all of the things that belong in that category	F1
ROS/MAP	fruits	all of the things that belong in that category	F1
ROS/MAP	sink1	Will a board sink in water?	
ROS/MAP	sink2	Will a stone sink in water?	
ROS/MAP	hammer1	Is a hammer good for cutting wood?	
ROS/MAP	hammer2	Can you use a hammer to pound nails?	
ROS/MAP	flour1	Do two pounds of flour weigh more than one?	
ROS/MAP	flour2	Is one pound of flour heavier than two?	
ROS/MAP	boots1	Will water go through a good pair of rubber boots?	
ROS/MAP	boots2	Will a good pair of rubber boots keep water out?	

Supplemental Table 12. Co-calibration of language across ACT, ADNI, ROS/MAP

Study	Variable	Description	Secondary structure
ACT, ADNI, ROS/MAP	read	Read the words on this card, then do it	
ACT, ADNI, ROS/MAP	cmd	Paper, fold, place on floor combined	
ACT, ADNI, ROS/MAP	catanim	Category Fluency (Animals)—Total Correct	F3
ACT, ROS/MAP	bnt_name	Boston Naming: Name of this object?	F2
ADNI, ROS/MAP	watch	[SHOW WRIST WATCH] What is this called?	
ADNI, ROS/MAP	pencil	[SHOW PENCIL] What is this called?	
ADNI, ROS/MAP	repeat	I would like you to repeat a phrase after me	
ADNI, ROS/MAP	write	Write any complete sentence on this piece of	
ROS/MAP	Q12amme	Spell WORLD forwards	
ROS/MAP	clothing	all of the things that belong in that category	
ROS/MAP	fruits	all of the things that belong in that category	F3
ROS/MAP	sink1	Will a board sink in water?	
ROS/MAP	sink2	Will a stone sink in water?	
ROS/MAP	hammer1	Is a hammer good for cutting wood?	
ROS/MAP	hammer2	Can you use a hammer to pound nails?	
ROS/MAP	flour1	Do two pounds of flour weigh more than one?	
ROS/MAP	flour2	Is one pound of flour heavier than two?	
ROS/MAP	boots1	Will water go through a good pair of rubber boots?	
ROS/MAP	boots2	Will a good pair of rubber boots keep water out?	
ACT	bnt_adpr	Boston Naming Test	F2
ACT-CASI	animal	animals with 4 legs	F3
ACT-CASI	rpta	repeat something	
ACT-CASI	rptb	repeat something	
ACT-CASI	cas_writ	write something	
ACT-CASI	body	identify part of body	
ACT-CASI	obja	identify object—1	F1
ACT-CASI	objb	identify object—2	F1
ADNI	catvegesc	Category Fluency (VegSupplemental Tables) — Total Correct	F3
ADNI	bnttotal	Total Number Correct (1+3)	F3
ADNI	q2score	ADAS Commands	
ADNI	q5score	ADAS Naming	F3
ADNI	q6score	Ideational Praxis—score	
ADNI	camel	Camel	
ADNI	lion	Lion	
ADNI	rhino	Rhinoceros	
ADNI	repeat1	Repeat Sentence.	
ADNI	repeat2	Repeat Sentence.	
ADNI	ffluency	Letter Fluency—F: Total # of correct words	

VISUOSPATIAL FUNCTIONING

ACT: Final model was a data driven bifactor model with CFI = 0.993, TLI = 0.987, and RMSEA = 0.031. The following items were included in the CFA analysis (Supplemental Table 13):

Supplemental Table 13. Items and secondary structure for visuospatial functioning for the ACT study

Study	Variable	Description	Secondary Structure
ACT	mat_cons	Mattis Dementia Rating Scale—constructional praxis score	
ACT	cp_in_ci	Constructional Praxis—circle	F1
ACT	cp_in_di	Constructional Praxis—diamond	F1
ACT	cp_in_re	Constructional Praxis—rectangles	
ACT	cp_in_cu	Constructional Praxis—cube	
ACT-CASI	draw	Copy interlocking pentagons	

ADNI: Final model was a single factor model with CFI = 0.958, TLI = 0.937, and RMSEA = 0.060. The following items were included in the CFA analysis (Supplemental Table 14):

Supplemental Table 14. Items and secondary structure for visuospatial functioning for the ADNI study

Study	Variable	Description	Secondary Structure
ADNI	copycirc	Clock copy: Approximately circular face	
ADNI	copysym	Symmetry of number placement	
ADNI	copynum	Correctness of numbers	
ADNI	copyhand	Presence of the two hands	
ADNI	copytime	Presence of the two hands, set to ten after eleven	
ADNI	q3score	Constructional Praxis—score	
ADNI	mmdraw	Present the participant with the Cnstrn Stimulus page. Say: Copy this design	

ROS/MAP: Final model was a single factor model with CFI = 0.948, TLI = 0.940, and RMSEA = 0.040. The following items were included in the CFA analysis (Supplemental Table 15):

Supplemental Table 15. Items and secondary structure for visuospatial functioning for the ROS and MAP studies

Study	Variable	Description	Secondary Structure
ROS/MAP	Q20mme	Please copy the drawing on this piece of paper	
ROS/MAP	Line1…15	Which two lines point in the same direction…?	

Co-calibration of visuospatial ability across ACT, ADNI, ROS/MAP

Single factor models were selected for ADNI and ROS/MAP, while a bifactor model with a single residual correlation was chosen for the ACT study. The pair of items with a residual correlation from ACT was unique to ACT and not present in either of the other studies. Our final model was thus a bifactor model that included only a single residual correlation for the pair of items from the ACT study; all other items, including all of the items administered in ROS/MAP and ADNI, only had loadings on the general factor.

Supplemental Table 16: Co-calibration of visuospatial ability across ACT, ADNI, and ROS/MAP.

Study	Variable	Description	Secondary Structure
ACT, ADNI, ROS/MAP	Q20mme	Please copy the drawing on this piece of paper	
ROS/MAP	Line1–15	Which two lines point in the same direction…	
ACT	mat_cons	Mattis Dementia Rating Scale	
ACT	cp_in_ci	Constructional Praxis—circle	F1
ACT	cp_in_di	Constructional Praxis—diamond	F1
ACT	cp_in_re	Constructional Praxis—rectangles	
ACT	cp_in_cu	Constructional Praxis—cube	
ADNI	copycirc	Clock copy: Approx circular face	
ADNI	copysym	Symmetry of number placement	
ADNI	copynum	Correctness of numbers	
ADNI	copyhand	Presence of the two hands	
ADNI	copytime	Presence of the two hands, set to ten after eleven	
ADNI	q3score	Constructional Praxis—score	

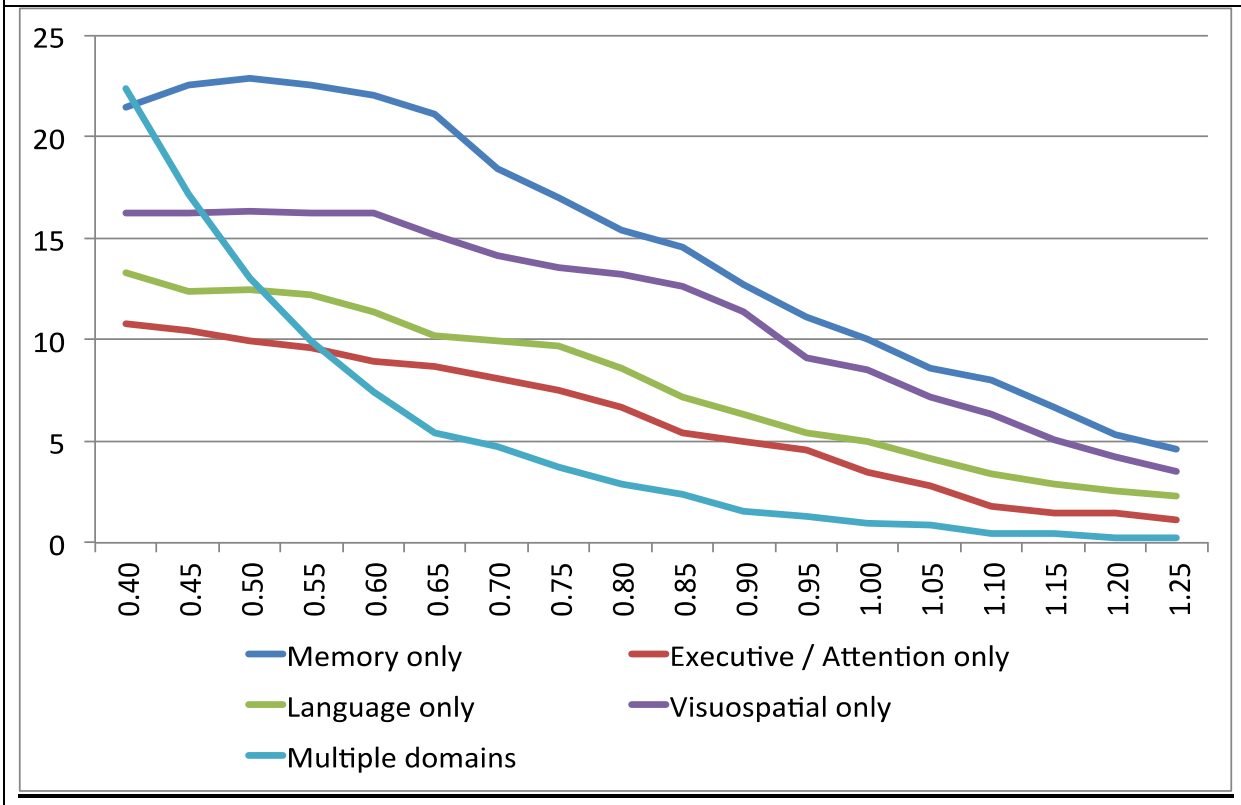
Supplemental Text 3: Choice of the threshold of 0.80 points

There is no readily agreed upon threshold for what would represent a substantial difference. We used data from ACT, since it was the largest community-based cohort study for which we had data. We considered a range of thresholds from 0.40 to 1.25 SD. At each threshold, we noted in how many and in which domains each individual had relative impairments. We categorized people as having no domain with a substantial relative impairment vs. having each single domain with a substantial relative impairment vs. having more than one domain with a substantial relative impairment.

Based on results from those analyses we selected a threshold of 0.80 to consider further. We selected that threshold based on the inflection in the curve describing the proportion of people with more than one domain with a substantial relative impairment. We reasoned that at insufficiently strenuous thresholds, multiple domains could be impaired just by chance alone, such that there would be a mixture of people with substantial relative deficits in multiple domains together with people with low scores just by chance. Below the 0.80 inflection point, the proportion of people identified with substantial relative impairments in multiple domains was much less influenced by the threshold than it was above the 0.80 inflection point.

The proportion of ACT participants with incident Alzheimer's dementia who met criteria for each cognitively defined subtype at each threshold level is shown in Supplemental Figure 1.

Supplemental Figure 1. Cognitively-defined subgroup membership at each threshold level*

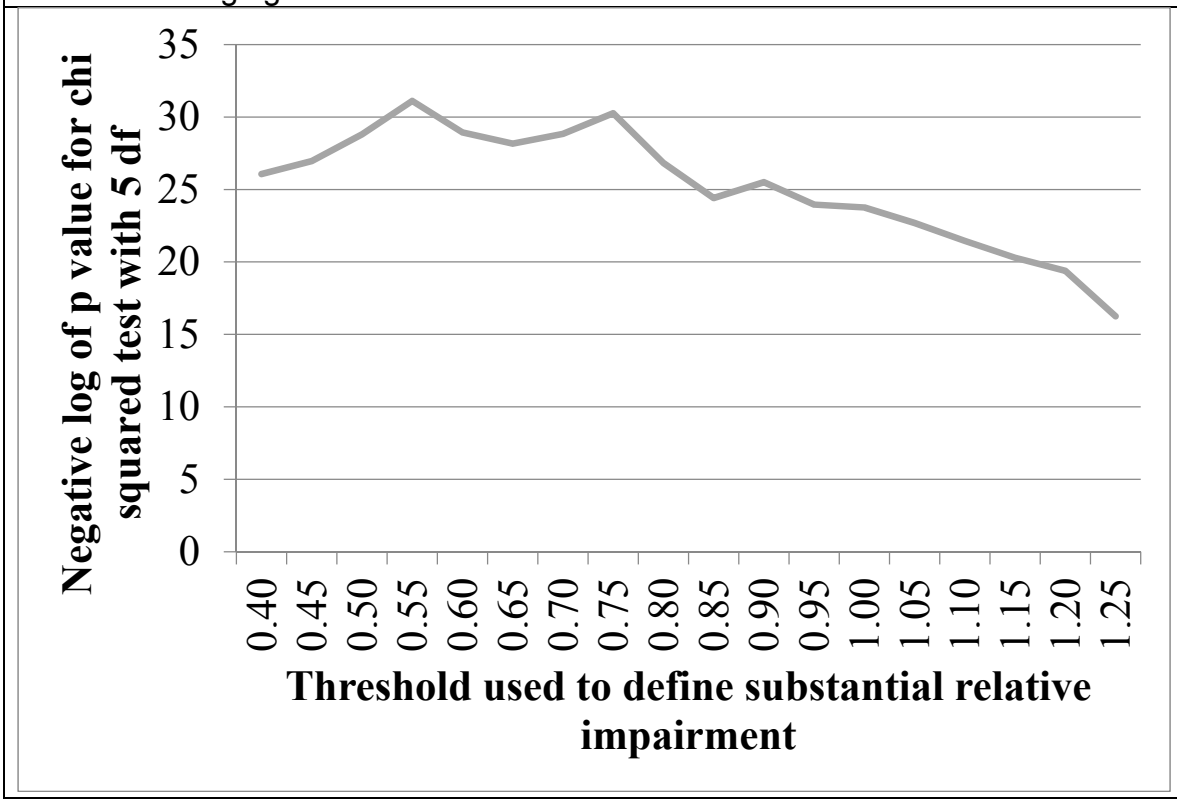


* Data represent the proportion of people with incident Alzheimer's dementia from ACT who met criteria for each subtype at thresholds that ranged from -0.40 to -1.25. At the -0.40 threshold, about 22% of the cohort had a memory score that was at least 0.40 points lower than their average score across all four domains, and had no other domain with a substantial relative impairment at that level (dark blue line). Also at the -0.40 threshold, about 16% of the cohort had a substantial relative impairment in visuospatial functioning and no other domain (purple line), about 13% had a substantial relative impairment in language (green line), and about 11% had a substantial relative impairment in executive functioning (red line); in all, 22% (memory) + 16% (visuospatial) + 13% (language) + 11% (executive functioning) = 62% of the cohort had a substantial relative impairment in a single domain at the minus 0.40 threshold. The light blue line shows that at that same threshold, about 23% of the cohort had two or more domains with a substantial relative impairment, meaning that in all 85% of the cohort had 1 or more domains with a substantial relative impairment at that threshold and the remaining 15% had no domains with a substantial relative impairment. Moving to the right, the proportion of individuals identified with domains with a substantial relative impairment decreases. There appears to be an inflection point in the light blue curve that represents the proportion of the cohort with substantial relative impairments in more than one domain around a threshold of minus 0.80; we selected that threshold for further analyses.

Supplemental Text 4. Sensitivity of *APOE* findings to choice of threshold

We performed additional analyses to determine whether the *APOE* finding of significant differences across subsets was due to choice of the threshold of 0.80. We used combined data from all the studies. We categorized people at each threshold between -0.40 to -1.25. We performed two analyses. First, we considered the proportion in each subgroup with a χ^2 test with 5 degrees of freedom. We plot the $-\log_{10}$ of p values for each threshold in Supplemental Figure 2:

Supplemental Figure 2. Sensitivity analyses of *APOE* ε4 proportions across subgroups at thresholds ranging from -0.40 to -1.25.



This figure shows p values ranging from 10^{-17} to 10^{-32}. The value at 0.80 is similar to those across a wide range of thresholds.

Supplemental Text 5. Addition of University of Pittsburgh study to the pipeline

As detailed above, items where the PITT item was the same as an item with parameters from the ACT/ADNI/ROS-MAP analyses, we used those previously co-calibrated parameters. For items administered only to PITT participants, we freely estimated item parameters from the data set.

Supplemental Table 17. Memory specification for the PITT dataset

Study	Variable	Description	Secondary Structure
ROS/MAP, PITT	wrec	Word recognition trial 1	F2
ROS/MAP, PITT	wrec2	Word recognition trial 2	F2
ROS/MAP, PITT	wrec3	Word recognition trial 3	F2
ROS/MAP, PITT	wrecde	Word recognition—delayed	
PITT	targets	Word recognition—target correct	
PITT	foils	Word recognition—foils correct	
PITT	reyim	Rey figure—immediate recall	F3
PITT	reyde	Rey figure—delayed	F3
ACT, ADNI, PITT	logimem	Logical Memory A1	F1
ACT, ADNI, PITT	memunits	Logical Memory A2	F1
ACT, PITT	mattism	Mattis DRS—memory	

Supplemental Table 18. Executive function specification for the PITT dataset

Study	Variable	Description	Secondary Structure
ROS/MAP, ADNI, PITT	spansb	Digit span—backwards	F1
ACT, ADNI, PITT	trailas	Trail A—time	F2
ACT, ADNI, PITT	trailbs	Trail B—time	F2
PITT	mbar	Abstract reasoning	
ACT, PITT	mattisip	Mattis DRS—initiation/perseveration	
ACT, PITT	mconcep	Mattis DRS—conceptualization	
ROS/MAP, ADNI, PITT	spansf	Digit span—forward	F1
ACT, PITT	mattisa	Mattis DRS—attention	
PITT	stpcw	Stroop—Color,Word	

Supplemental Table 19. Language specification for the PITT dataset

Study	Variable	Description	Secondary Structure
ACT, ADNI, ROS/MAP, PITT	fluen	Fluency test—animals	F1
PITT	fluenb	Fluency test—birds	F1
PITT	fluend	Fluency test—dogs	F1
ADNI, PITT	fluenf	Fluency test—letter F	F3
PITT	fluena	Fluency test—letter A	F3

PITT	fluens	Fluency test—letter S	F3
PITT	stpw	Stroop—Word	F2
PITT	stpc	Stroop—Color	F2
ADNI, PITT	veg	Category fluency—vegSupplemental Tables	F1
ADNI, PITT	boston	Boston Naming Test total	F1

Supplemental Table 20. Visuospatial functioning specification for the PITT dataset.

Study	Variable	description	Secondary Structure
ACT, ADNI, ROS/MAP, PITT	pentagon	draw intersecting pentagons	
PITT	reyco	Rey figure—copy	
PITT	blkdsn	Block design	
ACT, PITT	mconst	Mattis DRS—construction	

Supplemental Text 6. Genetic analyses

Text 6A. Cohorts

The following description of the IGAP data sets has been duplicated from the supplemental materials of the IGAP gene-wide analysis paper[5] referenced below.

The ACT/eMERGE Studies (ACT) The ACT cohort is an urban and suburban elderly population from a stable HMO that includes 2,581 cognitively intact subjects age ≥ 65 who were enrolled between 1994 and 1998[6, 7]. An additional 811 subjects were enrolled in 2000-2002 using the same methods except oversampling clinics with more minorities. More recently, a Continuous Enrollment strategy was initiated in which new subjects are contacted, screened and enrolled to keep 2000 active at-risk person-years accruing in each calendar year. This resulted in an enrollment of 4,146 participants as of May 2009. All clinical data are reviewed at a consensus conference. Dementia onset is assigned half way between the prior biennial and the exam that diagnosed dementia. Enrollment for the eMERGE Study began in 2007. A waiver of consent was obtained from the IRB to enroll deceased ACT participants. For this study we analyzed genome-wide genetic data from 1,407 cognitively normal elderly controls and 457 people with late-onset Alzheimer's disease.

The ADNI Study (ADNI 1/GO/2) ADNI is a longitudinal, multi-site observational study including people with Alzheimer's disease, people with mild cognitive impairment (MCI), and elderly individuals with normal cognition assessing clinical and cognitive measures, MRI and PET scans (FDG and 11C PIB) and blood and CNS biomarkers. For this study, ADNI contributed data on 607 Alzheimer's disease cases and 325 healthy controls with Alzheimer's disease -free status confirmed as of most recent follow-up. Alzheimer's disease subjects were between the ages of 65–90, had an MMSE score of 20–26 inclusive, met NINCDS/ADRDA criteria for probable Alzheimer's disease [8], and had an MRI consistent with the diagnosis of Alzheimer's disease. Control subjects had MMSE scores between 28 and 30 and a Clinical Dementia Rating of 0 without symptoms of depression, MCI or other dementia and no current use of psychoactive medications. According to the ADNI protocol, subjects were ascertained at regular intervals over 3 years, but for the purpose of our analysis we only used the final ascertainment status to classify case-control status. Additional details of the study design are available elsewhere[9-11].

Data used in the preparation of this article were obtained from ADNI database (http://adni.loni.ucla.edu). The ADNI 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 (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease Alzheimer's disease. Determination of sensitive and specific markers of very early Alzheimer's disease 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 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early Alzheimer's disease. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

For this study we analyzed genome-wide genetic data from 328 cognitively normal elderly controls and 589 people with late-onset Alzheimer's disease.

The ROS/MAP Studies ROS/MAP are two community-based cohort studies. The ROS has been on-going since 1993, with a rolling admission. Through July of 2010, 1,139 older nuns, priests, and brothers from across the United States initially free of dementia who agreed to annual clinical evaluation and brain donation at the time of death completed their baseline evaluation. The MAP has been on-going since 1997, also with a rolling admission. Through July of 2010, 1,356 older persons from across northeastern Illinois initially free of dementia who agreed to annual clinical evaluation and organ donation at the time of death completed their baseline evaluation. Details of the clinical and neuropathologic evaluations have been previously reported[12-15].

For this study we analyzed genome-wide genetic data from 825 cognitively normal elderly controls and 673 people with late-onset Alzheimer's disease.

University of Pittsburgh (PITT) The University of Pittsburgh data set contains 1,271 Caucasian Alzheimer's disease cases (of which 277 were autopsy-confirmed) recruited by the University of Pittsburgh Alzheimer's Disease Research Center, and 841 Caucasian, cognitively normal elderly controls ages 60 and older (2 were autopsy-confirmed). All Alzheimer's disease cases met NINCDS/ADRDA criteria for probable or definite Alzheimer's disease. Additional details of the cohort used for GWAS have been previously published[16]. We limited analyses from the Pittsburgh site to those with a Clinical Dementia Rating (CDR) of 0.5 or 1.0, since stability of cognitively-defined Alzheimer's disease subgroups in more advanced degrees of severity has not been established.

For this study we analyzed genome-wide genetic data from 825 cognitively normal elderly controls and 712 people with late-onset Alzheimer's disease.

Text 6B. Imputation and SNP selection for GWAS analyses.

Each of the raw (observed SNPs) genetic data sets from ACT/ADNI/ROS-MAP/UPITT were quality controlled and imputed using IMPUTE2 with haplotypes derived from samples of European ancestry in the 1000 Genome Project (2012 build) by the Alzheimer's Disease Genetics Consortium. Detailed quality control procedures can be obtained from Lambert *et al*[17]. In each imputed data set, SNPs with R^2 or info score quality estimates of less than 0.5 as indicated by IMPUTE2 were excluded from analyses. Similarly, SNPs with a MAF of <3% were also excluded. After these procedures, a maximum of 6,423,139 SNPs were retained in at least one data set across the different Alzheimer's disease subtype analyses.

Alzheimer's disease cases with Clinical Dementia Rating (CDR) of 0.5 or 1 were selected for each analyses. In each case-control data set for each subtype, the association of Alzheimer's disease subtype with SNPs was analyzed by a logistic regression model including covariates for age, sex and principal components to account for possible population stratification. Relatedness analyses and principal components were performed using observed genotype data KING-Robust[18] from the four studies. We used PLINK v1.9[19] for GWAS analyses.

After the exclusion of SNPs showing logistic regression coefficient $|\beta| > 5$ or p-value equal to 0 or 1, the maximum number of SNPs in any data set for any of the subtype analyses was 6,398,204.

These SNPs were included in the meta-analysis.

Text 6C. Meta-analysis.

We conducted a meta-analysis of genome-wide association studies (GWAS) in individuals of European ancestry for each Alzheimer's disease subtype except for the group with isolated substantial relative executive functioning impairment. That group was the smallest with cases ranging from 3 to 30 in each of the data sets. We used genotyped and imputed data (~6.4 million SNPs) to perform meta-analysis on four GWAS data sets (ACT/ADNI/ROS-MAP/PITT) with the exception of the group with multiple domains with substantial relative impairments. That group had only 12 individuals with genetic data from the ACT study so we excluded ACT from meta-analyses for that group. We undertook fixed-effects inverse variance-weighted meta-analysis using METAL[20]. SNPs that failed heterogeneity test (p-value ≤ 0.05) were excluded from the results.

The genomic control inflation factors (λ) for the meta-analysis of each Alzheimer's disease subtype were 1.01 for the group with no domain with a substantial relative impairment, 1.01 for those with isolated substantial relative

memory impairment, 1.0 for those with isolated substantial language impairment, 0.97 for those with isolated substantial visuospatial impairment, and 0.99 for those with multiple domains with substantial relative impairments. **λ** for All Alzheimer's disease vs. controls analysis across the four studies was 1.01. Quantile-quantile plots for each analysis are shown in Supplemental Figure 3 (section 6D).

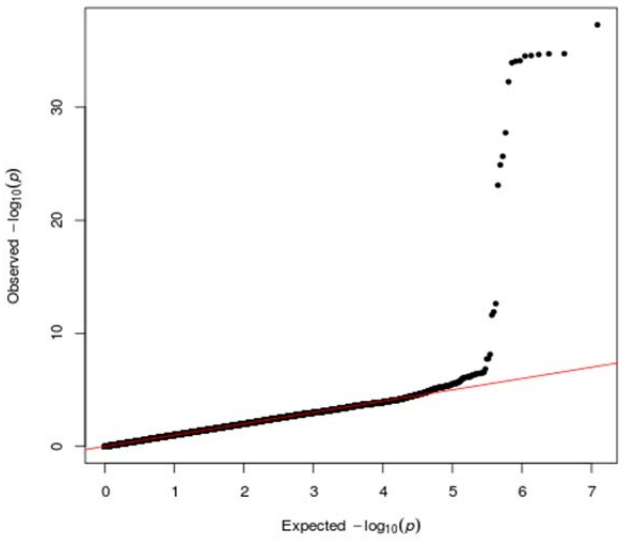
Manhattan plots for each meta-analysis of Alzheimer's disease subtypes are shown in Supplemental Figure 4 (section 6E). Plots for each Alzheimer's disease subtype are broken down into two plots; a) a full Manhattan plot and b) a truncated Manhattan plot with SNPs with p-value > 1×10^{-10}. GWAS summary statistics of top hits for each Alzheimer's disease subtype by study and overall meta-analysis are shown in Supplemental Text 7-11. Top hits for each Alzheimer's disease subtypes with corresponding results for those in other Alzheimer's disease subtypes are listed in tables in Supplemental Text 7-11.

Regional association plots[21] for top SNP hits for each Alzheimer's disease subtype are shown in Supplemental Figure 5 (Section 6F).

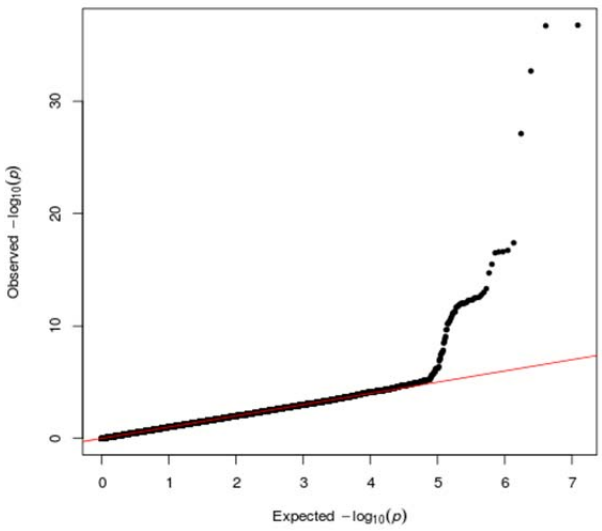
6D. Q-Q plots from meta-analysis of GWAS results.

Supplemental Figure 3. Quantile-Quantile plots

a) Controls vs. no substantial relative impairment

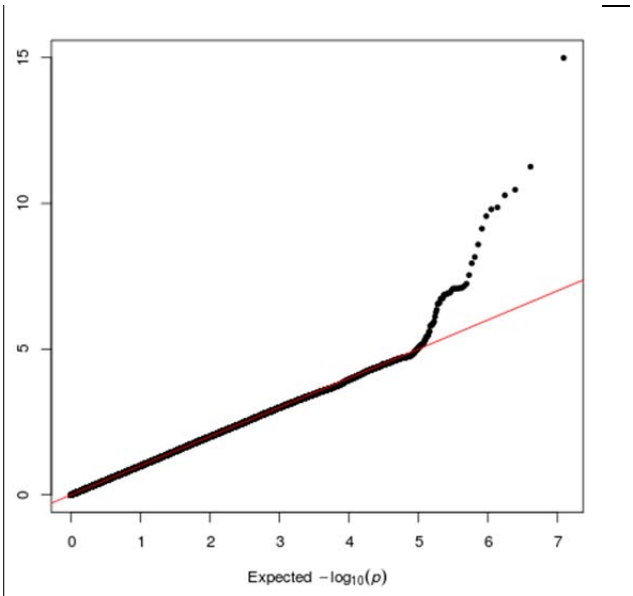


b) Controls vs. substantial relative memory impairment

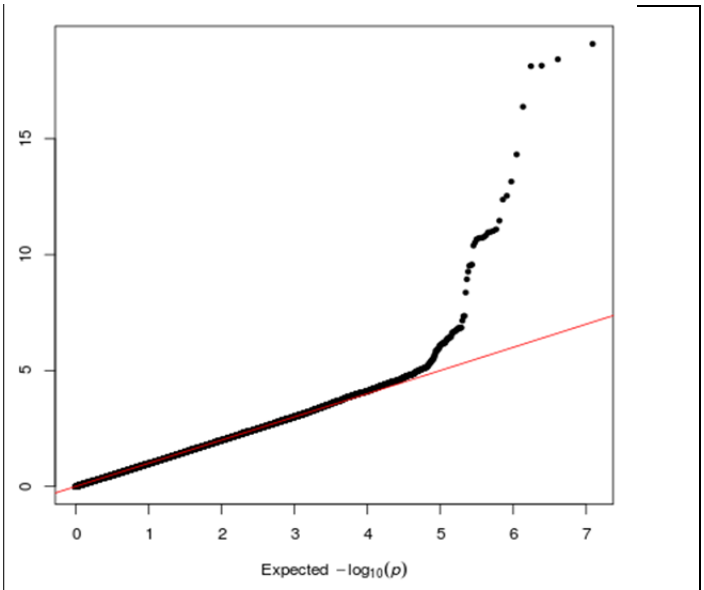


c) Controls vs. substantial relative language impairment

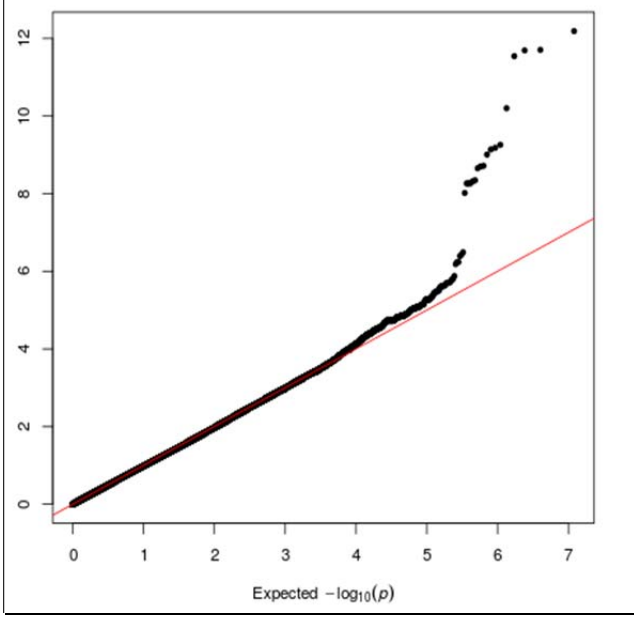
d) Controls vs. substantial relative visuospatial impairment

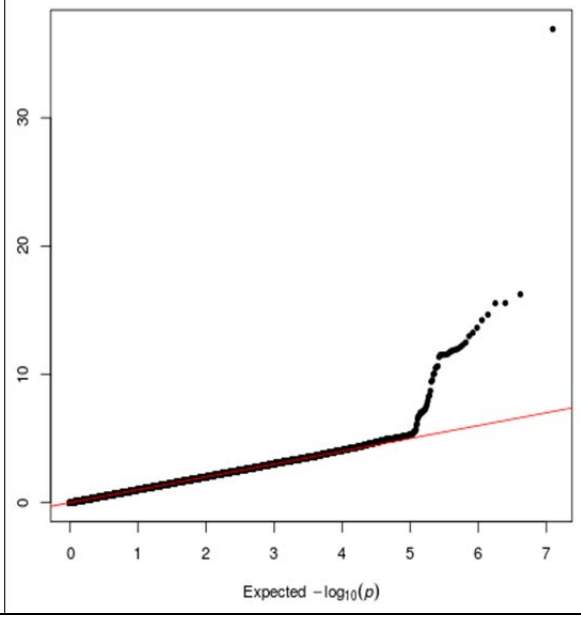


e) Controls vs. multiple domains with substantial relative impairment



f) Controls vs. All Alzheimer's disease across four studies



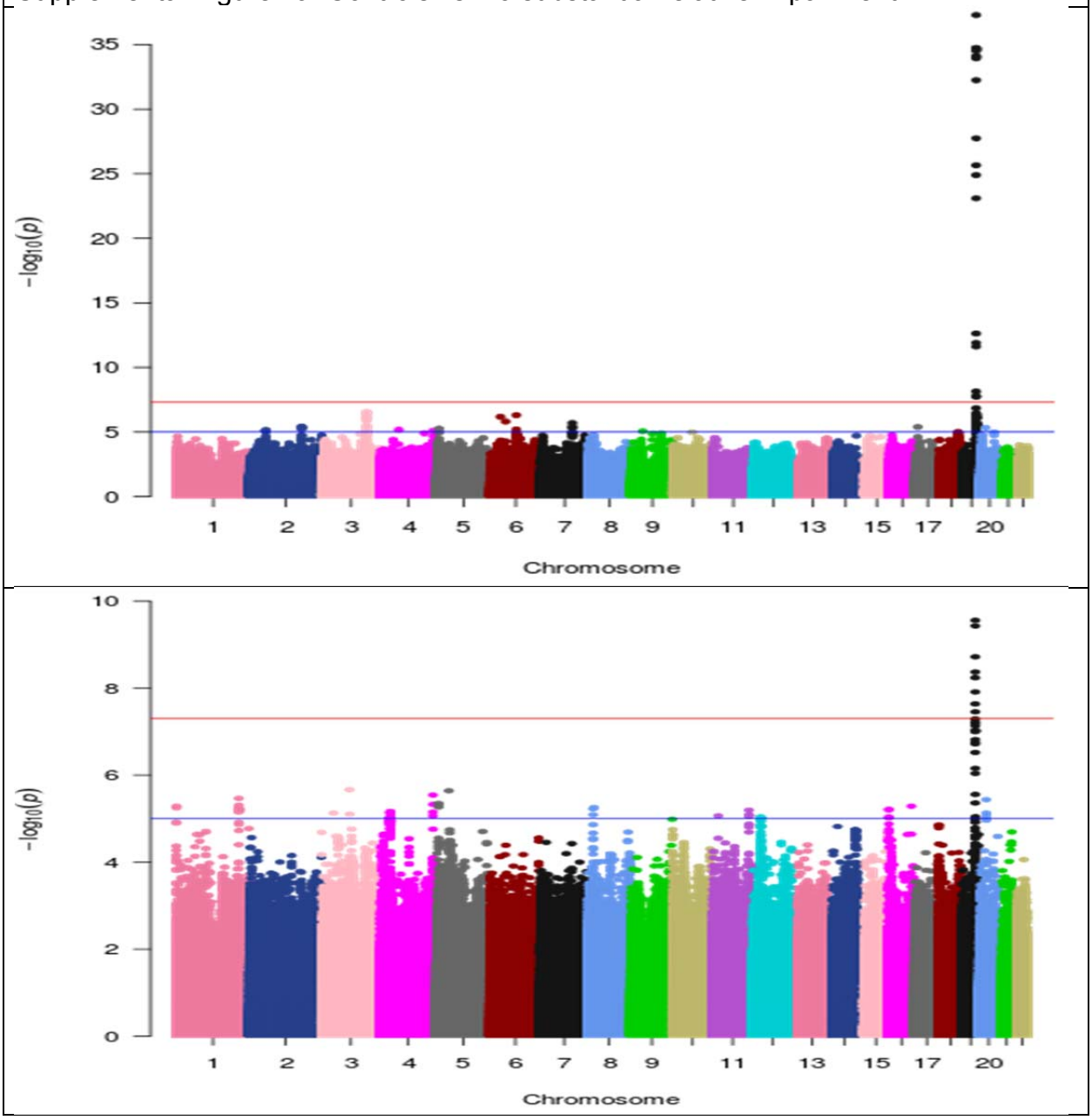


6E. Manhattan plots from meta-analyses of GWAS results

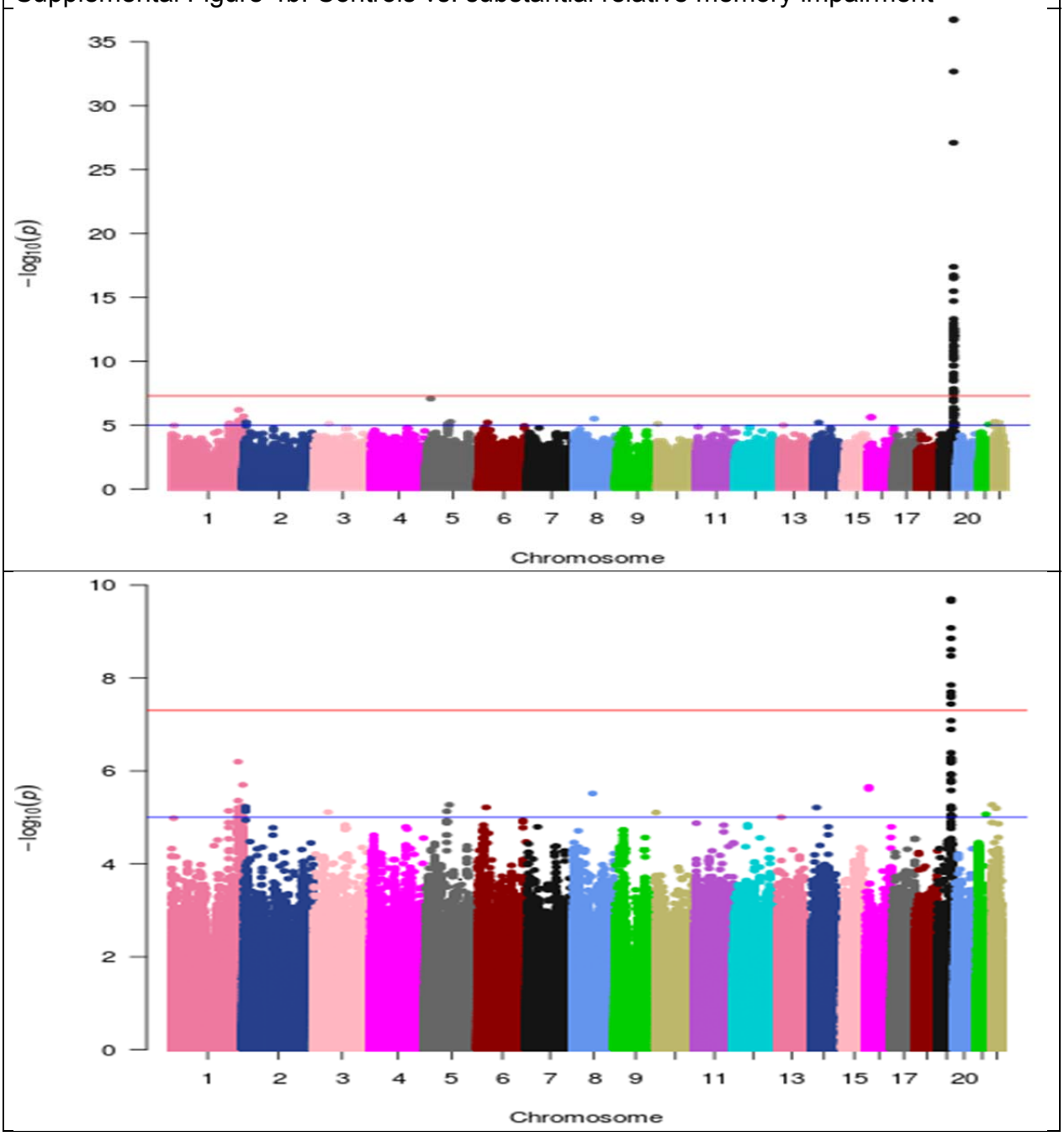
For each analysis, there are two plots: i) Full Manhattan plot; ii) Manhattan plot with *p*-values truncated to > 1×10^{-10}.

Supplemental Figure 4. Manhattan plots from meta-analysis of GWAS results

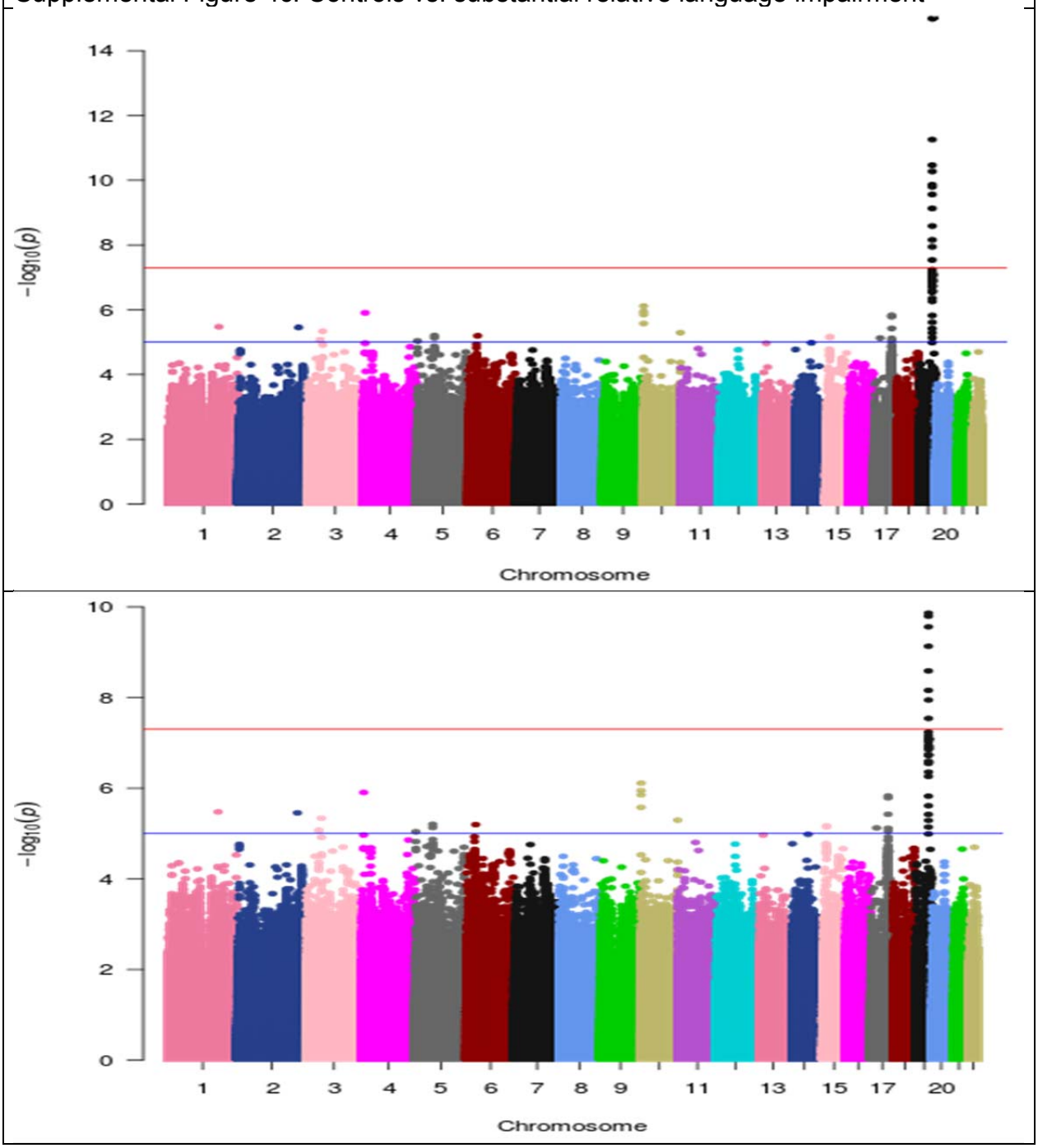
Supplemental Figure 4a. Controls vs. no substantial relative impairment



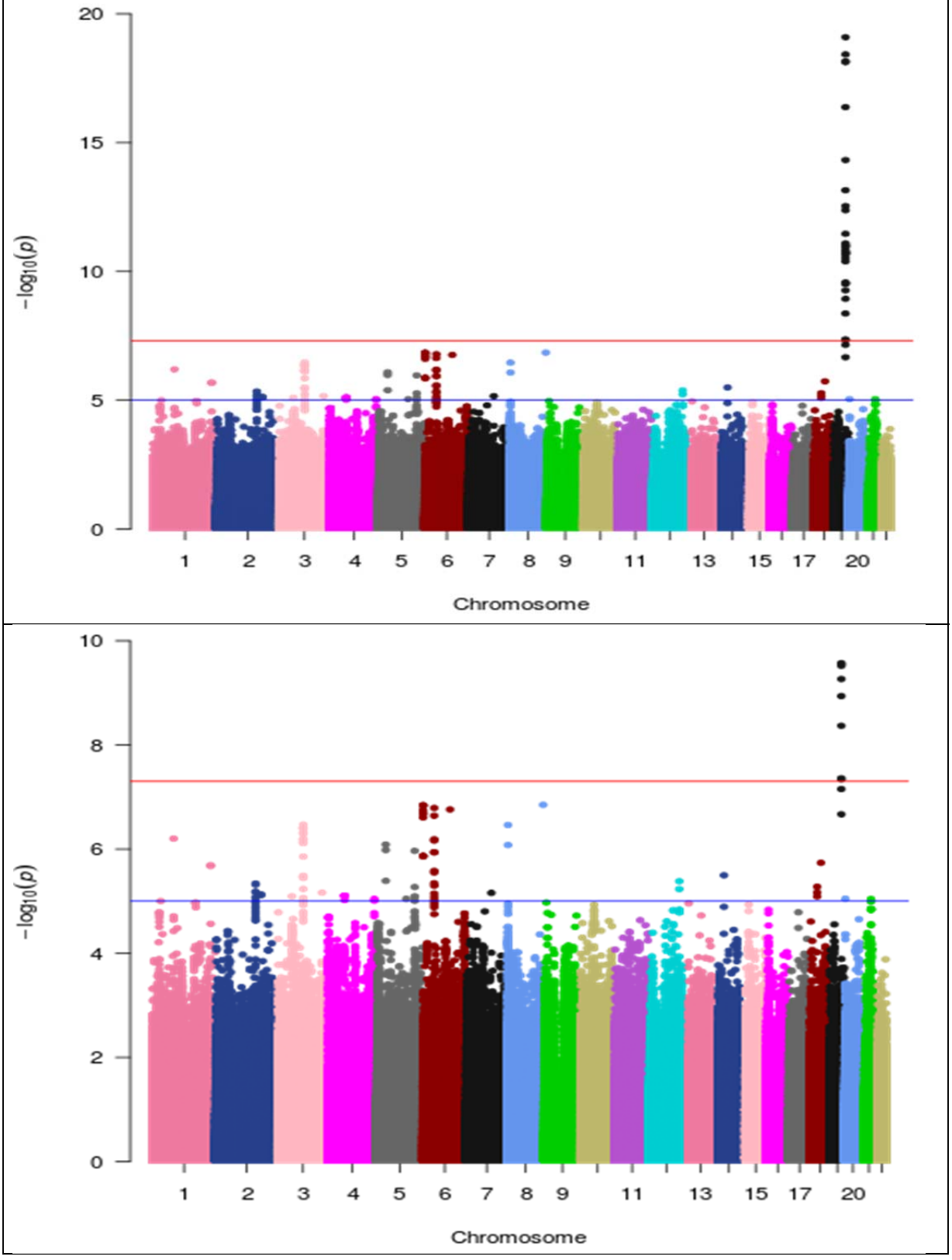
Supplemental Figure 4b. Controls vs. substantial relative memory impairment



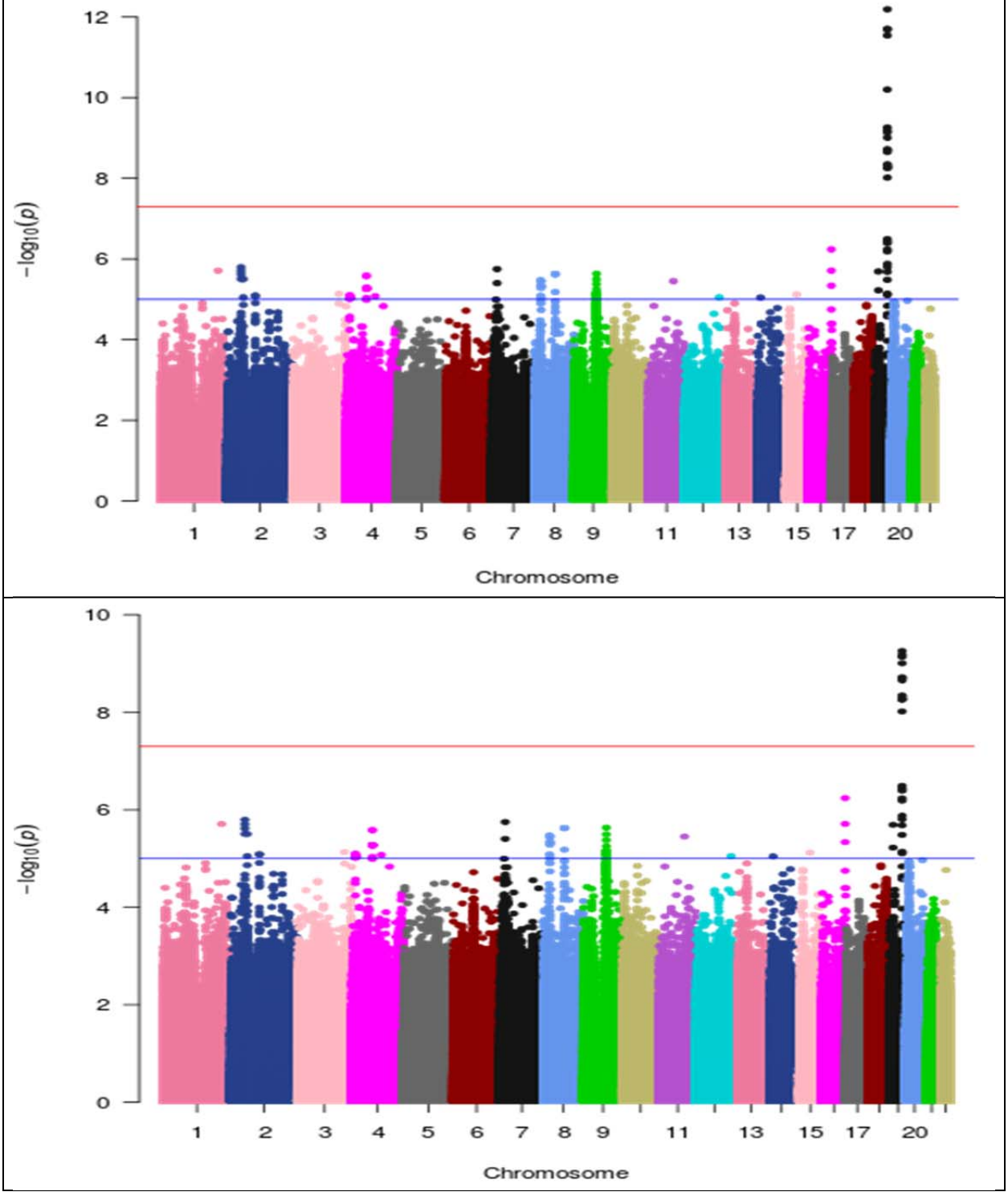
Supplemental Figure 4c. Controls vs. substantial relative language impairment



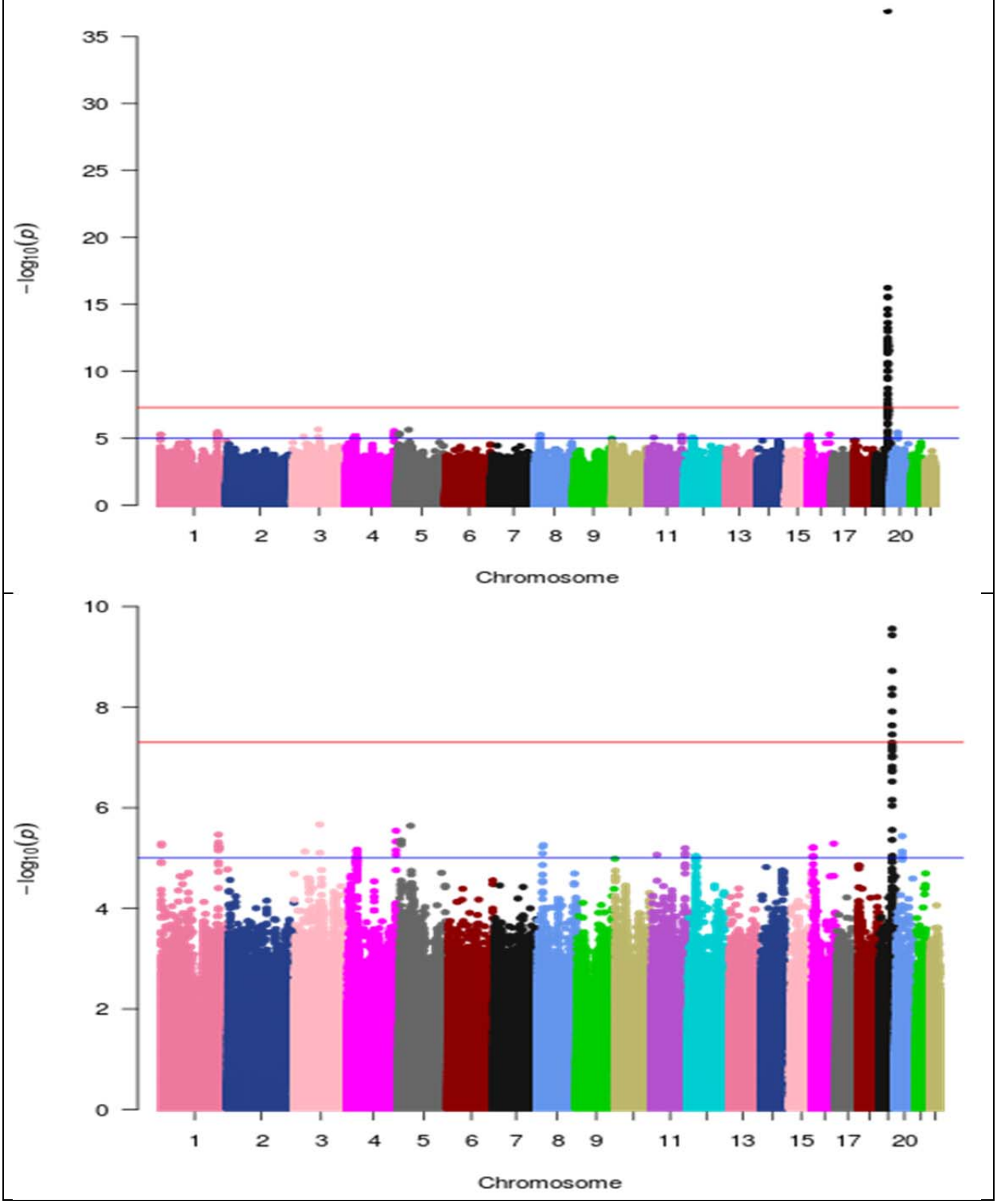
Supplemental Figure 4d. Controls vs. substantial relative visuospatial impairment



eFogure 4e. Controls vs. multiple domains with substantial relative impairment



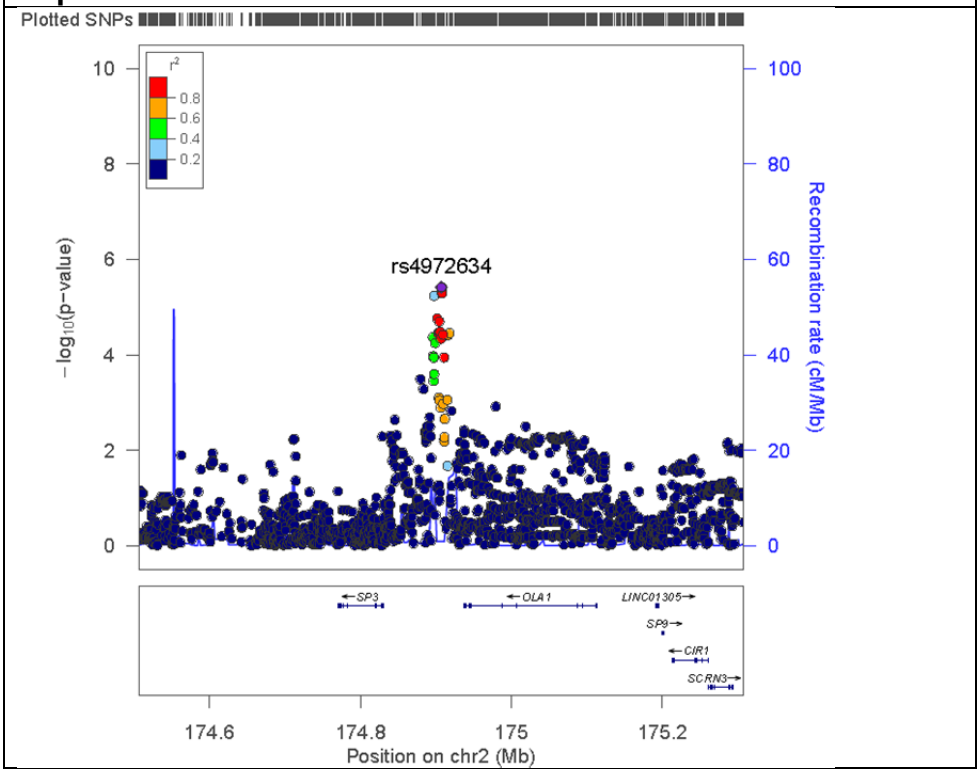
Supplemental Figure 4f. Controls vs. All Alzheimer's disease across four studies

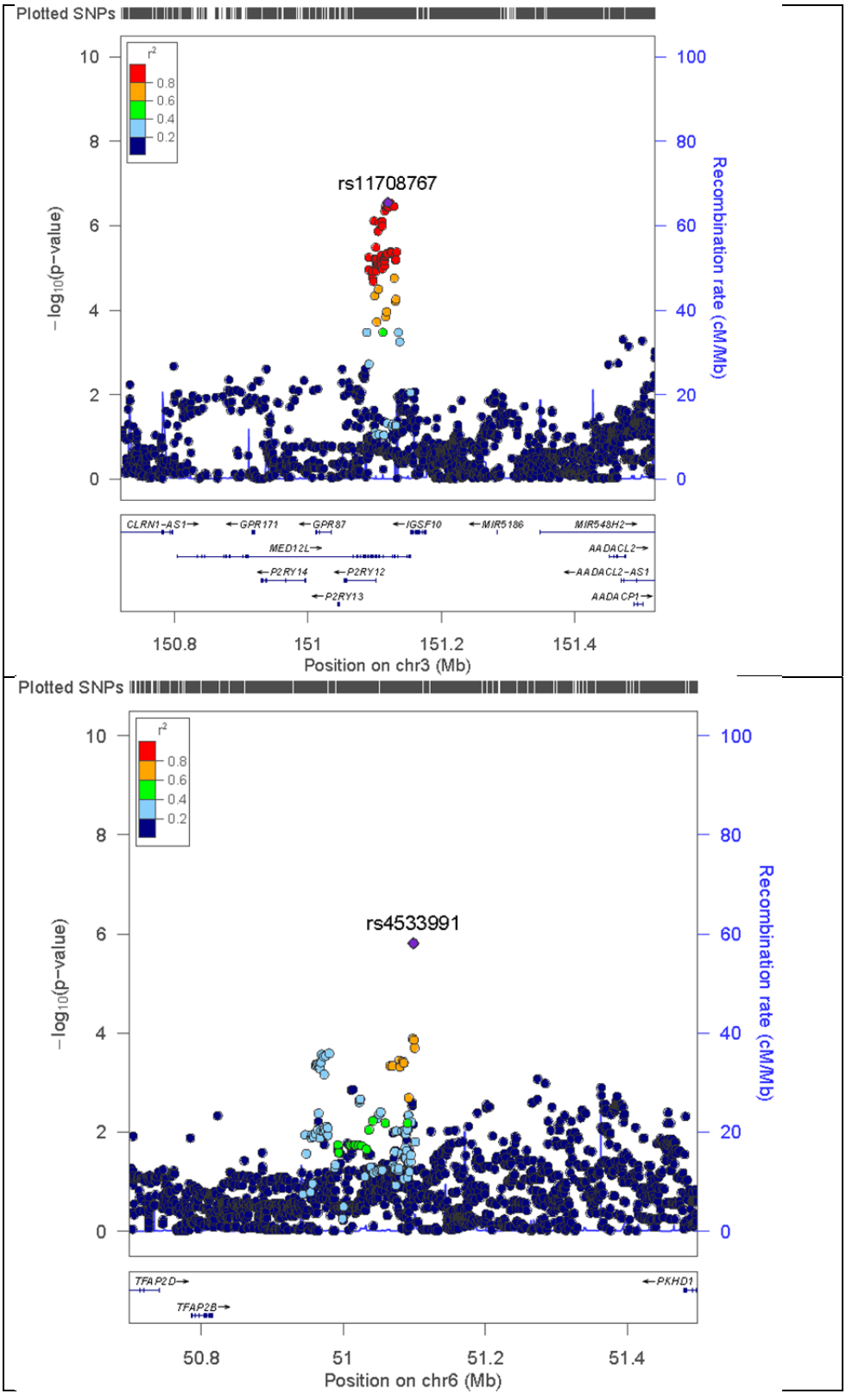


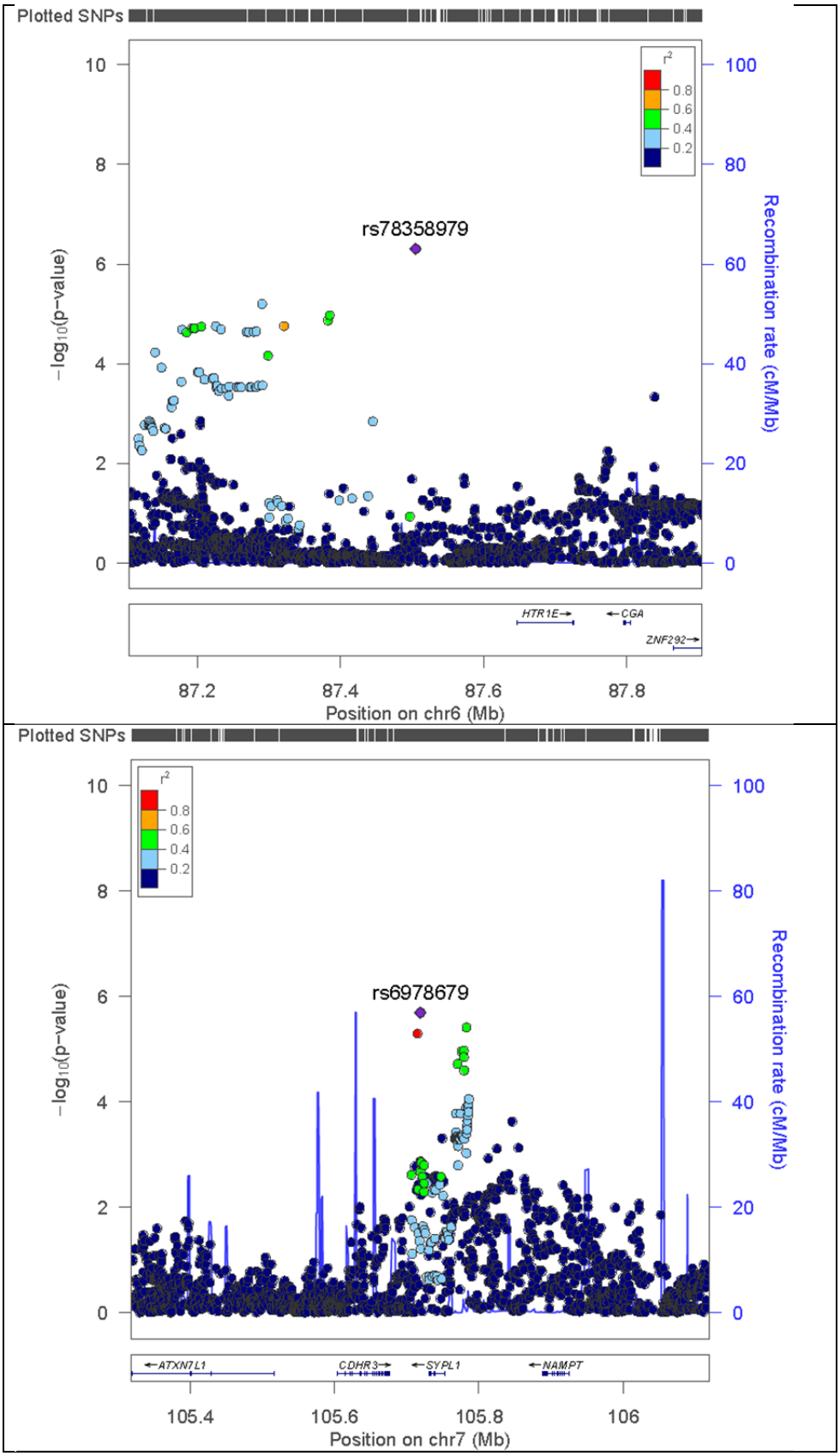
6F. Regional association plots of top hits from meta-analyses for each Alzheimer's disease subtype

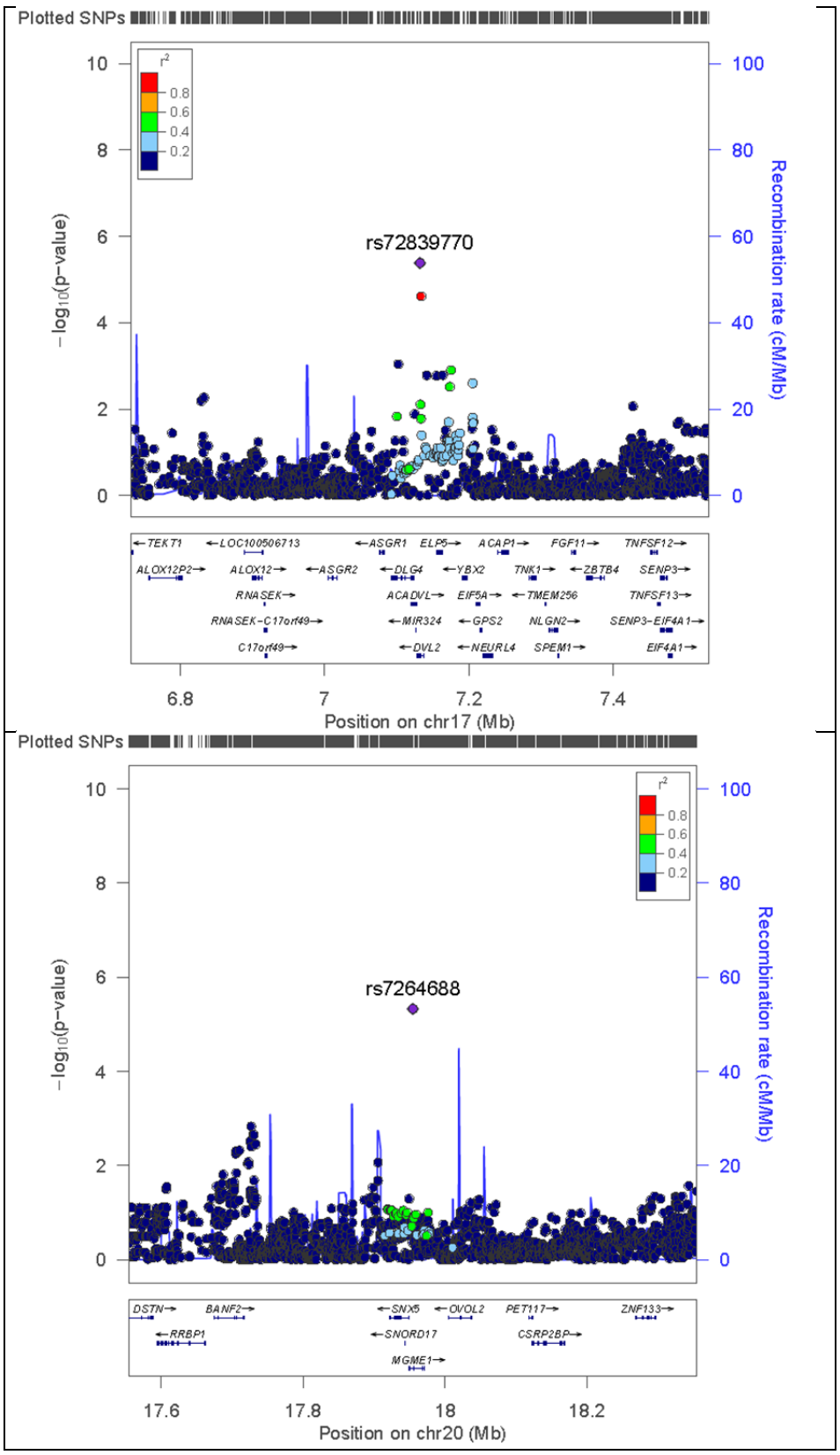
Supplemental Figure 5. Regional association plots from meta-analysis for each Alzheimer's disease subtype

Supplemental Figure 5a. Controls vs. no substantial relative impairment

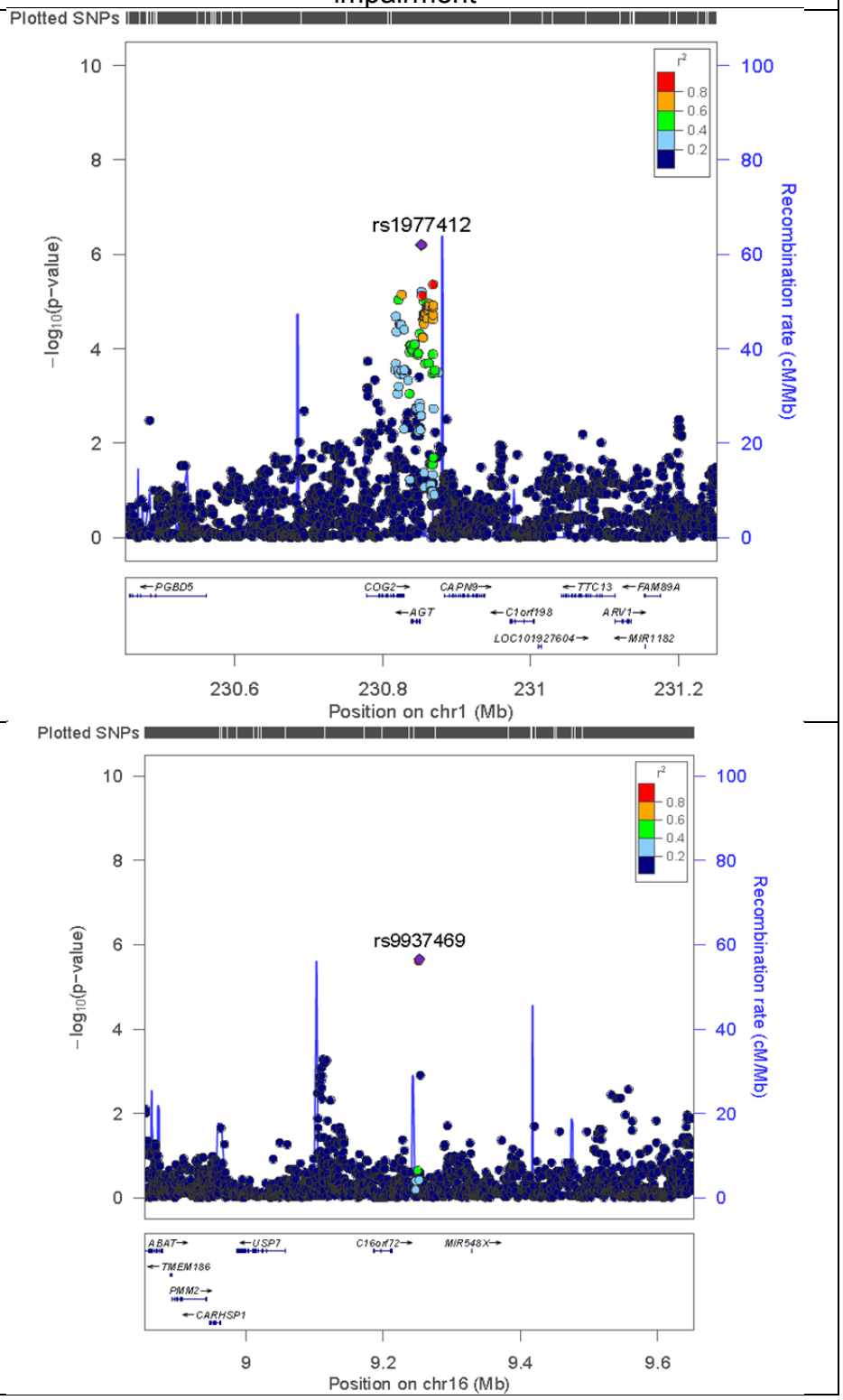



Plotted SNPs
rs11708767
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
CLRN1−AS1
GPR171
GPR87
IGSF10
MIR5186
MIR548H2
MED12L
AADACL2
P2RY14
P2RY12
AADACL2−AS1
P2RY13
AADACP1
Position on chr3 (Mb)
Plotted SNPs
rs4533991
−log10(p−value)
Recombination rate (cM/Mb)
TFAP2D
PKHD1
TFAP2B
Position on chr6 (Mb)

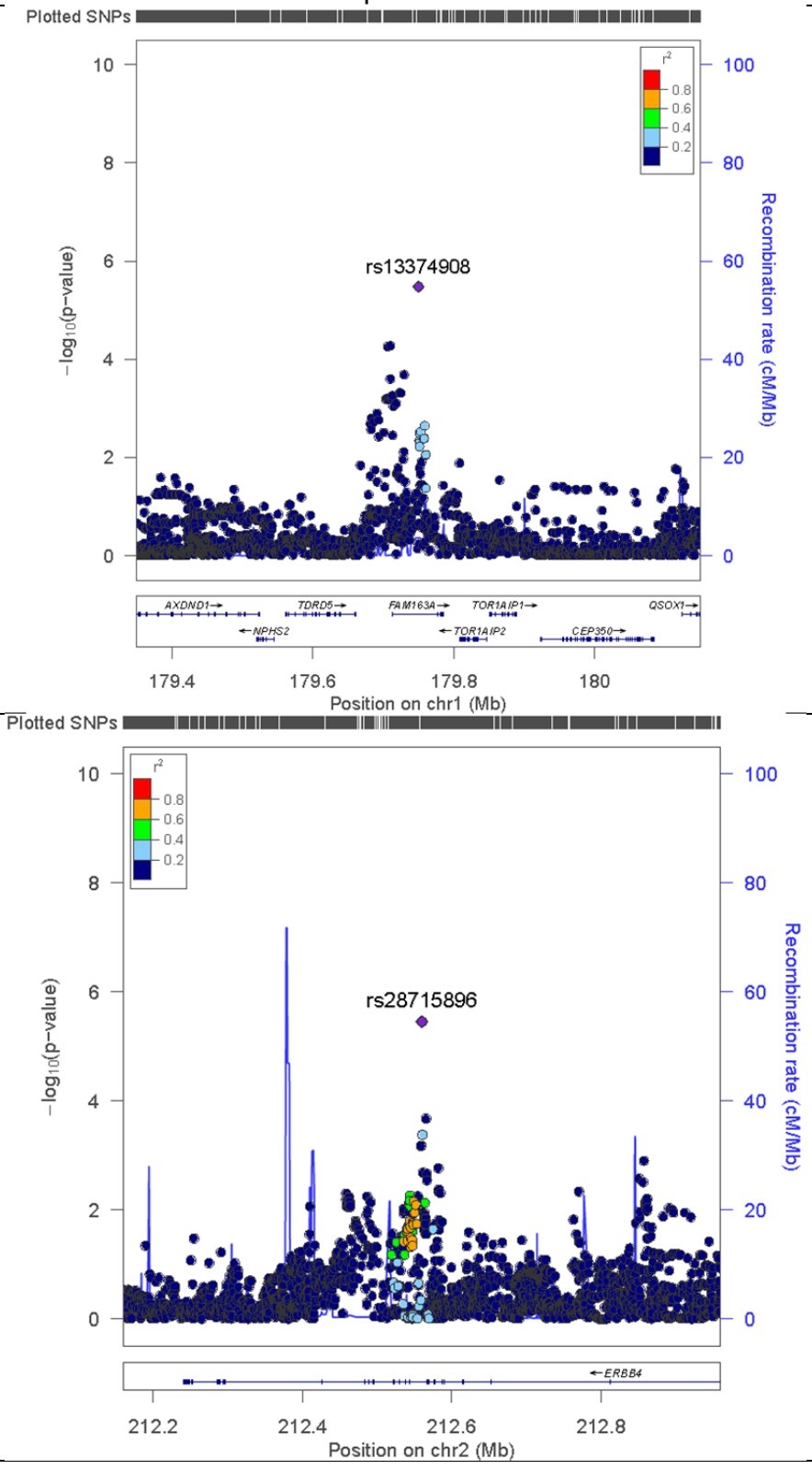

Plotted SNPs
rs78358979
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
HTR1E
CGA
ZNF292
Position on chr6 (Mb)
Plotted SNPs
rs6978679
ATXN7L1
CDHR3
SYPL1
NAMPT
Position on chr7 (Mb)

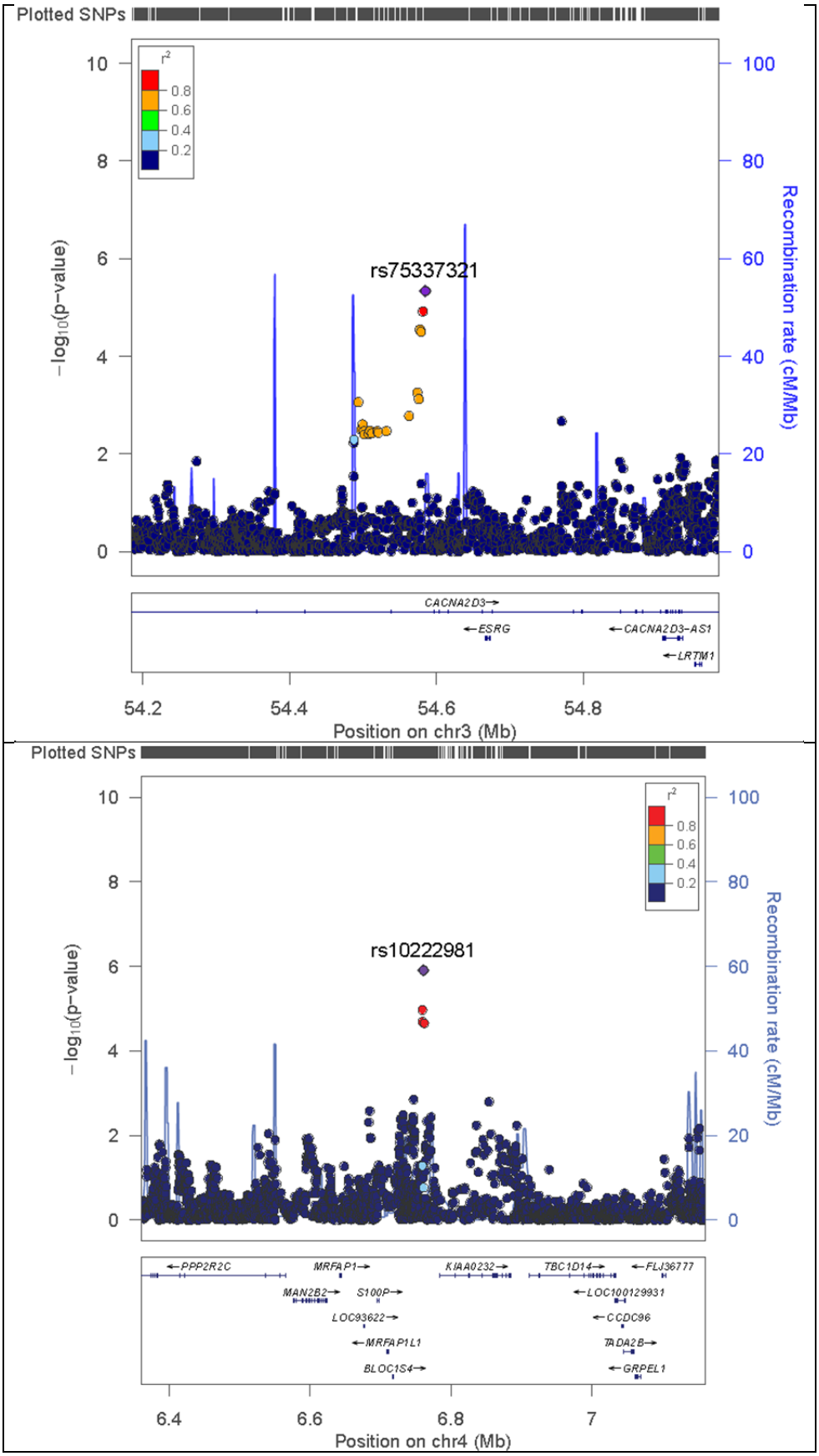

Plotted SNPs
rs72839770
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr17 (Mb)
Plotted SNPs
rs7264688
−log10(p−value)
Recombination rate (cM/Mb)
Position on chr20 (Mb)

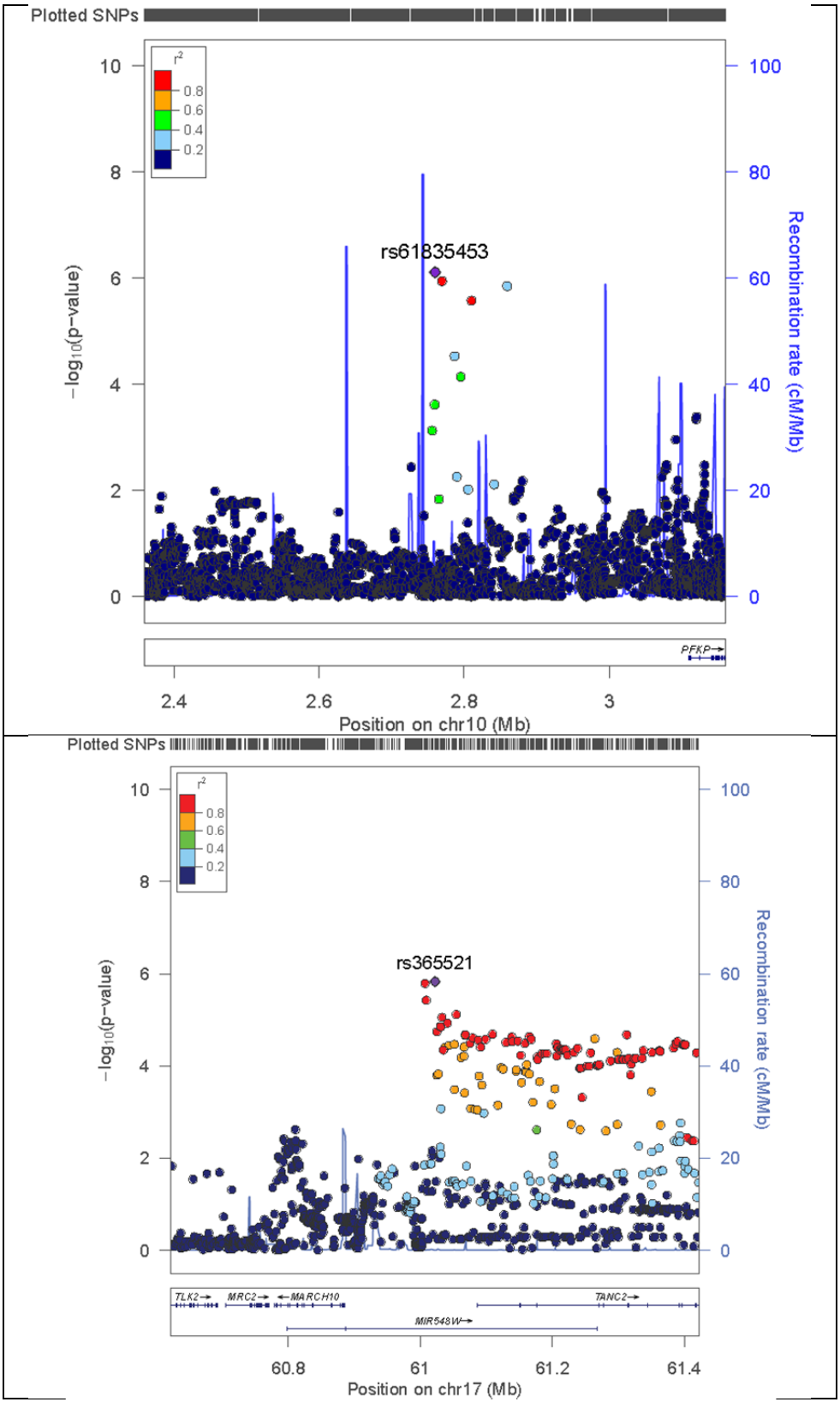
Supplemental Figure 5b. Controls vs. substantial relative memory impairment



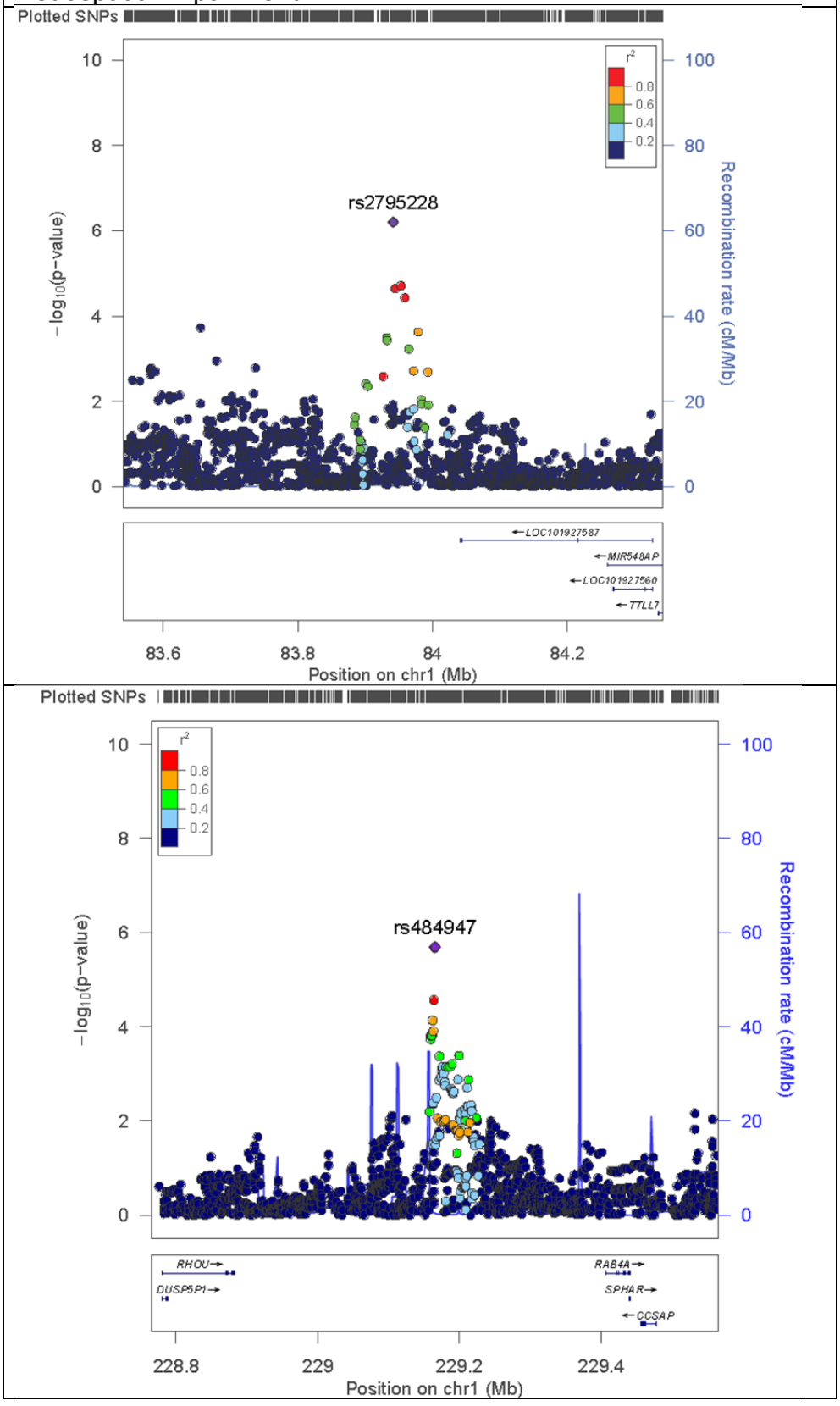
Supplemental Figure 5c. Controls vs. substantial relative language impairment

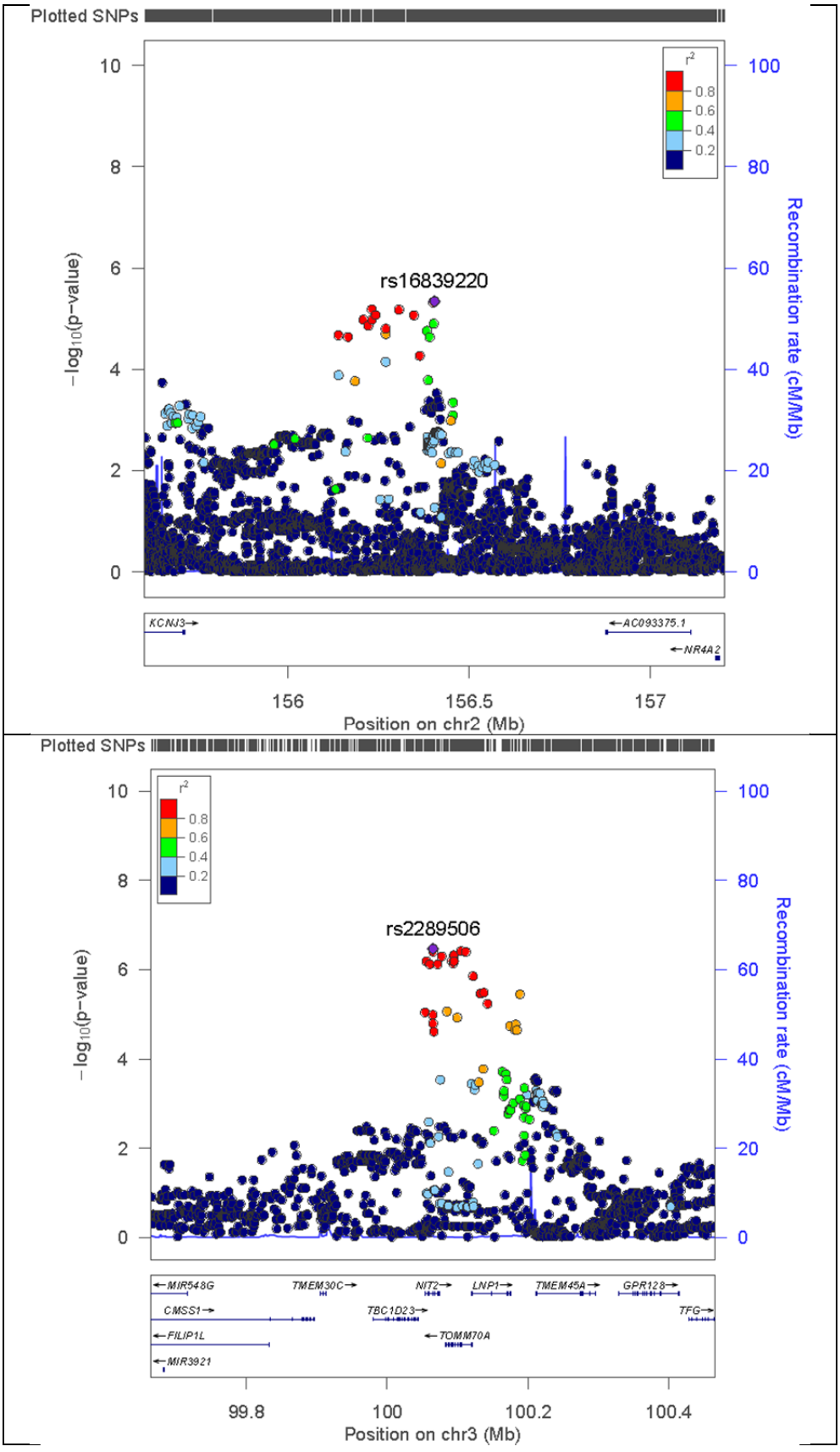


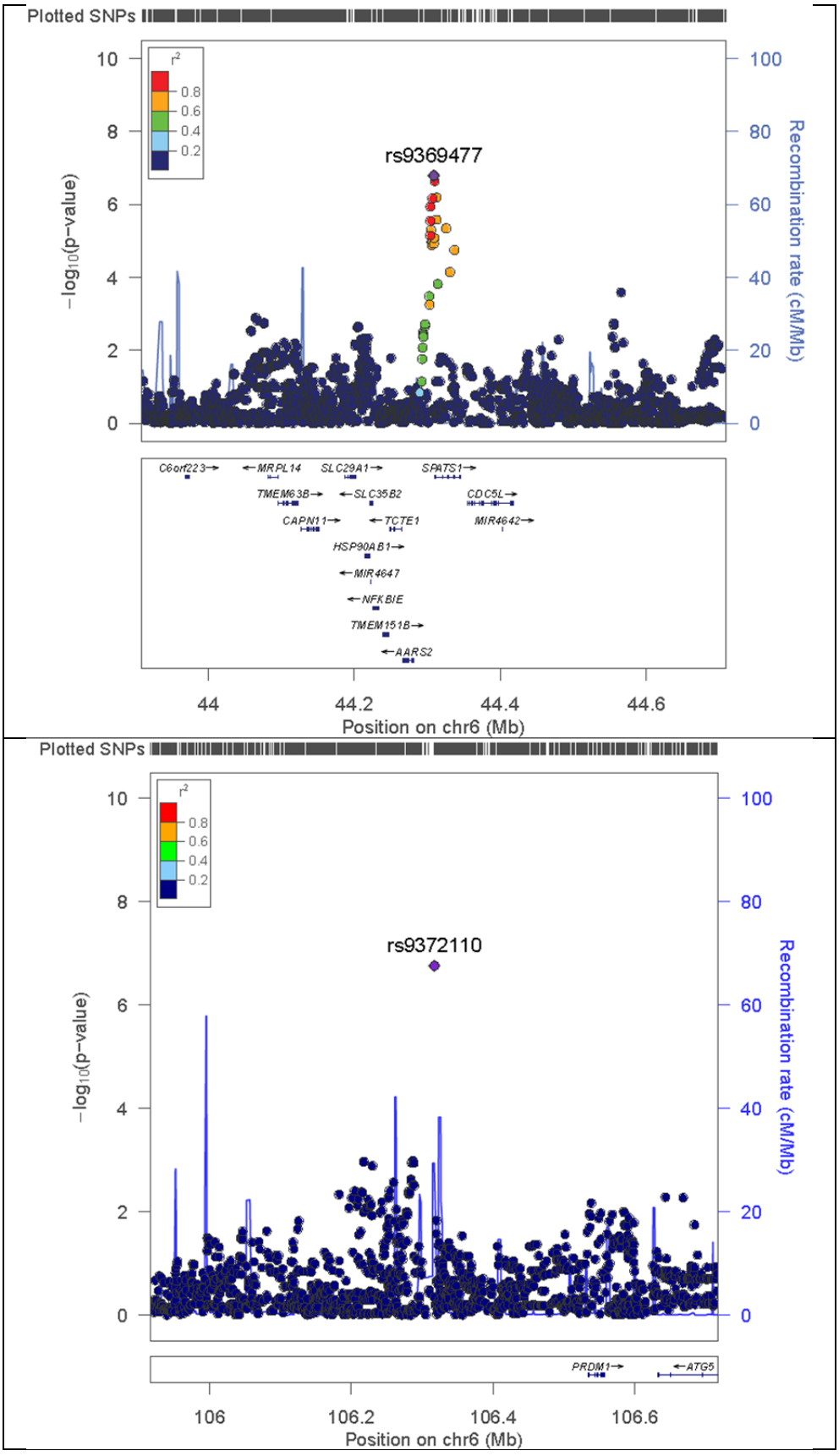

Plotted SNPs
r²
0.8
0.6
0.4
0.2
rs75337321
−log10(p−value)
Recombination rate (cM/Mb)
CACNA2D3
ESRG
CACNA2D3-AS1
LRTM1
Position on chr3 (Mb)
Plotted SNPs
rs10222981
PPP2R2C
MRFAP1
KIAA0232
TBC1D14
FLJ36777
MAN2B2
S100P
LOC100129931
LOC93622
CCDC96
MRFAP1L1
TADA2B
BLOC1S4
GRPEL1
Position on chr4 (Mb)

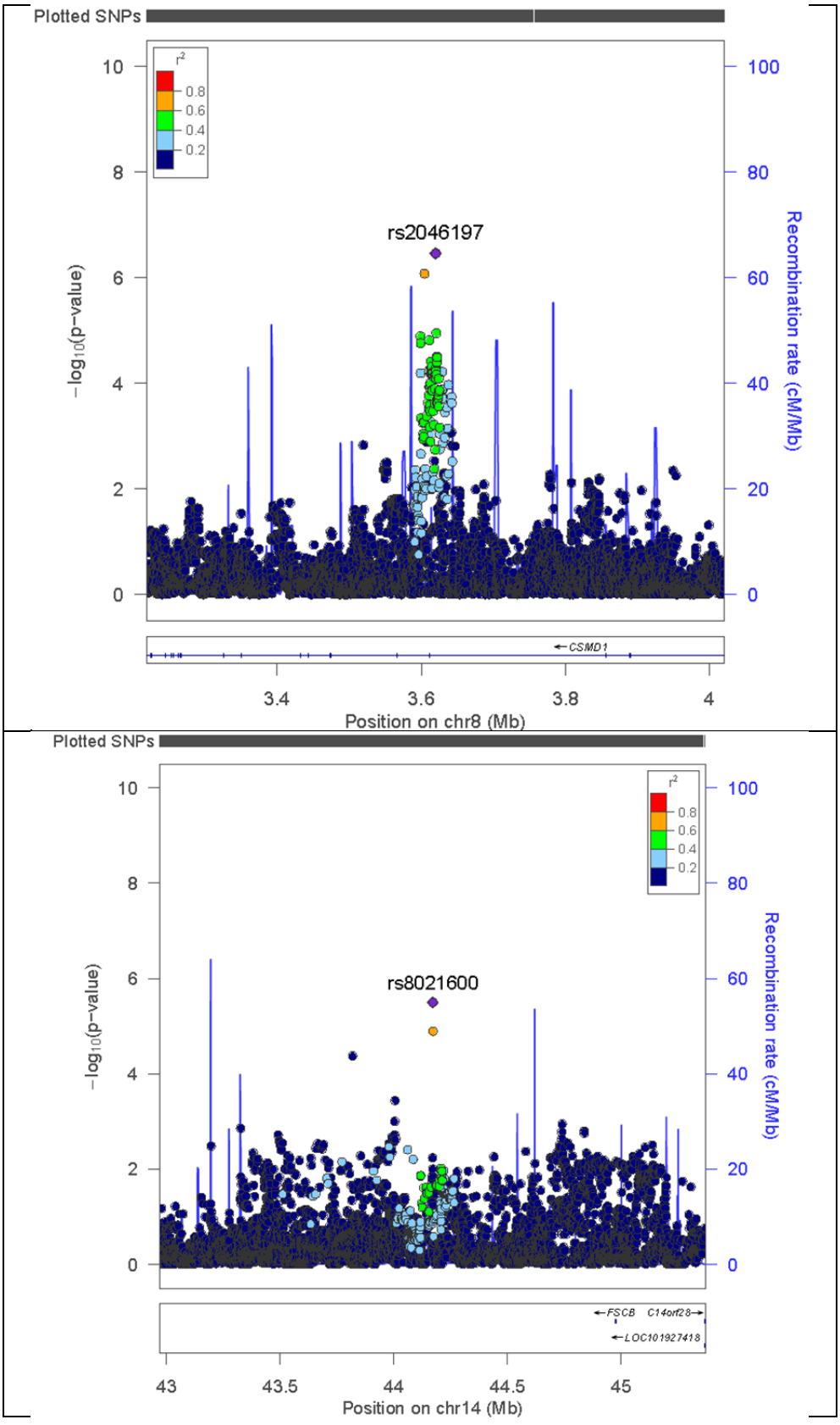

Plotted SNPs
r²
0.8
0.6
0.4
0.2
rs61835453
−log10(p−value)
Recombination rate (cM/Mb)
PFKP
Position on chr10 (Mb)
Plotted SNPs
rs365521
TLK2
MRC2
MARCH10
TANC2
MIR548W
Position on chr17 (Mb)

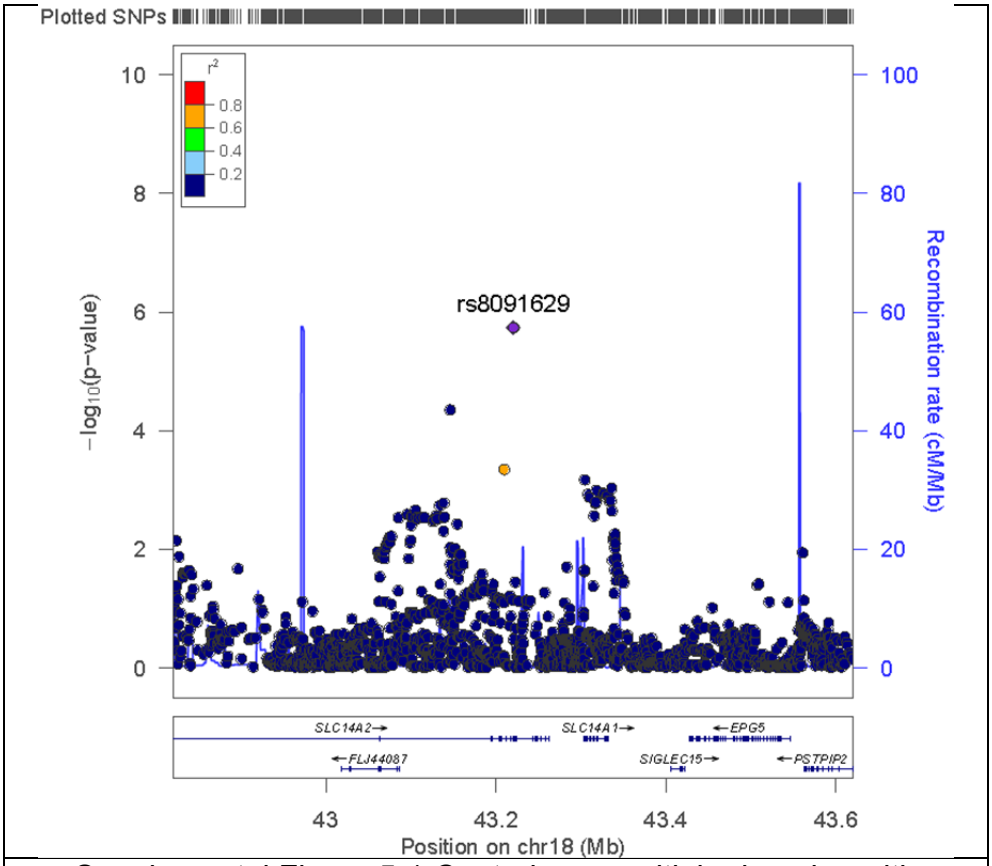
Supplemental Figure 5d. Controls vs. substantial relative visuospatial impairment



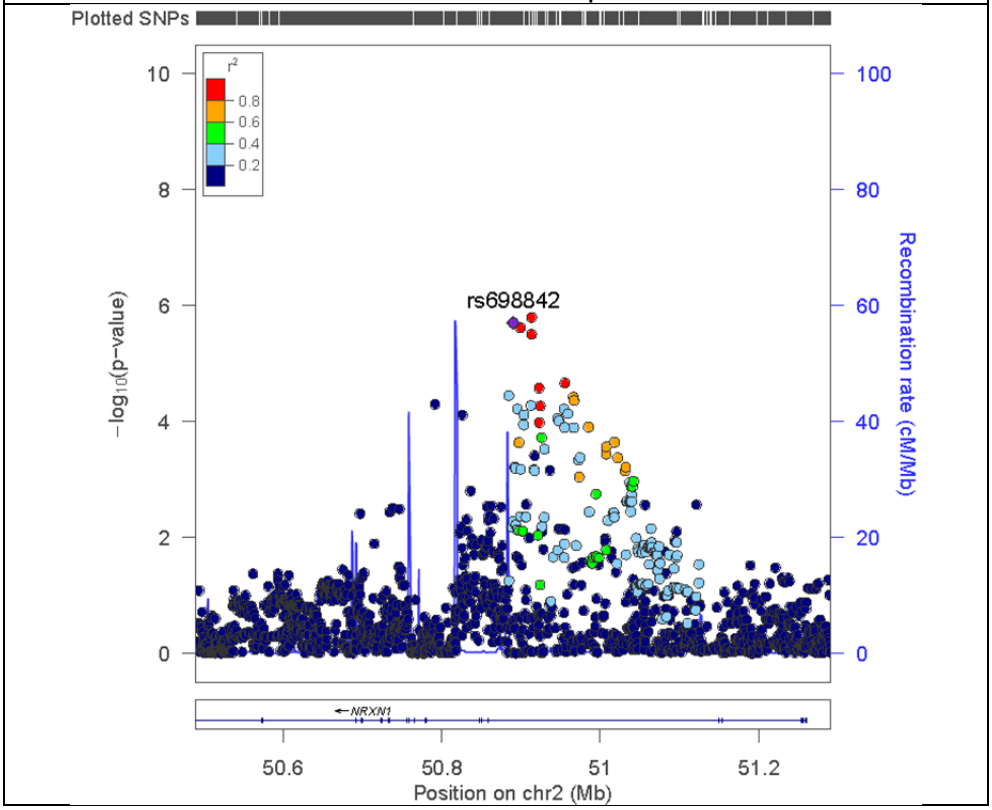

Plotted SNPs
rs16839220
KCNJ3
AC093375.1
NR4A2
Position on chr2 (Mb)
Plotted SNPs
rs2289506
MIR548G
TMEM30C
NIT2
LNP1
TMEM45A
GPR128
CMSS1
TBC1D23
TFG
FILIP1L
TOMM70A
MIR3921
Position on chr3 (Mb)
Recombination rate (cM/Mb)

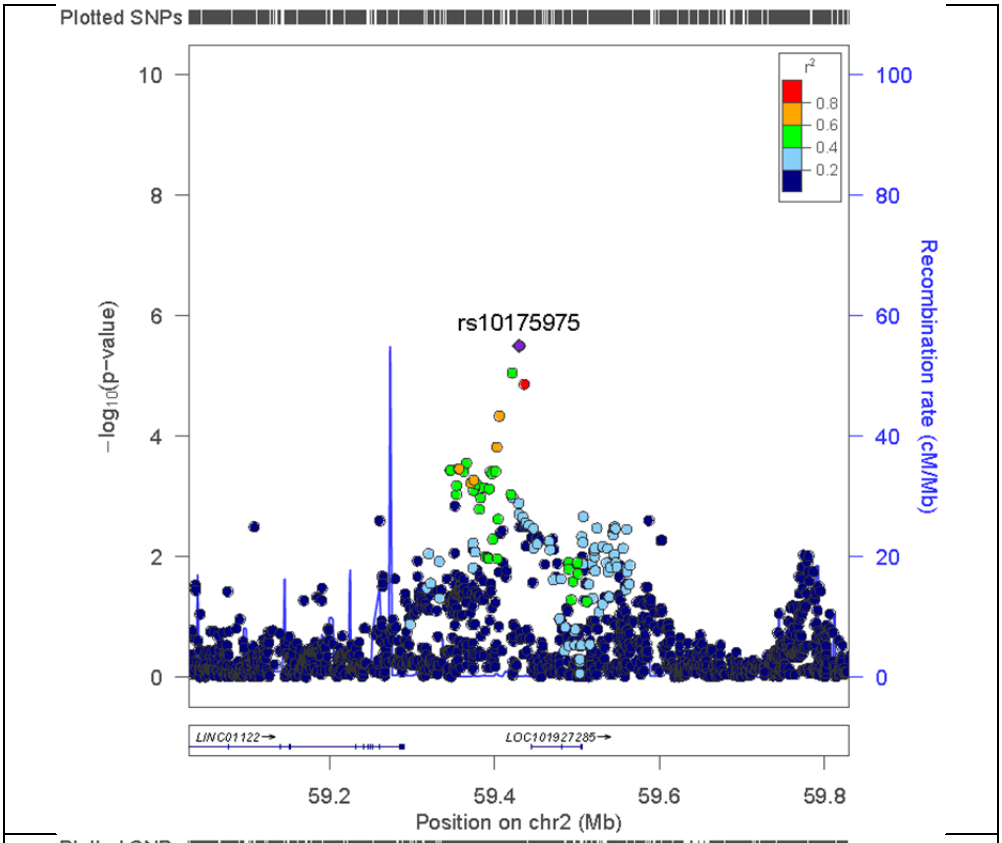

Plotted SNPs
rs9369477
−log10(p−value)
Recombination rate (cM/Mb)
r²
0.8
0.6
0.4
0.2
C6orf223
MRPL14
SLC29A1
SPATS1
TMEM63B
SLC35B2
CDC5L
CAPN11
TCTE1
MIR4642
HSP90AB1
MIR4647
NFKBIE
TMEM151B
AARS2
Position on chr6 (Mb)
Plotted SNPs
rs9372110
−log10(p−value)
Recombination rate (cM/Mb)
PRDM1
ATG5
Position on chr6 (Mb)

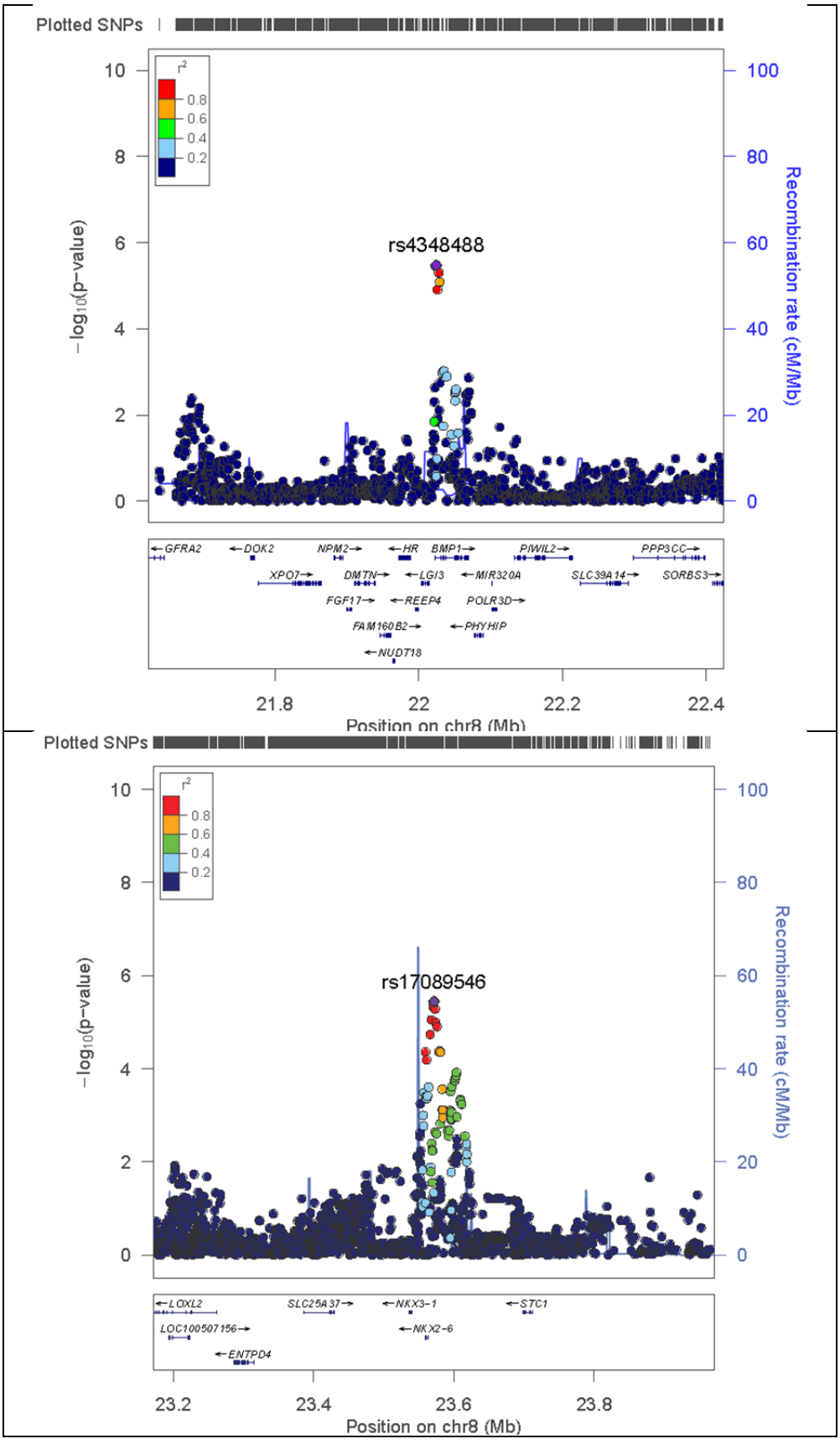

Plotted SNPs
r²
0.8
0.6
0.4
0.2
rs2046197
−log10(p−value)
Recombination rate (cM/Mb)
CSMD1
Position on chr8 (Mb)
Plotted SNPs
rs8021600
FSCB
C14orf28
LOC101927418
Position on chr14 (Mb)

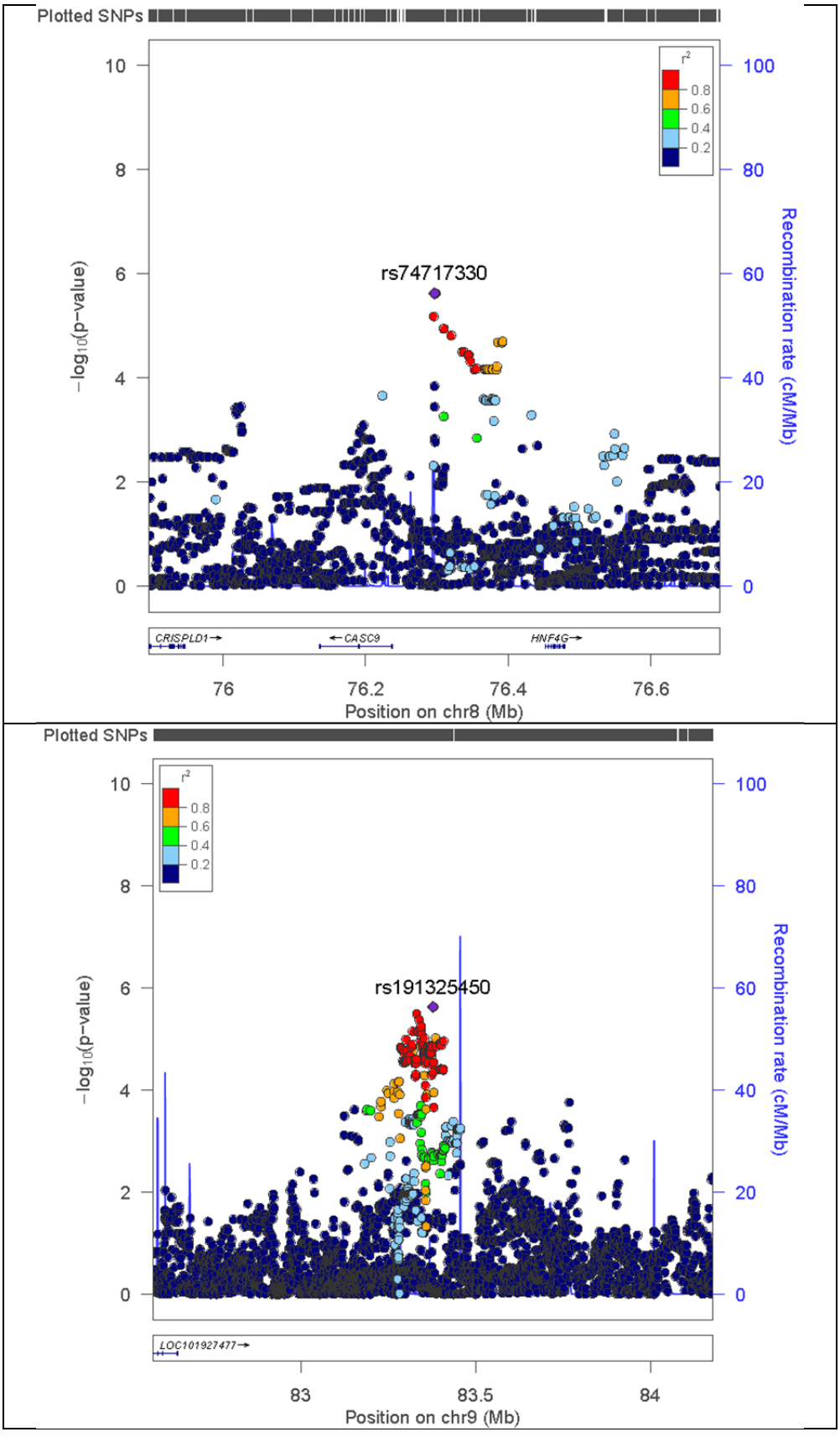


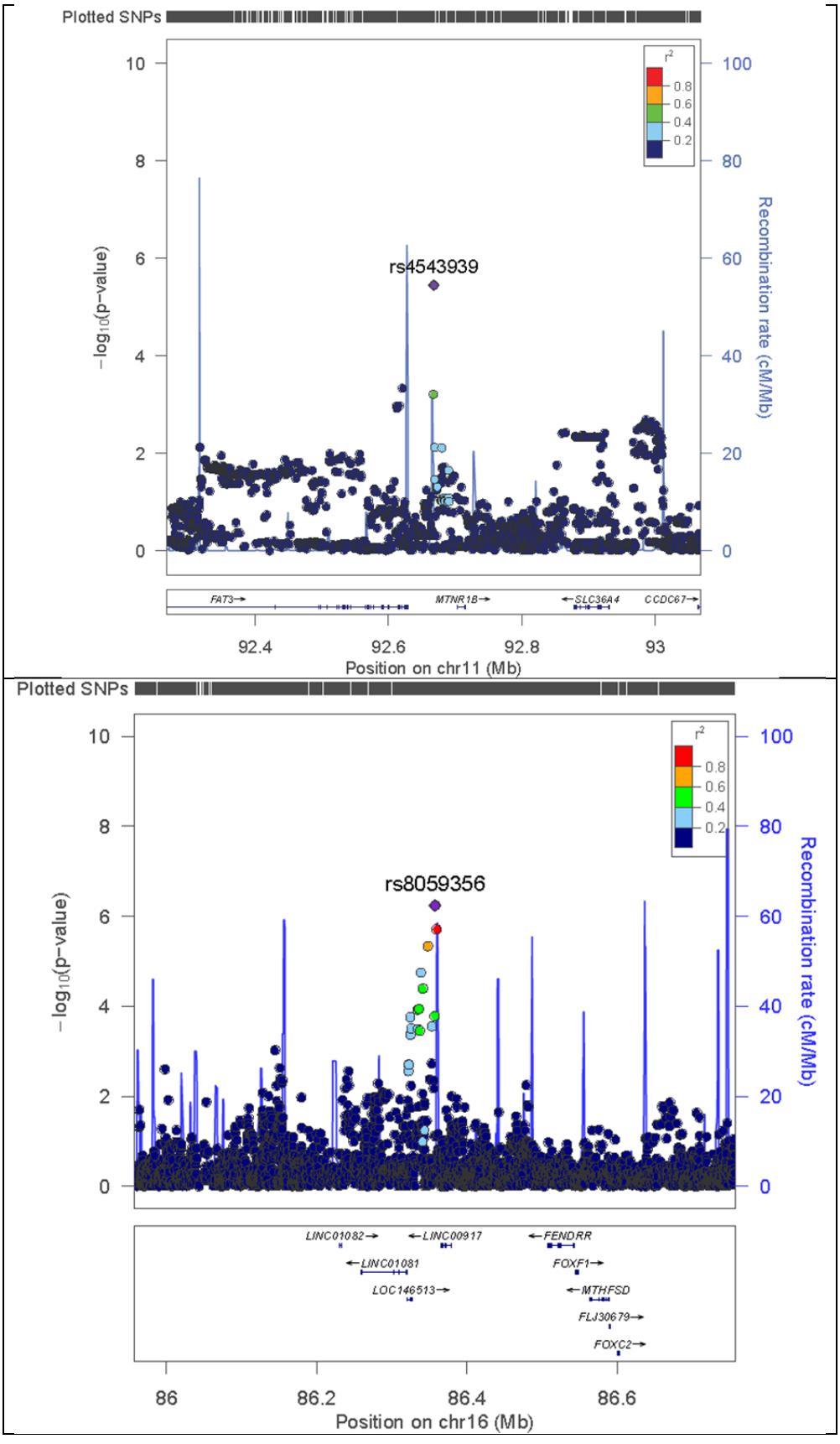
Supplemental Figure 5e) Controls vs. multiple domains with substantial relative impairment




Plotted SNPs
rs10175975
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
LINC01122
LOC101927285
Position on chr2 (Mb)
Plotted SNPs
rs78872508
HDAC9
TWIST1
FERD3L
Position on chr7 (Mb)


Plotted SNPs
rs4348488
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
GFRA2
DOK2
NPM2
HR
BMP1
PIWIL2
PPP3CC
XPO7
DMTN
LGI3
MIR320A
SLC39A14
SORBS3
FGF17
REEP4
POLR3D
FAM160B2
PHYHIP
NUDT18
21.8
22
22.2
22.4
Position on chr8 (Mb)
Plotted SNPs
rs17089546
−log10(p−value)
Recombination rate (cM/Mb)
LOXL2
SLC25A37
NKX3−1
STC1
LOC100507156
NKX2−6
ENTPD4
23.2
23.4
23.6
23.8
Position on chr8 (Mb)


Plotted SNPs
rs74717330
−log10(p−value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
CRISPLD1
CASC9
HNF4G
Position on chr8 (Mb)
Plotted SNPs
rs191325450
LOC101927477
Position on chr9 (Mb)


Plotted SNPs
rs4543939
−log10(p-value)
Recombination rate (cM/Mb)
r2
0.8
0.6
0.4
0.2
FAT3
MTNR1B
SLC36A4
CCDC67
92.4
92.6
92.8
93
Position on chr11 (Mb)
Plotted SNPs
rs8059356
−log10(p-value)
Recombination rate (cM/Mb)
LINC01082
LINC00917
FENDRR
LINC01081
FOXF1
LOC146513
MTHFSD
FLJ30679
FOXC2
86
86.2
86.4
86.6
Position on chr16 (Mb)

Supplemental Text 7. Genetic results: Memory SNPs

Supplemental Table 21a: Meta-analysis results for memory for memory SNPs

SNP Characteristics					Meta analysis results				
Chromosome	SNP	Base pair	Allele 1	Allele 2	Called allele frequency	OR	SE	P value	Heterogeneity p value
1	rs1977412	230852269	T	C	0.86	0.64	0.09	6.32E-07	0.29
16	rs9937469	9252656	T	C	0.06	2.14	0.16	2.20E-06	0.10

Supplemental Table 21b: Study-specific results for memory SNPs

	ACT			ADNI			ROS-MAP			PITT		
SNP	OR	SE	P value	OR	SE	P value	OR	SE	P value	OR	SE	P value
rs1977412	0.48	0.22	7.40E-04	0.73	0.19	0.08	0.81	0.21	0.31	0.61	0.14	3.00E-04
rs9937469	3.74	0.32	4.00E-04	*	*	*	2.16	0.33	0.02	1.62	0.22	0.03

* Indicates the analysis was missing for that study (ADNI did not have data for rs9937469).

Supplemental Table 21c: Meta-analysis for other subgroups for memory SNPs

	Isolated relative visuospatial impairment		Isolated relative language impairment		Multiple domains with relative impairments		No domain with relative impairment	
SNP	OR	P value	OR	P value	OR	P value	OR	P value
rs1977412	0.88	0.34	0.92	0.49	1.05	0.81*	0.85	0.04
rs9937469	1.62	0.05	1.45	0.12	1.23	0.56	1.02	0.91

* Indicates that the heterogeneity p value was <0.05 for that analysis

Supplemental Text 8. Genetic results: visuospatial SNPs

Supplemental Table 22a: Meta-analysis results for visuospatial for visuospatial SNPs

SNP Characteristics					Meta analysis results				
Chromosome	SNP	Base pair	Allele 1	Allele 2	Called allele frequency	OR	SE	P value	Heterogeneity p value
1	rs2795228	83941294	A	T	0.82	0.59	0.11	6.28E-07	0.17
1	rs484947	229165488	A	C	0.62	0.64	0.10	2.03E-06	0.85
2	rs16839220	156403868	C	G	0.20	0.53	0.14	4.57E-06	0.85
3	rs2289506	100064902	T	C	0.34	1.61	0.09	3.39E-07	0.62
6	rs9369477	44308629	T	C	0.92	0.49	0.14	1.62E-07	0.22
6	rs9372110	106317196	A	G	0.06	2.16	0.15	1.73E-07	0.16
8	rs2046197	3619752	C	G	0.59	1.66	0.10	3.44E-07	0.37
14	rs8021600	44170626	C	G	0.92	0.51	0.14	3.18E-06	0.23
18	rs8091629	43220331	A	G	0.90	0.54	0.13	1.83E-06	0.24

Supplemental Table 22b: Study-specific results for visuospatial SNPs

	ACT			ADNI			ROS-MAP			PITT		
SNP	OR	SE	P value	OR	SE	P value	OR	SE	P value	OR	SE	P value
rs2795228	0.50	0.22	0.001	0.90	0.24	0.69	0.60	0.21	0.02	0.48	0.20	2.60E-04
rs484947	0.73	0.20	0.12	0.57	0.20	0.005	0.65	0.18	0.02	0.61	0.18	0.007
rs16839220	0.44	0.31	0.01	0.55	0.28	0.03	0.62	0.25	0.05	0.49	0.27	0.01
rs2289506	1.46	0.20	0.05	1.82	0.20	0.002	1.38	0.18	0.08	1.80	0.17	6.26E-04
rs9369477	0.64	0.30	0.14	0.67	0.28	0.15	0.46	0.26	0.002	0.34	0.25	1.80E-05
rs9372110	2.29	0.29	0.004	1.11	0.38	0.80	3.13	0.27	2.70E-05	1.99	0.27	0.01
rs2046197	1.28	0.20	0.23	2.14	0.21	2.60E-04	1.72	0.20	0.007	1.65	0.19	0.008
rs8021600	0.35	0.29	3.30E-04	0.84	0.31	0.57	0.49	0.26	0.005	0.51	0.30	0.03
rs8091629	0.53	0.27	0.02	0.56	0.26	0.03	0.38	0.25	7.00E-05	0.79	0.27	0.36

Supplemental Table 22c: Meta-analysis for other subgroups for visuospatial SNPs

	Isolated relative memory impairment		Isolated relative language impairment		Multiple domains with relative impairments		No domain with relative impairment	
SNP	OR	P value	OR	P value	OR	P value	OR	P value
rs2795228	0.91	0.28	0.81	0.06	0.96	0.79	0.94	0.38
rs484947	0.94	0.38*	0.80	0.02	0.80	0.10	0.93	0.21
rs16839220	1.01	0.89	0.93	0.51	0.70	0.04	0.92	0.22
rs2289506	1.16	0.04	1.17	0.09	1.20	0.18	1.06	0.32
rs9369477	0.96	0.75	0.90	0.52	0.90	0.66	1.01	0.89
rs9372110	0.95	0.74	1.19	0.35	1.48	0.08	1.11	0.34
rs2046197	1.01	0.86*	1.18	0.08	0.94	0.65	1.05	0.36
rs8021600	0.84	0.19	0.92	0.66	1.01	0.98	0.91	0.37
rs8091629	0.84	0.13	0.79	0.13	0.74	0.14	0.81	0.02

* Indicates that the heterogeneity p value was <0.05 for that analysis

Supplemental Text 9. Genetic results: Language SNPs

Supplemental Table 23a: Meta-analysis results for language for language SNPs

SNP Characteristics					Meta analysis results				
Chromosome	SNP	Base pair	Allele 1	Allele 2	Called allele frequency	OR	SE	P value	Heterogeneity p value
1	rs13374908	179749774	A	G	0.24	1.59	0.10	2.33E-06	0.18
2	rs28715896	212560101	C	G	0.57	0.63	0.10	3.50E-06	0.44
3	rs75337321	54584587	T	C	0.06	2.21	0.17	4.59E-06	0.09
4	rs10222981	6761053	T	G	0.08	2.06	0.15	1.24E-06	0.31
10	rs6183545453	2759796	T	C	0.94	0.46	0.16	7.71E-07	0.16
17	rs365521	61022295	A	G	0.47	0.63	0.10	1.48E-06	0.84

Supplemental Table 23b: Study-specific results for language SNPs

	ACT			ADNI			ROS-MAP			PITT		
SNP	OR	SE	P value	OR	SE	P value	OR	SE	P value	OR	SE	P value
rs13374908	0.89	0.29	0.69	1.49	0.26	0.12	1.82	0.15	4.28E-05	1.67	0.19	0.007
rs28715896	0.64	0.26	0.10	0.64	0.23	0.05	0.71	0.15	0.02	0.45	0.23	5.10E-04
rs75337321	0.93	0.56	0.90	1.26	0.39	0.56	2.72	0.26	1.30E-04	3.25	0.33	4.22E-04
rs10222981	2.53	0.31	0.003	2.97	0.36	0.003	1.36	0.28	0.27	2.10	0.26	0.005
rs6183545453	0.26	0.32	2.76E-05	0.49	0.45	0.113	0.66	0.25	0.10	0.42	0.33	0.009
rs365521	0.52	0.27	0.01	0.58	0.25	0.03	0.67	0.14	0.004	0.65	0.19	0.02

Supplemental Table 23c: Meta-analysis for other subgroups for language SNPs

	Isolated relative memory impairment		Isolated relative visuospatial impairment		Multiple domains with relative impairments		No domain with relative impairment	
SNP	OR	P value	OR	P value	OR	P value	OR	P value
rs13374908	1.15	0.07	1.03	0.76	1.08	0.63	1.16	0.03
rs28715896	0.85	0.03	0.83	0.08	1.07	0.62	0.93	0.21
rs75337321	1.03	0.85	1.09	0.68	1.13	0.69	0.99	0.95
rs10222981	1.00	0.98	1.22	0.26	0.92	0.76	1.06	0.60
rs6183545453	0.83	0.20	0.84	0.36	0.83	0.49	0.92	0.51
rs365521	1.00	0.98	0.89	0.22	0.99	0.96*	0.88	0.03

* Indicates the heterogeneity p value was <0.05 for that analysis

Supplemental Text 10. Genetic results: Multiple domains SNPs

Supplemental Table 24a: Meta-analysis results for the multiple domains group for multiple domains SNPs

SNP Characteristics					Meta analysis results				
Chromosome	SNP	Base pair	Allele 1	Allele 2	Called allele frequency	OR	SE	P value	Heterogeneity p value
2	rs698842	50890096	A	T	0.22	1.96	0.14	1.98E-06	0.11
2	rs10175975	59429807	T	C	0.19	1.99	0.15	3.14E-06	0.31
7	rs78872508	19016476	T	C	0.87	0.45	0.17	1.78E-06	0.98
8	rs4348488	22024162	C	G	0.21	1.97	0.15	3.36E-06	0.96
8	rs17089546	23571807	A	G	0.25	1.86	0.13	3.29E-06	0.76
8	rs74717330	76296308	A	C	0.05	3.09	0.24	2.37E-06	0.97
9	rs191325450	83377984	A	G	0.91	0.43	0.18	2.32E-06	0.93
11	rs4543939	92667658	A	T	0.43	2.43	0.19	3.54E-06	0.33
16	rs8059356	86357245	A	G	0.21	2.23	0.16	5.75E-07	0.76

Supplemental Table 24b: Study-specific results for multiple domain SNPs

	ACT			ADNI			ROS-MAP			PITT		
SNP	OR	SE	P value	OR	SE	P value	OR	SE	P value	OR	SE	P value
rs698842	*	*	*	1.15	0.36	0.70	1.80	0.20	0.003	2.75	0.24	1.91E-05
rs10175975	*	*	*	2.94	0.33	0.001	2.03	0.22	0.001	1.55	0.25	0.08
rs78872508	*	*	*	0.47	0.39	0.06	0.45	0.24	0.001	0.43	0.29	0.004
rs4348488	*	*	*	1.90	0.34	0.06	1.92	0.22	0.003	2.08	0.24	0.002
rs17089546	*	*	*	1.99	0.29	0.02	1.65	0.21	0.02	2.05	0.22	0.001
rs74717330	*	*	*	*	*	*	3.06	0.32	5.35E-04	3.13	0.35	0.001
rs191325450	*	*	*	0.38	0.39	0.01	0.43	0.26	0.001	0.45	0.33	0.02
rs4543939	*	*	*	*	*	*	2.83	0.24	2.15E-05	1.92	0.31	0.04
rs8059356	*	*	*	*	*	*	2.34	0.22	1.14E-04	2.12	0.23	0.001

* Indicates that data were not available for that SNP in that study. There were too few people from ACT in this group to include in meta-analyses. ADNI was missing data for three SNPs.

Supplemental Table 24c: Meta-analysis for other subgroups for multiple domain SNPs

	Isolated relative memory impairment		Isolated relative visuospatial impairment		Isolated relative language impairment		No domain with relative impairment	
SNP	OR	P value	OR	P value	OR	P value	OR	P value
rs698842	1.13	0.13	1.11	0.34	1.37	???	1.01	0.93
rs10175975	1.01	0.94	1.07	0.59	1.11	0.36	0.99	0.84
rs78872508	0.80	0.02	0.84	0.22	0.81	0.11	0.88	0.14
rs4348488	1.11	0.22	1.05	0.68	1.20	0.10	1.06	0.43
rs17089546	0.93	0.38	1.03	0.78	1.26	0.02	1.04	0.50
rs74717330	1.14	0.48*	1.24	0.33	0.94	0.79	1.10	0.48
rs191325450	0.77	0.02	0.85	0.30	0.92	0.61	0.99	0.89
rs4543939	0.96	0.66	0.97	0.85	0.96	0.76	1.01	0.87
rs8059356	1.17	0.12	1.17	0.26	0.77	0.07	1.19	0.05

* Indicates the heterogeneity p value was <0.05 for that analysis.

Supplemental Text 11. Genetic results: No domain with a substantial relative impairment SNPs

Supplemental Table 25a: Meta-analysis results for the no domain group for no domain with a substantial relative impairment SNPs

SNP Characteristics					Meta analysis results				
Chromosome	SNP	Base pair	Allele 1	Allele 2	Called allele frequency	OR	SE	P value	Heterogeneity p value
2	rs4972634	174907205	T	C	0.59	1.31	0.06	3.84E-06	0.61
3	rs11708767	151119726	A	G	0.43	1.33	0.06	2.82E-07	0.76
6	rs4533991	51098648	T	G	0.46	1.32	0.06	1.55E-06	0.91
6	rs78358979	87504903	A	T	0.06	1.76	0.11	4.95E-07	0.15
7	rs6978679	105718743	A	G	0.73	1.36	0.06	2.02E-06	0.44
17	rs72839770	7132192	T	C	0.36	1.31	0.06	4.12E-06	0.61
20	rs7264688	17954706	T	G	0.67	1.47	0.08	4.70E-06	0.85

Supplemental Table 25b: Study-specific results for no domain with a substantial relative impairment SNPs

	ACT			ADNI			ROS-MAP			PITT		
SNP	OR	SE	P value	OR	SE	P value	OR	SE	P value	OR	SE	P value
rs4972634	1.28	0.11	0.02	1.27	0.13	0.06	1.21	0.12	0.12	1.49	0.12	6.29E-04
rs11708767	1.43	0.11	0.001	1.39	0.13	0.009	1.31	0.11	0.01	1.22	0.11	0.06
rs4533991	1.39	0.11	0.004	1.31	0.12	0.03	1.36	0.12	0.008	1.25	0.11	0.06
rs78358979	1.82	0.18	0.001	2.69	0.24	3.35E-05	1.32	0.25	0.25	1.39	0.26	0.21
rs6978679	1.51	0.13	0.001	1.52	0.14	0.003	1.23	0.13	0.10	1.23	0.12	0.08
rs72839770	1.34	0.11	0.006	1.16	0.12	0.22	1.28	0.14	0.08	1.49	0.11	0.001
rs7264688	1.63	0.19	0.01	1.48	0.13	0.003	1.55	0.20	0.03	1.30	0.18	0.16

Supplemental Table 25c: Meta-analysis for other subgroups for no domain with a substantial relative impairment SNPs

	Isolated relative memory impairment		Isolated relative visuospatial impairment		Isolated relative language impairment		Multiple domains with relative impairments	
SNP	OR	P value	OR	P value	OR	P value	OR	P value
rs4972634	1.09	0.22	1.06	0.54	0.95	0.56	0.98	0.86
rs11708767	1.11	0.12	1.04	0.70	1.08	0.37	0.96	0.73
rs4533991	1.20	0.01	1.15	0.14	0.99	0.89	0.93	0.57
rs78358979	1.09	0.60	1.10	0.64	0.95	0.82	1.94	0.01
rs6978679	1.05	0.51	1.03	0.77	1.06	0.58	0.94	0.67
rs72839770	0.94	0.40	1.12	0.25	1.03	0.76	0.97	0.82
rs7264688	1.19	0.07	1.06	0.69	1.26	0.08	1.58	0.02

Supplemental Text 12. Generation of genetic risk scores and their ability to predict Alzheimer's disease case/control status

We used information on SNPs to construct gene scores for each of the five Alzheimer's disease subgroups and Alzheimer's disease gene scores based on the Lambert *et al.* IGAP GWAS of late onset Alzheimer's disease paper[17].

For the subgroup gene scores we used SNPs which had a minor allele frequency > 3%, a *p*-value < 10^{-5} for the meta-analysis of one of the subgroups, and a heterogeneity *p*-value > 0.05. We checked for linkage disequilibrium (LD) between these SNPs and found that these SNPs were not in LD.

In total, we made eight different gene scores in our combined four-cohort data set (n=5,878):

1) Two SNPs were used to derive a gene score for the isolated relative memory impairment subgroup (grs_mem).

2) Nine SNPs were used to derive a gene score for the isolated relative visuospatial impairment subgroup (grs_vsp).

3) Six SNPs were used to derive a gene score for the isolated relative language impairment subgroup (grs_lan).

4) Nine SNPs were used to derive a gene score for the multiple domains with substantial relative impairments subgroup (grs_mix).

5) Seven SNPs were used to derive a gene score for the subgroup with no domain with a substantial relative impairment (grs_none).

6) Nineteen SNPs were used to derive an Alzheimer's disease risk score based on effect sizes reported in the IGAP Lambert et al. paper (grs_igap_lambert).

7) The same 19 IGAP SNPs were used to derive an Alzheimer's disease risk score (grs_igap_cc) based on beta coefficients from an analysis of the Alzheimer's disease case-control phenotype from the four cohorts we analyzed (ACT/ADNI/ROS-MAP/PITT).

8) We performed a GWAS of the Alzheimer's disease case-control phenotype from our data and identified 16 SNPs with a *p*-value < 10^{-5} from the four cohorts we analyzed (ACT/ADNI/ROS-MAP/PITT). We used these SNPs to derive an EPAD-specific Alzheimer's disease risk score (grs_epad_cc).

Details about SNPs, risk alleles, and effect sizes used to derive each of the gene scores are given at the end of the appendix.

The SNPs and the associated effect estimates were combined in a gene score assuming an additive genetic model where β_k is the corresponding SNP weight describing the effect of an additional risk allele on the phenotype.

$$\mathrm{GRS_i} = \sum_{k=1}^{\#\,\mathrm{loci}} \beta_k \cdot \text{allele count}_{i,k}$$

PLINK[22] was used to derive the gene scores.

We used the gene scores to predict Alzheimer's disease in logistic regression models.

We ran the following regressions in our combined four cohort data set with 3,447 cognitively normal elderly controls and 2,431 people with Alzheimer's disease using Stata:

A) Logistic regression for Alzheimer's disease case-control status adjusting for age, sex, and the five Alzheimer's disease subtype genetic risk scores (grs_mem, grs_vsp, grs_lan, grs_mix, and grs_none)

B) Logistic regression for Alzheimer's disease case-control status adjusting for age, sex, the five AD subtype genetic risk scores, and grs_igap_lambert

C) Logistic regression for Alzheimer's disease case-control status adjusting for age, sex, and grs_igap_lambert

D) Logistic regression for Alzheimer's disease case-control status adjusting for age, sex, and grs_igap_cc

E) Logistic regression for Alzheimer's disease case-control status adjusting for age, sex, and grs_epad_cc

Analysis I. Under a nested design setting, we test Model B vs. Model C where Model B is the full model. We obtained $\chi^2_{df=5} = 135.8$, $p=1.4 \times 10^{-27}$, which means that the variables that was removed to produce the reduced model resulted in a model that has a significantly poorer fit, and therefore the variable should be included in the model. This implies that the five subtype GRSs have additional power to predict Alzheimer's disease.

Analysis II. We, also, test the difference in area under receiver operator characteristic (ROC) curve for the following set of non-nested models:

i) Model A vs. Model C

ii) Model A vs. Model D

iii) Model A vs. Model E

Supplemental Table 26. Area under the receiver operator characteristic curve for predicting late-onset Alzheimer's disease case-control status with different groups of SNPs

	Model A	Model C	Model D	Model E
Area under ROC curve	0.621 SE = 0.01	0.598 SE = 0.01	0.582 SE = 0.01	0.584 SE = 0.01

* SE = Standard error

We then test equality of ROC areas between Model A and Models C, D, and E.

Supplemental Table 27. Tests of equality of receiver operator characteristic curves compared with that produced from IGAP SNPs (compared with Model A)

Model C	Model D	Model E
$\chi^2_{df=1} = 11.2$, p=0.0008	$\chi^2_{df=1} = 41.3$, $p=1.3 \times 10^{-10}$	$\chi^2_{df=1} = 34.8$, $p=3.6 \times 10^{-9}$

Model A, with the five subtype GRSs, was significantly better at predicting Alzheimer's disease than the alternative models that used scores based only on Alzheimer's disease case/control status.

Supplemental Table 28. SNPs used to calculate gene scores

SNPs	Chromosome	Risk Allele	Risk Allele Frequency	Beta
1) Isolated relative memory impairment subtype				
rs1977412	1	T	0.86	-0.44
rs9937469*	16	T	0.06	0.76
2) Isolated relative visuospatial ability impairment subtype				
rs2795228	1	A	0.82	-0.54
rs484947	1	A	0.62	-0.45
rs16839220	2	C	0.2	-0.63
rs2289506	3	T	0.34	0.48
rs9369477	6	T	0.92	-0.71
rs9372110	6	A	0.06	0.77
rs2046197	8	C	0.59	0.51
rs8021600	14	C	0.92	-0.67
rs8091629	18	A	0.9	-0.63
3) Isolated relative language impairment subtype				
rs13374908	1	A	0.24	0.46
rs28715896	2	C	0.57	-0.46
rs75337321	3	T	0.06	0.79
rs10222981	4	T	0.08	0.72
rs61835453	10	T	0.94	-0.78
rs365521	17	A	0.47	-0.46
4) Multiple domains with substantial relative impairment				
rs698842	2	A	0.22	0.67
rs10175975	2	T	0.19	0.69
rs78872508	7	T	0.87	-0.8
rs4348488	8	C	0.21	0.68
rs17089546	8	A	0.25	0.62
rs74717330*	8	A	0.05	1.13
rs191325450	9	A	0.91	-0.86
rs4543939*	11	A	0.43	0.89
rs8059356*	16	A	0.21	0.8
5) No domain with a substantial relative impairment				
rs4972634	2	T	0.59	0.27
rs11708767	3	A	0.43	0.29
rs4533991	6	T	0.46	0.28
rs78358979	6	A	0.06	0.57
rs6978679	7	A	0.73	0.3
rs72839770	17	T	0.36	0.27
rs7264688	20	T	0.67	0.39
6) IGAP Alzheimer's disease gene score based on Lambert *et al.* paper				
rs6656401	1	A	0.20	0.17
rs6733839	2	T	0.41	0.20
rs10948363	6	G	0.27	0.10
rs11771145	7	A	0.34	-0.11
rs9331896	8	C	0.38	-0.15
rs983392	11	G	0.40	-0.11
rs10792832	11	A	0.36	-0.14
rs4147929	19	A	0.19	0.14
rs9271192*	6	C	0.28	0.10

rs28834970	8	C	0.37	0.10
rs11218343*	11	C	0.04	-0.26
rs10498633	14	T	0.22	-0.09
rs35349669	2	T	0.49	0.08
rs190982	5	G	0.41	-0.07
rs2718058	7	G	0.37	-0.07
rs1476679	7	C	0.29	-0.09
rs10838725	11	C	0.32	0.08
rs17125944	14	C	0.09	0.13
rs7274581	20	C	0.08	-0.13
7) IGAP Alzheimer's disease gene score based on case-control meta-analysis of the four EPAD cohorts.				
rs6656401†	1	A	0.19	0.19
rs6733839	2	T	0.39	0.17
rs10948363	6	G	0.37	0.11
rs11771145	7	A	0.34	0.004
rs9331896	8	C	0.38	-0.06
rs983392	11	G	0.40	-0.10
rs10792832	11	A	0.36	-0.13
rs4147929	19	A	0.17	0.18
rs9271192*	6	C	0.27	0.05
rs28834970	8	C	0.36	0.11
rs11218343*	11	C	0.04	-0.24
rs10498633	14	T	0.22	-0.04
rs35349669	2	T	0.48	0.06
rs190982	5	G	0.48	-0.15
rs2718058	7	G	0.36	-0.05
rs1476679	7	C	0.38	-0.10
rs10838725	11	C	0.31	0.05
rs17125944	14	C	0.09	0.11
rs7274581	20	C	0.09	-0.14
8) EPAD-specific Alzheimer's disease risk score with SNPs $p < 10^{-5}$ in case-control meta-analysis of the four EPAD cohorts.				
rs72634809	1	T	0.26	0.78
rs6540721	1	A	0.16	-0.28
rs11922676	3	C	0.92	-0.67
rs4857132	3	A	0.77	-0.27
rs13434494	4	T	0.86	-0.27
rs6827227	4	T	0.46	-0.19
rs537483	5	A	0.51	0.19
rs78077027	5	T	0.03	1.02
rs6998234	8	T	0.05	0.42
rs28641873	8	A	0.08	0.48
rs7929347	11	A	0.61	-0.19
rs6589973	11	A	0.30	0.20
rs3751239	12	C	0.80	0.23
rs26833	16	A	0.40	-0.20
rs9939163	16	T	0.80	0.26

rs844912	20	T	0.18	0.25

* Missing in ADNI genetic data set;

† Heterogeneity *p*-value significant in meta-analysis;

Risk allele frequency corresponds to the frequency estimated in the given meta-analysis.

Supplemental text 8. Information regarding the Sweet et al. analyses

Sweet and colleagues[23] present data in terms of the sum of beta coefficients for two samples; the relevant comparison between our Figure 2 and their Table 4 would be their data divided by 2 to derive the average beta coefficient in each study. These ranged from +0.15 to -0.18, corresponding to ORs of 0.84 to 1.16, similar in magnitude to those previously reported for Alzheimer's disease from IGAP[24].

Supplemental Table 29. Demographic and cognitive characteristics by subgroup. N (%) or mean (SD).

	No Domain (n=1584)	Memory (n=1107)	Executive (n=104)	Language (n=510)	Visuospatial (n=497)	Multiple (n=248)
Female	977 (62%)	679 (61%)	53 (51%)	309 (61%)	314 (63%)	150 (60%)
Age at diagnosis	81 (8)	79 (8)	81 (9)	82 (8)	79 (9)	81 (8)
Education	14 (3)	14 (3)	14 (4)	15 (3)	14 (3)	14 (3)
White	1467 (93%)	1019 (92%)	97 (93%)	471 (92%)	434 (87%)	231 (93%)
Memory	-0.1 (0.9)	-1.0 (0.7)	0.6 (1.0)	0.0 (1.0)	0.3 (1.1)	-0.8 (1.4)
Visuospatial	0.1 (1.0)	1.0 (1.0)	0.6 (1.2)	0.6 (1.1)	-1.4 (1.0)	0.6 (1.6)
Executive function	0.2 (0.9)	0.8 (0.8)	-0.9 (0.9)	0.2 (1.0)	0.3 (1.1)	0.5 (1.3)
Language	0.0 (0.9)	0.4 (0.9)	0.2 (1.0)	-1.4 (1.0)	0.2 (1.1)	-0.7 (1.5)

Supplemental Table 30. IGAP SNPs with OR>1.30 or <0.77 in one subgroup and for which results from all four datasets were in the same direction

IGAP[a]				Results for notable subgroup[b]							Meta-analysis results for other subgroups[e]				
				Meta-analysis results[c]			Single study results[d]								
SNP	Gene	OR	Notable Subgroup	OR	p vs. null	p vs. IGAP	ACT	AD NI	ROS-MAP	PITT	No domain	Memory	Language	Visuo-spatial	Multiple domains
rs28834970	*PTK2B*	1.10	Multiple domains	1.51	0.0018	0.017	1.65	1.65	1.45	1.52	1.09	1.08	1.15	0.92	**
rs190982	*MEF2C*	0.93	Visuospatial	0.73	0.0021	0.019	0.75	0.99	0.60	0.64	0.85	0.85	0.86	**	1.25
rs11218343	*SORL1*	0.77	Visuospatial	0.61	0.12	0.47	0.56	n/a	0.84	0.41	0.89	0.73	1.02	**	0.83
rs7274581	*CASS4*	0.88	Memory	0.71	0.0058	0.09	0.83	0.55	0.84	0.72	0.86	**	0.90	0.98	0.88
rs17125944	*FERMT2*	1.14	Memory	1.37	0.0027	0.09	1.28	1.48	1.31	1.38	1.11	**	0.88	1.03	0.96
rs6656401	*CR1*	1.18	Visuospatial	1.42	0.0014	0.09	1.52	1.83	1.31	1.18	1.13	1.21[†]	1.33	**	1.11

[a] The odds ratios presented here are those reported in Lambert et al.[24]

[b] These columns present data for the subgroup with an OR >1.30 or <0.77.

[c] These columns present results from the meta-analysis results combining all studies, though for the subgroup with multiple domains with substantial relative impairments, ACT was excluded due to having only 12 people in that subgroup. The "Fold" column is the ratio of the meta-analytic odds ratio to that reported in Lambert et al. The "p vs. null" column shows the p value for the comparison of the subgroup to cognitively normal elderly controls, and the "p vs. IGAP" column shows the p value for the comparison of the subgroup to the values reported in Lambert et al., using the same method as in[25]. We evaluated 19 SNPs; the Bonferroni-corrected critical value is 0.05/19 = 0.0026.

[d] These columns show results for the notable subgroup from each study separately. The rs11218343 SNP was not reported for ADNI.

[e] These columns show results for other subgroups. The double asterisk (**) indicates that subgroup was the notable subgroup with results presented to the left.

[†] Meta-analysis odds ratios did not show statistical evidence of heterogeneity across studies except for the group with isolated substantial relative memory impairment, where rs665401 associated with *CR1* had a p value of 0.007.

Supplemental Table 31. Data for all IGAP SNPs for all of the studies and all the subgroups

Grp	SNP	Gene	IGAP OR	Meta	p	Heter. p	Meta vs IGAP p-value	ACT	p	ADNI	p	Rush	p	Pitt	p
none	rs6733839	*BIN1*	1.22	1.17	0.01	0.76	0.52	1.22	0.09	1.18	0.15	1.03	0.81	1.23	0.10
none	rs6656401	*CR1*	1.18	1.13	0.10	0.40	0.53	1.06	0.72	1.03	0.84	1.37	0.02	1.03	0.81
none	rs4147929	*ABCA7*	1.15	1.21	0.01	0.54	0.50	1.23	0.12	1.30	0.09	1.37	0.06	1.02	0.88
none	rs17125944	*FERMT2*	1.14	1.11	0.29	0.93	0.75	1.09	0.62	1.22	0.34	1.13	0.52	1.01	0.94
none	rs9271192	*HLA-DRB5-HLA-DRB1*	1.11	1.02	0.74	0.34	0.26	0.90	0.42			1.16	0.20	1.01	0.96
none	rs28834970	*PTK2B*	1.10	1.09	0.15	0.08	0.86	1.32	0.01	0.88	0.30	1.00	0.97	1.16	0.20
none	rs10948363	*CD2AP*	1.10	1.09	0.18	0.52	0.85	1.17	0.16	1.19	0.20	1.07	0.61	0.94	0.63
none	rs35349669	*INPP5D*	1.08	1.09	0.11	0.79	0.83	1.06	0.58	1.22	0.10	1.07	0.56	1.06	0.62
none	rs10838725	*CELF1*	1.08	1.05	0.45	0.55	0.61	1.07	0.53	0.89	0.39	1.15	0.24	1.05	0.70
none	rs2718058	*NME8*	0.93	0.91	0.10	0.96	0.69	0.89	0.32	0.95	0.70	0.92	0.49	0.87	0.23
none	rs190982	*MEF2C*	0.93	0.86	0.01	0.74	0.18	0.83	0.12	0.93	0.54	0.77	0.04	0.90	0.33
none	rs1476679	*ZCWPW1*	0.91	0.86	0.01	0.52	0.37	0.96	0.74	0.81	0.11	0.76	0.03	0.90	0.40
none	rs10498633	*SLC24A4-RIN3*	0.91	0.92	0.19	0.17	0.92	0.75	0.03	0.89	0.44	0.93	0.57	1.13	0.34
none	rs983392	*MS4A6A*	0.90	0.89	0.03	0.90	0.78	0.94	0.57	0.86	0.24	0.89	0.31	0.84	0.12
none	rs11771145	*EPHA1*	0.90	0.98	0.80	0.65	0.15	1.04	0.73	0.96	0.78	1.09	0.57	0.88	0.28
none	rs7274581	*CASS4*	0.88	0.86	0.15	0.71	0.87	0.96	0.82	0.72	0.12	0.96	0.84	0.82	0.32
none	rs10792832	*PICALM*	0.87	0.86	0.01	0.42	0.91	0.91	0.40	0.92	0.49	0.73	0.01	0.92	0.44
none	rs9331896	*CLU*	0.86	0.91	0.14	0.16	0.36	1.15	0.33	0.88	0.30	0.76	0.02	0.95	0.67
none	rs11218343	*SORL1*	0.77	0.89	0.47	0.51	0.38	1.00	0.99			0.64	0.17	0.98	0.93
mem	rs6733839	*BIN1*	1.22	1.21	0.01	0.01	0.91	1.03	0.88	0.85	0.24	1.33	0.14	1.56	0.00
mem	rs6656401	*CR1*	1.18	1.21	0.02	0.01	0.77	1.88	0.00	1.53	0.02	1.27	0.18	0.87	0.29
mem	rs4147929	*ABCA7*	1.15	1.22	0.02	0.58	0.53	1.10	0.67	1.22	0.26	0.93	0.78	1.34	0.02
mem	rs17125944	*FERMT2*	1.14	1.37	0.00	0.98	0.09	1.28	0.37	1.48	0.09	1.31	0.26	1.38	0.04
mem	rs9271192	*HLA-DRB5-HLA-DRB1*	1.11	1.19	0.03	0.33	0.40	0.94	0.75			1.13	0.44	1.30	0.01
mem	rs28834970	*PTK2B*	1.10	1.08	0.28	0.17	0.79	1.08	0.67	0.88	0.38	0.96	0.80	1.28	0.02
mem	rs10948363	*CD2AP*	1.10	1.03	0.68	0.98	0.38	0.96	0.82	1.05	0.77	1.05	0.76	1.04	0.73
mem	rs35349669	*INPP5D*	1.08	1.08	0.26	0.41	0.98	1.16	0.39	1.26	0.08	1.08	0.62	0.95	0.65

mem	rs10838725	*CELF1*	1.08	1.15	0.05	0.98	0.39	1.09	0.64	1.15	0.35	1.12	0.49	1.19	0.11
mem	rs2718058	*NME8*	0.93	0.95	0.47	0.74	0.74	1.10	0.59	0.86	0.30	0.99	0.97	0.94	0.52
mem	rs190982	*MEF2C*	0.93	0.85	0.02	0.49	0.22	0.76	0.17	0.86	0.31	0.70	0.04	0.93	0.50
mem	rs1476679	*ZCWPW1*	0.91	0.84	0.02	0.07	0.28	0.60	0.02	0.68	0.02	0.85	0.33	1.01	0.92
mem	rs10498633	*SLC24A4-RIN3*	0.91	0.91	0.24	0.90	0.99	0.80	0.27	0.94	0.72	0.97	0.86	0.91	0.44
mem	rs983392	*MS4A6A*	0.90	0.82	0.00	0.06	0.19	0.75	0.11	0.68	0.01	1.16	0.32	0.80	0.03
mem	rs11771145	*EPHA1*	0.90	0.94	0.37	0.29	0.57	0.69	0.05	0.91	0.52	0.96	0.83	1.04	0.71
mem	rs7274581	*CASS4*	0.88	0.71	0.01	0.66	0.09	0.83	0.55	0.55	0.02	0.84	0.55	0.72	0.08
mem	rs10792832	*PICALM*	0.87	0.83	0.01	0.97	0.47	0.81	0.24	0.85	0.25	0.78	0.11	0.84	0.11
mem	rs9331896	*CLU*	0.86	0.95	0.47	0.79	0.17	0.97	0.91	0.88	0.38	0.87	0.39	1.02	0.84
mem	rs11218343	*SORL1*	0.77	0.73	0.13	0.28	0.79	0.31	0.11			1.07	0.86	0.67	0.13
lan	rs6733839	*BIN1*	1.22	1.03	0.78	0.59	0.11	0.75	0.32	0.95	0.80	1.09	0.63	1.19	0.39
lan	rs6656401	*CR1*	1.18	1.33	0.01	0.11	0.30	1.43	0.27	1.63	0.10	1.53	0.01	0.80	0.34
lan	rs4147929	*ABCA7*	1.15	1.17	0.22	0.56	0.91	1.20	0.56	0.96	0.89	1.01	0.96	1.48	0.07
lan	rs17125944	*FERMT2*	1.14	0.88	0.45	0.36	0.13	1.04	0.94	1.22	0.59	0.90	0.65	0.46	0.07
lan	rs9271192	*HLA-DRB5-HLA-DRB1*	1.11	0.92	0.43	0.43	0.09	0.69	0.22			0.89	0.43	1.10	0.65
lan	rs28834970	*PTK2B*	1.10	1.15	0.14	0.37	0.65	1.50	0.10	0.94	0.78	1.04	0.76	1.35	0.12
lan	rs10948363	*CD2AP*	1.10	1.28	0.01	0.09	0.13	2.09	0.00	1.40	0.19	1.21	0.19	0.96	0.82
lan	rs35349669	*INPP5D*	1.08	0.97	0.76	0.11	0.26	1.09	0.70	1.52	0.07	0.90	0.45	0.76	0.15
lan	rs10838725	*CELF1*	1.08	1.04	0.68	0.90	0.69	0.94	0.81	0.93	0.78	1.12	0.43	1.02	0.91
lan	rs2718058	*NME8*	0.93	0.89	0.21	0.43	0.64	0.68	0.16	0.69	0.13	0.96	0.78	1.00	0.99
lan	rs190982	*MEF2C*	0.93	0.86	0.11	0.79	0.41	0.82	0.47	0.75	0.23	0.96	0.76	0.80	0.22
lan	rs1476679	*ZCWPW1*	0.91	1.15	0.15	0.18	0.02	1.75	0.02	1.34	0.22	0.98	0.88	1.06	0.77
lan	rs10498633	*SLC24A4-RIN3*	0.91	1.10	0.37	0.48	0.07	1.02	0.95	0.75	0.32	1.24	0.14	1.09	0.68
lan	rs983392	*MS4A6A*	0.90	0.98	0.82	0.09	0.36	0.85	0.51	0.99	0.96	1.22	0.14	0.69	0.05
lan	rs11771145	*EPHA1*	0.90	1.04	0.66	0.30	0.14	1.42	0.13	1.21	0.40	0.98	0.91	0.83	0.35
lan	rs7274581	*CASS4*	0.88	0.90	0.51	0.96	0.89	0.71	0.48	0.91	0.81	0.96	0.87	0.88	0.69
lan	rs10792832	*PICALM*	0.87	1.00	0.97	0.87	0.14	0.86	0.54	1.14	0.57	0.98	0.90	1.02	0.93
lan	rs9331896	*CLU*	0.86	0.97	0.75	0.31	0.22	1.10	0.75	0.66	0.10	1.11	0.46	0.89	0.54
lan	rs11218343	*SORL1*	0.77	1.02	0.92	0.14	0.24	1.66	0.32			1.12	0.72	0.37	0.10

vsp	rs6733839	*BIN1*	1.22	1.21	0.06	0.32	0.96	1.28	0.25	0.97	0.85	1.18	0.48	1.59	0.02
vsp	rs6656401	*CR1*	1.18	1.42	0.00	0.50	0.09	1.52	0.09	1.83	0.01	1.31	0.21	1.18	0.43
vsp	rs4147929	*ABCA7*	1.15	1.28	0.03	0.71	0.36	1.40	0.14	1.30	0.26	0.93	0.81	1.37	0.13
vsp	rs17125944	*FERMT2*	1.14	1.03	0.83	0.25	0.55	1.52	0.17	0.71	0.34	0.71	0.33	1.19	0.54
vsp	rs9271192	*HLA-DRB5-HLA-DRB1*	1.11	1.05	0.70	0.57	0.61	0.96	0.87			1.23	0.28	0.94	0.77
vsp	rs28834970	*PTK2B*	1.10	0.92	0.43	0.91	0.08	0.89	0.56	1.04	0.84	0.87	0.48	0.90	0.58
vsp	rs10948363	*CD2AP*	1.10	1.25	0.03	0.48	0.20	1.33	0.17	1.59	0.02	1.14	0.52	1.06	0.78
vsp	rs35349669	*INPP5D*	1.08	1.06	0.53	0.50	0.82	1.07	0.71	0.89	0.51	1.30	0.14	1.01	0.94
vsp	rs10838725	*CELF1*	1.08	0.93	0.44	0.45	0.12	0.77	0.22	0.84	0.37	0.92	0.66	1.18	0.39
vsp	rs2718058	*NME8*	0.93	1.17	0.09	0.81	0.01	1.35	0.13	1.04	0.83	1.12	0.54	1.20	0.30
vsp	rs190982	*MEF2C*	0.93	0.73	0.00	0.27	0.02	0.75	0.21	0.99	0.95	0.60	0.01	0.64	0.02
vsp	rs1476679	*ZCWPW1*	0.91	0.93	0.45	0.04	0.87	1.01	0.95	0.58	0.01	1.31	0.15	0.84	0.38
vsp	rs10498633	*SLC24A4-RIN3*	0.91	1.06	0.58	0.33	0.16	0.77	0.25	1.25	0.28	1.26	0.26	0.97	0.89
vsp	rs983392	*MS4A6A*	0.90	0.96	0.66	0.84	0.48	0.91	0.62	0.87	0.45	0.97	0.88	1.08	0.64
vsp	rs11771145	*EPHA1*	0.90	1.23	0.04	0.45	0.00	1.25	0.25	1.30	0.16	0.83	0.49	1.36	0.08
vsp	rs7274581	*CASS4*	0.88	0.98	0.92	0.53	0.48	0.63	0.23	1.00	1.00	1.30	0.39	0.97	0.91
vsp	rs10792832	*PICALM*	0.87	0.91	0.33	0.89	0.61	0.98	0.90	0.87	0.49	0.83	0.31	0.98	0.92
vsp	rs9331896	*CLU*	0.86	0.99	0.94	0.16	0.16	1.52	0.10	0.75	0.13	1.07	0.74	0.96	0.82
vsp	rs11218343	*SORL1*	0.77	0.61	0.12	0.64	0.47	0.56	0.34			0.84	0.72	0.41	0.14
mix	rs6733839	*BIN1*	1.22	1.35	0.04	0.34	0.50	0.66	0.44	0.95	0.85	1.63	0.04	1.40	0.15
mix	rs6656401	*CR1*	1.18	1.11	0.54	0.68	0.69	0.86	0.81	0.87	0.75	1.27	0.30	1.01	0.98
mix	rs4147929	*ABCA7*	1.15	1.30	0.13	0.27	0.48	0.72	0.60	0.87	0.73	1.82	0.03	1.15	0.61
mix	rs17125944	*FERMT2*	1.14	0.96	0.88	0.06	0.49	0.84	0.82	1.91	0.13	0.88	0.72	0.34	0.07
mix	rs9271192	*HLA-DRB5-HLA-DRB1*	1.11	1.22	0.20	0.04	0.55	0.69	0.46			1.56	0.02	0.80	0.38
mix	rs28834970	*PTK2B*	1.10	1.51	0.00	0.94	0.02	1.65	0.24	1.65	0.09	1.45	0.05	1.52	0.07
mix	rs10948363	*CD2AP*	1.10	1.06	0.68	0.71	0.80	0.99	0.98	1.26	0.49	1.11	0.63	0.91	0.71
mix	rs35349669	*INPP5D*	1.08	0.91	0.47	0.14	0.19	1.30	0.54	1.33	0.31	0.96	0.85	0.65	0.06
mix	rs10838725	*CELF1*	1.08	1.05	0.74	0.87	0.82	1.24	0.62	1.15	0.65	1.08	0.71	0.95	0.83
mix	rs2718058	*NME8*	0.93	0.78	0.06	0.62	0.19	0.69	0.42	0.69	0.24	0.89	0.55	0.68	0.10
mix	rs190982	*MEF2C*	0.93	1.25	0.10	0.84	0.03	0.99	0.98	1.22	0.51	1.38	0.13	1.15	0.50

mix	rs1476679	*ZCWPW1*	0.91	0.83	0.20	0.57	0.52	0.64	0.38	0.62	0.19	0.95	0.81	0.77	0.32
mix	rs10498633	*SLC24A4-RIN3*	0.91	0.80	0.18	0.18	0.44	0.55	0.29	0.42	0.06	0.75	0.22	1.09	0.75
mix	rs983392	*MS4A6A*	0.90	0.92	0.53	0.21	0.86	0.92	0.85	0.65	0.17	1.16	0.44	0.80	0.31
mix	rs11771145	*EPHA1*	0.90	1.12	0.41	0.39	0.12	1.84	0.13	0.85	0.62	1.02	0.92	1.39	0.13
mix	rs7274581	*CASS4*	0.88	0.88	0.60	0.85	0.98	2.73	0.05	0.73	0.57	0.83	0.60	1.03	0.93
mix	rs10792832	*PICALM*	0.87	0.83	0.17	0.23	0.73	2.26	0.06	0.85	0.62	1.01	0.95	0.59	0.03
mix	rs9331896	*CLU*	0.86	0.87	0.32	0.35	0.93	1.89	0.27	0.56	0.08	0.98	0.91	0.92	0.72
mix	rs11218343	*SORL1*	0.77	0.83	0.64	0.73	0.83	2.09	0.35			0.73	0.57	0.95	0.92

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