Triplet repeats in clinical subtypes of schizophrenia: variation at the DRPLA (B 37 CAG repeat) locus is not associated with periodic catatonia

Short Communication

K. P. Lesch1, G. Stöber1, U. Balling1, E. Franzek1, S. H. Li2, C. A. Ross2, M. Newman3, H. Beckmann1, and P. Riederer1

1 Department of Psychiatry, University of Würzburg, Würzburg, Federal Republic of Germany
2 Laboratory of Molecular Neurobiology, Departments of Psychiatry and Neuroscience, Johns Hopkins University, School of Medicine, Baltimore, MD, U.S.A.
3 Biological Psychiatry Laboratory, Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Accepted September 8, 1994

Summary. Clinical evidence for a dominant mode of inheritance and anticipation in periodic catatonia, a distinct subtype of schizophrenia, indicates that genes with triplet repeat expansions or other unstable repetitive elements affecting gene expression may be involved in the etiology of this disorder. Because patients affected with dentatorubral-pallidoluysian atrophy (DRPLA) may present with “schizophrenic” symptoms, we have investigated the DRPLA (B 37 CAG repeat) locus on chromosome 12 in 41 patients with periodic catatonia. The B 37 CAG repeat locus was highly polymorphic but all alleles in both the patient and control group had repeat sizes within the normal range. We conclude that variation at the DRPLA locus is unlikely to be associated with periodic catatonia. The evidence for dominant inheritance and anticipation as well as the high prevalence of human brain genes containing trinucleotide repeats justifies further screening for triplet repeat expansions in periodic catatonia.

Keywords: Association study, B 37 CAG repeat locus, chromosome 12, schizophrenia, periodic catatonia.

Introduction

Genes containing repetitive DNA elements, such as triplet repeats, may be expanded, unstable and a potential cause for some psychiatric disorders (Ross
et al., 1993). Triplet repeats may therefore be the molecular correlate of the clinical phenomenon of anticipation observed in subtypes of schizophrenia. Anticipation describes the unusual pattern of inheritance in genetic disorder whose severity increase and age of onset decrease in successive generations. This phenomenon, however, tends to be challenged as an assessment bias (Harper et al., 1992). The recent discovery of a new form of human mutation provided a specific biological explanation in several inherited neurological and neuropsychiatric diseases with anticipation (Mandel, 1993). In Huntington's disease, myotonic dystrophy, fragile X syndrome, spinocerebellar ataxia type 1, dentatorubral-pallidoluysian atrophy (DRPLA) (Koide et al., 1994; Nagafuchi et al., 1994), unstable expansion of trinucleotide repeats were identified in coding/non-coding regions of distinct genes. Repeat length and instability is directly associated with increased severity and earlier age of onset in successive generations.

Recently, an investigation of familial aggregation of psychoses in pedigrees with schizophrenic disorders strongly suggested a dominant mode of inheritance in periodic catatonia, a distinct subtype of schizophrenia (Stöber et al., 1994). As compared to other forms of catatonic schizophrenia (age-correlated morbidity risk, 4.6%) with a chronic progressive course and irreversible, well-defined defective states (Franzek and Beckmann, 1992), periodic catatonia was characterized by an age-corrected morbidity risk with homogenous psychoses of 26.9%. Moreover, a pairwise comparison of patients and their parents revealed patterns of genetic anticipation. The course of periodic catatonia is bipolar in both hyperkinetic as well as akinetic states. Typically, symptoms of one pole are combined with those of the other pole. The distortion of psychomotor activity leads to grimaces, parakinetic movements, stereotypies, impulsive actions with aggressiveness, and negativistic behavior. Although remissions occur after acute episodes, residual states of varying degrees finally develop with increasing poverty of movements, blunted affect, and lack of motivation.

The clinical evidence for a dominant mode of inheritance and anticipation in periodic catatonia indicates that genes with triplet repeat expansions or other unstable repetitive elements affecting gene expression may be involved in its etiology. Because patients affected with DRPLA may also present with “schizophrenic” symptoms (Koide et al., 1994), such as delusion and hallucination, variation at the DRPLA (B37 CAG repeat) locus on chromosome 12 was investigated in periodic catatonia.

**Subjects and methods**

*Recruitment of patients and diagnostic assessment*

Fourty-one unrelated German caucasians (19 male, 22 female) meeting the DSM-III-R criteria for schizophrenia, catatonic subtype (APA 1987), and the criteria for periodic catatonia (Leonhard, 1979, 1980) were recruited from inpatients at the Department of Psychiatry, University of Würzburg, and from wards with chronically ill patients at the Lohr/Main Psychiatric State Hospital. The patients with periodic catatonia included in this