

# Association study of CAG repeats in the KCNN3 gene in Japanese patients with schizophrenia, schizoaffective disorder and bipolar disorder

Hiroshi Ujike<sup>a,\*</sup>, Ayako Yamamoto<sup>a</sup>, Yuji Tanaka<sup>a,b</sup>, Yasushi Takehisa<sup>a</sup>,  
Manabu Takaki<sup>a</sup>, Toshihiko Taked<sup>c</sup>, Masafumi Kodama<sup>a</sup>,  
Shigetoshi Kuroda<sup>a</sup>

<sup>a</sup>Department of Neuropsychiatry, Okayama University Medical School, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

<sup>b</sup>Takaoka Hospital, Himeji, Japan

<sup>c</sup>Zikei Hospital, Okayama, Japan

Received 21 August 2000; received in revised form 29 November 2000; accepted 21 January 2001

## Abstract

To investigate a possible involvement of expanded triplet repeats of genome in the genomes of patients with endogenous psychoses, we examined a CAG repeat polymorphism in the coding region of the KCNN3 gene in schizophrenia, schizoaffective disorder, bipolar disorder and controls of the Japanese population. There were no significant differences in the CAG repeat number of longer or shorter alleles among the four diagnostic groups or among the schizophrenia hebephrenic and paranoid subtypes. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** hSKCA3; Anticipation; Trinucleotide repeat; Potassium channel

## 1. Introduction

Some family-based studies have shown an anticipation phenomenon, i.e. age of onset in children or young adults becoming earlier than that of their parents, in families with members suffering from schizophrenia or bipolar affective dis-

orders, although the findings is still a matter of controversy (Asherson et al., 1994; Bassett and Horner, 1994; Thibaut et al., 1995). Dynamic mutations involving elongation of CAG/CTG triplet repeats were demonstrated to be the molecular mechanisms of the anticipation phenomenon in certain neurodegenerative diseases such as Huntington's disease. In 1995, O'Donovan et al. (1995) presented indirect evidence for elongation of CAG/CTG repeats in the genomes of patients with schizophrenia and bipolar disorder using a

\* Corresponding author. Tel.: +81-86-223-7151; fax: +81-86-235-7246.

E-mail address: [hujike@cc.okayama-u.ac.jp](mailto:hujike@cc.okayama-u.ac.jp) (H. Ujike).

repeat expansion detection assay. Therefore, a gene containing a triplet repeat sequence could be a strong candidate for involvement in the etiologies of these endogenous psychoses.

In 1998, in a cohort study conducted in Europe, Chandy et al. (1998) found a polymorphism in the number of CAG repeats in exon 1 of the KCNN3 gene (MIM 602983, also called the hSKCA3). They also found the CAG repeat number in the KCNN3 gene to be significantly greater in patients with schizophrenia than in controls, and a similar tendency was seen in patients with affective disorders (Chandy et al., 1998; Bowen et al., 1998). However, the findings remained inconclusive because several negative studies followed (Li et al., 1998; Stöber et al., 1998; Wittekindt et al., 1999). To ascertain whether there is an association between KCNN3 CAG repeat number and endogenous psychoses, we determined this number in patients with schizophrenia, schizoaffective disorder and bipolar affective disorder in the Japanese, a population not yet examined for this putative relationship.

## 2. Methods

### 2.1. Subjects

Subjects were 265 patients (123 males and 142 females, age  $49.8 \pm 14.3$  years old) with schizophrenia (F20), schizoaffective disorder (F25.1) and bipolar disorder (F31) meeting ICD-10-DCR criteria who were outpatients or inpatients of psychiatric hospitals and 100 age-matched normal controls (35 males and 65 females, age  $38.2 \pm 10.9$  years old) who had no known history of psychiatric disease in their families. Patients with schizophrenia, schizoaffective disorder and bipolar disorder numbered 142, 39 and 84, respectively. As to the subtypes of schizophrenia, hebephrenic (F20.1), paranoid (F20.0), catatonic (F20.2) and undifferentiated type (F20.3) accounted for 75, 59, 2 and 6 patients, respectively. All subjects were Japanese, born and living in the middle western area of Japan. This study was performed after approval by the ethics committee of Okayama University Medical

School, Zikei Hospital and Takaoka Hospital, and all subjects provided written informed consent permitting use of their DNA samples for the research.

### 2.2. Procedure

Genomic DNA was extracted from peripheral leukocytes by the standard phenol/CHCl<sub>3</sub> method. The KCNN3 gene has two CAG repeat sequences in the coding region. We have confirmed the upstream sequence to have a consistent repeat number of 12 while the downstream sequence is polymorphic, based on direct sequencing, in Japanese subjects. The region containing the downstream polymorphic CAG repeat was amplified by PCR using the primer set described by Chandy et al. (1998). PCR products with size standard were analyzed on 6% polyacrylamide gel using an SQ5500 DNA sequencer (Hitachi Co., Japan), and each length was calculated using the computer software of Fragyls 2 (Hitachi Co., Japan). All genotyping was carried out in a blinded fashion with control and patient samples intermixed. Statistical analysis was done by Mann–Whitney rank sum test and chi-square test.

## 3. Results

Means, ranges and modal values of CAG repeat numbers of longer and shorter alleles of the KCNN3 gene are shown in Table 1. Distributions of longer CAG repeats of the four diagnostic groups are shown in Fig. 1. Distributions of both alleles in all groups were within the Hardy–Weinberg equilibrium. There was no significant difference in the longer or shorter CAG repeat numbers of the KCNN3 gene between the controls and the three major diagnostic groups, schizophrenia, schizoaffective disorders and bipolar disorders (shorter alleles: schizophrenia,  $z = -0.326$ ,  $P = 0.74$ ; schizoaffective,  $z = -0.607$ ,  $P = 0.54$ ; bipolar,  $z = -0.474$ ,  $P = 0.64$ ; longer alleles: schizophrenia  $z = -1.66$ ,  $P = 0.10$ ; schizoaffective  $z = -0.201$ ,  $P = 0.84$ ; bipolar  $z = -1.57$ ,  $P = 0.12$ ). As to the sub-categories of schizophrenia, hebephrenic and paranoid types,

متن کامل مقاله

دریافت فوری ←

**ISI**Articles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات