.

Genetic risk for schizophrenia and psychosis in Alzheimer disease

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INTRODUCTION

Psychotic symptoms, defined as the occurrence of delusions or hallucinations, are frequent in Alzheimer disease (AD+psychosis (AD+P)), affecting ~ 40 to 60% of individuals with AD. In comparison with AD subjects without psychosis, AD+P subjects have more rapid cognitive decline and poor outcomes. Ropacki and Jeste[1] comprehensively reviewed the literature on psychosis in AD from 1990 to 2003, identifying 55 studies comprising 9749 subjects. More rapid cognitive decline was the most consistent correlate of AD+P compared with AD without psychosis (AD − P). More recent studies have continued to support the relationship between greater cognitive impairment, more rapid cognitive decline and AD+P.[2–8] AD+P is further associated with additional psychiatric and behavioral disturbances, the most frequent and troublesome of which are agitation[9] and aggression.[10,11] AD+P leads to greater distress for family and caregivers,[12] greater functional impairment,[13] higher institutionalization rates,[14–17] worse health[18] and increased mortality[19] compared with AD − P patients.

Treatment of psychosis in AD patients has been suboptimal because of the limited efficacy of available drugs and their highoxicity in this age group. First-line treatments are atypical antipsychotics that have efficacy similar to conventional anti-psychotics for AD+P, with lower rates of motor side effects.[20] However, atypical and conventional antipsychotics have been associated with an increased risk of all-cause mortality after even short-term treatment.[20,21] Other treatments, such as selective serotonin reuptake inhibitors, may have some efficacy[22,23] and improved tolerability.[24] Nevertheless, none of these treatments were derived to prevent or reverse an identified biology of AD+P, and there are no current data to suggest that any of these treatments effectively mitigate against the greater cognitive and functional decline associated with AD+P. It is thus imperative to develop an approach to promote discovery regarding the biology of AD+P and identify opportunities to intervene to prevent its adverse trajectory.

We initially observed familial aggregation of AD+P,[25] since replicated in two independent cohorts.[4,26] These studies show a remarkable consistency in the estimated three- to fourfold increased odds of psychosis in a family member with AD, given the presence of psychosis in a proband with AD. Similarly, we used two of these cohorts to estimate the heritability of psychosis in AD as 61%.[27,28] Thus, AD+P is likely to be strongly influenced by
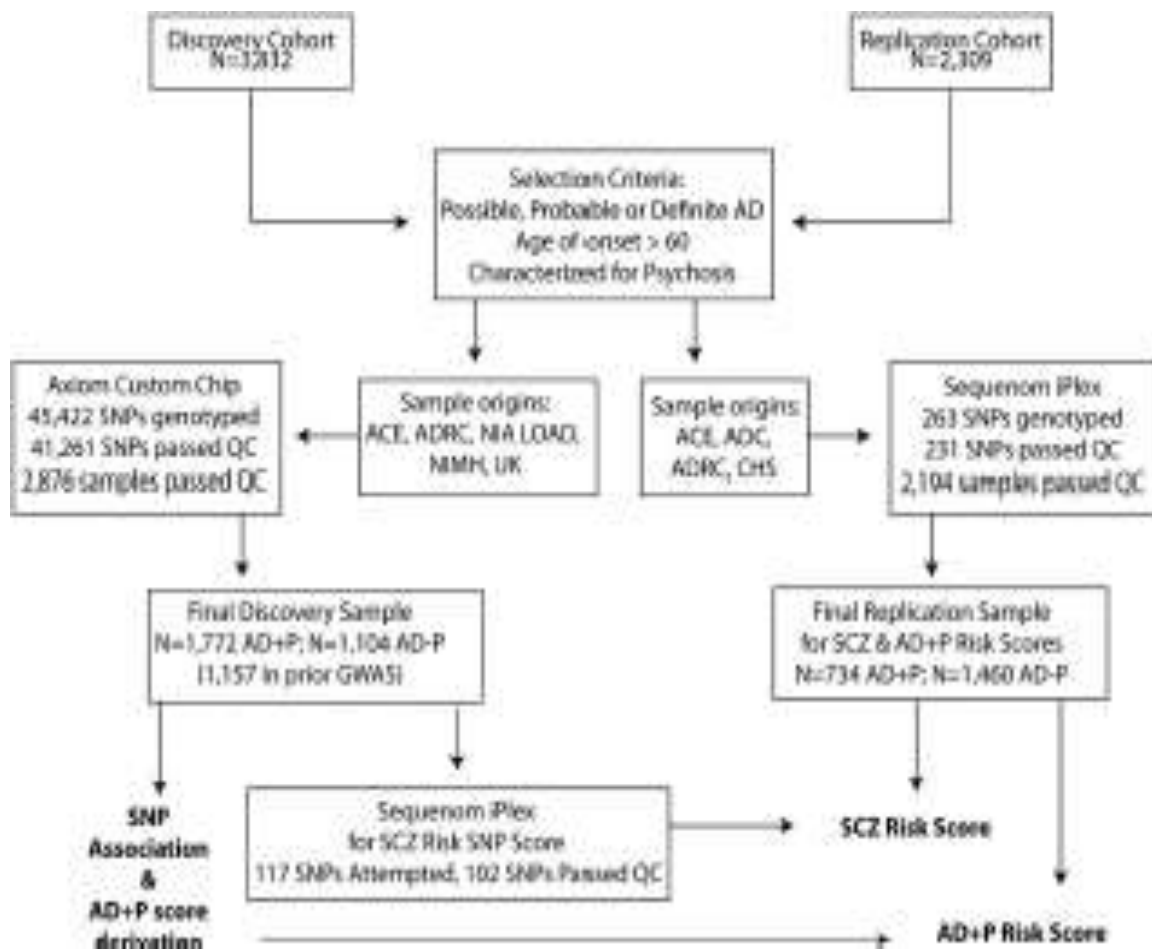
Figure 1. Diagram of the study design and workflow. ACE, Fundació ACE Barcelona Alzheimer Treatment and Research Center; ADC, consortium of National Institute on Aging Alzheimer Disease Centers; AD − P, Alzheimer disease without psychosis; AD+P, Alzheimer disease with psychosis; ADRC, University of Pittsburgh Alzheimer Disease Research Center; CHS, Cardiovascular Health Study; GWAS, genome-wide association study; NIA LOAD, National Institute on Aging's Late Onset Alzheimer's Disease Family Study; NIMH, National Institute of Mental Health Genetics Initiative AD Cohort; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; QC, quality control; UK, Genetic and Environmental Risk in AD Consortium 1.

genetic variation. In keeping with these observations, we recently reported the first genome-wide association study (GWAS) of AD+P, evaluating 1299 cases with AD+P and 735 individuals characterized as AD − P. Although no single single-nucleotide polymorphism (SNP) demonstrated genome-wide significance, likely because of modest sample size, there was suggestive evidence for association with novel loci.

We further found a trend toward association with a group of 11 SNPs that had been identified in initial GWAS studies of schizophrenia and bipolar disorder.29 That latter finding also provided the biologically intriguing observation that the direction of 7/11 allelic effects on risk for AD+P were opposite to that reported in the studies of psychiatric disorder subjects. Since the time of our prior report, genomic studies of schizophrenia risk have identified 128 SNPs in 108 loci that exceed genome-wide significance.30

Recently, the use of polygenic risk scores has emerged as an important approach for summarizing genetic effects of a set of SNPs. A polygenic score is a simple, subject-specific summary of the additive effects of alleles on a trait. When computed to predict subjects' risk for a disorder, it is called a polygenic risk score. The score can be obtained from a limited set of SNPs, such as those reaching genome-wide significance in association studies or a larger set based on some other threshold[31–33] or the entire genome.[34,35] For example, when alleles at the 108 schizophrenia-associated loci were combined in a polygenic risk score, they explained 3.4% of the liability to schizophrenia.[30] For traits in which few or no individual SNPs reach genome-wide significance, polygenic risk scores can provide initial evidence for true genetic association of the trait with the SNPs either included within the ndividual affected loci.

Here we follow-up on our prior research in an expanded Discovery Cohort of 2876 AD subjects with and without psychosis. All subjects were genotyped using a custom chip designed to evaluate SNPs with evidence of genetic association, mostprominently with AD+P, although SNPs affecting or putatively affecting risk for schizophrenia and AD were also assessed. Results were replicated in an independent cohort of 2194 AD subjects with and without psychosis. We found that AD+P is associated with polygenic risk for a set of novel loci and inversely associated with polygenic risk for schizophrenia. We believe these findings provide the first clear demonstration that AD+P is associated with common genetic variation. In addition, they provide an unbiased link between polygenic risk for schizophrenia and a lower risk of psychosis in AD. As efforts to identify the biologic effects of schizophrenia alleles progress, it may be possible to leverage these results to identify novel mechanisms protecting against more rapid cognitive decline and psychosis risk in AD.

MATERIALS AND METHODS

An overview of the study design and workflow is shown in Figure 1.

Subjects

This study analyzed samples obtained from subjects in two cohorts, an initial Discovery Cohort and an independent Replication Cohort (Table 1). All subjects were diagnosed with possible, probable[36] or definite[37] AD. Importantly, subjects with a primary diagnosis of dementia with Lewy bodies (DLB)[38] were excluded. The above diagnoses resulted from diagnostic evaluations, cognitive testing and in some cases neuropathologic assessment conducted during subjects' participation in the following programs as previously described: the University of Pittsburgh Alzheimer Disease Research Center (ADRC),[39,40] the Genetic and Environmental Risk in AD Consortium 1 (UK),[29,41,42] the National Institute on Aging's Late Onset Alzheimer's Disease Family Study (NIA-LOAD),[4,28] the National Institute of Mental Health Genetics Initiative AD Cohort (NIMH),[25] the Fundació ACE Barcelona Alzheimer Treatment and Research Center (ACE),[41,43] the Cardiovascular Health Study (CHS)[3,41] and a consortium of National Institute on Aging Alzheimer Disease Centers (ADC).[44] Collection of clinical data and genetic samples were approved by each site's local institutional review board or medical ethics committee, as appropriate. Additional detail of the individual cohorts and assessment methodology is available in Supplementary Methods and Supplementary Tables S1–S13.

Characterization of psychosis

Subjects were characterized for the presence or absence of delusions and hallucinations within the individual studies using the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) behavioral rating scale[45] (ADRC and NIA-LOAD), Neuropsychiatric Inventory Questionnaire (NPI-Q,[46] NIA-LOAD, ADC), NPI-Q Spanish Version[47] (ACE), NPI[48] (UK, CHS) and Brief Psychiatric Rating Scale[49] (NIMH). Each of these instruments has established reliability in AD,[4,50] and we have

previously used all successfully in analyses of psychosis in AD subjects.3,4,6,27,39 Details of the application of these assessments for each cohort are provided in the Supplementary Methods. AD+P was defined by the presence of persistent hallucinations or delusions occurring during the course of the dementia, and AD − P was defined by the absence of all symptoms at all assessments. Because psychotic symptoms typically emerge in the mild to moderate stages of AD,4 individuals without psychosis but who were still in the early stages of disease at their last assessment (Clinical Dementia Rating51 score o1, Mini–Mental State Examination score52 420) 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 previously used these approaches to characterizing and defining AD+P and AD − Pto demonstrate familial aggregation,4,25 heritability,27,28 genetic linkage28,53 and suggestive genome-wide association29 with the AD+P phenotype.

Genotyping

DNA preparation. Samples from outside sources were shipped on dry ice, stored and processed by the Genomic Core Lab at the University of Pittsburgh. ACE samples were supplied as whole blood and genomic DNA was extracted using the Qiamp Blood Mini kit (Qiagen, Valencia, CA, USA). All other centers provided genomic DNA (ADRC, NIA-LOAD, NIMH, UK, ADC) or whole genome amplified DNA (CHS).

Custom chip for Discovery Cohort. The Genomic Core Lab quantitated all samples by Pico Green (Thermo Fisher, Pittsburgh, PA, USA) and diluted the DNA to 23 ng μl − 1 and shipped the plates on dry ice to Affymetrix (Los Angeles, CA, USA) for genotyping. Plates also contained randomized duplicates. Affymetrix confirmed all DNA concentrations by Pico Green assay before genotyping. Genotyping used a custom-designed Axiom chip (see SNP selection below), and was performed using the Affymetrix GeneTitan system as described in the axiom user manual54 with resultant genotype calls provided for quality control (QC) and analysis.

iPlex assay for genotyping SCZ risk score SNPs and Replication Cohort testing iPlex chemistry: Assays were designed with Assay Designer 4.0 (Agena, San Diego, CA, USA) and analysis performed using iPlex Gold Genotyping Reagent Set (Agena) according to the manufacturer's instructions. Target loci were amplified within the samples by multiplex PCR in 1 × PCR buffer containing 3.5 mM MgCl2,25mM dNTPs, 500 nM each of forward and reverse amplification primer within the multiplex pool and 2.5 U HotStar Taq. The dNTPs and primers were removed by incubation with 0.5 U shrimp alkaline phosphotase at 37 °C for 40 min. The shrimp alkaline phosphotase was inactivated by incubation at 87 °C for 5 min. Single base extension was carried out in 0.2 × iPLEX buffer plus, 1 × termination mix (containing mass modified termination nucleotides), 1 × iPLEX enzyme and primers at 0.84, 1.04 and 1.25 μM as appropriate to the relative mass of each primer. Following thermocycling, clean resin and water was added to the MassExtend (Agena Bioscience, San Diego, CA, USA) reaction products. Samples were incubated in clean resin at room temperature with mixing for 5minandcentrifugedat3200g for 5 min.

Samples were then dispensed to a SpectraChip (Agena Bioscience) using the MassArray Nanodispenser (Agena Bioscience) according to manufac-turer's instructions. Spectra chips were loaded into the MassArray analyzer and spectra acquired for each sample. Genotype calls were made using Typer 4.0 (Agena) by mass identification of extended primer peaks.

SNP selection

Development of custom array for Discovery Cohort: The process of selecting SNPs for the genotyping array involved two principal stages. First, SNPs were amalgamated based on genetic signal for

association to a small set of phenotypes (Supplementary Table S14). The bulk of the SNPs were included on the basis of association results from four contrasts reported in three genome-wide studies: a contrast of AD+P versus AD − P,[29] AD+P versus controls,[29] AD versus controls[55] (https://www.niagads.org/datasets/ng00027, 2016) and schizophrenia (SCZ) versus controls.[32,56] An additional unpublished data set (described in Lin et al.[57] and Seney et al.[58]) of cis-expression quantitative trait loci (cis-eQTLs) affecting gene expression and cis-eQTLs associated with age-related changes in gene expression was also used. For the first four GWASs, SNPs with P-value less than a threshold of 0.01 were selected; for the eQTLs, the threshold was 0.001 and for the 'aging' eQTLs it was 0.05. Note that when a SNP was represented in more than one study, the minimum P-value in any of the 6 data sets was taken as representative for the SNP. To interrogate copy number regions shown to be associated with schizophrenia, 1574 SNPs were included (1q21.1, 3q29, 15q11.2-15q13.3, 16p13.1, 16p11.2 and 22q11.2, recently reviewed in Kirov,[59] and 7q11.23 (ref. 60)). Finally, a small fraction of SNPs were chosen to cover four genes of interest regarding psychotic disorders (SCZ target genes: NRXN1,[59] ERBB4,[61] PAK2 (ref. 62) and CHRNA7 (ref. 63)) or were nominated from unpublished AD studies (UK SNPs).
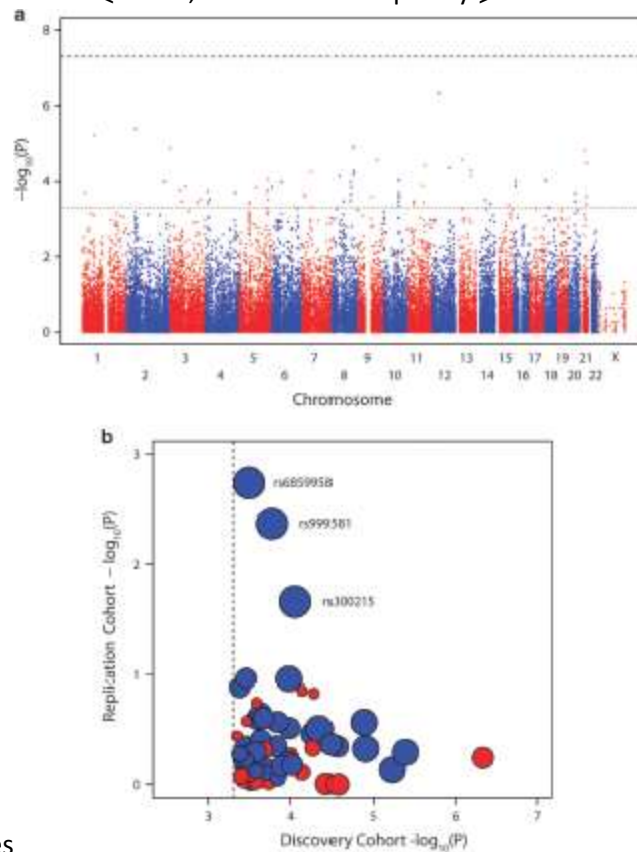
Second, SNPs were retained for genotyping by a winnowing process. This process involved removing redundant SNPs, those that could not be genotyped on the Axiom platform or SNPs not present in 1000 genomes. Of the SNPs passing this step, all SNPs with a minimum P-value of o0.0001 for any study were retained. For the remainder, by using a LD clumping process, we removed SNPs in LD with the retained SNPs (r240.9) and retained additional SNPs with the smallest P-value in 'independent' clumps (r2o0.9) by pruning SNPs with Plink[64] (maximum distance for pruning was 5 kb, window width was 25 SNPs and sliding step was 5 SNPs).

SNP selection for SCZ risk score testing and follow-up genotyping in Replication Cohort. For SCZ risk score testing in each cohort we targeted the 128 GWA significant SNPs reported in Schizophrenia Working Group of the Psychiatric Genomics Consortium,[30] although not all could be genotyped. Follow-up genotyping in the Replication Cohort also selected SNPs from our custom array that passed QC and with Po0.0001 for the contrast of AD+P versus AD − P. For the Replication Cohort we selected ancestry-informative markers for European Ancestry based on the results in Kosoy et al.[65] Specifically, based on results found in Supplementary Table 1 of Kosoy et al.,[65] we selected their 'Top 96' European ancestry-informative markers, of which 82 could be genotyped on the Sequenom platform and 79 passed QC.

Quality control

QC was performed at the individual level first, and then at the SNP level conditional on individual-level data passing QC and individuals of European ancestry. Details of QC are given in Supplementary Materials. In brief, genetic data for samples were retained if their nominal sex agreed with genetically determined sex (Supplementary Figure S1); heterozygosity rate, per subject, revealed no evidence of contamination by other samples; genetic data for subjects expected to be unrelated suggested this were true; and call rate of SNPs 496.5% per sample. Next ancestry of subjects in the Discovery Cohort was determined using dacGem in GemTools[66] based

on 5712 autosomal markers with non-call rate $\leqslant$ 0.001, minor allele frequency $\geqslant$ 0.05 and r2 $\leqslant$ 0.20

(Supplementary Figure S2). The samples

Figure 2. Discovery (a) and replication (b) analysis of Alzheimer disease with psychosis (AD+P) risk single-nucleotide polymorphisms (SNPs).(a) A total of 67 SNPs reached Po5e–4 in stage 2 samples (dashed line). (b) Stage 3 examined 60 of the 67 SNPs, 3 of which (top blue circles, Table 3) approached significance in meta-analysis (P = 1.61 × 10 − 6). In blue, SNPs showing same risk allele in stages 2 and 3; red, stage 2 versus 3 results differ in sign (risk allele); size of circle reflects meta-analysis –log10(P).

were separated into 5 clusters based on 3 significant ancestry dimensions, four of which likely represent European ancestry and two of these contain the bulk of the subjects ($\approx$ 66%). SNP QC was performed on data from these two clusters. SNPs passed QC if their call rate was 495%, minor allele

frequency was $\geqslant$ 0.01 and the exact Hardy–Weinberg equilibrium P-value was 40.005. Ancestry of samples in the Replication Cohort was determined using GemTools based on 79 autosomal ancestry-informative markers. The samples separated into three clusters based on two significant ancestry dimensions (Supplementary Figure S3).

Statistical analysis

Association between diagnosis and minor allele count for each SNP was assessed using logistic regression. For the Discovery Cohort, the model also accounted for first five ancestry dimensions, whereas for the Replication Cohort it accounted for two. Because some subjects in the Discovery Cohort were related as siblings, inference relied on the generalized estimating equation (gee) approach implemented in the statistical software R,67 assuming full siblings were correlated at 0.5 (that is, twice the kinship coefficient for full siblings).

To predict affection status using polygenic risk scores, either unweighted or weighted risk scores could be computed: the unweighted score for a subject is the sum of the count of risk alleles over all genotypes for that subject; a weighted score uses the same principle, but the count of risk alleles per SNP is adjusted by a function of the estimated effect of the SNP on risk (log odds ratio). Both unweighted and weighted scores for AD+P risk were calculated. Scores were derived from results from the Discovery Cohort and then used to predict AD+P status based on genotypes for each subject in the Replication Cohort. For the SCZ-risk score, only a subset of the 128 GWA significant SNPs could be genotyped. For genotyped SNPs, an unweighted score for each AD subject was estimated.

RESULTS

Association of AD+P with novel common variants

Not all of the subjects genotyped on the Axiom array were independent of our previously reported GWAS meta-analysis.29 Of the 2876 Discovery Cohort subjects described in Table 1a, 1157 of these subjects were in our prior GWAS and the remainder, 1799 subjects (969 AD+P and 750 AD − P), were independent. We, therefore, evaluated association both as a joint analysis of the sample sets (mega-analysis) and by analysis of the independent subjects. For the former, we used the traditional threshold for GWAS significance, $5 \times 10 - 8$; for the latter, we used a somewhat more lenient threshold-based sample sizes and the number of SNPs tested on both samples ($5.6 \times 10 - 8$).

For neither the joint analysis (Figure 2a) nor the independent analysis threshold (results not shown) was any SNP significantly associated with risk for AD+P. For the joint analysis there were 67 SNPs with $Po5 \times 10 - 4$ (Figure 2a). To test these SNPs we empaneled a Replication Cohort (Table 1b). We successfully designed and assayed either the SNP or a proxy in perfect LD for 60/67 target SNPs. We next used the results from the Discovery Cohort to assign the 'risk allele' at each of the 60 SNPs. Then, by counting the number of risk alleles carried by subjects in the Replication Cohort, we formed an unweighted risk score for each subject. This score significantly predicted AD+P status in the Replication Cohort, showing clear evidence for association (Table 2a). The same is true for a weighted score (Table 2a).

Moreover, although no single SNP was significantly associated with risk for AD+P within or across stages, and only three SNPs approached individual significance when combining stages (Figure 2b and Table 3), 41 out of the 60 SNPs had the same risk allele for both the Discovery and Replication Cohorts (Figure 2b; Fisher's exact test, $P = 0.0062$). The three SNPs that approached significance are in RP11-541P9.3 (an antisense transcript) located 5' to Cyclin G1 (CCNG1).

Association of AD+P with polygenic variation associated with schizophrenia

We previously described a significant association between AD+P and a summary statistic from a small number of putative schizophrenia and bipolar disorder risk alleles. Curiously, however, the direction of risk for most alleles was opposite in AD+P.29 Recently, 128 genome-wide significant SNPs at 108 independent loci have been identified in schizophrenia.30 When these loci were combined into a polygenic risk score, they explained ~ 3.4% of the variance in schizophrenia risk.30 We successfully genotyped 101 of these SNPs in the Discovery Cohort. We found that the corresponding unweighted risk score was significantly associated with AD+P (Nagelkerke's pseudo-$R2 = 0.32\%$, $P = 0.006$). We then genotyped the schizophrenia SNPs in the Replication Cohort. For this analysis, 94 SNPs remained after QC. Results clearly replicated, with close agreement between the two cohorts (Table 2b).

Of note, as in our earlier report,29 increasing schizophrenia polygenic risk score was associated with reduced risk of psychosis in AD. Consider, for example, its relationship within the Discovery Cohort. To better illustrate this relationship, we calculated an AD+P aligned risk score. For each of the SNPs comprising the schizophrenia polygenic risk score, the allele that increased the risk of developing AD+P was determined and a weighted sum of risks was then computed for each of the samples. The correlation between the AD+P aligned risk scores and the schizophrenia risk scores was − 0.159 (P = 5.5e − 18, Figure 3).

It should be noted that despite the overall protective effects of schizophrenia polygenic risk score on AD+P risk, a smaller number of individual schizophrenia risk SNPs were associated with increased risk of AD+P. Table 4a details the 20 SNPs that most consistently (as defined by the minimum of the sum of their individual SNP regression coefficients from the analysis of the Discovery and Replication Cohorts) were associated with reduced AD+P risk. Table 4b provides similar information for the 10 SNPs that most consistently were associated with increased AD+P risk in the two cohorts.

DISCUSSION

Psychosis occurs in approximately half of individuals affected by AD, serving to identify a subgroup with more rapid decline and poor outcomes. We, and others, have hypothesized that common genetic variation may contribute to the risk of psychosis in AD, based in part on evidence that AD+P aggregates in families, with an estimated heritability of 61%. However, prior studies of the association of common genetic variation with AD+P have been inconclusive.68,69 We now provide the first clear evidence in support of an association of AD+P with both a unique set of common variants and with a set of common variants associated with risk for schizophrenia. Several potential methodologic issues in determining the psychosis phenotype are important to consider in evaluating our findings. First, the need to aggregate multiple cohorts so as to have sufficient power for detection of association with common genetic variation meant that we included sites in which different rating scales were used for ascertainment of psychosis that could have contributed noise to our phenotypic classifications. Such a limitation, if present, would have reduced our power to detect differences between groups. Thus, it speaks to the robustness of our findings that despite this potential limitation, we were able to replicate associations across two independent, somewhat hetero-geneous cohorts. Perhaps this result is not surprising, in that significant familial aggregation of AD+P was previously identified in three separate family cohorts, each of which relied primarily on a different behavioral rating scale.4,25,26 Second, we chose to consider delusions and hallucinations together as a psychosis syndrome rather than evaluate them individually. The best approach to this issue likely depends on the question being asked. For example, when evaluating functional neuroanatomy, separation of these symptoms could make most sense. However, for genetic studies, there is substantial support for grouping these symptoms. Specifically, studies demonstrating familial aggrega-tion of AD+P4,25,26 have all used this joint definition, establishing it as suitable for genetic investigation. Similar data in support of individual psychotic symptoms do not exist. Finally, the relation-ships between clinical DLB diagnoses, Lewy body neuropathology and AD+P is complex.69,70 In brief, DLB pathology may contribute to some proportion, but clearly not account for most of the occurrence of AD+P. Nevertheless, all sites in the current study used standard diagnostic criteria to identify individuals with probable Lewy body dementia and exclude them from analysis (the one exception being the NIMH family study that predated the generation of DLB criteria, but did exclude individuals with parkinsonism or prominent early behavioral disturbance.71 As practical evidence that these diagnostic approaches are suffi-ciently rigorous to identify AD separately from DLB, the sites included in the current study have successfully contributed to discovery of common variants for AD risk.42

We identified a set of SNPs with suggestive association with AD+P in our Discovery Cohort, confirming this polygenic association with AD+P in an independent Replication Cohort. Although no individual SNP reached genome-wide significance in the meta-nalysis, the strongest associations were seen with three SNPs, rs300215, rs6859958 and rs999581, within a single locus. The function of the antisense transcript, RP11-541P9.3, is not known. However, it is located 5' to CCNG1 and is therefore likely to regulate CCNG1 expression. In support of this interpretation, rs6859958 and rs999581 have been shown to be eQTLs for CCNG1 in some tissues.[72] Most cyclins activate cyclin-dependent kinases, including CDK5, a Tau kinase that promotes phospho-Tau aggregation.[73] In contrast, CCNG1 has been proposed to competi-tively inhibit the activation of cyclin-dependent kinases by other cyclins.[74] Whether increased levels of Cyclin G1, the protein product of CCNG1, is therefore protective against pathological phosphorylation of Tau by CDK5 is not established. Nonetheless, in neocortex of AD subjects Cyclin G1 levels are increased in pyramidal neurons lacking Tau aggregates and are undetectable in those pyramidal neurons containing aggregated phospho-Tau.[75] Because the strongest brain correlate of psychosis in AD is excess phosphorylation of tau (in comparison with the degree of Tau phosphorylation in AD subjects without psychosis),[69] CCNG1 is thus also a strong functional candidate for AD+P risk.

We also identified and confirmed an association of polygenic risk for schizophrenia with a reduced risk of AD+P. At present, there are little convergent data from family studies to inform on the relationship of schizophrenia risk to AD+P.[9,76] The inverse nature of the association between schizophrenia risk score and AD+P may seem counterintuitive at first. In fact, it was the counterintuitive nature of our findings that motivated us to attempt to independently replicate them, finding a nearly identical association in a second large cohort. In contrast to our findings, schizophrenia has been shown to share polygenic risk with a number of complex disorders, such as autism and bipolar illness, that may include psychotic symptoms as part of the expressed phenotype.[77] Unlike AD+P, these are disorders of early, or late, neurodevelopment and thus do not occur in the context of neurodegeneration.

Possible genetic mechanisms underlying how the 108 schizophrenia-associated loci confer an increased risk of schizo-phrenia are just now emerging.[78–80] How these loci may lead to reduced AD+P risk cannot be asserted, but a few exemplars are worth discussion. First, a locus may alter expression of a single gene that has effects during neurodevelopment that increase schizophrenia risk, but when the same altered expression occurs in a brain with an active AD neurodegenerative process, it is protective. For example, rs75968099 is an eQTL for LRRFIP2 (Table 4), the gene encoding Leucine-rich Repeat Flightless-interacting Protein 2, a regulator of Toll-like receptor 4-mediated signaling in response to inflammatory stimuli. Toll-like receptor 4 signaling helps activate microglia to clear toxic amyloid β from the brain of an AD patient in early disease stages,[81] whereas microglial activation may contribute to excess synaptic elimination in development, increasing risk for schizophrenia.[78] Second, a locus may regulate the expression of gene transcription differently during early neurodevelopment than in the adult brain. Such an effect has recently been described for the schizophrenia risk locus defined by rs55833108, and may similarly be present at loci that confer opposing risks for schizophrenia and AD+P.[80] A third scenario might result from the observation that a SNP and/or locus may be an eQTL for more than one gene. For example, the locus on chromosome 17 defined by rs8082590 was recently reported to show consistent disease and eQTL associations for two genes, TOM1L2 and DRG2,[79] encoding Target of Myb1 Like 2 Membrane Trafficking Protein (TOM1L2) and Developmentally Regulated GTP-Binding Protein 2 (DRG2), respectively. DRG2 deactivates the early endosome regulator, Ras-related protein Rab-5A.[82] Thus, it is strongly positioned to impact glutamate neurotransmission, a process implicated in the pathogenesis of schizophrenia, via effects on neurotransmitter release[83] and on AMPA receptor

internalization.[84] In contrast, TOM1L2 is necessary for delivery of endosome cargo to autophagosomes that target protein aggregates and damaged organelles to lysosomes for degradation.[85] The autophagy pathway is strongly implicated in the pathogenesis of AD[86] and, more recently, of schizophrenia,[87] and is also downstream of Toll-like receptor 4 signaling.[88] Finally, we note that the above examples are not comprehensive. Other mechanisms may also contribute to different impacts of loci on risk for schizophrenia and AD+P.

As indicated in Table 4b, we also identified SNPs that showed the same direction of effect for schizophrenia and AD+P risk. Notable among these were two intronic SNPs located in CACNA1C, the gene encoding the voltage-dependent L-type calcium channel subunit alpha-1C. Although the genetic mechanism underlying these associations remains an area of active inquiry,[89] convergent data suggest that schizophrenia is associated with reduced voltage-dependent calcium channel function.[90–92] How reductions in voltage-dependent calcium channel function may further increase AD+P risk is not known, but impairments of intracellular Ca2+ homeostasis are present in AD and can contribute to synaptic dysfunction and cognitive impairments.[93]

We recently estimated the annual incidence of psychosis in AD at 10%.[40] Thus, there is an opportunity to intervene before psychosis onset if individual predictors can be identified. Although currently no treatments are established for prevention of AD+P, selective serotonin reuptake inhibitors have some efficacy for treating it,[22,23] and they have acceptable tolerability. Nonpharmacologic treatments may also offer benefit for treating AD+P (reviewed in Geda et al.[94] and Weamer et al.[40]) and could be adapted for prevention. It is thus worth considering whether genetic variants that associate with psychosis may serve as biomarkers to predict AD+P risk and the associated more rapidly declining cognitive trajectory. Because individual SNP relative risks are typically small, polygenic risk scores have greater predictive power.[31,95] We observed a very modest explanatory power of both the 60 SNP and the schizophrenia polygenic risk scores, each accounting for o1% of the AD+P risk. None of these effects is large enough to yield meaningful clinical prediction at present. Still, we note that these polygenic scores could have a different magnitude of effect on prediction of a related, clinically relevant construct, such as time to onset of psychosis. However, the development of predictive approaches would clearly benefit from the identification of additional risk loci. Nevertheless, the current findings are a step forward in the development of prevention for psychosis in AD.

In that regard it is noteworthy that our custom array, used to evaluate the Discovery Cohort, was derived, in part, from the one existing GWAS of AD+P. That earlier GWAS was underpowered and limited in the number of loci interrogated.[29] As a consequence, it is likely that many SNPs and loci that contribute meaningfully to AD+P risk were not tested in the current study. Despite this limitation, the current study provides confirmation of the hypothesis that AD+P is associated with common genetic variation. As such, it provides strong support for unbiased genome-wide scans of larger cohorts of AD+P and AD − P subjects that will surely identify individual AD+P risk loci and develop more strongly predictive polygenic risk scores.

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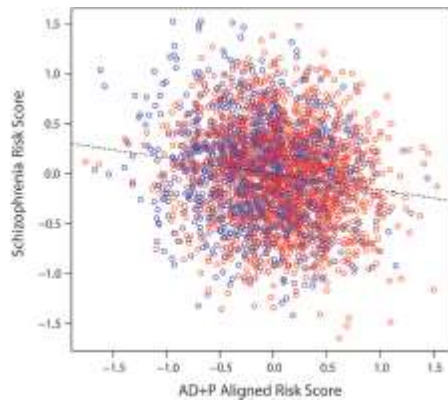
Figure 3. Relationship between schizophrenia risk score and risk of psychosis in Alzheimer disease (AD). Displayed are the risk scores for each subject; the score for schizophrenia uses the allele found to confer risk in Schizophrenia Working Group of the Psychiatric Genomics Consortium,30 whereas the AD+P aligned score uses the same SNPs but assigns risk according to the AD+P association results. Red and blue circles indicate AD+P and AD − P subjects, respectively. AD − P, Alzheimer disease without psychosis; AD+P, Alzheimer disease with psychosis; SNP, single-nucleotide polymorphism.