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Progranulin (*GRN*) in two siblings of a Latino family and in other patients with schizophrenia

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Abstract

Schizophrenia has been linked to a region on chromosome 17q21 in Latino populations (Escamilla et al., 2009). Mutations of a gene at this location (*GRN*) are associated with frontotemporal dementia. A recent study demonstrated that patients with frontotemporal dementia who presented with symptoms of schizophrenia show neuropathological findings consistent with *GRN* mutations, but were not tested for *GRN* mutations (Velakoulis, Walterfang, Mocellin, Pantelis, & McLean, 2009). The current study describes a Latino family in which two siblings have schizophrenia and one has frontotemporal dementia. We sequenced *GRN* in one of the siblings with frontotemporal dementia and one of the siblings with schizophrenia. The siblings both have a loss-of-function *GRN* mutation. This finding, in conjunction with other studies (Escamilla et al., 2009; Velakoulis et al., 2009), suggests that there may be an association between schizophrenia, frontotemporal dementia, and *GRN* mutations in Latino populations that should be investigated further.

Keywords

Frontotemporal dementia; Schizophrenia; Genetics; Progranulin; Psychiatric disorders

INTRODUCTION

In a recent publication, Escamilla et al. (2009) reported results from a genome-wide screen of 855 individuals from 175 multiple families of Latino origin with schizophrenia and schizoaffective disorder. The DNA of the subjects was genotyped for 385 short tandem repeat markers distributed throughout the genome. The strongest linkage was found in a region of chromosome 17q11–17q21 between the markers D17S975 and D17S2180 with a LOD score higher than 2.0. This finding is consistent with a meta-analysis that identified this locus as one of several linked to schizophrenia in previous genome-wide linkage scans (Lewis et al., 2003). This region contains two major genes associated with frontotemporal dementia (FTD), *MAPT* (Hutton et al., 1998) and *GRN* (Baker et al., 2006). Another recent study (Velakoulis et al., 2009) demonstrated that 5 of 17 patients with FTD presented with psychotic symptoms. Those 5 patients had an earlier age of onset than the other FTD patients and showed neuropathological findings consistent with *GRN* mutations (TDP-43 and ubiquitin-positive inclusions). However, the patients were not tested for *GRN* mutations (Velakoulis et al., 2009).

In the current study, we describe a family with two siblings with schizophrenia and one with frontotemporal dementia (FTD). Blood samples were obtained from one sibling with schizophrenia and one with FTD. Both were found to have the same *GRN* mutation likely to cause loss-of-function. We subsequently screened samples from 88 Caucasian schizophrenic patients and >200 healthy controls for *GRN* mutations.

METHOD

Case report

The proband (III-2) in Figure 1 was identified through his participation in a research study to better characterize patients with FTD and related disorders performed in the Cognitive Neuroscience Section of the National Institute of Neurological Disorders and Stroke. This study includes a clinical assessment, neuropsychological testing, and imaging (MRI and 18-fluoro-deoxy-glucose-positron emission tomography). Genetic analyses were performed in the Laboratory of Neurogenetics of the National Institute on Aging. The proband had assigned a research durable power of attorney prior to admission to the protocol and the assigned individual gave written informed consent for the study. The patient gave assent for the study. We obtained permission from the proband and his research durable power of attorney to contact other family members. Individual III-3 wished to participate in the study and gave informed consent. At the time of the study, he resided in a locked psychiatric facility. He was judged by his treating physicians to have capacity to provide informed consent. All aspects of the study and the consent procedure were approved by the appropriate NINDS and NIA Institutional Review Boards. The other family members contacted declined participation in this study. The samples from the 88 other schizophrenic patients and normal control subjects were obtained with informed consent using procedures approved by the appropriate IRBs.

Genotyping

Genomic DNA was extracted from venous blood samples. The coding exons and the flanking intronic sequences of *GRN* were amplified and sequenced in patients III-2 and III-3 and 88 Caucasian schizophrenic patients and >200 healthy controls as previously described (Baker et al., 2006; Huey et al., 2006). The schizophrenic patients were diagnosed by DSM criteria (APA, 2000). The samples from the schizophrenic patients were obtained from the Genes, Cognition and Psychosis Program of the National Institute of Mental Health-

National Institutes of Health (48 patients) and from the Center for Psychiatric Genetics, ENH Research Institute, Northwestern University (40 patients).

RESULTS

Case report

The family of interest is Latino of Caribbean origin (Figure 1). The proband (III-2) began having symptoms of FTD at the age of 53. Prior to this, he did not have psychiatric or neurologic symptoms. His initial symptoms were a stutter and expressive aphasia. He subsequently developed difficulty performing complex tasks, apathy, inappropriate laughter, and increased food intake. These symptoms progressed rapidly. When he was seen in our program two years and three months after symptom onset, he was severely demented, receiving an 11 out of 144 on a Mattis Dementia Rating Scale (Mattis, 1976). He was diagnosed with FTD by standard criteria (The Lund and Manchester Groups, 1994). In the few months prior to our evaluation, the patient had developed symptoms of corticobasal syndrome including a dystonic and apraxic left upper extremity. MRI demonstrated moderate bilateral atrophy of the cerebral hemispheres (see Figure 2). On FDG-PET, he showed widespread reductions in glucose utilization across the frontal, temporal, and parietal cortices with the right hemisphere somewhat more affected than the left (see Figure 3).

Individual III-3 had onset of symptoms at the age of 23 including auditory command hallucinations to pluck out his right eye because of sexual sins he had committed and auditory hallucinations telling him that he is the son of God, disorganized speech, and delusions that he was Jesus Christ and the President. At the time of his symptom onset, he had completed high school and most of college. He presented initially for psychiatric evaluation because he had cut his wrists in a suicide attempt. At the time of presentation, he was noted to have 'above average' intelligence, but neither formal neuropsychological testing nor imaging was performed. He was diagnosed with schizophrenia and his symptoms improved with antipsychotic medication treatment. He had more than 20 psychiatric admissions over the subsequent 30 years including one after an attempt to enucleate his eye in response to command hallucinations. His admissions were frequently related to medication non-compliance. His symptoms over 30 years have consistently remained command auditory hallucination, grandiose religious delusions, disorganization, and paranoia. He had several suicide attempts over that period. He was treated with Clozaril. He has a history of poly-substance abuse but has psychotic symptoms when not using drugs of abuse. His symptoms were always typical for a psychotic disorder and so he did not receive brain imaging or formal neuropsychological testing. However, he was always noted to have grossly intact cognition, and on a recent (2006) clinical mental status examination, he was oriented to person place, and time, able to perform serial sevens, remember 3 items for 5 minutes, and abstract that a table and a chair are similar because they are both furniture. One of the authors (EDH) spoke to the patient on the telephone recently, and he was grossly cognitively intact at that time. Per records, he has not shown any motor symptoms with the exception of tardive dyskinesia.

Individual III-1 had an onset of psychotic symptoms as a young adult and received a diagnosis of schizophrenia. He had multiple psychiatric admissions and was frequently homeless. The family lost contact with him early in the course of his illness and know little about his subsequent course.

The father of the proband had dementia and motor symptoms of Parkinson's disease and died at age 73. The exact type of the dementia and motor symptoms are unclear.

The two sisters of the proband did not wish to participate in the genetic part of the study, but have no obvious symptoms of cognitive or motor dysfunction. While it is unfortunate that they did not participate, their genetic samples would be minimally scientifically informative because even if they have the *GRN* mutation detected in III-2 and III-3, they are the younger siblings and could still develop symptoms of FTD.

Genotyping

Individuals III-2 and III-3 have a heterozygous two base pair deletion in exon 7 of *GRN*, c. 675–676del CA p.S226WfsX27, leading to a stop codon 28 amino acids downstream of the mutation. The mutation likely leads to nonsense-mediated decay which in turn will lead to loss-of-function and haploinsufficiency. No obvious loss-of-function mutations were found in the samples from the 88 schizophrenic patients or the >200 healthy controls.

DISCUSSION

While schizophrenia and FTD clearly differ in many ways including age of presentation, symptoms, and progression, they share some features. Both have some symptoms associated with frontal dysfunction including emotional and social withdrawal, executive dysfunction, and apathy (Ross, Margolis, Reading, Pletnikov, & Coyle, 2006; The Lund and Manchester Groups, 1994). FTD patients with pathogenic *GRN* mutations are more likely to have hallucinations than patients without such *GRN* mutations (Beck et al., 2008; Huey et al., 2006; Le Ber et al., 2008; Rademakers et al., 2007), although the hallucinations in FTD patients are usually visual, not auditory as is usually observed in schizophrenia (APA, 2000). Up to 25% of FTD patients with *GRN* mutations will have hallucinations, often well-formed and complex (e.g., people or animals), and occurring early in the course of the illness (Huey et al., 2006; Le Ber et al., 2008). The pathogenic mechanism of *GRN* mutations, loss-of-function, is consistent with the neurodevelopmental hypothesis of schizophrenia (Fatemi, 2005; Rapoport, Addington, Frangou, & Psych, 2005) as the haploinsufficiency induced by loss-of-function *GRN* mutations exists throughout development and childhood. Interestingly, in Velakoulis et al. (2009), the FTD patients who presented with psychotic symptoms had an early age of onset (as early as 28). A key unanswered question in the genetics of *GRN* and FTD is: Why does *GRN* insufficiency take approximately 50 years to show clinical symptoms? One partial answer could be that it may not take that long to show symptoms in all patients with pathogenic *GRN* mutations. Symptoms of schizophrenia, or possibly other psychiatric syndromes, may represent a prodrome of eventual frontotemporal dementia in some pathogenic *GRN* mutation carriers. These considerations aside, it is difficult to understand how the same mutation could account for illnesses that are so neuropathologically distinct in two individuals in the same family. It is possible that the mutation by itself is not sufficient to cause either condition, and that only in the context of other genetic and potentially environmental factors is its penetrance and expression explainable.

It is possible that loss-of-function mutations were not detected in the screened samples from schizophrenic patients in the current study because the samples used were from Caucasian patients or because of the rarity of the mutation. The current negative screening study of schizophrenic patients, which used only Caucasian patients, in conjunction with the results reported by (Escamilla et al., 2009) suggests that *GRN* mutations may be a rare cause of schizophrenia, but primarily in Latino populations. This hypothesis is consistent with recent results that suggest that rare genetic variants, with relatively high penetrance in specific populations, may be associated with schizophrenia (Stefansson et al., 2008). Even if cases of *GRN* mutations resulting in the phenotype of schizophrenia are rare, these cases could advance understanding of the biological bases of schizophrenia similar to the way in which

presenilin and *APP* mutations, albeit rare, have helped researchers understand the biology of Alzheimer's disease.

The current study does not prove an association between loss-of-function *GRN* mutations and schizophrenia. However, the conjunction of evidence from genome-wide screens (Escamilla et al., 2009), neuropathological studies (Velakoulis et al., 2009), and case reports (the current study) strongly suggest there may be such an association. The screening of large numbers of Latino schizophrenic patients for *GRN* mutations should be carried out to explore this putative association. Clinical and neuropathological follow-up of patients with loss-of-function *GRN* mutations and the clinical syndrome of schizophrenia will be critical. One possible outcome is that these patients never develop the symptoms of FTD, which suggests that they have a separate phenotype from patients with FTD associated with loss-of-function *GRN* mutations. A second possible outcome is that they develop clinical FTD at the usual age at which patients develop FTD, in which case the symptoms of schizophrenia developed earlier in life may represent a prodrome of eventual FTD. In either case, neuropathological examination of these patients should be performed to determine if and the degree to which they show the neuropathological changes associated with FTD associated with *GRN* mutations (FTLD-U). As noted above, the neuropathologies of FTD and schizophrenia are distinct. However, if *GRN* mutations are rarely associated with schizophrenia as we have hypothesized, the necessary studies (e.g., ubiquitin staining) may not have been performed at autopsy on the small numbers of patients with schizophrenia associated with *GRN* mutations.

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Figure 1.
Pedigree of affected family. Individuals with a diagnosis of dementia are shown in red and individuals with a diagnosis of schizophrenia are shown in blue.

Figure 2.
MRI scan of Individual III-2.

Figure 3.
18-Fluoro-deoxy-glucose-positron emission tomography scan of Individual III-2.