Evidence that neuroticism is and underlying phenotypic dimension in the association between G72, Schizophrenia, and other psychiatric disorders

Strohmaier J[1], Georgi A[1], Buerger C[1], Schmael C[1], Hoefels C[3], Abou Jamra R[2], Schumacher J[2], Propping P[2], Cichon S[4], Noethen MM[4], Schulze TG[1], Rietschel M[1]

(1) Division of Genetic Epidemiology, Central Institute of Mental Health (ZI), Mannheim, Germany; (2) Institute of Human Genetics, University of Bonn, Germany; (3) Departments of Psychiatry and (4) Genomics, Life & Brain Center, University of Bonn, Germany

Introduction

We previously found the *G72* on chromosome 13q associated with schizophrenia (SZ), bipolar disorder (BD), panic disorder (PD), and major depression (MD)[1,2,3]. The risk haplotype (M23-M24) associated with these disorders occurs at high frequency in the general population. According to the threshold model of psychiatric disorders, the risk haplotype should have an impact on carriers of this variant who do not display the full-fledged phenotype (defined as psychiatric disorder).

To better understand the mechanism of how *G72* acts toward psychopathology, the identification of an underlying endophenotypic personality trait would constitute an important step. In a systematic genotype-phenotype correlation analysis, we were able to show that the association between *G72* risk haplotypes and BD is mainly driven by those cases with a history of persecutory delusions[4]. Persecutory delusions are characterized by the presence of anxiety[5] and are one of the core symptoms of SZ. Given our finding that *G72* is also associated with PD[2], anxiety seems to be a major component of a *G72*-asociated personality trait underlying SCZ, BD, PD, and MD.

Neuroticism is the one personality factor having found to be strongly associated with anxiety. Individuals who score high on neuroticism readily destabilize emotionally and are at increased risk for several psychiatric diseases[6,7]. Several twin studies have shown neuroticism to be strongly heritable with heritability estimates around 0.60[8]. We hypothesized that *G72,* the established susceptibility gene for major psychiatric disorders may also be associated with the personality trait neuroticism in the general population.

Methods

Study sample

We studied a population-based sample of 166 individuals of German descent, (70 males, 96 females; mean age=46, SD=14). Phenotype characterization was based on the NEO-Five-Factor Inventory[9].

Exploratory sample

1105 individuals of German descent (542 males, 562 females; mean age=48, SD=16) were phenotyped based on the Tridimensional Personality Questionnaire (TPQ)[10]. The TPQ does not assess neuroticism, but other related personality dimensions (see below).

NEO-FFI	**Extraversion**	quantity and intensity of interpersonal interactions and positive emotion	
	Agreeableness	orientation toward others, altruistic vs. antagonistic	
	Conscientiousness	organisation, motivation and persistence in achieving goals	
	Neuroticism	tendency to experience negative emotions and cope poorly	
	Openness to experience	appreciation of experience for its own sake	
TPQ	**Novelty Seeking**	**Harm avoidance**	**Reward Dependence**
	Exploratory excitability vs. rigidity	Anticipatory worry vs. optimism	Sentimentality vs. insensitivity
	Impulsiveness vs. reflection	Fear of uncertainty vs. confidence	Attachment vs. detachment
	Extravagance vs. reserve	Shyness vs. gregariousness	Dependence vs. independence
	Disorderliness vs. regimentation		

Genotyping

The two G72 SNP markers M23 (rs3918342) and M24 (rs421292), we previously found associated with SZ, BD, and PD were genotyped using the MassARRAY system (Sequenom, San Diego)[11]. Genotype frequencies were in Hardy-Weinberg equilibrium.

Genetic analyses (Study sample)

The sample was divided into high and low scorers applying a median split. We performed both single-marker and haplotype analyses with the program COCAPHASE 2.40[12].

Exploratory Phenotype-Genotype Association Analysis (Exploratory sample)

Logistic regression analysis with the M23 and M24 genotypes as dependent variables were performed. Genotypes were dichotomized in two categories (i.e. presence of 1 or 2 risk allele(s) vs. no risk allele). The TPQ-scales and respective subscales were entered as explanatory variables in the model, as well as gender and age.

Results

Single-marker analyses (Figure 1) revealed a significant association between high neuroticism scores with the C-allele of marker M23 (OR=1.63, p=.028) and the T-allele of marker M24 (OR=1.62, p=.029), the respective previously identified risk alleles. Permutation showed that a p-value of .028 (i.e. the one observed for M23) would be seen by chance alone in 289 times out of 10,000 replicates, yielding an empirical p*-value of .0289.

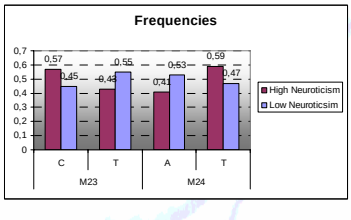

Figure 1: Single-Marker Case-Control Analyses

Haplotype analysis (Figure 2) revealed that the previously reported risk haplotype C-T was more frequent in individuals scoring high on neuroticism (57 vs. 45%; p=0,028). The corresponding risk haplotype T-A was significantly less frequent (42 vs. 53%, p=0.037).

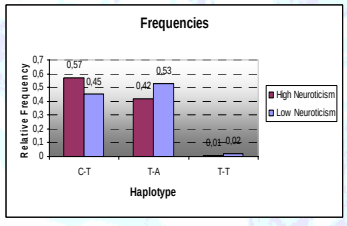

Figure 2: Haplotype Case-Control Analysis

Exploratory analysis (Figure 3). In this analysis, we tested a potential association between *G72* and the TPQ-based personality dimension "novelty seeking" capturing certain aspects of neuroticism. We found that individuals with genotypes carrying the respective previously identified risk alleles, i.e. "C" (M23) and "T" (M24) had significantly higher scores on novelty seeking (p=.031 and p=.013) and its subscale "exploratory excitability vs. stoic rigidity" (p=.048 and p=.046) than non-carriers of the alleles. There were no associations with harm avoidance and reward dependence (and respective subscales).

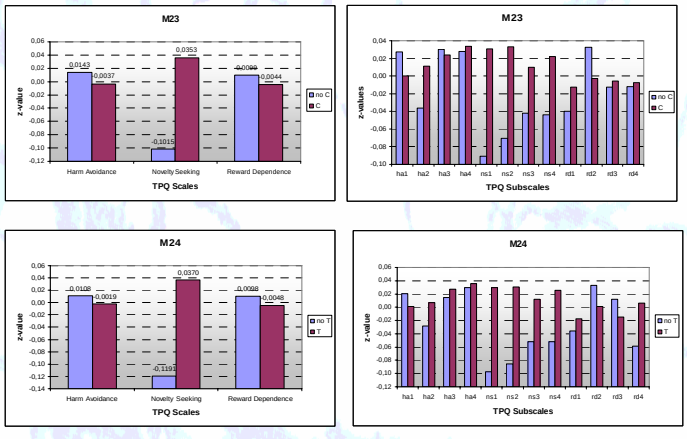

Figure 3: Logistic regression analyses (TPQ)

Summary & Discussion

Association of a single specific haplotype (M23-M24) across different psychiatric diagnostic categories raises the possibility that a phenotype dimension exists which is common to all diseases associated with *G72* and that drives the observed associations. Neuroticism might be an excellent candidate for conferring such an effect. Single-marker as well as haplotype analyses support above hypotheses. In our sample from the normal population, neuroticism is associated with *G72*. Given the fact that neuroticism has found to be heritable in several twin studies and occurs comorbid with anxiety and several psychiatric disorders, our finding suggests that it acts as a major risk factor in the development of psychiatric diseases.

We further examined the association between *G72* risk-alleles and TPQ scales. Results revealed a significant association between M23 and M24 and novelty seeking - specifically its subscale "exploratory excitability vs. stoic rigidity". Individuals who score high on this subscale are characterized as extremely responding to environmental stimuli and easily provoked to prepare for fight and flight[10]. Exploratory excitability as conceptualized in the TPQ might be responsible for the more readily and stronger emotional reaction of individuals who score high on neuroticism to external and internal events, especially negative ones.

Our finding of the association between neuroticism and *G72* risk alleles suggests that neuroticism is a phenotype dimension underlying psychiatric diseases associated with *G72*. Neuroticism seems to be a genetic risk factor, which in combination with other risk factors leads to disturbed functioning in anxiety, affective, and schizophrenic disorders.

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