Genome-Wide Association Identifies the First Risk Loci for Psychosis in Alzheimer Disease

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Running Title: GWAS of Psychosis in Alzheimer Disease

Abstract

Psychotic symptoms, defined as the occurrence of delusions or hallucinations, are frequent in Alzheimer disease (AD with psychosis, AD+P). AD+P affects ~50% of individuals with AD, identifies a subgroup with poor outcomes, and is associated with a greater degree of cognitive impairment and depressive symptoms, compared to subjects without psychosis (AD-P). Although the estimated heritability of AD+P is 61%, genetic sources of risk are unknown. We report a genome-wide meta-analysis of 12,317 AD subjects, 5,445 AD+P. Results showed common genetic variation accounted for a significant portion of heritability. Two loci, one in *ENPP6* (rs9994623, O.R. (95%CI) 1.16 (1.10, 1.22), $p=1.26x10^{-8}$) and one spanning the 3'-UTR of an alternatively spliced transcript of *SUMF1* (rs201109606, O.R. 0.65 (0.56-0.76), $p=3.24x10^{-8}$), had genome-wide significant associations with AD+P. Gene-based analysis identified a significant association with *APOE*, due to the *APOE* risk haplotype ε4. AD+P demonstrated negative genetic correlations with cognitive and educational attainment and positive genetic correlation with depressive symptoms. We previously observed a negative genetic correlation with schizophrenia; instead, we now found a stronger negative correlation with the related phenotype of bipolar disorder. Analysis of polygenic risk scores supported this genetic correlation and documented a positive genetic correlation with risk variation for AD, beyond the effect of ε4. We also document a small set of SNPs likely to affect risk for AD+P and AD or schizophrenia. These findings provide the first unbiased identification of the association of psychosis in AD with common genetic variation and provide insights into its genetic architecture.

Introduction

Psychotic symptoms, defined as the occurrence of delusions or hallucinations, constitute a phenotype within Alzheimer disease (AD+Psychosis, AD+P) that affects ~ 40% to 60% of individuals with AD and is associated with poor outcomes.[1] In comparison to AD subjects without psychosis (AD-P), AD+P subjects have greater cognitive impairments and experience more rapid declines in cognition and function that begin prior to psychosis onset.[2-9] AD+P is also often associated with increased rates of concurrent neuropsychiatric symptoms, including agitation,[10] aggression,[11,12] and depression.[5,13-15] As a consequence, AD+P is associated with increased rates of other poor outcomes, including greater distress for family and caregivers,[16] higher institutionalization rates,[17-20] worse health,[21] and increased mortality[22] compared to AD-P patients.

The AD+P phenotype is well suited for genetic studies when careful attention is paid to excluding potential phenocopies of both AD+P and AD-P. For example, we have shown that the heritability of AD+P is greatest when requiring the presence of multiple or recurrent psychotic symptoms, rather than a one-time occurrence of a single symptom.[23] Similarly, because psychotic symptoms typically emerge in the transition from mild to moderate stages of AD,[5] individuals without psychosis who are still in the early stages of disease may later manifest psychosis, and therefore, need to be excluded from analysis. Using these approaches to phenotypic characterization, we have previously reported familial aggregation of AD+P,[24] which has since been replicated in two independent cohorts.[5,25] We further estimated the heritability of the presence or absence of psychosis in AD at 61%.[23,26]

Thus, AD+P is likely to be strongly influenced by genetic variation. To date, no study has identified genome-wide significant associations with AD+P, largely due to the small sample sizes of prior studies. However, in prior reports we identified negative genetic correlation of

AD+P risk with risk for schizophrenia.[27,28] We now report a large genome-wide association meta-analysis of 12,317 AD subjects with and without psychosis. We identified two loci with genome-wide significant associations with AD+P, in *ENPP6* and *SUMF1*. In gene-based analyses, only *APOE* ($p=1.23x10^{-6}$) reached the criterion for genome-wide significance. AD+P was negatively genetically correlated with educational attainment and positively with depressive symptoms. Surprisingly, AD+P was not significantly genetically correlated with schizophrenia, but it was negatively correlated with bipolar disorder. Analysis of polygenic risk scores derived from schizophrenia (PRS_{SZ}), and bipolar disorder (PRS_{BP}) GWAS, support these genetic correlations. However, the relationship of schizophrenia risk to AD+P is more subtle. Some established risk SNPs for schizophrenia also confer risk for AD+P, while others confer protection.

Materials and Methods

Subjects

This study analyzed samples from 12,317 subjects diagnosed with possible, probable,[29] and when available, autopsy-confirmed definite[30] Alzheimer disease (for subject characteristics see Table 1A). Diagnoses were made based on diagnostic evaluations, cognitive testing, and in some cases neuropathologic assessment, conducted during subjects' participation in the following eight source programs as previously described: the Fundació ACE Barcelona Alzheimer Treatment and Research Center (ACE/GR@ACE),[31-33] a Consortium of National Institute on Aging Alzheimer Disease Centers (ADC),[34] Eli Lilly and Company (LILLY),[35,36] the Norwegian, Exeter and King's College Consortium for Genetics of Neuropsychiatric Symptoms in Dementia (NEXGENS),[37-42] the National Institute on Aging's Late Onset Alzheimer's Disease Family Study (NIA-LOAD),[5,26] the National Institute of Mental Health Genetics Initiative AD Cohort (NIMH),[24] the University of Pittsburgh Alzheimer Disease Research Center (PITT ADRC),[43,44] and the MRC genetic resource for Late-onset AD included in the Genetic and

Environmental Risk in AD Consortium (UK-Cardiff).[27,31,45] Collection of clinical data and genetic samples were approved by each source program's local Institutional Review Board or Medical Ethics Committee, as appropriate.

Characterization of Psychosis

Subjects were characterized for the presence or absence of delusions and hallucinations within the individual source programs (including their sub-studies) using the CERAD behavioral rating scale[46] (PITT ADRC and NIA-LOAD), Neuropsychiatric Inventory Questionnaire (NPI-Q,[47] NIA-LOAD, ADC, NEXGENS), NPI-Q Spanish Language Version[48] (ACE/GR@ACE), NPI[49] (UK-Cardiff, NEXGENS, LILLY), and Brief Psychiatric Rating Scale[50] (NIMH). Each of these instruments has established reliability in AD,[5,51] and we have previously used all successfully in analyses of psychosis in AD subjects.[4,5,7,23,43] AD+P was defined by the presence of persistent hallucinations or delusions throughout the course of dementia, AD-P was defined by the absence of all symptoms at all assessments. However, because psychotic symptoms typically emerge in the transition from mild to moderate stages of AD[5], individuals without psychosis, but who were still in the early stages of disease at their last assessment (CDR® Dementia Staging Instrument[52] score < 1, mini-mental state examination score[53] > 20), were considered to be at substantial risk of developing AD+P later in their course. Thus, these individuals were excluded from the analysis. We have used these approaches to characterizing and defining AD+P and AD-P in multiple studies demonstrating the heritability and association with genetic variation of the AD+P phenotype.[5,23,24,26-28,54]

For additional detail of each source program's clinical assessment methodology and demographics, see Supplementary Material.

Genotypes

Six of the eight program sources provided us with either blood (ACE/GR@ACE) or DNA samples (PITT ADRC, UK-Cardiff, NIA-LOAD, ADC, NIMH), all of which were processed by the Genomics Core Lab at the University of Pittsburgh. Genomic DNA was extracted from whole blood samples using the Qiamp Blood Mini kit (Qiagen, Valencia, CA). All DNA was quantitated by Pico Green (Thermo Fisher, Pittsburgh, PA) and diluted to a DNA concentration of 23ng/µl. Samples without the required amount of DNA were plated for whole genome amplification (WGA) and re-quantified. The above samples were genotyped at the Children's Hospital of Philadelphia (CHoP, Philadelphia, PA) using Illumina's Global Screening Array (Illumina, San Diego, CA). Prior to genotyping, ChoP confirmed DNA concentrations by Pico Green assay, and performed additional WGA on samples when necessary.

In addition to the above-mentioned blood and DNA samples, ACE/GR@ACE, LILLY, and NIA-LOAD provided us with single nucleotide polymorphism (SNP) array data. For the ADC, SNP array data was provided by the Alzheimer's Disease Genetics Consortium (ADGC). NEXGENS provided genome-wide association (GWA) statistics for the comparison of AD-P and AD+P. Additional details of the generation of SNP array data for all programs can be found in the Supplementary Material.

Analysis

Data from the eight program sources were processed as four cohorts (Phase 1, Phase 2, GR@ACE, and NEXGENS), based on timing of receipt of the data. Data processing, QC, and statistical analyses were uniform across three of the cohorts for which there were genotypes (Phase 1, Phase 2, GR@ACE), whereas only summary statistics were available for the fourth cohort (NEXGENS). All cohorts were analyzed separately for GWA, then statistics per SNP from these analyses were combined by meta-analysis using METAL.[55] Below we describe quality control procedures for the three genotyped cohorts and an overview of other methods.

For more detail, see the Supplementary Material. Additional details for the NEXGENS cohort have also been described previously.[56] Methods were implemented within Plink[57,58] unless otherwise noted.

Quality Control (QC) was completed by both genotype and by sample from Phase 1, Phase 2, and GR@ACE. After QC, 6,872 AD-P and 5,445 AD+P subjects, distributed across the four cohorts, remained for analysis (Table 1B). We determined ancestry using GemTools analysis[59] of a subset of autosomal SNPs with non-call rate < 0.001 and MAF > 0.05 for Phase 1, Phase 2, and GR@ACE. These SNPs were pruned such that, within a 50 SNP block and a 5 SNP step-size, the linkage disequilibrium $r^2 < 0.01$. For each of the three cohorts, a different subset of SNPs was chosen for ancestry analysis, and the resulting ancestry plots were used to identify the samples in the major European ancestry cluster. Analysis of NEXGENS[56] was restricted to individuals of European ancestry using genetic principal components computed by EIGENSTRAT.[60]

Genotypes were imputed using the Sanger Imputation Server,[61] the 1000 Genomes Phase3 reference panel,[62] and EAGLE2 for pre-phasing[63] for Phase 1, Phase 2, and GR@ACE. Before imputation, the genotypes were harmonized using the perl script HRC-1000G-check-bim-v4.2.5.pl. This resulted in 85,057,462 imputed or genotyped SNPs for each sample. QC of the imputed SNPs included the requirement that the INFO score for a SNP in each data set > 0.81; MAF > 0.01; and, among all European ancestry subpopulations defined by GemTools, Fst < 0.005. For NexGENS Phasing and imputation was done via the Sanger Imputation Service using the Haplotype Reference Consortium (r1.1) reference panel on all cohorts. After imputation only SNPs with an imputation quality (INFO) score > 0.4 and MAF > 0.05 were retained.

Separate GWA analyses were performed for the Phase 1, Phase 2, and GR@ACE cohorts, to contrast AD+P versus AD-P for the 9,200,578 SNPs using the Plink option --logistic and with adjustment for the three ancestry dimensions (**Supplementary Figures S3-S5**). For chromosome X, an additional covariate for sex was included. For NEXGENS, separate logistic regressions, implemented in PLINK for each of the 5 NEXGENS consortium datasets (**Tables S11.1-S11.5**), was used to contrast AD+P versus AD-P for each SNP, with adjustment for the first 10 ancestry principal components. METAL software was used to conduct inverse-variance weighted fixed effects meta-analysis across the 5 NEXGENS datasets, applying genomic control,[55] to generate the summary statistics used in the current analysis. The four GWAS statistics (Phase 1, Phase 2, GR@ACE, NEXGENS summary), per SNP, were then meta-analyzed using METAL.

Heritability of AD+P using GenomicSEM was estimated from 1,126,265 summary statistics from our METAL analysis. Of the 7,105,229 SNPs used for GWAS, 1,126,265 matched to those available on the GenomicSEM website. Also, using genome-wide complex trait analysis (GCTA),[64] heritability was estimated from 9,031 subjects of European ancestry drawn from the Phase 1, Phase 2, and GR@ACE cohorts for which individual genotypes were available (Table 1B). Two eigenvectors were used to control for ancestry, 997,105 SNPs were included in the analysis.

Individuals of European ancestry from all four cohorts were used to estimate genetic correlations using LD Score[65] and LD Hub (version 1.9.3).[66] We selected phenotypes for analysis based on prior studies showing correlations with psychosis in AD (years of schooling, depressive symptoms) or genetic association with AD+P (schizophrenia), or because they are closely related with the above four phenotypes. Specifically, we included intelligence, which is genetically correlated with years of schooling, bipolar disorder which is strongly genetically

correlated with both depressive symptoms and schizophrenia. Finally, we included AD as it is a necessary condition of AD±P, and two other neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and Parkinson's disease, each of which is associated with a neuropathology that may contribute to psychosis risk in AD.

We evaluated how well three different polygenic risk scores could differentiate 9,031 AD+P and AD-P subjects of European ancestry. We used the pruning and thresholding approach[67] to compute a PRS for our subjects, developed from GWAS results for AD (PRS_{AD}), [42] schizophrenia (PRS_{SZ}),[68] and bipolar disorder (PRS_{BP}),[69] separately. We used a set of GWAS p-value thresholds for SNP inclusion in each score ($5x10^{-8}$, 0.0001, 0.001, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5).

Gene-based analyses were performed on the summary association statistics using the most recent version (1.08b) of MAGMA.[70] For the primary analysis, SNPs were assigned to genes if they lay within the gene boundaries (as defined by NCBI) and the MAGMA "mean" method was used to derive the gene-wide association statistic (the sum of the squared Z statistics for individual SNPs). A secondary analysis assigned SNPs to genes if they lay within 35kb upstream or 10kb downstream of the gene boundary, to capture regulatory regions.[71]

Gene set enrichment analyses were performed in MAGMA,[70] correcting for the number of SNPs in each gene, linkage disequilibrium (LD) between SNPs and LD between genes. The measure of pathway enrichment is the MAGMA "competitive" test (where the association statistic for genes in the pathway is compared to those of all other protein-coding genes).[72]

Transcriptome-wide association (TWAS) was implemented using the FUSION package[73] was used to perform a TWAS using dorsolateral prefrontal cortex expression data from the

CommonMind Consortium and expression data from 13 Brain tissues from the GTEx (Genotype-Tissue expression) consortium (v7).[74] Results were corrected for multiple testing of multiple genes within each tissue using the Bonferroni method.

See Supplementary Methods for additional details of QC, PRS calculation, pathway analyses and TWAS.

Results

Association Analyses

A total of 12,317 subjects, 6,872 AD-P and 5,445 AD+P, were included in this GWAS analysis (Table 1A). Contrasting AD-P to AD+P genotypes across the genome revealed two significant loci (Fig. 1, Supplementary Table 1). One locus was at 4q24, mapping to an intron of *ENPP6* (best SNP rs9994623, O.R. (95%CI) 1.16 (1.10, 1.22), $p=1.26\times10^{-8}$). The other locus was at 3p26.1 (best SNP rs201109606, O.R. 0.65 (0.56-0.76), $p=3.24\times10^{-8}$). This locus spans the 3' untranslated region (3'-UTR) of an alternatively spliced variant of *SUMF1* (SUMF1-204 ENST00000448413.5). None of the SNPs showing significant association in these loci are annotated as expression quantitative trait loci (eQTL) in GTEx. Behavior of the association statistics, as assessed by probability-probability plot (Supplementary Figure 1), is consistent with the expectation for such analyses, and the genomic control estimate,[75] GC=1.03, shows no evidence for confounding by ancestry.

For the gene-based analyses (Supplementary Table S2), only *APOE* ($p=1.23\times10^{-6}$) reached the criterion for genome-wide significance ($p<2.5\times10^{-6}$).[76] This association was only significant for SNPs within *APOE* itself. When the 35/10kb window around genes was used to assign SNPs,

no genes reached genome-wide significance. There was substantial association signal for SNPs in and near *APOE*, however: the smallest p-value achieved was at rs283811 ($z = 5.15$, $p = 2.55\times10^{-7}$), which falls in an intron of *NECTIN2* (PVRL2 protein), the second smallest p-value occurred for rs429358 ($z = 5.12$, $p = 2.96\times10^{-7}$), which is one of the two SNPs comprising the *APOE* risk haplotype ε4. These two SNPs, separated by 23,441 bp, were in modest LD ($r^2 = 0.52$, $D' = 0.91$[77]) in the 1000G CEU population sample. To determine if ε4 count could explain the AD+P association signal at this locus, we first analyzed a subset of our subjects who were characterized for the ε4 haplotype (2414 AD+P and 2509 AD-P) by logistic regression of AD+P status (yes/no) on ε4 count. The odds increased significantly with count of ε4 haplotypes (OR = 1.21; 95% CI: 1.11-1.31; $p = 8.64\times10^{-6}$). Next, using the same subjects, we determined the LD of ε4, in terms of r^2, with 120 SNPs in the *APOE* locus, all of which had association statistic $|z| > 2.0$ based on the GWAS of AD+P. We then regressed the statistics for these SNPs, $|z|$, on their LD with ε4, yielding a strongly positive slope ($b=3.14$, $p = 1.90\times10^{-41}$) and explaining 78.5% of the variance in the observed AD+P z-statistics. Thus, we conclude that the preponderance of AD+P association signal in this locus arises from ε4.

For the pathway enrichment analyses (Supplementary Table S3), only the Pathway Interaction Database (PID) IGF1 pathway showed significant enrichment after correction for multiple testing ($p=1.17\times10^{-6}$, $q=0.011$), although it was no longer significant when the 35/10kb window was used ($p=0.0469$, $q=0.920$). Interestingly, one of the pathways found to be significantly enriched for AD risk in Kunkle et al.[78] (GO:48156, tau protein binding) showed significant enrichment ($p=6.44\times10^{-4}$ and $p=2.21\times10^{-3}$ respectively), albeit not withstanding correction for multiple testing. Given that this pathway includes APOE, the enrichment analysis was repeated excluding genes within 1Mb of APOE (a total of 70 genes), with results shown in Supplementary

Table S3. Removing the genes in the APOE region greatly reduces the significance of GO:48156 (p=0.0106), suggesting that its enrichment is mainly due to APOE.

TWAS comprised a total of 44,185 gene-tissue combinations (Supplementary Tables S4 and S5). No TWAS association was significant after correction for the number of tests performed in all genes and tissues combined ($p<1.13\times10^{-6}$, Bonferroni correction for 44,185 tests). Two associations were significant after Bonferroni correction for the number of genes tested in their particular tissue: VN1R108P in GTEx7 hippocampus (p=2.94×10-6) and FAM182B in GTEx7 cerebellum (p=5.51×10-6). For both genes, an increase in gene expression was associated with the presence of psychosis.

SNP-Based Heritability

While earlier studies the AD+P phenotype have shown strong clustering in families and substantial heritability, SNP-based heritability has not been estimated. We estimated it in two ways. First, by analyzing our GWAS statistics using GenomicSEM, SNP-based heritability was estimated at 0.181 ± 0.064 (Chi-square = 8.0, df=1, p = .005). An alternative approach, using the GCTA software, evaluated genotypes genome-wide to determine relationships among the samples and how they partitioned within and between AD+P and AD-P sets. This estimate was 0.312 ± 0.053 (Chi-square = 34.98, df=1, $p = 3.3\times10^{-9}$). The larger estimate probably arises due to greater information contained in estimated genetic relationships, relative to our modestly powered GWAS, although the heritability estimates are not significantly different. The GCTA analysis focused on subjects of European ancestry, genetically determined, to avoid confounding of ancestry.

Genetic Correlation, Polygenic Risk Score, and Risk SNP Analyses

Subjects of European ancestry were also used to estimate genetic correlations of AD+P with select phenotypes available from LD Hub (Table 2). Consistent with clinical observations, AD+P is significantly genetically correlated with “Years of Schooling” (and nearly so with the related phenotype, “Intelligence”) and with “Depressive Symptoms”. In contrast, AD+P was not significantly genetically correlated with AD (Table 2). Nor was AD+P significantly genetically correlated with the two other neurodegenerative disorders evaluated, ALS and Parkinson disease (Table 2).

We previously found a significant relationship between risk for AD+P and schizophrenia.[28] Specifically, we genotyped 94 of 128 SNPs that showed genome-wide-significance for association with schizophrenia in a sample of AD+P subjects. We constructed a predictive score for schizophrenia risk from these SNPs, then assessed whether this score predicted AD+P status in the AD sample. There was a significant negative correlation between the risk score for schizophrenia and AD+P status, which we then replicated by genotyping 60 of the 94 risk SNPs in an independent sample. Now, using SNPs from across the genome and a larger set of AD subjects, results from LD HUB show a negative, but non-significant, genetic correlation with schizophrenia, while showing a negative and significant genetic correlation with bipolar disorder (Table 2). In fact, no SNP with p value $<10^{-4}$ for association with psychosis in AD had a p value $<10^{-5}$ in the 108 loci associated with schizophrenia.[79]

Because bipolar disorder and schizophrenia are genetically correlated, we next asked if our original result for the 94 SNPs could be explained by an overlap of risk SNPs for schizophrenia and bipolar disorder. To do so, we tested whether the odds ratios for association of these SNPs for these disorders[69,79] were independent. They were not (Supplementary Figure 2), 91 of 94 SNPs had odds ratios exceeding one for both disorders, whereas 47 were expected under independence (sign test, $p = 5.8\times10^{-20}$).

Given the somewhat surprising results for the genetic correlations of AD+P with schizophrenia, bipolar disorder and AD, we examined whether PRS -scores for each of these disorders could differentiate AD+P versus AD-P subjects. In agreement with the genetic correlation, the PRS_{BP} differentiated AD+P from AD-P, whereas PRS_{SZ} showed little ability to differentiate AD+P from AD-P subjects (Table 3).

By contrast, the PRS_{AD} did not agree with the genetic correlation of AD and AD+P from LD Hub. PRS_{AD} significantly predicted AD+P status, in the direction of increased risk for AD+P. Even when we removed the SNP representing the APOE locus, predictions remained positive. Yet the genetic correlation between our AD+P GWAS and Alzheimer's disease, as estimated in LD HUB, was negative, although non-significant. Notably, PRS_{AD} was built on results from a larger AD GWAS[42] than LD Hub uses.[45] Based on our analyses, we believe sample size explains the difference. For example, when we analyzed the genetic correlation of the two AD studies in LD Hub, the genetic correlation was 0.9 with standard error of 0.11; likewise, when we computed two PRS from these two AD GWAS, the results were in qualitative agreement in their ability to distinguish AD+P and AD-P.

Because "uncorrelated" is not the same as "independent", we evaluated one more dimension of these data. Specifically, we evaluated the GWAS-significant SNPs (GWAS SNPs) for schizophrenia,[68] bipolar disorder,[69] and AD[42] to determine whether they also had signal in our AD+P GWAS. We approached this question in two ways. First, we queried the GWAS SNPs to determine if their p-values for AD+P were less than 10^{-4}: 11 crossed the threshold, all in the *APOE* locus and all associated with AD. Next, we reasoned that if some GWAS SNPs also generated risk for or protection from AD+P, whereas others did not, then those AD+P statistics would be represented by a mixture of distributions. We found support for a mixture of

distributions for schizophrenia and separately for AD (Supplementary Figures S6-S8), while for bipolar disorder there were too few independent GWAS SNPs to have any confidence in our results (See Supplementary Methods for details). Curiously, while AD GWAS SNPs were consistent in their effects on AD and AD+P, effects of schizophrenia GWAS SNPs were not. Instead, risk alleles for schizophrenia could impart risk or protection for AD+P (Supplementary Methods and Figure S9). In addition, using the mixture model results, we identified a set of SNPs likely to affect risk to AD+P and either AD or schizophrenia (Supplementary Table S6).

Discussion

We identified evidence of genome-wide significant association with psychosis risk in AD at SNPs within *ENPP6*, and in the 3'-UTR of an alternatively spliced transcript of *SUMF1*. Exploration of multiple data sets did not reveal any current evidence linking the SNPs at these loci to variation in expression of *ENPP6, SUMF1,* or other genes. Similarly, although the alternatively spliced SUMF1-204 transcript is expressed in brain,[80] AD+P risk SNPs in the SUMF1 locus were not associated with brain expression of SUMF1-204 (S. Sieberts, Personal Communication). Nor were SNPs at these loci linked to other potential genetic mechanisms, such as variation in epigenetic modifications. However, we note that for *SUMF1*, the locus is located in the 3'-UTR, a region that often serves a substantial role in regulating protein levels via post-transcriptional mechanisms.[81]

ENPP6 encodes a glycerophosphodiesterase that is highly expressed in new oligodendrocytes as they differentiate from their precursors.[82] Recent data in mice have demonstrated that differentiation of oligodendrocytes from their precursors (as indicated by increased *ENPP6*

mRNA expression) is a necessary component of early,[83] i.e. synaptic,[84] phases of new (motor) learning. ENPP6 protein can be expressed both on the myelin membrane and as a soluble form that is found extracellularly.[85,86] ENPP6 acts as a hydrolase that severs choline from substrates, including lysophosphatidylcholine, glycerophosphorylcholine, and sphingosylphosphorylcholine.[86] Of these, it has highest catalytic efficiency towards sphingosylphosphorylcholine,[85] releasing both sphingosine and phosphocholine. Sphingosine is phosphorylated to generate sphingosine-1-phosphate, which signals via the g-protein-coupled sphingosine-1-phosphate receptor (S1PR1). It is of some interest, therefore, that the S1PR1 modulator, fingolimod,[87] has been previously shown to increase excitatory synaptic transmission[88] and improve psychosis-associated behaviors in a genetic animal model of β-amyloid overproduction.[89]

The locus on chromosome 3 maps to introns spanning the 3'-UTR of an alternatively spliced transcript of *SUMF1*. *SUMF1* encodes formylglycine-generating enzyme, which serves as a master activator of lysosomal sulfatases by converting conserved cysteines to formylglycine in their active sites. As a consequence, genetic disruption of *SUMF1* leads to a multiple sulfatase deficiency syndrome.[90,91] Importantly, the transcript of *SUMF1* (SUMF1-204, ENST00000448413.5) within which our locus is located encodes an isoform of formylglycine-generating enzyme (isoform 3, Uniprot Accession Q8NBK3-3) lacking the enzymatically active Cys341 residue.[92] The functional consequences of this change are not established, but would be anticipated to reduce or eliminate the primary enzymatic function. The function of the novel sequence that replaces the c-terminal of formylglycine-generating enzyme in isoform 3 is also not known, and BLAST of this sequence against the UNIPROT database does not identify homologous proteins. Nevertheless, speaking to the potential functional impact in AD+P, ENST00000448413.5 is detectable in cerebral cortex.[80]

Recently, an appreciation of how lysosomal storage dysfunction also leads to impaired autophagy has emerged.[93] It is thus not surprising, therefore, that selective depletion of SUMF1 in either astrocytes or neurons results in neurodegeneration.[94] How alterations in function of formylglycine-generating enzyme due to a potential change in levels of isoform 3 may modify the course of AD through these mechanisms and thus result in the AD+P phenotype remains speculative. We have previously shown, however, that preservation of synaptic protein levels in the context of AD neuropathology is associated with reduced psychosis risk.[89] Thus, genetic alterations that impact degradation of synaptic proteins by the lysosome to autophagosome pathway are likely to influence risk of psychosis.

We and others[34] have previously evaluated the association of psychosis in AD with *APOE* risk haplotype ε4, finding inconsistent evidence of association.[34] Our current findings, obtained from by far the largest cohort to address this question, shed further light on these prior observations. We found that SNPs within *APOE* demonstrate gene-based significant association with AD+P, and that this association appears attributable to the presence of the ε4 *haplotype* itself, without a detectable contribution from other SNPs. Because the impact of ε4 on AD+P risk is not large, increasing the odds by 1.21, prior inconsistent associations with AD+P likely resulted from the much smaller sample sizes in all prior studies.

APOE ε4 has been shown to increase the accumulation of amyloid β and phosphorylated tau, and, even in the absence of Aβ overproduction, lead to reductions in dendritic markers and synaptic proteins.[95] For example, we have shown that human ε4 carriers and mice with targeted replacement of ε4 had down-regulation of numerous glutamate signaling and synaptic proteins.[96] Increased phosphotau and reduced synaptic proteins (but not altered amyloid β accumulation) have all been associated with psychosis in AD.[97] Future human and animal

model studies of ε4 that control for the contribution of other loci to the genetic risk for AD+P would be helpful in determining the relative contributions of these mechanisms to AD+P.

We previously identified, and independently replicated, an inverse association between polygenic risk for schizophrenia, defined by a limited set of schizophrenia risk SNPs[79], and risk for psychosis in AD.[28] It was thus somewhat surprising that we saw a non-significant genetic correlation between these two disorders when considering both a larger set of SNPs and a substantially enlarged cohort of AD subjects with and without psychosis. Instead, we identified a negative genetic correlation with risk for bipolar disorder, a disorder that has substantial genetic overlap with schizophrenia. Because our prior analyses relied on a subset of SNPs significantly associated with risk for schizophrenia, and this set also shows enrichment for affecting risk for bipolar disorder (Supplementary Figure 2), this overlap probably explains the discrepancy we now observe between our earlier results and the current results for genetic correlations. However, the lack of genetic correlation of AD+P with schizophrenia conceals an underlying complexity. We observed that schizophrenia risk SNPs evidenced significant mixture regarding AD+P risk, such that risk alleles for schizophrenia could impart risk or protection for AD+P.

In contrast, we observed a positive genetic correlation between risk for depressive symptoms and AD+P risk, consistent with clinical observations of co-occurrence of depressive and psychotic symptoms in AD patients,[5,13-15] and evidence that antidepressant medications may have some effect in reducing psychotic symptoms in AD.[98,99] We also observed a significant negative genetic correlation of educational level with psychosis risk in AD and a similar pattern, but not quite significant relationship with intelligence. Greater cognitive impairment increases the risk for psychosis in AD; moreover, psychosis in AD is further associated with a more rapid rate of cognitive decline[2-9] (see also review in[100]). The current findings extend these earlier observations, by showing genetic overlap with measures that may be better construed as

indicative of cognitive reserve, as they reflect early life cognitive attainment. Cognitive reserve has long been recognized as protective against developing a degree of cognitive and functional impairment sufficient to lead to a diagnosis of AD.[101] However, somewhat counter-intuitively, once AD is diagnosed, individuals with greater cognitive reserve decline more rapidly.[101] Thus, the genetic correlations we observed may point to a biology underlying the presence of greater cognitive impairment in AD, but not the more rapid decline associated with AD+P.

The above findings are subject to several potential limitations. Although our analysis is the largest GWA study of AD+P to date, it is nevertheless modest in sample size in comparison to studies of related complex traits.[78,79] As our heritability results show, a substantial increase in sample size will identify many additional loci as having a significant association with psychosis risk in AD. Similarly, increased sample size is needed to provide the necessary power to identify genes, transcripts, genetically correlated traits, and pathways in the corresponding analyses that derive from the SNP-based associations.

One of our GWAS-significant SNPs, rs201109606, falls in a genomic region marked as simple repeats. Perhaps because the SNP is difficult to impute, it did not pass QC for some of our data. Nonetheless, the largest two of the four datasets contribute to this result and the estimates of the odds ratios for the two data sets are remarkably similar, 0.684 and 0.637. Moreover, other SNPs at this locus also support the findings (Supplementary Table S1), although those associations are not quite GWAS significant. Thus, this result requires replication. For additional discussion of other findings and potential limitations, see Supplementary Material.

Currently established treatments for psychosis in AD patients are suboptimal, perhaps reflecting in part that these treatments were not derived to prevent or reverse an identified biology of AD+P.[100] The development of effective, specific, therapeutic targets will therefore require as a

first step delineating this underlying biology. Our study provides the first unbiased evidence of association of specific genetic loci with psychosis in AD and, can thus serve as an initial road map to AD+P biology. These findings, in conjunction with available functional genomic and post-mortem data, provide multiple links to mechanisms influencing synaptic function as contributors to psychosis in AD.

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Author Contributions

Each author is expected to have made substantial contributions:

1. to the conception **or** design of the work; RAS, Bernie, Ilyas, Clive, Oscar
2. to the acquisition, analysis, **or** interpretation of data; MAAD-S, LK, BC, JCH, EAW, LM, RS, IH, SM-G, LT, MB, EA-M, SV, YL, BH, DA, GS, SB, AR, IS, HKS, BE, ES, OAA, SD, LA, DS, BB, DA, GF, PM, AS, DDR, AP, GP, JW, RM, TF, AR, CB, PH, OLL, MIK, BD, RAS
3. to the creation of new software used in the work; YL
4. have drafted the manuscript or substantively revised it. MAAS-S, JCH, LK, BC, LM, CB, PH, MIK, BD, RAS

Each author must have approved the submitted version (and any substantially modified version that involves the author's contribution to the study) AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally

involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Conflicts of Interest

Yushi Liu and Basavaraj Hooli are currently employed by and holding stock in Eli Lilly and Company

Dr. Ballard reports grants and personal fees from Acadia pharmaceutical company, grants and personal fees from Lundbeck, personal fees from Roche, personal fees from Otsuka, personal fees from Biogen, personal fees from Eli Lilly, personal fees from Novo Nordisk, personal fees from AARP, grants and personal fees from Synexus, personal fees from Exciva, outside the submitted work.

Oscar Lopez served as a consultant for Grifols, Inc.

Dr Saltvedt has been investigator in the drug trial Boehringer-Ingelheim 1346.0023

Ole A. Andreassen: Consultant to HEALTHLYTIX, speaker honoraria from Lundbeck.

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Figure Legends

Figure 1. SNP associations with psychosis in AD. A. Manhattan plot. The x axis shows genomic position for autosomes and the X chromosome. The y axis shows statistical significance as −log10 (P). Each point represents an analyzed SNP. The dashed line represents the threshold for genome-wide significance ($p = 5 \times 10^{-8}$). **B-C. Zoom plots of the two genome-wide significant loci.** The x axis shows genomic position. The left y axis shows statistical significance as −log10 (P). Each point represents an analyzed SNP, coded by degree of linkage dysequilibrium relative to the most significant SNP within the locus. Recombination rate through the region is shown on the right y axis. LD: linkage disequilibrium; cM: centimorgans; Mb: megabase

Table 1A. Subject Characteristics.

	AD-P 6,872 (55.8%) **N (%) or Mean (SD)**	**AD+P** 5,445 (44.2%) **N (%) or Mean (SD)**	**Total** 12,317 (100.0%) **N (%) or Mean (SD)**
Female	4,008 (58.3)	3,649 (67.0)	7,657 (62.2)
Age of Onset[1]	74 (8.3)	73.4 (8.0)	73.8 (8.2)
Age at Consent	75.6 (7.0)	77.0 (6.9)	76.2 (7.0)
Age at Last Visit[1]	80.5 (8.1)	81.3 (7.7)	80.9 (7.9)
Last MMSE[1]	16.0 (6.5)	13.7 (6.8)	15.0 (6.8)
Last CDR[1]			
0.0	2 (0.0)	5 (0.1)	7 (0.1)
0.5	244 (3.8)	186 (3.8)	430 (3.8)
1.0	2,469 (38.4)	967 (19.6)	3,436 (30.2)
2.0	1,560 (24.3)	1,586 (32.2)	3,146 (27.7)
3.0	986 (15.3)	1,340 (27.2)	2,326 (20.5)
4.0	759 (11.8)	482 (9.8)	1,241 (10.9)
5.0	410 (6.4)	363 (7.4)	773 (6.8)

AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; MMSE: Mini mental state exam; CDR: CDR® Dementia Staging Instrument; [1]Data not available for some subjects/source programs; see **Supplementary Tables 3-10** for details.

Table 1B. Sample size for each cohort contributing to the meta-analysis.

GWA	**Phase 1**		**Phase 2**		**GR@ACE**		**NEXGENS**		**Total**	
Diagnosis	**AD-P**	**AD+P**	**AD-P**	**AD+P**	**AD-P**	**AD+P**	**AD-P**	**AD+P**	**AD-P**	**AD+P**
ALL	3529	3525	1045	495	1646	762	652	663	6872	5445
EUR	2665	2732	833	394	1646	762	652	663	5796	4551

GWA: Genome-wide association; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; EUR: European ancestry

Table 2. Genetic correlations (r_g) of psychosis in Alzheimer disease with selected relevant phenotypes. Correlations were obtained from LD Hub.[66] Phenotypes in bold were chosen, a priori, based on phenotypic or genetic (schizophrenia, bipolar disorder) analyses.

Phenotype	r_g	Se	z	p-value
Alzheimer disease	-0.374	0.321	-1.168	0.243
Amyotrophic lateral sclerosis	-0.307	0.300	-1.021	0.307
Parkinson disease	0.142	0.186	0.763	0.446
Years of schooling	-0.312	0.111	-2.816	0.005
Intelligence	-0.200	0.121	-1.650	0.099
Schizophrenia	-0.094	0.081	-1.164	0.244
Depressive symptoms	0.327	0.141	2.316	0.021
Bipolar disorder	-0.287	0.145	-1.976	0.048

Table 3. Prediction of psychosis in Alzheimer disease by polygenic risk scores built using GWAS results for Bipolar disorder, Schizophrenia, and Alzheimer disease and the pruning and thresholding approach.

Bipolar Disorder

P Value Cut Off	N	OR	l95 OR	u95 OR	P Value	R^2
0.00000005	22	0.968	0.928	1.010	1.293E-01	3.304E-03
0.0001	785	0.961	0.921	1.003	6.525E-02	3.468E-03
0.001	3112	0.980	0.938	1.023	3.499E-01	3.091E-03
0.01	14748	0.959	0.918	1.002	6.404E-02	3.473E-03
0.1	79818	0.950	0.908	0.994	2.499E-02	3.711E-03
0.2	134250	0.955	0.913	0.999	4.466E-02	3.563E-03
0.3	182119	0.953	0.911	0.997	3.505E-02	3.624E-03
0.4	225630	0.957	0.915	1.001	5.550E-02	3.509E-03
0.5	265136	0.958	0.916	1.002	5.984E-02	3.490E-03

Schizophrenia

P Value Cut Off	N	OR	l95.OR	u95.OR	P Value	R^2
0.00000005	329	1.051	1.008	1.096	2.063E-02	8.018E-04
0.0001	3161	1.012	0.970	1.056	5.738E-01	4.733E-05
0.001	8488	1.009	0.967	1.052	6.910E-01	2.363E-05
0.01	26064	1.004	0.962	1.048	8.440E-01	5.795E-06
0.1	99775	1.006	0.963	1.052	7.824E-01	1.141E-05
0.2	153878	1.007	0.963	1.053	7.583E-01	1.416E-05
0.3	198913	1.009	0.965	1.055	6.985E-01	2.244E-05
0.4	238902	1.011	0.967	1.057	6.236E-01	3.602E-05
0.5	274264	1.013	0.969	1.059	5.680E-01	4.876E-05

Alzheimer Disease

P Value Cut Off	N	OR	l95.OR	u95.OR	P Value	R^2
0.00000005	63	1.088	1.043	1.135	9.750E-05	2.275E-03
0.0001	488	1.048	1.005	1.093	2.847E-02	7.182E-04
0.001	1962	1.059	1.015	1.105	7.760E-03	1.061E-03
0.01	12301	1.069	1.025	1.115	1.986E-03	1.432E-03
0.1	83722	1.095	1.050	1.142	2.301E-05	2.686E-03
0.2	144621	1.096	1.051	1.143	2.115E-05	2.710E-03
0.3	195758	1.096	1.051	1.143	2.073E-05	2.716E-03
0.4	239694	1.088	1.043	1.134	9.392E-05	2.285E-03
0.5	277645	1.088	1.043	1.135	8.795E-05	2.304E-03

P Value Cut Off: GWAS p-value threshold used for SNP included in calculating the PRS; N: number of SNPs meeting the threshold; OR: Odds ratio; l95 OR: lower limit of the 95%

confidence interval for OR; u95 OR: upper limit of the 95% confidence interval for OR; R^2: partial pseudo-R^2 attributable to the PRS after adjusting for the first 2 ancestry eigenvectors.

URLs

METAL http://csg.sph.umich.edu/abecasis/metal/index.html

GemTools http://www.compgen.pitt.edu/GemTools/GemTools.htm

PLINK https://www.cog-genomics.org/plink2/

NCBI RS names https://ftp.ncbi.nih.gov/snp/redesign/latest_release/VCF/

LD-Hub: http://ldsc.broadinstitute.org/~~ldhub~~LD Hub/

Sanger Imputation Service: https://imputation.sanger.ac.uk

Psychiatric Genetics Consortium: https://www.med.unc.edu/pgc/

Imputation preparation: https://www.well.ox.ac.uk/~wrayner/tools/

CMC/AMP-AD eQTL Meta-analysis: https://www.synapse.org/#!Synapse:syn16984815

NCBI gene2go file: ftp://ftp.ncbi.nlm.nih.gov/gene/DATA/

Reactome: https://reactome.org/download-data

Gene Ontology: http://geneontology.org/docs/download-ontology/

Molecular Signatures Database: https://www.gsea-msigdb.org/gsea/msigdb/index.jsp

R package qvalue: http://github.com/jdstorey/qvalue

LD Score Regression (LDSC) software : v1.0.0 : https://github.com/bulik/ldsc

HapMap 3 https://www.sanger.ac.uk/resources/downloads/human/hapmap3.html

Common mind consortium: https://www.nimhgenetics.org/resources/commonmind

FUSION software http://gusevlab.org/projects/fusion/

SUPPLEMENTARY RESULTS, METHODS, DISCUSSION, AND ACKNOWLEDGMENTS

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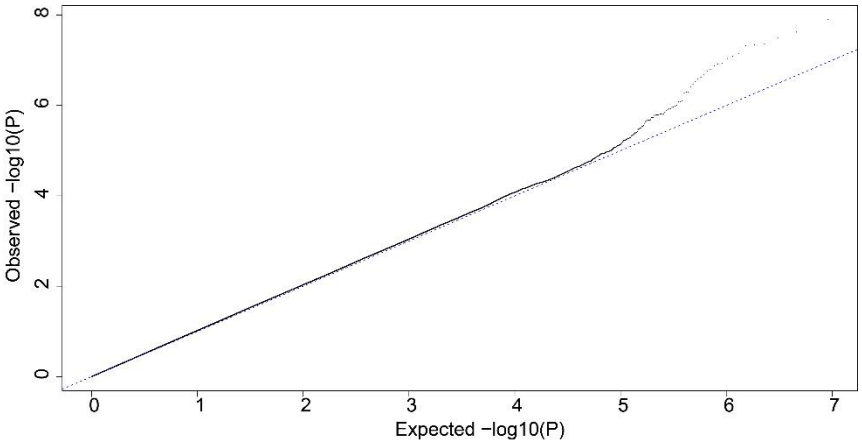
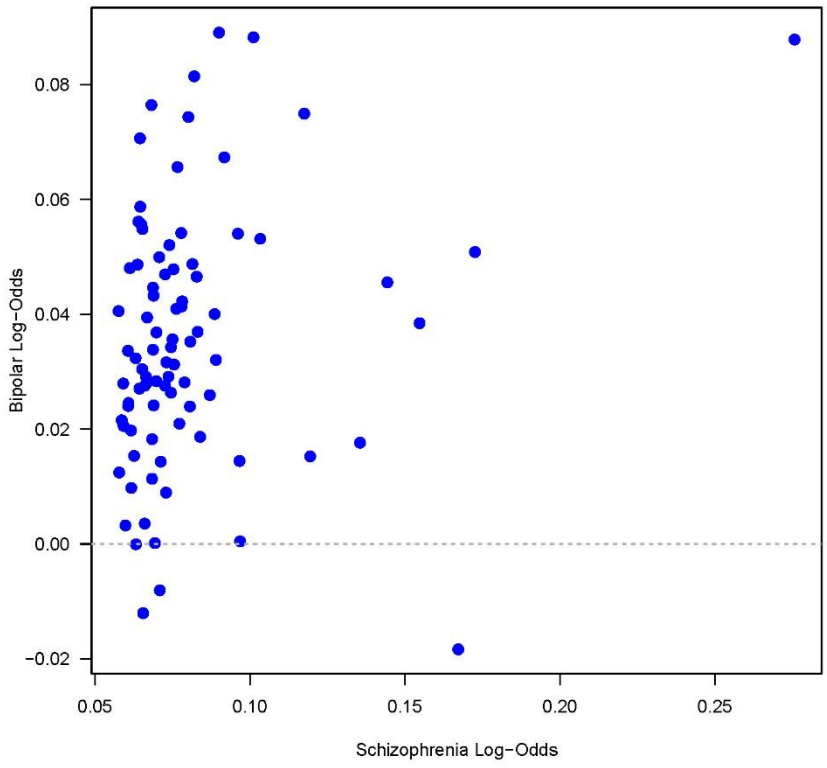
1. RESULTS- SUPPLEMENTARY FIGURES 1 & 2



Supplementary Figure 1. Observed versus expected -log$_{10}$ probabilities of statistics for genome-wide association with Alzheimer disease without versus with psychosis. Genomic control estimate,[1] GC=1.03, indicating there is no evidence for confounding by ancestry.



Supplementary Figure 2. Log of the odds ratios of 94 SNPs showing significant association with schizophrenia[2] versus their odds ratios for association with bipolar disorder.[3] Ninety-one of 94 SNPs had odds ratios exceeding one for both disorders, whereas 47 were expected under independence (sign test, $p = 5.8 \times 10^{-20}$).

2. METHODS- SUBJECT RECRUITMENT AND PSYCHOSIS CHARACTERIZATION

Overview. Subjects included in this GWA meta-analysis were provided from 8 different source programs: the Fundació ACE Barcelona Alzheimer Treatment and Research Center (ACE/GR@ACE), a consortium of National Institute on Aging Alzheimer Disease Centers (ADC), Eli Lilly and Company (LILLY), the Norwegian, Exeter and King's College Consortium for Genetics of Neuropsychiatric Symptoms in Dementia (NEXGENS), the National Institute on Aging's Late Onset Alzheimer's Disease Family Study (NIA-LOAD), the National Institute of Mental Health Genetics Initiative AD Cohort (NIMH), the University of Pittsburgh Alzheimer Disease Research Center (PITT ADRC), and the MRC Genetic Resource for Late-onset Alzheimer's disease as part of the Genetic and Environmental Risk in AD Consortium (UK-Cardiff). Collection of clinical data and genetic samples were approved by each site's local Institutional Review Board or Medical Ethics Committee, as appropriate. Methods used for selection of subjects from each program source are described in sections 2.1-2.8.

Phenotype data were provided to us by each institution. A total of 12,317 samples were used in this analysis, and their psychosis status is shown in **Supplementary Table S7**.

Supplementary Table S7. Psychosis Status of Subjects by Cohort.

Source	AD-P N (%)	AD+P N (%)	Total N (%)
ACE/GR@ACE	1,841 (67.8)	875 (32.2)	2,716 (22.1)
ADC	2,017 (67.8)	957 (32.2)	2,974 (24.1)
LILLY	1,360 (62.5)	815 (37.5)	2,175 (17.7)
NEXGENS	652 (49.6)	663 (50.4)	1,315 (10.7)
NIA-LOAD	168 (25.0)	505 (75.0)	673 (5.4)
NIMH	157 (26.5)	435 (73.5)	592 (4.8)
PITT ADRC	405 (31.7)	874 (68.3)	1,279 (10.4)
UK-Cardiff	272 (45.9)	321 (54.1)	593 (4.8)
TOTAL	**6,872 (55.7)**	**5,445 (44.3)**	**12,317 (100.0)**

AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis

2.1. Subject Recruitment and Psychosis Characterization – ACE/GR@ACE. Subjects in the ACE sample and the GR@ACE Stage I cohort were recruited from Fundació ACE Institut Català de Neurociències Aplicades, an Alzheimer's disease center serving the population of central Barcelona, Spain. All subjects received a structured neurological evaluation and cognitive testing as previously described.[4-6] They met criteria for a primary diagnosis of either possible or probable AD according to the National Institute on Aging and Alzheimer's Association's 2011 guidelines for defining AD,[7] as determined by a multidisciplinary working-group. Any subjects with a primary diagnosis of Dementia with Lewy bodies[8] were excluded.

Subjects were rated for psychotic symptoms on a validated Spanish language version of the Neuropsychiatric Inventory Questionnaire (NPI-Q[9]). Ratings of psychotic symptoms were performed at initial and follow up visits. The presence of psychosis at a visit was defined by either delusions or hallucinations of moderate or greater severity, or by both delusions and hallucinations of mild severity. Subjects were classified as AD+P if they were rated as having psychosis at any visit. For subjects without psychosis to be classified as AD-P, they had to have a score of 0 on the NPI-Q psychosis items at all visits and a last observed Mini Mental State Exam[10] score $\leq$ 20 or a CDR® Dementia Staging Instrument[11] score $\geq$ 1. See **Supplementary Table S8** for a summary of clinical and demographic data for these subjects.

2.2. Subject Recruitment and Psychosis Characterization – ADC. Recruitment for the ADC cohort has been described previously.[12-15] In brief, AD centers throughout the United States, each of which had received approval by their institutional review board, participated and provided data on subjects diagnosed with primary diagnoses of possible or probable AD.[7] Any subjects with a primary diagnosis of Dementia with Lewy bodies[8] were excluded. When available, subjects' autopsy data was also reviewed. Subjects were excluded if they did not have AD pathology, if AD pathology was rated as having a low likelihood of serving as the cause of dementia per NIA-Regan Institute Criteria,[16] or if the AD pathology was rated as having an intermediate likelihood of serving as the cause of dementia and other pathologies that could be the cause of dementia, such as Lewy Body or cerebrovascular disease, were present.

Phenotype data on ADC subjects were provided by the National Alzheimer's Coordinating Center (NACC) in three separate phenotype data freezes (March 2018, March 2019, and September 2019). These freezes included data for subjects' whose UDS visits were conducted between June 2005 and August 2019. Subjects were rated for psychotic symptoms on the NPI-Q[17] at initial and follow up visits. The presence of psychosis at a visit was defined by either delusions or hallucinations of moderate or greater severity, or by both delusions and hallucinations of mild severity. Subjects were classified as AD+P if they were rated as having psychosis at any visit. For subjects without psychosis to be classified as AD-P, they had to have scores of 0 on the NPI-Q psychosis items at all visits and either a last observed Mini Mental State Exam score $\leq$ 20 or a CDR® Dementia Staging Instrument score $\geq$ 1. See **Supplementary Table S9** for a summary of clinical and demographic data for these subjects.

2.3. Subject Recruitment and Psychosis Characterization – LILLY: Subjects participated in one of eight independent drug trials conducted by Eli Lilly and Company. Registration details of each of these trials is available via ClinicalTrials.gov:
LFAN: https://clinicaltrials.gov/ct2/show/NCT00594568
LFBC: https://clinicaltrials.gov/ct2/show/NCT00762411
LZAM: https://clinicaltrials.gov/ct2/show/NCT00905372
LZAN: https://clinicaltrials.gov/ct2/show/NCT00904683
LEAM: https://clinicaltrials.gov/ct2/show/NCT00051909
LEAQ: https://clinicaltrials.gov/ct2/show/NCT00843518
LYCG: https://clinicaltrials.gov/ct2/show/NCT00191009
Expedition 3 (LZAX): https://clinicaltrials.gov/ct2/show/NCT01900665.

Briefly, subjects were enrolled if they were diagnosed with probable AD.[18] Subjects were assessed for psychotic symptoms with the Neuropsychiatric Inventory (NPI[19]) The NPI was administered at timepoints and frequencies as specified for each of the included studies. The frequency and severity of each symptom were rated from 0-4 and 0-3, respectively. Frequency and severity scores at each visit were multiplied to give an overall domain score for each symptom ranging from 0-12. Individuals with a delusion or hallucination domain score $\geq$2 or with both delusion and hallucination domain scores equal to 1 at any visit were classified as AD+P. To be classified as AD-P, subjects had to have delusion and hallucination domain scores of 0 at all visits, and a last observed Mini Mental State Exam score $\leq$ 20 or a CDR® Dementia Staging Instrument score $\geq$ 1. See **Supplementary Table S10** for a summary of clinical and demographic data for these subjects.

2.4. Subject Recruitment and Psychosis Characterization –NEXGENS. NEXGENS is a collaboration between the following 5 institutions: University of Exeter, King's College London, Innlandet Hospital Trust, University of Oslo, and Stavanger University Hospital which undertakes secondary analysis of data from Alzheimer's disease patients from cohort studies and patient registries. Data for this study came from the following five program sources: **AddNeuroMed** study; Health and Memory Study in Nord-Trøndelag (**HMS**)[20]; Resource Use and Disease Couse in Dementia (**REDIC**)[21]; Norwegian registry of persons assessed for cognitive symptoms and the Progression of Alzheimer's Disease and Resource Use (**NorCog/PADR**)[22,23]; and from the following outpatient clinics in Italy and Greece (**Italian and Greek Hospital Outpatients)**: Centre for Neurodegenerative Disorders, University of Brescia; IRCCS Casa Sollievo della Sofferenza, Neuropsychiatry Clinic of the Eginition Hospital, Athens. Detail of each program source are in Sections 2.4.1 to 2.4.5.

Diagnosis of AD was performed according to ICD-10 etiological diagnosis, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (**NINCDS-ADRDA**[18]) criteria, or clinical diagnosis by psychiatrist or geriatrician (See details of each institution described below). Individuals with a primary diagnosis of Dementia with Lewy Bodies were excluded. Any cases with a history of bipolar disorder or schizophrenia (except for the HMS study in which no information about psychiatric history was available) were excluded. Dementia severity was assessed in all cohorts by Mini Mental State Examination and the CDR® Dementia Staging Instrument. Psychotic symptoms were assessed by the NPI or the NPI-Q. For the NPI the presence of psychosis at a visit was defined by a calculated (frequency x severity) score for delusions or hallucinations $\geq$ 1 for either delusions or hallucinations. For the NPI-Q, the presence of psychosis at a visit was defined by either delusions or hallucinations of moderate or greater severity, or by both delusions and hallucinations of mild severity. For both NPI and NPI-Q, subjects were classified as AD+P if they were rated as having psychosis at any visit. Subjects were classified as AD-P if they had scores of 0 for delusions and hallucinations at all visits, and a last Mini Mental State Exam score $\leq$20 or a CDR® Dementia Staging Instrument score $\geq$ 1.

2.4.1 The Norwegian registry of persons assessed for cognitive symptoms (NorCog)/The Progression of Alzheimer's Disease and Resource use (PADR). NorCog is a national quality- and research registry collecting extensive clinical data and biobank material at outpatient clinics across Norway. Patients from NorCog included in the current study were recruited from memory clinics, geriatric-, and old-age psychiatric outpatient clinics in three of the four regional health authorities responsible for specialist healthcare in Norway. Participants underwent a comprehensive clinical assessment according to a standardized protocol including verbal interviews of the patient and proxy informant, neurocognitive testing, as well as a psychiatric, physical, and neurological examination. Diagnosis of AD was performed according to the ICD-10 criteria. The PADR study is affiliated to NorCog. PADR follows the same protocol as NorCog but it is a longitudinal observational study with assessments at the time of diagnostic workup (baseline) and follow-up after a mean of 24 months (range 16–37, 80% between 20 and 28 months). Inclusion criteria were MCI or dementia at baseline, living at home, able to give informed consent, and have a proxy informant available. For PADR, the NINCDS-ADRDA were used to diagnose AD. Diagnoses were assigned by the study researchers reviewing all available data from the baseline examination. Cerebrospinal fluid markers were used to support AD diagnosis. Psychosis in NorCog and PADR was assessed by NPI-Q. See **Supplementary Table S11.1** for clinical and demographic data.

2.4.2 Resource Use and Disease Couse in dementia - Nursing Home (REDIC-NH). REDIC-NH participants were recruited at admission to one of 47 nursing homes in 4 counties in Norway. The inclusion was from March 2012 to November 2014. Patients eligible for inclusion in the study were 65 years or older, or younger than 65 years with established dementia, with an expected stay in the NH of more than four weeks. The only exclusion criterion was a life expectancy of less than six weeks. The participants were assessed with the NPI-NH, in addition to several other assessment tools for depression, cognition, ADL function and physical disease. Assessments were carried out at baseline and every 6 months for maximum 2.5 years Based on all available information, AD according to ICD-10 was independently diagnosed by two old age psychiatrists with the possibility of consulting a third specialist, to reach a consensus. Patients were followed up with biannual assessments until death. See **Supplementary Table S11.2** for clinical and demographic data.

2.4.3 Health and Memory Study in Nord-Trøndelag (HMS). HMS participants were recruited from nursing homes in 24 municipalities in one county in middle Norway. Inclusion was between 2010 and 2011. Patients were eligible for inclusion if they had stayed in a nursing home for at least 14 days. Patients were diagnosed by the same method as in REDIC. Psychosis was assessed by NPI. No follow-up assessments were performed. See **Supplementary Table S11.3** for clinical and demographic data.

2.4.4 AddNeuroMed. The AddNeuroMed study involves six cross-European collection study sites; London (United Kingdom), Toulouse (France), Perugia (Italy), Kuopio (Finland), Lodz (Poland), and Thessaloniki (Greece) and has been described previously.[24] Participants were assessed once every three months for 1 year (5 assessments in total) on a battery of neuropsychological and psychiatric measures. Psychosis was

assessed with the NPI. Diagnosis of AD was made according to the NINCDS-ADRDA. See **Supplementary Table S11.4** for clinical and demographic data.

2.4.5 Italian & Greek Hospital Outpatients. For this sample, patient data and samples were collected through outpatient clinics at the Centre for Neurodegenerative Disorders, University of Brescia; IRCCS Casa Sollievo della Sofferenza, and the Neuropsychiatry Clinic of the Eginition Hospital, Athens. Diagnoses of AD mere made according to NINCDS-ADRDA criteria (IRCCS), ICD-10[25] criteria including MRI and CSF biomarkers (Brescia), or DSM-IV[26] criteria (Greece). Psychosis was assessed by NPI. See **Supplementary Table S11.5** for clinical and demographic data.

2.5. Subject Recruitment and Psychosis Characterization – NIA-LOAD. Recruitment for the family-based NIA-LOAD (National Institute of Aging Late Onset Alzheimer Disease) cohort has been described previously.[27,28] In brief, AD centers throughout the US participated, each of which had received approval by their institutional review board. The recruitment criteria included a family with multiple members affected with late onset AD that could provide clinical information and a biological sample for DNA extraction. The proband was required to have a diagnosis of probable[18] or definite[29] AD with onset after 60 years of age. At least one full sibling with definite, probable or possible AD and with onset after 60 years of age was also required. Finally, a third biologically related family member was required who was ≥50 years old if diagnosed as having AD or mild cognitive impairment or was ≥60 years old if unaffected. Family members were required to have had cognitive testing and clinical examination results documenting the classification as unaffected. To be included in the current study, individuals had to have a primary diagnosis of AD. Any subjects with a primary diagnosis of Dementia with Lewy bodies[8] were excluded.

NIA-LOAD subjects were rated for psychotic symptoms on the CERAD behavioral rating scale (CBRS[30]) and the NPI-Q as previously described.[31] Ratings of psychotic symptoms were performed at initial and follow up visits. The presence of psychosis as rated on the CBRS at any visit was defined as described below (see 2.7 **Subject Recruitment and Psychosis Characterization – PITT ADRC**). The presence of psychosis as rated on the NPI-Q at any visit was defined by either delusions or hallucinations of moderate or greater severity, or by both delusions and hallucinations of mild severity. Subjects were classified as AD+P if they were rated as having psychosis on either of the above scales at any visit. For subjects without psychosis to be classified as AD-P, they had to have scores of 0 on all psychosis items on both scales at all visits and a last observed CDR® Dementia Staging Instrument score $\underline{\geq}$ 1. See **Supplementary Table S12** for a summary of clinical and demographic data for these subjects.

2.6. Subject Recruitment and Psychosis Characterization – NIMH. The ascertainment and characterization of the family-based NIMH Genetics Initiative AD Cohort has been previously described.[32] All AD subjects met criteria for possible, probable,[18] or definite[29] AD. Psychotic symptoms were characterized at the time of initial evaluation, and again during follow-up evaluations, by responses to semi-structured interview questions. In a subset of subjects, this assessment was augmented by ratings on the Brief Psychiatric Rating Scale.[33] Subjects were classified as AD+P if they demonstrated either multiple delusions and/or hallucinations at any single evaluation or recurrent delusions and/or hallucinations over time, a phenotype associated with strong heritability.[34] Subjects without delusions or hallucinations at any time point, and with a last observed CDR® Dementia Staging Instrument score $\underline{\geq}$ 1, were classified as AD-P. See **Supplementary Table S13** for a summary of clinical and demographic data for these subjects.

2.7. Subject Recruitment and Psychosis Characterization – PITT ADRC. Subjects were evaluated at the University of Pittsburgh Alzheimer Disease Research Center (**PITT ADRC**), Pittsburgh, PA. All subjects were assessed at baseline with standardized neurological, neuropsychological, and psychiatric evaluations, cognitive testing, laboratory studies and brain imaging as previously described.[14,35-39] Repeat assessments were conducted annually. Subjects included in this analysis had a final clinical diagnosis of possible or probable AD.[18] Any subjects with a primary diagnosis of Dementia with Lewy bodies[8] were excluded. When available, subjects' autopsy data was also reviewed. Subjects were excluded if they did not have AD pathology, if AD pathology was rated as having a low likelihood of serving as the cause of dementia per NIA-Regan Institute Criteria,[16] or if the AD pathology was rated as having an intermediate likelihood of serving as

the cause of dementia and other pathologies that could be the cause of dementia, such as Lewy Body or cerebrovascular disease, were present.

Psychosis was evaluated with the CERAD behavioral rating scale (CBRS).[30] The CBRS was administered at initial and annual visits and in some subjects between annual visits by telephone as previously described.[27,36] Subjects were classified as AD+P if they had any hallucination or delusion symptom (CBRS item # 33-45) for 3 or more days in the previous month at any visit, as previously described.[14,35-39] To be classified as AD-P, AD subjects had to have scores of 0 for all CBRS items #33-45 and have a last observed Mini Mental State Exam score $\leq$20 or a CDR® Dementia Staging Instrument score $\geq$ 1.[14] See **Supplementary Table S14** for a summary of clinical and demographic data for these subjects.

2.8. Subject Recruitment and Psychosis Characterization – UK-Cardiff. The UK-Cardiff subjects were recruited at sites that participated in the the Medical Research Council (MRC) Genetic Resource for AD (Cardiff University; Kings College London; Cambridge University; Trinity College Dublin). Subject recruitment and clinical characterization was as previously described.[40,41] All AD cases met criteria for either probable[18] or definite[29] AD. Any subjects with a primary diagnosis of Dementia with Lewy bodies[8] were excluded.

The NPI was used to assess psychotic symptoms in all cases.[14,40] The frequency and severity of each symptom were rated from 0-4 and 0-3, respectively, and were scored to reflect the worst episode of each symptom over the lifetime of the illness. Frequency and severity scores were multiplied to give an overall domain score for each symptom ranging from 0-12. The NPI was administered at baseline and during follow up visits. Individuals with a delusion or hallucination domain score $\geq$2 or with both delusion and hallucination domain scores equal to 1 at any visit were classified as AD+P. To be classified as AD-P, subjects had to have delusion and hallucination domain scores of 0 at all visits, and a last observed Mini Mental State Exam score $\leq$ 20 or a CDR® Dementia Staging Instrument score $\geq$ 1. See **Supplementary Table S15** for a summary of clinical and demographic data for these subjects.

3. METHODS- INDIVIDUAL PROGRAM SOURCE SUBJECTS' DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Supplementary Table S8. ACE/GR@ACE Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	1,841 (67.8)	875 (32.2)	2,716 (100.0)
Male	584 (31.7)	186 (21.3)	770 (28.4)
Female	1,257 (68.3)	689 (78.7)	1,946 (71.6)
Age of Onset[1]	76.9 (7.7)	77.3 (7.3)	77.0 (7.6)
Age at last visit	82.6 (7.4)	83.7 (6.9)	82.9 (7.3)
Last MMSE[2]	14.4 (6.9)	10.9 (6.1)	13.3 (6.9)
Last CDR[3]			
1.0	180 (9.8)	20 (2.3)	200 (7.4)
2.0	183 (10.0)	69 (7.9)	252 (9.3)
3.0	353 (19.3)	103 (11.8)	456 (16.8)
4.0	729 (39.8)	363 (41.5)	1,092 (40.3)
5.0	388 (21.2)	319 (36.5)	707 (26.1)

ACE: Fundacio Alzheimer Centre Educacional/GR@ACE: Genome Research at Fundacio ACE; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; Age of Onset data not available for 37 subjects, 96 subjects were <60 (range 48-59); [2]MMSE: Mini mental status exam, data not available for 8 subjects; [3]CDR: CDR® Dementia Staging Instrument, data not available for 9 subjects.

Supplementary Table S9. ADC Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	2,017 (67.8)	957 (32.2)	2,974 (100.0)
Male	1,032 (51.2)	427 (44.6)	1,459 (49.1)
Female	985 (48.8)	530 (55.4)	1,515 (50.9)
Age of Onset[1]	72.4 (8.9)	70.9 (9.4)	71.9 (9.1)
Age at last visit	79.8 (8.9)	79.5 (9.0)	79.7 (9.0)
Last MMSE[2]	17.6 (6.9)	15.1 (7.5)	16.8 (7.2)
Last CDR			
0.5	62 (3.1)	43 (4.5)	105 (3.5)
1.0	980 (48.6)	189 (19.7)	1,169 (39.3)
2.0	618 (30.6)	318 (33.2)	936 (31.5)
3.0	357 (17.7)	407 (42.5)	764 (25.7)

ADC: Alzheimer Disease Centers; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; MMSE: Mini mental status exam; CDR: CDR® Dementia Staging Instrument. **[1]**Age of Onset not available for 10 subjects; 208 subjects were <60 (range 35-59); **[2]**Last MMSE not available for 176 subjects.

Supplementary Table S10. LILLY Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	1,360 (62.5)	815 (37.5)	2,175 (100.0)
Male	618 (45.4)	325 (39.9)	943 (43.4)
Female	742 (54.6)	490 (60.1)	1,232 (56.6)
Age of Onset[1]	71.1 (6.6)	70.8 (6.4)	71.0 (6.6)
Age at Last Visit[2]	76.9 (6.6)	76.8 (6.4)	76.9 (6.6)
Age at Consent	71.9 (6.7)	72.2 (6.5)	72.0 (6.6)
Last MMSE[3]	17.7 (4.8)	16.0 (6.1)	17.0 (5.4)
Last CDR[4]			
0.5	114 (9.8)	73 (10.6)	187 (10.1)
1.0	732 (63.2)	268 (38.8)	1,000 (54.1)
2.0	280 (24.2)	274 (39.7)	554 (30.0)
3.0	32 (2.8)	76 (11.0)	108 (5.8)

AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; [1]The LILLY program source was comprised of 8 independent drug trials. Seven of the eight drug trials did not collect data for Age of Onset (N=1,281); for these trials Age at Consent, was used for screening purposes; [2]Age at Last Visit not available for 1,281 subjects; **[3]**MMSE: Mini mental state exam, data not available for 340 subjects; CDR: CDR® Dementia Staging Instrument; **[4]**CDR data not available for 326 subjects.

Supplementary Table S11.1. NEXGENS NorCog/PADR Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	165 (45.0)	202 (55.0)	367 (100.0)
Male	64 (38.8)	76 (37.6)	140 (38.1)
Female	101 (61.2)	126 (62.4)	227 (61.9)
Age at Consent[1]	76.4 (8.7)	77.3 (8.0)	76.9 (8.3)
Age at last visit	76.5 (8.7)	77.5 (8.0)	77.1 (8.3)
Last MMSE[2]	16.9 (3.2)	20.2 (4.7)	18.7 (4.4)
Last CDR[3]			
0.5	17 (12.1)	20 (11.8)	37 (11.9)
1.0	59 (41.8)	82 (48.2)	141 (45.3)
2.0	55 (39.0)	57 (33.5)	112 (36.0)
3.0	10 (7.1)	11 (6.5)	21 (6.8)

NEXGENS: Norwegian, Exeter and King's College Consortium for Genetics of Neuropsychiatric Symptoms in Dementia; NorCog: The Norwegian Registry of Persons Assessed for Cognitive Symptoms; PADR: The Progression of Alzheimer's Disease and Resource Use; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; [1]Unlike the other program sources, Age of Consent was collected for this study; MMSE: Mini mental state exam; [2]MMSE not available for 14 subjects CDR: CDR® Dementia Staging Instrument; [3]CDR not available for 56 subjects

Supplementary Table S11.2. NEXGENS REDIC-NH Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	111 (40.2)	165 (59.8)	276 (100)
Male	40 (36.0)	47 (28.5)	87 (31.5)
Female	71 (64.0)	118 (71.5)	189 (68.5)
Age at Consent[1]	86.4 (6.4)	84.4 (7.5)	85.2 (7.1)
Age at last visit	87.9 (6.7)	86.0 (7.6)	86.6 (7.4)
Last MMSE[2]	12.4 (5.3)	12.6 (7.0)	12.5 (6.3)
Last CDR[3]			
0.5	2 (1.8)	3 (1.8)	5 (1.8)
1.0	19 (17.3)	25 (15.2)	44 (16.1)
2.0	42 (38.2)	56 (34.1)	98 (35.8)
3.0	47 (42.7)	80 (48.8)	127 (46.3)

NEXGENS: Norwegian, Exeter and King's College Consortium for Genetics of Neuropsychiatric Symptoms in Dementia; REDIC-NH: Resource Use and Disease Couse in Dementia- Nursing Home; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; [1]Unlike the other program sources, Age of Consent was collected for this study; MMSE: Mini mental state exam; [2]MMSE not available for 55 subjects; CDR: CDR® Dementia Staging Instrument;[3]CDR not available for 2 subjects

Supplementary Table S11.3. NEXGENS HMS Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	91 (56.2)	71 (43.8)	162 (100.0)
Male	20 (22.0)	19 (26.8)	39 (24.1)
Female	71 (78.0)	52 (73.2)	123 (75.9)
Age at Consent[1]	86.4 (6.0)	86.7 (6.4)	86.5 (6.2)
Age at last visit	86.4 (6.0)	86.7 (6.4)	86.5 (6.2)
Last MMSE	12.4 (6.2)	12.4 (6.0)	12.4 (6.1)
Last CDR[2]			
0.5	5 (5.5)	1 (1.4)	6 (3.7)
1.0	16 (17.8)	12 (16.9)	28 (17.4)
2.0	37 (41.1)	22 (31.0)	59 (36.6)
3.0	32 (35.5)	36 (50.7)	68 (42.2)

NEXGENS: Norwegian, Exeter and King's College Consortium for Genetics of Neuropsychiatric Symptoms in Dementia; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; [1]Unlike the other program sources, Age of Consent was collected for this study; MMSE: Mini mental state exam; CDR: CDR® Dementia Staging Instrument; [2]CDR not available for 1 subject.

Supplementary Table S11.4. NEXGENS AddNeuroMed Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	65 (41.7)	91 (58.3)	156 (100)
Male	24 (36.9)	21 (23.1)	45 (28.8)
Female	41 (63.1)	70 (76.9)	111 (71.2)
Age at Consent[1]	77.0 (7.6)	77.9 (5.8)	77.5 (6.6)
Age at last visit	77.9 (7.5)	78.7 (5.8)	78.3 (6.6)
Last MMSE	15.4 (4.1)	17.6 (6.0)	16.7 (5.4)
Last CDR[2]			
0.5	0 (0)	5 (5.5)	5 (3.3)
1.0	30 (47.6)	34 (37.8)	64 (41.8)
2.0	32 (50.8)	41 (45.6)	73 (47.7)
3.0	1 (1.6)	10 (11.1)	11 (7.2)

NEXGENS: Norwegian, Exeter and King's College Consortium for Genetics of Neuropsychiatric Symptoms in Dementia; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; [1]Unlike the other program sources, Age of Consent was collected for this study; MMSE: Mini mental state exam; CDR: CDR® Dementia Staging Instrument; [2]CDR not available for 3 subjects.

Supplementary Table S11.5. NEXGENS Italian and Greece Hospital Outpatient Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	220 (62.1)	134 (37.9)	354 (100.0)
Male	87 (39.5)	54 (40.3)	141 (39.8)
Female	133 (60.5)	80 (59.7)	213 (60.2)
Age at Consent[1]	77.8 (7.7)	79.0 (6.7)	78.3 (7.4)
Age at last visit	77.8 (7.7)	79.0 (6.7)	78.3 (7.4)
Last MMSE[2]	12.6 (5.3)	11.0 (6.2)	12.0 (5.9)
Last CDR[3]			
0.0	2 (1.0)	2 (1.7)	4 (1.3)
0.5	9 (4.6)	1 (0.9)	10 (3.2)
1.0	72 (36.9)	20 (17.4)	92 (29.7)
2.0	84 (43.1)	52 (45.2)	136 (43.9)
3.0	28 (14.4)	40 (34.8)	68 (21.9)

NEXGENS: Norwegian, Exeter and King's College Consortium for Genetics of Neuropsychiatric Symptoms in Dementia; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; [1]Unlike the other program sources, Age of Consent was collected for this study; MMSE: Mini mental state exam; [2]MMSE not available for 2 subjects; CDR: CDR® Dementia Staging Instrument; ;[3]CDR not available for 44 subjects.

Supplementary Table S12. NIA-LOAD Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	168 (25.0)	505 (75.0)	673 (100.0)
Male	78 (46.4)	171 (33.9)	249 (37.0)
Female	90 (53.6)	334 (66.1)	424 (63.0)
Age of Onset[1]	74.3 (8.0)	73.6 (7.4)	73.8 (7.6)
Age at last visit[2]	82.6 (7.6)	84.9 (8.3)	84.4 (8.2)
Last CDR[3]			
0.0	0 (0.0)	3 (0.8)	3 (0.5)
0.5	0 (0.0)	17 (4.4)	17 (3.1)
1.0	66 (39.3)	61 (15.8)	127 (22.9)
2.0	39 (23.2)	88 (22.8)	127 (22.9)
3.0	63 (37.5)	216 (56.0)	279 (50.4)
4.0	0 (0.0)	1 (0.3)	1 (0.2)

NIA-LOAD: National Institute of Aging Late-onset Alzheimer disease; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; CDR: CDR® Dementia Staging Instrument. [1]AOO not available for 10 subjects, <60 for 16 subjects (range=48-58). [2]Age at last visit not available for 4 subjects. [3]CDR not available for 119 subjects.

Supplementary Table S13. NIMH Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	157 (26.5)	435 (73.5)	592 (100.0)
Male	54 (34.4)	105 (24.1)	159 (26.9)
Female	103 (65.6)	330 (75.9)	433 (73.1)
Age of Onset[1]	71.3 (8.8)	72.0 (7.7)	71.8 (8.0)
Age at Last Visit	79.7 (9.2)	81.0 (7.1)	80.6 (7.7)
Last CDR			
1.0	37 (23.6)	41 (9.4)	78 (13.2)
2.0	38 (24.2)	97 (22.3)	135 (22.8)
3.0	32 (20.4)	156 (35.9)	188 (31.8)
4.0	28 (17.8)	97 (22.3)	125 (21.1)
5.0	22 (14.0)	44 (10.1)	66 (11.1)

NIMH: National Institute of Mental Health; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; CDR: CDR® Dementia Staging Instrument. [1]Age of Onset<60 for 37 subjects (range=41-59)

Supplementary Table S14. PITT ADRC Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	405 (31.7)	874 (68.3)	1,279 (100.0)
Male	166 (41.0)	288 (33.0)	454 (35.5)
Female	239 (59.0)	586 (67.0)	825 (64.5)
Age of Onset	72.7 (6.5)	73.1 (6.4)	72.9 (6.4)
Age at last visit	78.4 (6.5)	80.4 (6.3)	79.8 (6.4)
Last MMSE[1]	17.0 (5.6)	13.2 (6.1)	14.4 (6.2)
Last CDR[2]			
0.5	34 (8.4)	21 (2.4)	55 (4.3)
1.0	225 (55.6)	198 (22.8)	423 (33.2)
2.0	123 (30.4)	459 (52.8)	582 (45.6)
3.0	21 (5.2)	171 (19.7)	192 (15.1)
4.0	2 (0.5)	21 (2.4)	23 (1.8)

PITT ADRC: University of Pittsburgh Alzheimer Disease Research Center; AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; [1]MMSE: Mini mental state exam, data not available for 21 subjects; [2]CDR: CDR® Dementia Staging Instrument, data not available for 4 subjects.

Supplementary Table S15. UK-Cardiff Subject Characteristics

	AD-P N (%) or Mean (SD)	AD+P N (%) or Mean (SD)	Total N (%) or Mean (SD)
Sex	272 (45.9)	321 (54.1)	593 (100.0)
Male	97 (35.7)	77 (24.0)	174 (29.3)
Female	175 (64.3)	244 (76.0)	419 (70.7)
Age of Onset[1]	76.1 (6.5)	76.0 (7.2)	76.0 (6.9)
Age at last visit[2]	81.7 (6.7)	83.1 (6.6)	82.4 (6.7)
Last MMSE[3]	11.9 (7.4)	9.5 (8.0)	10.7 (7.8)
Last CDR[4]			
0.5	1 (1.1)	2 (1.9)	3 (1.5)
1.0	53 (57.0)	17 (16.0)	70 (35.2)
2.0	29 (31.2)	53 (50.0)	82 (41.2)
3.0	10 (10.8)	34 (32.1)	44 (22.1)

UK-Cardiff: MRC Genetic Resource for Late-onset Alzheimer's disease as part of the Genetic and Environmental Risk in AD Consortium AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; MMSE: Mini mental state exam; CDR: CDR® Dementia Staging Instrument; [1]Age of Onset not

available for 1 subject; [2]Age at last visit not available for 8 subjects; [3]MMSE not available for 38 subjects; [4]CDR not available for 394 subjects because it was instituted later in the data collecting process.

4. METHODS- GENOTYPING

Overview. For subjects selected for this study based on the above described phenotypic criteria, program sources provided us with blood samples (ACE/GR@ACE), DNA samples (PITT ADRC, UK-Cardiff, NIA-LOAD, ADC, NIMH), and/or single nucleotide polymorphism array data (ACE/GR@ACE, ADC, LILLY, NIA-LOAD). Additionally, NEXGENS provided summary GWA statistics for the comparison of AD-P and AD+P. Blood and DNA samples that were supplied to us were genotyped at the Center for Applied Genomics at The Children's Hospital of Philadelphia (CHoP, Philadelphia, PA). These samples were initially processed by the Genomics Core Lab at the University of Pittsburgh. Genomic DNA was extracted from whole blood samples using the Qiamp Blood Mini kit (Qiagen, Valencia, CA). All DNA was quantitated by Pico Green (Thermo Fisher, Pittsburgh, PA) and diluted the DNA to 23ng/ul. Samples without the required amount of DNA were plated for whole genome amplification (WGA) and re-quantified. Prior to genotyping, CHoP confirmed DNA concentrations by Pico Green assay and performed additional WGA on samples when necessary. Supplementary Table S11 contains information of each program sources, the source of their genotypes, and the genotype arrays used by each source.

Supplementary Table S16. Program Sources, Genotype Sources, and Chip Information

Program Sources (N)	Genotype Source	Genotype Array
ACE/GR@ACE (2,716)		
• ACE	CHoP	Illumina Infinium Global Screening Array-24 v1.0
• GR@ACE	ACE	Axiom 815K Spanish Biobank Array
ADC (2,974)	ADGC wave 1-2	Illumina Human660W-Quad v1_A
	ADGC wave 3	IlluminaHumanOmniExpress-12v1_A
	ADGC wave 4-6	IlluminaHumanOmniExpress-12v1_H
	ADGC wave 7	Illumina Human OmniExpressExome-8v1.2_a
	ADGC wave 8	Illumina Human OmniExpressExome-8v1.2_a
	ADGC wave 9	Illumina Infinium Global Screening Array-24 v1.0
	ADGC wave 10	Illumina Infinium Global Screening Array-24 v1.0
LILLY (2,175)		
• LFAN, LFBC, LZAM, and LZAN trials	Lilly	Illumina 5M Genotyping Array v1.2
• LEAM, LEAQ, and LYCG trials	Lilly	Illumina 5M Genotyping Array v1.2
• Expedition 3 LZAX trial	Lilly	Illumina Infinium Global Screening Array v2.0
NEXGENS (1,315)		
• NorCog/PADR, REDIC-NH, and HMS	NEXGENS	Illumina Human OmniExpress 24 v1.0
• AddNeuroMed	NEXGENS	Illumina 610K
• Italian/Greek	NEXGENS	Illumina Global Screening Array 24 v1.0
NIA-LOAD (673)	CHoP	Illumina Infinium Global Screening Array-24 v1.0
	NIA-LOAD	Illumina OmniExpress Illumina Human610-quad v1_B Illumina 660K 700 Illumina OmniExpress Illumina 1M Illumina OmniExpress-24 v.1 Illumina Global Screening Array
NIMH (592)	CHoP	Infinium Global Screening Array-24 v1.0
PITT ADRC (1,279)	CHoP	Illumina Infinium Global Screening Array-24 v1.0
	ADGC	Illumina Human1M-Duo v3.0
	PITT ADRC Neurogenetics Core	Illumina HumanOmni1-Quad v1.1
UK-Cardiff (593)	CHoP	Infinium Global Screening Array-24 v1.0

ACE: Fundacio Alzheimer Centre Educacional/GR@ACE: Genome Research at Fundacio ACE; ADC: Alzheimer Disease Centers; NEXGENS: Norwegian, Exeter and King's College Consortium for Genetics of Neuropsychiatric Symptoms in Dementia; NIA-LOAD: National Institute of Aging Late-onset Alzheimer disease;

NIMH: National Institute of Mental Health; PITT ADRC: University of Pittsburgh Alzheimer Disease Research Center; UK-Cardiff: MRC Genetic Resource for Late-onset Alzheimer's disease as part of the Genetic and Environmental Risk in AD Consortium; CHoP: Center for Applied Genomics at The Children's Hospital of Philadelphia; ADGC: Alzheimer's Disease Genetics Consortium.

4.1. Genotyping – ACE/GR@ACE. ACE supplied us with whole blood. DNA was prepared by the Genomics Core Lab at the University of Pittsburgh and genotypes were generated by CHoP as described in the Overview, above. Other subjects were genotyped as part of the GR@ACE genomic data collection for Alzheimer's disease.[6] GR@ACE genotypes were generated using the Axiom 815K Spanish Biobank Array (Thermo Fisher). Further information on the quality control for genome-wide data has been previously described.[6]

4.2. Genotyping – ADC. ADCs submitted blood samples to the National Centralized Repository for Alzheimer's Disease and Related Dementias (**NCRAD**). As part of their participation in the Alzheimer's Disease Genetics Consortium (**ADGC**), DNA was prepared by NCRAD for genotyping and sent to the genotyping site at CHoP as previously described.[15] ADGC then provided us with genotypic data on selected subjects[15] In addition, NCRAD supplied us with DNA for subjects for whom ADGC did not have genotypic data. The DNA was then prepared by the Genomics Core Lab at the University of Pittsburgh and submitted to CHoP for genotyping as described in the Overview, above.

4.3. Genotyping – LILLY. DNA was first extracted from whole blood samples and DNA concentrations were normalized to 50ng/µl using Pico green assay to measure concentrations, followed by suspension in 10mM Tris-Cl at pH 8.5. Samples from LZAX were genotyped on the Illumina Global Screening array version 2.0 with an addition of multi-disease associated SNP panel (n~700k SNP probes in total). The rest of the trial samples were genotyped using Illumina 5M Infinium® Omni5-4 v1.2 genotyping platform as per the manufacturers recommended guidelines (n~4.5M SNP probes). Three control DNA samples from HAPMAP consortium were used on each 96 well plate to quantify genotyping assay quality across plates and batches. In addition, 5% of the total samples were used as replicates to quantify replicability across all the batches. The genotyping data went through a stringent QC pipeline, as described in[42] using SNPRelate[43] and GWASTools[44]available on Bioconductor. Genotyping QC pipeline included a 19-step process of eliminating samples and probes with spurious quality. At probe level, in cases of duplicate probes (for e.g. APOE-e4 rs7412), only the probe with the best quality was retained. SNP probes were filtered based on probe level missing rates (<95%) and in addition SNPs with heterozygosity rate outliers were excluded from the dataset (using sample call rate vs heterozygosity plot). In addition, discordant SNPs in >=3 duplicated samples were also eliminated. At the samples level, only the higher quality data from duplicated samples were retained, samples with low call rates (< 95%) and those showing conflicts between reported gender and chromosomal sex were also eliminated. In addition, sample pairs with high identity-by-state (IBS) scores were eliminated since the trial participants are unrelated.

4.4. Genotyping – NIA-LOAD. DNA was prepared by NCRAD for genotyping and sent to the genotyping site at ChoP as part of participation in the ADGC, as previously described.[15] For these subjects we utilized existing genotype data provided by NIA-LOAD. NCRAD also supplied us with DNA for subjects for whom genotypic data was unavailable from NIA-LOAD. The DNA was prepared by the Genomics Core Lab at the University of Pittsburgh and submitted to CHoP for genotyping as described in the Overview, above.

4.5. Genotyping – NIMH. NIMH provided us with DNA which was prepared by the Genomics Core Lab at the University of Pittsburgh and submitted to CHoP for genotyping as described in the Overview, above.

4.6. Genotyping – PITT ADRC. DNA for subjects for whom genotypic data was unavailable was provided by the Neurogenetics Core of the PITT ADRC or by NCRAD. The DNA was submitted to CHoP for genotyping as described in the Overview, above. For other subjects, available genotypic data was generated as previously described and provided by the Neurogenetics Core of the PITT ADRC and the ADGC.[45,46]

4.7. Genotyping –UK-Cardiff. The UK-Cardiff supplied us with DNA which was then prepared and submitted to CHoP for genotyping as described in the Overview, above.

4.8 Genotyping – NEXGENS. NEXGENS provided summary statistics for tests of AD+P versus AD-P. NEXGENS samples were genotyped on Illumina platforms, using either the OmniExpress array (NorCog/PADR, REDIC-NH, and HMS), the Illumina 610K (AddNeuroMED), or the Illumina Global Screening Array 24 v1.0 array (Italian and Greece Hospital Outpatient).

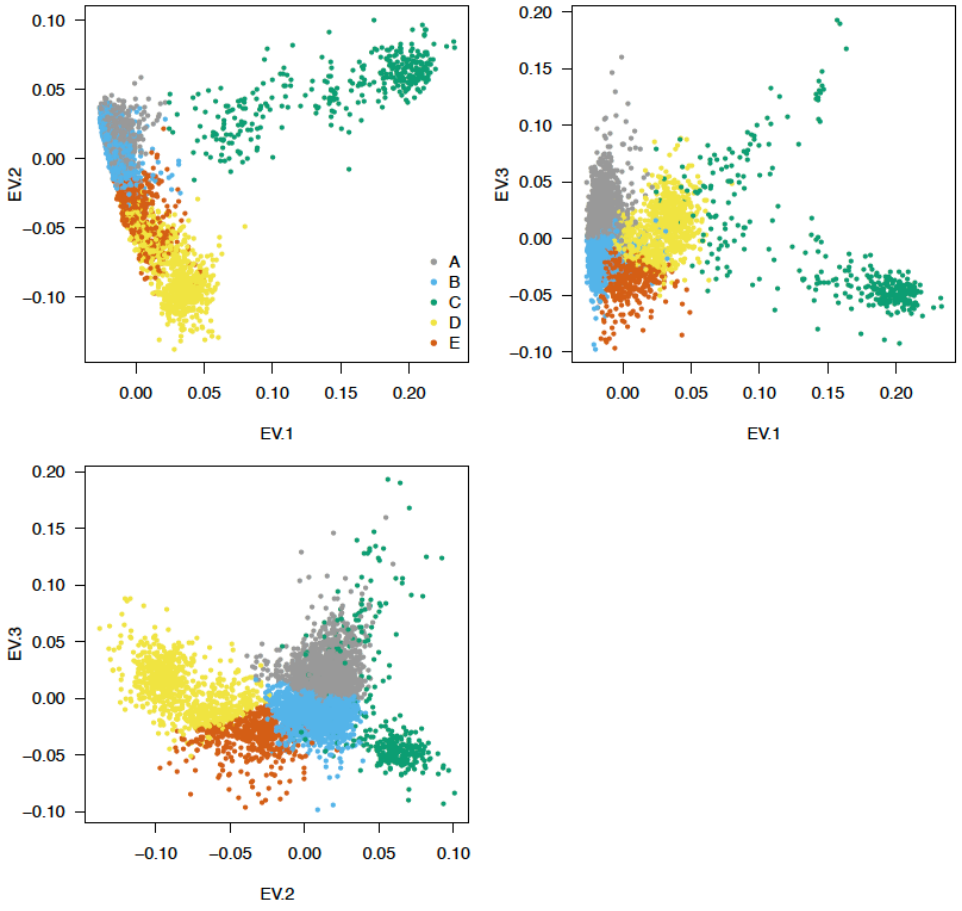
5. METHODS- QC AND ANCESTRY

5.1 QUALITY CONTROL: For QC by genotype, SNPs were removed if they had an unknown location, were monomorphic, were duplicated, did not map to an autosome or X-linked chromosome, had a non-call rate > 0.025, had a minor allele frequency MAF < 0.01, or had an exact Hardy-Weinberg p-value< 0.005 in the major European ancestry group, as defined below. For QC by sample, samples were removed if their overall SNP non-call rates > 0.025, if they showed extreme homo- or heterozygosity (<-.15 or > 0.4, respectively), if their nominal versus inferred genetic sex did not match, or if they were determined to be duplicates of other samples within or between cohorts. Raw genotype data for individual NEXGEN cohorts underwent appropriate QC steps (implemented in PLINK).[47]

5.2 ANCESTRY: Here we document batch-specific sources (Phase 1, Phase 2, GR@ACE, and NEXGENS) of samples and attributes of genetic ancestry of those samples.

5.2.1. PHASE 1

Subjects analyzed in Phase 1 were from ACE, ADC, Lilly, NIA-LOAD, NIMH, PITT ADRC and UK-Cardiff, and their genotypes were from ADGC waves 1-7, CHoP, Lilly, Pitt ADRC, and NIA-LOAD (**Supplementary Table S16**).



Supplementary Figure S3. Ancestry plot for the PHASE 1 samples. Analysis of genetic ancestry using GemTools identified three significant ancestry dimensions and divided the data up into 5 ancestry clusters (see also **Supplementary Table S17**), of which 5,396 samples in clusters A and B were of narrow European ancestry on the basis of self-identified ancestry of subjects.

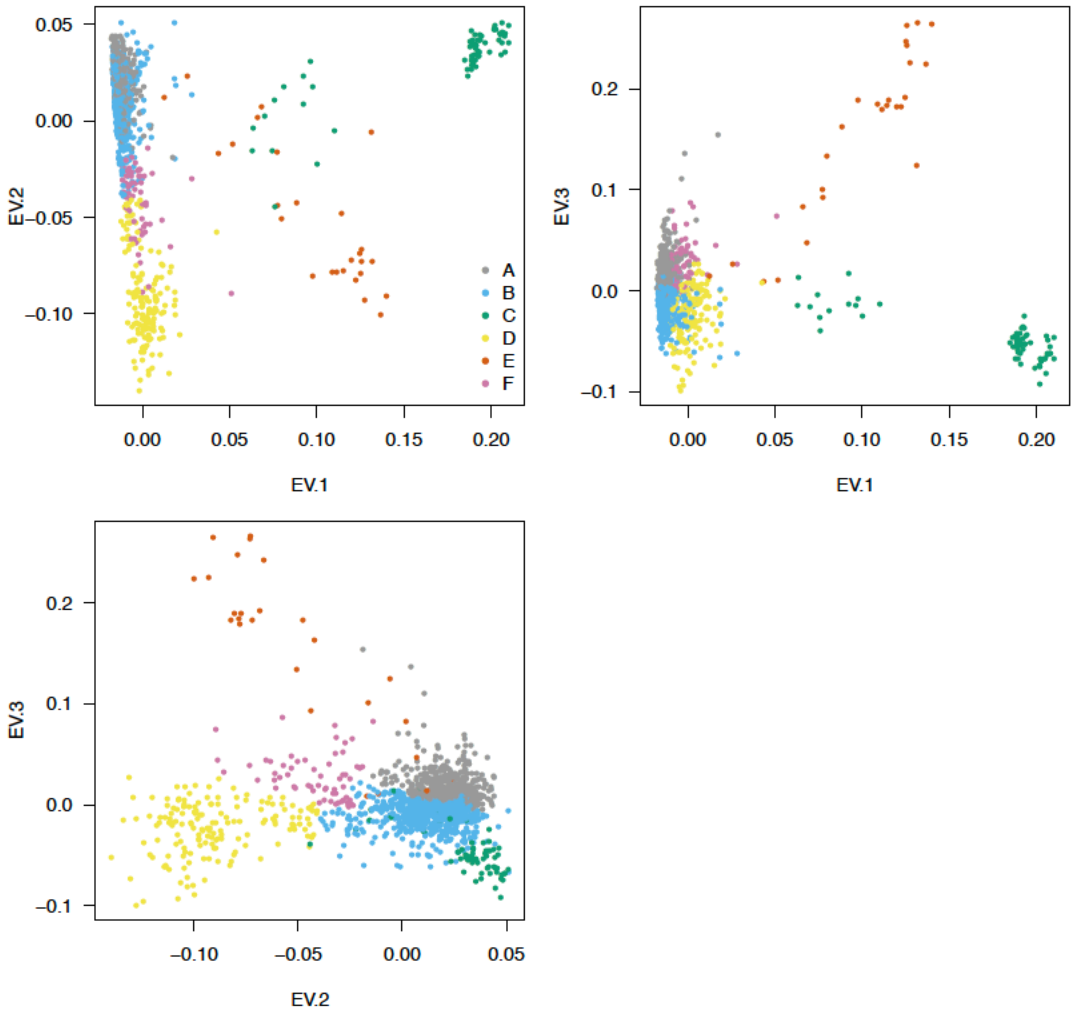
Supplementary Table S17. Distribution of PHASE 1 samples over the ancestry clusters.

	Cluster[1]						
	A	**B**	**C**	**D**	**E**	**All**	**EUR**
Psychosis Status	2,382	3,014	354	809	495	7,054	5,396
AD-P	1,152	1512	139	458	268	3,529	2,664
AD+P	1,230	1,502	215	351	227	3,525	2,732
Program Source (Genotype Source)							
ACE/GR@ACE (CHoP)	2	66	2	20	218	308	68
ADC (ADGC waves 1-7 and CHoP)	792	1,047	132	320	37	2,328	1,839
PITT ADRC (ADGC, PITT ADRC Neurogenetics Core, and CHoP)	472	436	103	191	77	1,279	908
LILLY LEAM, LEAQ, LFAN, LFBC, LYCG, LZAM, and LZAN drug trials (LILLY)	439	526	41	153	122	1,281	965
NIA-LOAD (CHoP and NIA-LOAD)	271	305	50	33	14	673	576
NIMH (CHoP)	190	264	24	90	24	592	454
UK-Cardiff (CHoP)	216	370	2	2	3	593	586

AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis; AA: African American;
[1] Of the subjects who self-reported ancestry: Cluster A (0.2% AA, 99.8% EUR [white]); Cluster B (0.2% AA, 99.8% EUR); Cluster C (92.2% AA, 7.8% EUR); Cluster D (0.5% AA, 99.5% EUR); Cluster E (0% AA, 100% EUR). Other self-reported ancestries represented less than 0.1% of subjects and hence were not reported here.

5.2.2. PHASE 2

Subjects analyzed in Phase 2 were from ADC and LILLY, and their corresponding genotypes were from ADCG waves 8-10 and LILLY (**Table S16**).



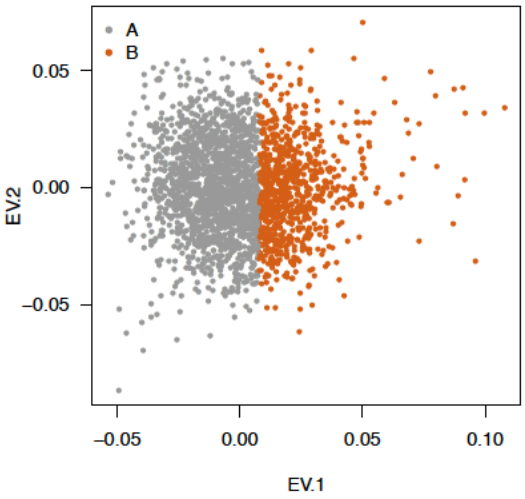
Supplementary Figure S4. Ancestry plot for the PHASE 2 samples. Analysis of genetic ancestry using GemTools identified three significant ancestry dimensions and divided the data up into 6 ancestry clusters (see also **Supplementary Table S18**), of which 1,227 samples in clusters A and B are of narrow European ancestry, as determined by genetically-based clustering with PHASE 1 samples (99% of PHASE 2 clusters A and B group together with clusters A and B of PHASE 1).

Supplementary Table S18. Distribution of PHASE 2 samples over the ancestry clusters

	Cluster							
	A	**B**	**C**	**D**	**E**	**F**	**All**	**EUR**
Psychosis Status	461	766	65	161	26	61	1,540	1,227
AD-P	310	523	42	113	15	42	1,045	833
AD+P	151	243	23	48	11	19	495	394
Program Source (Genotype Source)								
ADC (ADGC waves 8-10)	206	337	1	92	0	10	646	543
LILLY (Expedition 3 LZAX)	255	429	64	69	26	51	894	684

AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis

5.2.3. GR@ACE



Supplementary Figure S5. Ancestry plot for the GR@ACE samples. Analysis of GR@ACE samples' genetic ancestry using GemTools identified one significant ancestry dimension and divided the data up into 2 ancestry clusters (see also **Supplementary Table S19**). All samples are of European ancestry, as determined by genetically-based clustering with PHASE 1 and PHASE 2 samples (99.4% of GR@ACE cluster with others of European ancestry, specifically clusters A and B of PHASE 1 and PHASE 2).

Supplementary Table S19. Distribution of GR@ACE samples over the ancestry clusters.

	Cluster			
	A	**B**	**All**	**EUR**
Total	1623	785	2408	2408
AD-P	1098	548	1646	1646
AD+P	525	237	762	762
GR@ACE	1623	785	2408	2408

AD-P: Alzheimer disease without psychosis; AD+P: Alzheimer disease with psychosis

5.2.4. NEXGENS

For our meta-analysis, we received summary statistics from the NEXGENS consortium. What follows is a synopsis of the methods used by the NEXGENS consortium to produce these association summary statistics.

Raw genotype data for individual NEXGENS cohorts underwent appropriate QC steps (implemented in PLINK), as described previously.[47] SNPs with a minor allele frequency ≤5% and a Hardy Weinberg equilibrium $p < 10-5$ were excluded. The SNP and individual genotype failure threshold were set at 5%, and individuals with mean heterozygosity ±3 standard deviations were excluded. The analysis was restricted to individuals of European ancestry using genetic principal components computed by EIGENSTRAT. Related (pi-hat > 0.2) or duplicate individuals both within and between cohorts were excluded, ensuring there was no sample overlap across datasets. Phasing (EAGLE2) and imputation (PBWT) was done via the Sanger Imputation Service using the Haplotype Reference Consortium (r1.1) reference panel on all cohorts. After imputation only SNPs with an imputation quality (INFO) score > 0.4 and MAF > 0.05 were retained. Logistic regression, implemented in PLINK on each dataset individually, was used for SNP association testing with psychosis status, covarying for the first 10 ancestry principal components. The METAL software was used to conduct inverse-variance weighted fixed effects meta-analysis across the 5 datasets within the NEXGENS Consortium (**Tables S11.1-S11.5**), applying genomic control.[48]

6. METHODS- ANALYSIS

6.1. PATHWAY ANALYSIS: Gene set enrichment analyses were performed in MAGMA,[49] correcting for the number of SNPs in each gene, linkage disequilibrium (LD) between SNPs and LD between genes. The measure of pathway enrichment is the MAGMA "competitive" test (where the association statistic for genes in the pathway is compared to those of all other protein-coding genes).[50] As in the gene-based analyses, we used the "mean" test statistic, and again the primary analysis assigned variants to genes if they lie within the gene boundaries, but a secondary analysis used a window of 35kb upstream and 10kb downstream to assign SNPs to genes, as in Kunkle et al.[15] We used the R package qvalue to account for multiple testing.

Pathways were defined as follows. The assignment of Gene Ontology (GO) terms to human genes was obtained from the "gene2go" file, downloaded from NCBI on March 11th 2020. "Parent" GO terms were assigned to genes using the ontology file downloaded from the Gene Ontology website on the same date. GO terms were assigned to genes based on experimental or curated evidence of a specific type, so evidence codes IEA (electronic annotation), NAS (non-traceable author statement), RCA (inferred from reviewed computational analysis) were excluded. Pathways were downloaded from the Reactome website on April 26th 2020. Biocarta, KEGG and Pathway Interaction Database (PID) pathways were downloaded from v7.1 (March 2020) of the Molecular Signatures Database. Analysis was restricted to GO terms containing between 10 and 2000 genes. No size restrictions were placed on the other gene sets, since there were many fewer of them. This resulted in a total of 10,053 gene sets for analysis.

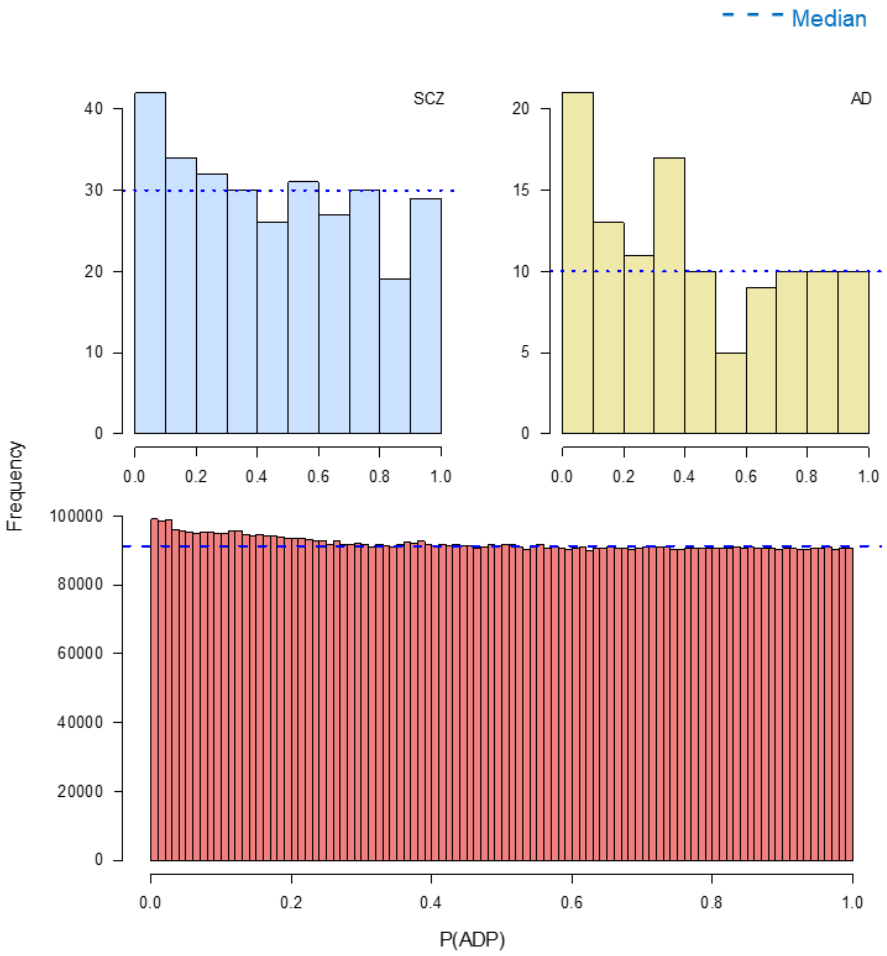
6.2. TRANSCRIPTOME-WIDE ASSOCIATION (TWAS): Using the GRCh37 hg19 genome assembly, common variants from the AD+P summary statistics were filtered using the munge_sumstats.py (v2.7.13) script from the LD Score Regression (LDSC) software and the hapmap 3.0 reference panel resulting in 1,184,883 SNPs. The FUSION package[51] was used to perform a TWAS using dorsolateral prefrontal cortex expression data from the CommonMind Consortium and expression data from 13 Brain tissues from the GTEx (Genotype-Tissue expression) consortium (v7).[52] GTEx7 and CMC expression weights and the reference panel from the 1000 Genomes European population were downloaded from the FUSION web site. Expression weights were used in TWAS for autosomal chromosomes and excluding the MHC region, with the processed AD+P summary statistics using the R script FUSION.assoc_test.R from the FUSION software.[51] Results were corrected for multiple testing of multiple genes within each tissue using the Bonferroni method.

6.3 POLYGENIC RISK SCORE: We evaluated how well three different polygenic risk scores could differentiate 9,031 AD+P and AD-P subjects of European ancestry. We used the pruning and thresholding approach[53] to compute a PRS for our subjects, developed from GWAS results for AD (PRS_{AD}), [54] schizophrenia (PRS_{SZ}),[55] and bipolar disorder (PRS_{BP}),[3] separately. We used a set of GWAS p-value thresholds for SNP inclusion in each score ($5x10^{-8}$, 0.0001, 0.001, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5).

As a first step in pruning SNPs for the score, we required SNPs to meet these criteria: must be included in both GWAS of interest (AD+P and other phenotype); genotypes called in all three data sets (Phase 1, Phase 2, and GR@ACE); MAF > 0.01; not an indel; difference between MAF for AD+/-P versus the MAF for the other phenotype < 0.05; if palindromic, MAF < 0.40. Also, for PRSAD, we selected only the most influential SNP (smallest GWAS p-value) within the APOE locus (chr19:45,000,000-46,000,000); and, for all three scores, we selected only the most influential SNP within the MHC region (chr6:25,000,000-34,000,000). As a next step, SNPs were clumped using Plink command --clump with a clump window of 500Kb and a maximum r2 between pairs of 0.50. The PRS were subsequently determined for each of the phenotypes using --score command with the options "center" and "sum" for p-value and for the thresholds given above. Logistic regression of AD+P status on PRS was performed using two ancestry vectors as additional covariates. Function nagelkerke in R library rcompanion was used to obtain the partial pseudo-R2 attributable to the PRS.

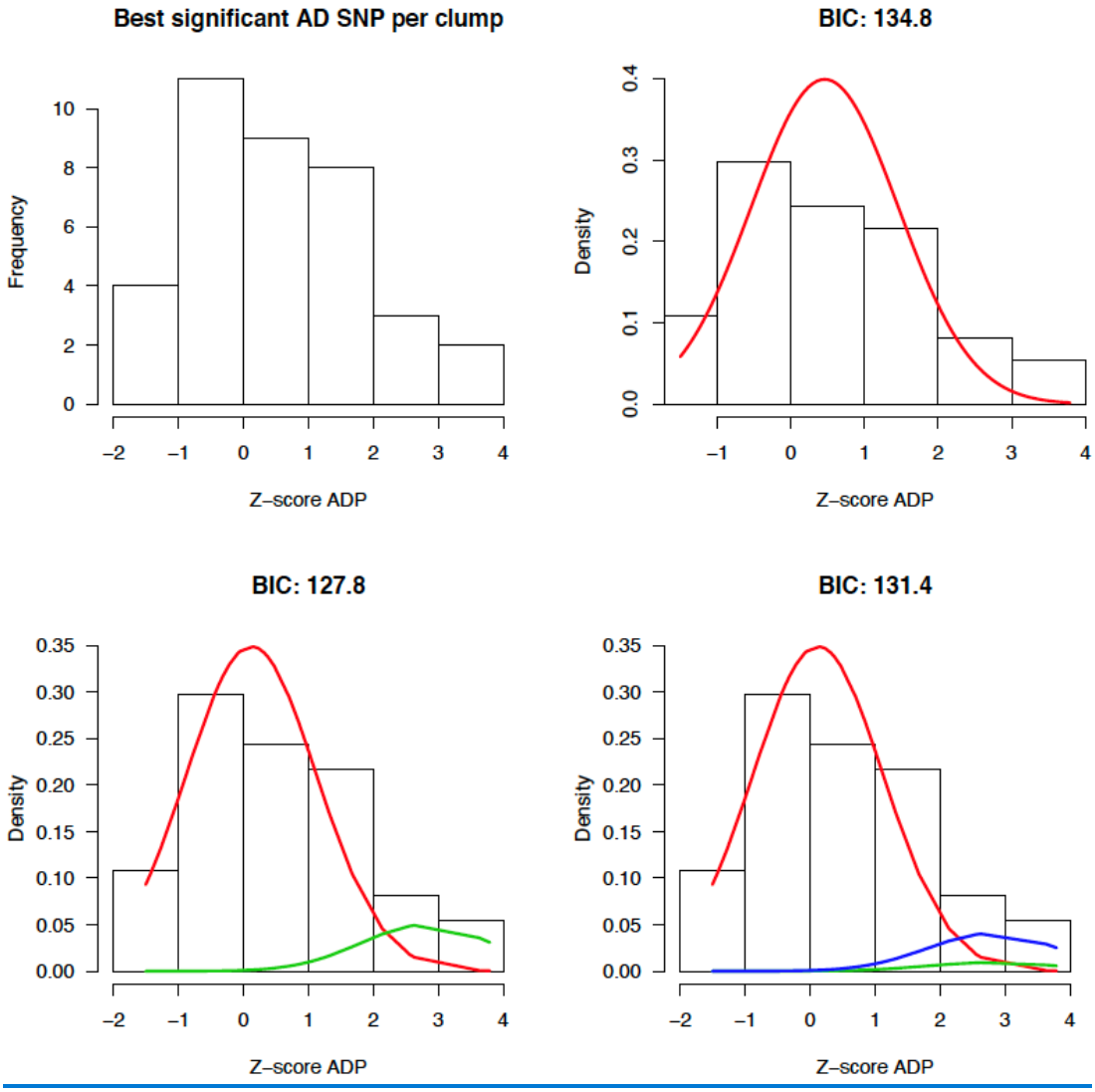
6.4. ANALYSES OF OVERLAP WITH SCHIZOPHRENIA, BIPOLAR, AND AD RISK SNPs: To evaluate whether there are consistent signals across studies and traits, we took three approaches. First, using a threshold of 5×10^{-8}, we selected GWAS-significant SNPs for schizophrenia (SCZ),[55] bipolar disorder (BPD),[3] or AD[54] and matched them to SNPs analyzed in our AD+P GWAS. Among the 18,276 significant SZ SNP, we matched 18,256 to SNPs in our AD+P GWAS. None crossed the p-value threshold of 10^{-4} for our AD+P GWAS. The same was true for the 264 significant BPD SNPs, which could be mapped to 238 SNPs from our AD+P GWAS. Among the 2394 GWAS significant AD SNPs, we matched 2284 to SNPs in our AD+P GWAS, and 11 crossed the threshold, all in the APOE region.

Next, we addressed this a different way. If there were consistent signals across studies, at least for some fraction of the SNPs (π), then we would expect the distribution of p-values from the AD+P GWAS, drawn because they had p-value < 5×10^{-8} for the complementary GWAS (SCZ, BPD, or AD), to be a mixture of two densities: fraction π, bearing true signal, would tend to have small p-values and they are often assumed to follow a Beta distribution; for the remainder, $1-\pi$, the p-values are expected to be drawn from the null distribution, a uniform on the interval (0,1). Because some SNPs are not independent, we first clumped SNPs by LD (pairwise LD r^2 < .20, using clump in PLINK with a 500Kb region) and selected the SNP, within clump, with the largest association p-value for the disease (SCZ, BPD, or AD). After clumping, if there were many SNPs falling in the same locus, such as around APOE for AD, we choose one SNP for the locus. When we fit this model to the p-values for 205, 16, and 37 selected SNPs for SCZ, BPD, and AD (**Supplementary Figure S6** for SCZ and AD, as well as the full distribution of AD+P GWAS p-values for contrast), respectively, and estimate π, we obtain $\pi_{\text{SCZ}} = 0.13$, $\pi_{\text{BPD}} = 0.39$, and $\pi_{\text{AD}} = 0.41$. The estimate for bipolar disorder, based on a small number of SNPs, is not reliable.

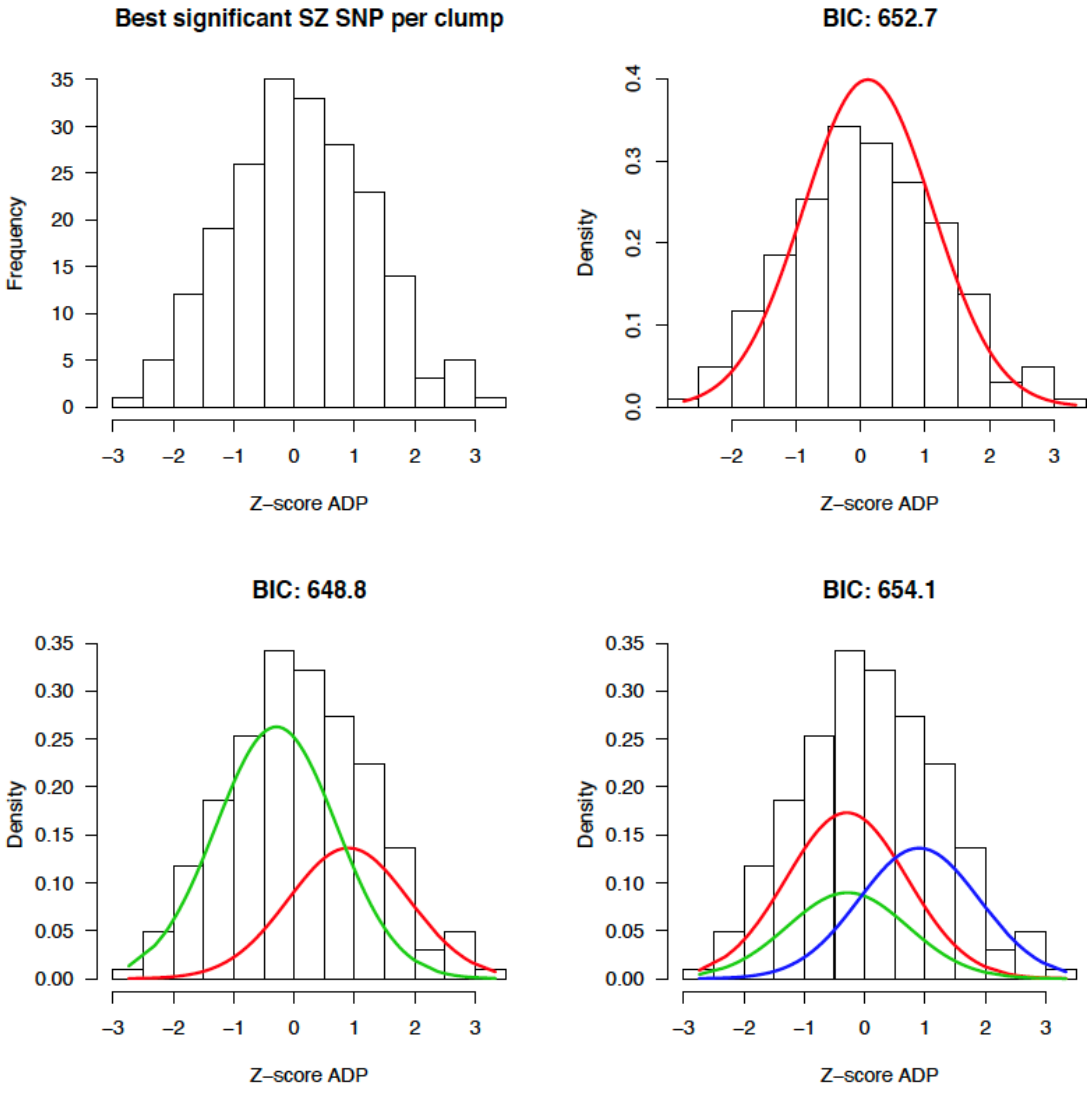


Supplementary Figure S6. Distribution of AD+P p-values for GWAS significant SNPs for SCZ and AD (top) and the entire AD+P p-value distribution (bottom). Dashed horizontal reference line is the median value of the AD+P p-values. Not shown: AD+P p-values for GWAS significant SNPs for BPD because the relatively few p-values made the mixture model analysis unreliable.

Finally, we asked if any particular GWAS-significant SNP for SCZ, BPD, and AD, or set of SNPs, also showed sufficient evidence for significance in AD+P. We approached this by using results from the clumped/thinned SNPs described above. Next, we sought evidence for a mixture of distributions of z-scores for the identified sets of SNPs. If there is evidence of a mixture, did any observations show compelling evidence for membership in one of the component distributions (PPr > 0.95)? As expected, we found evidence for a mixture for SCZ and AD, but not BPD. Both SCZ and AD z-scores were consistent with a mixture of two normal distributions (**Supplementary Figures S7-S8**). After estimating the posterior probability (PPr) of membership in these distributions, based on the parameters of the mixture model, 55 significant SNPs from the AD GWAS showed notable association for AD+P Z-scores, 21 with PPr.1 > 0.95 (left distribution) and 2 with PPr.2 > 0.95 (right distribution). For the significant SCZ SNP 71 SNP with PPr.1 > 0.95 (left distribution) and 8 with PPr.2 > 0.95 (right distribution) showed notable association with AD+P.



Supplementary Figure S7. Distribution of AD+P z-scores for GWAS significant SNPs for AD fit for 0, 1, 2 and 3 components of a normal. BIC is the Bayesian Information Criterion. Here, if the BIC decreases substantially with the addition of parameters, then they are needed to describe the distribution of the z-scores. In this case, the BIC decreases substantially by adding a second component to the mixture distribution, but it decreases thereafter. Hence we chose a two-component mixture as the best representation.



Supplementary Figure S8. Distribution of AD+P z-scores for GWAS significant SNPs for SCZ fit for 0, 1, 2 and 3 components of a normal. BIC is the Bayesian Information Criterion. Here, if the BIC decreases substantially with the addition of parameters, then they are needed to describe the distribution of the z-scores. In this case, the BIC decreases substantially by adding a second component to the mixture distribution, but it decreases thereafter. Hence we chose a two-component mixture as the best representation.

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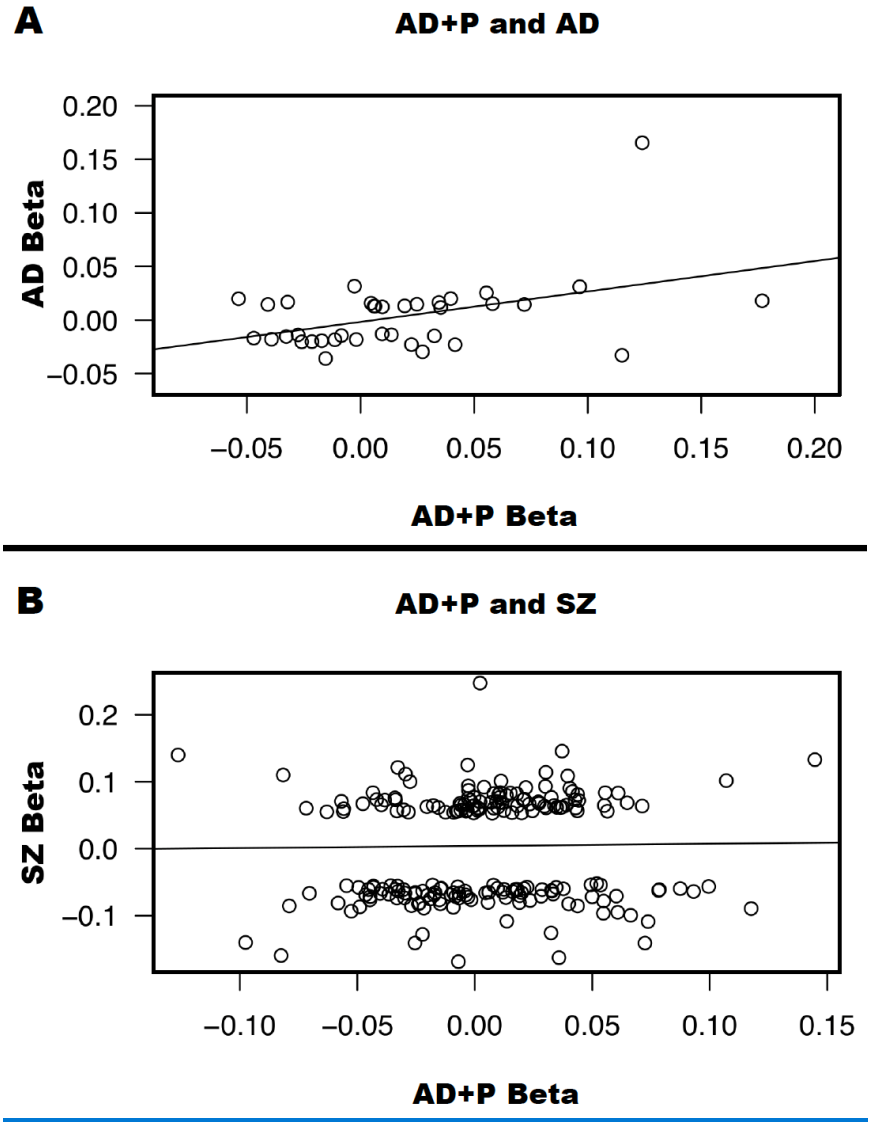
For context, we also evaluated the relationship between the estimated effects for AD and SCZ versus AD+P.



Supplementary Figure S9. Distribution of AD+P p-values for GWAS significant SNPs for SCZ and AD (top) and the entire AD+ P p-value distribution (bottom). Dashed horizontal reference line is the median value of the AD+P p-values. Not shown: AD+P p-values for GWAS significant SNPs for BPD because the relatively few p-values made the mixture model analysis unreliable.

7. SUPPLEMENTARY DISCUSSION OF RESULTS

Association Test Results

Of interest, we found some evidence for association of AD+P with rs11701 (Supplementary Table 1, 4.0×10^{-6}). rs11701 is located on chromosome 14, within two genes, *ANG* and *RNASE4*, which share promoters and some 5' exons, although each gene is spliced to a unique downstream exon containing its complete coding region. rs11701 is a synonymous coding variant in *ANG*, is intronic in *RNASE4*, and its protein products are members of the RNAse A Superfamily. Loss-of-function mutations in both *ANG* and *RNASE4* have been associated with amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD) syndromes.[56-61] ANG preferentially hydrolyzes transfer RNA (tRNA) *in vivo*.[62] Understanding of how tRNA-derived fragments generated by ANG may contribute to neuroprotection is rapidly expanding.[63]

It would thus be parsimonious to hypothesize that less potent alterations in expression of *ANG* and *RNASE4*, or in functions of their protein products, modify neuronal function or survival, which in turn, increases the risk for psychosis in individuals with AD. Several observations are consistent with this hypothesis. For example, rs11701 has been linked to expression levels for both genes in some tissues.[64] While it is not known if mutations in *ANG* or *RNASE4* are present in AD+P, some of these mutations result in tar DNA binding protein 43 (TDP43) inclusion pathology on postmortem exam in ALS/FTD patients.[65] We have previously reported that the presence of comorbid TDP43 pathology in AD is independently associated with psychosis risk.[66]

TWAS Results

VN1R108P in GTEx7 hippocampus was TWAS significant in this analysis. VN1R108P is a member of the Vomeronasal receptors and it is classified as a pseudogene. Pseudogenes, which are homologous to protein-coding genes but have lost their coding ability, were thought to be functionless.[67] However, more recently, it has been shown that pseudogenes can be expressed and that they can have roles in gene regulation.[68,69] Such relationships have been shown previously in schizophrenia.[70] VN1R108P is not well annotated, however, it is expressed in a wide variety of tissues and could have a role in gene regulation. However, we note that the best eQTL snp in this analysis, rs4815438 is located in the ZNF337-AS1 gene which is a long non-coding RNA.

FAM182B is a long non-coding RNA (lncRNA) which is highly expressed in the cerebellum (https://www.proteinatlas.org/ENSG00000175170-FAM182B/tissue) and may be involved in the development of the foetal neocortex.[71] In addition, it has been suggested that FAM182B could be an important regulator in hepatocellular carcinoma.[72]

Long non-coding RNAs (lncRNAs) have many roles in the regulation of gene expression for example, they are involved in the regulation of the epigenome by association with chromatin modifying complexes[73] and they can affect gene expression through association with chromatin- modifying complexes.[74] FAM182B shows TWAS associations in a consistent direction in numerous brain tissues (Supplementary Table S5), suggesting that it could be an important regulator in the brain.

Definition of AD+P Phenotype

We note that we examined the association of genetic variation with a psychosis phenotype defined by the presence of one or more of multiple individual psychotic symptoms. It is possible that relevant subgroups could exist within the AD+P phenotype.[75] However, several lines of evidence support the phenotype definition used in the current study. First, our approach mirrors that used to define other psychotic disorders, e.g. schizophrenia. Second, AD+P as defined in the current study demonstrates familial aggregation and heritability.[27,31,34] Moreover, the heritability of AD+P is highest when requiring the presence of multiple or recurrent psychotic symptoms.[31,34] Nevertheless, it remains possible that any of the loci we report as significantly or suggestively associated with AD+P reflect a selective association with only a subset of psychosis symptoms.

Another potential limitation of our phenotypes, imprecision of our diagnosis of AD, seems unlikely. We did not observe any genetic correlation between AD+P risk and risk for ALS or Parkinson's disease. The lack of genetic overlap with ALS suggests that cases for whom a comorbid pathogenic process associated with ALS/FTD contributes to the manifestation of psychosis in AD account for only a small proportion of AD+P. This conclusion is consistent with our prior pathologic observations, in which the presence of TDP-43 pathology predicted only 5% of the variance in risk for AD+P.[66] Similarly, the lack of genetic correlation with Parkinson's disease indicates that our AD+P phenotype did not derive from a phenocopy due to inclusion of subjects with primary alpha-synuclein pathology, which itself is associated with psychosis.[76]

8. ACKNOWLEDGMENTS

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GR@ACE Consortium:
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