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The *C9ORF72* hexanucleotide repeat expansion is a rare cause of schizophrenia

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ABSTRACT

A hexanucleotide repeat expansions in the first intron of *C9ORF72* has been shown to be responsible for a high number of familial cases of amyotrophic lateral sclerosis and/or frontotemporal lobar degeneration. The same mutation has been described in a patient with bipolar disorder, but up to now, not in patients suffering from schizophrenia. We determined the frequency of the *C9ORF72* hexanucleotide repeat expansions in a population of 298 patients with schizophrenia or schizoaffective disorder. The pathogenic repeat expansion was detected in 2 patients (0.67%). Both of them presented with auditory hallucinations and had comorbid alcohol abuse. In addition, a positive family history for psychiatric and/or neurodegenerative diseases was present. The repeat expansion in the *C9ORF72* gene is a rare, but possible, cause of schizophrenic spectrum disorders. We cannot rule out however whether the number of repeats influence the phenotype.

1. Introduction

A hexanucleotide repeat expansion in the first intron of *C9ORF72* was shown to be responsible for a high number of autosomal dominant inherited amyotrophic lateral sclerosis and/or frontotemporal lobar degeneration (FTLD) cases, with or without concomitant motor neuron disease (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The function(s) of the protein encoded by this gene is so far unknown. Wild-type alleles contain not more than 30 repeats, whereas mutated alleles have hundreds to thousands of repeats (DeJesus-Hernandez et al., 2011). The relationship between the number of expansions and the phenotype is, however, not clear yet, as recent data described patients with frontotemporal lobar degeneration (FTLD) carrying an allele with 20–22 hexanucleotide repeats (Gómez-Tortosa et al., 2013).

It was suggested that psychosis and obsessive-compulsive disorder were common symptoms at disease onset in patients with FTLD carrying the repeat expansion (Calvo et al., 2012; Floris et al., 2012; Snowden et al., 2012). Moreover, a case showing mystic delusion with visual and auditory hallucinations, in the absence of neurologic symptoms and brain atrophy, has been recently described (Arighi et al., 2012). In a study carried out in a large population of patients with FTLD, it was shown that the presentation with late onset psychosis (particularly hallucinations and delusions) is significantly more frequent in *C9ORF72* repeat expansion carriers than noncarriers (Galimberti et al., 2013a). In addition, presentation with memory impairment occurs quite often, possibly leading to a clinical diagnosis of Alzheimer's disease (Galimberti et al., 2013a; Majounie et al., 2012b; Murray et al., 2011). Bipolar disorder (BD) patients carrying the *C9ORF72* hexanucleotide repeat expansion have been recently described (Galimberti et al., 2013b; Meisler et al., 2013), whereas no carriers were found in a population of 192 patients with schizophrenia (Huey et al., 2013). In 2012, it was shown that a suicide attempt can

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be the first manifestation of early dementia because of the recently identified *C9ORF72* expansion (Synofzik et al., 2012).

Herein, we genotyped a population of 298 patients with schizophrenia for the presence of the *C9ORF72* expansion, and identified 2 mutation carriers (0.67%).

2. Methods

2.1. Patients and clinical workup

Our cohort included 298 patients (274 Germans and 24 Italians; thereof 157 males, mean age at disease onset ± SD: 27 ± 10 years, range: 9–72 years) recruited at the Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Germany, and at the Psychiatry Unit of the Fondazione Cà Granda, Ospedale Maggiore Policlinico (Milan), diagnosed with schizophrenia or schizoaffective disorder (i.e., psychotic disorders). Diagnoses were made according to Diagnostic and Statistical manual of Mental disorders, fourth edition, Text Revised (DSM-IV-TR) criteria (First et al., 2002). German samples were described in greater detail previously (Scholz et al., 2010).

2.2. C9ORF72 genotyping

High-molecular weight DNA was isolated from whole blood using a Flexigene Kit (Qiagen, Hildren, Gemany). *C9ORF72* genotyping was carried out by repeat-primed polymerase chain reaction and sequencing, as previously described (Xi et al., 2012). A characteristic stutter amplification pattern (>40 repeats) on the electropherogram is considered evidence of a pathogenic repeat expansion.

3. Results

We genotyped 298 patients with schizophrenia. A clinically documented family history for psychiatric diseases or dementia was reported for 122 patients. The pathogenic repeat expansion was detected in 2 patients (0.67% of cases; Table 1). Both of them were presented with acoustic hallucinations and showed comorbid alcohol abuse. In addition, they had a positive family history for dementia and psychiatric conditions. Detailed medical histories available are herein reported. The estimated number of repetitions in control subjects was 2–15; whereas in patients without the expansion was 2–30.

3.1. Patient #1

Patient #1, male, was first admitted to the Psychiatric Department of the University of Würzburg at the age of 33 years, for paranoid ideation with frequent acoustic hallucinations (imperative, commenting, but also benevolent voices). He developed ideas of grandiosity, but also showed depressed mood and reduced drive. Later, he developed formal thought disorder. In addition, a history of comorbid alcohol abuse was present. He was overweight (height 173 cm, body weight 115 kg, body mass index = 38). His past medical history included hypertension, diabetes, heart failure, and sleep apnea. His family history was positive for dementia, as his mother was diagnosed with dementia and Parkinson's disease at about the age of 50 years. For unclear reasons, as no data on any psychiatric condition was present, she was treated with lithium since the age of 54 years. She died at the age of 65. Also, both her sisters suffered from dementia, although no information on age at onset and course of the disease were available. The patient himself is no longer able to work since 2005; since then, he had a fluctuating yet chronic course of the disease. In 2006, he underwent magnetic resonance imaging (MRI) that showed global brain atrophy and enlargement of the ventricles. A second MRI in 2012 showed no progression as compared with the previous scan. In 2012, neurologic examination revealed saccadic gaze, slowed tongue motility, dysarthria (not of the bulbar amyotrophic lateral sclerosis type), and dysdiadochokinesia, all of which were not present in 2006.

3.2. Patient #2

Patient #2 is a male, born in 1947, no longer working since the 90s. He was first admitted at the age of 44 years, and showed a fluctuating yet chronic course since then. His medical history disclosed congenital dysplasia syndrome (patella-nail-syndrome) mainly of the lower limbs, peripheral neuropathy, oral and manual dyskinesia, dysdiadochokinesia, as well as bronchial carcinoma, which was diagnosed in 2007. His mother suffered from chronic schizophrenia since her adolescence, whereas his father probably suffered from alcohol abuse. The patient showed paranoid ideation with acoustic hallucinations (imperative and derogatory voices), depressed mood, reduced drive, especially at later stages, and pronounced latency to answer. In 2004, his Mini-Mental State Examination score was 27/30, mainly because of dyscalculia. In 2007, he developed cognitive and amnestic deficits: at MMSE, he scored 16/30, because of dyscalculia, impaired delayed recall and executive functions. He suffered from comorbid alcohol abuse. A brain computed tomography scan showed mild but diffuse brain atrophy.

4. Discussion

In this study, we show that the *C9ORF72* hexanucleotide repeat expansion is a rare, although possible, cause of schizophrenia. Our data further support previous descriptions of *C9ORF72* carriers presenting with psychosis (Calvo et al., 2012; Floris et al., 2012; Galimberti et al., 2013a), either developing FTLD over time, or as pure psychotic symptoms, that is, megalomaniac delusions in the absence of neurologic signs and with no atrophy at imaging (Arighi et al., 2012). Memory deficits represent another atypical feature of *C9ORF72* carriers (Arighi et al., 2012; Galimberti et al., 2013a). In this regard, patient #1 did not show memory deficits in spite of the evidence of diffuse brain atrophy at MRI, whereas patient #2 developed cognitive impairment, as documented by MMSE. Moreover, both patients #1 and #2 had a positive family history for dementia and psychiatric disturbances. Interestingly, the *C9ORF72*

Table 1
Characteristics of *C9ORF72* repeat expansion carriers

Patient	Age at onset (y)	Symptoms at onset	Symptoms after onset	Family history	Diagnosis
#1	33	Paranoid ideation; acoustic hallucinations	Ideas of grandiosity; depressed mood; formal thought disorder	Dementia (sister) and Parkinson's disease; dementia (mother)	Schizophrenia
#2	44	Acoustic hallucinations	Paranoid ideation with acoustic hallucinations, depressed mood	Schizophrenia (mother)	Schizophrenia