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Neuregulin-1 Polymorphism in Late Onset Alzheimer's Disease Families With Psychoses

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Probands with late onset Alzheimer's disease (LOAD) exhibit positive symptoms of psychosis, 30–60% of the time. Positive symptoms of psychosis have been shown to appear prior to the onset of dementia to be accompanied by greater cognitive deficits, and to predict a more rapid decline. A study of the distribution of AD with psychosis (ADP) in families from the NIMH Alzheimer's Disease Genetic Initiative sample indicates that the trait is heritable, and linkage studies of multiplex ADP families have found suggestive peaks on 2p, 6q, 8p, and 21q. A genome scan of idiopathic psychosis, schizophrenia, in the Icelandic population identified a risk haplotype within the 5′ region of neuregulin-1 (*NRG1*) on 8p12. Associations with *NRG*1 SNPs have also been found in other schizophrenia populations from Scotland, Ireland, and China. Here, we report results demonstrating a significant linkage peak for ADP on 8p12 in the NIMH AD dataset, encompassing the NRG1 region. We also demonstrate that there is a significant association with a NRG1 SNP (single nucleotide polymorphism), rs392499, with ADP, $\chi^2 = 7.0$, $P = 0.008$. This same SNP is part of a 3-SNP haplotype preferentially transmitted to individuals with this phenotype. Our results suggest that NRG1 plays a role in increasing the genetic risk to positive symptoms of psychosis in a proportion of LOAD families.

KEY WORDS: genetics; linkage; SNP; psychotic; haplotype

INTRODUCTION

Positive psychotic symptoms, hallucinations, and delusions occur in 30–60% of all Alzheimer's Disease patients [Wragg and Jeste, 1989]. Recent studies indicate that presence of psychotic symptoms is a marker for a more severe phenotype characterized by greater cognitive deficits and a more rapid decline [Sweet et al., 2003]. This work shows that the increased rate of cognitive decline precedes the onset of psychosis [Paulsen et al., 2000], and provides emerging evidence that in some subjects the onset of psychosis predates dementia, and is a risk factor for the development of dementia [Ostling and Skoog, 2002; Lopez et al., 2004]. The neurobiologic processes underlying ADP are not clearly defined; severity of neuritic plaque and neurofibrillary tangle pathology might or might not be increased in ADP [Farber et al., 2000; Sweet et al., 2000]; however, postmortem magnetic resonance spectroscopy evidence of significant reduction in neocortical N-acetyl-l-aspartate and elevated phosphodiesters suggests excess neocortical, neuronal, and synaptic pathology in ADP [Sweet et al., 2002b]. Similarly, in vivo functional imaging studies have found neocortical impairments indicated by blood flow and glucose metabolism in ADP [Sultzer et al., 1995; Lopez et al., 2001].

It is indisputable that ADP patients suffer psychotic symptoms at rates far greater than chance. Nonetheless, is there evidence to suggest that there is a genetic basis for ADP? Sweet et al. [2002a] using family data from the NIMH AD Genetics Initiative found that the risk ratio for a sibling of a proband with ADP is 2.4 times higher when compared to a sibling of an AD proband without psychosis. Further analyses estimated the heritability of psychosis in LOAD in this cohort at 60–70% [Bacanu et al., 2005]. A subgroup of families with multiple family members affected by ADP shows evidence for significant linkage to a 40 cM region on 8p (see [Bacanu et al., 2002], online supplemental data). We follow-up on this observation by examining whether variation in Neuregulin-1 (*NRG*1), a gene in which variation has recently been associated with liability to schizophrenia, is also implicated in liability to ADP. NRG1 is an excellent candidate gene in the 8p region for ADP, 32.6 cM on 8p (Fig. 1).

NRG1 has multiple isoforms known by multiple names—NDF (neu differentiation factor), ARIA (acetyl choline receptor inducing activity), GGF(glial growth factor), Her (heregulin), and SMDF (sensory and motor neuron-derived factor) depending on its tissue location and function. These isoforms that occur due to alternative splicing are grouped into three major types, Types 1–3. Type 1 and 2 isoforms, involved in paracrine signaling, are required for generation of neural crest-derived neurons in cranial ganglia and for trabeculation of the heart ventricle. Type 3 isoforms play an important role in the early development of Schwann cells, and are involved in juxtacrine signaling [Falls, 2003]. A recent study by Steinthorsdottir et al. [2004] suggests that there are three additional types, Type 4–6 with the identification of six new 5′ exons.

Stefansson et al. [2002] found significant linkage for schizophrenia in this 8p11-12 region centered around 32.5 cM, and found a highly significant association and linkage to a 5-SNP (single nucleotide polymorphism) haplotype in the *NRG*1 gene

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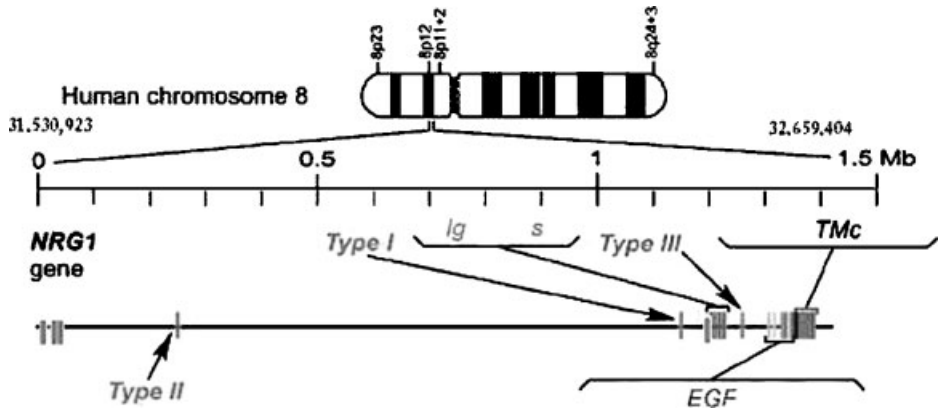

Fig. 1. NRG1 molecular gene structure. Human *NRG1* gene structure (Genbank accession no. BK000383). The *NRG*1 gene is on the short arm of chromosome 8. On the expanded illustration of this region, the position of each exon included in reported NRG1 isoforms is indicated by a vertical line. The red vertical lines indicate the location of the SNPs genotyped in this study. Type I, II, and III indicate the differing coding exons that comprise these isoforms and result from the initiation of transcription from different *NRG1* gene promoters and alternative splicing. TMc and EGF label the Transmembrane and Epidermal Growth Factor domains of the gene. Ig labels the immunoglobulin-like domains and s, spacers.

[Stefansson et al., 2002]. This was later confirmed in a Scottish population [Stefansson et al., 2003]. Although studies of some populations failed to find associations with this same core risk haplotype [Iwata et al., 2004; Li et al., 2004; Thiselton et al., 2004], studies in other populations confirmed associations with additional SNPs or haplotypes of *NRG1* [Stefansson et al., 2003; Williams et al., 2003; Yang et al., 2003; Corvin et al., 2004; Petryshen et al., 2005].

MATERIALS AND METHODS

Population

The NIMH AD Genetic Initiative collected approximately 457 families [Blacker et al., 2003], of which 437 (1,439 individuals, 994 affecteds) represent those left after removing a subset of early onsets (<50), believed to be enriched for the APP, PS1, and PS2 mutations. The mean age of onset was 72.4, ranging from 50 to 97. Three hundred twenty families contained affected individuals with age of onset 65 and over ("the late-onset pedigrees"). Of the 437 pedigrees, 65 families were multiplex for ADP; specifically the proband exhibited multiple positive symptoms of psychosis as did at least one other sibling. This subset, the ADP subset, was analyzed for linkage in the 8p region.

Diagnostic Procedures for Psychoses

Descriptions of the ascertainment and characterization of the NIMH Genetics Initiative Alzheimer Disease Cohort have been presented elsewhere [Blacker et al., 1997]. The initial identification of probands with AD and the recruitment of family members were designed to maximize ascertainment of families with multiple members affected by AD. Ascertainment did not specifically target the recruitment of psychotic AD subjects. Psychotic symptoms, delusions (including misidentification delusions [Sweet et al., 2003]), and hallucinations were characterized in probands and their family members at the time of initial evaluations and again during follow-up evaluations. The presence of psychotic symptoms was identified by responses to semi-structured interview questions. In a subset of subjects, this assessment was augmented by ratings on the Brief Psychiatric Rating Scale (BPRS [Overall and Gorham, 1962]). Based on our prior findings in this cohort that the familiality and heritability of psychosis were increased when AD with psychosis was defined by the presence of multiple psychotic symptoms [Sweet et al., 2002a; Bacanu et al., 2004], subjects were classified as ADP if they demonstrated either more than one psychotic symptom, or the presence of psychotic symptoms at more than one assessment. The ADP analysis was restricted to families with two or more members diagnosed with Definite, Probable, or Possible AD, using NINCDS/ADRDA criteria [McKhann et al., 1984] with psychosis.

Statistical Methods

Linkage analyses were performed using GeneHunter Plus software that uses the multipoint method of Kruglyak et al. [1996] and exact LOD score calculations from Kong and Cox [1997]. We also performed model-free linkage analysis with the Haseman–Elston method as implemented in the SAGE program SIBPAL [Elston et al., 1997]. The IBD estimates required by SIBPAL were multipoint estimates calculated by SAGE GENIBD [Elston et al., 1997]. For testing association to the NRG1 SNPs, we used the family-based association methods of Horvath et al. [2001]. While the linkage and association information extracted from families was probably due largely to the distribution of genotypes in discordant siblings [Horvath and Laird, 1998], FBAT efficiently evaluates nuclear families with any configuration of affected and unaffected siblings and was used for the haplotype analyses.

SNP Genotyping

Using the ADP family samples, four SNPs in and around NRG1 were genotyped by primer extension chemistry using the Beckman/Coulter CEQ 8000 capillary electrophoresis platform with WellRED dyes (www.beckman.com/resource-center/literature/BioLit/BioLitList.asp; #A1928A). PCR and annealing primers were selected using the Autoprimer program (Beckman/Coulter, Fullerton, CA) for minimum interaction during primer extension, and poly T-tails were added to the annealing primers, so products could be pooled and analyzed on the CEQ for genotyping based on dye color as well as size. One-fifth of each product was cleaned up separately before 1 μl of each cleaned product, except for SNP8NRG341930 (0.5 μl), was pooled and added to the primer extension reaction along with each annealing primer. One-half of the reaction was used in the final cleanup step before running on CEQ. Alleles called by the software (ver. 6.0.75) were confirmed by two separate readers.

RESULTS

Linkage Analyses

To confirm the linkage signal in the 8p11-p12 region, we performed linkage using phenotypic information on LOAD in the NIMH dataset. Multipoint linkage, using simple tandem repeat (STR) markers generated by the Center for Inherited Disease Research (CIDR), yielded a maximum Zlr score of 2.0, $P < 0.05$. Analyzing only data from the 65 ADP families using CIDR STR markers resulted in a Zlr of 4.2, $P = 0.000016$.

Genetic Association Tests

Of the four loci analyzed for linkage and association using the sibling disequilibrium statistic, SDT, estimated from the FBAT software, only rs392499 was highly associated with ADP ($\chi^2 = 7.0$, $P = 0.008$). The others showed no obvious association (Table I). Haplotype-based analyses revealed that a haplotype (A-C-G) consisting of three NRG1 SNPs (SNP8NRG221533- SNP8NRG243177- rs392499) was transmitted more often to siblings with ADP, $z = 1.73$, $P = 0.076$. Although this haplotype association was not significant, two of these SNPS are in the same region as the 5-SNP risk haplotype region found in several northern European populations to be overly transmitted to individuals with schizophrenia.

DISCUSSION

Our results indicate that there is a significant linkage to ADP in the 8p region, which harbors *NRG1*, since analyzing the 65 ADP families only, resulted in a significant Zlr statistic of 4.2. The significant association of the *NRG1* SNP rs392499, segregating in 65 families with ADP, provides evidence that NRG1 is involved in the neuropathology of psychoses. This SNP (G → A) is in the second exon of the *NRG1* gene and results in an arginine to a glutamine change in position 38 of the Ig-like domain of the protein. The Ig-like domain functions in binding cell-surface and extracellular matrix proteoglycans; knocking out this domain in mice causes neuronal and heart developmental problems [Kramer et al., 1996; Falls, 2003]. It is unknown whether this polymorphism is pathogenic or not; the substitution replaces a highly charged amino acid with an uncharged, nonpolar residue. However, using bioinformatics tools that assess functional impacts of non-synonymous coding changes in proteins, the R38Q substitution is predicted to be benign with an unlikely functional effect (Panther: https://panther.appliedbiosystems.com/tools/csnpScoreForm.jsp; PolyPhen: http://www.bork.embl-heidelberg.de/PolyPhen). Future studies utilizing cell-based expression and binding assays, and development of transgenic mouse models will be the next steps to assess what effect, if any, this polymorphism has upon neuregulin function. It should be noted that the 3-SNP haplotype, we find to be preferentially transmitted to siblings with ADP, is also a part of the 5-SNP risk haplotype identified in Northern European populations; however, the rs392499 SNP was not typed in these populations [Stefansson et al., 2002, 2003], and therefore, may be in linkage disequilibrium with another functional SNP. This SNP, however, has been genotyped in a Chinese population [Li et al., 2004], and the same G allele is found to be highly associated with schizophrenia.

TABLE I. Family-Based Test of Linkage/Association of 4 NRG1 SNPS Genotyped in the 65 ADP Families

SNP	Degrees of freedom	Chi-square	*P*-value
SNP8NRG24190	1	0.818	0.366
SNP8NRG221533	1	0.333	0.564
SNP8NRG243177	1	0.286	0.593
Rs3924999	1	7.000	0.008

These results provide additional evidence that variation in NRG1 compromise those areas of the brain relating to auditory and visual hallucinations and delusions. While the variation at rs392499 segregates in the general population, we assume that this variation or variation in tight linkage disequilibrium with these alleles increases the risk of psychotic features in the presence of the neurodegenerative process inherent in LOAD, and possibly during the course of other neurological diseases [Tsuang et al., 2000].

Neuregulin-induced cellular responses are mediated by tyrosine kinase receptors of the erbB family; neuregulin binds erbB3 and erbB4 with high affinity, but not the erbB2 (HER2) and erbB1 (EGF) receptors [Peles and Yarden, 1993; Plowman et al., 1993; Carraway et al., 1994]. When co-expressed with erbB3 or erbB4, neuregulin induces tyrosine phosphorylation of the erbB2 receptor [Holmes et al., 1992; Carraway and Cantley, 1994; Beerli et al., 1995]. Thus, NRG1 is important in neurodevelopment, and with the activation of erbB4 receptors, it may be involved in synaptic plasticity by its recruitment of tyrosine kinases that regulate NMDA receptor function. Recent data show that after neuregulin stimulation, ErbB4 undergoes a series of proteolytic steps, including cleavage by presenilin-dependent gamma secretase, an important enzyme for cleavage of amyloid precursor protein into a neurotoxic form, Aβ42. [Lee et al., 2002; Lai and Feng, 2004]. In addition, reactive microglia in neuritic plaques have been shown to contain NRG1 and ERBB4 immunoreactivity [Chaudhury et al., 2003]. These data suggest the alternate possibility that rather than acting as a general risk factor for psychosis in the population, NRG1 may interact specifically with the inflammatory pathologic processes underlying AD to yield a psychotic phenotype characterized by a more rapid progression of AD. The complexity of the genomic organization of NRG1 (Fig. 1) with 21 exons, possibly 9 alternative promoters, and multi-transcriptional start sites can lead to many splice variants [Steinthorsdottir et al., 2004] and multiple isoforms [Falls, 2003]. This complexity is congruent with highly complex regulation of developmentally regulated gene expression by either translational or transcriptional processes. This variability of splice variants in NRG1 may also be required for the dynamic changes in developing synapses needed to sense synaptic conditions, and respond to signals of multiple origins [Ma et al., 2003] required for neuroplasticity. It seems reasonable to speculate that any perturbations in the timing and levels of NRG1 during development can lead to aberrant signaling and heightened susceptibility to visual and auditory hallucinations, and delusions.

Our findings of association between variants in NRG1 and ADP, and the reports of several other studies showing association with schizophrenia, provide mounting evidence that variation in NRG1 confers liability to psychosis. Our results suggest the following hypothesis: Neuropathological processes associated with LOAD act as a stressor that triggers a new neuropathological process that produces the positive symptoms of psychosis. NRG1 appears to play a role in the latter neuropathological process. Furthermore, it is possible that the neuropathological processes associated with LOAD mimic the early neurodevelopmental stressor(s) required in the stress diathesis model of schizophrenia.

Recent studies hypothesize that the functional mutation lies in the Expressed Sequence Tag cluster, Hs.97362 of NRG1 [Corvin et al., 2004]. If this is confirmed, then a greater understanding of the functional mutation in patients with early signs of AD may offer therapeutic targets for drug development to treat psychotic symptoms in AD and other illnesses.

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