Network: **Systematic Gene Identification and Functional Analyses in Common CNS Disorders**

Project: Recruitment of a Population Based Cohort of Patients with Bipolar Affective Disorder

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Introduction

Aims of the project

The Neuronet research projects will identify susceptibility genes for bipolar affective disorder (BPAD), but since these projects access highly selected patient samples the relevance of these genes in unselected patient populations will be unclear. The aim of this project is therefore to establish a cohort of patients with BPAD that is population-based. Recruitment is being carried out in collaboration with the PopGen project (population-based recruitment of patients and controls for the analysis of complex genotype-phenotype relationships) which also provides population-based controls.

Background

Pathological disturbances in mood ranging from severe depression to extreme mania are characteristic of BPAD. The disorder can be sub-classified into BPAD I, in which episodes of obvious mania occur, and BPAD II, in which only milder forms of mania are observed (APA 1994). Considerable efforts are currently underway to introduce the concept of a bipolar spectrum with lower operational thresholds. The life-time prevalence of BPAD I is approximately 0.8% (ranges from 0.3-1.5%; Weissman et al. 1996), and similar rates are reported for males and females. Results from the leading German studies accord well with these findings, suggesting point and life-time prevalences of approximately 0.3% and 0.5%, (Dilling et al. 1984, Fichter 1990, Heun and Maier 1993, Weissman et al. 1996, Meyer et al. 2000). In a population-based control sample (n=1,200) collected within the recent funding period of the NGFN1, life-time prevalence of BPAD I, based on psychiatric interviews, was 0.3%. While BPAD II seems to occur with a comparable frequency, rates of up to 5% have been proposed for the broadly conceived bipolar spectrum (Akiskal 2003). It is unclear whether the various bipolar subtypes represent a clinical or a genetic continuum. Addressing this question is beyond the scope of this project, which concentrates instead on patients with a narrowly defined phenotype (BPAD I). The peak onset of BPAD I occurs between 25 and 30 years of age. The likelihood of at least one recurrence is 50% within the first, and almost 80% within five years of recovery (review: Marneros and Brieger 2002).

Characteristics of the project

Research to identify susceptibility genes for BPAD is carried out using highly selected subpopulations *e.g.* patients admitted to hospital (who generally display a most severe phenotype), or patients who have been recruited for linkage studies (who have a familial loading for the disorder).
To examine the relevance of these genes in unselected populations of BPAD patients, it is necessary for the cohorts to be recruited through a system which introduces as little bias as possible. This is particularly important when examining interactions between the various susceptibility genes themselves, and the interactions between disease genes and environmental precipitating factors, for which very large and preferably population-based samples are required. The PopGen project has been established to provide a population-based recruitment resource within the National German Genome Research Network (NGFN). The project utilises the natural geographic borders of Northern Schleswig Holstein (oceans and Danish border). These define a population of more than 1.1 million inhabitants, making this an appropriate region for use in population-based recruitment strategies. PopGen received its funding as a network project in the middle of NGFN-1, and set up a professional infrastructure that includes sophisticated data protection systems, quality controlled phenotype identification and recruitment, and application of the regulations for sample handling formulated by the GEM platform Kiel. PopGen recruited more than 3000 individuals for NGFN studies during its first 8 months of activity, made possible through an extensive infrastructure including availability of research nurses, project management specialists and access to medical documentation.
We expect to identify approximately 10,000 individuals who will be scrutinized using stringent BPAD 1 diagnostic criteria for their suitability to participate. The German health care system assists us in this process by its use of ICD 10 WHO diagnostic criteria to assign diagnosis. Applying stringent inclusion criteria, and assuming a response rate of 50%, we expect to include approximately 4,000 persons in the study. It is unfortunately not possible in this study to conduct a refined phenotype characterization of life-time symptoms, but the study nevertheless offers a unique opportunity of assessing the natural course of the disease (*e.g.* number of relapses and admission to hospitals, social functioning), a factor which is always negatively biased in inpatient samples. We are also able to assess the occurrence and outcome of frequently observed co-morbid disorders such as alcohol dependence and anxiety. In addition, participants are asked to complete self-rating questionnaires describing life-events, ethnicity, family history, social status, and selected items concerning life-time symptoms (*e.g.* age at onset of depression and mania, occurrence of psychotic symptoms). The short-comings of such a focused approach to phenotype characterization are clear, but the clinical items assessed through scrutiny of medical records and use of self-reporting tools are invaluable in assessing phenotype-genotype correlations for those susceptibility genes identified so far.

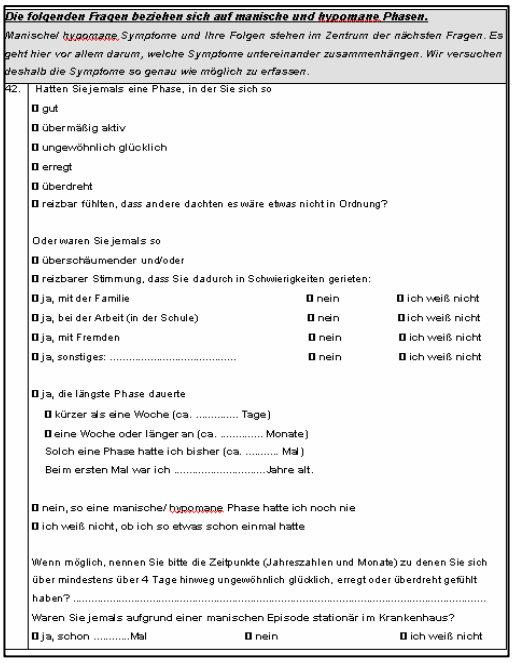
Results/Project Status

The first project milestone was the development of a self-rating questionnaire to determine evidence of a life-time history of BPAD in a population-based sample. Guided by the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders IVth Edition* (*DSM-IV*; APA, 1994), we designed the questionnaire to assess the core symptoms of BPAD, namely a life-time history of depressive, manic and/or hypomanic episodes. To evaluate those co-morbid conditions commonly associated with BPAD, we also included sections for anxiety disorders (i.e. panic disorder, phobias, and/or obsessive compulsive disorder) and psychotic symptoms (i.e. delusions and/or hallucinations). The questionnaire also includes questions on ethnicity, general medical conditions, socio-demographic factors, history of physical and non-physical abuse during childhood and adolescence, as well as an assessment of the “Big Five” personality dimensions (neuroticism, extraversion, openness, agreeableness, conscientiousness) as evaluated by the NEO-FFI (Costa & McCrae1992).

To date we have validated the questionnaire in a sample of 20 BPAD patients and 20 healthy controls. The procedure validates both the assigned *DSM-IV* diagnosis and the rating of individual symptoms (see Figure 1).

Our population-based screening procedure is now underway, using the PopGen infrastructure outlined above for participating hospitals and local psychiatrist and neurologists in Northern Schleswig-Holstein. We have so far identified 1700 patients who will be contacted and asked to participate in the study.

Fig 1: *The Questionnaire developed and validated for the assessment of a life-time history of BPAD in a population-based sample (here: cover sheet and part of the section on mania and hypomania)*



Die folgenden Fragen beziehen sich auf manische und hypomane Phasen.

Manische/ hypomane Symptome und Ihre Folgen stehen im Zentrum der nächsten Fragen. Es geht hier vor allem darum, welche Symptome untereinander zusammenhängen. Wir versuchen deshalb die Symptome so genau wie möglich zu erfassen.

42. Hatten Sie jemals eine Phase, in der Sie sich so

- ☐ gut
- ☐ übermäßig aktiv
- ☐ ungewöhnlich glücklich
- ☐ erregt
- ☐ überdreht
- ☐ reizbar fühlten, dass andere dachten es wäre etwas nicht in Ordnung?

Oder waren Sie jemals so

- ☐ überschäumender und/oder
- ☐ reizbarer Stimmung, dass Sie dadurch in Schwierigkeiten gerieten:

☐ ja, mit der Familie	☐ nein	☐ ich weiß nicht
☐ ja, bei der Arbeit (in der Schule)	☐ nein	☐ ich weiß nicht
☐ ja, mit Fremden	☐ nein	☐ ich weiß nicht
☐ ja, sonstiges:	☐ nein	☐ ich weiß nicht

☐ ja, die längste Phase dauerte

- ☐ kürzer als eine Woche (ca. ..... Tage)
- ☐ eine Woche oder länger an (ca. ..... Monate)

Solch eine Phase hatte ich bisher (ca. ..... Mal)

Beim ersten Mal war ich .....Jahre alt.

☐ nein, so eine manische/ hypomane Phase hatte ich noch nie

☐ ich weiß nicht, ob ich so etwas schon einmal hatte

Wenn möglich, nennen Sie bitte die Zeitpunkte (Jahreszahlen und Monate) zu denen Sie sich über mindestens über 4 Tage hinweg ungewöhnlich glücklich, erregt oder überdreht gefühlt haben? .....

Waren Sie jemals aufgrund einer manischen Episode stationär im Krankenhaus?

☐ ja, schon .....Mal ☐ nein ☐ ich weiß nicht

Outlook

Our principal foucus is the continued identification and recruitment of patients with BPAD I. This population-based sample of patients will be a valuable resource for identifying susceptibility genes for BPAD. The relevance of recently reported candidate genes for BPAD and related/comorbid neuropsychiatric disorders and of genes identified through animal studies within the framework of the Neuronet will be examined in this large population-based sample.

Lit.: ***1.*** *APA (1994) American Psychiatric Association Press 4th edition.* ***2.*** *Weissman MM et al. JAMA 1996; 276:293-299.* ***3.*** *Dilling H et al. (1984) Enke;* ***4.*** *Fichter MM (1990) Springer.* ***5.*** *Heun R & Maier W. Acta Psychiatr Scand 1993; 87: 279-284.* ***6.*** *Meyer C et al. Nervenarzt 2000 ; 71 :535-542.* ***7.*** *Akiskal HS. J Affect Disord 73: 1-5;* ***8.*** *Marneros A & Brieger P. WPA Series 2002: 97-148.* ***9.*** *World Health Organization 1993* ***9.*** *Costa PT & McCrae RR (1992), Psychological Assessment Resources.*