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C9orf72 repeat expansions that cause frontotemporal dementia are detectable among patients with psychosis

Annie Watson, MS^{a,#}, Mochtar Pribadi, PhD^{b,#}, Kodavali Chowdari, PhD^a, Sue Clifton, Med^a, Joel Wood, BS^a, Bruce L. Miller, MD^c, Giovanni Coppola, MD^{b,*}, and Vishwajit Nimgaonkar, MD, PhD^{a,d,*}

^aDepartment of Psychiatry, University of Pittsburgh, School of Medicine, Pittsburgh, PA

^bDepartments of Psychiatry and Neurology, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA

^cMemory and Aging Center/Sandler Neurosciences Center, University of California San Francisco, San Francisco, CA

^dDepartment of Human Genetics, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA

Abstract

A pathologic hexanucleotide repeat expansion in C9orf72 causes frontotemporal dementia (FTD) or amyotrophic lateral sclerosis (ALS). Behavioral abnormalities can also occur among mutation carriers with FTD, but it is uncertain whether such mutations occur among persons with psychoses per se. Among participants in a genetic study of psychoses (N=739), two pairs of related individuals had C9orf72 expansions, of whom three were diagnosed with schizophrenia (SZ)/schizoaffective disorder (SZA), but their clinical features did not suggest dementia or ALS. A few patients with SZ/SZA carry C9orf72 repeat expansions; such individuals are highly likely to develop FTD/ALS.

Keywords

schizophrenia; schizoaffective disorder; dementia

* Address for correspondence: 3811 O'Hara St, Thomas Detre Hall, Room 441, Pittsburgh, Pa 15213, Phone 412-246-6353, nimnga@pitt.edu; Co-Corresponding author: gcoppola@ucla.edu.

#These authors contributed equally to the work.

Conflicts of Interest

Dr. Miller receives grant support from the NIH/NIA and the Centers for Medicare & Medicaid Services as grants for the Memory and Aging Center. He also serves as Medical Director for the John Douglas French Foundation, Scientific Director for the Tau Consortium, Director/Medical Advisory Board of the Larry L. Hillblom Foundation and Scientific Advisory Board Member for the NIH Research Cambridge Biomedical Research Centre and its subunit, the Biomedical Research Unit in Dementia (UK). The other authors do not disclose any conflicts of interest.

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1. Introduction

FTD is a fatal, untreatable neurodegenerative disease that is associated with progressive deterioration in behavior, personality and/or language (Cruts et al., 2013 and Rademakers et al., 2012). The most common cause of familial FTD, particularly among Caucasians, is a hexanucleotide expansion of >30 repeats within the intronic region of the C9orf72 gene. Psychosis can be a prominent feature of FTD, particularly in the behavioral variant subtype and among individuals with hexanucleotide repeat expansions in C9orf72 (0–50%) (Cruts et al., 2013 and Shinagawa et al., 2014). Among UK biopsy-confirmed individuals with FTD, 5/17 individuals had previously been diagnosed with a psychotic illness (Shinagawa et al., 2014 and Velakoulis et al., 2009) It is thus possible that patients with early onset FTD are misdiagnosed with psychoses such as schizophrenia (SZ), or individuals with SZ may later be diagnosed with FTD. Indeed, C9orf72 mutations have been reported in individual SZ case reports (Gramaglia et al., 2014). A pathogenic repeat expansion was reported in 0.67% of Italian patients with SZ (Galimberti et al., 2014); the low frequency may explain why the expansions were not detected in other studies (Huey et al., 2013, Yoshino et al., 2014 and Fahey et al., 2014). We screened a US sample and detected four individuals with C9orf72 repeat expansions.

2. Methods

2.1. Participants

The participants were ascertained for a genetic study of SZ; they included consenting probands with SZ/SZA, their affected siblings and non-psychotic control individuals, all of whom were evaluated systematically and consensus diagnoses assigned (Talkowski et al., 2008). Available parents of the patients provided family histories, but diagnostic evaluations were not conducted. Consenting individuals also completed neuropsychological assessments.

2.2 Genetic analysis

Genomic DNA was extracted from venous blood samples using the phenol chloroform method or with Qiagen DNA extraction kits. C9orf72 hexanucleotide repeat expansion was assayed by repeat-primed PCR, followed by electrophoresis on an ABI3730 DNA Analyzer and analysis using Peak Scanner Software v1.0 software (DeJesus-Hernandez et al., 2011).

3. Results

The sample comprised 739 individuals with or without psychotic disorders, including 448 men and 291 women, the majority of whom reported Caucasian ancestry (Caucasian n=577, African American n=159, other ancestry, n=3). The patients with psychoses included persons with SZ (N=422), SZA (N=274) or psychosis not otherwise specified (NOS, N=1), 25 of whom were first degree relatives and 10 second degree or more distant relatives of probands. The patients included 431 men and 266 women (38.8 ± 9.9 years; mean \pm standard deviation, SD). The sample also included individuals without a history of psychosis: community based controls (n=37) and unaffected relatives of probands (N=5) (18 men and 24 women, 39.66 ± 15.12 years, mean \pm SD). The pathogenic C9orf72 repeat

expansion was detected in four individuals from two families; their clinical information is summarized below (details in the Supplementary data).

3.1. Family 1. (Figure 1a)

3.1.1. Proband, Case #1: (SZ, Caucasian ancestry, 52 years)—The patient reported several vivid persistent hallucinations and delusions since childhood. His illness was unremitting course and was relatively refractory to treatment with antipsychotic drugs and mood stabilizing agents. He completed 14 years of education and obtained an associate degree. He scored 81 on the Wide Ranging Aptitude Test-Revised (WRAT, 10th percentile, indicating low normal premorbid function).

3.1.2. Case #2: (SZ, Caucasian ancestry, 43 years)—The proband's sibling also reported several vivid and persistent hallucinations and delusions, with teenage onset. His records indicated partial response to antipsychotic drugs. He completed 14 years of education, requiring remedial classes and speech therapy in school. He had a WRAT 3 standard score of 90 (normal premorbid function).

3.1.3. Family history—The siblings' mother did not have a pathogenic C9orf72 repeat expansion. Their deceased father reportedly suffered from an 'organic brain syndrome (DNA not available). Two paternal aunts reportedly succumbed to dementia.

3.2. Family 2. (Figure 1b)

3.2.1. Proband, Case #3: (SZA, bipolar type; Caucasian ancestry, 51 years)—After severe childhood trauma, she reported smelling 'burning flesh' and auditory hallucinations for a year, followed by recurrent sadness. In her 20s, she experienced manic episodes co-occurring with major depressive episodes, rapid mood fluctuation and intermittent psychotic phenomena (including somatic, olfactory, visual and gustatory hallucinations) independent of manic or depressive episodes. She received electroconvulsive treatment, antidepressants, antipsychotic drugs and mood stabilizers. She completed 14 years of education and obtained an associate degree. Her WRAT-R score was 98 (normal range).

3.2.2. Proband's mother, Case #4: (Caucasian ancestry, 77 years)—A psychiatric evaluation was not completed; she reported a diagnosis of 'Charcot's disease'.

3.2.3. Family history—Three of the proband's children had depression and her brother had von Willebrand's disease. Other relatives were reported to have 'Charcot disease' and nervous problems.

4. Discussion

A survey of psychiatric genetics research participants indicated 3 US patients with SZ/SZA and another individual with C9orf72 repeat expansions. The patients had severe, florid psychoses, but not dementia or ALS. Some of their relatives were diagnosed with dementia, neurological diseases and psychiatric disorders. The patients have additional risk FTD or ALS later due to the highly penetrant nature of this mutation, but they could not be re-

evaluated. The psychoses could also be a pleiotropic effect of the repeat expansion; indeed, two other individuals with intellectual disability bearing the expansion have been reported (Proudfoot et al., 2014). The C9orf72 repeat expansions was present in 0.15% of a UK birth cohort, so it is possible, but unlikely that the expansion occurs in healthy persons (Beck et al., 2013). Further research is needed to see whether C9orf72 repeat expansions should be tested routinely in psychotic individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Pathological hexanucleotide repeat expansions of C9orf72 cause FTD/ALS.
- We screened for C9orf72 repeat expansions among individuals with psychoses.
- We describe four individuals with C9orf72 repeat expansions.
- Three of the individuals were diagnosed with SZ and SZA.
- All the patients with SZ or SZA had florid psychotic features.

Figure 1a. Family 1.

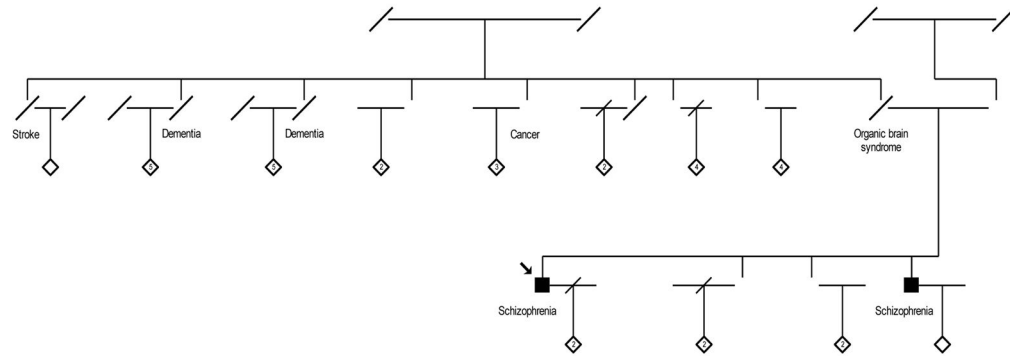


Figure 1b. Family 2.

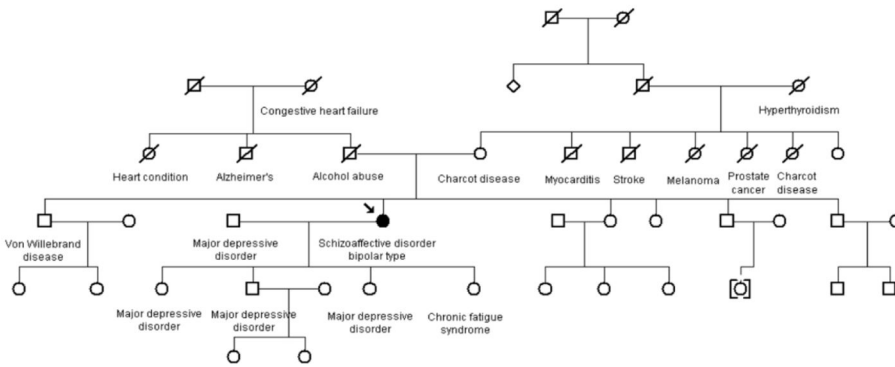


Figure 1. Pedigree structures

The individuals described in this manuscript are shown along with their relatives. Genders of some individuals have been altered to preserve confidentiality. Individuals with schizophrenia or schizoaffective disorder are indicated by darkened circles or squares. Other diagnoses are based on family history information from the probands' parents. Genomic DNA from the individuals with schizophrenia or schizoaffective disorder in both pedigrees and the mother of the proband in Family 2 were assayed for the C9orf72 expansion.