Genetic Studies in Borderline Personality Disorder (BPD)
Progress Report 4/1/01 to 3/31/02

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Collaborating Sites / Co-Investigators:
- Oslo, Norway
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- Freiburg, Germany
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- Ann Arbor, Michigan
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OBJECTIVE:

To define and identify genetic underpinnings of BPD.

BACKGROUND:

In order to investigate the genetic underpinnings of borderline personality disorder (BPD), we have to consider that BPD has a complex etiology with interacting genetic and environmental substrates. In addition, we need to reframe the BPD diagnosis in terms of more specific, measurable, presumably biologically-based endophenotypes. To improve our chances to identify genetic predisposing factors, subjects should be evaluated with regard to clinical phenotype by diagnostic interview, self-report measures of personality traits, and laboratory measures including neuropsychologic, psychophysiologic, or operationalized behavioral tests.

We have formulated a plan to help us identify genes for BPD, which involves studying both clinically ascertained samples but also epidemiologic, non-clinically ascertained samples.

- An excellent, epidemiologic, non-clinically ascertained sample of twins has been identified in Norway, and is being collected and ascertained by Svenn Torgersen and his colleagues (see below).
- A clinically ascertained sample is being collected and evaluated by Martin Bohus and his colleagues in Freiburg, Germany (see below).

RESEARCH PLAN/PROGRESS REPORT:

(A) We have proposed to use the epidemiologic, non-clinically ascertained sample of twins from Norway to search for Quantitative Trait Loci (QTLs) influencing personality dimensions related to BPD.

Since this time last year, when the details of the project were worked out and funding became available, the following have taken place:

- The genetic study of the twins was approved by the Ethics Committee in Oslo, Norway.
- A study coordinator was hired. This person is responsible to contact all the twins and schedule visits/blood drawing sessions.
- A laboratory technician, who will perform all DNA extractions, was hired.

The current status of the study recruitment is as follows:
1. Number of twins in twin pairs who have answered a self-report questionnaire: 6,668
2. Number of twins who have completed the in-person diagnostic interview: 1,935
3. Number of collected blood samples: 322
4. Number of extracted DNA samples: 322

Among these 322 DNA samples there are the following *complete* twin pairs:
41 monozygotic (MZ) twins
47 dizygotic (DZ) twins

Concentration of DNA is currently being determined and the samples will be shipped to Rockefeller University shortly after that. The DNA from these 88 pairs will be genotyped with a panel of polymorphic microsatellite markers to determine zygosity with certainty (zygosity at the moment is based on self-report). The panel will consist of 8 fluorescently labeled microsatellite markers (D12S1042, D13S793, D2S1363, D5S1470, D5S2848, D7S1804, DXS6789, GATA121A08).

Shipment of DNA samples will continue throughout the year. The rate of collection at Oslo is currently 100 blood samples every month.

Other statistics about the sample:
50% of those who answer the questionnaire accept to be interviewed. Of these, 75% agree to provide a blood sample.
Of those already interviewed in the past, 50% agree to come back and give a blood sample.

It is very difficult at this point to estimate the exact numbers of *complete* twin pairs we will be able to collect for which we will have all 3 items available:
a) diagnostic interview
b) questionnaire
c) blood sample.
Judging from the percentages provided above, we estimate we will be able to collect 500-600 DZ twin pairs and an equal number of MZ pairs.

When DNA from 100 complete DZ twin pairs is available, we will initiate a systematic genome scan with a panel of ~400 microsatellite markers evenly spaced at 10cM intervals throughout the genome. Our plan is to perform this scan at the Genotyping Facility of the Starr Center for Human Genetics, at the Rockefeller University. A research assistant will be hired to assist with this phase of the project.

This sample will be analyzed by a Quantitative Trait Locus (QTL) approach to map genetic loci for personality traits considered as "endophenotypic traits" or underlying dimensions of BPD, such as impulsivity, impulsive aggression, or affective instability, for which heritability has been demonstrated. Dr. Goncalo Abecasis from the University of Michigan, Ann Arbor, will head the statistical genetic analysis of the data.

The phenotypic information that will be used in conjunction with the genotypic data from the first stage twin pair analysis, will be as follows:
The Oslo, Norway team will produce an overall score for the subscale that is included in their questionnaire and pertains to the borderline diagnosis. This subscale consists of 11 questions interspersed among 113 additional questions pertaining to other dimensions of personality, life satisfaction and mental problems. Some twin pairs are expected to be concordant for a trait and other discordant. The Oslo, Norway team will also make available to Dr. Karayiorgou the results of the diagnostic interview. It is expected that some twins may meet full diagnostic criteria for a clinical diagnosis.

Positive markers and candidate genes identified through the QTL studies of the Norwegian twin sample will be tested in clinically ascertained samples of BPD patients (one being the Freiburg sample described below). This approach will allow us to a) test markers and candidate genes identified by the QTL approach in the Oslo, Norway twins for relevance to BPD, b) test the validity of certain personality traits as "endophenotypic" markers for BPD.

(B) We have proposed to use the clinically ascertained sample of BPD patients from Freiburg to test for associations between specific genes and BPD.

Since this time last year, when the details of the project were worked out and funding became available, the following have been accomplished:

- The study was approved by the ethical committee of the Freiburg Medical School
- A large battery of diagnostic instruments was implemented (see below for details)
- Database was set-up
- Raters were hired and trained (4 raters)
- Good Inter-rater reliability was achieved (average inter-rater reliability is between .82 and .92, across the different instruments)
- Recruitment of BPD patients has begun (see below for details and status).

B.1. Diagnostic Instruments:
As part of the implementation process, the computer-based neuropsychological test batteries were translated and installed. Also, in order to test pain threshold and pain sensitivity an fMRI-compatible thermode, which can be used for routine-assessment, was also tested and implemented.

The following instruments are currently in use:
Categorical Assessment:
Axis I: SCID I
Axis II: IPDE- DSM-IV module

Dimensional Assessment:
Dimensional Assessment of Personality Pathology (DAPP-BQ).

Specific Behavioral Patterns:

Impulsivity	Barratt Impulsiveness Scale (BIS)
Affect Irritability	Anger, Irritability, and Assault-Questionnaire (AIAQ)
Dissociation	Dissociation Experience Scale (DES)
Sensation Seeking	Sensation Seeking Scale (SSS)
ADHD	Wender-Utah-Rating-Scale (WURS) DSM-IV-checklist
Psychotic Features	PANSS
Identity Disturbance	Identity Disturbance Questionnaire (IDQ)
Suicidality, Self-Mutilation	Long-Term-Parasuicidal Count (LPC)

Sociodemographic variables:
Mainz Structured Assessment (MSA)

This structured interview covers a broad range of sociodemographic data including:
Family pedigree
Psychiatric disorders in first-degree relatives
Problems during pregnancy
Problems during birth
Problems or disturbances during early stages of development
Relevant somatic diseases, operations
Traumatic experiences
Relationship to peer groups
Learning disabilities
Full history of psychiatric symptomatology
Treatment history

Neuropsychological tests:
Attention Network Test (Posner, 2001)
Point Subtraction Aggression Paradigm (PSAP)

Neurophysiological tests:

Startle Response Paradigm
Pain sensitivity to heat induced pain
Affective priming

Neuroimaging:
MRI - Volumetry of Amygdala and Hippocampus
MR - Spectroscopy of Amygdala, Hippocamus and Prefrontal Cortex

B.2. Recruitment and evaluation phase:

The goal is to collect DNA from at least 300 female BPD patients and an equal number of well-matched controls for a case-control association study. Recruitment of patients started at the beginning of February 2002, following the successful implementation of clinical instruments and training of additional raters.

Status: Forty patients have been screened. Eighteen of them fulfilled the diagnostic criteria and agreed to donate DNA.

The diagnostic procedure outlined above takes about 12 hours per patient. We are able to screen about 25 patients per month, about 50% of which are expected to meet diagnostic criteria for BPD.

Psychopathological and sociodemographic data will be collected from all diagnosed patients.
We estimate that approximately a third of the patients will be free of psychotropic medication at the time of recruitment. This group of patients will be invited to also participate in the neuroimaging, neuropsychological and neurophysiological studies.

All patients will be asked for permission to contact their first-degree relatives. If additional family members are identified with BPD, we will be able to meet our secondary goal, which is to develop a clinical sample for linkage analysis.

For now, we will follow a **case/control study design**, where differences in allele distribution between affected individuals ("cases") and controls will be evaluated.