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No association of psychosis in Alzheimer disease with neurodegenerative pathway genes

Mary Ann A. DeMichele-Sweet, Ph.D.¹, Lambertus Klei, Ph.D.¹, Bernie Devlin, Ph.D.¹, Robert E. Ferrell, Ph.D.⁴, Elise A. Weamer, M.P.H.^{1,2}, James E. Emanuel, B.S.¹, Oscar L. Lopez, M.D.^{1,2}, and Robert A. Sweet, M.D.^{1,2,3}

¹Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, U.S.A

²Department of Neurology, University of Pittsburgh, Pittsburgh, PA, U.S.A

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

⁴Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA, U.S.A

Abstract

Psychotic symptoms occur in approximately 40% of subjects with Alzheimer disease (AD with Psychosis, AD+P) and identify a subgroup with more rapid cognitive decline. We evaluated in 867 AD subjects the association of AD+P with genes which may modify the pathologic process via effects on the accumulation of amyloid beta (A β) protein and/or hyperphosphorylated microtubule-associated protein tau (MAPT): amyloid precursor protein (APP), beta-site amyloid precursor protein cleaving enzyme (BACE1), sortilin-related receptor (SORL1), and MAPT. Each gene was thoroughly interrogated with tag SNPs, and gene-based tests were used to enhance power. We found no association of these genes with AD+P.

Keywords

Alzheimer's disease; psychosis; amyloid precursor protein (APP); beta-site amyloid precursor protein cleaving enzyme (BACE1); sortilin-related receptor (SORL1); microtubule-associated protein tau (MAPT); and Apolipoprotein E e4 (APOE e4)

2. Introduction

Psychotic symptoms, delusions and hallucinations, are common in Alzheimer Disease (AD), occurring in approximately 40% of individuals over the course of the illness (Ropacki and Jeste, 2005). Psychotic symptoms in AD (AD with psychosis, AD+P) cause significant

For questions, correspondence, and reprints please contact: Robert A. Sweet, M.D., Professor of Psychiatry and Neurology, Vice-Chair, Institutional Review Board, University of Pittsburgh, Co-Associate Director for Research, Mental Illness Research, Education, and Clinical Center, VA Pittsburgh Healthcare System, Ph- 1-412-383-8548, Fax 1-412-624-9910, sweetra@upmc.edu, <http://www.wpic.pitt.edu/research/sweetlab>, Mail: Biomedical Science Tower, Rm W-1645, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, Express Mail: Biomedical Science Tower, Rm W-1645, Lothrop and Terrace Streets, Pittsburgh, PA 15213-2593. Previously presented at the 9th Annual Meeting of the International College of Geriatric Psychoneuropharmacology, Baltimore, MD, 2009.

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distress for patients and family members (Kaufer et al, 1998), predict worse functional outcome (Scarmeas et al, 2005), and show limited benefit from current treatments (Schneider et al, 2006). Importantly, a number of studies indicate that the occurrence of psychosis in AD is familial, with an estimated heritability of 61% (Bacanu et al, 2005; Hollingworth et al, 2007; Sweet et al, 2002a; Sweet et al, 2010), thereby motivating the study of the genetic basis of the AD+P phenotype (Sweet et al, 2003).

Numerous studies have shown that the most consistent clinical correlate of the development of psychotic symptoms during AD is more rapid cognitive decline than seen in individuals who have AD without psychosis (AD-P) (Ropacki and Jeste, 2005). More rapid decline and greater resultant cognitive dysfunction precedes the onset of psychosis, occurring in the earliest phases of disease (Emanuel et al, 2010; Weamer et al, 2009). It has been appreciated for a number of years that the strongest correlate of cognitive impairment in individuals with AD is loss of synapses across neocortical regions (Scheff and Price, 2003; Terry et al, 1991). Consistent with the observation of more rapid cognitive decline in AD+P, we have previously reported biochemical evidence consistent with increased synaptic disruption across multiple neocortical regions in subjects with AD+P (Sweet et al, 2002b).

While many factors may contribute to synapse loss in AD, human postmortem studies indicate that cortical synapse loss and cognitive impairments correlate strongly with levels of soluble amyloid beta ($A\beta$) protein (Lue et al, 1999), even in subjects with early disease (Naslund et al, 2000). Evidence from animals transgenic for mutant human amyloid precursor protein (APP) similarly indicate a direct role of soluble $A\beta$ in synaptic loss and dysfunction early in the pathologic cascade (Selkoe, 2002; Walsh and Selkoe, 2007). Soluble $A\beta$ may also increase aggregation of microtubule-associated protein tau (MAPT) (Walsh and Selkoe, 2007), which itself can contribute to loss of synapses (Eckermann et al, 2007). Although most studies have found no consistent association between AD+P and indexes of insoluble $A\beta$ (Farber et al, 2000; Sweet et al, 2000), soluble $A\beta$ has not been assessed. In contrast, increased aggregated MAPT has been reported in AD+P subjects (Farber et al, 2000; Forstl et al, 1994; Mukaetova-Ladinska et al, 1995). Of interest, MAPT mutation can be associated with a dementia-lacking AD pathology which initially presents as a schizophrenia-like psychosis (Bird et al, 1997; Poorkaj et al, 1998).

The above findings suggest a model (Suppl. Fig 1) in which the more rapidly deteriorating cognitive course of individuals with AD+P reflects a greater degree of cortical synaptic disruption than found in AD subjects without psychosis (AD-P), either due to effects of genetic variation on the generation of soluble $A\beta$ or on downstream effectors of $A\beta$ -induced synapse loss such as MAPT. Currently, the APOE gene, which is known to increase AD risk, possibly via its effects on $A\beta$ clearance (Kim et al, 2009), is the only such gene to have been tested for association with AD+P, with largely negative findings (DeMichele-Sweet and Sweet, 2010). To further test this model we undertook to comprehensively evaluate the APP and MAPT genes for association with AD+P in a large cohort of well-characterized subjects. In addition, we similarly evaluated sortilin-related receptor (SORL1), an AD risk gene (Bettens et al, 2008; Feulner et al, 2010; Kimura et al, 2009; Kolsch et al, 2009; Li et al, 2008; Rogaeva et al, 2007; Tan et al, 2009) which impacts $A\beta$ metabolism (Mayeux and George-Hyslop, 2009) and correlates with measures of synaptic markers (Gear et al, 2009). Finally, we evaluated beta-site amyloid precursor protein cleaving enzyme (BACE1), a key enzyme in the conversion of APP to $A\beta$ (Vassar et al, 1999), the knockout of which is associated with synapse loss and psychosis phenotypes in the mouse model (Savonenko et al, 2008).

3. Methods

3.1. Subjects

Subjects were included if they were Caucasian and non-Latino with a final diagnosis of possible or probable AD (McKhann et al, 1984) as evaluated at the University of Pittsburgh Alzheimer Disease Research Center (ADRC), Pittsburgh, PA. All subjects were assessed at baseline with standardized neurological, neuropsychological, and psychiatric evaluations, cognitive testing, laboratory studies and brain imaging as previously described (Lopez et al, 1997; Lopez et al, 2003; Sweet et al, 1998; Weamer et al, 2009). Patients with schizophrenia, bipolar disorder (APA, 1994), or probable Dementia with Lewy Bodies (McKeith et al, 1996) at their initial or follow-up assessments were excluded. The rate of autopsy confirmation of AD in subjects diagnosed with Possible or Probable AD exceeds 90% in our center (Lopez et al, 2003). All data collected in this study were obtained with protocols approved by the Institutional Review Board of the University of Pittsburgh.

3.2. Assessment of Psychosis

Psychosis was evaluated with the CERAD behavioral rating scale (CBRS) (Tariot et al, 1995). The CBRS measures the extent of behavioral pathology in persons with dementia, and was designed to be administered to an informant. The 867 subjects in this study had 3,182 behavioral rating assessments. Informant data were available for 793 subjects at 2,988 assessments. Informants were predominately spouses (52.7%), children (47.2%), or others (9.8%), (total exceeds 100% because some subjects have multiple informants). Most informants (61.9%) lived with the subject. The vast majority of informants had contact with subjects more than 3-4 days/week (86.7%). Psychosis was defined by the presence of persistent hallucinations or delusions occurring at any time during the course of the dementia. A delusion was defined as a false belief based on incorrect inference about external reality, resistant to persuasion or contrary evidence, and not attributable to social or cultural mores. Hallucinations were defined as sensory perceptions for which there was no basis in reality. Discrete hypnagogic and hypnopompic hallucinations, as well as symptoms occurring only during an episode of delirium, were not rated. Psychosis at any assessment was considered present when any of the CBRS items #33 or #36-#45 were rated as occurring ≥ 3 times in the past month. The CBRS items include: misidentified people (#33), people harming or stealing (#36), spouse is unfaithful (#37), caregiver plotting to abandon (#38), caregiver is an imposter (#39), characters on TV are real (#40), phantom boarder in home (#41), dead person is alive (#42), house is not home (#43), auditory hallucinations (#44), and visual hallucinations (#45). Inter-rater reliability for the determination of psychosis using the CBRS at the ADRC has been established and is uniformly high, with mean (SD) AD with psychosis kappa 0.98 (0.07) for all raters and mean (SD) individual psychosis symptom kappas ranging from 0.98 (0.07) to 1.0 (0.0). The CBRS was administered at initial and annual visits and in some subjects between annual visits by telephone, a procedure for which reliability has also been established (Sweet et al, 2010; Wilkosz et al, 2007). Using all available CBRS data, subjects were characterized as having no psychotic symptoms, a single psychotic symptom at only one time point, or multiple/recurrent psychotic symptoms, reflecting the increasing genetic loading associated with this hierarchy (Bacanu et al, 2005; Sweet et al, 2010). Finally, because the occurrence of psychosis is less frequent in the early stages of AD, subjects were required to have a Mini Mental State Exam (Folstein et al, 1975) score ≤ 20 in order to be classified as AD-P.

3.3. SNP Selection

SNPs were downloaded for each of the genes from HapMap2 (www.hapmap.org). Gene location was determined by the March 2006 Human Reference Sequence NCBI Build 36.1;

SNPs were selected from the gene location $\pm 15\text{kb}$. We then used Hclust (Rinaldo et al, 2005) to determine tag-SNPs with $r^2 < 0.8$.

3.4. Genotyping

SNP genotyping used the Illumina GoldenGate Assay (Illumina, Inc., San Diego, CA), in the Genomics and Proteomics Core Laboratories of the University of Pittsburgh (www.genetics.pitt.edu). Prior to genotyping, all DNA specimens were whole genome amplified by the multiple displacement amplification method of Dean, et al. (2002) using the REPLI-g kit Quiagen, Valencia, CA. After genotyping, SNPs were screened for completion rate (completion rate $>95\%$), minor allele frequency (>0.01) and Hardy Weinberg equilibrium in AD-P cases (exact Hardy Weinberg p-value >0.005). After edits there were 49, 12, 25, and 41 SNPs representing *APP*, *BACE1*, *MAPT*, and *SORL1* respectively. Details can be found in Suppl Table 1. Additionally, 12/879 (1.4%) subjects were removed for a genotype completion rate of less than 95%, leaving a final sample of 867 subjects.

3.5. Statistical Analysis

Data were analyzed using two gene-based tests (Roeder et al, 2005), one evaluating the maximum test statistic per gene, T(P), and the other evaluating the pattern of test statistics based on the maximum of a spline fit of the statistics, T(S). One thousand permutations of psychosis status were used to determine significance of the tests.

Data were further analyzed using a conditional logit model (Lee et al, 2010; Luca et al, 2008). In this model, AD+P and AD-P subjects were matched based on genetic similarity. Because the SNPs in this study were determined as part of a larger study in which genotypes were obtained for a total of 768 SNPs, a subset of 543 SNPs that had a completion rate of at least 99% and were separated by at least 1Kb was used for assessment of ancestry. Based on this subset, 8 dimensions of ancestry were identified. Genetic distances among individuals were then based on these 8 dimensions, and AD+P and AD-P subjects were subsequently matched using the fullmatch algorithm as implemented in the optmatch package in R. The fullmatch algorithm matches AD+P and AD-P subjects in such a way that in each matched strata one AD+P subject is matched to one or more AD-P subjects, or one AD-P subject is matched to one or more AD+P subjects.

For both the gene-based and conditional logit tests, a primary analysis was conducted in which subjects with multiple or recurrent psychosis were contrasted with subjects with either a single psychotic symptom or no psychosis. To optimize the sensitivity to detect association, the primary analysis was followed up by a secondary analysis in which subjects with multiple or recurrent psychosis were contrasted with subjects without psychosis.

4. Results

Demographics and clinical characteristics for the 867 participants with available genotypes are shown in Suppl Table 2. All subjects had late-onset AD (age of onset ≥ 60); the vast majority (91.2%) was diagnosed with Probable AD. There were 293 AD cases with multiple or recurrent psychosis, 252 AD cases with a single occurrence of psychosis and 322 AD cases with no signs of psychosis. There was no association of AD+P with the presence of an APOE $\epsilon 4$ allele (None, Single, Multiple/Recurrent, $\chi^2 = 1.724$, $df=2$, $p=0.422$).

Results of the primary and secondary gene-based tests of association are shown in Figure 1. No tests approached significance. Similar results were present in both the primary (Suppl Figure 2) and secondary conditional logit analyses controlling for ancestry.

5. Conclusions

We examined genetic variation in four genes, APP, SORL1, BACE1, and MAPT finding no evidence of association with the occurrence of psychosis in late-onset AD. Several strengths of our design are compelling and enhance confidence in the results. Our cohort was rigorously characterized for the behaviors of interest, and we used a conservative definition of the psychosis phenotype – multiple and/or recurrent psychotic symptoms- that has been shown to have enhanced familiarity and heritability in comparison to less restrictive definitions of psychosis in late-onset AD (Bacanú et al, 2005; Sweet et al, 2010). Our cohort is among the largest tested for genetic associations of AD+P (DeMichele-Sweet and Sweet, 2010). We extensively evaluated genetic variation in our candidate genes using a set of tag SNPs that produces excellent coverage in terms of prediction of SNPs that were not genotyped (Rinaldo et al, 2005; Roeder et al, 2005). To maximize power we used gene-based tests, which conserve power in comparison to multiple testing of individual SNPs, as our primary measure of association, decreasing the chance of a false-negative (Roeder et al, 2005). Furthermore, even the conditional logit analyses achieved good power (>80%) for genotype relative risk ≥ 1.5 , a risk allele frequency exceeding 0.3, and an uncorrected significance level of 0.05 (and for higher relative risks with lower risk allele frequencies). While it remains possible that some SNPs we tested have small effects on AD+P risk, and be found to have significant associations in much larger samples, there was no evidence of even a trend towards such an effect in the current sample, arguing against that possibility.

Two of the SNPs in SORL1 shown to be associated with AD risk, rs1699102 and rs1010159, were specifically included in our genotyping array (Bettens et al, 2008; Feulner et al, 2010; Kimura et al, 2009; Kolsch et al, 2009; Li et al, 2008; Rogaeva et al, 2007; Tan et al, 2009). Five other SNPs are often genotyped, specifically rs668387, rs689021, rs641120 rs3824968, and rs2282649. However, of these five SNPs the first three are tagged by rs923892 and the last two are tagged by rs726601. Thus our approach, in which we chose SNPs to represent the vast majority of genetic variation in our candidate genes, would likely have detected an association with SORL1, if present at any of these SNPs.

We proposed a model in which genetic variation leads to AD+P risk by accelerating the process of synapse loss either by increasing the accumulation of soluble A β , or via processes which increase the effects of soluble A β and its downstream mediators (including MAPT) on synapse loss. The current findings do not support this model for APOE, APP, BACE1, SORL1 and MAPT, though they do not exclude the possibility of liability variants in other genes that impact A β metabolism, or which mediate A β and MAPT effects on synapse loss. For example, schizophrenic psychosis is also characterized by excess loss of excitatory synaptic structures (Lewis and Sweet, 2009). Several genes for synaptic acting proteins have been associated with schizophrenia risk (e.g. NRG1, DISC1) and might be fruitfully studied in AD+P.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Gene-based tests of association with psychosis in Alzheimer disease

A) Results for the primary analysis that contrasted individuals with multiple/recurrent psychotic symptoms versus those with no psychotic symptoms or a single symptom. B) Results for the secondary analysis that contrasted individuals with multiple/recurrent psychotic symptoms versus those with no psychotic symptoms. Note that a p-value of 0.05 maps to 1.3 on the $-\log_{10}$ scale for this figure; thus no p-value even approaches nominal significance from these results. T(P) = maximum test statistic per gene. T(S) = maximum of a spline fit of the statistics.