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Genetics of Psychosis in Alzheimer Disease

Mary Ann A. DeMichele-Sweet · Robert A. Sweet

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Abstract Psychosis occurs in approximately half of patients with Alzheimer disease (AD with psychosis, AD + P). AD + P patients have more rapid cognitive decline, greater behavioral symptoms, and higher mortality than do AD patients without psychosis. Studies in three independent cohorts have shown that psychosis in AD aggregates in families, with estimated heritability of 29.5–60.8 %. These findings have motivated studies to investigate and uncover the genes responsible for the development of psychosis, with the ultimate goal of identifying potential biologic mechanisms that may serve as leads to specific therapies. Linkage analyses have implicated loci on chromosomes 2, 6–8, 15, and 21 with AD + P. Association studies on apolipoprotein E do not support it as a risk gene for psychosis in AD. No other candidate genes, such as neurodegenerative and monoamine genes, show conclusive evidence of association with AD + P. However, a recent genome-wide association study has produced some promising leads, including among them genes that have been associated with schizophrenia. This review summarizes the current knowledge on the genetic basis of AD + P.

Keywords Alzheimer disease · Psychosis · Heritability · Linkage analysis · Genome-wide association · Association study

M. A. A. DeMichele-Sweet · R. A. Sweet (✉)
Department of Psychiatry, University of Pittsburgh, Biomedical Science Tower, Rm W-1645, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA
e-mail: sweetra@upmc.edu

R. A. Sweet
Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA

R. A. Sweet
VISN 4 Mental Illness Research, Education and Clinical Center (MIRECC), VA Pittsburgh Healthcare System, Pittsburgh, PA, USA

R. A. Sweet
Biomedical Science Tower, Rm W-1645, Lothrop and Terrace Streets, Pittsburgh, PA 15213-2593, USA

Background

A subgroup of late-onset Alzheimer disease (AD) patients develops psychosis during progression of the disease (AD with psychosis, AD + P). Psychotic symptoms in AD are typically defined by the presence of delusions and hallucinations. Psychosis in AD subjects has been reported to range in prevalence from 12.2 to 74.1 % (median 41 %) and have a cumulative incidence approximating 50 % [1•]. The variability in reported prevalence may be explained by the fact that the development of AD + P is dependent on the stage of the disease, with low prevalence in the prodromal stage, a large increase in occurrence during early AD and highest prevalence in the middle disease stages [2, 3]. Numerous studies have shown that greater cognitive impairment is the most consistent correlate of AD + P compared to AD patients without psychosis [4]. With estimates of more than 13 million people affected with AD by the year 2050, AD + P may soon be the second most common psychotic disorder (schizophrenia being first) in the US [5].

The presence of psychotic symptoms in AD patients has a negative impact on the patient, family, and caregiver. AD + P patients often have other psychiatric and behavioral disturbances, the most frequent and troublesome of which are agitation [6] as well as verbal and physical aggression [7, 8]. Overall, AD + P leads to greater distress for family and caregivers [9], greater rates of institutionalization [10–13],

and worse general health for the patient [14], with increased mortality [15, 16] compared to patients with AD − P.

Treatment of psychosis in AD patients with typical and atypical antipsychotics has been suboptimal. Their efficacy is low, and they have serious side effects for this population [17–19]. These drugs were developed for treatment of psychotic symptoms in a population without co-occurring dementia, so their biological specificity in AD + P patients may be poor. It is, therefore, important to determine the pathogenesis of psychosis in AD so that better pharmaceutical treatments can be developed for this subgroup of patients. During the past 10 years, substantial information from brain imaging, neuropathological, clinical, and genetic studies has begun to accrue regarding the neurobiology of AD + P [1•]. This review summarizes research findings regarding the genetic basis of psychosis in AD.

Familial Aggregation and Heritability

Several studies have examined whether psychosis in AD (AD + P) runs in families. An early study that examined familial aggregation in sibling pairs diagnosed with AD found that the frequency of psychosis in these patients was 0.41 [20]. The pair-wise concordance for psychosis was 0.21, which was modestly higher than expected by chance alone, 0.17 (Table 1•).

A larger study was done by Sweet et al. [21••] in which they looked at a family cohort in the National Institute of Mental Health (NIMH) AD Genetics Initiative. All probands and their siblings were diagnosed with AD and were tested for familial aggregation of AD + P. Of the 371 probands and their 461 siblings in the study, 75.5 % of the probands were positive for psychosis. They found a significant association between psychosis in the proband and the occurrence of AD + P in their siblings (Table 1). Similar results were obtained when covariates for age, age-of-onset, and the presence of extrapyramidal symptoms were accounted for. Interestingly, when a more restrictive definition of AD + P requiring multiple psychotic symptoms to be present over time was used in the model, the familial aggregation was strengthened.

Following this study, which showed that psychosis in AD aggregates in families, Bacanu et al. [22•] then employed statistical modeling to estimate the heritability of psychosis among 826 of the individuals from their prior report. The heritability of an occurrence of a single psychotic symptom was modest (29.5 %, $p = 0.04$), but when heritability was assessed using the more restrictive definition of psychosis requiring multiple or recurrent symptoms, it increased to 60.8 %, $p = 0.004$. The odds ratio (OR) for at least one psychotic symptom was 2.37 (1.45–3.87), and it increased to 5.42 (2.62–10.43) for multiple psychotic symptoms [22•] (Table 1).

Hollingworth et al. [23•] expanded the work of Sweet et al. by combining the data of the NIMH cohort with families recruited from the UK. A significant association existed between the psychosis status of the probands and the occurrence of AD + P in family members in both the NMIH and UK samples. The OR in the NIMH sample for the development of AD + P in siblings of probands with AD + P was 3.2 (2.05–4.99). Similar findings were obtained in the UK sample with an OR of 4.17 (1.67–10.44). For the combined sample of NIMH and UK families, the OR was 3.38 (2.27–5.05) (Table 1).

Sweet et al. [3] confirmed previous aggregation studies by looking at families in which multiple members were affected with late-onset AD and were part of the National Institute on Aging Late Onset AD Family Study. The association of psychosis in the proband with AD + P in other family members was highly significant ($\chi^2 = 15.8, \mathrm{df} = 4, p = 0.003$; Table 1).

In summary, studies of three independent cohorts have found evidence of significant familial aggregation of

Table 1 Familial aggregation studies of psychosis in siblings of probands with Alzheimer disease and psychosis (AD + P)

Author, references	Data set	Proband (*n*)	Siblings (*n*)	Odds ratio, *p* value
Tunstall et al. [20]	UK	DNS	DNS	Excess pair-wise concordance = 0.04
Sweet et al. [21••]	NIMH	371	461	2.4 (1.46–4.0) for AP, $p < 0.0006$
				3.18 (2.17–4.66) for MP, $p < 0.0001$
Bacanu et al. [22•]	NIMH	370	456	2.37 (1.45–3.87) for AP, $p < 0.001$
				5.42 (2.62–10.43) for MP, $p <$ 10–6
Hollingworth et al. [23•]	NIMH	305	359	3.2 (2.05–4.99), $p < 0.001$
	UK	91	98	4.17 (1.67–10.44), $p = 0.002$
	Combined	396	457	3.38 (2.27–5.05), $p < 0.001$
Sweet et al. [3]	NIA LOAD Family Study	143	334	3.80 (1.54–9.40), $p = 0.003$

UK United Kindgom, *NIMH* National Institute of Mental Health, *NIA* National Institute on Aging, *LOAD* late-onset Alzheimer disease, *DNS* data not shown, *AP* at least one psychotic symptom was present during the course of AD, *MP* multiple or recurrent psychotic symptoms were present during the course of AD

psychosis in AD. Study of a fourth cohort found suggestive evidence of the same. The estimated heritability of AD + P, when defined by multiple and/or recurrent psychotic symptoms, was 60.8 %. Taken as a whole, these findings provide compelling support for the hypothesis that psychosis in late-onset AD has a genetic basis and a firm rationale for studies exploring the underlying genetic associations.

Genetic Linkage Studies

With the identification that psychosis in AD aggregates in families, several studies were done to identify chromosomal loci that might be linked to and predispose AD patients to the development of psychosis. The first linkage study of AD + P found significant linkage on chromosome 2p and suggestive linkage on chromosomes 6 and 21 [24•]. Hollingworth et al. [23•] examined linkage using the combined NIMH and UK cohorts described earlier. In the NIMH sample, significant linkage was found on chromosomes 7 and 15. They also found suggestive evidence of linkage to loci on chromosomes 6 and 21; however, these loci were no longer significant after the inclusion of the apolipoprotein E (*APOE*) genotype as a covariate.

Neuregulin-1 (NRG1) on chromosome 8 is a gene of interest in psychosis because both linkage and association have been found for NRG1 in patients with schizophrenia [25]. A study examining 437 families from the NIMH AD Genetics Initiative found significant linkage for NRG1 and AD + P [26•]. Go et al. [26•] then analyzed four specific single nuclear polymorphisms (SNPs) within NRG1 for linkage and association with AD + P. Three of these SNPS were part of the Icelandic haplotype reported to be associated with risk for schizophrenia (SNP8NRG221533, SNP8NRG243177, SNP8NRG2419) [27]; the fourth was an exonic SNP (rs392499). In single SNP analyses, only rs392499 showed significant association with AD + P.

The previous studies that found significant linkage with psychosis to loci on chromosomes 2, 6–8, and 15 utilized a definition of psychosis that included the occurrence of either delusions or hallucinations. A study by Avramopoulos et al. [28] examined linkage separately for delusions and hallucinations. They found a region on chromosome 14 that was linked to AD patients without hallucinations. The linked region was close to, but independent of, the PSEN1 locus. They also found linkage of chromosome 2 with delusions in AD patients.

Genome-Wide Association Studies (GWASs)

The first GWA analysis of AD + P was recently reported [29••], combining meta-analytically three AD GWA data sets [30–32]. The final analyzed sample included 1,299 cases with AD + P, 735 with AD − P and 5,659 controls unaffected by AD. After imputation, 1,882,172 SNPs were evaluated in the contrast of AD + P versus AD − P. The AD + P versus control contrast included 1,847,262 SNPs.

The results for the AD + P versus AD − P and AD + P versus control analysis are shown in Table 2. Among the most significant SNPs in the AD + P versus AD − P analysis was rs3764640 in serine/threonine kinase 11, STK11 [29••]. STK11 deletions are known to cause Peutz-Jeghers syndrome. However, a case with an unusually large STK11 deletion has been described in which Peutz-Jeghers syndrome, mental retardation, and schizophrenia co-occurred [33]. Similarly, a genome-wide screen in siblings co-affected by schizophrenia found reduced copy numbers of STK11 in 3/18 individuals, significantly more often than in controls [34]. Finally, STK11, also known as liver kinase B1, is a necessary intermediate in amyloid beta (Aβ) precursor protein (APP) overexpression-induced tau phosphorylation [35, 36].

In the AD + P versus control analysis, the most significant intragenic SNP was rs4038131, an intronic SNP in visinin-like 1 (VSNL1). rs4038131 also showed evidence of association with AD + P versus AD − P (OR 0.72, $p = 1.84 \times 10^{-2}$) [29••]. VSNL1 encodes the neuronal calcium sensor, visinin-like protein 1, Vilip1 [37]. Cerebrospinal fluid and plasma concentrations of Vilip1 are elevated in AD subjects in comparison to normal controls [38, 39] and to non-AD dementia subjects [39]. In early AD, elevated cerebrospinal fluid Vilip1 levels predict more rapid cognitive decline [40]. Of interest, expression of VSNL1 mRNA and Vilip1 protein is also reported to be altered in schizophrenia [41, 42].

In contrast to the above findings, a number of loci recently identified as associated with risk of AD, including clusterin, phosphatidylinositol-binding clathrin assembly protein, complement receptor 1, bridging integrator 1, ATP-binding cassette transporter 7, membrane-spanning 4-domain subfamily A, CD2-associated protein, CD33, and ephrin type-A receptor 1 were not associated with AD + P when compared to AD − P cases. Similarly, *APOE*/TOMM40 (translocase of outer mitochondrial membrane 40 homolog) SNPs were not associated with AD + P when compared to AD − P [29••].

Finally, prior GWASs had identified a number of loci with risk for schizophrenia and bipolar illness [43–49]. Hollingworth et al. [29••] sought to determine whether these SNPs might share an association with psychosis in AD. In the same GWAS cohorts described above, we tested 11 SNPs that had genome-wide evidence for association with schizophrenia or bipolar illness. Individually, none of the SNPs had an association with psychosis in AD; however, there was a trend toward association when all SNPs were grouped (combined $p = 0.109$).

Table 2 Genome-wide association study (GWAS) of AD + P patients versus controls and AD − P patients

SNPs	Chr	MB	MAF	Closest RefSeq gene	GWAS *p*	OR
AD + P versus controls						
rs6834555	4	9.7	0.21	SLC2A9	3.06E−07	1.39
rs4038131	2	17.6	0.07	**VSNL1**	5.90E−07	0.64
rs16970672	17	73.5	0.29	AC015804.1	1.67E−06	1.29
rs9811423	3	114.3	0.47	**RP11-572M11.4**	4.18E−06	1.28
rs733175	4	9.7	0.18	**SLC2A9**	4.97E−06	1.36
rs4360367	9	31.6	0.09	RP11-402B2.1	5.90E−06	0.68
rs4746003	10	71.2	0.25	RP11-242G20.2	5.95E−06	1.29
rs9789748	2	17.7	0.07	**VSNL1**	7.39E−06	1.50
rs1464108	12	129.6	0.32	RIMBP2	8.19E−06	1.27
AD + P versus AD − P						
rs753129	4	56.4	0.24	AC110611.1	2.85E−07	0.66
rs2969775	2	47.7	0.37	AC079250.1	2.11E−06	0.68
rs257016	5	123.2	0.36	AC008541.1	4.06E−06	0.70
rs6509701	19	58.1	0.30	ZNF320	5.41E−06	0.71
rs16922670	9	105.1	0.14	**RP11-341A22.2**	7.22E−06	1.63
rs17716202	5	55.9	0.06	AC022431.2	7.70E−06	0.45
rs3764640	19	1.2	0.21	**STK11**	7.88E−06	0.68
rs11252926	10	0.6	0.36	**DIP2C**	8.08E−06	0.72

Loci at $p < 1 \times 10^{-5}$ are shown. For AD + P versus controls 1,628 loci had $p < 1 \times 10^{-4}$. For AD + P versus AD − P 1,740 loci had $p < 1 \times 10^{-4}$. Intragenic SNPs are in bold

SNP single nucleotide polymorphism, *Chr* chromosome, *MB* mega base, *MAF* minor allele frequency, *RefSeq* reference sequence, *GWAS* genome-wide association study, *p p* value, *OR* odds ratio, *AD + P* Alzheimer disease with psychosis, *AD − P* Alzheimer disease without psychosis, *STK11* serine/threonine kinase 11 gene, *DIP2C* disco-interacting protein 2 homolog c, *VSNL1* visinin-like 1 gene, *SLCA2A9* solute carrier family 2, facilitated glucose transporter member 9 gene

Candidate Gene Studies

Prior to the advent of GWA, a large body of research was reported assessing the association of candidate genes with AD + P. The majority of such studies have focused understandably on the ∈4 allele of *APOE*. A large effort has also examined the monoamine neurotransmitter systems, namely serotonin and dopamine. With some limited exceptions, these individual studies have been characterized by small numbers of genetic variants assessed in any given study and small sample sizes, precluding any firm conclusions. Because candidate gene studies of *APOE*, serotonin system genes, and dopamine system genes have recently been comprehensively reviewed elsewhere [1•, 4], only a brief summary of these findings are presented below.

Association of *APOE*

The *APOE* ∈4 allele is a strong risk factor for the development of late-onset AD; therefore, candidate gene studies investigated its possible role in the development of psychosis in AD. In a review of 22 studies examining the association of *APOE* ∈4 with psychosis, 9 found a significant association, but the nature of the association (genotype, carrier status, allele frequency, etc.) differed across studies [4]. It was unclear whether the contrasting results reflected a lack of true association or may have arisen because of heterogeneity among the sample sizes, patient populations, and diagnostic criteria used. To attempt to address the issue of possible heterogeneity, DeMichele-Sweet et al. [50] examined the association of *APOE* ∈4 with AD + P in the National Alzheimer's Disease Coordinating Center data set, which provided a large sample ($N = 2{,}317$) with uniform diagnostic criteria and measurement of psychosis. No association was found between psychosis and *APOE* ∈4 carrier status or *APOE* ∈4 allele number (Table 3). Since psychosis may not manifest until later in the course of disease, analyses were restricted to subjects who had reached at least a mild to moderate stage of illness (Clinical Dementia Rating Scale score ≥1, $N = 1{,}941$). In this follow-up, no association of *APOE* ∈4 carrier status and *APOE* ∈4 allele number with psychosis remained (Table 3).

Of note, a poly-T repeat sequence polymorphism in TOMM40, a locus in linkage disequilibrium with *APOE*, has been suggested to underlie the biological effects associated with genetic variation in *APOE* [51]. A recent study explored whether the variable associations of *APOE*

with AD + P might result from an association with the TOMM40 repeat sequence. However, no association was found between the poly-T repeat length and psychosis [52].

Association of Monoamine System Genes

Genetic variations in serotonin receptors and transporters have been tested for association with AD + P because of the importance of the serotonin system in regulating central nervous system functions, including its involvement in psychiatric disorders [53, 54] and its altered levels in brains of AD subjects [55–57]. As with *APOE*, associations of polymorphisms and allele frequencies of serotonin receptors and transporters with psychosis in AD have been contradictory and do not generally support any clear associations (see Table S2 in [1•] for details).

Genetic variation in dopamine receptors has been of interest in association studies with AD + P because antipsychotic agents target these receptors [58]. The dopamine transporter gene has similarly been studied because of its role in regulating synaptic dopamine. However, as for serotonin system genes, results for dopamine system genetic variants have been inconclusive (see Table S2 in [1] for details). Similarly, the catechol-*O*-methyltransferase gene (COMT), which codes for an enzyme that inactivates dopamine, was evaluated in AD + P after several studies reported SNPs in COMT to be associated with schizophrenia [59]. However, these too yielded inconclusive results.

Association of Neurodegenerative Pathway Genes

The greatest association of cognitive impairment in subjects with AD is loss of synapses across the neocortical regions [60, 61]. Subjects with AD + P also have a more rapid cognitive decline than subjects without psychosis [1•], and this decline is associated with increased synaptic disruption across multiple neocortical regions in subjects with AD + P [62]. Soluble Aβ protein directly leads to synapse loss [63–66], and it may also increase aggregation of microtubule-associated protein tau, MAPT [66], which itself can contribute to loss of synapses [67]. Therefore, genes that regulate Aβ and MAPT represent potential candidates for association with AD + P.

DeMichele-Sweet et al. [68] comprehensively evaluated the APP and MAPT genes for association with AD + P in a cohort of 867 well-characterized subjects. They also evaluated sortilin-related receptor (SORL1), an AD-risk gene that impacts Aβ metabolism and correlates with measures of synaptic markers [69–71], and β-site amyloid precursor protein cleaving enzyme (BACE1), an enzyme involved in the conversion of APP to Aβ [72]. There was no evidence of an association of APP, SORL1, BACE1, and MAPT with the occurrence of psychosis in AD [68].

Miscellaneous Associations

The α7 nicotinic acetylcholine receptor is encoded by CHRNA7 on chromosome 15 and has been reported to

Table 3 Apolipoprotein (*APOE*) ∈4 allele association with Alzheimer disease and psychosis (AD + P)

APOE ∈4 allele variables	Psychosis status			Total *N* (%) or mean (SD)	$\chi^{2\dagger}$	df	*p* value
	Never *N* (%) or mean (SD)	Single *N* (%) or mean (SD)	Multiple/recurrent *N* (%) or mean (SD)				
Cases restricted to CDR <1							
Carrier status					4.008†	2	0.135
−∈4	632 (41.7)	190 (38.5)	112 (36.2)	934 (40.3)			
+∈4	883 (58.3)	303 (61.5)	197 (63.8)	1,383 (59.7)			
Number					5.097†	4	0.277
0	632 (41.7)	190 (38.5)	112 (36.3)	934 (40.3)			
1	712 (47.0)	236 (47.9)	158 (51.1)	1,106 (47.7)			
2	171 (11.3)	67 (13.6)	39 (12.6)	277 (12.0)			
Cases restricted to CDR ≥1							
Carrier status					3.100†	2	0.212
−∈4	471 (41.4)	190 (38.5)	112 (36.2)	773 (39.8)			
+∈4	668 (58.6)	303 (61.5)	197 (63.8)	1,168 (60.2)			
Number					3.502†	4	0.478
0	471 (41.3)	190 (38.5)	112 (36.3)	773 (39.8)			
1	527 (46.3)	236 (47.9)	158 (51.1)	921 (47.5)			

CDR Clinical Dementia Rating Scale, *APOE* apolipoprotein E

† Pearson's χ^2 test: χ^2 values are presented

demonstrate significant linkage and association in schizophrenia [73, 74]. An initial study by Carson et al. [75] looked at whether this gene is associated with psychosis in AD. Analyzing 14 SNPs in this gene in a group of 409 probable AD patients of Northern Irish descent, they found a significant association between a single SNP (rs6494223) and delusions in AD ($p = 0.017$) with risk conveyed by the T allele (OR = 1.63, CI = 1.22–2.17). This finding has yet to be replicated in other AD populations.

A polymorphism of the interleukin 1β gene promoter was studied in a population of 424 patients diagnosed with possible/probable AD in the UK [76]. The CC genotype frequency was significantly higher in patients with delusions ($\chi^2 = 2.69$, $p = 0.002$), with hallucinations ($\chi^2 = 6.27$, $p = 0.043$), and with both delusions and hallucinations ($\chi^2 = 9.9$, $p = 0.007$). The frequency of the C allele was also significantly higher in patients with delusions ($\chi^2 = 4.86$, OR = 1.49, CI = 1.02–1.94, $p = 0.028$), with hallucinations ($\chi^2 = 5.95$, OR = 1.6, CI = 1.08–2.39, $p = 0.014$), and with both ($\chi^2 = 3.91$, OR = 1.62, CI = 0.98–2.70, $p = 0.048$). Although this provides intriguing evidence for a potential role of inflammation in psychosis risk in AD, independent confirmation of these findings is pending.

Conclusion

Psychosis occurs in a subset of patients with AD, in whom it is associated with a more aggressive cognitive deterioration and worse outcomes. There is now evidence from three independent replications that psychosis in AD aggregates within families and thus is likely to result, in part, from effects of genetic variation. At present, there is no gene in which genetic variation can unequivocally be stated to associate with the risk of psychosis in AD, although several promising leads from a recent GWAS have been identified. In contrast, substantial evidence supports the conclusion that the *APOE* locus can be excluded from an association with AD + P. Although based on much more limited evaluation, current evidence similarly suggests that other genetic variants that increase the risk for AD do not increase the risk for psychosis in AD. In contrast, although also derived from limited data, current evidence is consistent with the hypothesis that there is some overlap of genetic risk for psychosis in AD with that for schizophrenia.

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