3.13 The impact of psychiatric susceptibility genes on personality traits in the general population.

Supervisors: Prof. Dr. med. Marcella Rietschel
PD Dr. med. Til Stürmer
Dr. med. Thomas G. Schulze

Background
The prevalence of mental disorder is generally higher than that for any other type of chronic condition. Schizophrenia, bipolar affective disorder, and major depression (MD) are all listed amongst the 10 leading causes of disability worldwide. 10 to 15% of patients commit suicide during the course of these diseases. Researchers and clinicians have worked for decades to reduce the suffering of those affected by these diseases and current treatments alleviate symptoms in many cases. Unfortunately, however, none of these treatments offer sustained relief. The development of more effective treatments depends upon the understanding of causal factors. The etiology of schizophrenic and affective disorders is multifactorial and probably includes several, partly interacting genetic mechanisms, which may be further modulated by environmental factors. In contrast to somatic disorders, no biological markers have been identified to assist in diagnosis.

As with many complex disorders, psychiatric diseases have long defied any attempts to unravel their molecular genetic makeup. Psychiatric genetic research has only recently begun to bear fruit; with the identification of several susceptibility genes. This has been possible through the use of collaborative efforts to produce large sample sizes in genetic linkage and association studies, and the employment of sound statistical methods. Our group has contributed substantially to these findings. The most promising and therefore the most intensively studied genes so far are: Dysbindin, Neuregulin-1, the G72/G30 locus and DAAO for both schizophrenia and bipolar affective disorder, BDNF for major depression and schizophrenia, COMT for schizophrenia and bipolar affective disorder and MAOA for major depression and panic disorder. Moreover, our group has shown that the association between bipolar affective disorder and the G72/G30 locus, which had originally been found through systematic fine-mapping in a SZ linkage region, is largely due to those bipolar patients with a history of persecutory delusions, a symptom which is a key component of the schizophrenia phenotype. Given that persecutory delusions are characterized by the presence of fear, anxiety-related traits may be at the core of the association between bipolar affective disorder and the G72/G30 locus. It is therefore intriguing to note that we have also found evidence for an association between panic disorder, a prime example of an anxiety disorder, as well as depression and the same genotypes and haplotypes at the G72/G30 locus. Moreover, in the general population, we could show that the very same haplotype was also associated with high levels of neuroticism, a personality trait that has long been considered an important predictor or even endophenotype for major psychiatric disorders such as UD or SZ. These findings demonstrate that certain genes cross diagnostic boundaries. These genes may be responsible for the biological mechanisms underlying traits that are common to several psychiatric diseases, but they may simultaneously act as genes that are protective against the development of other conditions (e.g.: heterozygosity of hemoglobin gene mutation causing sickle cell disease as protective factor against malaria; deficiency of the enzyme alcohol dehydrogenase as protective factor against alcoholism in Asian populations).

In the development of a complex disorder, a number of different genes and environmental variables act as risk and protective factors. The disorder develops when sufficient risk
factors accumulate to outweigh the protective factors. Since many factors contribute to the disorder, the liability or predisposition towards the disorder is really a continuous, quantitative dimension. The full-fledged phenotype of the disorder can then be considered the composite product of several of these factors or personality traits (e.g. neuroticism, psychoticism), produced once a certain threshold has been surpassed. The vulnerability gene variants observed in complex disorders are common and are therefore found at a high frequency in the general population as well. According to the threshold model of psychiatric disorders, the risk variant should also have an impact on carriers of this variant who do not display the full-fledged phenotype (defined as psychiatric disorder). This impact should be most clearly discernable for traits that are believed to be the observable correlates of underlying genetic factors.

Genotype-phenotype correlation studies of personality traits such as anxiety, neuroticism, and psychoticism could assist in unravelling the mechanisms which lead to disturbed function in anxiety, affective and schizophrenic disorders. To date, however, no such genotype-phenotype correlation studies of disease-associated personality traits using a large scale, systematic, population based approach have been undertaken.

**Aim**
To explore the effect of genetic variation in susceptibility genes for affective disorder, anxiety disorder and schizophrenia on personality traits, highly relevant for these diseases, using a sample from the general-population. Thus, association with variants in the G72/G30, DAAO, Dysbindin, Neuregulin-1 and further variants in newly discovered candidate genes, and psychoticism, neuroticism, anxiety, hostility, and negative affectivity will be investigated. We expect that risk-gene carriers should score highly on those personality traits which are considered key-components of the above mentioned disorders. Furthermore, we want to evaluate further impact of these genes on general health conditions. Our analysis will include gene-gene interaction and information about environmental factors (e.g. socio-demographic factors, social support).

**Study plan**
The project will be embedded in the HEIDE (Heidelberger Langzeitstudie zu Risikofaktoren und Diagnose chronischer Erkrankungen) study. The HEIDE study is an ongoing, population-based cohort study, which is conducted by Prof. Manfred Amelang (Institute of Psychology) and PD Dr. Til Stürmer (Medizinische Fakultät Heidelberg, Harvard Medical School, Boston). The study was initiated 12 years ago and includes 5000 participants, aged between 40-65. At this point, participants completed a comprehensive self-rating with respect to personality dimensions, life-style, nutrition and working habits as well as their state of health. After a mean follow-up of 8.5 years, 4,010 out of 4,857 still alive (83%) responded to a mailed questionnaire. Of these, 3,859 (over 96%) also sent a mouthwash sample and gave written informed consent for genetic analyses.

DNA from mouth wash is available and will be amplified before genotyping. The genotype-phenotype correlation studies will test the influence of the most important risk genotypes and haplotypes of the aforementioned susceptibility genes on the assessed personality dimensions, taking into consideration modulating effects of a history of stressful life-events and other sociodemographic factors. Full equipment for genotyping is available in the laboratory of the Division of Genetic Epidemiology in Psychiatry. These studies will be performed as part of our ongoing projects within the framework of the German National Genome Research Network (NGFN) in close collaboration with Prof. Markus M. Nöthen (Department of Genomics, Life & Brain, University of Bonn) and Prof. Peter Propping (Institute of Human Genetics, University of Bonn).

Our group has wide experience in the conduct of cohort studies, including gene-environment interactions and the development of efficient methods of their assessment as well as in the management of genotypic and phenotypic data, state-of the art genotyping methods, statistical genetic analyses.
References