Article

G72 and Its Association With Major Depression and Neuroticism in Large Population-Based Groups From Germany

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Objective: *G72* is among the most frequently replicated vulnerability genes for schizophrenia and bipolar disorder. The authors previously found identical haplotypes of markers M23 and M24 to be associated with schizophrenia, bipolar disorder, and panic disorder. Given both the well-recognized familial clustering across these disorders and recent linkage findings implicating the region harboring *G72* in the etiology of major depression and panic disorder, we can hypothesize that *G72* should also be involved in the etiology of major depression. Neuroticism, measuring trait anxiety, may be the endophenotypic link underlying genetic associations with *G72* across diagnostic boundaries. The authors tested whether the previously observed risk haplotypes are also associated with major depression and neuroticism.

Method: The authors performed a standard haplotype analysis in a group of 500 major depression patients and 1,030 population-based comparison subjects. The authors also performed an exploratory analysis on 10 additional *G72* markers using a novel haplotype-sharing approach. They performed a quantitative trait haplotype analysis in an independent group of 907 individuals phenotyped for neuroticism.

Results: The previously identified M23-M24 risk haplotype was significantly associated with major depression and high levels of neuroticism. The haplotype-sharing analysis also implicated the same region, whereas more proximal markers showed no association with major depression.

Conclusions: This is the first study to the authors' knowledge to implicate the *G72* locus in the etiology of major depression and neuroticism. The results strengthen the notion of a genetic overlap between diagnoses, commonly conceptualized as distinct entities. Neuroticism may constitute the common underlying endophenotypic link.

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Since the initial report by Chumakov et al. (1) of an association between markers at the *G72* locus and schizophrenia in samples from Russia and Canada and subsequent reports by Hattori et al. (2), Chen et al. (3), and Schumacher et al. (4) showing association between this locus and bipolar disorder in samples from the United States and Germany, this locus has become the focus of increased attention in psychiatric genetic research. A recent meta-analysis by Detera-Wadleigh and McMahon (5) concluded that the association findings between *G72* and both schizophrenia and bipolar disorder are "among the most compelling in psychiatry" despite the fact that associated alleles and haplotypes are not identical across studies and functional variants remain to be demonstrated. Findings are not limited to a specific population, being observed in European, North American, Han Chinese, and Ashkenazi samples, with few studies reporting nonassociations (5–9). Our group reported association of identical *G72* haplotypes with both schizophrenia and bipolar disorder in the German population (4). In line with findings from other groups on *G72*, our findings support the notion of a genetic overlap across major psychiatric diagnoses. Such a genetic overlap has also been suggested by studies of *DTNBP1* (dysbindin), *COMT, BDNF, DISC1*, and *NRG1* (10–17).

Although there is now increasing support for the *G72* locus as a susceptibility gene for schizophrenia and bipolar

disorder (15–18) as well as evidence for an etiological role in panic disorder (19), a potential association with major depression still needs to be assessed, in particular given the well-established familial clustering of major depression, schizophrenia, bipolar disorder, and anxiety disorders (20–22). Moreover, a large multicenter study provided evidence of linkage between major depression and a locus on 13q31.1–q31.3 (76.1–92.6 megabases on National Center for Biotechnology Information build 35), thus lying in the vicinity of *G72* (104.9 megabases on National Center for Biotechnology Information build 35; reference 23).

To pursue this issue, we undertook a two-tiered design. First, we tested whether the previously identified susceptibility haplotypes for schizophrenia, bipolar disorder, and panic disorder, i.e., the M23-M24 haplotypes C-T and T-A, were also associated with major depression with a group of 500 major depression patients and 1,030 population-based comparison subjects from Germany, all of German descent. Second, in addition to standard haplotype analyses focusing on the previously reported haplotypes, we also conducted an exploratory analysis with an additional 10 single nucleotide polymorphisms (SNPs) and a novel haplotype-sharing approach. This step was performed in order to obtain a complete overview of the contribution of genetic variability at the *G72* locus to major depression.

Finally, in order to facilitate a better understanding of why susceptibility genes such as *G72* are consistently found associated across diagnostic boundaries, we took our analysis a step further by studying a potential association between the same susceptibility haplotypes and neuroticism in 907 individuals from the general population. The rationale for this approach is based on the large body of evidence that neuroticism can be considered a predictor and potential endophenotype for several psychiatric disorders, including major depression and schizophrenia (24–28) and, on the other hand, follows from our previously formulated hypothesis that the association between *G72* and major psychiatric phenotypes may be due to an association with an underlying trait of anxiety (29).

Method

Groups, Recruitment, and Phenotype Characterization Procedures

Cases were recruited from consecutive admissions to the inpatient units of the Department of Psychiatry and Psychotherapy of the University of Bonn, Germany. DSM-IV lifetime diagnoses of major depression were made by a consensus best-estimate procedure (30), based on all available information, including a structured interview (the Structured Clinical Interview for DSM-IV [31]), medical records, and the family history method. We also used the OPCRIT (32) system to obtain detailed polydiagnostic documentation of symptoms. The details of our recruitment and phenotype characterization procedures are outlined elsewhere (33, 34).

For the analyses, we included 500 major depression patients, 178 men (36%) and 322 women (64%). As regards the clinical manifestation, 124 were diagnosed with single episode of major depression and 376 with a recurrent major depression. Four hundred patients (80.0%) had a melancholic subtype. As regards a positive family history in first- or second-degree relatives, 69 (13.8%) patients had a family history of major depression, five (1.0%) had a family history of bipolar disorder, and 16 (3.2%) had a family history of schizophrenia. The mean (SD) age at assessment was 47.9 (SD=13.8) years; the mean (SD) age at onset was 36.9 (SD=13.3) years, age at onset being defined as the time at which criteria for a DSM-IV major depression were met for the first time.

The population-based comparison group was established with the support of the local census bureau of the city of Bonn, Germany (North Rhine-Westphalia). For the analyses, we included 1,030 (499 men, 531 women) individuals; the mean (SD) age at assessment was 47.9 (SD=15.5) years. This group was established within the framework of the German National Genome Research Network I (Nationales Genomforschungsnetz I, www.ngfn.de) of the Federal Ministry of Education and Research (www.bmbf.de) between 2000 and 2003 to serve as an epidemiological comparison group for complex genetic studies within the NGFN.

All comparison subjects were seen by a trained psychiatrist and screened for psychiatric disorders, as described previously (34). From the 1,030 individuals, 133 (13%) had a history of major depression, one (0.09%) of schizophrenia, four (0.4%) of bipolar disorder, and 14 (1.3%) of anxiety disorder. To maintain the character of an epidemiological community group and minimize type II errors, we opted to keep all 1,030 individuals as comparison individuals in our primary analysis. All cases and the comparison individuals were of German descent, which, in our study, is fulfilled when an individual's parents originate from Germany and when there is no indication that one of the four grandparents may originate from outside of Germany.

General Population-Based Group for the Study of Neuroticism

We recruited 907 people (430 men, 477 women; mean age=28.8 years, SD=11.3) from the general population of the Rhineland region at three research centers (Aachen, Trier, and Mannheim). Neuroticism scores were obtained with the established and widely used NEO-FFI questionnaire (35). Neuroticism scores were transformed to follow a normal distribution with a mean value of 100 and an SD of 10.

Ethical Considerations

Protocols and procedures were approved by the institutional review boards (*Ethikkommission*) of the respective academic institutions. After complete description of the study to the subjects, written informed consent was obtained.

Genotyping

Major depression cases and comparison subjects were genotyped for 12 *G72* SNPs (Table 1) with the MassARRAY system (Sequenom Inc., San Diego). The two markers M23 and M24 were the subject of our primary analysis testing the specific hypothesis that their two-marker haplotypes, C-T and T-A, were associated with major depression. The remaining 10 SNPs were analyzed within our exploratory analyses as described below. Of these, SNPs M12 through rs1935062, M21, and M22 were chosen on the basis of previously reported association findings (5). DAO_3UTR_SNP12 was only very recently found to be associated with bipolar disorder and major mood episodes in schizophrenia by Williams et al. (14). Marker G72_z6:1117 was identified by resequencing in our laboratory. Overall, the 12 markers cover a ~95 kilobase region, including the 5′ and 3′ flanking regions of the *G72* locus, constituting the region of interest for linkage disequilibrium mapping (5). Genotyping completeness ranged from 96.3% (marker rs1935062) to 99.1%

TABLE 1. Single Nucleotide Polymorphisms (SNPs) Genotyped in our Groups: SNP Identifications, Physical Position, and Intermarker Distance (kilobases)[a]

Number	dbSNP Identification Number	Trivial Name	Position (base pair)	Alleles	Intermarker Distance (kilobases)	Minor Allele Frequency in Cases Versus Comparison Subjects
1	rs3916965	M12	104901361	C/T		T allele: 0.364 versus 0.404
					7.9	
2	rs1935058	—	104909351	A/G		G allele: 0.426 versus 0.454
					4.2	
3	rs1341402	—	104913510	C/T		C allele: 0.213 versus 0.219
					1.8	
4	rs3916967	M14	104915349	C/T		C allele: 0.364 versus 0.402
					2.1	
5	rs2391191	M15	104917447	A/G		A allele: 0.372 versus 0.404
					8.7	
6	rs1935062	—	104926137	A/C		C allele: 0.321 versus 0.357
					1.4	
7	—	DAO_3UTR_SNP12	104927538	A/C		A allele: 0.334 versus 0.323
					32.4	
8	rs3916971	M21	104960002	C/T		T allele: 0.439 versus 0.426
					7.2	
9	rs778293	M22	104967200	C/T		C allele: 0.428 versus 0.384
					6.8	
10	—	G72_z6:1117	104973980	C/T		C allele: 0.051 versus 0.047
					9.8	
11	rs3918342	M23	104983750	C/T		C allele: 0.527 versus 0.495
					12.5	
12	rs1421292	M24	104996236	A/T		A allele: 0.446 versus 0.482

[a] Base pair positions are all based on the May 2004 human reference sequence (NCBI build 35).

(marker rs1421292/M24). The group studied for neuroticism was only typed for markers M23 and M24.

For quality comparison purposes, we genotyped a subset of the group in duplicate in order to estimate the replicate error rate. Two of 96 DNA samples were randomly chosen for this purpose. For the SNPs genotyped in the course of this study, all genotypes between duplicates were consistent (0% replicate error rate). Apart from that, positive and negative controls are always included routinely in our genotyping experiments.

By a standard 1 df chi-square test, there were no significant deviations from Hardy-Weinberg equilibrium for the genotype distributions of the studied groups.

Calculation of Linkage Disequilibrium

Intermarker linkage disequilibrium, as expressed by D′, was calculated and visualized using the Haploview (http://www.broad.mit.edu/mpg/haploview/contact.php; reference 36) software. Linkage disequilibrium was calculated in the comparison group (N=1,030).

Primary Statistical Analysis on Major Depression

Case-control haplotype analyses for the two-marker haplotype, consisting of markers M23 and M24, were performed with version 3.0 of the widely used program UNPHASED (http://www.mrc-bsu.cam.ac.uk/personal/frank/software/#software; reference 37). Using a standard unconditional logistic regression, UNPHASED performs likelihood ratio tests under a log-linear model of the probability that a haplotype belongs to a case rather than a comparison subject; the expectation-maximization algorithm is used to resolve uncertain haplotypes and provide maximum-likelihood estimates of frequencies. Based on our previous findings in schizophrenia, bipolar disorder, and panic disorder (4, 19), we specifically tested the M23-M24 haplotypes C-T and T-A. Empirical p values were established by performing 10,000 permutations.

Secondary Statistical Analysis on Major Depression

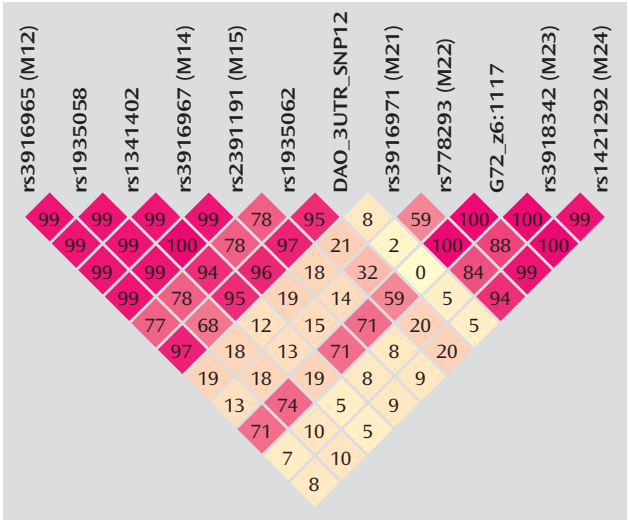
Three exploratory analyses were carried out: first, we tested whether we would obtain similar results for the M23-M24 haplotypes when the comparison group was restricted to the 871 individuals from the community group without a lifetime history of a psychotic, affective, or anxiety disorder. Second, we tested whether confining case definition to recurrent major depression (N=376) would yield a similar effect. Third, we wanted to obtain a more comprehensive overview of the contribution of genetic variability in the *G72* region to major depression, besides the specific analysis of the region captured by markers M23 and M24. To achieve this, we opted for a novel haplotype-sharing method (38) in order to exhaust the joint information conferred by all the markers in the critical region.

Haplotype-sharing analysis is based on the assumption that, in the neighborhood of a genetic susceptibility variant, haplotypes carrying this variant ("case" haplotypes) are more related than haplotypes not carrying the mutation ("random" or "comparison" haplotypes) and that the time to the most recent common ancestor is shorter among case haplotypes than among random haplotypes. It is thus expected that case haplotypes share significantly longer stretches of DNA "identical by descent" around the variant because of fewer recombinational and mutational events (39–42). Haplotype-sharing analysis was first successfully applied in the study of monogenic disease (41, 42). In the last decade, it has furthermore become an established method in the analysis of complex disorders (39, 43–49). Here, we have applied the approach of Mantel's statistics for space-time clustering (50) to correlate genetic and phenotypic similarity, as developed by Beckmann et al. (38):

$$M^{\circ}(x) = \sum_{i<j} L_{ij^{(x)}} Y_{s_i s_j}$$

where x denotes a putative disease locus and i and j are haplotypes. The sum is over all pairwise comparisons of haplotypes. The genetic similarity, $L_{ij(x)}$, is measured as the number of intervals surrounding x flanked by markers identical by state (haplotype sharing). Y_{sisj} denotes the phenotypic similarity of the individuals s_i and s_j and is defined as the mean-corrected product $Y_{sisj}=(y_{si}-\mu_y)(y_{sj}-\mu_y)$, where μ_y denotes the sample mean and y_{si} and y_{sj} the disease status of s_i and s_j. In the case-control scenario, y_{si} is 1 if s_i is affected and 0 if s_i is a comparison individual. Thus,

FIGURE 1. Linkage Disequilibrium Plot of 12 Single Nucleotide Polymorphisms Tested in the Comparison Group[a]



[a] The value of intermarker linkage disequilibrium for any given pair of markers (also see Table 1) is given in the respective square. A two-digit value, e.g., 97, stands for a D′ value of 0.97; a value of 2 for 0.02, and 100 stands for a value of 1.00. High levels of linkage disequilibrium are represented by red coloring, with decreasing color intensity representing lower levels of linkage disequilibrium.

the Mantel statistics contrast between the pairwise comparisons of cases versus cases, cases versus comparison subjects, and comparison subjects versus comparison subjects. The statistical significance is evaluated by a Monte Carlo permutation in which the phenotype *Y* is permuted randomly over the individuals, while keeping together the two haplotypes derived from the same individual. Although the Mantel statistics use the information of multilocus haplotypes, they are pointwise statistics. The Mantel statistics have been applied in the software TOMCAT (www.dkfz.de/en/klepidemiologie/software/software.html). For this analysis, individual haplotype pairs were estimated with the software FASTPHASE (51).

Correction for Multiple Testing in the Haplotype-Sharing Analysis

To correct for multiple testing in the exploratory haplotype-sharing analysis, a step-down min-p algorithm was used to adjust the p values according to the number of tests, i.e., the number of SNPs. This algorithm has been described in detail by Obreiter et al. (52) and has been implemented in the software program SDMinP (52). SDMinP is suited for the fast calculation of empirical and adjusted p values for correlated and uncorrelated hypotheses in multiple testing experiments. It is based on the free step-down resampling method for controlling the familywise error rate.

Quantitative Trait Association Study of Neuroticism

In analogy to the case-control study on major depression, association between neuroticism and the M23-M24 haplotypes C-T and T-A was tested using UNPHASED version 3.0 (37).

Post Hoc Power Analyses

Power analyses for the case-control analysis on major depression were performed with the Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/; reference 53). Power estimates are based on a marker allele frequency of 0.5 (e.g., reflecting the frequencies of the M23-M24 haplotypes) and an alpha level of 5%. Power was calculated both under an additive and a multiplicative model, assuming varying degrees of genotype relative risk. We furthermore assumed a risk allele frequency of 0.5 and complete linkage disequilibrium (D′=1) between marker and risk allele. Power was also estimated expressing the genetic effect size as an odds ratio with the PS Power and Sample Size Calculations suite of programs (http://www.mc.vanderbilt.edu/prevmed/ps/index.htm; reference 54). The genetic power calculator (53) was also used to determine the power for the quantitative trait analysis on neuroticism. We estimated power for total quantitative trait locus variances of 1%, 2%, and 3% and no dominance variance. We furthermore assumed a quantitative trait locus increaser allele frequency of 0.5 and complete linkage disequilibrium (D′=1) between marker and quantitative trait locus increaser allele.

Results

Patterns of Linkage Disequilibrium

Altogether, 12 *G72* markers were studied (rs numbers, trivial names, and physical positions are presented in Table 1). The patterns of intermarker linkage disequilibrium are as depicted in Figure 1. Patterns of linkage disequilibrium (expressed in D′) are similar to the patterns in a trio sample of European origin from the HapMap data (5) and a sample from the United Kingdom (14). The linkage disequilibrium structure is characterized by two blocks of high linkage disequilibrium between markers M12 and DAO_3UTR_SNP12 and between markers M22 and M24, respectively, with marker M21 mapping to a region of low linkage disequilibrium.

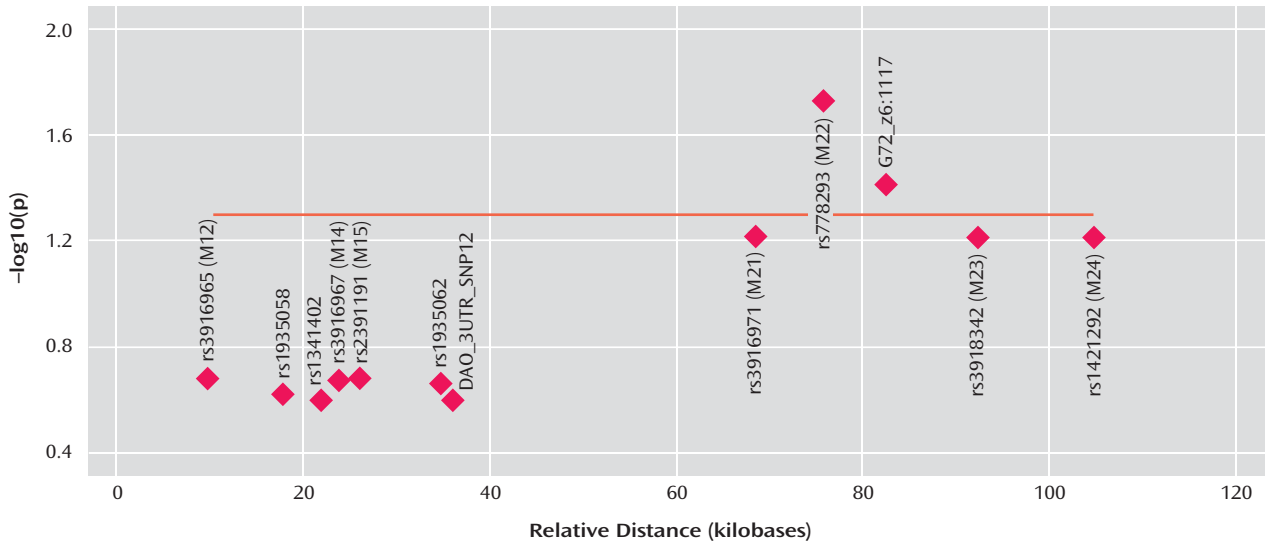
Primary Statistical Analysis: Case-Control Study of Major Depression

Cases and comparison subjects were assessed for a potential differential distribution of the C-T and the T-A haplotypes. C-T was more frequent in cases than in comparison subjects (53.1% versus 49.4%), whereas the T-A haplotype was less frequent in cases than in comparison subjects (43.8% versus 48.1%), conferring an odds ratio of 1.18, (95% confidence interval [CI]=1.01–1.38, p=0.04, permuted p<0.05). Given that the gender ratios differed between major depression cases and comparison subjects, we further tested for a differential haplotype distribution between men and women in the combined group of cases and comparison subjects; this was not the case (p=0.64). Thus, our result is unlikely to be due to stratification by gender. Individual allele frequency differences between cases and comparison subjects are given in Table 1.

Secondary Statistical Analysis

Community comparison group. When the aforementioned case-control analysis was performed with only the 871 community comparison individuals without a lifetime history for a psychotic, affective, or anxiety disorder, the results remained virtually unchanged: comparison of major depression cases with comparison subjects also showed a differential distribution of the M23-M24 haplotypes. The C-T haplotype was more frequent in cases than in comparison subjects (53.1% versus 49.5%), whereas the T-A haplo-

FIGURE 2. Results of the Haplotype-Sharing Analysis on Major Depression[a]



[a] The pointwise p values obtained from the haplotype-sharing analyses and corrected for multiple testing are plotted. Empirical p values were derived by 10,000 Monte Carlo permutations. From left to right, the diamonds represent the 12 markers as listed in Table 1. Corrected p values are plotted in logarithmic transformation and correct relative physical marker positions are given. The horizontal line indicates a nominal level of significance (p=0.05).

type was less frequent in cases than in comparison subjects (43.8% versus 48.2%). The associated odds ratio was 1.18 (95% CI=1.01–1.38). Owing to the 25% smaller size of the comparison group, the observed p value is slightly larger than for the primary analysis comprising the full set of comparison subjects (p<0.05, permuted p=0.053).

Case definition confined to recurrent major depression. Similar to the aforementioned secondary analysis, the decrease in group size, from 500 to 376 cases, also led to an increase in the observed significance level: the C-T haplotype was more frequent in cases than in comparison subjects (52% versus 49.4%), whereas the T-A haplotype was less frequent in cases than in comparison subjects (44.8% versus 48.1%). The associated odds ratio was 1.14 (95% CI=0.96–1.35, p=0.15, permuted p=0.16).

Haplotype sharing. Guided by the linkage disequilibrium structure of the locus and the physical intermarker distances, haplotype sharing was not evaluated for the complete 94.8 kilobase range defined by all 12 markers but separately for intervals described by markers M12 through DAO_3UTR_SNP12 and M21 through M24. Correction for multiple testing was based on these intervals.

Markers M21, M23, and M24 (p=0.06 for all) fell short of nominal levels of significance. The neighboring markers M22, p=0.02) and G72_z6:1117 (p=0.04) were significantly associated with major depression. The proximal markers (M12 through DAO_3UTR_SNP12) showed no association at all. All p values have been adjusted for multiple testing, as described (Figure 2).

Quantitative Trait Association Study of Neuroticism

A significant association was observed between neuroticism and the tested M23-M24 haplotypes. C-T was significantly associated with higher neuroticism scores than T-A (p<0.02, permuted p<0.02). The additive value of C-T versus T-A, i.e., the change in expected mean trait value due to this haplotype, was 0.95.

Post Hoc Power Analyses

Detailed power estimates for the case-control analysis on major depression are presented in Table 2. In summary, our group of 500 cases and 1,030 comparison subjects had sufficient power (>0.8) to detect an effect at a genotype relative risk or odds ratio of 1.3 or larger. For the quantitative trait analysis on neuroticism, power estimates were as follows: assuming total QTL variances of 1%, 2%, and 3%, power estimates were 0.67, 0.92, and 0.99, respectively.

Discussion

Since its initial description (1), the *G72* locus has become one of the most frequently replicated susceptibility genes for both schizophrenia and bipolar disorder (5, 16–19). In our previous work, we found identical *G72* alleles and haplotypes to be associated with schizophrenia, bipolar disorder, and panic disorder in independent samples from Germany (4, 19). Thus, we demonstrated for the first time the involvement of *G72* variants in three distinct clinical diagnoses.

Familial clustering across mood, anxiety, and psychotic disorders is a well-established finding in psychiatry (20–

TABLE 2. Power Estimates for the Case-Control Analysis of Major Depression

Expression of Genetic Effect Size	Power	
Genotype relative risk		
	Model	
	Additive	Multiplicative
1.1	0.22	0.24
1.2	0.58	0.66
1.3	0.85	0.92
1.4	0.96	0.99
1.5	0.99	1.00
Odds ratio		
	Test statistics	
	Chi-square test	Fisher's exact test
1.1	0.23	0.22
1.2	0.66	0.64
1.3	0.92	0.92
1.4	0.99	0.99
1.5	1.00	1.00

22). Findings from a large multicenter study provided evidence of linkage between major depression and a locus on 13q in proximity to *G72* (23). Furthermore, 13q has also been implicated in the etiology of panic disorder (55). This prompted us to test whether *G72* was also involved in the etiology of major depression with a two-tiered design. Our primary analysis tested the specific hypothesis that the M23-M24 haploytpes C-T and T-A that we had previously found associated with schizophrenia, bipolar disorder, and panic disorder were also associated with major depression. With a large group of patients with major depression, we were able to identify an association between major depression and the M23-M24 haplotypes C-T and T-A, with C-T being more frequent and T-A being less frequent in cases. This finding was furthermore corroborated by the haplotype-sharing analysis, implicating an involvement of the distal region of *G72* in the etiology of major depression, with markers M22 and G72_z6:117 reaching significance after correction for multiple testing. Markers M23 and M24 did not reach significance (p=0.06) after correction.

The fact that the standard haplotype analysis with UNPHASED and the haplotype-sharing analysis do not completely overlap in their results illustrates that these two approaches are fairly independent from each other because haplotype information is considered in different ways. At every marker position, the Mantel statistic tests whether there is an excess of sharing between case and comparison haplotypes around this SNP. Thus, it is a pointwise test taking into account the information of haplotypes to calculate the shared length as a measure of similarity. In contrast, UNPHASED tests for differences in haplotype frequencies between cases and comparison subjects in a logistic regression framework. However, given that the two identified sets of SNPs (haplotype-sharing analysis: M22 and G72_z6:1117; standard haplotype analysis: M23 and M24) are very close to each other, i.e., less than 10 kilobases, one can assume that both methods do identify the same region. The difference between the two approaches also explains why the haplotype-sharing analysis may highlight an SNP showing similar allele frequencies for cases and comparison subjects. The selection of the 12 *G72* markers was not based on a systematic HapMap-based coverage of the region, but rather, we took into account the comprehensive association findings at the *G72* locus and investigated the potential effect of those markers that had shown the most promising results with psychiatric phenotypes in previous studies.

Taking the results of the present study and the findings from our previous studies, there is now evidence for an association of *G72* with four major diagnostic entities: schizophrenia, bipolar disorder, panic disorder, and major depression. These association findings were obtained for *identical* haplotypes, i.e., the T-A and the C-T haplotypes of markers M23 and M24, in one of the largest sample collections worldwide, including more than 3,000 individuals from German and Polish populations (4, 19, 29).

The association between this locus and major psychiatric disorder is still surrounded by some important caveats, however, given that the association findings with schizophrenia and bipolar disorder and with specific subtypes, e.g., schizophrenia with mood episodes or bipolar disorder with psychotic features (14, 29), have been obtained with different alleles, even in similarly sized and phenotyped samples of European origin, which may be due to a variety of reasons, ranging from so far undetected ethnic stratification to complex expression control (5, 56, 57). We therefore acknowledge that evidence remains that other *G72* variants play an etiological role. However, since this situation is not unique to *G72* but also affects other vulnerability genes for psychiatric disorders such as dysbindin (58), we and others (M. O'Donovan and N. Craddock, American College of Neuropsychopharmacology meeting, December 2006) believe that it should not prevent further research in these loci, in particular, as the situation of different alleles being associated across studies may be consistent with so far undetected locus-locus interactions and subtle differences in the linkage disequilibrium structure (59). In contrast, we strongly advocate the continuation of this line of research. Identifying the functional variants of *G72* and other vulnerability genes will necessitate the refinement of both psychiatric phenotypes and molecular genetic research techniques. This line of research should be accompanied by further studies on the biological relevance of *G72* (1, 60).

We further acknowledge that the genetic effect sizes we obtained for the individual M23-M24 susceptibility haplotypes are very modest. However, these odds ratios are within the range for reported associations with schizophrenia and bipolar disorder (5, 56) and are typical for the situation in complex disorders (61). Moreover, they are consistent with the notion of a polygenic etiology of complex disorders, such as psychiatric phenotypes, a concept that is gaining increased attention (62–65). For diabetes

Patient Perspective

"Mathilda," a 22-year-old female student with a neuroticism score of 44, is a psychology student in her second year. She lives in a dormitory, has good social contacts, and has been dating her current boyfriend for the last 7 months. Her relationship with her parents and younger brother is good, and she visits them every second month. She has no financial problems, no somatic disorders, and, so far as she is aware, there is no family history of any psychiatric disorder.

She reports that although she knows she has everything and should be happy, she hardly ever is. Since childhood she has worried about almost everything. She has never been able to fully enjoy anything as she always has the fear that things may change. Nothing really tragic has ever happened in her life, but nevertheless (or perhaps on account of this), she always expects that something will go wrong. In school, for example, she envied her classmates their light-heartedness and the ease with which they did things she would never have dared to do. On the other hand, she always had the feeling that others did not really appreciate or understand her. One day she remembers vividly is when, at the age of 16, she gave a presentation about the "free will of human beings" in which she presented her own philosophical ideas, ideas that she hoped might impress her classmates and her teachers. When she realized that neither the students nor the teacher had even tried to understand her sophisticated thoughts, she felt simultaneously hurt, ashamed, and angry. She would like to have had more friends, but she considered most people too superficial and rude. Being a good to excellent student, she was always afraid of failing examinations and was convinced that the teachers who appreciated her would eventually find out that she was not as good as everyone thought. In order to avoid this, she studied much harder than the other students, neglecting everything else. She received excellent grades in high school, which enabled her to study psychology. She and her family were initially very proud of this, but then things started to go wrong. She became increasingly afraid of not being able to compete with her co-students, whom she considered much more intelligent than herself. With the approach of the first examinations, she became even more anxious, nervous, and irritable. She became easily involved in arguments with her friends and suffered from the feeling that nobody really understood, appreciated, or loved her. The arguments with her boyfriend left her feeling desperate; she felt guilty about her exaggerated reproaches as well as lonely and miserable. She became convinced that studying psychology had been the wrong decision and came to the conclusion that it might be better to get pregnant and become a housewife. Her boyfriend then decided to end the relationship, and she developed suicidal ideas. A fellow student finally convinced her to see a psychologist who diagnosed major depression.

Now, 2 years later, she is fine. Her studies are going well, and she has a new boyfriend. Although she has learned to cope with her negative emotions and dysfunctional ideas, she still often feels anxious and is easily overwhelmed by situations that others view as challenges.

(66, 67) and, very recently, for bipolar disorder (68, 69), polygenic etiologies are supported by large-scale genome-wide association studies. In other words, the *G72* risk haplotypes that we have found associated with major depression are not likely to play a major role in the pathophysiology of this disorder when considered alone. However, within the context of a polygenic model, each person's disease risk is influenced by the total burden of risk alleles or haplotypes they carry; taken for themselves alone, these alleles or haplotypes only confer very modest effects. Disease occurs when the burden of alleles or haplotypes crosses some threshold.

The major strength of our study lies in its large group size and robust recruitment and phenotyping procedures. A study with a smaller group size and less stringent methods may have missed the modest effect we describe (34), in particular for an etiologically heterogeneous disorder like major depression (70, 71).

The challenge lying ahead is to dissect this heterogeneity. This will facilitate a better understanding of why susceptibility genes such as *G72* are consistently found associated across diagnostic boundaries. Ideally, one would want to pinpoint an (endo)phenotype linking different diagnostic entities together (72, 73). For the case of *G72*, we could previously show that persecutory delusions constituted the common link between the association findings for schizophrenia and those for bipolar disorder in samples from Germany and Poland (29). Given our *G72* findings on panic disorder, the evidence for linkage between panic disorder and chromosomal region 13q (55), where *G72* resides, and the notion that trait anxiety or worry are important predictors for the development, intensity, and persistence of persecutory delusions (74, 75), we have furthermore advocated that not persecutory delusions per se but rather a trait of anxious affectivity might constitute this common link.

Therefore, in the present study, we set out to test this hypothesis by studying a potential association between *G72* and trait anxiety, i.e., neuroticism. In a large group of 907 individuals from the general population of the Rhineland region, we detected association between the M23-M24 risk haplotypes and neuroticism. In concordance with the findings on schizophrenia, bipolar disorder, panic disorder, and now major depression, in which the C-T haplotype was associated with an *increased* disease risk, the very same haplotype was associated with *higher* levels of neu-

roticism, whereas the T-A haplotype was associated with *lower* levels of neuroticism. Neuroticism has repeatedly been reported as a predictor and potential endophenotype for several psychiatric disorders, including major depression and schizophrenia (24–28).

The observation that identical *G72* haplotypes are not only associated with schizophrenia, bipolar disorder, panic disorder, and major depression but also with the personality dimension neuroticism suggests that *G72* may confer susceptibility to major psychiatric disorders through trait anxiety, which is shared by different diagnostic entities. Although replication of our findings in other samples of different genetic background is clearly needed, we would like to argue the case for a psychiatric genetic research framework that complements disorder-focused genetic association testing by the study of easily measurable intermediate phenotypes, e.g., personality dimensions, in large samples from the general population. Such an approach may further close the sometimes existing gap between disorder-specific genetics and sophisticated neurobiological endophenotypic strategies (76).

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