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C9orf72 hexanucleotide repeat expansions are not a common cause of obsessive-compulsive disorder

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Abstract

Obsessive-compulsive disorder (OCD) is a polygenic neuropsychiatric disorder characterized by repetitive thoughts and behaviors that cause distress. The pathogenic repeat expansion $[GGGGCC]_n$ found at the *C9orf72* locus is the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), and has also been documented in patients with psychosis and schizophrenia. Furthermore, obsessions and compulsions have been identified in patients diagnosed with ALS and/or FTD and carrying the pathogenic repeat expansion. Here, we performed genetic screening for the *C9orf72* repeat expansion on 573 patients diagnosed with OCD. None of the patients were found to carry the expansion. The results show that patients with OCD do not commonly carry the pathogenic repeat expansion and therefore should not be routinely screened. OCD and psychotic patients who do test positive for the *C9orf72*, however, should be closely observed for the later development of FTD and ALS.

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Disclosure statement

BJT has a patent pending on the clinical testing and therapeutic intervention for the hexanucleotide repeat expansion of *C9orf72*.

Author Contributions

B.J.T. and G.N. designed the study. J.S., Y.W., M.G., F.G., B.M., and G.N. were involved in patient identification and DNA extraction. K.C.A. and A.M.R. performed *C9orf72* screening. K.C.A. wrote the paper. All authors were involved in critical revisions of the manuscript.

Keywords

C9orf72; Obsessive-Compulsive Disorder; Amyotrophic Lateral Sclerosis; Frontotemporal Dementia

1. Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by repetitive thoughts and behaviors that cause distress [1]. It is a relatively common disorder with a lifetime prevalence of about 2.3% in the United States population [2]. Recent studies support the hypothesis that OCD is a polygenic disorder, and genes in the glutamatergic, serotonergic, and dopaminergic systems have been identified as important [3].

A $[GGGGCC]_n$ hexanucleotide repeat expansion at the *C9orf72* locus is the most common genetic cause of both amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [4,5]. This repeat expansion has also been identified in patients diagnosed with psychosis and schizophrenia [6,7,8]. Furthermore, obsessions and compulsions have been identified in patients diagnosed with ALS and/or FTD and carrying the pathogenic repeat expansion [9,10]. However, it is unclear whether the *C9orf72* repeat expansion is a common cause of patients with OCD in isolation. In order to investigate the frequency of the hexanucleotide repeat in patients with OCD, we performed genetic screening on 573 patients diagnosed with OCD.

2. Materials and Methods

A total of 573 participants in the Johns Hopkins University (JHU) site of the OCD Collaborative Genetics Association Study were included [11]. An Institutional Review Board has approved the use of human subjects for this study, and consent forms were obtained from all patients participating in the study. All patients were diagnosed with OCD according to DSM-IV criteria [1]. 226 (39.4%) of the participants were male, and 347 (60.6%) were female. The median age was 35 years (range, 7 to 84). Most (n = 546) of the participants were white, 4 were African-American, 9 were Latino, 9 were of other ethnicities, and ethnicity was missing for 5 individuals. A total of 378 (66%) of the cases had a family history of OCD (i.e., 1 or more relatives with OCD).

DNA samples were arrayed on seven 96-well plates. Each of these seven plates also contained a control sample known to carry a pathogenic *C9orf72* repeat expansion. The *C9orf72* hexanucleotide repeat was genotyped according to the previously described repeat-primed polymerase chain reaction (PCR) assay [5]. The resulting PCR amplicons were analyzed on an Applied Biosystems 3730cl DNA Analyzer (Life Technologies, Grand Island, N.Y., USA). The *C9orf72* hexanucleotide expansion was considered pathogenic if it contained more than 30 repeats and had the typical sawtooth wave pattern [5].

3. Results

None of the 573 patients diagnosed with OCD carried a pathogenic *C9orf72* repeat expansion. The control tested positive on all plates.

4. Discussion

This study shows that patients with OCD do not commonly harbor the pathogenic *C9orf72* repeat expansion. Our data, together with the high occurrence of behavioral FTD among *C9orf72* carriers, leads us to speculate that this type of repeat expansion is not a common cause of isolated neuropsychiatric syndromes. Instead, we postulate that the cases with psychosis, schizophrenia or OCD reported in the literature may be misdiagnosed cases of behavioral variant FTD. Under this paradigm, their neuropsychiatric symptoms were the initial manifestation of frontal lobe dysfunction and such patients would likely manifest additional symptoms of frontal lobe dysfunction or motor neuron degeneration if followed longitudinally.

In this regard, several clinical aspects of published cases of *C9orf72*-related neuropsychiatric disease are noteworthy. First, one of the patients diagnosed with schizophrenia reported by Galimberti et al. (2014) had a family history of early-onset dementia. The second patient developed severe cognitive impairment over the course of his illness and a CT scan of his brain showed diffuse brain atrophy [6]. Similarly, two of the four patients who tested positive for the expansion in the study performed by Watson et al. (2016) had a family history of an ill-defined neurological disorder [8]. Second, many of these cases manifested symptoms late in life, well past the peak age of symptom onset for these neuropsychiatric diseases [6,8].

We conclude that patients with isolated neuropsychiatric syndromes should not be routinely screened for the *C9orf72* repeat expansion unless there is a family history of early-onset dementia or their symptoms occur late in life. Furthermore, OCD and psychotic patients who do test positive for the *C9orf72* should be closely observed for the later development of FTD and ALS.

Acknowledgments

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Highlights

- DNA from patients with OCD were tested for the *C9orf72* repeat expansion.
- None of the cases tested positive.
- The *C9orf72* repeat expansion is not a common cause of OCD.