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Chapter 1

GENETIC EPIDEMIOLOGY OF BORDERLINE PERSONALITY DISORDER

Marijn A. Distel*[*,1], Timothy J. Trull[2] and Dorret I. Boomsma[1]

[1] Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands

[2] Department of Psychological Sciences, University of Missouri-Columbia, Columbia, MO, USA

ABSTRACT

Borderline personality disorder (BPD) is a severe personality disorder characterized by impulsivity, affective instability, relationship problems and identity problems. BPD affects 1-2% of the general population, 10% of the patients in outpatient settings, 15-20% of the patients in inpatients settings and 30-60% of the patients diagnosed with personality disorders. BPD is most commonly assessed according to the diagnostic and statistical manual of mental disorders (DSM). In addition, assessment of BPD features on a quantitative or dimensional scale is increasingly used. BPD is more often diagnosed in women in clinical samples and in young individuals and is frequently co-morbid with other personality disorders and axis-I disorders.

Most studies on BPD have attempted to clarify the etiology in terms of social and environmental determinants (e.g. physical or sexual abuse). These factors are important contributors to risk, but do not explain all variation in BPD risk. Moreover, even if the association is significant, in many instances the direction of causality is unclear. Genetic factors are additional contributors to BPD risk, and there now are some large twin and family studies that suggest significant heritability for the disorder as well as for the quantitative assessment.

In this chapter, we first discuss the main symptoms of BPD and several assessment methods. Next, we consider the association between BPD and demographic characteristics, such as age and sex, and the co-morbidity with other disorders. After the

* Address for correspondence: Marijn Distel, Department of Biological Psychology, VU University Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands. Phone: +31 20 598 8792; Fax: +31 20 598 8832; E-mail address: ma.distel@psy.vu.nl

focus on environmental covariates, we review family and twin studies into the genetics of BPD and related traits, genetic linkage and candidate gene studies of BPD. We end with a discussion of future directions in research in which we will consider multivariate studies, the discordant MZ co-twin design, the children of twins design, genome wide association studies, and genotype-environment interaction.

INTRODUCTION

Borderline personality disorder (BPD) is a severe personality disorder characterized by disturbances in emotional regulation, impulse control, interpersonal relationships, and identity (American Psychiatric Association 2000). BPD affects 1-2% of the general population and is the most common personality disorder in clinical settings representing 10% of the patients in outpatient settings, 15-20% of the patients in inpatients settings and 30-60% of the patients diagnosed with personality disorders (Lenzenweger et al. 2007; Widiger & Weissman 1991; Widiger & Trull 1993). BPD is frequently co-morbid with other personality disorders and with axis-I disorders (Skodol et al. 2002). Although BPD is most commonly diagnosed through structured clinical interviews, self report measures of BPD are increasingly used as a screening instrument to assess BPD features on a quantitative scale in clinical as well as in non-clinical settings. In particular, epidemiological studies often use self-report questionnaires, because it is a relatively efficient way to assess large samples.

To increase the success of treatment on BPD, much research has focused on the determinants of BPD. Most of these studies have attempted to clarify the etiology of BPD in terms of social and environmental causes. Several studies demonstrated that traumatic life events such as sexual abuse (e.g. Zanarini et al. 2002; Paris et al. 1994a; Paris et al. 1994b), physical abuse (e.g. Westen et al. 1990; Helgeland & Torgersen, 2004), parental divorce or illness (e.g. Paris et al. 1994a; Paris et al. 1994b; Parker et al. 1999) or parental psychopathology (e.g. Trull 2001; Torgersen 1984) are important risk factors for the development of BPD. However, none of these factors has emerged as a definite causal determinant of BPD or can explain all of the risk in affected individuals. Moreover, several questions remain: 1) t he direction of causality is not resolved: individuals with a high risk for BPD may also be at higher risk than others to experience traumatic life events, 2) not all subjects who experience a traumatic life event develop BPD, it might be that a (genetic) liability is required to develop the disorder, 3) not all BPD patients have experienced a traumatic life event, in some patients their genetic liability may be so high that they do not need the environmental trigger and 4) some of the risk of BPD might not be through the main effects of genes and environment but through their interaction. Therefore, recently research has focused on the genetic determinants of BPD.

In this chapter we focus on the assessment of BPD, through DSM diagnosis and quantitative assessment. Quantitative assessment is of importance in genetic epidemiological studies, as it allows phenotyping for BPD in family members of patients (who might score high on liability to BPD but do not meet the criteria for diagnosis), and in population based twin and family studies into the genetic architecture of BPD. An important area of research is the comorbidity of BPD with other DSM disorders and the association of variation in personality traits and BPD. There has been increasing consensus that BPD represents the combination of extremes of normal personality traits (Widiger & Trull 2007; 2008).

Multivariate genetic studies may shed light on the etiology of the association among personality disorders and variation in normal personality by addressing the question to what extent overlapping sets of genes or environmental factors are responsible for the association of personality (e.g. neuroticism, novelty seeking) and BPD.

We first discuss the main symptoms of BPD and several conceptualisations and assessment methods of BPD. Next, we consider the association between BPD and demographic characteristics and the co-morbidity with other axis-I and axis-II disorders. After the focus on environmental covariates, we review family-, twin-, and twin family studies into the genetics of BPD and related traits, genetic linkage and candidate studies of BPD. We end with a discussion of future directions in research in which we will consider multivariate studies, the discordant MZ co-twin design, the children of twins design, genome wide association studies, and genotype-environment interaction.

BORDERLINE PERSONALITY DISORDER: CONCEPTUALISATION AND MAIN SYMPTOMS

It was only with the publication of the third version of Diagnostic and Statistical Manual of Mental Disorders (DSM-III; American Psychiatric Association 1980) that BPD became an official axis II disorder. Before that there were several conceptualisations of the term borderline, the ones of Stern, Kernberg and Gunderson being most influential. Stern (1938) was the first to introduce the term borderline which he used to describe the most difficult and treatment resistant patients who were neither neurotic nor psychotic. The earliest conceptualizations of BPD emphasized the belief that these patients were suffering from a milder form of schizophrenia and there was no uniformity in the diagnosis of BPD. Kernberg (1975; 1967) provided more sharply defined boundaries for what he called the borderline personality organization (BPO). BPO was one of the three levels of personality organisation which Kernberg defined and was situated between the more severe psychotic personality organization and the less severe neurotic personality organization. BPO was characterized by identity diffusion, primitive defences (e.g. splitting, magical thinking, projective identification) and intact reality testing which is vulnerable for alterations and failures. The first operational definition of BPD was formulated by Gunderson and Singer (1975) in a paper in which they review the existing literature on BPD. This paper led to the development of a structured interview (Diagnostic Interview for Borderline Patients [DIB]; Gunderson et al. 1981) to reliably diagnose BPD patients. The discriminant characteristics based on this questionnaire (Gunderson & Kolb 1978), with the addition of the criterion about identity diffusion derived from Kernberg, were used by the development of DSM-III (American Psychiatric Association 1980).

The DSM-IV-R (American Psychiatric Association 2000) describes nine criteria for BPD which are described in Table 1. At least five out of nine must be present for the diagnosis to be made, resulting in 256 different combinations of criteria from which it is possible to achieve a BPD status. Such clinical heterogeneity has led to factor analytic studies to search for latent variables within the diagnosis. Several clinical and non-clinical factor analytic studies of the DSM-III (Rosenberger & Miller 1989), DSM-III-R (Sanislow et al. 2000; Becker et al. 2006; Clarkin et al. 1993), ICD-10 (Whewell et al. 2000) and DSM-IV

(Sanislow et al. 2002; Taylor & Reeves 2007; Benazzi 2006; Johansen et al. 2004; Blais et al. 1997) criteria for BPD have been conducted. One study supports the diagnostic construct of BPD as a whole (Johansen et al. 2004) but more commonly, two (Rosenberger & Miller 1989; Whewell et al. 2000; Benazzi 2006), three (Clarkin et al. 1993; Blais et al. 1997; Sanislow et al. 2000; Johansen et al. 2004; Taylor & Reeves 2007) and four (Becker et al. 2006) factor solutions were found. Based on these studies borderline characteristics might be subdivided into four factors; *affective instability*, *identity disturbance*, *impulsivity* and *unstable relationships*. These factors will briefly be discussed. *Affective instability* refers to the highly reactive moods of borderline individuals in response to stimuli from the individual's environment. The basic mood of BPD individuals often shifts between periods of anger, panic, anxiety or despair and is rarely relieved by periods of well-being or satisfaction. *Identity disturbance* is a second main characteristic of individuals with BPD, which involves a poorly defined concept of self. The self image of persons with BPD may shift a lot, including sudden changes in opinions, sexual identity, types of friends or career plans. A third characteristic of BPD patients is *impulsivity*, which often results in self-damaging behaviour. Common forms of impulsive behaviour for borderline patients are excessive spending, reckless driving, binge eating, substance abuse and promiscuity. The last main feature of BPD patients is *unstable relationships.* BPD patients often engage in unstable and stormy relationships, partly caused by the former three mentioned characteristic of BPD patients. BPD patients idealize potential lovers in an early stage of a relationship and demand to spend a lot of time together. However, they easily switch from idealization to devaluation when they get the feeling that the other person is not equally committed. In addition to these four main characteristics, intense and inappropriate anger, feelings of emptiness, fear of abandonment, suicidal and self-mutilating behaviour and transient dissociative or paranoid symptoms are also common in BPD patients.

Table 1. Criteria for borderline personality disorder.

The main characteristics of borderline personality disorder include instability in interpersonal relationships, self-image, affects, and control over impulses. Specific features include:
1. Extreme efforts to avoid real or imagined abandonment.
2. Unstable and intense interpersonal relationships.
3. Identity disturbance: disturbed, distorted, or unstable self-image or sense of self.
4. Impulsivity that is potentially self-damaging (e.g. excessive spending, substance abuse, reckless driving, binge eating).
5. Recurrent suicidal behaviour (gestures or threats) or self-mutilating behaviour.
6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or lack of control of anger.
9. Dissociation (e.g. depersonalization or derealization) or paranoid thoughts that occur in response to stress.

Besides categorical assessment with the DSM-IV, in which the disorder is either present or not, based on whether a diagnostic threshold is met, self report questionnaires are increasingly used in clinical and non-clinical settings to assess BPD features on a quantitative

or dimensional scale. An important advantage of measuring BPD features on a quantitative scale is that information on different levels of BPD symptom presentation is gained. Some people will meet several diagnostic criteria for BPD but not enough to warrant an actual BPD diagnosis, others will meet five, six, seven, eight or even nine criteria and all receive the same BPD diagnosis. Quantitative scales provide information on the degree to which symptoms of a disorder are present instead of a sole statement about whether the disorder is present or not. A commonly used self-report dimensional measure of BPD features is the *Personality Assessment Inventory-Borderline features scale* (PAI-BOR; Morey 1991). The PAI-BOR scale taps four important components of BPD, which are affective instability, identity problems, negative relationships, and self-harm. The 24-items are scored on a likert scale (0 to 3; *false, slightly true, mainly true, very true*) to provide a dimensional understanding of BPD features. Several studies have shown the PAI-BOR to be a reliable and valid measure of BPD features, and support the usefulness of the PAI-BOR in assessing BPD features in the general population as well as BPD features in clinical settings (Kurtz et al. 1993; Stein et al. 2007; Morey 2003). Kurtz and Morey (2001) for example showed that PAI-BOR scores correlated .78 with a structured interview-based assessment of BPD, indicating high convergent validity. Additionally, Trull (1995) compared nonclinical young adults scoring in the clinical significant range on the PAI-BOR (raw score ≥ 38) with those who scored below this threshold and found them to differ on measures of mood, personality, coping, general psychopathology. In the next section several dimensional models of BPD will be discussed.

DIMENSIONAL MODELS OF BORDERLINE PERSONALITY DISORDER

BPD is presented in a categorical manner in DSM-IV-TR; one either has the disorder (5 or more of 9 symptoms) or one does not (4 or less of 9 symptoms). Although such a categorical scheme is efficient and convenient, it may not be the best way to represent BPD pathology. A number of researchers have called for a dimensional approach to diagnosing and describing personality pathology (Trull & Durrett 2005; Widiger & Trull 2007, Widiger & Lowe 2008). Dimensional models provide quantitative estimates of the degree to which relevant personality traits, whether derived from DSM-IV-TR or not, are present in each individual. Dimensional models provide more reliable scores (e.g. across raters, across time), help explain symptom heterogeneity and the lack of clear boundaries between categorical diagnoses through the lens of underlying personality traits or dimensions, retain important information about subthreshold traits and symptoms which may be of clinical interest, and allow us to integrate scientific findings concerning the distribution of personality traits and associated maladaptivity into a classification system.

The term "dimensional" is used to describe many different approaches to quantifying personality and personality pathology. There are three major possibilities: (1) "quantify" each personality disorder construct by indicating the degree to which the symptoms for each PD are present. For example, scores might simply represent the actual number of criteria present for each personality disorder (a BPD rating of 6 on a scale from 0 to 9) or a rating indicating the degree to which features for the disorder are present (PAI-BOR score of 42 on a scale of 0 to 72). (2) identify those personality traits that underlie the personality disorder constructs and then to provide a description of personality pathology from a trait perspective. For example,

Liveley's DAPP inventory has identified four higher-order dimensions underlying personality pathology: *emotional dysregulation, dissocial behavior, inhibitedness, and compulsivity*. BPD symptoms appear to be best represented by the factors emotional dysregulation and dissocial behavior (e.g. Bagge & Trull 2003). (3) use personality trait models that are independent from current diagnostic classification schemes to both characterize and perhaps redefine personality pathology and personality disorder. For example, the Five Factor Model (FFM) of personality is a popular way to conceptualize major personality traits, and the five major domains of this model are typically referred to as *neuroticism versus emotional stability, extraversion versus introversion, openness versus closedness to experience, agreeableness versus antagonism, and conscientiousness versus negligence*. FFM traits that appear to underlie BPD symptoms include: anxiety, angry hostility, depressiveness, impulsiveness, vulnerability, openness to feelings, openness to actions and deliberation (low) (Lynam & Widiger, 2001; Trull et al. 2003).

PREVALENCE OF BPD

Table 2 shows 22 studies reporting prevalence rates for BPD which vary from 0.0 to 5.9%. The main limitation of many of these studies is that they are not representative of the population. The sample from Lenzenweger et al.'s (1997) study for example only consists of college students, which makes it impossible to generalize the results. Other samples consist of relatives of psychiatric patients (Zimmerman & Coryell 1989; Baron et al. 1985b; Black et al. 1993), or controls screened for psychiatric disorders (Moldin et al. 1994; Klein et al. 1995), which may have respectively upwardly or downwardly biased the prevalence rates, given that BPD often co-occurs with axis-I disorders. In addition, several studies suffer from small sample sizes (Reich et al. 1989; Black et al. 1993; Bodlund et al. 1993; Blanchard et al. 1995; Klein et al. 1995; Lenzenweger et al. 1997).

Seven large scale studies assessed the prevalence of BPD in well characterized community samples from Australia, the USA, the UK or Norway, using validated structural interviews for ICD-10 (Jackson & Burgess 2000), DSM-III-R (Torgersen et al. 2001) and DSM-IV (Crawford et al. 2005; Coid et al. 2006; Samuels et al. 2002; Lenzenweger et al. 2007; Grant et al. 2008). Jackson & Burgess (2000) assessed 10,641 Australian individuals aged 18 years and over with the International Personality Disorder Examination (IPDE) ICD-10 screener (Loranger et al. 1997) administered by an interviewer.

Torgersen et al. (2001) administered structured interviews for DSM-III-R in 2,053 individuals between the ages of 18 and 65 years which was 57% of the originally randomly selected sample of 3,590 citizens from the national register of Oslo, Norway. Contrary to most other studies, a fixed list of potential subjects was selected instead of households which resulted in valuable information about who participated and who did not. Participants were significantly more often women (63%), aged 40 years or older (61%) and living in the town periphery (61%) instead of in the center of the city. The reason for the different participation rate between the demographic groups was incorrect address and relocation without a new correct address. Prevalence rates were weighed for the differences between the interviewed sample and the population at large although differences were small.

Samuels et al. (2002) selected in the first stage of the study in 1981, all household residents between the ages of 18 and 64 years old of eastern Baltimore of whom 3,481 were interviewed using the Diagnostic Interview Schedule (DIS) and 810 of these individuals were also examined by psychiatrists. In the 1990s, 1,920 of the surviving subjects were re-interviewed. The sample of the 2002 study was selected from these subjects, which included all participants who were examined by psychiatrists and all participants who were identified as having an axis-I disorder by the DIS. In addition, a random sample was selected from the remaining subjects, of which 742 were fully assessed with the IPDE for DSM-IV (IPDE; Loranger 1999). Their mean age was 47 years (range 34-94 years) and 63% were women. Weighted (0.5%) and unweighted (1.2%) prevalence rates were reported.

The study by Crawford et al. (2005) used participants drawn from the children in community (CIC) sample, a large epidemiological sample of children in New York that was assessed for the first time in 1975 and followed since. The 2005 study is based on 644 subjects (53% women) assessed with the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II; First et al. 1997) at age 33.

The sample studied by Coid et al. (2006) was drawn from those participating in the British National Survey of Psychiatric Morbidity. Initially 8,886 adults living in England, Scotland and Wales, completed the phase I screening interview. The sample selection for the second phase was based on scores on the diagnostic instruments used in phase I. All persons who screened positive for psychosis (N = 339), half of those who screened positive for antisocial or borderline personality disorder (N = 164), one in 14 of those who screened positive for other personality disorder (N = 136) and one in 14 of those who showed no evidence of either PD or psychosis (N = 398) were selected of whom 638 were assessed by the SCID-II (First et al. 1997). The final sample consisted of 626 participants (57% women, age range 16-74 years) who completed both the SCID-II and a scan interview. Prevalence rates were estimated using weights to adjust for the effects of differential probabilities of selection and non-response in both phases of the survey.

The study of Lenzenweger et al. (2007) was based on the National Comorbidity Survey Replication (NCS-R), a nationally representative survey in the United States, in which all 9,282 respondents were administered a Part I diagnostic interview that assessed core disorders. The sample used in the 2007 study was selected in part II and consisted of all phase I respondents who met criteria for a core disorder and 25% of other part I respondents. All 5,692 phase II participants completed a series of PD screening questions from the IPDE and three sets of possible correlates (socio-demographics, role impairment and 12-month treatment) were examined. The sample was weighted to adjust for sampling effects and several correlates. Clinical reappraisal interviews with the IPDE were carried out with 214 part II respondents. Based on these interviews, the coefficients from best fitting regression equations of PD diagnoses predicted by IPDE screening questions in the clinical reappraisal group were used to predict the probability of each PD diagnosis to part II respondents who were not part of the clinical reappraisal group.

Table 2. The prevalence of BPD in 22 studies.

Author	Year	Instrument	Place	Sample description	N	Prevalence
Baron et al.	1985	SIB DSM-III	?	Randomly selected relatives of 90 normal control probands.	376	1.6
Drake & Vaillant	1985	Clin Int DSM-III	Boston, USA	Normal control male probands originally recruited in a study of juvenile delinquency.	369	0.8
Zimmerman & Coryell	1989	SIDP DSM-III	Iowa, USA	First degree relatives of normal controls (23%) and of psychiatric patients with schizophrenia (16%), psychotic (31%) and nonpsychotic depression (29%) or another psychiatric disorder (1%).	797	1.6
Reich et al.	1989	PDQ DSM-III	Iowa, USA	Randomly drawn from a Midwestern university community.	235	1.3
Swartz et al.	1990	DIS [a] DSM-III	Continental USA	Community sample from the USA	1,541	1.8
Maier et al.	1992	SCID-II DSM-III-R	Mainz, Germany	Normal unscreened controls (24%), their spouses (13%) and their relatives (63%).	452	1.1
Black et al.	1993	SIDP DSM-III	Iowa,USA	First degree relatives of obsessive compulsive probands (49%) and of normal control probands (51%).	247	3.2
Bodlund et al.	1993	SCID-screen DSM-III-R	Umea, Sweden	Normal control subjects.	133	3.8
Kendler et al.	1993	SIS DSM-III-R	Ireland	Relatives of 150 unscreened control subjects selected from a rural county.	580	0.0
Moldin et al.	1994	PDE DSM-III-R	New York, USA	Parents (38%) and offspring (62%) followed as normal control families in the New York High-Risk Project.	302	2.0
Blanchard et al.	1995	SCID-II DSM-III-R	New York, USA	Normal unscreened control subjects.	93	1.1
Klein et al.	1995	PDE DSM-III-R	New York, USA	Relatives of 45 normal controls.	229	1.7
Lenzenweger et al.	1997	IPDE DSM-III-R	New York, USA	Undergraduate students enrolled at Cornell University. Screened by means of a questionnaire. A sample of those expected to have a PD and those not expected to have a PD were interviewed.	258	1.3 [c]

Table 2. (Continued).

Author	Year	Instrument	Place	Sample description	N	Prevalence
Jackson & Burgess	2000	IPDE ICD-10	Australia	Community sample from Australia	10,641	1.0
Torgersen et al.	2001	SIDP-R DSM-III-R	Oslo, Norway	Randomly drawn from the National Register of Oslo.	2,053	0.7 [b]
Ekselius et al.	2001	DIP-Q DSM-IV, ICD-10	Gotland, Sweden	Randomly selected from the community of Gotland.	557	5.4/4.8[d]
Samuels et al.	2002	IPDE DSM-IV	Baltimore, USA	Adult household residents who were not examined by a psychiatrist in an earlier stage of the study and screened for several Axis I disorders.	742	0.5 [b]
Crawford et al.	2005	SCID-II DSM-IV	New York, USA	Community sample from two upstate New York counties.	644	3.9
Coid et al.	2006	SCID-II DSM-IV	United Kingdom	Community sample from England, Wales or Scotland.	626	0.7 [b]
Lenzenweger et al.	2007	IPDE DSM-IV	Continental USA	Community sample from the USA.	5,692	1.4 [b]
Şar et al.	2007	SCID-II DSM-III-R	Sivas, Turkey	Women from 500 households in Sivas.	628	3.5
Grant et al.	2008	AUDADIS-IV DSM-IV	USA	Community sample from the USA.	34,653	5.9

SIB = Schedule for Interviewing Borderlines; Clin Int: semi structured psychiatric interview; SIDP = Structured Interview for DSM-III Personality disorders; PDQ = Personality Diagnostic Questionnaire; DIS = Diagnostic Interview Schedule; SCID-II = Structured Clinical Interview for DSM-III-R personality disorders; SIS= Structured Interview for Schizotypy; PDE= Personality Disorder Examination; IPDE = International Personality Disorder Examination. DSM-III-R and DSM-IV version; SIDP-R = Structured Interview for DSM-III-R; DIP-Q = DSM-IV and ICD-10 Personality Questionnaire; AUDADIS-IV= Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV version.

[a] Borderline personality disorder was not included in the DIS but an algorithm was constructed to approximate prevalence of borderline personality disorder.
[b] Weighted prevalence rates. [c] When the two stage procedure is taken into account. [d]According to the DSM-IV and ICD-10 classification system, respectively.

Table 3. Family studies of BPD

Study	N probands/ relatives	Assessment proband (instrument)	Assessment relatives (instrument)	% relatives with BPD	Limitations
Stone et al. (1981)	BPD 39/135 Psychotic 36/118 Normal 21/68	Interview (BPO criteria)	Partly direct interviewed	BPD 6.7 Psychotic 13.6 Normal 4.4	- BPO criterion in stead of DSM - Relative raters mostly not blind to proband's diagnosis. - Part of the relatives assessed through probands
Loranger et al. (1982)	BPD 83/338 Sz 100/482 BiP 100/537	Chart review	Chart review	BPD 8.6 SZ 1 BiP 0.6	- No normal comparison subjects - Not controlled for comorbid depression - Only female BPD probands
Pope et al. (1983)	BPD 33/130 BiP 34/173 Sz 39/181	Chart review	Chart review	BPD 0.8 [a] BiP 0.6 Sz 2.2	- No normal comparison subjects - For comparison groups (BiP & Sz) cluster B diagnoses in stead of BPD diagnoses are reported.
Baron et al. (1985)	BPD 17/60 BPD,SPD 20/84 SPD 16/56 Normal 90/376	Structured Interview (SIB)	Directly interviewed (most relatives of normal controls) and through probands. (FHRDC/ Family history version of SIB)	BPD 5.1 BPD/ SPD 1.8 SPD: 0.0 Normal 1.7	- Student sample - 15 of 17 probands had 'probable' BPD - Relative raters not blind to proband's diagnosis. - Part of the relatives assessed through probands
Links et al. (1988)	BPD 69/320	Structured Interview (DIB)	Partly direct interviewed (DIB)	BPD 10.9	- No comparison groups - No information on proband comorbidity
Zanarini et al. (1988)	BPD 48/240 APD 37/139 DOPD 26/109	Structured Interview (DIB-R, DIPD)	Through probands (FHQ)	BPD 18.3 APD 2.9 DOPD 7.3	- No interrater reliability - No normal comparison subjects

Table 3. (Continued).

Study	N probands/ relatives	Assessment proband (instrument)	Assessment relatives (instrument)	% relatives with BPD	Limitations
Reich et al. (1989)	BPD 12/31 No PD 15/51	Questionnaire (PDQ)	Questionnaire (PDQ)	BPD 6.5 No PD 0.0	- PDQ is likely to produce false positives - No other PD comparison group - Relatives assessed through probands
Johnson et al. (1995)	BPD ?/39 AvPD ?/62 No PD 17/46	Structured Interview (SCID-II)	Directly interviewed (SCID-II)	BPD 10.3 AVPD 3.2 No PD 0.0	- Adolescent sample - Number of BPD probands not clear
Riso et al. (2000)	BPD (no MD)11/54 MD 119/563 Normal 45/229	Structured Interview (PDE, FH/PD)	Partly direct interviewed	BPD 22.2 MD 21.5 Normal 7.0	- Part of the relatives assessed through probands
Zanarini et al. (2004)	BPD 341/1580 OPD 104/472	Structured Interview (DIB-R, DIPD-R)	Through probands (FHQ-R)	BPD 13.0 [b] OPD 7.8 [b]	- No normal comparison subjects - Relatives assessed through probands
Bandelow et al. (2005)	BPD 66/66 Normal 109/?	Structured Interview (SCID)	Through probands	BPD 9.1 Normal 0.0	- Relatives assessed through probands - Number of relatives not clear - No other PD comparison group

BPD = Borderline Personality Disorder; BiP = Bipolar Disorder; Sz = Schizophrenia; SPD = Schizotypy; APD = Antisocial Personality Disorder; DOPD = Dysthymic Other Personality Disorder; AvPD = Avoidant Personality Disorder; MD = Mood Disorder; OPD = Other Personality Disorder; PD = Personality Disorder.

SIB = Schedule for Interviewing Borderlines; FHRDC = Family History Research Diagnostic Criteria; DIB = Diagnostic Interview for Borderlines; DIB-R: Revised Diagnostic Interview for Borderlines; DIPD: Diagnostic Interview for DSM-III-R Personality Disorders; FHQ = Family History Questionnaire; PDQ = Personality Diagnostic Questionnaire; SCID-II = Structured Clinical Interview for DSM-III-R Personality Disorders; PDE = Personality Disorder Examination; FH/PD = Family History Interview for Personality Disorder; DIPD-R = Diagnostic Interview for DSM-III-R Personality Disorders- Revised; FHQ-R = Revised Family History Questionnaire; SCID = Structured Clinical Interview for DSM-IV.

[a] 7.7% of the relatives received a diagnoses when histrionic, BPD and antisocial PD were considered together. [b] For DSM-III-R BPD diagnosis. For estimated DSM-IV BPD diagnoses prevalence rates are 16% for relatives of BPD probands and 9.1% for relatives of OPD patients.

Recently, Grant et al. (2008) conducted a large scale epidemiological study in which 34,653 individuals aged 18 years and older were assessed using the Wave 2 Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV; Grant et al. 2001). Participants were assessed on 18 multiple symptom items. A requisite number of symptoms had to be endorsed of which at least 1 must had caused significant distress or impairment in daily functioning to receive a BPD diagnosis.

Prevalence rates for BPD based on these seven studies range from 0.5 (Samuels et al. 2002) to 5.9% (Grant et al. 2008). Crawford et al. (2005) and Grant et al. (2008) reported the highest prevalence rates of respectively, 3.9 and 5.9%. The discrepancy between the study by Crawford et al. and other studies is most likely due to differences in sample composition. The study of Crawford et al. was based on 33 year-old participants whereas the other studies covered a much broader age range. As BPD is more often diagnosed in younger individuals this could have caused the high prevalence. Grant et al. (2008) assessed BPD diagnoses on lifetime basis in stead of current diagnoses, which can explain the high prevalence rate of 5.9% they report. Also, the criteria to receive a diagnosis of BPD (if only one of the required symptoms resulted in impairment in daily functioning a diagosis was made) might have biased the prevalence rate upwardly.

In clinical settings BPD is much more common with prevalence rates up to 10% in outpatients and 20% of inpatients (Widiger & Weissman 1991).

DEMOGRAPHIC CORRELATES

Age

Generally BPD symptoms appear by early adulthood (American Psychiatric Association 2000), and the symptoms and/or severity of the disorder usually diminish with age (Stone 1990; Torgersen et al. 2001; Lenzenweger et al. 2007; Grant et al. 2008). Two longitudinal studies present results about the longitudinal course of BPD in treatment seeking adults. The McLean Study of Adult Development (MSAD; Zanarini et al. 2005; Zanarini et al. 2007) studied the longitudinal course of BPD in a group of 362 patients (77% females) of whom 24 BPD symptoms and comorbid diagnoses were assessed every two years by the Structured Clinical Interview for DSM-IV axis I Disorders (SCID-I; Spitzer et al. 1992), the Revised Diagnostic Interview for Borderlines (DIB-R; Zanarini et al. 1989) and the Diagnostic Interview for DSM-III-R Personality Disorders (DIPD-R; Zanarini et al. 1987). Results showed that half of the symptoms at baseline had declined substantially over time. These 12 symptoms mainly included symptoms reflecting impulsivity and interpersonal difficulties. The 12 symptoms that seemed to be more stable encompassed affective symptoms and interpersonal symptoms reflecting issues concerning abandonment and dependency. The authors conclude that some symptoms of BPD are manifestations of acute illness while others are more enduring aspects of the disorder. The Collaborative Longitudinal Personality disorder Study (CLPS; Skodol et al. 2005; Gunderson et al. 2000) presented a similar model dividing symptoms into symptomatic behaviour (e.g. abandonment fears, self-mutilation), which is episodic and reactive in nature, and traits (e.g. impulsivity, anger), which are more fundamental and enduring. Thus, both clinical studies report a decline in actual BPD

diagnoses as well as in part of the symptoms. A third longitudinal study, the Children In Community (CIC; Cohen et al. 2005) study, assessed personality disorders in 658 individuals drawn from the general population at ages 14, 16, 22 and 33 and report a decline in symptom levels from adolescence to adulthood (Johnson et al. 2000; Skodol et al. 2007).

Sex

In clinical studies BPD is often found to be more prevalent among women, as is also suggested by DSM-IV (American Psychiatric Association 2000) which states that 75% of the individuals diagnosed with BPD are women. This estimate is based on a meta-analysis by Widiger and Trull (1993) who summarized the results of 75 studies, most based on clinical samples. However, several large scale community studies revealed no significant gender differences in BPD (Torgersen et al. 2001; Jackson & Burgess 2000; Lenzenweger et al. 2007; Grant et al. 2008). It is suggested that the gender difference found in clinical samples is caused by different base rates of men and women in clinical samples as women are more likely to seek help (Widiger 1998; Corbitt & Widiger 1995).

COMORBIDITY WITH OTHER DISORDERS

Epidemiological and clinical studies have established that BPD and axis-I and II disorders are highly comorbid (Gunderson 2001). For axis-II disorders, Nurnberg et al. (1991) found that 82% of the BPD outpatient population without a current axis-I disorder received at least one other personality disorder diagnosis. Lenzenweger et al. (2007) reported significant co-occurrence between BPD and paranoid, schizoid, antisocial, avoidant, dependent and obsessive-compulsive disorder. For axis-I disorders, Fabrega et al. (1992) found that of the 390 persons diagnosed with BPD, about two thirds received a concurrent axis-I diagnosis. In general, studies into the co-occurrence of BPD and axis-I disorders report that BPD patients often meet criteria for major depression, bipolar I and II disorder, eating disorders, substance use disorders and several anxiety disorders (including PTSD) (Lenzenweger et al. 2007; Skodol et al. 1993; Skodol et al. 1995; Skodol et al. 1999a; Skodol et al. 1999b; Zimmerman & Mattia 1999; Zanarini et al. 1998).

Although there seem to be no gender differences in the prevalence of BPD in the general population, as discussed previously, there are gender differences in comorbid diagnoses. Johnson et al. (2003) compared 175 women and 65 men with a BPD diagnosis and found that women were more likely to be diagnosed with post traumatic stress disorder (51% vs. 31%) and eating disorders (42% vs. 19%), while men were more likely to be diagnosed with substance disorder (58% vs. 85%) and schizotypal (10% vs. 25%), narcissistic (5% vs. 22%) and antisocial (10% vs. 30%) personality disorder. Recently, McCormick et al. (2007) assessed 163 BPD patients (84.7% women) using the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al. 1992) and found that women were more likely than men to have an anxiety disorder (particularly generalized anxiety disorder and agoraphobia), somatoform disorders, and histrionic personality disorder. Antisocial personality disorder was more common in men. In contrast to earlier studies (Johnson et al. 2003; Zanarini et al. 1998), they

did not find PTSD and eating disorders to be more common in women or substance use disorders to be more common in men.

FAMILY STUDIES

A number of family studies (summarized in table 3) report increased rates of BPD in the relatives of individuals with BPD compared to relatives of control probands (Baron et al. 1985a; Bandelow et al. 2005; Johnson et al. 1995; Zanarini et al. 2004; Zanarini et al. 1988; Loranger et al. 1982). Prevalences or morbidity risks for BPD in relatives of BPD probands ranged from 9.1% (Bandelow et al. 2005) to 24.9% (Zanarini et al. 1988). The high prevalence reported by Zanarini et al. is probably caused by the indirect assessment method used. Reich et al. (1989) found a trend in the direction of familiarity which did not reach significance. Stone et al. (1981) did not find a higher prevalence of BPD among relatives of BPD probands. Pope et al. (1983) only found BPD to be more prevalent in the relatives of depressed BPD probands.

As described in a comprehensive review by White et al. (2003) most studies published on the familiarity of BPD have limitations in the methodology employed. Amongst other limitations, the sample sizes are generally small varying from 17 (Baron et al. 1985a) to 83 BPD probands (Loranger et al. 1982) and are often not representative of the population (e.g. Loranger et al. [1982] assessed only female BPD probands). Only Zanarini et al. (2004) used a larger sample of 341 BPD probands, but the main limitation of their study is that information on psychopathology of relatives was derived from the BPD probands themselves.

Two studies assessed the prevalence of individual borderline symptoms or features, in stead of actual diagnoses, in relatives of BPD probands. Silverman et al. (1991) found that the prevalence rates for affective and impulsive personality disorder traits were significantly higher in the relatives of BPD probands than in the relatives of probands with other personality disorders or in the relatives of schizophrenic probands. Zanarini et al. (2004) assessed the prevalence rates of all nine BPD DSM criteria symptoms in first degree relatives of BPD patients, and reported that the prevalence rates of five (inappropriate anger, affective instability, paranoia/dissociation, general impulsivity, and intense, unstable relationships) were significantly higher in first degree relatives of BPD patients than in first degree relatives of axis-II comparison subjects.

TWIN STUDIES

Several family studies support the idea that BPD and BPD related traits are familial, but these studies cannot disentangle the effects of genes from the effects of environment shared by family members, social interaction and cultural inheritance. Twin studies can disentangle the effects of common environment and genes by making use of the different genetic relatedness of monozygotic (MZ) and dizygotic (DZ) twins. MZ twins are genetically (nearly) identical while DZ twins and siblings share on average 50% of their segregating genes. If genetic factors are important for a trait, MZ twins must be more similar than DZ twins or

other first degree relatives. If MZ twins are as similar as DZ twins, familiarity is mainly due to common environmental factors.

Genetic studies of BPD remain relatively scarce, when compared to the number of studies of other disorders in psychiatric genetics. Only four twin studies so far provided data on BPD diagnoses and features. Torgersen (1984) reported a MZ concordance rate of 0.0% and a DZ concordance rate of 11.1% for BPD, suggesting that shared environmental factors influence the variance in BPD. However, the low number of twin pairs (N = 25) limit any conclusions concerning evidence supporting a genetic or environmental liability for BPD. In 2000, Torgersen et al. assessed 221 twin pairs with the SCID-II (Spitzer and Williams 1985). Results suggested a heritability of 69%, though this estimates must be considered approximate due to the small number of twins, the ascertainment method (sampling those who were treated for mental disorder), and the fact that the zygosity and diagnostic status of co-twins was not hidden from the interviewers.

More recently, Torgersen et al. (2008) assessed personality disorder traits in 1,386 twin pairs between the age of 19 and 35 years using the Structured Interview for DSM-IV Personality Disorders (SIDP-IV; Pfohl et al. 1995). The prevalence rate for BPD of 0.4%, and even lower for several other PD's, was too low to analyse the data categorically, so a dimensional representation based on sub-clinical criteria was used to study the degree to which genetic and environmental factors influence cluster B PDs. The heritability of BPD was estimated at 35% with the remaining variance explained by individual specific environment.

Using a quantitative scale, Distel et al. (2008a) were able to assess BPD features in 5,496 twins (1,852 complete pairs) between the ages of 18 and 86 years from the Netherlands, Belgium and Australia. Results showed that genetic influences explained 42% of the variation in BPD features in both men and women. The heritability was equal between the three countries suggesting no interaction between genotype and country. The MZ correlation was more than twice as high as the DZ correlation in all three countries. Such a pattern of correlations is not compatible with an additive genetic model and indicates that non-additive genetic effects (dominance) may explain part of the variation in BPD features. However, even large twin studies generally do not have enough power to detect non-additive genetic effects (Posthuma & Boomsma 2000) and it was not necessary to model a separate dominance component. The heritability estimate of 42% therefore is likely to include some non-additive genetic effects.

TWIN FAMILY STUDIES

The combination of data from twins and other family members (their parents, spouses, siblings and/or offspring) offers a powerful approach to study the importance of several mechanisms that cannot be assessed in twin or family data alone (Boomsma et al. 2002).

Parents of twins can be included to simultaneously study genetic and cultural transmission. In the classical twin design, variance due to cultural transmission will be accounted for as common environmental variance. In an extended twin design cultural transmission can be distinguished from other common environmental influences, assuming that cultural transmission from parents to offspring is based on the measured phenotype of the

parents rather than on a latent variable (Eaves et al. 2005). Environmental factors as part of cultural transmission may be taught from parents to their offspring in the form of customs or preferences, and have direct effects on behavioural phenotypes through processes of social learning or modelling. In contrast, non-transmissible shared-environment comprises environmental conditions shared by relatives reared together within the same generation (Cloninger et al. 1979). If both genetic and cultural transmission are of importance, i.e. parents transmit both genes and non-genetic information to their children this will induce a correlation between genes and environment. This so called "passive" G × E correlation or covariance occurs because parents shape the child's environment based on their own genetic factors which correlates with the child's genetic propensities (Eaves et al. 2005). Parents of twins can also be studied in a quasi-longitudinal design, in which analyses of young adult twins, their middle aged parents and analyses of a group of middle aged twins are compared, to determine genetic and environmental stability (e.g. Snieder et al. 1997).

Spouses of twins can be included to study marital resemblance which can be due to social homogamy, marital interaction or phenotypic assortment (Heath & Eaves 1985). Social homogamy refers to the tendency of spouses to have similar social backgrounds. Marital interaction means that spouses living together experience mutual influences which makes them resemble each other, or active influences of one spouse on the other (Penrose 1944). Phenotypic assortment refers to the tendency of individuals to select their partner based on the partner's phenotype. Marital resemblance as a result of phenotypic assortment will lead to increased genetic resemblance between family members if the trait is heritable, while social homogamy and marital resemblance would not (Falconer & Mackay 1996). If phenotypic assortment exists, it is therefore important to include it into the genetic analyses, to obtain unbiased heritability estimates.

Social interactions among family members and special twin effects (which might arise prenatally, such as prenatal hormone transition, shared prenatal environment, or the effect of low birth weight) can be studied if siblings of twins are included. To study some effects of social interaction, data from MZ and DZ twins are sufficient. The effects of social interaction among siblings to individual differences in behavior were first discussed by Eaves (1976) and later by Carey (1986) and others. In the context of behavior genetic research, social interaction effects reflect that alleles may cause variation in a trait of individuals carrying these alleles, but may also, through social interaction, influence the phenotypes of individuals who do not carry them (e.g. in their family members). Social interactions between siblings thus may create an additional source of variance. Social interaction effects between siblings can either be cooperative (imitation) or competitive (contrast), depending on whether the presence in the family of, for example, a high-scoring sibling inhibits or facilitates the behavior of the other siblings. Cooperation implies that behavior in one sibling leads to similar behavior in the other siblings. In the case of competition, the behavior in one child leads to the opposite behavior in the other child. In the classical twin design, cooperation or positive interaction leads to increased twin correlations for both MZ and DZ twins. The relative increase is larger for DZ than for MZ correlations, and the pattern of correlations thus resembles the pattern that is seen if a trait is influenced by shared environmental factors. Positive interactions have been observed for traits such as antisocial tendencies (Carey 1992). Negative sibling interaction, or competition, will result in MZ correlations, which are more than twice as high as DZ correlations, i.e., a similar pattern to the one that is seen in the presence of genetic dominance.

The inspection of correlations in twins thus is not sufficient to detect social interaction. However, social interactions also influence the absolute variances of a trait, leading to variance differences between MZ and DZ twins. If the interaction effect is cooperative the variances of MZ and DZ twins are both inflated, and this effect is greatest on the MZ variance. The opposite is observed if the effect is competitive; MZ and DZ variances are both deflated and again this effect is greatest on the MZ variance. In the study by Distel et al. (2008a) a maximum likelihood test of variance differences between MZ and DZ twins indicated no differences in variances between MZ and DZ twins ($\chi^2_{(2)} = .069$, $p = .996$) and thus, given the large sample size, did not suggest that social interaction between twin siblings is of importance. Maternal effects GE correlation and imprinting can be examined if data on the offspring of male and female MZ twins are available.

Data from twins and siblings only, as analyzed in the twin-sibling studies described above, may not provide sufficient statistical power to disentangle additive and non-additive genetic effects, even when sample sizes are large. MZ twins are perfectly correlated for all non-additive genetic effects. DZ twins and siblings share ¼ of the dominance or non-additive genetic effects (the interaction between alleles at a locus) and less of the epistatic genetic effects (where epistasis refers to interaction between genes at different loci; epistasis takes place when the action of one gene is modified by one or several other genes, which are sometimes called modifier genes). In contrast, while the correlation for additive genetic effects in parents and offspring is also 0.5 (unless the expression of genetic effects depends on age), parents and offspring are not correlated for dominant genetic effects. Therefore, if dominance is of importance, the correlation between parents and offspring is expected to be lower than the correlations among DZ twins and siblings.

Distel et al. (submitted) examined the genetic and environmental influences on individual differences in BPD features using an extended twin-family design. Data were collected on BPD features in twins (N = 5,017), their spouses (N = 939), siblings (N = 1,266) and parents (N = 3,064). Additive and non-additive genetic effects, individual specific environmental influences, and assortment and cultural transmission were tested. Familial resemblance for pairs of family members with different degrees of genetic relatedness is depicted in Figure 1. There was no indication for specific twin environment and the resemblance between parents and their offspring was independent of the sex of the parent. The MZ twin correlation was .45 and the DZ/sib correlation was .18 suggesting that around 50% of the variance in BPD features can be attributed to genetic factors and that part of the genetic variance might be non-additive. Resemblance between fathers and their offspring was equal to the resemblance between mothers and their offspring (r = .13). The parent-offspring correlation was a bit lower than the DZ/sibling correlation, again indicating genetic dominance. There was a significant association between the BPD scores of spouses (r = .19). The correlation between MZ twins and their co-twins' spouse (r = .18) was higher than the correlation between DZ twins and their co-twins' spouse (r = .07) which indicates the non-random mating is primarily based on phenotypic assortment. Several models were fitted to the data to test the significance of additive genetic effects, non-additive genetic effects (dominance), unique environmental effects, cultural transmission and GE covariance. In the best fitting model resemblance among biological relatives could completely be attributed to additive and non-additive genetic effects. Variation in BPD features was explained by additive genetic (21%; 95% CI 17-26%) and non-additive genetic (24%; 95% CI 17-31%) factors. Unique environmental influences (55%; 95% CI 51-60%) explained the remaining variance. Around 1% of the total variance

was due to the genetic consequences of assortment. There was no effect of cultural transmission.

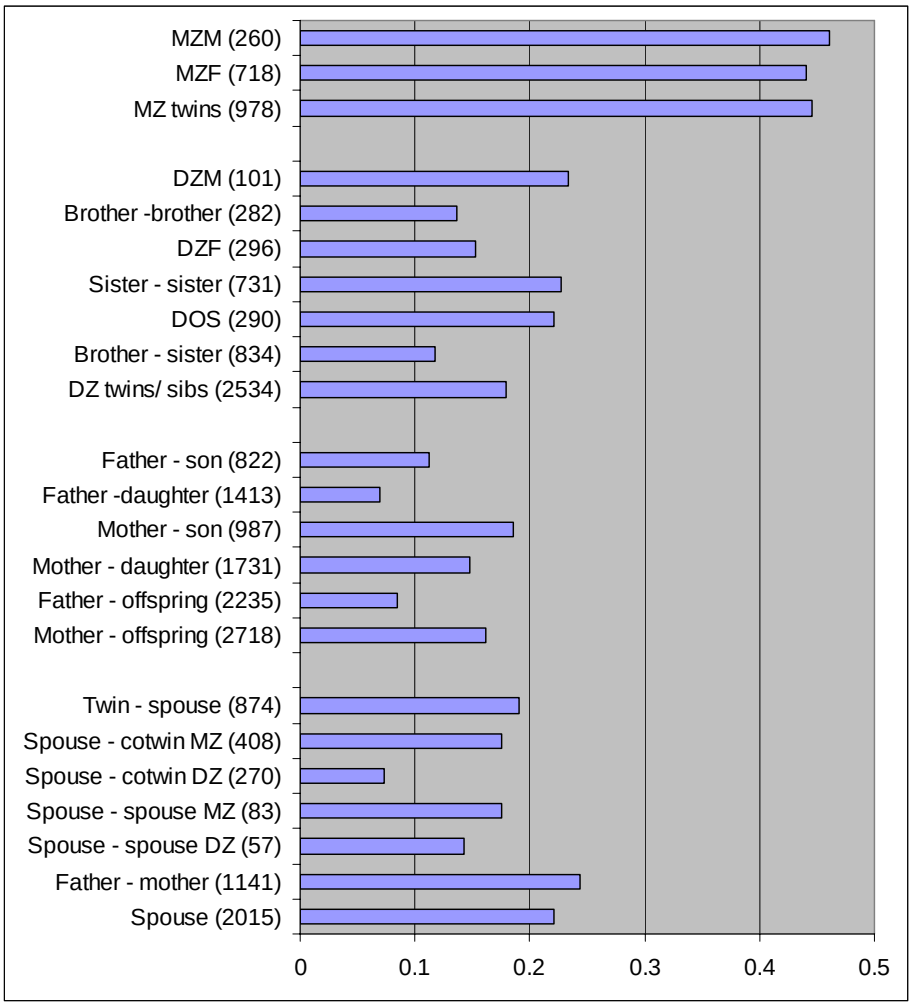

Figure 1. Correlations between family members of different degree of relatedness (number of pairs).

LINKAGE STUDIES

Since we know now that variation in BPD and BPD features have a genetic component, the next step is to find and study the genes involved. Through linkage analysis, the location of genes involved can be determined. Linkage is based on allele sharing within families or pedigrees and can be investigated by correlating allele sharing for DNA markers in e.g. pairs of siblings with the differences between sibs on a quantitative trait.

If a marker is linked to a quantitative trait there will be greater than expected allele sharing for siblings who are more similar for the trait (Vink & Boomsma 2002). Linkage for complex traits is often performed with sibling pairs. If a pair of siblings has received the same

combination of alleles from a parent at a certain marker locus of the genome, the pair is said to share the parent's alleles at the locus identical by descent (IBD). Because offspring receive the alleles from two parents, the pair can share 0, 1 or 2 alleles IBD at a locus. If the marker locus is close to a causal gene, then IBD status at the marker locus reflects IBD status at the causal locus. IBD status will then be associated with trait resemblance in sibling pairs (Haseman & Elston 1972). If siblings are genotyped but not their parents, it is possible, based on information about allele frequencies, to estimate the probability that a pair of siblings shares 0, 1 or 2 alleles IBD.

To date, only one linkage study has been conducted to identify the genomic region(s) which may contain the quantitative trait loci (QTLs) that influence the manifestation of BPD features. Distel et al. (2008b) carried out a linkage study with 711 sibling pairs with phenotype and genotype data, and 561 additional parents with genotype data. BPD features were assessed on a quantitative scale. Evidence for linkage was found on chromosomes 1, 4, 9 and 18. The highest linkage peak was found on chromosome 9p at marker D9S286 with a Lod score of 3.548 (empirical *p*-value = 0.0001). To determine the importance of chromosomes 1, 4, 9 and 18 in the development of BPD it is essential that the results are replicated in other samples and that fine-mapping and association studies in these regions are conducted to identify the actual genetic variants.

CANDIDATE GENE STUDIES

Besides linkage, association is a powerful approach to map genes involved in complex human traits and disorders. Linkage studies are usually genome wide and carried out in pedigrees or in sibling pairs. Association studies assess genetic variants in candidate genes and can be performed at the population level. Case-control studies are the most commonly used type of association studies. Case-control studies compare allele frequencies between a group of unrelated affected individuals (e.g. BPD patients) and a group of unrelated controls. Most candidate genes are functional genes that have biological consequences related to the trait, disorder or disease. They can be suggested by linkage studies if interesting genes are located under a linkage peak, by animal models for a disorder, by pharmacological studies, or be based on theoretical models.

Reduced serotonergic function in anger (Giegling et al. 2006), aggression (Siever 2008), suicidal behaviour (Bah et al. 2008; Zaboli et al. 2006) and impulsivity (Passamonti et al. 2008; New et al. 1998), and increased serotonergic function in emotional lability (Hoefgen et al. 2005) have led to several serotonergic candidate genes for BPD. Tryptophan hydroxylase (TPH) and the serotonin transporter gene (5-HTT), are the most studied candidate genes.

TPH plays a role in the biosynthesis of serotonin (5-HT) and is therefore expected to be related to dysfunction of the 5-HT system. Zaboli et al. (2006) conducted a case control study to determine whether specific TPH SNP-based haplotypes were associated with BPD in 95 suicidal female BPD patients. They found that several haplotypes were associated with BPD but no individual single nucleotide polymorphism (SNP) was associated with BPD.

5-HTT transports serotonin from synaptic spaces into presynaptic neuron. Ni et al. (2006) examined association between 5-HTT and BPD in 89 BPD patients and 269 healthy controls. For this purpose three polymorphisms were genotyped: 5-HTTLPR (the 5-HTT-linked

polymorphic region [LPR]), VNTR (variable number of tandem repeat) in intron 2 and a SNP within the LPR region (A/G). Higher frequencies of the 10 repeat and the S-10 haplotype were found in BPD patients compared to healthy controls. No significant differences in allele frequencies or genotype frequencies of 5-HTTLPR and A/G were detected. The authors conclude that 5-HTT may play a role in the etiology of BPD. Pascual et al. (2008) however, were not able to replicate this finding in 86 BPD patients and 100 control subjects. The authors give the clinical heterogeneity of BPD patients as a possible cause of the differential outcome and suggest that future association studies should focus on genetically homogenous subgroups of BPD patients.

Besides serotonergic dysfunction, there is some evidence that dopamine (DA) dysfunction may be associated with BPD. DA dysfunction is associated with emotional dysregulation, impulsivity and cognitive-perceptual impairment (for a review see Friedel 2004), three important dimensions of BPD. Joyce et al. (2006) found a significant replicated association between the 9-repeat allele of dopamine transporter 1 (dopamine active transporter, DAT1) and BPD in depressed patients.

Finally, genes involved in the production of monoamine oxidase-A (MAOA), which degrades amongst others 5-HTT and DA, are suggested to be involved in BPD because it is shown to be associated with aggression (Buckholtz & Meyer-Lindenberg 2008), impulsivity (Manuck et al. 2000) and mood lability (Furlong et al. 1999). To test whether MAOA is also associated with the BPD diagnosis Ni et al. (2007) genotyped two MAOA polymorphisms (promotor VNTR and rs6323) in 111 BPD patients and 289 control subjects. A high frequency of the high activity VNTR alleles and a low frequency of the low activity haplotype was found in BPD patients suggesting that the high activity allelic variant may play a role in the etiological development of BPD.

Although several studies indicate the influence of 5-HTT, DA and MAOA on BPD and related traits, there is no satisfactory neurobiological model for BPD. Replication in other samples is needed to determine the biological basis of BPD.

FUTURE RESEARCH

Twin and twin family studies have shown that genetic effects explain around 35 to 50% (of which part is non-additive) of the variance in BPD and BPD features. The only linkage study conducted up to now pointed to chromosome 9 as a candidate for genes influencing BPD and candidate gene studies found evidence for the influence of genes involved in the serotonergic system, dopamine dysfunction and the production of monoamine oxidase-A on the development of BPD. In spite of these important findings much is still to be learned. Several lines of research could be of importance.

Multivariate twin family studies, in which more than one phenotype per person is analysed, can shed light on the genetic and environmental causes of association between traits, comorbidity between disorders or overlap between traits and disorder. Distel et al. (submitted) investigated to what extent the covariance among four important components of BPD (affective instability, identity problems, negative relationships and self-harm) could be explained by common genes. The phenotypic correlations among the scales ranged from .21 to .56 and were best explained by a genetic common pathway model, in which a single latent

factor influenced all four components. A single genetic factor underlies most of the genetic variance in BPD but each contributing component to BPD was also influenced by specific genetic factors, which do not overlap with each other. Torgersen and others (2008) examined the genetic and environmental contribution to the co-occurrence of the four cluster B personality disorders. They found that a common genetic and a common individual specific environmental factor influenced all four cluster B personality disorders. A second common genetic and common environmental factor contributed to BPD and Antisocial personality disorder. In addition there was disorder specific genetic variance, which was strongest for antisocial personality disorder, and narcissistic personality disorder and very low for histrionic personality disorder and BPD. Further, in light of the increasing consensus that personality disorders represent the extremes of normal personality it would be interesting to investigate the genetic and environmental overlap between personality traits and disorders. For example, studies of the relationship between the five factor model of personality and BPD showed that BPD patients tend to score high on neuroticism and low on agreeableness and conscientiousness (Widiger et al. 2002; Reynolds & Clark 2001). Multivariate twin family studies can explain the genetic etiology of the relationship between BPD and the five factor model.

Often not all covariance between two or more disorders or traits can be explained by common genetic factors. The discordant MZ co-twin design is a powerful method to explore the mechanisms underlying the association between traits or disorders while controlling for the influence of genes and shared environment. This design compares, for example, the score on a loneliness scale of the BPD affected twin with that of his or her co-twin who has no BPD. Because MZ twins share both their genes and the environment they grew up in, genetic and common environmental influences are controlled for. If the association between loneliness and BPD is explained by environmental factors for which twin pairs are discordant, the loneliness scores are expected to differ (Martin et al. 1997; Middeldorp et al. 2008).

The children of twins design compares the rates of disorder in the offspring of discordant pairs of twins. A lower BPD prevalence in the offspring of the unaffected MZ cotwin than in the affected MZ cotwin would indicate a causal environmental association between parental and child BPD, because the child of the affected cotwin was exposed to a parent with BPD while the child of the unaffected co-twin was not (their genetic risks are identical if their parents are identical twins). If the BPD rates in the offspring of affected and unaffected co-twins are equal, the disorder of the parent does not have a direct influence on the children. Higher rates of BPD in the offspring of unaffected MZ twins (who are a first degree relative of the affected MZ co-twin) than in the offspring of unaffected DZ twins (who are a second degree relative of the affected DZ co-twin) suggests that genetic effects play a role in the association between parental and child BPD. If this pattern is absent, shared environmental factors are most important (D'Onofrio et al. 2003).

Several strategies in molecular genetics have been developed to localize and identify the genes involved in BPD. Linkage and candidate gene studies were previously discussed. Linkage studies systematically assess the entire genome, but have relatively low statistical power and require family data. Association studies have higher power, but when they are carried out with candidate genes they require prior knowledge. A third relatively new method is genome wide association (GWA) studies. GWA searches the whole genome for small variations (SNPs) that occur more frequently in people with a particular disorder than in people without the disorder. Each study can look at hundreds or thousands of SNPs at the

same time. Identifying genes that influence the development of BPD will help to develop better strategies to diagnose, treat and prevent the disorder. However, association analysis measures statistical associations, cannot be used to test for causality, and is prone to population stratification. Specifically, in case-control studies the choice of controls is very important to avoid selection bias. Cases and controls should therefore ideally come from the same population.

Finally, in addition to the correlation between genes and environment as discussed previously, the interaction between the influences of genes and environment on the development of BPD needs further exploration. Gene-environment interaction implies that genes determine the degree to which a subject is sensitive to an environment. In the presence of interaction, individuals with a 'sensitive' genotype will be of greater risk to develop BPD if the predisposing environment is present, than individuals with an 'insensitive' genotype. If gene-environment interaction is present for BPD, and the predisposing environment involves experiences unique to an individual (G-E interaction), this will increase the estimates for E in the classical twin model. If the predisposing environment involves experiences shared by members of the same family (G-C interaction), the estimate of A will be increased (Purcell 2002; Molenaar et al. 1990). G-E interaction can be detected by determining if the heritability of BPD varies in groups with different environmental conditions (for example experiencing sexual abuse).

CONCLUSION

BPD is a common personality disorder with a prevalence rate of 1 to 2%. The main symptoms are affective instability, identity disturbance, negative relationships and self-harm (impulsivity). Recently, research into the etiology of BPD has attempted to clarify the etiology of BPD in terms of genetic vulnerability in addition to social and environmental causes.

Family-, twin, and twin family studies revealed that BPD and related traits are heritable and that the genetic influence on BPD features is partly non-additive (Distel et al. submitted). Moreover, a linkage study (Distel et al. 2008b) found evidence for genes influencing BPD features on chromosome 9. Association studies indicate the influence of genes involved in the serotonergic system, dopamine dysfunction and the production of monoamine oxidase-A. Multivariate research showed genetic overlap between all four cluster B personality disorders (Torgersen et al. 2008) and between an dimensional measure of BPD and personality traits. Future research should focus on integrating sociocultural, biological and environmental causes of BPD to move toward a comprehensive model of the development of BPD.

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