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C9ORF72 repeat expansions not detected in a group of patients with schizophrenia

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Abstract

A hexanucleotide repeat expansion in *C9ORF72* was recently found to cause some cases of FTLD, FTD-ALS, and ALS. FTLD patients with the *C9ORF72* repeat expansion are more likely than those without to present with psychosis. In this study, we screened DNA samples from 192 unrelated subjects with schizophrenia for the *C9ORF72* repeat expansion. None of the subjects with schizophrenia had the pathogenic expansion. *C9ORF72* repeat expansions either do not cause schizophrenia, or do so rarely (less than 1% of cases).

Keywords

FTLD; Schizophrenia; C9ORF72 repeat expansion; psychosis

1. Introduction

There are interesting connections between schizophrenia and frontotemporal lobar degeneration (FTLD). Arnold Pick, for whom Pick's disease is named, coined "dementia praecox" or early dementia as the original term for schizophrenia (Pick 1891). Both illnesses are characterized by dysfunction of the frontal lobes accompanied by apathy, anhedonia, alogia, and affective flattening (Ziauddeen et al 2011). In the last several years cases of schizophrenia associated with genetic mutations that cause FTLD have been reported (Momeni et al 2010; Schoder et al 2010; Velakoulis et al 2009).

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6. Disclosure statement
The authors have no potential conflicts of interest to disclose.

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Recently, a hexanucleotide repeat expansion in *C9ORF72* was found to cause some cases of FTLD, FTD-ALS, and ALS (DeJesus-Hernandez et al 2011; Renton et al 2011). This expansion has been found in approximately 6% of sporadic, and 25% of familial, FTLD cases (Rademakers 2012). While psychotic symptoms are rare in FTLD, FTLD patients with the *C9ORF72* repeat expansion have a high prevalence, up to 38%, of psychosis (Snowden et al 2012). This finding raises the following question: If *C9ORF72* expansions are associated with psychosis in FLTD patients, are they also associated with schizophrenia without FTLD? To answer this question, we tested DNA from 192 patients with schizophrenia for *C9ORF72* repeat expansions.

2. Methods

Samples of DNA from 192 unrelated subjects (384 chromosomes) with schizophrenia were obtained from the NIH/NIMH Center for Collaborative Studies on Mental Disorders. Probands were chosen first based on ethnicity. Only Caucasian families were included in this subsample. Secondly, one affected individual per family was chosen at random from the Caucasian subsample, up to a total of 192. Establishment of DSM III-R and DSM-IV diagnoses were made from a systematic and comprehensive examination of information obtained from relatives, medical records, and assessment of the subject using the Diagnostic Interview for Genetic Studies (Nurnberger et al 1994). This project has been approved by an appropriate Human Subjects Review Board (see www.nimhgenetics.org for more information).

To detect *C9ORF72* repeat expansions, the repeat-primed PCR method as per (Renton et al 2011) was used. Using this method, *C9ORF72* repeat expansions produce a characteristic sawtooth pattern with a 6 bp periodicity (Renton et al 2011). This method does not allow exact quantification of the number of repeats. However previous studies have shown that >60 repeats are pathogenic, while fewer than 20 repeats are wild-type alleles (Renton et al 2011).

3. Core data

No patterns characteristic of a *C9ORF72* repeat expansion were observed except in the positive control sample.

4. Discussion of data

In this experiment, *C9ORF72* repeat expansions are not a common cause of schizophrenia. The current study has a power > 0.95 to detect a genetic risk factor with a prevalence of 1% (Collins & Schwartz 2002). It is possible that *C9ORF72* repeat expansions are very rarely associated with schizophrenia and we did not screen enough samples to detect this association. However, *C9ORF72* repeat expansions detected with a prevalence < 1% could represent patients with schizophrenia who coincidently will go on to develop FTLD or ALS and not necessarily an association of *C9ORF72* repeat expansions and schizophrenia. This study did not test for mutations in genes other than *C9ORF72* that can cause FTLD (e.g., *MAPT*, *GRN*).

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