

RESEARCH ARTICLE

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Is Ankyrin a genetic risk factor for psychiatric phenotypes?

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Abstract

Background: Genome wide association studies reported two single nucleotide polymorphisms in *ANK3* (rs9804190 and rs10994336) as independent genetic risk factors for bipolar disorder. Another SNP in *ANK3* (rs10761482) was associated with schizophrenia in a large European sample. Within the debate on common susceptibility genes for schizophrenia and bipolar disorder, we tried to investigate common findings by analyzing association of *ANK3* with schizophrenia, bipolar disorder and unipolar depression.

Methods: We genotyped three single nucleotide polymorphisms (SNPs) in *ANK3* (rs9804190, rs10994336, and rs10761482) in a case-control sample of German descent including 920 patients with schizophrenia, 400 with bipolar affective disorder, 220 patients with unipolar depression according to ICD 10 and 480 healthy controls. Sample was further differentiated according to Leonhard's classification featuring disease entities with specific combination of bipolar and psychotic syndromes.

Results: We found no association of rs9804190 and rs10994336 with bipolar disorder, unipolar depression or schizophrenia. In contrast to previous findings rs10761482 was associated with bipolar disorder ($p = 0.015$) but not with schizophrenia or unipolar depression. We observed no association with disease entities according to Leonhard's classification.

Conclusion: Our results support a specific genetic contribution of *ANK3* to bipolar disorder though we failed to replicate findings for schizophrenia. We cannot confirm *ANK3* as a common risk factor for different diseases.

Background

Schizophrenia and bipolar disorder are genetically complex diseases with numerous proposed genetic risk factors encompassing different pathophysiological pathways of neurotransmission, brain development or synaptic plasticity with each small contribution to disease risk and inconsistent results among replication studies (Stöber et al 2009) [1,2]. Recently genome wide association studies (GWAs) lead to identification of new susceptibility genes with genome-wide levels of significance: zinc finger gene *ZNF804A* on chromosome 2q32 or the *MHC*-locus at 6p21 on schizophrenia. For bipolar disorder the most promising results have been reported for *CACNA1C* and *ANK3* (ankyrin 3, node of Ranvier) [3-5]. Subsequently *CACNA1C* and *ZNF804A* were proposed as common risk variants for both bipolar disorder

and schizophrenia and a Meta-analysis additionally added the *MHC*-locus as a common risk factor for both diseases [5].

ANK3 at 10q21.2 consists of 44 exons spanning ~700 kb on genomic DNA with multiple splicing variants. A GWA study based on pooled DNA found association with bipolar disorder and rs9804190 located intronic between exon 36 and 37 at the locus *ANK3* [6]. A Meta-analysis of GWA on bipolar patients with European ancestry reported an additional marker rs10994336, about 340 kb distal to rs9804190, at the 3-UTR of *ANK3* [7]. Further analysis suggested that each variant might contribute independently to bipolar disorder [8]. A further SNP located 3-UTR showed suggestive evidence of genome-wide association in a Han Chinese sample [9]. Subsequent studies found a genetic marker at *ANK3* to be associated with schizophrenia as well. Analysis in a GWA study of a Norwegian discovery sample with a large European replication sample reported association of rs10761482 located near 3-UTR between exon

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41 and 42 with disease at a distance of 84.5 kb to rs9804190 [10].

Ankyrin 3 is a brain expressed member of a protein-family linking the integral membrane proteins to the underlying spectrin-actin cytoskeleton. The gene product Ankyrin-G of 4377 amino acids locates on axonal initial segment and at nodes of Ranvier in the central and peripheral neurons. Ankyrin-G is proposed to play a regulatory role on sodium channel function, cell adhesion and neuronal development [11-16]. A post mortem study reported reduced immunoreactive of Ankyrin-G in pyramidal neurons in the superficial cortical layer of the dorsolateral prefrontal cortex in subjects with schizophrenia [17].

Within the debate on common susceptibility genes for schizophrenia and bipolar disorder we attempted to replicate common findings of a genetic association for different disease entities by analyzing association of *ANK3* with major psychosis in a case-control study with SNPs rs9804190, rs10994336, and rs10761482. For diagnosis we used beside ICD10 Leonhard's classification separating disease entities with specific combination of bipolar and psychotic syndromes [18].

Karl Leonhard divides psychoses into five main groups, systematic schizophrenias, unsystematic schizophrenias and cycloid psychoses. Affective psychoses are subdivided into bipolar manic depression and monopolar depression. In family and twin studies based on Leonhard's classification, a different genetic background for each diagnostic category was demonstrated [19]

Methods

Index cases were recruited from the Department of Psychiatry, Psychosomatics and Psychotherapy at of the University of Würzburg. The sample encompassed 920 cases (631 males, 68%) with psychosis according to ICD10 for schizophrenia or related diseases with an average age at onset of 26.5 years and an average age at recruitment of 41 years including 182 cases with schizoaffective disorder (ICD10 F20-F25). 400 cases (231 males, 58%) with bipolar disorder (F30-F31) with an average age at onset of 32 years and an average age at recruitment of 42.5 years and 220 cases (134 males, 61%) with unipolar depression (F32-F33). with an average age at onset of 43 years and an average age at recruitment of 51 years.

Sample was further subdivided according to Leonhard's classification systematic schizophrenias (n = 228), unsystematic schizophrenias (n = 635), cycloid psychosis (n = 309), manic depression (n = 284) and monopolar depression (n = 90) [17]. Diagnosis in differentiated psychopathology was made by repeated personal examinations of experienced psychiatrists (BP, MG, GS).

The 480 volunteer control subjects (283 males, 59%) were recruited from the blood donor centre at the University of Würzburg. The average age of recruitment was 29 years. The preponderance of males in both samples avoided gender distortion in comparison of cases and controls. All subjects were unrelated and of German Caucasian descent. The Ethics Committee of the University of Würzburg had approved the study, and written informed consent was obtained from all subjects.

PCR for allelic discrimination was performed in a final reaction volume of 20 μ l containing 20 ng genomic DNA and 10 μ l of 2 \times TaqMan[®] Universal PCR Master Mix (Applied Biosystems) and 1 μ l of 20 \times TaqMan[™] SNP genotyping assay including fluorescent tags specific for the wild type allele and the variant allele. Marker amplification was performed in microtiter plates on Biometra thermocyclers (Whatman). PCR amplification conditions were according to the manufacturer's recommendation [10 min at 95°C followed by 15 sec at 92°C and 60 sec at 60°C for 40 cycles]. Allelic discrimination with endpoint detection of fluorescence was performed at 60°C on an ABI prism 7000 sequence detection system followed by analysis with an appropriate software package (Applied Biosystems). All genotype experiments were made at least in duplicate, with quality control of automated allele calling by two independent operators blind to phenotype. The calling rate was 99%.

Software FAMHAP was used to test for association [20]. Hardy-Weinberg equilibrium (HWE) and pairwise standardized linkage disequilibrium (LD) were calculated with the program HAPLOVIEW [21]. The software "stastical power calculator" was used analyzing power for association test [22].

Results

Corresponding to HAPMAP data rs9804190 locates between LD-block 7 and 8, rs10761482 in LD-block 26 and rs10994336 in a downstream LD block of *ANK3*. Thus, linkage disequilibrium (LD) was low between the analyzed markers with LD' 0.018 between rs9804190 and rs10761482, 0.0060 between rs9804190 and rs10994336 and 0.72 between rs10761482 and rs10994336 located at 3'-UTR. All SNPs were in HWE.

Analyzing Allele and genotype frequencies in cases according to the ICD 10 classification with schizophrenia, bipolar disorder or major depression revealed no association for SNPs rs9804190 and rs10994336, (table 1 and 2). We observed no significant difference between cases and controls for subgroup with schizoaffective disorder. SNP rs10761482 was associated with bipolar disorder (p = 0.015, OR 1.304, CI 1.065 - 1.595) but not with schizophrenia, nor with subgroup schizoaffective disorder nor with unipolar depression (table 1 and 2).

Table 1 Bipolar disorder according to ICD10: Genotype distribution and test for association

SNP	Cases	Controls	Cases	Controls	P	Cases	Controls	P	Cases	Controls	P
	n	n	CC	CC		CT	CT		TT	TT	
rs9804190 (C/T)	400	480	0.618	0.578	0.237	0.327	0.380	0.101	0.056	0.042	0.337
rs10994336 (C/T)	400	480	0.843	0.874	0.182	0.154	0.119	0.13	0.003	0.006	0.415
rs10761482 (C/T)	400	480	0.652	0.572	0.015	0.300	0.359	0.063	0.048	0.069	0.19

P: test for association (FAMHAP); CC, CT, TT: genotypes

Sample was further differentiated according to Leonhard's classification. Analyzing association of SNPs with schizophrenic spectrum divided into subgroups systematic schizophrenias, unsystematic schizophrenias and cycloid psychosis provided no significance. Likewise affective diseases with manic depression and monopolar depression reached no significant association.

Analyzing haplotype with FAMHAP provided no further risks haplotype concordant with observed low LD.

Our study population with 1540 cases and 480 controls had a power of 55.1% to replicate the reported association with bipolar disorder and of 69.1% with schizophrenia (alpha = 0.05%).

Discussion

Common susceptibility genes for schizophrenia and bipolar disorder challenge traditional diagnostic categories and boundaries between schizophrenia and bipolar disorder. We attempt to replicate genetic association findings of *ANK3* as a possible common risk factor for schizophrenia and affective disorders in a case control study of > 2000 subjects of German descent. Analysis of previous associated SNPs in different LD-Blocks, located intronic (rs9804190 and rs10761482) or 30 kb downstream of *ANK3* (rs10994336) found a nominally significant association of SNP rs10761482 with bipolar disorder (p = 0.015, OR 1.304) but not with schizophrenia (table 1 and 2). Thus, association of this marker with schizophrenia in a GWA analysis of European samples could not be confirmed [16].

We failed to confirm an association of rs9804190 and rs10994336 with bipolar disorder reported in two previous GWA studies. We found no association with unipolar depression or schizophrenia including subgroup of schizoaffective disorder (table 1 and 2) [13,14]. Analyzing

haplotype provided no further risks haplotype concordant with observed low LD between the markers.

Our failure to replicate previous findings could be due to insufficient sample size. The study had a power of 55.1% to replicate reported association with bipolar disorder and of 69.1% with schizophrenia (alpha = 0.05%) [14,16]. However, in our study were cases and controls of the same genetic background, minimizing a distortion regarding genetic heterogeneity. The strength of our strategy is the combination of operational diagnostic criteria (ICD-10) and Leonhard's categorical diagnostic approach. In search for common risk factors for schizophrenia and bipolar disorder we found no association in the schizophrenic spectrum neither with systematic schizophrenias nor with subgroups with a specific combination of bipolar and psychotic syndromes: Particularly the unsystematic schizophrenias and strictly defined manic depression with strong genetic background [19,23,24]. Other disease entities according to Leonhard's classification were not associated to any of the markers.

Our data support findings from two meta-analyses of GWA-studies searching for common risk variants in *ANK3* for schizophrenia, bipolar disorder or unipolar depression: One study combining Meta-analysis and additional genotyping of a bipolar and unipolar sample from the US, the UK, Ireland, and Netherlands, found no association of variants in *ANK3* and unipolar depression. Another Meta-analysis on GWA studies based on schizophrenia and bipolar disorder cohorts with samples from UK observed no significant results for schizophrenia. Both Meta-analyses suggested a specific effect of *ANK3* for bipolar disorder [25,5].

Since genetically associated SNPs around *ANK3* are intronic or in downstream regions located, causative coding variants or associated haplotype blocks are still

Table 2 Schizophrenia according to ICD10: Genotype distribution and test for association

SNP	Cases	Controls	Cases	Controls	P	Cases	Controls	P	Cases	Controls	P
	n	n	CC	CC		CT	CT		TT	TT	
rs9804190 (C/T)	920	480	0.577	0.578	0.949	0.369	0.380	0.674	0.055	0.042	0.284
rs10994336 (C/T)	920	480	0.884	0.874	0.617	0.112	0.119	0.689	0.004	0.006	0.62
rs10761482 (C/T)	920	480	0.557	0.572	0.593	0.394	0.359	0.196	0.048	0.069	0.113

P: test for association (FAMHAP); CC, CT, TT: genotypes

missing. Regard distorted gene regulation as patho-physiological causative factor a recent study reported evidence for cis-acting regulation of *ANK3* by testing for allelic expression imbalance, but the study failed to attribute dysregulation to risk-associated SNPs [26].

Conclusions

In conclusion, our results support a genetic contribution of *ANK3* to ICD 10 bipolar disorder, though we failed to replicate findings for schizophrenia according to ICD 10 or Leonhard's classification. Our study cannot confirm *ANK3* as a common risk factor for both diseases, challenging the hypothesis that bipolar disorder and schizophrenia are just different phenotypes of the same disease.

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Authors' contributions

AG and MS performed the experiments and drafted the manuscript, ND and GS conceived the study and participated in the coordination. BP and GS carried out the diagnostic evaluation of the patients; MG carried out the statistical analyses, coordinated the study and wrote the manuscript. All authors read and approved the final manuscript.

Authors' information

To our deep regret Professor Núria Durany passed away on August 27th 2010 after an intense but short fighting an illness. We shall continue to cherish her passion for science.

Competing interests

The authors declare that they have no competing interests.

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