CAG-Repeat Length in Exon 1 of KCNN3 Does Not Influence Risk for Schizophrenia or Bipolar Disorder: A Meta-Analysis of Association Studies

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Schizophrenia and bipolar disorder both show some evidence for genetic anticipation. In addition, significant expansion of anonymous CAG repeats throughout the genome has been detected in both of these disorders. The gene *KCNN3*, which codes for a small/intermediate conductance, calcium-regulated potassium channel, contains a highly polymorphic CAG-repeat array in exon 1. Initial evidence for association of both schizophrenia and bipolar disorder with increased CAG-repeat length of KCNN3 has not been consistently replicated. In the present study, we performed several meta-analyses to evaluate the pooled evidence for association with CAG-repeat length of KCNN3 derived from case-control and family-based studies of both disorders. Each group of studies was analyzed under two models, including a test for direct association with repeat length, and a test for association with dichotomized repeat-length groups. No evidence for a linear relationship between disease risk and repeat length was observed, as all pooled odds ratios approximated 1.0. Results of dichotomized allele-group analyses were more variable, especially for schizophrenia, where case-control studies found a significant association with longer repeats but family-based studies implicated shorter alleles. The results of these meta-analyses demonstrate that the risks for both schizophrenia and bipolar disorder are largely, if not entirely, independent of CAG-repeat length in exon 1 of KCNN3. This study cannot exclude the possibility that some aspect of this polymorphism, such as repeat-length disparity in heterozygotes, influences risk for these disorders. Further, it remains unknown if this polymorphism, or one in linkage disequilibrium with it, contributes to some distinct feature of the disorder, such as symptom severity or anticipation. © 2003 Wiley-Liss, Inc.

KEY WORDS: schizophrenia; bipolar disorder; *KCNN3*; CAG-repeat; allelic association; meta-analysis

DATABASE: KCNN3

INTRODUCTION

Schizophrenia and bipolar disorder both show some evidence of genetic anticipation, with increased severity and an earlier age of onset in successive generations of families that are multiply affected [McInnis et al., 1993; Bassett and Honer, 1994]. The cause of these phenomena is unknown, but a good candidate is the expansion of genomic trinucleotide-sequence repeats. Trinucleotide-repeat expansions underlie anticipation in various neurological conditions, including fragile-X syndrome [Kremer et al., 1991], spinal and bulbar muscular atrophy [La Spada et al., 1992], myotonic dystrophy [Tsilfidis et al., 1992], and Huntington's disease [Duyao et al., 1993]. To investigate the possibility of such a mechanism in schizophrenia and bipolar disorder, repeat-expansion detection (RED) methods have been used to scan the genomes of affected individuals for

expanded triplet-repeat arrays. In fact, a greater number of CAG repeats has been documented in both groups of patients [Lindblad et al., 1995; Morris et al., 1995]; however, this phenomenon has not been observed in all samples [Ohara, 2001; Jones et al., 2002]. Nevertheless, while RED methods suggest the presence of expanded sequences in these two disorders, they provide little information on the chromosomal loci of these expansions.

Without a known genomic location of trinucleotide-repeat expansion in schizophrenia and bipolar disorder, genes containing polymorphic trinucleotide-repeat arrays have been considered good candidates for underlying anticipation in these disorders. One such candidate is *KCNN3*, a gene that codes for member 3 of the N family of small/intermediate conductance, calcium-regulated potassium channels. KCNN3, formerly known as hSKCa3, contains two CAG-repeat arrays in exon 1, the second (more 3′) of which is highly polymorphic [Chandy et al., 1998]. This gene maps to chromosome 1q21-22, where evidence for a major schizophrenia-susceptibility locus is mixed [Brzustowicz et al., 2000; Levinson et al., 2002]. KCNN3 is also a good functional candidate for schizophrenia and bipolar disorder because of its expression in the central nervous system [Dror et al., 1999], particularly in midbrain dopaminergic neurons where it mediates calcium-dependent afterhyperpolarization [Wolfart et al., 2001]. Based on these promising features of the gene, this polymorphism of KCNN3 has also been tested frequently for association with the absolute risks for bipolar disorder and schizophrenia; in fact, it has been tested more often for association with disease risk in these two disorders than it has been tested for a role in their anticipation.

The first report to examine the relationship of this polymorphism with the risks for these two disorders found significant evidence for an association of alleles longer than 19 repeats with schizophrenia and a trend for an association with bipolar disorder [Chandy et al., 1998]. Many attempts were made to replicate these findings; however, most subsequent reports have failed to support these associations. In light of numerous discrepant findings, the initial evidence for association may represent a false-positive association resulting from a type-I inferential error. Alternatively, subsequent studies may have lacked sufficient power to detect a small but significant association. In the present study, we attempted to resolve this uncertainty through meta-analyses in which pooled case-control and family-based studies of schizophrenia and bipolar disorder were considered separately for association with this polymorphism.

MATERIALS AND METHODS
Literature Search

To identify studies eligible for meta-analysis, MEDLINE citations (January, 1966–February, 2003) were surveyed using the National Library of Medicine's PubMed online search engine with "schizophrenia," "bipolar disorder," "hSKCa3," and "KCNN3" as keywords. The retrieved abstracts were read to identify studies that examined the allelic association of a polymorphism within the *KCNN3* gene with either schizophrenia or bipolar disorder. Studies of this type were then read in their entirety to assess their appropriateness for inclusion in the meta-analysis. All references cited in these studies were also reviewed to identify additional works not indexed by MEDLINE.

Inclusion Criteria

Only those studies examining the second (more 3′) CAG repeat in exon 1 of KCNN3 were included in the meta-analysis. Furthermore, studies had to meet all of the following criteria: (1) be published in a peer-reviewed journal, (2) present original data, and (3) provide enough data to calculate an effect size. The application of these criteria yielded 23 studies eligible for meta-analysis. The 14 case-control studies provided data on 11 schizophrenia samples and 6 bipolar disorder groups [Chandy et al., 1998; Wittekindt et al., 1998; Bonnet-Brilhault et al., 1999; Dror et al., 1999; Guy et al., 1999; Hawi et al., 1999; Joober et al., 1999; Rohrmeier et al., 1999; Tsai et al., 1999; Bowen et al., 2000; Saleem et al., 2000; Imamura et al., 2001; Meira-Lima et al., 2001; Laurent et al., 2003], while the 10 family-based studies documented 7 schizophrenia samples and 3 bipolar disorder groups [Li et al., 1998; Stober et al., 1998; Antonarakis et al., 1999; McInnis et al., 1999; Meissner et al., 1999; Rohrmeier et al., 1999; Wittekindt et al., 1999; Bowen et al., 2000; Chowdari et al., 2000; Laurent et al., 2003].

Coding of Study Characteristics

To delineate potential moderating influences of various sample characteristics on the size of the effects obtained in the case-control studies under consideration, each study was coded on the following variables: (1) the ethnicity of the sample, (2) the mean age of the case group, (3) the mean age of the control group, and (4) a gender index [calculated as (female cases/male cases)/(female controls/male controls)]. The descriptive characteristics of schizophrenia case-control studies are presented in Table I, and those of bipolar disorder case-control studies are shown in Table II. Because far fewer family-based studies were available for meta-analysis, the power to detect significant moderator variables was severely constrained and, as such, a statistical analysis of these relationships was precluded.

Statistical Analysis

Four study sets were available for meta-analysis: (1) case-control studies of schizophrenia, (2) family-based studies of schizophrenia, (3) case-control studies of bipolar disorder, and (4) family-based studies of bipolar disorder. Each group of studies was analyzed under two models: one in which allele length (4–30 repeats) was treated as an ordinal predictor, and one in which allele length was dichotomized into allele-length groups (≤ 19 or ≥ 20 repeats). This dichotomization scheme was chosen to maximize the number of studies that could be included in each analysis, as some studies only presented data in this format. The allele-length analysis

TABLE I. Descriptive Characteristics of Case-Control Studies of Schizophrenia

Study	Ethnicity	Mean age of case group	Mean age of control group	Gender index[a]
Bonnet-Brilhault et al., 1999	European	41.0	38.8	0.89
Bowen et al., 2000	European	45.0	43.0	1.12
Chandy et al., 1998	European	—	—	—
Dror et al., 1999	European	—	—	—
Hawi et al., 1999	European	—	—	—
Imamura et al., 2001	Asian	40.9	40.2	1.11
Joober et al., 1999	European	38.8	44.0	2.82
Laurent et al., 2003	African	—	—	—
Rohrmeier et al., 1999	European	36.7	32.5	1.85
Saleem et al., 2000	Asian	30.4	29.5	0.53
Tsai et al., 1999	Asian	53.0	55.0	1.29

Dashes indicate missing or insufficient data.
[a]Gender index = (female cases/male cases)/(female controls/male controls).

was used to determine if CAG-repeat length influenced schizophrenia or bipolar disorder risk in a linear fashion, while the analysis of dichotomized allele groups was designed to clarify the schizophrenia- or bipolar disorder-risk attributable to alleles with 20 or more CAG repeats.

For allele-length analyzes, the number of alleles of each repeat length was assigned as the predictor in a logistic regression, in which group membership (case or control) was the dependent variable for case-control studies, and parental allele transmission status (transmitted to the affected offspring or not) was the dependent variable for family-based studies. For both case-control and family-based studies, the exponentiated regression coefficient $[\exp(\beta)]$ provided an estimate of the odds ratio (OR), where a value >1.0 indicated a positive association between repeat length and disease risk. This OR represented the increase in disease risk attributable to each 1-repeat increment in allele size for case-control studies, while for family-based studies this OR represented the increase in probability of allele transmission to an affected offspring with each 1-repeat increment in allele length.

For the dichotomized allele-group analyzes, data from each study were used to construct two-by-two tables. For case-control studies, these two-by-two tables were used to classify subjects by diagnostic category (case or control) and allele group ($\leq$19 or $\geq$20 repeats), whereas the data from family-based studies were used to classify parental alleles by group ($\leq$19 or $\geq$20 repeats) and transmission status (transmitted to the affected offspring or not). The strength of association in these two-by-two tables was summarized using the OR, where a value >1.0 indicated a positive association between longer alleles and risk for the disorder. For case-control studies, the OR estimates the relative risk, which represents the increase in the probability of observing alleles with 20 or more repeats in cases relative to controls, while for family-based studies this OR represents the increase in likelihood of transmitting an allele with 20 or more repeats rather than an allele with 19 or less repeats to an affected offspring.

Each group of studies was analyzed by random-effects meta-analysis. ORs were pooled according to the methods of DerSimonian and Laird [1986], and 95% confidence intervals (CIs) were constructed using Woolf's [1955] method. The significance of the pooled OR was determined by the z test. The heterogeneity of the group of ORs was assessed using a χ^2 test of goodness of fit. The influence of individual studies on the pooled OR was determined by sequentially removing each study and recalculating the pooled OR and 95% CI. The moderating influence of sample characteristics on the OR derived from each case-control study was assessed by multiple regression. The type-I error rate was set at 0.05. All statistical analyses were conducted using Stata 7.0 (Stata Corporation; College Station, TX).

RESULTS

Case-Control Studies of Schizophrenia

Within this group of 11 case-control studies, the test for heterogeneity among the ORs for allele length (Table III) was not significant ($\chi^2_{(10)} = 15.20$, $P = 0.13$).

TABLE II. Descriptive Characteristics of Case-Control Studies of Bipolar Disorder

Study	Ethnicity	Mean age of case group	Mean age of control group	Gender index[a]
Guy et al., 1999	European	45.4	44.2	0.99
Hawi et al., 1999	European	—	—	—
Meira-Lima et al., 2001	European	43.0	33.0	1.61
Rohrmeier et al., 1999	European	48.8	32.5	1.27
Saleem et al., 2000	Indian	31.2	29.5	0.76
Wittekindt et al., 1998	European	—	—	—

Dashes indicate missing or insufficient data.
[a]Gender index = (female cases/male cases)/(female controls/male controls).

TABLE III. KCNN3 CAG-Repeat Length and Allele Group as Schizophrenia Risk Factors: Case-Control Studies

Study	Allele length		Allele group	
	OR	95% CI	OR	95% CI
Bonnet-Brilhault et al., 1999	1.0	0.9–1.1	1.0	0.7–1.5
Bowen et al., 2000	1.0	1.0–1.1	1.4	0.9–1.9
Chandy et al., 1998	1.1	1.0–1.2	1.8	1.2–2.7
Dror et al., 1999	1.1	1.0–1.2	3.2	1.8–5.6
Hawi et al., 1999	1.0	0.9–1.1	1.1	0.8–1.5
Imamura et al., 2001	1.0	0.9–1.1	0.9	0.6–1.4
Joober et al., 1999	1.1	1.0–1.2	1.2	0.7–2.0
Laurent et al., 2003	1.0	1.0–1.1	1.1	0.6–1.8
Rohrmeier et al., 1999	1.0	0.9–1.0	1.1	0.7–1.6
Saleem et al., 2000	0.9	0.8–1.1	1.0	0.6–1.8
Tsai et al., 1999	1.0	0.9–1.1	0.9	0.6–1.4
Pooled	1.0	1.0–1.1	1.2	1.0–1.5

TABLE IV. KCNN3 CAG-Repeat Length and Allele Group as Schizophrenia Risk Factors: Family-Based Studies

Study	Allele length		Allele group	
	OR	95% CI	OR	95% CI
Antonarakis et al., 1999	1.0	0.8–1.2	1.3	0.4–3.6
Chowdari et al., 2000	1.0	0.9–1.2	0.8	0.3–1.8
Laurent et al., 2003	1.0	1.0–1.1	0.9	0.6–1.5
Li et al., 1998	1.0	0.9–1.1	0.6	0.4–1.0
Meissner et al., 1999	1.0	0.8–1.3	1.5	0.5–3.9
Stober et al., 1998	0.9	0.7–1.0	0.4	0.2–0.8
Wittekindt et al., 1999	—	—	0.9	0.6–1.3
Pooled	1.0	0.9–1.0	0.7	0.5–1.0

Dashes indicate missing or insufficient data.

Individual study ORs ranged from 0.9 to 1.1, and the pooled OR from 1,596 cases and 1,564 controls was 1.0 (95% CI = 1.0–1.1), which was not significant ($z = 1.15$, $P = 0.25$). The pooled estimate was not excessively influenced by any single study, as the removal and replacement of each study from the calculation of the pooled OR consistently produced values of 1.0. ORs were not significantly influenced by sample ethnicity ($z = -1.29$, $P = 0.20$) or gender composition ($z = -0.04$, $P = 0.97$), or by the mean age of the cases ($z = -0.82$, $P = 0.41$) or controls ($z = 1.36$, $P = 0.18$).

When alleles were dichotomized into those with 19 or fewer repeats and those with 20 or more repeats (Table III), the pooled OR for longer-repeat alleles was 1.2, which was significant ($z = 2.05$, $P = 0.04$). Significant heterogeneity was observed ($\chi^2_{(10)} = 20.03$, $P = 0.03$), which suggested the presence of some moderating factor; yet, none of the variables coded in these studies reliably influenced their ORs (ethnicity, $z = -1.15$, $P = 0.25$; gender index, $z = -0.32$, $P = 0.75$; mean age of cases, $z = -0.28$, $P = 0.78$; mean age of controls, $z = 0.34$, $P = 0.74$). Furthermore, the significance of the pooled OR was not robust, as the removal of any one of four different studies from the calculation of the pooled OR would reduce the estimate to 1.0 and non-significance.

Family-Based Studies of Schizophrenia

Six studies, comprising 365 parent-offspring trios, provided enough data to calculate allele-length ORs (Table IV), and the pooled OR from these studies was 1.0 ($z = -0.52$, $P = 0.61$). Individual study ORs ranged from 0.9 to 1.0, and these ORs comprised a homogeneous set ($\chi^2_{(5)} = 4.63$, $P = 0.46$). The pooled ORs calculated after the sequential removal and replacement of each study ranged from 0.9 to 1.0, with 95% CIs that always encompassed a value of 1.0. When allele length was dichotomized and an additional study was added (Table IV), the pooled OR of 0.8 derived from 558 trios nearly attained statistical significance ($z = 1.90$, $P = 0.06$); however, in contrast to the analysis of dichotomized data from case-control studies, this analysis

implicated shorter-repeat alleles of KCNN3 in schizophrenia risk.

Case-Control Studies of Bipolar Disorder

The meta-analysis of allele length in case-control studies of bipolar disorder included five studies with data from 583 cases and 814 controls (Table V). The ORs from these studies comprised a homogeneous group ($\chi^2_{(4)} = 6.96$, $P = 0.14$), and the pooled OR of 1.0 (95% CI = 0.9–1.0) clearly indicated that the risk for bipolar disorder was independent of allele length ($z = -0.04$, $P = 0.68$). In fact, a pooled OR of 1.0 was obtained regardless of which study was omitted from its calculation. ORs were not influenced by such factors as sample ethnicity ($z = 0.61$, $P = 0.54$) or gender composition ($z = -1.24$, $P = 0.21$), or by the mean age of the cases ($z = -1.4$, $P = 0.16$) or controls ($z = -0.58$, $P = 0.56$).

One additional study was included in the analysis of dichotomized alleles, producing a total of 748 cases and 1,010 controls (Table V). The ORs, which ranged from 0.8 to 1.2, comprised a homogeneous set ($\chi^2_{(5)} = 2.38$, $P = 0.79$). As with the allele-length analysis, the pooled OR was 1.0 (95% CI = 0.8–1.1), and was not significant ($z = 0.48$, $P = 0.63$). This result was not due to the excess influence of any single study, since the 95% CIs around the pooled OR always contained a value of 1.0 regardless of which study was removed from the group. No significant moderators of these ORs were observed (ethnicity,

TABLE V. KCNN3 CAG-Repeat Length and Allele Group as Bipolar Disorder Risk Factors: Case-Control Studies

Study	Allele length		Allele group	
	OR	95% CI	OR	95% CI
Guy et al., 1999	1.0	0.9–1.0	0.9	0.7–1.2
Hawi et al., 1999	1.0	0.9–1.0	0.9	0.7–1.3
Meira-Lima et al., 2001	—	—	1.2	0.8–1.7
Rohrmeier et al., 1999	0.9	0.9–1.0	0.7	0.5–1.1
Saleem et al., 2000	1.0	0.9–1.1	1.1	0.8–1.6
Wittekindt et al., 1998	1.1	1.0–1.2	1.2	0.8–1.9
Pooled	1.0	0.9–1.0	1.0	0.8–1.1

Dashes indicate missing or insufficient data.

TABLE VI. KCNN3 CAG-Repeat Length and Allele Group as
Bipolar Disorder Risk Factors: Family-Based Studies

	Allele length		Allele group	
Study	OR	95% CI	OR	95% CI
Bowen et al., 2000	1.1	1.0–1.2	0.7	0.4–1.1
McInnis et al., 1999	1.0	1.0–1.1	1.5	1.0–2.2
Rohrmeier et al., 1999	—	—	1.3	0.7–2.4
Pooled	1.0	1.0–1.1	1.1	0.7–1.8

Dashes indicate missing or insufficient data.

$z = 0.74$, $P = 0.46$; gender index, $z = 1.27$, $P = 0.20$; mean age of cases, $z = 0.86$, $P = 0.39$; mean age of controls, $z = -1.51$, $P = 0.13$).

Family-Based Studies of Bipolar Disorder

Only three family-based studies of bipolar disorder were available for analysis, of which only two presented allele-length data (Table VI). These two studies, comprised of 242 parent-offspring trios, produced virtually identical ORs, and a pooled OR of 1.0 (95% CI = 1.0–1.1), which was not significant ($z = 1.38$, $P = 0.17$). Significant heterogeneity was not detected ($\chi^2_{(1)} = 0.05$, $P = 0.82$), but the power to do so was clearly inadequate. A third study was added for the analysis of dichotomous allele groups, thus increasing sample size to 333 trios (Table VI). While the pooled OR was slightly higher in this analysis (OR = 1.1, 95% CI = 0.7–1.8), the combined result was still not significant ($z = 0.40$, $P = 0.69$).

DISCUSSION

KCNN3 is a good candidate for bipolar disorder and, especially, schizophrenia based on its genomic organization, chromosomal location, and function. However, the results of this study very clearly indicate that CAG-repeat length in exon 1 does not influence risk for either of these disorders, at least not in a linear fashion. The dichotomization of alleles into those with 19 or fewer repeats and those with 20 or more repeats did produce a significant association of longer alleles with schizophrenia in case-control studies, but this was offset by evidence from family-based studies in which shorter alleles were implicated. These discrepant findings, along with the fact that the significant association with shorter alleles in the case-control studies was quite sensitive (i.e., not robust) to the effects of individual studies, suggest that both are false positive findings.

Because case-control studies are more susceptible than family-based studies to sampling bias introduced by population stratification [Faraone et al., 1999], the evidence from the latter group of studies may be more useful than that from the former. However, in the absence of a rationale for assigning risk to any particular allele or to alleles over a certain length, the analysis of repeat length by logistic regression has higher face validity than either of the allele-group analyses in determining the risk attributable to this polymorphism. These allele length analyzes had excellent power ($\beta > 0.80$) to detect a significant OR as low as 1.1 for

either bipolar disorder or schizophrenia, but failed to do so. This fact provides compelling evidence against any appreciable role of this polymorphism in the risk for either condition, and also makes it highly unlikely that expansion at this locus accounts for the anonymous expansions of CAG-repeat domains observed by RED in some samples of patients with schizophrenia or bipolar disorder. Further, the observed associations of schizophrenia with both of the allele groups (longer alleles in case-control studies, shorter alleles in family-based studies) may have capitalized on chance relationships, since moving the dichotomization threshold only slightly (e.g., ≤ 18 and ≥ 19 or ≤ 20 and ≥ 21) erased all indications of association (case-control, 18/19 repeats as threshold, $P = 0.13$; case-control, 20/21 repeats as threshold, $P = 0.38$; family-based, 18/19 repeats as threshold, $P = 0.59$; family-based, 20/21 repeats as threshold, $P = 0.78$; data available upon request).

Thus, the pooled evidence does not support a relationship between CAG-repeat length in exon 1 of KCNN3 and schizophrenia or bipolar disorder. However, this does not preclude some potential role for KCNN3 in these disorders. For example, although a role for this polymorphism in the general population is not indicated, stronger associations may be noted in circumscribed segments of the population (e.g., homogeneous ethnic groups or population isolates). Furthermore, these meta-analyses cannot address the possibility that repeat length of this polymorphism is directly related to anticipation. Thus, while this polymorphism is clearly not a mediator of disease development, it may be a moderator of its severity and age of onset. In addition, some other feature of this polymorphism, such as the disparity in allele length among heterozygotes [Saleem et al., 2000], may confer excess risk for these conditions. Furthermore, it is entirely possible that some other polymorphism within KCNN3 contributes to the risk or presentation of these disorders.

In summary, it seems unlikely that the length of this CAG-repeat polymorphism in KCNN3 influences risk for either schizophrenia or bipolar disorder. More studies of schizophrenia than bipolar disorder were summarized in this study, so this conclusion is stronger for the former condition than for the latter. Further tests for association between allele length of this polymorphism and a formal diagnosis of schizophrenia seem unwarranted. However, to strengthen the conclusions for bipolar disorder, more family-based studies, or the use of more powerful genomic-control association methods [Bacanu et al., 2000], are recommended. In addition, more studies specifically designed to detect a role for this polymorphism in anticipation are needed [Bonnet-Brilhault et al., 1999; Joober et al., 1999].

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