

RESEARCH ARTICLE

Genetic associations with psychosis and affective disturbance in Alzheimer's disease

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Abstract

INTRODUCTION: Individuals with Alzheimer's disease (AD) commonly experience neuropsychiatric symptoms of psychosis (AD+P) and/or affective disturbance (depression, anxiety, and/or irritability, AD+A). This study's goal was to identify the genetic architecture of AD+P and AD+A, as well as their genetically correlated phenotypes.

METHODS: Genome-wide association meta-analysis of 9988 AD participants from six source studies with participants characterized for AD+P AD+A, and a joint phenotype (AD+A+P).

RESULTS: AD+P and AD+A were genetically correlated. However, AD+P and AD+A diverged in their genetic correlations with psychiatric phenotypes in individuals without AD. AD+P was negatively genetically correlated with bipolar disorder and positively with depressive symptoms. AD+A was positively correlated with anxiety disorder and more strongly correlated than AD+P with depressive symptoms. AD+P and AD+A+P had significant estimated heritability, whereas AD+A did not. Examination of the loci most strongly associated with the three phenotypes revealed overlapping and unique associations.

Inga Margret Antonsdottir, Constantine Lyketsos, and Robert A. Sweet contributed equally to this study.

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DISCUSSION: AD+P, AD+A, and AD+A+P have both shared and divergent genetic associations pointing to the importance of incorporating genetic insights into future treatment development.

KEYWORDS

affective disturbance, Alzheimer's disease, genome-wide association, heritability, psychosis

Highlights

- It has long been known that psychotic and affective symptoms are often comorbid in individuals diagnosed with Alzheimer's disease. Here we examined for the first time the genetic architecture underlying this clinical observation, determining that psychotic and affective phenotypes in Alzheimer's disease are genetically correlated.
- Nevertheless, psychotic and affective phenotypes in Alzheimer's disease diverged in their genetic correlations with psychiatric phenotypes assessed in individuals without Alzheimer's disease. Psychosis in Alzheimer's disease was negatively genetically correlated with bipolar disorder and positively with depressive symptoms, whereas the affective phenotypes in Alzheimer's disease were positively correlated with anxiety disorder and more strongly correlated than psychosis with depressive symptoms.
- Psychosis in Alzheimer's disease, and the joint psychotic and affective phenotype, had significant estimated heritability, whereas the affective in AD did not.
- Examination of the loci most strongly associated with the psychotic, affective, or joint phenotypes revealed overlapping and unique associations.

1 | BACKGROUND

People living with Alzheimer's disease (AD) exhibit a range of neuropsychiatric symptoms (NPS) in addition to cognitive and functional declines¹⁻³ with up to 97% experiencing at least one NPS at some point in their illness.⁴ NPS are impactful to AD patients, their families, and care partners, and are associated with significant disability, morbidity, and mortality.⁵ For example, they are associated with more rapid cognitive and functional decline, greater caregiver burden, premature institutionalization,⁶⁻⁹ and accelerated mortality.¹⁰ Despite their importance, few effective therapeutic options exist for NPS.² For example, atypical antipsychotics are widely used to treat psychosis and agitation, despite very modest efficacy and risks of treatment-associated cardio or cerebrovascular events and mortality.¹¹ This likely reflects the very limited understanding of the neurobiological mechanisms underpinning the emergence of NPS, making it difficult to target pharmacologic therapies.

We previously addressed this gap in knowledge about NPS etiology by examining the genetic underpinnings of psychosis in AD (AD+Psychosis, AD+P). AD+P is defined by the presence of delusions and/or hallucinations, and in clinical populations affects approximately half of individuals living with AD at some point in their illness.¹²

We have shown that AD+P is a heritable phenotype,^{13,14} and more recently, we reported the first genome-wide significant associations of AD+P with loci within *ENPP6* and *SUMF1*.¹⁵ Of interest, genetic risk for AD+P positively correlated with genetic risk for depressive symptoms and negatively correlated with genetic risk for bipolar disorder,¹⁵ indicating a genetic overlap of AD+P with affective disturbances in individuals without AD.

It has been recognized for many years that psychosis and affective symptoms tend to co-occur in AD.⁴ Using Latent Class Analysis, Lyketsos et al. proposed three syndromic clusters of NPS in a population sample: (1) AD with psychosis (AD+P); (2) AD with affective disturbance (AD+A); (3) and a third group consisting of a range of individuals with minimal NPS. While AD+A primarily involves a cluster of dysphoria, anxiety, and/or irritability,¹ about 40% exhibit co-occurring psychotic symptoms as found in a community-dwelling sample.¹ Other studies have similarly demonstrated that psychotic and affective disturbance symptoms often overlap. For example, a factor analysis constructed from the Neuropsychiatric Inventory (NPI) responses of 2354 European persons with AD revealed four subgroups: apathy, hyperactive, affective, and psychotic. The affective and psychotic subgroups were present in 59% and 38% of their sample, respectively, with 24% experiencing a combination of clinically

meaningful psychotic and affective disturbance symptoms.¹⁶ Finally, in clinical settings, depressive symptoms are associated with the risk of AD+P.^{17–19}

Here, we expand upon the earlier AD+P genome-side association studies (GWAS)¹⁵ by evaluating 9988 participants in that study for the additional presence or absence of affective disturbance. Given the clinical co-occurrence of psychosis with affective disturbance, we were specifically interested in the genetic underpinnings of three clinical NPS phenotypes: AD+P, AD+A, and AD+A+P (a joint phenotype). We hypothesized that these phenotypes would have both shared and divergent genetic associations pointing to the importance of incorporating genetic insights into future treatment development.

2 | METHODS

2.1 | Participants

Participants were selected from among those included in our prior GWAS of psychosis in AD,¹⁵ based on the presence or absence of affective disturbance (see below). All were diagnosed with possible, probable,²⁰ and when available, autopsy-confirmed definite²¹ AD (for participant characteristics see Table 1). Diagnoses were based on diagnostic evaluations, cognitive testing, and in some cases neuropathologic assessment, conducted during participation in one of the following six source programs (see [Supplemental Material](#) for details for each source program), as previously described¹⁵: 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), and the University of Pittsburgh Alzheimer Disease Research Center (PITT ADRC). The collection of clinical data and genetic samples was approved by each source program's local Institutional Review Board or Medical Ethics Committee, as appropriate.

2.2 | Characterization of AD with psychosis (AD+P) and affective disturbance (AD+A)

Participants had already been characterized for the presence or absence of AD+P as previously described.¹⁵ In brief, AD+P presence was defined as the occurrence of delusions and/or hallucinations at any visit, within the individual source programs (including their sub-studies) using the CERAD behavioral rating scale²² (PITT ADRC and NIA-LOAD), the Neuropsychiatric Inventory Questionnaire (NPI-Q,²³ NIA-LOAD, and ADC), the NPI-Q Spanish Language Version²⁴ (ACE/GR@ACE), or the NPI²⁵ (LILLY and NEXGENS) (see the [Supplementary Material](#) for details of scoring cutoffs for each site and scale).

RESEARCH IN CONTEXT

- 1. Systematic Review:** We reviewed the current and past literature using traditional sources. Information relating to neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) and their genetic underpinnings are cited throughout the manuscript.
- 2. Interpretation:** In people with AD, three NPS phenotypes are common: an affective disturbance only (AD+A), a joint affective-psychotic (AD+A+P), and a psychosis only (AD+P) phenotype. We report evidence for both shared and distinct genetic correlates as well as associations of these three (AD+P, AD+A, or AD+A+P) phenotypes.
- 3. Future Directions:** As the development of treatment options for NPS progresses, leveraging these results will guide novel therapeutic approaches targeting these debilitating behavioral phenotypes of AD.

For subjects to be classified as AD-P, they had to have a score of 0 on all psychosis items at all visits and a last observed Mini-Mental State Examination²⁶ score < 20 or a CDR® Dementia Staging Instrument²⁷ score > 1.

For the same participants, AD+A was defined as having at least one clinically significant key symptom from the NPI or the NPI-Q [NPI (Lilly and NEXGENS), the NPI-Q (Pitt ADRC, NIALOAD, and ADC), or the NPI-Q Spanish Language Version (ACE/GR@ACE)]. Specifically, we used the symptom domains of depression, anxiety, and irritability as indicators of affective disturbance, derived from our prior latent class analysis (the additional symptom of euphoria was omitted due to its low frequency).¹ An a priori definition of the presence of AD+A was generated for the NPI and NPI-Q scales. The NPI rates frequency and severity of each NPS on scales from 0 to 4 (absent to daily or more often) and 0 to 3 (absent to severe), respectively. Frequency and severity scores were multiplied to give an overall domain score for each symptom ranging from 0 to 12. AD+A was defined as having depression, anxiety, or irritability with an overall domain score of ≥ 4 at any visit. AD-A was defined as having depression, anxiety, and irritability with an overall domain score < 4 at all visits. For the NPI-Q and NPI-Q Spanish Language Version, the presence of AD+A was defined as having depression, anxiety, or irritability with severity ≥ 2 at any visit. AD-A was defined as having depression, anxiety, and irritability with severity < 2 at all visits. Of the 12,317 subjects in our previous GWAS,¹⁵ 9988 had available data to determine the absence or presence of AD+A and, thus, could be included in this analysis (see Table S1). A greater fraction of the AD+P participants were missing data to determine the absence or presence of AD+A, 27.0% (1463) compared to 12.0% (825) of AD-P subjects, a significant difference ($\chi^2 = 444.2$, $df = 1$, $p < 2.2 \times 10^{-16}$). See the [Supplementary Material](#) for additional

TABLE 1 Participant characteristics

Parameter	AD-P		AD+P		Total	
	N (%) or mean (SD)	AD+A N (%) or mean (SD)	N (%) or mean (SD)	AD+A N (%) or mean (SD)	N (%) or mean (SD)	AD+A N (%) or mean (SD)
Female	6027 (60.3%)	2828 (46.9)	3961 (39.7)	2778 (70.1)	9988 (100.0%)	5606 (56.1)
Male	1810 (56.6)	1677 (59.3)	781 (66.0)	1817 (65.4)	2591 (59.1)	3494 (62.3)
Age of onset ^a	1389 (43.4)	1151 (40.7)	402 (34.0)	961 (34.6)	1791 (40.9)	2112 (37.7)
Age at consent ^a	74.4 (8.5)	73.7 (8.4)	74.5 (7.8)	73.1 (8.5)	74.5 (8.3)	73.4 (8.5)
Age at last visit ^a	75.9 (6.9)	74.9 (7.2)	78.3 (6.6)	76.1 (7.1)	76.7 (6.8)	75.4 (7.1)
Last MMSE ^a	80.6 (8.2)	80.5 (8.1)	82.4 (8.9)	80.8 (8.0)	81.1 (8.0)	80.6 (8.1)
Last CDR ^a	16.4 (6.1)	15.9 (6.7)	15.4 (6.3)	13.7 (6.7)	16.2 (6.2)	14.8 (6.8)
0.0	2 (0.1)	0 (0.0)	0 (0.0)	5 (0.2)	2 (0.05)	5 (0.1)
0.5	174 (5.2)	57 (1.9)	70 (5.2)	94 (3.2)	244 (5.9)	151 (2.8)
1.0	1,242 (37.1)	925 (30.8)	266 (19.8)	490 (16.5)	1508 (36.8)	1415 (26.3)
2.0	719 (21.5)	634 (21.1)	368 (27.4)	768 (25.9)	1087 (26.5)	1402 (26.0)
3.0	437 (13.1)	460 (15.3)	280 (20.8)	693 (23.4)	717 (17.5)	1153 (21.4)
4.0	291 (8.7)	438 (14.6)	55 (4.1)	310 (10.5)	346 (8.4)	748 (13.9)
5.0	483 (14.4)	487 (16.2)	306 (22.8)	602 (20.3)	199 (4.9)	508 (9.4)

Abbreviations: AD+A, Alzheimer's disease with affective disturbance; AD-A, Alzheimer's disease without affective disturbance; AD+P, Alzheimer's disease with psychosis; AD-P, Alzheimer's disease without psychosis; CDR, CDR® Dementia Staging Instrument; MMSE, Mini-Mental State Examination.

^a Data not available for some subjects/program sources. See [Supplementary Material](#) for details.

details of each source program's clinical assessment methodology and demographics.

2.3 | Statistical methods

2.3.1 | Univariate genetic association

Subjects from five source programs (ACE/GR@ACE, ADC, Lilly, NIALOAD, and PITT ADRC) had both phenotypes and genotypes ($N = 8714$). For each phenotype, AD+P (vs. AD-P) or AD+A (vs. AD-A), a GWAS was performed using data from these source programs with adjustment for three ancestry dimensions and, for chromosome X, an additional covariate for sex, as previously described.¹⁵ Because the NEXGENS consortium provided only summary statistics, we next combined the summary statistics from its GWAS with those from the five-source program GWAS by meta-analysis, as implemented in the program METAL.²⁸ A total of 9,424,397 unique single nucleotide polymorphisms (SNPs) were analyzed for AD+P and a similar number for AD+A (9,424,389).

2.3.2 | Bivariate genetic association

To perform a bivariate association analysis, one might combine the results from the AD+P and the AD+A analyses using METAL. This assumes, however, that the two association statistics for each SNP are uncorrelated; if they were correlated, the approach would elevate the false positive rate. Indeed, the association statistics are correlated, $\rho = 0.24$ ($p < 2.2 \times 10^{-16}$), and the genomic control $\lambda = 1.28$,²⁹ which is consistent with spurious inflation of the association signal. To adjust for this correlation, our first step was to compute an average regression coefficient β by taking a weighted average of the regression coefficients for psychosis and affective, β_P and β_A , respectively, using the standard errors for both to determine the weights (as in a standard METAL analysis). Specifically, $w_P = \frac{1/se_P}{1/se_P + 1/se_A}$, $w_A = (1 - w_P)$, and $\beta = w_P \beta_P + w_A \beta_A$. The standard error (se) for the combined estimate must take the correlation into account:

$se = \sqrt{w_P^2 se_P^2 + w_A^2 se_A^2 + 2\rho w_P w_A \sqrt{se_P^2 se_A^2}}$. The test statistic z and resulting p -value can then be calculated. By this approach, $\lambda = 1.04$, which is consistent with no spurious inflation of test statistics.

2.3.3 | Genetic correlation and heritability

Heritability and genetic correlation for AD+P and AD+A were calculated using GenomicSEM³⁰ and based on summary statistics from the association tests using the 1,135,456 SNPs that remained after merging our data with the LD-score files provided by GenomicSEM. Genetic correlations of phenotypes were based on GWAS summary statistics and used LD score regression.³¹

TABLE 2 Heritability (h^2) on liability scale as a function of the prevalence of psychosis and affective disturbance in individuals with AD

Prevalence	AD+P estimate (SE)	AD+A estimate (SE)
0.10	0.15 (0.05)	0.04 (0.05)
0.20	0.18 (0.07)	0.05 (0.06)
0.30	0.21 (0.07)	0.05 (0.07)
0.40	0.22 (0.08)	0.06 (0.07)
0.50	0.22 (0.08)	0.06 (0.07)

Abbreviations: AD, Alzheimer's disease; AD+A, Alzheimer's disease with affective disturbance; AD+P, Alzheimer's disease with psychosis; SE, standard error.

3 | RESULTS

3.1 | Association between the AD+P and AD+A phenotypes

Prior work has established that psychosis and affective symptoms are closely associated with AD.¹ We therefore first examined whether the same phenotypic association was present in our cohort. A total of 9988 participants were classified on the two phenotypes and their characterization on additional demographic and clinical variables is in Table 1. An affective syndrome was present in 70.1% of AD+P participants, as opposed to 46.9% of AD-P participants, a significant association ($\chi^2 = 522.02$ df = 1, $p < 2.2 \times 10^{-16}$).

3.2 | Heritability of AD+P, AD+A, and the joint affective-psychotic phenotype (AD+A+P)

We previously used family-based and common variant approaches to estimate the heritability of psychosis in AD.^{13,14} However, whether the presence of affective symptoms in AD identifies a heritable phenotype, or whether a joint affective-psychotic phenotype is heritable is not established. Evaluating a plausible range of prevalence had only a modest impact on the estimated heritability for either phenotype (Table 2). Based on a prevalence of AD+P and AD+A in AD subjects of 0.50, the estimated heritability ($h^2 \pm SE$) on the liability scale was 0.22 ± 0.08 (95% confidence interval (CI): 0.07–0.38) for AD+P, consistent with our earlier report. For AD+A the estimated h^2 on the liability scale was 0.06 ± 0.07 (95% CI: 0.00–0.19). The correlation between the two symptom domains on the liability scale was estimated to be 1.00 ± 0.52 (95% CI: 0.36–1.00). The estimated h^2 on the liability scale for the joint phenotype was 0.24 ± 0.08 (95% CI: 0.08–0.40).

3.3 | Genetic associations of AD+P and AD+A

Contrasting AD-P to AD+P genotypes across this subset of our original GWAS yielded results highly consistent with the earlier report

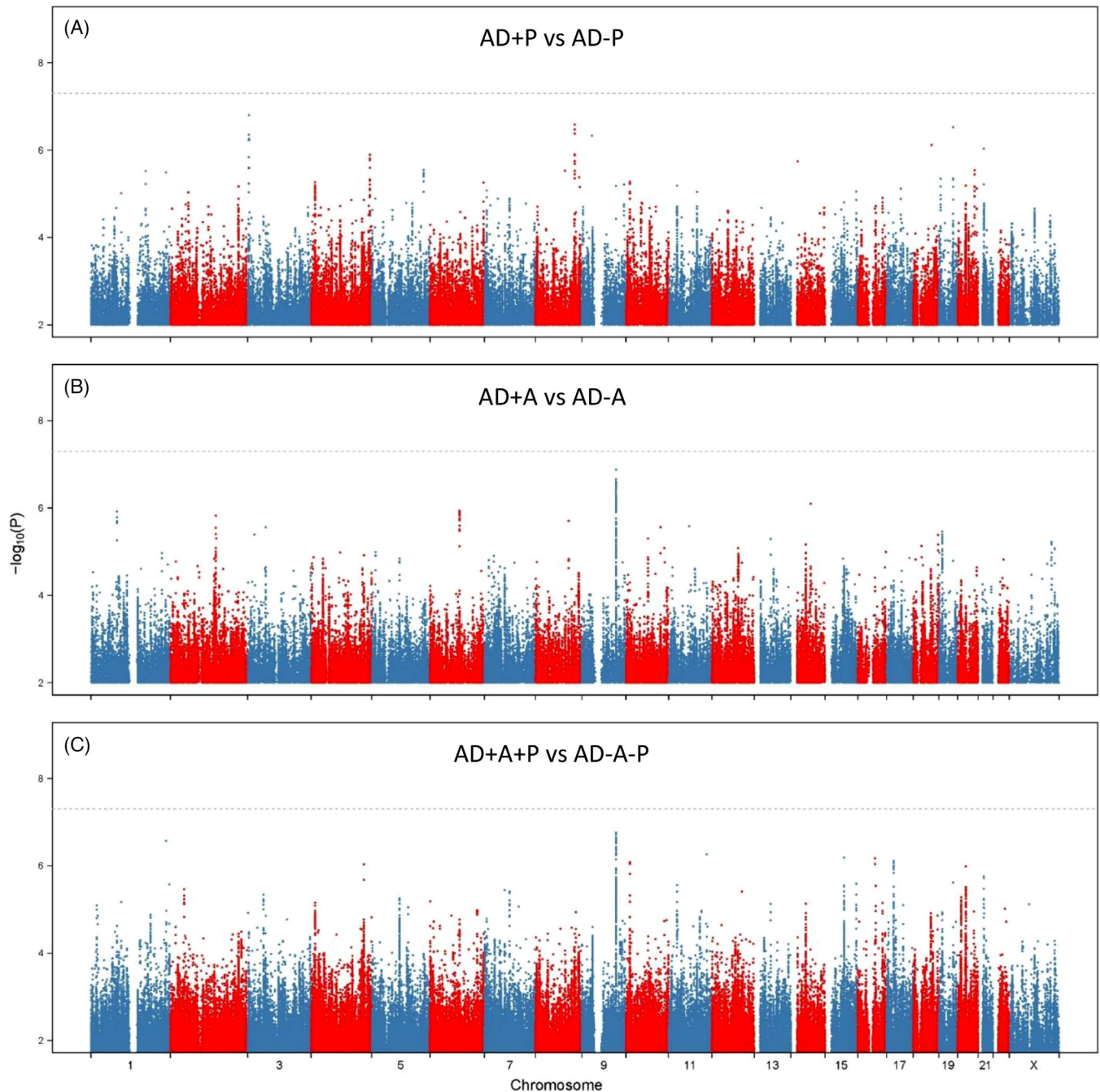


FIGURE 1 SNP associations with AD+P, AD+A, and joint analysis of associations. Manhattan plots for (A) AD+P versus AD-P, (B) AD+A versus AD-A, and (C) the joint AD+A+P versus AD-A-P association statistics. The x-axis shows the genomic position for autosomes and the X chromosome. The y-axis shows statistical significance as $-\log_{10}(P)$. Each point represents an analyzed SNP. The dashed horizontal line represents the threshold for genome-wide significance ($p = 5 \times 10^{-8}$). AD, Alzheimer's disease; AD+A, Alzheimer's disease with affective disturbance; AD-A, Alzheimer's disease without affective disturbance; AD+A+P, Alzheimer's disease with psychotic and affective disturbance; AD-A-P, Alzheimer's disease without psychotic or affective disturbance; AD+P, Alzheimer's disease with psychotic symptoms; AD-P, Alzheimer's disease without psychotic symptoms

(Figure S2),¹⁵ albeit with the reduced number of individuals in the current analysis, no single SNP reached genome-wide significance. Nevertheless, support for our previously identified genome-wide significant associations of AD+P with loci located within introns of *ENPP6* (best SNP rs9994623, odds ratio (O.R.) (95% CI) 1.16 (1.10, 1.22), $p = 1.25 \times 10^{-8}$) and an alternatively spliced variant of *SUMF1* (SUMF1-

204 ENST00000448413.5, best SNP rs201109606, but with O.R. 0.67 (0.57–0.78), $p = 1.58 \times 10^{-7}$) persisted.¹⁵

The contrast of AD-A genotypes to AD+A is in Figure 1B. No SNP reached genome-wide significance in this contrast (Table 2), although a locus at 9q31 spanning *RAD23B* approached significance (Table 3, best SNP rs1805331, O.R. 0.80 (0.74, 0.87), $p = 1.33 \times 10^{-7}$). The behavior

TABLE 3 Best SNP at each locus with $p < 5 \times 10^{-7}$ in association with AD+P, AD+A, or the joint AD+A+P phenotype

CHR	hg38.BP	SNP	Allele1	Allele2	Phenotype	B	SE	Z	p-Value	OR	I95OR	U95OR
1	235155396	rs112368830	T	C	AD+A+P	0.327	0.063	5.143	2.70E-07	1.386	1.224	1.570
3	3790149	3:3831833	A	G	AD+P	-0.405	0.077	-5.245	1.58E-07	0.667	0.573	0.776
8	123553071	rs16898561	A	G	AD+P	-0.276	0.054	-5.149	2.61E-07	0.759	0.683	0.843
9	32594702	rs780116570	CT	C	AD+P	-1.678	0.333	-5.041	4.64E-07	0.187	0.097	0.359
9	107318695	rs1805331	A	T	AD+A	-0.220	0.042	-5.276	1.33E-07	0.803	0.740	0.871
9	107244052	rs12004883	A	G	AD+A+P	-0.149	0.029	-5.225	1.75E-07	0.861	0.814	0.911
9	107244562	rs35188506	A	G	AD+A+P	-0.149	0.029	-5.225	1.75E-07	0.861	0.814	0.911
9	107244623	rs60819822	A	G	AD+A+P	-0.149	0.029	-5.225	1.75E-07	0.861	0.814	0.911
19	44908684	rs429358	T	C	AD+P	-0.180	0.035	-5.131	2.97E-07	0.835	0.780	0.895

Abbreviations: AD+A, Alzheimer's disease with affective disturbance; AD+A+P, Alzheimer's disease with psychosis and affective disturbance; AD+P, Alzheimer's disease with psychosis; B, estimate; CHR, chromosome; hg38.BP, homo sapiens genome assembly GRCh38 from Genome Reference Consortium; I95OR, lower limit of the odds ratio; OR, odds ratio; p, p value; SE, standard error; SNP, single nucleotide polymorphism; Z, z score; U95OR, upper limit of the odds ratio.

TABLE 4 Estimated genetic correlations of AD+P and AD+A with a selected set of neuropsychiatric phenotypes

Parameter	AD+P			AD+A			AD+P-AD+A ^d		
	Estimate	SE	p-Value	Estimate	SE	p-Value	Estimate	SE	p-Value
Alzheimer's disease ³⁷	0.19	0.17	0.267	0.23	0.25	0.369	-0.04	0.22	0.869
^a Anxiety disorders ³⁸	0.08	0.26	0.751	1.00	0.48	0.034	-0.94	0.42	0.024
Bipolar disorder ³⁹	-0.17	0.08	0.036	-0.27	0.16	0.095	0.10	0.14	0.457
^b Depressive symptoms ⁴⁰	0.21	0.11	0.065	0.62	0.24	0.010	-0.41	0.21	0.049
Major depressive disorder ⁴¹	0.12	0.08	0.150	0.27	0.14	0.057	-0.16	0.12	0.212
Schizophrenia (PGC3, 2020)	0.00	0.06	0.974	-0.01	0.13	0.945	0.01	0.11	0.922
^c Height ⁴²	-0.01	0.07	0.893	-0.00	0.12	0.967	-0.00	0.10	0.964

Abbreviations: AD+A, Alzheimer's disease with affective disturbance; AD+P, Alzheimer's disease with psychosis; p, p value; PGC3, Psychiatric Genomics Consortium Wave 3; SE, standard error.

Note: The non-neuropsychiatric phenotype, height, was also included as a control comparison. AD+P-AD+A tests whether the genetic correlation of each trait differs between the AD+P and AD+A phenotypes.

^aUsing the case-control genome-wide association studies results.

^bDepressive symptoms were analyzed as a continuous phenotype.

^cResults from an early report of the GIANT study, later reports combined height and body mass index (BMI) in meta-analyses.

^dUsing the same formula as before with $w_p = 1$, $w_A = -1$, and $\rho = 0.50$.

of the association statistics, as assessed by the probability-probability plot (Figure S2), suggests there is a signal to detect, and significant associations could emerge with increased sample sizes.

3.4 | Bivariate analysis of the AD+A+P (joint) phenotype

The bivariate association tests are in Figure 1C. Again, no SNP reached genome-wide significance in this contrast. However, the locus at 9q31 spanning *RAD23B* identified in the analysis of AD+A again approached significance (Table 3, best SNP rs60819822, O.R. 0.86 (0.81, 0.91), $p = 1.75 \times 10^{-7}$). Another single SNP, rs112368830, an intronic SNP in *RBM34* at 1q42 also approached significance (O.R. 1.39 (1.22, 1.57), $p = 2.70 \times 10^{-7}$, see Extended Data File 1 for a list of all SNPs with $p < 10^{-4}$ in any of the three contrasts: AD+P vs. AD-P, AD+A vs. AD-A, and

AD+A+P vs. AD-P-A). As seen for the analysis of AD+A, the behavior of the association statistics for AD+A+P, as assessed by probability-probability plot (Figure S2), suggests there is the signal to detect, and significant associations could emerge with increased sample sizes.

3.5 | Genetic correlation of AD+P and AD+A with other phenotypes

We previously reported that AD+P had significant positive correlations with depressive symptoms and major depressive disorder and a significant negative genetic correlation with bipolar disorder.¹⁵ We hypothesized that given the phenotypic overlap and genetic correlation between AD+P and AD+A, AD+A would also be genetically correlated with mood phenotypes (Table 4). Like AD+P, AD+A had positive genetic correlations with depressive phenotypes, while showing

negative correlations with bipolar disorder. AD+A, but not AD+P, was also positively genetically correlated with anxiety disorders. Finally, we note that both conditions had non-significant (albeit moderate positive) genetic correlations with AD itself.

4 | DISCUSSION

In this GWAS of 9988 individuals with AD, 32% had neither NPS phenotype, equal groups (28% each) exhibited the affective only (AD+A) or the joint psychotic-affective phenotype (AD+A+P), and a smaller group (12%) exhibited the psychotic only phenotype (AD+P). These estimates match a population-based sample of individuals,¹ highlighting that there are twice as many individuals with AD+A+P versus AD+P alone. Not surprisingly, given the degree of phenotypic overlap, the three phenotypes were genetically correlated. Nevertheless, some differences emerged. The joint AD+A+P phenotype, like AD+P, had evidence of significant heritability. In contrast, estimates of the heritability of AD+A were lower and not statistically significant. Differences between AD+P, AD+A, and AD+A+P in their genetic correlations with other neuropsychiatric syndromes were apparent, as were differences in the SNPs most strongly associated with each phenotype.

Treatment of psychotic and affective symptoms in AD can include “eco-psycho-social” approaches and/or medication treatment. Eco-psycho-social interventions are the first line option; however, implementation can be costly, time-consuming, and risky if the person is in a position where they may harm themselves or others. Antipsychotic medications have been studied in randomized controlled trials and large-scale cohort studies, yet they are associated with a 1.5- to 1.7-fold increased mortality among many other risks.³² Thus, there remains a critical need for further development of safe and effective therapies.

Importantly, our findings have several implications for treatment development targeting NPS in AD. First, the high frequency of AD+A+P suggests that the joint phenotype should be an independent focus for treatment development, as these individuals may respond differently to medications than their pure AD+A or AD+P counterparts. However, trials assessing pharmacologic treatments for NPS may not report on enrollment of individuals with both groups of symptoms or report treatment effects specific to each phenotype,³³ although the CitAD targeted agitation study reported that citalopram had efficacy for both psychotic and affective symptoms.³⁴

Second, the degree of genetic correlation between AD+P and AD+A suggests they may also share biology that could be targeted concurrently to relieve both sets of symptoms. For example, in CitAD, 19% and 23% in the selective serotonin reuptake inhibitor (SSRI) treatment and placebo groups had hallucinations not requiring antipsychotic treatment at baseline, reduced to 13% and 16% at week 9 of the trial, respectively. Additionally, participants were less likely to develop delusions in the SSRI group (4%) than in the placebo group (10%).³⁴ Though that study was not intended to examine the response of psychotic symptoms to SSRI treatment, other studies of psychosis in the

presence of agitation have similarly reported its response to SSRI treatment.^{35–37}

Conversely, the divergence in the genetic correlates of AD+P and AD+A suggests that treatment of the joint AD+A+P phenotype may benefit from strategies that target these independent pathways concurrently with separate treatments to achieve synergistic effects. For example, we used an *in silico* approach to predict combinations of antipsychotic and antidepressant medications that would have synergistic effects for the treatment of AD+P.³⁸ The strongest predicted benefits amongst combinations of currently approved agents were for aripiprazole with maprotiline, sertraline, or mirtazapine. Whether testing these combinations, or others, it may be worth considering empirical evaluation of combination treatment for AD+A+P.

Of interest, genetic risk for AD was not significantly correlated with risk for AD+P and AD+A (though in both cases the magnitude of correlation was moderately positive). Loci that are associated with the risk of developing AD but are not associated with the risk of developing a behavioral phenotype should be equally present in individuals with and without the behavior (i.e., AD+P vs. AD-P, AD+A vs. AD-A). That would result for a given locus in an O.R. not different from 1.0 for its association with AD+P or AD+A. If only such loci were present, AD risk would not genetically correlate with the genetic risk for AD+P or AD+A, as seen here. The lack of significant correlation implies that psychosis and affective symptoms in AD derive from a set of genetic and neurobiological factors superimposed on, yet independent of, those causing AD itself, further motivating the search for treatments specific for these behaviors.

We did not observe loci with genome-wide significant associations with any of the three phenotypes. Several lines of evidence suggest this is due to the limited power inherent in our sample of 9988. Probability-probability plots for all three phenotypes suggest an excess of small *p*-values, suggesting that with increased sample size some would reach the threshold for genome-wide significance. In fact, just such a situation exists for AD+P, as two loci with suggestive association with AD+P in this smaller sample, within *ENPP6* and *SUMF1*, were genome-wide significant in the larger sample of 12,317 in our original report.¹⁵ To our knowledge, this is the first GWAS of AD+A and AD+A+P; thus, comparable prior data are not available for these phenotypes. Nevertheless, it is likely that some of the loci approaching significant associations with AD+A or with the AD+A+P phenotype, for example, at the locus at 9q31 within *RAD23B*, will reach genome-wide significance when assessed in larger samples. However, pending such a study, the alternative possibility, that risk for AD+A or AD+A+P is not associated with genetic variation, cannot be excluded by the current data.

The loci identified in our previous¹⁵ and current studies, *ENPP6*, *SUMF1*, and *RAD23B* could have a functional impact on AD+P, AD+A, and AD+A+P. The functions of *ENPP6* and *SUMF1* in relation to AD+P are described in more detail elsewhere.^{15,39} Briefly, *ENPP6* is expressed in differentiating oligodendrocytes⁴⁰ and based on increased *ENPP6* mRNA expression, plays a critical role in early motor learning.^{41,42} *SUMF1* is found in the cerebral cortex⁴³ and has been linked to neurodegeneration.⁴⁴ *RAD23B* functions in DNA damage repair, the ubiquitin-proteasome system, and ER-associated

degradation,⁴⁵ disturbances in any of which may influence the onset or progression of neurodegenerative disease. RAD23B also co-localizes with pTDP-43 pathology,⁴⁵ a frequent pathologic comorbidity in AD which may also influence AD+P risk.⁴⁶

Our sample size may also have limited the power to detect significant heritability of the AD+A phenotype, unlike AD+P and AD+A+P. Of interest, the estimated h^2 for AD+A was notably (albeit not significantly) lower than that estimated for AD+P. It is likely that this difference in magnitude of estimated heritability between AD+A and AD+P reflects a greater contribution of environmental (i.e., non-genetic) factors to the presence of affective symptoms than to the presence of psychosis in individuals with AD. A similar difference in the magnitude of heritability estimates exists, for example, between major depression and schizophrenia.⁴⁷

Different rating scales (CERAD behavioral rating scale, NPI-Q, NPI-Q Spanish Language Version, and NPI) were used to define AD+P and AD+A. How these scales are completed, some by clinician-interview, others informant-reported, also differ. Although this strategy allowed for a larger sample size, it may be a limitation, as the participants could have been categorized differently had they been assessed with one of the other measures. Nevertheless, each of these instruments has been tested in AD and, with regard to AD+P, our approach is consistent with that of other studies.^{12-15,48-51}

An additional potential limitation of our approach to defining AD+P and AD+A is that we defined these behavioral phenotypes by the presence of one or more of multiple individual symptoms. While our choice of phenotype definitions reflects the clustering of these symptoms within individuals with AD (e.g., delusions/hallucinations co-occur in AD far more frequently than by chance, similarly for depression/anxiety/irritability), it is possible that relevant subgroups within the AD+P and AD+A phenotypes may exist and be defined by individual symptoms and account for any detected associations. Finally, we note that participants had reached various stages of illness during this study, therefore, had some participants developed NPS after data extraction or genetic sampling occurred, they may have been incorrectly classified in the current sample, reducing the potential power to detect associations. This concern is greater for psychosis, which increases in frequency rapidly between the early and middle stages of the disease,⁵² and less of a concern for affective symptoms which are often present in the prodrome and early disease stages.⁴ We attempted to mitigate this concern for psychosis by requiring subjects classified as AD+P to have reached at least a stage of mild to moderate disease severity.

Clinically, providers and family can be on the lookout for affective and psychotic symptoms knowing that these symptoms may cluster together and impact treatment plans and outcomes. Understanding the genetic and neurobiological underpinnings of NPS in AD may help create personalized treatment plans for patients and drive drug repurposing and development. The current study represents a step in this direction, examining the genetic overlap and divergence of AD+P and AD+A phenotypes. However, further work in larger cohorts is needed to identify specific loci associated with AD+A and AD+A+P.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the [supporting information](#).

CONSENT STATEMENT

All human subjects provided informed consent.

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