Published in final edited form as:

J Alzheimers Dis. 2010 ; 19(3): 761–780. doi:10.3233/JAD-2010-1274.

Genetics of Psychosis in Alzheimer Disease: A Review

Mary Ann DeMichele-Sweet, Ph.D.¹ and Robert A. Sweet, M.D.^{1,2,3}

¹Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA

²Department of Neurology, University of Pittsburgh, Pittsburgh, PA

³VISN 4 Mental Illness Research, Education and Clinical Center (MIRECC), VA Pittsburgh Healthcare System, Pittsburgh, PA

Abstract

In and of itself, late-onset Alzheimer disease (AD) can be a devastating illness. However, a sub-group of AD patients develop psychosis as the disease progresses. These patients have an added burden of greater cognitive impairment, higher rates of institutionalization, and higher mortality than AD patients without psychosis. While the etiopathogenesis of psychosis in AD (AD+P) is not known, mounting evidence accrued over the past ten years indicates that AD+P represents a distinct phenotype with a genetic basis. Elucidating the genetic mechanism of AD+P is crucial if better pharmaceutical treatments are to be developed for these patients. The goal of this review is to summarize what is currently known regarding the genetic basis of psychosis in AD. Specific attention is given to familial aggregation and heritability, linkage to chromosomal loci, and associations of candidate genes such as APOE and the monoamine neurotransmitter system.

Keywords

Heritability; Linkage Analysis; Association Analysis; APOE; Dopamine; COMT; Serotonin; NRG1

BACKGROUND

Alzheimer disease (AD) is a neurodegenerative illness that can be broken down into two sub-groups, early- and late-onset. Early-onset AD accounts for less than 5% of all AD cases. In many early-onset AD cases, an autosomal dominant mode of transmission is seen. Causative mutations in the genes presenilin 1 (PSEN1) and presenilin 2 (PSEN2) have been described, while both causal mutations and copy number variations within the amyloid precursor protein (APP), have been reported [1,2,3,4,5]. Late-onset AD is also a highly heritable, albeit complex, phenotype. To date only the apolipoprotein E (APOE) gene, and specifically, the $\epsilon 4$ allele, has been accepted as a genetic risk factor [6,7], though substantial data now also supports an association of late-onset AD with genetic variation in SORL1 [8,9,10,11]. Many other genes and chromosomal regions have been identified as possibly being involved in late-onset AD, but because of the genetic heterogeneity of the disease, these have not been confirmed across studies.

A subgroup of patients with late-onset AD also 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 (but not by the presence of disorganization of thought

and behavior in the absence of delusions or hallucinations). Reported common delusions are of persecution, infidelity, abandonment, and the belief that deceased individuals are still alive [12]. In addition, individuals with AD+P have frequent misidentification delusions, such as the belief that there are phantom boarders in the house, one's spouse is an imposter, or one's home is not really one's own [13]. Hallucinations can occur in any modality, but are typically visual [12,13,14]. Recently, Ropacki and Jeste [15] comprehensively reviewed the literature on psychosis in AD from 1990 to 2003. They reviewed 55 studies comprised of 9,749 subjects. The median prevalence of AD+P was 41% (range=12.2-74.1%). The median prevalence of delusions was 36% (range=9.3-63%), with delusions of theft the most frequently reported type of delusion. Other psychotic symptoms, predominantly misidentification delusions, were the next most frequent psychotic symptom, with a median prevalence of 25% (range=3.6-38.9%). The median prevalence of hallucinations was 18% (range=4-41%) with visual hallucinations (median=18.7%) more common than auditory hallucinations (median= 9.2%). Patients experienced both hallucinations and delusions with a median prevalence of 13% (range=7.8-20.8%).

Greater cognitive impairment was the most consistent correlate of AD+P compared to AD without psychosis (AD-P). Ropacki and Jeste found in 20 of the 30 studies that assessed this relationship that greater cognitive impairment, typically as determined by the mini mental state examination (MMSE) [15], was associated with the presence of psychosis. Additionally, nine of nine studies found a significant association between a greater rate of cognitive decline and the presence of AD+P. Studies conducted more recently have continued to support the relationship between greater cognitive impairment and AD+P [16,17]. In contrast, only inconsistent associations have been detected between AD+P and age, age at onset of AD, illness duration, gender, education, and family history of dementia or psychiatric illness. AD+P may be associated with African American ethnicity, though it has only been examined in a limited number of studies to date [15].

Psychotic behaviors in AD patients have a tremendous impact on the patient, family, and caregiver. Oftentimes, these patients also have other psychiatric and behavioral disturbances, the most frequent and troublesome of which are agitation [18], and verbal and physical aggression [19,20]. Overall, AD+P leads to greater distress for family and caregivers [21], greater rates of institutionalization [22,23,24,25], and worse general health for the patient [26], with increased mortality [27] compared to patients with AD-P.

Treatment of psychosis in AD patients has been suboptimal due to the limited efficacy of the classes of drugs available and their high toxicity in this age group. Haloperidol is the most studied of the conventional antipsychotics, and it has demonstrated mild to moderate efficacy relative to placebo in AD patients with psychosis and/or agitated behaviors. However, it also causes serious side-effects in these patients, namely parkinsonism, tardive dyskinesia, and akathisia [28]. More recent studies have examined the efficacy of second generation, or atypical antipsychotics, such as risperidone [29], olanzapine [30], and aripiprazole [31,32]. These medications have similar efficacy to conventional antipsychotics in reducing psychotic symptoms, with a lower likelihood of inducing motor side effects [33]. However, they have been associated with an increased risk of cerebral vascular adverse events such as stroke, and increased all-cause mortality [34,35,36,37]. Furthermore, there is no current data to suggest that any of these treatments effectively mitigate against the greater cognitive and functional burden associated with AD+P.

Alzheimer disease can be a devastating illness. It is clear that patients with AD+P have an added burden. Current treatment for AD+P is not adequate. It is, therefore, important to determine the etiopathogenesis of psychosis in AD, so that better pharmaceutical treatments can be developed for this sub-group of patients. One approach results from the observation that

AD patients who exhibit psychosis represent a distinct phenotype with a genetic basis[38]. During the past 10 years, substantial information has begun to accrue regarding the genetics of AD+P. The goal of this review is to summarize the current state of knowledge regarding the genetic basis of psychosis in AD, with specific attention to familial aggregation and heritability, linkage to chromosomal loci, and associations of candidate genes.

FAMILIAL AGGREGATION and HERITABILITY

Familial aggregation refers to the occurrence of a trait in more members of a family than can be accounted for by chance. It is important to remember that even though a trait may aggregate within families, its appearance may still be due to environmental influences that are shared by family members. In contrast, heritability is an estimate of the proportion of risk for a trait which is attributable to genetic variation.

One of the first studies that examined familial aggregation of AD+P was done by Tunstall et al[39]. Looking at sibling pairs diagnosed with AD, Tunstall found the frequency of psychosis in these patients to be 0.41 (with delusions and hallucinations showing frequencies of 0.36 and 0.30, respectively). The pair-wise concordance for psychosis (i.e. frequency of pairs in which both siblings were positive for psychosis) was 0.21, a value that is modestly higher than expected by chance alone, 0.17, and the excess pair-wise concordance was 0.04 (Table 1).

Sweet et al[40] studied a larger cohort of probands and their siblings for familial aggregation of AD+P, examining a total of 371 probands and their 461 siblings from the National Institute of Mental Health Alzheimer Disease (NIMH AD) Genetics Initiative (Table 1). All probands and siblings were diagnosed with AD, and 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 siblings. The Odds Ratio (OR; 95% C.I.) for AD+P in siblings of AD+P probands was 2.4 (1.46-4.0). Similar results were obtained in supplementary analyses covarying for sibling age and age-of-onset and for the presence of extrapyramidal symptoms. When the same model was used to examine a more restrictive definition of AD+P requiring multiple psychotic symptoms to be present over time, the familial aggregation was strengthened, with an OR (relative to single or no psychotic symptoms) of 3.18 (2.17-4.66).

In a follow-up to this study, they used statistical modeling to estimate the heritability of psychosis among 826 of the individuals from their prior report[41]. Though the heritability of any occurrence of a psychotic symptom was modest (29.5%, $p=0.04$), the heritability of the more restrictive definition of psychosis requiring multiple symptoms was estimated at 60.8%, $p=0.004$. The OR for at least one psychotic symptom was 2.37 (1.45-3.87), and the OR (relative to no psychotic symptoms) increased to 5.42 (2.62-10.43) for multiple psychotic symptoms (Table 1).

Hollingsworth et al[42] undertook a study to replicate and expand the work of Sweet et al by incorporating data from the NIMH AD Genetics Initiative's pedigrees and families recruited from the United Kingdom (UK). They found a significant association between proband psychosis status and the occurrence of AD+P in family members in both the US and UK samples (Table 1). The estimated 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).

GENETIC LINKAGE STUDIES

The studies of familial aggregation and heritability of psychosis in AD, summarized above, strongly implicate genetic variation as contributing to AD+P. An important question is what

chromosomal loci might be linked to the development of psychosis in AD, and what are the implicated genes? To answer these questions, genetic linkage studies have been done to identify loci that predispose individuals to AD+P.

Bacanu et al[43] reported the first linkage study in AD+P, evaluating 65 families from the National Institute of Mental Health Alzheimer Disease (NIMH AD) Genetics Initiative with two or more members having the restrictive definition of AD+P. Furthermore, they partitioned the families into a subset of 42 families in which two or more individuals were carriers of apolipoprotein (APOE) $\epsilon 4$ alleles (AD+P+ $\epsilon 4$). When looking at this subset, they found evidence of significant linkage on chromosome 2p near marker D2S1356 (64.3 cM). In addition, they found two suggestive linkages on chromosome 6 near marker D6S1021 (112.2 cM), and chromosome 21 at marker D21S1440 (36.8cM). When analyzing the entire group of 65 families, they found a suggestive linkage on chromosome 6, corresponding to the same region that was found in the AD+P+ $\epsilon 4$ families.

Hollingworth et al[42] examined linkage using the combined NIMH and UK cohort described earlier. In the NIMH sample, they found significant linkage on chromosome 15 between markers D15S655 (85.7 Mb) and D15S652 (90.3 Mb), with a psychosis covariate maximum LOD score at 86 cM. Significant linkage was also found on chromosome 7 with its nearest marker at D7S2204 (78.0 Mb) and a psychosis covariate maximum LOD score at 91 cM. They also found regions of increased linkage on chromosomes 6 and 21 that were close to those previously reported by Bacanu et al[43]. However, the main effect at both loci appeared to be due to inclusion of APOE genotype as a covariate, with a smaller effect of psychosis.

Neuregulin -1(NRG1) is a gene on chromosome 8p that has shown both linkage and association with psychosis due to schizophrenia[44]. Go et al examined 437 families from the NIMH AD Genetics Initiative to determine association and linkage of NRG1 with AD and AD+P[45]. Linkage analysis of chromosome 8 in AD yielded a maximum Zlr score of 2.0, $p < 0.05$, in the 8p11-p12 region containing NRG1. Of the 437 families, 65 families had a proband that was positive for multiple psychotic symptoms as was at least one other sibling. When this subset of families was analyzed, linkage in the 8p11-p12 region increased to a Zlr of 4.2, $p = 0.000016$.

Go et al[45], followed up on this linkage signal, analyzing the transmission of four SNPs within NRG1 in the AD+P families. The SNPs analyzed included three from the 5' region of NRG1 strongly implicated in schizophrenia (SNP8NRG24190, SNP8NRG221533, and SNP8NRG243177). An additional exonic SNP, rs3924999 was also tested. In single SNP analyses, rs3924999 demonstrated evidence of significant linkage and association with AD+P. Haplotype analyses indicated that a three SNP haplotype defined by SNP8NRG221533, SNP8NRG243177, and rs3924999) tended to be over-transmitted to siblings with AD+P ($p = 0.076$).

Whereas the studies by Bacanu, Hollingworth and Go showed linkage of chromosomes 2p, 15 and 7, and 8p, respectively, with psychosis in AD, Avramopoulos et al[46] found that chromosome 14q is linked to AD patients without hallucinations. They genotyped 348 individuals from 148 families of the NIMH AD Genetics Initiative and used the presence or absence of hallucinations or delusions as covariates. The majority of these patients had late-onset AD, but Avramopoulos also included some individuals with ages of onset between 50 and 65. They found a linkage to a locus on chromosome 14q24.3 (LOD = 3.91; genome-wide $p = 0.052$), close to the PSEN1 locus related to the absence of hallucinations. Screening of PSEN1 for mutations did not detect any coding region or splice site mutations. They also found some support for the findings of Bacanu et al[43], with evidence of elevated linkage to the presence of delusions on chromosome 2p.

ASSOCIATION STUDIES

An alternate approach to assessing the genetic basis of AD+P is to examine whether specific genetic variations are more frequent in AD+P cases than in unrelated AD–P samples. A number of such studies have been reported in AD+P, predominantly focused on APOE and genetic variation within components of monoamine neurotransmitter systems.

Association of Apolipoprotein E (APOE)

The gene for APOE is located on chromosome 19 and is well documented as being a risk factor for the development of late-onset AD[7,47]. However, its association with development of psychosis is less clear. To date, at least 22 studies have examined the relationship between the ϵ 4 allele and the presence of psychosis in AD, with nine reporting that ϵ 4 is significantly associated with AD+P (See Table 2). These discrepancies may be due to differences in sample sizes (with both false positive and false negative findings more likely in small samples), patient populations, and diagnostic criteria. As a whole, however APOE does not appear to contribute to the risk of psychosis in AD.

Association of serotonin receptors and serotonin transporter

Serotonin (5-hydroxytryptamine, 5-HT) is a central nervous system neurotransmitter important in regulating mood, memory, learning, sleep, and appetite. Altered serotonin neurotransmission has also been suggested to contribute to various mood disorders such as depression, obsessive-compulsive disorder, schizophrenia, and with psychosis seen in patients with AD[68,69]. In addition, postmortem and biopsy studies of AD patients' brains have shown a decrease in the levels of 5-HT, of 5-HT receptors (HTR), and of the 5-HT transporter (SLC6A4)[70,71,72]. A number of investigations, therefore, have looked for an association of genetic variation in serotonin receptors HTR2A and HTR2C, and SLC6A4 with AD+P.

The association of polymorphic variation of the HTR2A gene with AD+P has focused on a single SNP (rs6313), which results in a T(102)C substitution. Both alleles code for a serine in codon 34, and therefore, do not alter the amino acid sequence of the HTR2A receptor[73]. However, this polymorphism has been associated with changes in HTR2A expression. In human postmortem studies, mRNA expression of the rs6313 (C) allele in the temporal cortex of heterozygotes was significantly lower than mRNA expression of the rs6313 (T) allele[74]. Similarly, total levels of HTR2A mRNA and protein in individuals with the CC genotype, as well as the combined CC + TC genotype groups, were lower than in individuals with the TT genotype[74].

The association of the HTR2A T(102)C genotype with psychosis in AD has been studied by several groups (Table 3). Nacmias et al[75] and Rocchi et al[76] found a significant association between allele frequencies and AD+P, with C being the risk allele. Other groups looked specifically for association with delusions and hallucinations with conflicting results. For example, Holmes et al[77] found a significant association of the C allele with hallucinations, whereas Assal et al[78] did not find an association for allele frequency with hallucinations. Furthermore, Assal[78] and Lam[79] found that T alleles increased risk for delusions, but Holmes[77] didn't find an association with either allele. Wilkosz et al[80] not only determined that there wasn't a significant association with the presence of psychotic symptoms, but they also found that HTR2A T(102)C genotype was not associated with the time to onset of psychosis. Others, such as Craig et al[81] and Pritchard et al[82] did not find association with either delusions or hallucinations. Though the above data may be consistent with a modest effect of HTR2A genotype on AD+P risk, the opposing risk alleles found in the different studies would suggest that rs6313 is unlikely to be causative.

Relatively fewer studies have examined the association of AD+P with HTR2C. These studies have all evaluated a single non-synonymous SNP in HTR2C, which results in a Cys23Ser substitution, the function of which is not established[83]. Holmes et al[77] found a significant association of allele frequency with visual hallucinations, but not with auditory hallucinations or delusions, whereas Assal et al[78], and Pritchard et al[82], did not find a significant association of allele frequency or genotype with delusions or hallucinations (Table 3).

SLC6A4 gene expression is regulated by several functional polymorphisms. One is within the promoter region of SLC6A4 and is named the 5-HTTLPR[84]. The long allele (L) variant of 5-HTTLPR occurs from a 44 base pair insertion and results in greater transcriptional activity, and therefore, serotonin reuptake, than does the short allele (S) variant[85,86]. Several studies have been conducted to test for an association of the 5-HTTLPR polymorphism with AD+P and have yielded conflicting results (Table 3). Sweet et al[20] found that the LL genotype and the L allele frequency were associated with psychosis, but several subsequent studies did not confirm these findings[76,87,88,89]. Furthermore, Borroni et al[90] found that S allele carriers had increased risk for the development of psychosis.

Another functional polymorphism that affects SLC6A4 gene expression is a variable number tandem repeat polymorphism (5-HTTVNTR) located in the second intron containing 9, 10, or 12 copies of a 17 base-pair sequence[91],[92]. Pritchard et al[88] and Ueki et al[89] examined if this polymorphism is associated with AD+P. Pritchard found that the 10-repeat allele was significantly associated with psychosis, but Ueki did not find an association of genotype with delusions or hallucinations. This difference could be due to the smaller sample size of Ueki's study (Table3).

Overall, the serotonergic system is a complex one, and its association with AD+P is still unclear. Small sample sizes, non-uniformity in patient populations and diagnostic criteria across studies, and investigation of only limited genetic variation within individual genes makes a definite conclusion regarding these associations difficult.

Association of dopamine receptors and catechol-O-methyltransferase (COMT)

The possible association of dopamine receptors and AD+P is of interest because many antipsychotic agents used to treat psychosis target these receptors[93]. Dopamine receptors are coded by multiple genes. A limited number of studies have been done looking at the association of the polymorphisms of these genes and AD+P (Table 4). Of these, studies of the dopamine-3 receptor (DRD3) have been of greatest interest because of numerous studies suggesting a small, but significant, association of this gene with the risk for schizophrenic psychosis[94,95]. Three studies have been done looking at the association of a single exonic SNP, coding for a serine to glycine substitution in the DRD3 gene, and AD+P with conflicting results[96,97,98]. Sweet et al[96] found the Ser/Ser and Gly/Gly genotype to be significantly associated with psychosis, Holmes et al[97] found the Gly/Gly genotype to be protective against delusions, but did not find any genotype to be associated with hallucinations, and Craig et al[98] did not find an association of any polymorphism with hallucinations or delusions (Table 4).

Sweet et al[96] also tested the association of a single SNP in the dopamine-1 receptor (DRD1) gene with psychosis, whereas Holmes et al[97] tested its association separately with hallucinations and delusions. Sweet found a significant association for the B2/B2 genotype with psychosis whereas Holmes found a significant association for the B1/B2 genotype with hallucinations, with a trend for association of B2/B2, but did not find any genotype to be associated with delusions. Only one study was done to test the association of the dopamine-2 receptor (DRD2) gene with AD+P[96]. Sweet et al[96] found that Cys311 frequency was not significantly associated with psychosis (Table 4). As with the DRD2 gene, Sweet et al[96] were the only ones to test the association of the dopamine-4 receptor (DRD4) gene with AD

+P. They found that neither the long nor short allele of the DRD4 exon III repeat sequence polymorphism was significantly associated with AD+P (Table 4).

Pritchard et al[99] investigated the association of the dopamine transporter gene (SLC6A3) with AD+P (Table 4). SLC6A3 has also recently been implicated by association with psychosis in schizophrenia, including both direct effects and interactions with other dopamine system genes[100]. Specifically, Pritchard et al[99] looked at the variable number tandem repeat (VNTR) polymorphism in the 3'-untranslated region (UTR) of SLC6A3. They did not find a significant association with psychosis, hallucinations, or delusions.

The catechol-O-methyltransferase (COMT) gene is located on chromosome 22q11.2 and codes for an enzyme that inactivates dopamine along with other catecholamine neurotransmitters[101]. Since COMT is responsible for enzymatically degrading dopamine, a mutation in the gene could lead to altered levels of dopamine, and therefore, psychosis. Deletions within 22q11.2 are associated with velocardiofacial syndrome, a developmental abnormality in which 30% of individuals develop schizophrenic psychosis[102,103,104,105]. Furthermore, although numerous positive and negative studies of the association of a single coding SNP, rs4680, which results in a valine to methionine substitution, have been reported in schizophrenia, emerging understanding of the genetic regulation of COMT suggests that COMT haplotype is a risk for psychosis[106].

Sweet et al[107] examined the possible association of COMT haplotypes in subjects suffering from AD with and without psychosis (Table 5). They genotyped the same SNPs analyzed for association with schizophrenia by Shifman et al[108] (rs737865, rs165599, and rs4680) and an additional SNP (ERE6) located near an estrogen responsive element within the P2 promoter region, evaluating single locus effects and the multiple loci haplotypes. Because of possible effects of the ERE6 locus, they also stratified analyses by gender. In female subjects, single locus analyses revealed that the risk for psychosis increased significantly with the number of G alleles present at the rs4680 locus. Furthermore, there was a trend toward association with rs737865. None of the SNPs were associated with psychosis in men. Haplotype analysis in females revealed an additive effect of risk alleles at rs4680 and ERE6 (or rs737865). There was a significant linear relationship between the number of ERE6 C alleles and rs4680 G alleles and psychosis, with each locus contributing equally to the risk (rs4680: slope = 0.7905, $p=0.0007$; ERE6: slope = 0.6720, $p=0.0032$). In males, an interaction between rs4680, ERE6, and rs165599, was close to significant ($p=0.08$) for psychosis.

An initial study by Borroni et al[90] looked only at the association of rs4680 with delusions and hallucinations in AD. They found that carriers of the G allele experienced significantly more hallucinations than non-carriers. Borroni et al[109] expanded their analyses of COMT polymorphisms by evaluating the association of four SNPs (rs737865, rs737864, intron 1 C2754delC, and rs4680) with AD+P. An association of the G allele of rs4680 was confirmed for AD+P (Table 5). In addition, haplotype analysis revealed a significant association of haplotypes (A-C-C-G, $p=0.044$ and G-C-delC-G, $p=0.006$) for psychosis in AD. The A-C-C-G haplotype further increased the risk by 25% compared to the effect of the rs4680 G allele alone. The G-C-delC-G haplotype further increased the risk by 75% compared to the rs4680 G allele.

Studies with dopamine receptor variation and psychosis in AD have been limited and conflicting. Likewise, studies of COMT have also been limited, although there does appear to be a complex association of COMT haplotypes, including the effects of rs4680, with psychosis. Further work which more thoroughly evaluates the genetic variation within COMT for association with psychosis, and in particular considers the effects of haplotypes known to impact other phenotypes [110] is needed.

Miscellaneous Associations

The $\alpha 7$ nicotinic acetylcholine receptor is encoded by CHRNA7 on chromosome 15 and has been found via linkage and association studies to be involved in schizophrenia [111,112]. An initial study by Carson et al looked at whether this gene is associated with psychosis in AD [113]. Analyzing SNPs in this gene in a group of 409 probable AD patients of Northern Ireland descent, they found a significant association with a single SNP (rs6494223) and delusions in AD ($p=0.017$) with the T allele being the risk factor (OR=1.63, CI=1.22-2.17). This finding has yet to be replicated in other AD populations.

A polymorphism of the interleukin 1 β gene promoter was studied in a population of 424 patients diagnosed with possible/probable AD in the United Kingdom [114]. Craig et al found that 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, $p=0.048$). Once again, independent confirmation of these findings is pending.

POSSIBLE UNDERLYING GENETIC MECHANISMS OF AD+P

If AD+P is heritable, what model may guide future genetic studies of AD+P? Several pathways by which genetic factors may lead to AD+P are presented in Figure 1. Pathway A1 represents disease modifying genes that lead to AD+P in individuals who develop AD itself due to other genetic and environmental influences. This pathway is consistent with certain findings in AD +P. For example AD+P is rare as a prodrome of AD, and occurs with increasing frequency as individuals traverse the early and middle disease stages. Also, as reviewed above, AD+P does not appear to be associated with the one identified genetic risk factor for the development of late-onset AD itself, APOE. Similarly, disease modifying genes may alter the course of other neurodegenerative illnesses to yield psychosis (Pathway A3). There is evidence to support this model in Huntington disease, as psychosis aggregates within families with Huntington disease, but the occurrence of psychosis does not appear to be due to the expansion of the disease causing triplicate repeats in the Huntington disease gene (HD) itself [115]. Some data also exist to support this model in families carrying identified disease-causing mutations in microtubule-associated protein tau (MAPT) which results in a frontotemporal dementia. Despite carrying the same disease alleles, families in which some members present with early-onset schizophreniform psychosis have been described, presumably due to an interaction of the disease causing mutation with their specific genetic (and environmental) backgrounds [116]. Finally, as reviewed above, several genes which show some evidence of association with AD +P (NRG1, COMT) have been suggested as putative risk genes for schizophrenic psychosis, possibly indicating they may modify neurodevelopment to yield psychosis risk (Pathway A2).

Alternatively, in pathway B, genes that increase the liability to onset of AD would increase risk for AD+P. Currently, there is little evidence by which to accept or reject this model. For the one gene known to influence risk of late-onset AD, APOE, pathway B does not appear to apply. Another gene with substantial (but not conclusive) evidence of association with late-onset AD, SORL1, has not been studied for association with AD+P. Finally, despite evidence that rates of psychiatric illness, including schizophrenia, may be higher among family members of individuals with early-onset versus late-onset AD [117], studies of genes known to contribute to early-onset AD for association with psychosis (e.g. APP, PSEN1, PSEN2) have not been reported.

CHALLENGES GOING FORWARD

While it is evident that psychosis in AD is a distinct phenotype with a genetic basis, the inconsistent findings of genetic association studies of AD+P indicate that many challenges still face researchers attempting to elucidate the genetics behind this syndrome. These challenges group into two main domains: reducing variability in the phenotypic definition and reducing variability due to the approaches used for genetic analysis. We briefly address these key issues below.

Variability in the phenotypic definition of AD+P

As mentioned earlier, there is substantial variability between studies in the rates of psychosis reported in AD patients [15]. To the extent this reflects inaccurate classification of individuals, it will either reduce power to identify true associations, or possibly inflate the false positive rate of genetic association studies. While variable classification of subjects with regard to psychosis presence may reflect multiple factors, in practice two design variables prove most important. First, the prevalence of psychosis in subjects with AD increases from the earliest stages of cognitive impairment to reach a maximum value by the middle stages of illness [118]. Thus, studies would do best to only consider an individual accurately characterized as without psychosis if they have reached at least this stage of illness. Second, individuals may have brief psychotic symptoms due to a number of factors, including intercurrent medical illness or drug toxicity. The likelihood of detecting one of these events increases with the use of frequent, systematic screening for psychosis symptoms. One way to avoid the reduction in study power introduced by these phenocopies is to use more stringent requirements for the presence of psychosis. For example, we have found that estimates of familial aggregation and heritability are increased if multiple and/or recurrent symptoms of psychosis have been reported [41].

Variability in design of association studies

Several factors contribute to both false-positive and false-negative findings in genetic association studies of candidate genes. Perhaps the most important is small sample size. It seems obvious that too small a sample may cause the failure to detect a true association due to lack of statistical power, what is less obvious is that small sample sizes not uncommonly lead to false positive findings due to random chance alone. Because these findings are not stable, they result in failed replications. While there is no absolute standard, experience with the use of genome-wide association studies in other complex disorders has suggested the correct sample sizes for association tests number in the thousands, not the tens or hundreds.

Another factor which can further contribute to variation in findings in association studies includes problems of population stratification. This occurs when the affected (e.g. AD+P) and unaffected (e.g. AD-P) groups have different allele frequencies due to unidentified differences in genetic ancestry. This problem can be handled in a straightforward way by genotyping a set of ancestry SNPs within all subjects and controlling for ancestry in the analysis of the variants of interest [119].

The association studies contained within this review have mostly relied on testing a single SNP within genes of interest. Failure to find association may lead to the false-negative conclusion that the gene of interest does not contribute to AD+P risk, a conclusion that could be avoided with more systematic interrogation of genes. Currently it is reasonable to attempt complete coverage of all haplotype blocks (defined by elevated correlation of SNPs within a block) within a gene, using for each block a representative (tag) SNP. Study of single SNPs can also lead to non-replicated positive findings. If the associated SNP is not causal, but only associated due to its correlation with an unassessed genetic variant which does contribute to disease risk,

two different situations may arise. Because these correlations can differ across populations, subsequent studies may find either a significant association with the same SNP, but with the opposite allele identified as the risk allele, or may not replicate any association at all.

The choice of genes of interest that have been tested in association studies of AD+P is also problematic. These genes have been chosen based on inference about their potential relationship to psychosis. Such an approach has no power to identify true associations unless the set of genes examined have a causal relationship to AD+P. An alternate approach currently being used with success in other complex phenotypes of aging (e.g. prostate cancer and macular degeneration) is genome-wide association [120]. This approach interrogates SNPs from across the entire genome for association with disease. While not biased by mistaken assumptions of causality, this approach is highly dependent on the presence of large samples, typically many thousands of subjects.

CONCLUSION

Psychosis occurs in a subset of patients with Alzheimer Disease, in whom it is associated with a more aggressive cognitive deterioration and worse outcomes. There is growing evidence that psychosis in AD aggregates within families and is likely to result, in part, from effects of genetic variation. Association studies with a number of candidate genes have been reported. The most studied has been the APOE gene with most reports failing to find an association with AD+P. However, even in this case no firm conclusion can be made as to whether the APOE $\epsilon 4$ allele is associated with development of AD+P as most individual studies have been small, and there is substantial variability in phenotypic characterization and analytic approach between reports. A number of studies have evaluated putative schizophrenia risk genes, with intriguing initial findings for both NRG1 and COMT. These will require confirmation in larger cohorts who are genetically characterized for ethnicity and with more thorough interrogation of the genetic variation present in these genes. Finally, if sufficiently large cohorts can be homogeneously collected and characterized, consideration of alternate approaches to identifying genetic variants association with AD+P risk, such as Genome-Wide Association Studies should be considered.

Acknowledgments

This work was supported by USPHS grant AG 027224 and AG 05133, and there are no potential conflicts.

References

- [1]. Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, Yu CE, Jondro PD, Schmidt SD, Wang K. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* 1995;269:973–977. [PubMed: 7638622]
- [2]. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991;349:704–706. [PubMed: 1671712]
- [3]. Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, Chi H, Lin C, Li G, Holman K. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 1995;375:754–760. [PubMed: 7596406]
- [4]. Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerriere A, Vital A, Dumanchin C, Feuillette S, Brice A, Vercelletto M, Dubas F, Frebourg T, Campion D. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet* 2006;38:24–26. [PubMed: 16369530]
- [5]. Sleegers K, Brouwers N, Gijselinck I, Theuns J, Goossens D, Wauters J, Del Favero J, Cruts M, van Duijn CM, Van Broeckhoven C. APP duplication is sufficient to cause early onset Alzheimer's dementia with cerebral amyloid angiopathy. *Brain* 2006;129:2977–2983. [PubMed: 16921174]

- [6]. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A* 1993;90:1977–1981. [PubMed: 8446617]
- [7]. Corder EH, Saunders AM, Strittmatter WJSDE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921–923. [PubMed: 8346443]
- [8]. Lee JH, Cheng R, Schupf N, Manly J, Lantigua R, Stern Y, Rogaeva E, Wakutani Y, Farrer L, St George-Hyslop P, Mayeux R. The association between genetic variants in SORL1 and Alzheimer disease in an urban, multiethnic, community-based cohort. *Arch Neurol* 2007;64:501–506. [PubMed: 17420311]
- [9]. Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, Katayama T, Baldwin CT, Cheng R, Hasegawa H, Chen F, Shibata N, Lunetta KL, Pardossi-Piquard R, Bohm C, Wakutani Y, Cupples LA, Cuenco KT, Green RC, Pinassi L, Rainero I, Sorbi S, Bruni A, Duara R, Friedland RP, Inzelberg R, Hampe W, Bujo H, Song YQ, Andersen OM, Willnow TE, Graff-Radford N, Petersen RC, Dickson D, Der SD, Fraser PE, Schmitt-Ulms G, Younkin S, Mayeux R, Farrer LA, St George-Hyslop P. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nat Genet* 2007;39:168–177. [PubMed: 17220890]
- [10]. Bettens K, Brouwers N, Engelborghs S, De Deyn PP, Van BC, Sleegers K. SORL1 is genetically associated with increased risk for late-onset Alzheimer disease in the Belgian population. *Hum Mutat* 2008;29:769–770. [PubMed: 18407551]
- [11]. Webster JA, Myers AJ, Pearson JV, Craig DW, Hu-Lince D, Coon KD, Zismann VL, Beach T, Leung D, Bryden L, Halperin RF, Marlowe L, Kaleem M, Huentelman MJ, Joshipura K, Walker D, Heward CB, Ravid R, Rogers J, Papassotiropoulos A, Hardy J, Reiman EM, Stephan DA. Sorl1 as an Alzheimer's disease predisposition gene? *Neurodegener Dis* 2008;5:60–64. [PubMed: 17975299]
- [12]. Tariot PN, Mack JL, Patterson MB, Edland SD, Weiner MF, Fillenbaum G, Blazina L, Teri L, Rubin E, Mortimer JA, Stern Y, Behavioral Pathology Committee of the Consortium to Establish a Registry for Alzheimer's Disease. The behavior rating scale for dementia of the Consortium to Establish a Registry for Alzheimer's Disease. *Am J Psychiatry* 1995;152:1349–1357. [PubMed: 7653692]
- [13]. Rubin EH, Drevets WC, Burke WJ. Nature of psychotic symptoms in senile dementia of the Alzheimer type. *J Geriatr Psychiatry Neurol* 1988;1:17–20.
- [14]. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias. *Am J Geriatr Psychiatry* 2000;8:29–34. [PubMed: 10648292]
- [15]. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am J Psychiatry* 2005;162:2022–2030. [PubMed: 16263838]
- [16]. Wilkosz PA, Miyahara S, Lopez OL, DeKosky ST, Sweet RA. Prediction of Psychosis Onset in Alzheimer Disease: The Role of Cognitive Impairment, Depressive Symptoms, and Further Evidence for Psychosis Subtypes. *Am J Geriatr Psychiatry* 2006;14:352–356. [PubMed: 16582044]
- [17]. Weamer EA, Emanuel JE, Varon D, Miyahara S, Wilkosz PA, Lopez OL, DeKosky ST, Sweet RA. The relationship of excess cognitive impairment in MCI and early Alzheimer's disease to the subsequent emergence of psychosis. *Int Psychogeriatr* 2009;21:78–85. [PubMed: 18814807]
- [18]. Gilley DW, Whalen ME, Wilson RS, Bennett DA. Hallucinations and associated factors in Alzheimer's disease. *J Neuropsychiatry* 1991;3:371–376.
- [19]. Gilley DW, Wilson RS, Beckett LA, Evans DA. Psychotic symptoms and physically aggressive behavior in Alzheimer's disease. *J Am Geriatr Soc* 1997;45:1074–1079. [PubMed: 9288014]
- [20]. Sweet RA, Pollock BG, Sukonick DL, Mulsant BH, Rosen J, Klunk WE, Kastango KB, DeKosky ST. The 5-HTTPR polymorphism confers liability to a combined phenotype of psychotic and aggressive behavior in Alzheimer's disease. *Int Psychogeriatr* 2001;13:401–409. [PubMed: 12003247]
- [21]. Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, MacMillan A, Ketchel P, DeKosky ST. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the

- Neuropsychiatric Inventory Caregiver Distress Scale. *J Am Geriatr Soc* 1998;46:210–15. [PubMed: 9475452]
- [22]. Rabins PV, Mace NL, Lucas MJ. The impact of dementia on the family. *JAMA* 1982;248:333–335. [PubMed: 7087127]
- [23]. Lopez OL, Wisniewski SR, Becker JT, Boller F, DeKosky ST. Psychiatric medication and abnormal behavior as predictors of progression in probable Alzheimer disease. *Arch Neurol* 1999;56:1266–1272. [PubMed: 10520944]
- [24]. Magni E, Binetti G, Bianchetti A, Trabucchi M. Risk of mortality and institutionalization in demented patients with delusions. *J Geriatr Psychiatry Neurol* 1996;9:123–126. [PubMed: 8873875]
- [25]. Cummings JL, Diaz C, Levy M, Binetti G, Litvan I I. Neuropsychiatric Syndromes in Neurodegenerative Disease: Frequency and Significance. *Semin Clin Neuropsychiatry* 1996;1:241–247. [PubMed: 10320427]
- [26]. Bassiony MM, Steinberg M, Rosenblatt A, Baker A, Lyketsos CG. Delusions and hallucinations in Alzheimer's disease: Prevalence and clinical correlates. *Int J Geriatr Psychiatry* 2000;15:99–107. [PubMed: 10679840]
- [27]. Wilson RS, Krueger KR, Kamenetsky JM, Tang Y, Gilley DW, Bennett DA, Evans DA. Hallucinations and mortality in Alzheimer disease. *Am J Geriatr Psychiatry* 2005;13:984–990. [PubMed: 16286442]
- [28]. Tariot PN, Proffenno LA, Ismail MS. Efficacy of atypical antipsychotics in elderly patients with dementia. *J Clin Psychiatry* 2004;65(Suppl 11):11–15. [PubMed: 15264966]
- [29]. Bhana N, Spencer CM. Risperidone: a review of its use in the management of the behavioural and psychological symptoms of dementia. *Drugs Aging* 2000;16:451–471. [PubMed: 10939309]
- [30]. De Deyn PP, Carrasco MM, Deberdt W, Jeandel C, Hay DP, Feldman PD, Young CA, Lehman DL, Breier A. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19:115–126. [PubMed: 14758577]
- [31]. Streim JE, McQuade R, Stock E, Goyvaerts H, Breder C, Iwamoto T, Yamamoto Y. Aripiprazole for the treatment of institutionalized patients with psychosis of Alzheimer's dementia. *J Am Geriatr Soc* 2004;52:S15–S15.
- [32]. Jeste DV, De Deyn P, Carson W, Marcus R, McQuade RD, Schneider L, Mintzer J. Aripiprazole in dementia of the Alzheimer's type. *J Am Geriatr Soc* 2003;51:S226–S226.
- [33]. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* 2006;14:191–210. [PubMed: 16505124]
- [34]. Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004;161:1113–1115. [PubMed: 15169702]
- [35]. Smith DA, Beier MT. Association between risperidone treatment and cerebrovascular adverse events: examining the evidence and postulating hypotheses for an underlying mechanism. *J Am Med Dir Assoc* 2004;5:129–132. [PubMed: 15008183]
- [36]. Wooltorton E. Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. *Can Med Assoc J* 2004;170:1395–1395. [PubMed: 15111472]
- [37]. Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. *Can Med Assoc J* 2002;167:1269–1270. [PubMed: 12451085]
- [38]. Sweet RA, Nimgaonkar VL, Devlin B, Jeste DV. Psychotic symptoms in Alzheimer disease: evidence for a distinct phenotype. *Mol Psychiatry* 2003;8:383–392. [PubMed: 12740595]
- [39]. Tunstall N, Owen MJ, Williams J, Rice F, Carty S, Lillystone S, Fraser L, Kehoe P, Neill D, Rudrasingham V, Sham P, Lovestone S. Familial influence on variation in age of onset and behavioural phenotype in Alzheimer's disease. *Br J Psychiatry* 2000;176:156–159. [PubMed: 10755053]
- [40]. Sweet RA, Nimgaonkar VL, Devlin B, Lopez OL, DeKosky ST. Increased familial risk of the psychotic phenotype of Alzheimer disease. *Neurology* 2002;58:907–911. [PubMed: 11914406]
- [41]. Bacanu SA, Devlin B, Chowdari KV, DeKosky ST, Nimgaonkar VL, Sweet RA. Heritability of psychosis in Alzheimer disease. *Am J Geriatr Psychiatry* 2005;13:624–627. [PubMed: 16009739]

- [42]. Hollingworth P, Hamshere ML, Holmans PA, O'Donovan MC, Sims R, Powell J, Lovestone S, Myers A, Devrieze FW, Hardy J, Goate A, Owen M, Williams J. Increased familial risk and genomewide significant linkage for Alzheimer's disease with psychosis. *Am J Med Genet B Neuropsychiatr Genet* 2007
- [43]. Bacanu SA, Devlin B, Chowdari KV, DeKosky ST, Nimgaonkar VL, Sweet RA. Linkage analysis of Alzheimer disease with psychosis. *Neurology* 2002;59:118–120. [PubMed: 12105318]
- [44]. Harrison PJ, Law AJ. Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology. *Biol Psychiatry* 2006;60:132–140. [PubMed: 16442083]
- [45]. Go RC, Perry RT, Wiener H, Bassett SS, Blacker D, Devlin B, Sweet RA. Neuregulin-1 polymorphism in late onset Alzheimer's disease families with psychoses. *Am J Med Genet B Neuropsychiatr Genet* 2005;139B:28–32. [PubMed: 16082692]
- [46]. Avramopoulos D, Fallin MD, Bassett SS. Linkage to chromosome 14q in Alzheimer's disease (AD) patients without psychotic symptoms. *Am J Med Genet B Neuropsychiatr Genet* 2005;132B:9–13. [PubMed: 15389761]
- [47]. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997;278:1349–1356. [PubMed: 9343467]
- [48]. Ballard C, Massey H, Lamb H, Morris C. Apolipoprotein E: non-cognitive symptoms and cognitive decline in late onset Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1997;63:273b–273b. [PubMed: 9285479]
- [49]. Cacabelos R, Rodriguez B, Carrera C, Caamano J, Beyer K, Lao JI, Sellers MA. APOE-related frequency of cognitive and noncognitive symptoms in dementia. *Methods Find Exp Clin Pharmacol* 1996;18:693–706. [PubMed: 9121226]
- [50]. Chang JB, Wang PN, Chen WT, Liu CY, Hong CJ, Lin KN, Liu TY, Chi CW, Liu HC. ApoE epsilon4 allele is associated with incidental hallucinations and delusions in patients with AD. *Neurology* 2004;63:1105–1107. [PubMed: 15452311]
- [51]. Gabryelewicz T, Religa D, Styczynska M, Peplonska B, Pfeffer A, Wasiak B, Luczywek E, Golebiowski M, Androsiuk W, Czyzewski K, Przekop I, Barcikowska M. Behavioural pathology in Alzheimer's disease with special reference to apolipoprotein E genotype. *Dement Geriatr Cogn Disord* 2002;14:208–212. [PubMed: 12411763]
- [52]. Harwood DG, Barker WW, Ownby RL, St.George-Hyslop PH, Duara R. Apolipoprotein-E (APO-E) genotype and symptoms of psychosis in Alzheimer's disease. *Am J Geriatr Psychiatry* 1999;7:119–123. [PubMed: 10322238]
- [53]. Hirano N, Mori E, Yasuda M, Ikejiri Y, Imamura T, Shimomura T, Ikeda M, Hashimoto M, Yamashita H. Factors associated with psychotic symptoms in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1998;64:648–652. [PubMed: 9598682]
- [54]. Hirano N, Mori E, Yasuda M, Imamura T, Shimomura T, Hashimoto M, Tanimukai S, Kazui H, Yamashita H. Lack of effect of apolipoprotein E E4 allele on neuropsychiatric manifestations in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 1999;11:66–70. [PubMed: 9990558]
- [55]. Hollingworth P, Hamshere ML, Moskvina V, Dowzell K, Moore PJ, Foy C, Archer N, Lynch A, Lovestone S, Brayne C, Rubinsztein DC, Lawlor B, Gill M, Owen MJ, Williams J. Four components describe behavioral symptoms in 1,120 individuals with late-onset Alzheimer's disease. *J Am Geriatr Soc* 2006;54:1348–1354. [PubMed: 16970641]
- [56]. Lehtovirta M, Soininen H, Helisalmi S, Mannerman A, Helkala EL, Hartikainen P, Hanninen T, Ryyanen M, Rickkinen PJ. Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: Relation to apolipoprotein E polymorphism. *Neurology* 1996;46:413–419. [PubMed: 8614504]
- [57]. Levy ML, Cummings J, Fairbanks LA, Sultzer DL, Small GW. Apolipoprotein E genotype and noncognitive symptoms in Alzheimer's disease. *Biol Psychiatry* 1999;45:422–425. [PubMed: 10071711]
- [58]. Lopez OL, Kamboh MI, Becker JT, Kaufer DI, DeKosky ST. The apolipoprotein E epsilon4 allele is not associated with psychiatric symptoms or extrapyramidal signs in probable Alzheimer's disease. *Neurology* 1997;49:794–797. [PubMed: 9305342]

- [59]. Lyketsos CG, Baker L, Warren A, Steele C, Brandt J, Steinberg M, Kopunek S, Baker A. Depression, delusions, and hallucinations in Alzheimer's disease: no relationship to apolipoprotein E genotype. *The Journal of Neuropsychiatry and Clinical Neurosciences* 1997;9:64–67. [PubMed: 9017530]
- [60]. Pritchard AL, Harris J, Pritchard CW, Coates J, Haque S, Holder R, Bentham P, Lendon CL. The effect of the apolipoprotein E gene polymorphisms and haplotypes on behavioural and psychological symptoms in probable Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2007;78:123–126. [PubMed: 16980336]
- [61]. Ramachandran G, Marder K, Tang M, Schofield PW, Chun MR, Devanand DP, Stern Y, Mayeux R. A preliminary study of apolipoprotein E genotype and psychiatric manifestations of Alzheimer's disease. *Neurology* 1996;47:256–259. [PubMed: 8710089]
- [62]. Scarmeas N, Brandt J, Albert M, Devanand DP, Marder K, Bell K, Ciappa A, Tycko B, Stern Y. Association between the APOE genotype and psychopathologic symptoms in Alzheimer's disease. *Neurology* 2002;58:1182–1188. [PubMed: 11971084]
- [63]. Spalletta G, Bernardini S, Bellincampi L, Federici G, Trequattrini A, Caltagirone C. Delusion symptoms are associated with ApoE epsilon4 allelic variant at the early stage of Alzheimer's disease with late onset. *Eur J Neurol* 2006;13:176–182. [PubMed: 16490049]
- [64]. Sweet RA, Kamboh MI, Wisniewski SR, Lopez OL, Klunk WE, Kaufer DI, DeKosky ST. Apolipoprotein E and alpha-1-antichymotrypsin genotypes do not predict time to psychosis in Alzheimer's disease. *J Geriatr Psychiatry Neurol* 2002;15:24–30. [PubMed: 11936240]
- [65]. van der Flier WM, Staekenborg S, Pijnenburg YA, Gillissen F, Romkes R, Kok A, Bouwman FH, Scheltens P. Apolipoprotein E genotype influences presence and severity of delusions and aggressive behavior in Alzheimer disease. *Dement Geriatr Cogn Disord* 2007;23:42–46. [PubMed: 17077632]
- [66]. Weiner MF, Vega GRRC, Honig LS, Collum CM, Crumacker D, Rosenberg RN. Apolipoprotein Eε4, other risk factors, and course of Alzheimer's disease. *Biol Psychiatry* 1999;45:633–638. [PubMed: 10088051]
- [67]. Zdanyk KF, Kleiman TG, MacAvoy MG, Black BT, Rightmer TE, Grey M, Garman KS, Tampi RR, Gelernter J, van Dyck CH. Apolipoprotein E epsilon4 allele increases risk for psychotic symptoms in Alzheimer's disease. *Neuropsychopharmacology* 2007;32:171–179. [PubMed: 16841077]
- [68]. Meltzer CC, Smith G, DeKosky ST, Pollock BG, Mathis CA, Moore RY, Kupfer DJ, Reynolds CF III. Serotonin in aging, late-life depression, and Alzheimer's disease: the emerging role of functional imaging. *Neuropsychopharmacology* 1998;18:407–430. [PubMed: 9571651]
- [69]. Cross AJ. Serotonin in Alzheimer-type dementia and other dementing illnesses. *Ann N Y Acad Sci* 1990;600:405–417. [PubMed: 1701291]
- [70]. Bowen DM, Allen SJ, Benton JS, Goodhardt MJ, Haan EA, Palmer AM, Sims NR, Smith CC, Spillane JA, Esiri MM, Neary D, Snowden JS, Wilcock GK, Davison AN. Biochemical assessment of serotonergic and cholinergic dysfunction and cerebral atrophy in Alzheimer's disease. *J Neurochem* 1983;41:266–272. [PubMed: 6306169]
- [71]. Cheng AV, Ferrier IN, Morris CM, Jabeen S, Sahgal A, McKeith IG, Edwardson JA, Perry RH, Perry EK. Cortical serotonin-5₂ receptor binding in Lewy body dementia, Alzheimer's and Parkinson's diseases. *J Neurol Sci* 1991;106:50–55. [PubMed: 1779239]
- [72]. Tejani-Butt SM, Yang J, Pawlyk AC. Altered serotonin transporter sites in Alzheimer's disease raphe and hippocampus. *Neuroreport* 1995;6:1207–1210. [PubMed: 7662909]
- [73]. Warren JT, Peacock ML, Rodriguez LC, Fink JK. An MspI Polymorphism in the Human Serotonin Receptor Gene (Htr2) - Detection by Dge and Rflp Analysis. *Hum Mol Genetics* 1993;2:338–338.
- [74]. Polesskaya O, Sokolov B. Differential Expression of the "C" and "T" Alleles of the 5-HT_{2A} Receptor Gene in the Temporal Cortex of Normal Individuals and Schizophrenics. *J Neurosci Res* 2002;67:812–822. [PubMed: 11891796]
- [75]. Nacmias B, Tedde A, Forleo P, Piacentini S, Guarnieri BM, Bartoli A, Ortenzi L, Petrucci C, Serio A, Marcon G, Sorbi S. Association between 5-HT_{2A} receptor polymorphism and psychotic symptoms in Alzheimer's disease. *Biol Psychiatry* 2001;50:472–475. [PubMed: 11566166]

- [76]. Rocchi A, Micheli D, Ceravolo R, Manca ML, Tognoni G, Siciliano G, Murri L. Serotonergic polymorphisms (5-HTTLPR and 5-HT2A): Association studies with psychosis in Alzheimer disease. *Genetic Testing* 2003;7:309–314. [PubMed: 15000807]
- [77]. Holmes C, Arranz MJ, Powell JF, Collier D, Lovestone S. 5-HT2A and 5-HT2C receptor polymorphisms and psychopathology in late onset Alzheimer's disease. *Hum Mol Genetics* 1998;7:1507–1509.
- [78]. Assal F, Alarcon M, Solomon EC, Masterman D, Geschwind DH, Cummings JL. Association of the serotonin transporter and receptor gene polymorphisms in neuropsychiatric symptoms in Alzheimer disease. *Arch Neurol* 2004;61:1249–1253. [PubMed: 15313842]
- [79]. Lam LC, Tang NL, Ma SL, Zhang W, Chiu HF. 5-HT2A T102C receptor polymorphism and neuropsychiatric symptoms in Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19:523–526. [PubMed: 15211529]
- [80]. Wilkosz PA, Kodavali C, Weamer EA, Miyahara S, Lopez OL, Nimgaonkar VL, DeKosky ST, Sweet RA. Prediction of psychosis onset in Alzheimer disease: the role of depression symptom severity and the HTR2A T102C polymorphism. *Am J Med Genet B Neuropsychiatr Genet* 2007;144B:1054–1062. [PubMed: 17525976]
- [81]. Craig D, Donnelly C, Hart D, Carson R, Passmore P. Analysis of the 5HT-2A T102C receptor polymorphism and psychotic symptoms in Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet* 2007;144B:126–128. [PubMed: 16967466]
- [82]. Pritchard AL, Harris J, Pritchard CW, Coates J, Haque S, Holder R, Bentham P, Lendon CL. Role of 5HT 2A and 5HT 2C polymorphisms in behavioural and psychological symptoms of Alzheimer's disease. *Neurobiol Aging* 2008;29:341–347. [PubMed: 17098333]
- [83]. Lappalainen J, Zhang L, Dean M, Oz M, Ozaki N, Yu DH, Virkkunen M, Weight F, Linnoila M, Goldman D. Identification, expression, and pharmacology of a Cys23-Ser23 substitution in the human 5-HT2c receptor gene (HTR2C). *Genomics* 1995;27:274–279. [PubMed: 7557992]
- [84]. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL. Association of Anxiety-Related Traits with a Polymorphism in the Serotonin Transporter Gene Regulatory Region. *Science* 1996;274:1527–1531. [PubMed: 8929413]
- [85]. Collier DA, Stober G, Li T, Heils A, Catalano M, DiBella D, Arranz MJ, Murray RM, Vallada HP, Bengel D, Muller CR, Roberts GW, Smeraldi E, Kirov G, Sham P, Lesch KP. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol Psychiatry* 1996;1:453–460. [PubMed: 9154246]
- [86]. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, Lesch KP. Allelic variation of human serotonin transporter gene expression. *J Neurochem* 1996;66:2621–2624. [PubMed: 8632190]
- [87]. Ha TM, Cho DM, Park SW, Joo MJ, Lee BJ, Kong BG, Kim JM, Yoon JS, Kim YH. Evaluating associations between 5-HTTLPR polymorphism and Alzheimer's disease for Korean patients. *Dement Geriatr Cogn Disord* 2005;20:31–34. [PubMed: 15832033]
- [88]. Pritchard AL, Pritchard CW, Bentham P, Lendon CL. Role of serotonin transporter polymorphisms in the behavioural and psychological symptoms in probable Alzheimer disease patients. *Dement Geriatr Cogn Disord* 2007;24:201–206. [PubMed: 17690552]
- [89]. Ueki A, Ueno H, Sato N, Shinjo H, Morita Y. Serotonin transporter gene polymorphism and BPSD in mild Alzheimer's disease. *J Alzheimers Dis* 2007;12:245–253. [PubMed: 18057558]
- [90]. Borroni B, Grassi M, Agosti C, Costanzi C, Archetti S, Franzoni S, Caltagirone C, Di Luca M, Caimi L, Padovani A. Genetic correlates of behavioral endophenotypes in Alzheimer disease: Role of COMT, 5-HTTLPR and APOE polymorphisms. *Neurobiol Aging* 2006;11:1595–1603. [PubMed: 16257094]
- [91]. Lesch KP, Balling U, Gross J, Strauss K, Wolozin BL, Murphy DL, Riederer P. Organization of the human serotonin transporter gene. *J Neural Transm Gen Sect* 1994;95:157–162. [PubMed: 7865169]
- [92]. Ogilvie AD, Battersby S, Bubb VJ, Fink G, Harmar AJ, Goodwin GM, Smith CA. Polymorphism in serotonin transporter gene associated with susceptibility to major depression. *Lancet* 1996;347:731–733. [PubMed: 8602004]
- [93]. Seeman P. Dopamine receptor sequences: therapeutic levels of neuroleptics occupy D₂ receptors, clozapine occupies D₄. *Neuropsychopharmacology* 1992;7:261–284. [PubMed: 1362057]

- [94]. Williams J, Spurlock G, Holmans P, Mant R, Murphy K, Jones L, Cardno A, Asherson P, Blackwood D, Muir W, Meszaros K, Aschauer H, Mallet J, Laurent C, Pekkarinen P, Seppala J, Stefanis CN, Papadimitriou GN, Macciardi F, Verga M, Pato C, Azevedo H, Crocq MA, Gurling H, Kalsi G, Curtis D, McGuffin P, Owen MJ. A meta-analysis and transmission disequilibrium study of association between the dopamine D3 receptor gene and schizophrenia. *Mol Psychiatry* 1998;3:141–149. [PubMed: 9577838]
- [95]. Talkowski ME, Mansour H, Chowdari KV, Wood J, Butler A, Varma PG, Prasad S, Semwal P, Bhatia T, Deshpande S, Devlin B, Thelma BK, Nimgaonkar V. Novel, replicated associations between dopamine D3 receptor gene polymorphisms and schizophrenia in two independent samples. *Biol Psychiatry* 2006;60:570–577. [PubMed: 16893532]
- [96]. Sweet RA, Nimgaonkar VL, Kamboh MI, Lopez OL, Zhang F, DeKosky ST. Dopamine receptor genetic variation, psychosis, and aggression in Alzheimer's disease. *Arch Neurol* 1998;55:1335–1340. [PubMed: 9779662]
- [97]. Holmes C, Smith H, Ganderton R, Arranz M, Collier D, Powell J, Lovestone S. Psychosis and aggression in Alzheimer's disease: the effect of dopamine receptor gene variation. *J Neurol Neurosurg Psychiatry* 2001;71:777–779. [PubMed: 11723200]
- [98]. Craig D, Hart DJ, Carson R, McIlroy SP, Passmore AP. Psychotic symptoms in Alzheimer's disease are not influenced by polymorphic variation at the dopamine receptor DRD3 gene. *Neurosci Lett* 2004;368:33–36. [PubMed: 15342129]
- [99]. Pritchard AL, Pritchard CW, Bentham P, Lendon CL. Investigation of the role of the dopamine transporter in susceptibility to behavioural and psychological symptoms of patients with probable Alzheimer's disease. *Dement Geriatr Cogn Disord* 2008;26:257–260. [PubMed: 18841010]
- [100]. Talkowski ME, Kirov G, Bamne M, Georgieva L, Torres G, Mansour H, Chowdari KV, Milanova V, Wood J, McClain L, Prasad K, Shirts B, Zhang J, O'Donovan MC, Owen MJ, Devlin B, Nimgaonkar VL. A network of dopaminergic gene variations implicated as risk factors for schizophrenia. *Hum Mol Genet* 2008;17:747–758. [PubMed: 18045777]
- [101]. Axelrod J, Tomchick R. Enzymatic O-methylation of epinephrine and other catechols. *J Biol Chem* 1958;233:702–705. [PubMed: 13575440]
- [102]. Grossman MH, Emanuel BS, Budarf ML. Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1---q11.2. *Genomics* 1992;12:822–825. [PubMed: 1572656]
- [103]. Carlson C, Sirotkin H, Pandita R, Goldberg R, McKie J, Wadey R, Patanjali SR, Weissman SM, Anyane-Yeboah K, Warburton D, Scambler P, Shprintzen R, Kucherlapati R, Morrow BE. Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. *Am J Hum Genet* 1997;61:620–629. [PubMed: 9326327]
- [104]. Lachman HM, Morrow B, Shprintzen R, Veit S, Parsia SS, Faedda G, Goldberg R, Kucherlapati R, Papolos DF. Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of velo-cardio-facial syndrome. *Am J Med Genetics* 1996;67:468–472. [PubMed: 8886163]
- [105]. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry* 1999;56:940–945. [PubMed: 10530637]
- [106]. Williams HJ, Owen MJ, O'Donovan MC. Is COMT a susceptibility gene for schizophrenia? *Schizophr Bull* 2007;33:635–641. [PubMed: 17412710]
- [107]. Sweet RA, Devlin B, Pollock BG, Sukonick DL, Kastango KB, Bacanu S-A, Chowdari KV, DeKosky ST, Ferrell RE. Catechol-O-methyltransferase haplotypes are associated with psychosis in Alzheimer disease. *Mol Psychiatry* 2005;10:1026–1036. [PubMed: 16027741]
- [108]. Shifman S, Bronstein MSM, Pisante-Shalom A, Lev-Lehman E, Weizman A, Reznik I, Spivak B, Grisaru N, Karp L, Schiffer R, Kotler M, Strous RD, Swartz-Vanetik M, Knobler HY, Shinar E, Beckmann JS, Yakir B, Risch N, Zak NB, Darvasi A. A highly significant association between a COMT haplotype and schizophrenia. *Am J Hum Genet* 2002;71:1296–1302. [PubMed: 12402217]
- [109]. Borroni B, Grassi M, Costanzi C, Zanetti M, Archetti S, Franzoni S, Caimi L, Padovani A. Haplotypes in catechol-O-methyltransferase gene confer increased risk for psychosis in Alzheimer disease. *Neurobiol Aging* 2007;28:1231–1238. [PubMed: 16837108]

- [110]. Nackley AG, Shabalina SA, Tchivileva IE, Satterfield K, Korchynskiy O, Makarov SS, Maixner W, Diatchenko L. Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science* 2006;314:1930–1933. [PubMed: 17185601]
- [111]. Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, Polymeropoulos M, Holik J, Hopkins J, Hoff M, Rosenthal J, Waldo MC, Reimherr F, Wender P, Yaw J, Young DA, Breese CR, Adams C, Patterson D, Adler LE, Kruglyak L, Leonard S, Byerley W. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci U S A* 1997;94:587–592. [PubMed: 9012828]
- [112]. Freedman R, Leonard S, Gault JM, Hopkins J, Cloninger CR, Kaufmann CA, Tsuang MT, Farone SV, Malaspina D, Svrakic DM, Sanders A, Gejman P. Linkage disequilibrium for schizophrenia at the chromosome 15q13-14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (CHRNA7). *Am J Med Genet* 2001;105:20–22. [PubMed: 11424985]
- [113]. Carson R, Craig D, Hart D, Todd S, McGuinness B, Johnston JA, O'Neill FA, Ritchie CW, Passmore AP. Genetic variation in the alpha 7 nicotinic acetylcholine receptor is associated with delusional symptoms in Alzheimer's disease. *Neuromolecular Med* 2008;10:377–384. [PubMed: 18696274]
- [114]. Craig D, Hart DJ, McCool K, McIlroy SP, Passmore AP. The interleukin 1beta gene promoter polymorphism (–511) acts as a risk factor for psychosis in Alzheimer's dementia. *Ann Neurol* 2004;56:121–124. [PubMed: 15236409]
- [115]. Tsuang D, Almqvist EW, Lipe H, Strgar F, DiGiacomo L, Hoff D, Eugenio C, Hayden MR, Bird TD. Familial aggregation of psychotic symptoms in Huntington's disease. *Am J Psychiatry* 2000;157:1955–1959. [PubMed: 11097960]
- [116]. Bird TD, Wijsman EM, NOchlin D, Leehey M, Sumi SM, Payami H, Poorkaj P, Nemens E, Rafkind M, Schellenberg GD. Chromosome 17 and hereditary dementia: linkage studies in three non-Alzheimer families and kindreds with late-onset FAD. *Neurology* 1997;48:950–955.
- [117]. Devi G, Williamson J, Massoud F, Anderson K, Stern Y, Devanand DP, Mayeux R. A comparison of family history of psychiatric disorders among patients with early- and late-onset Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 2004;16:57–62. [PubMed: 14990760]
- [118]. Drevets WC, Rubin EH. Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. *Biol Psychiatry* 1989;25:39–48. [PubMed: 2912509]
- [119]. Devlin B, Roeder K, Bacanu SA. Unbiased methods for population-based association studies. *Genet Epidemiol* 2001;21:273–284. [PubMed: 11754464]
- [120]. Couzin J, Kaiser J. Genome-wide association. Closing the net on common disease genes. *Science* 2007;316:820–822. [PubMed: 17495150]

Figure 1. Genetic models of psychosis in Alzheimer Disease

Genes may modify the neurodegenerative process to result in the expression of psychosis in AD (Pathway A1). Some of these genes may similarly impact the neurodegenerative process in other diseases (Pathway A2). Modifier genes may also interact with environmentally or genetically driven abnormalities of neurodevelopment (e.g. velocardiofacial syndrome) or with normal neurodevelopmental processes (e.g. synaptic pruning during adolescence) resulting in an early life psychosis such as schizophrenia (Pathway A3). Three possible disease modifier genes are shown (CHRNA7, COMT, NRG1) based on data suggesting a role for each in the onset of schizophrenia and preliminary findings in AD+P (see text for more complete review of the evidence). Alternatively in Pathway B, there may be genes that predispose to the

development of a subtype of Alzheimer disease in which psychotic symptoms are manifest. Two genes associated with increased risk for late-onset AD, APOE and SORL1, are shown. Available evidence, while subject to limitations reviewed in the text, does not support a role for APOE in AD+P development. SORL1 has not been studied.

APOE: Apolipoprotein E; CHRNA7: $\alpha 7$ nicotinic acetylcholine receptor gene; COMT: Catechol-O-methyltransferase; NRG1: Neuregulin-1; SORL1: Sortilin-related receptor.

Table 1

Familial aggregation studies of psychosis in siblings of probands with Alzheimer Disease and Psychosis (AD +P)

Author, Date	Data Set	Proband (n)	Siblings (n)	Odds Ratio, <i>p</i> value
Tunstall, 2000[39]	United Kingdom	DNS	DNS	Excess pair-wise concordance = 0.04
Sweet, 2002[40]	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, 2005[41]	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, 2007[42]	NIMH	305	359	3.2 (2.05-4.99), $p<0.001$
	United Kingdom	91	98	4.17 (1.67-10.44), $p=0.002$
	combined	396	457	3.38 (2.27-5.05), $p<0.001$

NIMH: National Institute of Mental Health; 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

Table 2

Apolipoprotein (APOE) Association with Alzheimer Disease and Psychosis (AD+P)

Author, Date	Subjects (N)	AD-P (N)	AD+P (N)	AD-P Genotype (N)	AD+P Genotype (N)	Association with Psychosis ⁺	Odds ratio, RR or χ^2 , p value
Lehtovirta, 1996[56]	SLO, FLO, SEO, FEO (58, but only 25 with SLO)	DNS	DNS	DNS	DNS	Genotype NS for Hal	DNS
Ramachandran, 1996[61]	Late-onset AD (46) Controls (135)	26	20	c3/3 (18) c3/4 (8)	c3/3 (8) c3/4 (12)	Genotype NS for Psy	OR=3.4 (1.0-11.4)
Cacabelos, 1996[49]	Dementia (207) AD (47/207)	118	89	c3/3 (37) c3/4 (38) c4/4 (25)	c3/3 (23) c3/4 (22) c4/4 (11)	3/3 genotype commonly associated with Psy but NS	DNS
Ballard, 1997[48]	Possible/probable AD (36)	DNS	DNS	DNS	DNS	One or more c4 alleles significant for Psy	p=0.006
Lopez, 1997[58]	Probable AD (194)	DNS	DNS	c3/3-Psy (36) c3/3-Del (40) c3/3-Hal (60) c3/4-Psy (54) c3/4-Del (55) c3/4-Hal (83) c4/4-Psy (14) c4/4-Del (14) c4/4-Hal (16)	c3/3+Psy (43) c3/3+Del (39) c3/3+Hal (19) c3/4+Psy (42) c3/4+Del (41) c3/4+Hal (13) c4/4+Psy (5) c4/4+Del (5) c4/4+Hal (3)	Genotype NS for Del Genotype NS for Hal Genotype NS for Del+Hal	$\chi^2=1.1, p=0.28$ $\chi^2=2.6, p=0.10$ OR=0.66 (0.35-1.25), $\chi^2=2.2, p=0.10$
Lyketsos, 1997[59]	Probable AD (120)	DNS	Del (36) Hal (17)	c2/3-Del (2) c2/3-Hal (2) c2/4-Del (5) c2/4-Hal (7) c3/3-Del (20) c3/3-Hal (29) c3/4-Del (46) c3/4-Hal (50) c4/4-Del (11) c4/4-Hal (15)	c2/3+Del (0) c2/3+Hal (0) c2/4+Del (2) c2/4+Hal (0) c3/3+Del (15) c3/3+Hal (6) c3/4+Del (13) c3/4+Hal (9) c4/4+Del (6) c4/4+Hal (2)	Genotype NS for Del/Hal	p>0.10
Hirono, 1998[53]	AD (228)	110	118 Del (94) Hal (3) Del+Hal (21)	+c4 (66) -c4 (44)	+c4 (42) -c4 (76)	Carrier status NS for Psy	$\chi^2(1)=0.47, p=0.49$
Levy, 1999[57]	Probable/possible AD (605)	DNS	DNS	DNS	DNS	Carrier status NS for Del/Hal	DNS
Harwood, 1999[52]	Probable late-onset AD (343) Possible late-onset AD (158)	332	169	c2/3 (14) c2/4 (8) c3/3 (166) c3/4 (126) c4/4 (18)	c2/3 (5) c2/4 (6) c3/3 (62) c3/4 (77) c4/4 (19)	Genotype significant for Psy Carrier status significant for Psy	$\chi^2=12.7, p=0.01$ OR=2.0 (1.3-3.1), p=0.002 for c4
Hirono, 1999[54]	Sporadic AD (175)	DNS	Del (90) Hal (10)	DNS	DNS	Carrier status NS for Del Carrier status NS for Hal	OR= 0.76 (0.45-1.28) OR=0.49 (0.15-1.60)

Weiner, 1999[66]	Probable AD (93) Possible AD (4) Definite (autopsy-confirmed) late-onset AD (61*) Control (73)	DNS	Del (14) Hal (26)	No c4-Del (51) No c4-Hal (48) One c4-Del (76) One c4-Hal (69) Two c4-Del (16) Two c4-Hal (14)	No c4-Del (2) No c4-Hal (5) One c4-Del (8) One c4-Hal (15) Two c4-Del (4) Two c4-Hal (6)	Allele frequency significant for Del Allele frequency significant for Hal	p=0.05** p=0.05
Nacmias, 2001[75]	AD (83) FAD (120/24 late-onset FAD) Controls (72)	AD (58) FAD (77)	AD (25) FAD (43)	DNS	DNS	Carrier status NS for Psy	DNS
Gabryelewicz, 2002[51]	Probable AD (139)	DNS	Del (77) Hal (31)	No c4-Del (31) c4-Del (31) No c4-Hal (54) c4-Hal (54)	No c4-Del (36) c4-Del (41) No c4-Hal (13) c4-Hal (18)	Carrier status NS Del/Hal	DNS
Scarmeas, 2002[62]	AD early stages (87)	DNS	Del (49) Hal (35)	No c4-Del (8) No c4-Hal (18) One c4-Del (1) One c4-Hal (14) Two c4-Del (0) Two c4-Hal (10)	No c4-Del (20) No c4-Hal (15) One c4-Del (21) One c4-Hal (18) Two c4-Del (8) Two c4-Hal (2)	Significant for Del in simple and adjusted models Protective association with 2c4 against Hal in adjusted model only	Simple Model: Del +1c4: RR=2.5 (1.3-4.8) Del+2 c4: RR=5.6 (2.2-14.0) Hal+1 c4: RR=1.2 (0.6-2.5) Hal+2 c4: RR=0.3 (0.1-1.3) Adjusted Model: Del +1c4: RR=3.0 (1.4-6.3) Del +2c4: RR=11.7 (3.8-36.0) Hal+1c4: RR= 0.9 (0.4-1.9) Hal +2c4: RR= 0.2 (0.0-0.9)
Sweet, 2002[64]	Possible/probable AD (316)	DNS	47	DNS	DNS	Carrier status NS for time to development of Psy	p=0.8
Chang, 2004[50]	AD (56)	DNS	Del (18) Hal (14)	DNS	DNS	Carrier status significant for Del Carrier status significant for Hal	RR=3.4 (1.0-11.3), p=0.047 RR=19 (2.6-138.4), p=0.004
Spalletta, 2006[63]	Late-onset AD (171)	DNS	Psy (31) Del (26) Hal (15)	+c4-Psy (66) -c4-Psy (74) +c4-Del (66) -c4-Del (79) +c4-Hal (77) -c4-Hal (79)	+c4-Psy (18) -c4-Psy (13) +c4-Del (18) -c4-Del (8) +c4-Hal (7) -c4-Hal (8)	Carrier status significant for Del	OR=3.11 (1.21-8.01), p=0.019
Borroni, 2006[90]	Probable AD (232)	DNS	DNS	DNS	DNS	Carrier status NS for Del Carrier status NS for Hal Allele frequency NS for Del/Hal	OR=1.55, p=0.05 OR=1.07, p=0.05 DNS
Hollingsworth, 2006[55]	Probable late-onset AD (1,120)	DNS	Del (502) Hal (271)	DNS	DNS	Genotype NS for delusions Allele frequency NS for delusions c3/3 genotype significant for Hal Allele frequency NS for Hal	$\chi^2=7.98, p=0.92$ $\chi^2=4.70, p=0.095$ $\chi^2=12.02, p=0.017$ $\chi^2=0.33, p=0.85$
Pritchard, 2007[60]	AD (388)	Del (147) Hal (221)	Del (241) Hal (167)	c22/24-Del (1) c2/3-Del (17) c3/3-Del (41) c3/4-Del (69) c4/4-Del (19) c22/24-Hal (0)	c22/24+Del (7) c2/3+Del (14) c3/3+Del (57) c3/4+Del (120) c4/4+Del (45) c22/24-Hal (6)		

				c2/3+Hal (22) c3/3+Hal (53) c3/4+Hal (113) c4/4+Hal (33)	c2/3+Hal (10) c3/3+Hal (47) c3/4+Hal (77) c4/4+Hal (27)		
van der Flier, 2007[65]	AD (110)	DNS	DNS	DNS	DNS	c4/4 genotype significant for Del	p<0.05
Zdayns, 2007[67]	Probable AD (266)	217	49	+ c4-Psy (94) - c4-Psy (84)	+c4+Psy (56) -c4+Psy (32)	Carrier status significant for Psy	OR=1.87 (1.07-3.29), p=0.029

⁺ Based on a simple model of analysis. Associations refer to c4 unless otherwise noted. Studies with significant associations are in bold

AD: Alzheimer disease; AD-P: Alzheimer disease minus psychosis; AD+P: Alzheimer disease plus psychosis; RR: relative risk; Psy: psychosis; Del: delusions; Hal: hallucinations; NS: not significant for association; SLO: sporadic late-onset; FLO: familial late-onset; SEO: sporadic early-onset; FEO: familial early-onset; DNS: data not shown.

* of the 61 patients, 17 met criteria for Lewy Body variant of AD

** significance for delusions, but not for hallucinations was lost after removal of LBV cases $p=0.13$

Table 3

Association of Serotonin Receptors and Alzheimer Disease and Psychosis (AD+P)

Gene	Author, Date	Subjects (N)	AD-P (N)	AD+P (N)	Association with Psychosis	Odds Ratio, χ^2 , p value
5HTR2A (102-T/C)	Holmes, 1998[77]	Late-onset AD (211) Controls (181)	-Del (93) -vis Hal (168) -aud Hal (181)	+Del (118) +vis Hal (43) +aud Hal (30)	Allele frequency significant for vis Hal Allele frequency significant for aud Hal Risk allele for Hal is C Allele frequency NS for Del	$\chi^2=8.3$, $p=0.015$ $\chi^2=6.5$, $p=0.04$ DNS
	Nacmias, 2001[75]	AD (83) FAD (120/24 late-onset FAD) Controls (72)	AD (58) FAD (77)	AD (25) FAD (43)	CC genotype significant for Psy in AD and FAD groups Allele frequency significant for Psy in AD and FAD groups Risk allele for Psy is C	$p<0.00005$
	Rocchi, 2003[76]	Sporadic AD (135) Controls (90)	77	58	Allele frequency significant for Psy Risk allele for Psy is C	$\chi^2=19.13$, $p<0.001$
	Assal, 2004[78]	AD (93) genotyped for del (92) genotyped for hal (93)	-Del (69) - Hal (81)	+Del (24) +Hal (12)	Allele frequency significant for Del Risk allele for Del is T Allele frequency NS for Hal	$p=0.045$ $p=0.55$
	Lam, 2004[79]	Probable/possible AD (87) Controls (75)	-Del (55)	+Del (32)	Genotype significant for Del CC genotype protective for Del Allele frequencies NS for Del	$\chi^2=8.31$, $p=0.016$ DNS
	Craig, 2007[81]	Probable AD (406)	-Del (211) -Hal (292)	+Del (195) +Hal (114)	Genotype NS for Del Genotype NS for Hal Allele Frequency NS for Del Allele frequency NS for Hal	$\chi^2=1.779$, $p=0.411$ $\chi^2=4.805$, $p=0.090$ $\chi^2=2.110$, $p=0.146$ $\chi^2=0.200$, $p=0.654$
	Wilkosz, 2007[80]	Probable AD (237) Possible AD (35) MCI (52)	214	110	Genotype and allele frequency NS for presence of or time to onset of Psy	DNS
	Pritchard, 2008[82]	AD (393)	-Del (149) -Hal (224)	+Del (244) +Hal (169)	Genotype NS for Del Genotype NS for Hal Allele frequency NS for Del Allele frequency NS for Hal	$\chi^2=2.86$, $p=0.24$ $\chi^2=2.68$, $p=0.26$ $\chi^2=2.13$, $p=0.14$ $\chi^2=2.16$, $p=0.14$
5HTR2C (Cys23Ser)	Holmes, 1998[77]	Late-onset AD (211)	-Del (93) -vis Hal (168) -aud Hal (181)	+Del (118) +vis Hal (43) +aud Hal (30)	Allele frequency NS for Del Allele frequency significant for vis Hal Allele frequency NS for aud Hal	DNS $\chi^2=7.7$, $p=0.02$ DNS
	Assal, 2004[78]	AD (96) Genotyped (87)	-Del (69) - Hal (81)	+Del (24) +Hal (12)	Allele frequency NS for Del Allele frequency NS for Hal	$p=0.18$ $p=0.70$
	Pritchard, 2008[82]	AD (394)	-Del (126) -Hal (225)	+Del (268) +Hal (169)	Genotype NS for Del in Females Genotype NS for Hal in Females Allele Frequency NS for Del in Females Allele frequency NS for Hal in Females Genotype NS for Del in Males Genotype NS for Hal in Males	$\chi^2=2.43$, $p=0.30$ $\chi^2=0.75$, $p=0.69$ $\chi^2=0.47$, $p=0.49$ $\chi^2=0.21$, $p=0.65$ $\chi^2=0.18$, $p=0.67$ $\chi^2=1.24$, $p=0.27$
5-HTTLPR	Sweet, 2001[20]	Possible AD (55) Probable AD (277)	189	143	LL genotype significant for Psy L allele frequency significant for Psy	$\chi^2=6.5$, $p=0.01$ $\chi^2=13.2$, $p<0.001$
	Rocchi, 2003[76]	Sporadic AD (135) Controls (90)	77	58	Allele frequency NS for Psy	DNS
	Ha, 2005[87]	AD (65) Controls (43)	-Del (22)	+Del (43)	Genotype NS for Del Allele frequency NS for Del	$p=0.997$ $p=0.888$
	Borroni, 2006[90]	Probable AD (216)	DNS	DNS	LL genotype significant for protecting against Del S allele carrier status NS for Hal	OR=0.38 (0.01-0.90) , $p<0.05$ OR=0.49
	Pritchard, 2007[88]	Probable AD (367)	224 -Del (139) -Hal (206)	143 +Del (228) +Hal (161)	Genotype NS for Psy Genotype NS for Del Genotype NS for Hal Allele frequency NS for Psy Allele frequency NS for Del Allele frequency NS for Hal	$\chi^2=1.37$, $p=0.5$ $\chi^2=1.17$, $p=0.56$ $\chi^2=1.72$, $p=0.42$ $\chi^2=0.12$, $p=0.73$ $\chi^2=0.07$, $p=0.79$ $\chi^2=1.05$, $p=0.31$
	Ueki, 2007[89]	AD (200) Controls (200)	-Del (156) -Hal (176)	+Del (44) +Hal (24)	Genotype NS for Del Genotype NS for Hal	$\chi^2=4.079$, $p=0.1301$ $\chi^2=3.208$, $p=0.0711$
5-HTTVNTR	Pritchard, 2007[88]	Probable AD (360)	230 -Del (140) -Hal (209)	130 +Del (220) +Hal (151)	Genotype NS for Psy Allele frequency significant for Psy 10-repeat is risk allele Genotype NS for Del Genotype NS for Hal Allele frequency NS for Del Allele frequency NS for Hal	$\chi^2=6.67$, $p=0.08$ $\chi^2=6.63$, $p=0.04$ $\chi^2=6.33$, $p=0.10$ $\chi^2=4.93$, $p=0.18$ $\chi^2=4.92$, $p=0.09$ $\chi^2=4.96$, $p=0.08$
	Ueki, 2007[89]	AD (200) Controls (200)	-Del (156) -Hal (176)	+Del (44) +Hal (24)	Genotype NS for Del Genotype NS for Hal	$\chi^2=0.014$, $p=0.9058$ $\chi^2=0.005$, $p=0.9441$

Studies with significant associations are in bold.

5HTR2A: serotonin 2A receptor; 5HTR2C: serotonin 2C receptor; SLC6A4: serotonin transporter; 5-HTTLPR: serotonin transporter promoter linked polymorphic region; 5-HTTVNTR: serotonin transporter variable number of tandem repeats sequence; AD: Alzheimer disease; AD-P: Alzheimer

disease minus psychosis; AD+P: Alzheimer disease plus psychosis; Psy: psychosis; Del: delusions; Hal: hallucinations; vis: visual; aud: auditory; MCI: mild cognitive impairment; NS: not significant; DNS: data not shown.

Table 4

Association of Dopamine Receptors and Alzheimer Disease and Psychosis (AD+P)

Receptor	Author, Date	Subjects (N)	AD-P (N)	AD+P (N)	AD-P Genotype (N)	AD+P Genotype (N)	Association with Psychosis	Odds ratio, χ^2 , <i>p</i> value
DRD1	Sweet, 1998[96]	Probable AD (251)	179	72	B1/B1 (19) B1/B2 (99) B2/B2 (61)	B1/B1 (11) B1/B2 (25) B2/B2 (36)	B2/B2 genotype significant for Psy B2 allele frequency NS for Psy	OR=1.9 (1.1-3.3), $\chi^2=5.5$, <i>p</i> =0.02 $\chi^2=1.4$, <i>p</i> =0.2
	Holmes, 2001[97]	Possible/probable late-onset AD (105)	-Del (45) -Hal (82)	+Del (60) +Hal (23)	B1/B1-Del (13) B1/B2-Del (18) B2/B2-Del (14) B1/B1-Hal (22) B1/B2-Hal (34) B2/B2-Hal (26)	B1/B1+Del (10) B1/B2+Del (31) B2/B2+Del (19) B1/B1+Hal (1) B1/B2+Hal (15) B2/B2+Hal (7)	B1/B2 genotype significant for Hal Genotype NS for Del	OR=9.7 (1.2-79.0), <i>p</i> =0.006 <i>p</i> >0.1
DRD2	Sweet, 1998[96]	Probable AD (267)	DNS	DNS	DNS	DNS	Cys311 allele frequency NS for Psy	<i>p</i> =0.4
DRD3	Sweet, 1998[96]	Probable AD (244)	173	71	1/1 (77) 1/2 (75) 2/2 (21)	1/1 (40) 1/2 (21) 2/2 (10)	Ser/Ser and Gly/Gly genotype significant for Psy Allele frequency NS for Psy	OR=1.8 (1.0-3.3), $\chi^2=4.0$, <i>p</i> <0.05 $\chi^2=1.1$, <i>p</i> =0.3
	Holmes, 2001[97]	Possible/probable late-onset AD (129)	DNS	DNS	DNS	DNS	Gly/Gly genotype significant for protecting against Del Genotype NS for Hal	OR=0.3 (0.1-0.99), <i>p</i> =0.045 DNS
	Craig, 2004[98]	Probable AD (416)	-Del (213) -Hal (304)	+Del (203) +Hal (113)	GG-Del (23) GS-Del (94) SS-Del (96) GG-Hal (35) GS-Hal (140) SS-Hal (129)	GG+Del (25) GS+Del (100) SS+Del (78) GG+Hal (13) GS+Hal (55) SS+Hal (45)	Genotype NS for Del Genotype NS for Hal Allele frequency NS for Del Allele frequency NS for Hal	$\chi^2=2.7$, <i>p</i> =0.26 $\chi^2=0.26$, <i>p</i> =0.88 $\chi^2=1.5$, <i>p</i> =0.22 $\chi^2=0.12$, <i>p</i> =0.73
DRD4	Sweet, 1998[96]	Probable AD (225)	DNS	DNS	DNS	DNS	Allele frequency NS for Psy	$\chi^2=0.1$, <i>p</i> =0.70
SLC6A3 (DAT1 3'-UTR VNTR)	Pritchard, 2008[99]	Probable AD (395)	DNS	DNS	DNS	DNS	Genotype NS for Psy/Del/Hal	DNS

Studies with significant associations are in bold.

AD: Alzheimer disease; AD-P: Alzheimer disease minus psychosis; AD+P: Alzheimer disease plus psychosis; DRD1: dopamine-1 receptor; DRD2: dopamine-2 receptor; DRD3: dopamine-3 receptor; DRD4: dopamine-4 receptor; SLC6A3: dopamine transporter; DAT1 3'-UTR VNTR: 3'-untranslated region variable number tandem repeat polymorphism; Psy: psychosis; Del: delusions; Hal: hallucinations; NS: not significant; DNS: data not shown.

Table 5

Association of Catechol-O-methyltransferase (COMT) and Alzheimer Disease and Psychosis (AD+P)

Author, Date	SNPs in order on the chromosome	Subjects (N)	AD-P (N)	AD+P (N)	Single locus association with psychosis	Odds ratio, χ^2 , <i>p</i> value
Sweet, 2005[107]	ERE6 rs737865 rs4680 rs165599	Possible/probable AD (373)	182	191	Females: ERE6 NS for Psy Trend toward association with rs737865 for Psy rs4680 significant for Psy rs165599 NS for Psy Males: ERE6 NS for Psy rs737865 NS for Psy rs4680 NS for Psy rs165599 NS for Psy	$\chi^2=1.93$, <i>p</i> =0.164 $\chi^2=2.93$, <i>p</i> =0.087 $\chi^2=7.99$, <i>p</i>=0.005 $\chi^2=0.25$, <i>p</i> =0.614 $\chi^2=0.01$, <i>p</i> =0.924 $\chi^2=0.05$, <i>p</i> =0.816 $\chi^2=0.76$, <i>p</i> =0.383 $\chi^2=2.43$, <i>p</i> =0.120
Borrioni, 2006[90]	rs4680	Probable AD (232)	DNS	DNS	G carriers significant for Hal NS for Del	OR=6.30 (1.21-27.1), <i>p</i>=0.05 OR=1.62, <i>p</i> >0.05
Borrioni, 2007[109]	rs737865 rs737864 intron1C2754delC rs4680	AD (246)	171	75	rs737865 genotype NS for Psy rs737865 G allele frequency NS for Psy rs737864 genotype NS for Psy rs737864 T allele frequency NS for Psy intron1C2754delC genotype NS for Psy intron1C2754delC delC allele frequency NS for Psy rs4680 genotype significant for Psy rs4680 G allele frequency significant for Psy	OR (additive) AG=1.26; GG=1.60, <i>p</i> =0.267 OR (additive)=1.24, <i>p</i> =0.329 OR (additive) CT=1.16; TT=1.34, <i>p</i> =0.526 OR (additive)=1.20, <i>p</i> =0.566 OR (additive) delC/C=1.18; delC/delC=1.39, <i>p</i> =0.480 OR (additive)=1.18, <i>p</i> =0.552 OR (additive) AG =1.83 (1.21-2.76), GG=3.34; <i>p</i>=0.004 OR (additive)=1.75 (1.019-2.58), <i>p</i>=0.007

Studies with significant associations are in bold.

AD: Alzheimer disease; AD-P: Alzheimer disease minus psychosis; AD+P: Alzheimer disease plus psychosis; Psy: psychosis; Del: delusions; Hal: hallucinations; NS: not significant; DNS: data not shown.