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Past, Present, and Future of Genetic Research in Borderline Personality Disorder

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Review of Borderline Personality Disorder

A major mental illness with a lifetime prevalence of approximately 1–3%, borderline personality disorder (BPD) is characterized by a persistent pattern of instability in relationships, mood, impulse regulation, and sense of self. This results in impulsive self-damaging behavior, difficulty controlling anger, severe functional impairment and intense irritability or anxiety [1]. Moreover, this disorder is marked by rates of suicide around 10%, almost 50 times higher than in the general population [2]. Although the symptoms and course of BPD are well characterized, its etiology is less clear.

It is generally accepted that borderline personality disorder (BPD) has a complex, multifactorial etiology, resulting from an interaction among genetic and environmental substrates [3]. Given its moderate to high heritability based on twin and family studies, the role of genetic risk factors in BPD is unquestionable [4,5]. However, our understanding of the genetic architecture of BPD is very limited. This is a critical obstacle since genetics can pave the way for identifying new treatment targets and developing preventive and disease-modifying treatments which are currently lacking [6].

One important challenge for genetic research is the heterogeneity of BPD. Like most other psychiatric disorders, the diagnosis of BPD in the DSM-5 is polythetic, resulting in multiple possible combinations of criteria to fulfill the diagnosis of BPD and significant heterogeneity [7]. In fact, it has been suggested that the neurobiological substrates may

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differ across different subtypes of BPD, based on the most prominent symptom domains in a given patient [8].

Introduction to Genetic Studies in BPD

Most early genetic studies in BPD focused on single candidate genes [see 8,9 for a review]. More recently, there has been one genome-wide linkage study and a genome-wide association study (GWAS) of subclinical BPD traits and an insufficiently powered GWAS in patients fulfilling full diagnostic criteria for the disorder [10,11]. Although there are adequate animal models for some of the core dimensions of BPD, as described below, there is a lack of translational research including data from animal models in BPD. Research in more pioneering fields, such as imaging genetics, and epigenetics, holds promise for elucidating the pathophysiology of BPD.

Single-Gene Candidate Studies

The Single Candidate Gene Association Study approach works to identify links between variations in specific genes with the phenotypic manifestations of complex diseases. As with other complex diseases, it is expected that each individual risk variant will have a very small effect on the risk of developing BPD. Not surprisingly, the results of single candidate gene association studies have so far been disappointing, with small effect sizes for the risk variants, lack of replication and no significant associations surviving after meta-analysis of individual studies [8,9].

Because the core BPD traits, such as impulsive aggression and impaired emotional regulation, have been associated with dysregulations of the serotonin system, many of the candidate genes examined are involved in the serotonin system, including Monoamine oxidase A (MAOA), the serotonin receptor 2C (5-HT2C) and tryptophan hydroxylase 2 (TPH2) [12,13,14]. A few studies have examined other targets including the dopaminergic system (dopa decarboxylase [DDC] gene), or neurexins [15,16]. However, these results need to be replicated, and most share limitations of small sample sizes and heterogeneity.

The endophenotype approach in BPD

The modest success in the search for susceptibility genes for the categorical psychiatric disorders (i.e., testing associations of genetic variants with overt syndromic phenotypes such as BPD) has given rise to alternative methods such as the endophenotype approach. The endophenotype approach aims to deconstruct a complex phenotype (e.g., the clinical syndrome of BPD) into its underlying basic elements (i.e., endophenotypes), which may more closely map onto distinct neurobiological pathways [3]. Endophenotypes, also known as intermediate phenotypes, are objectively measurable dimensional features that fall between the grossly manifest signs of psychopathology and their genetic underpinnings [17]. Endophenotypes must be heritable and associated with the disorder, must be independent from clinical state, and must co-segregate within families (such that a trait putatively linked to disease risk is inherited with the risk for the disease itself, resulting in impairment in all affected family members and to a lesser degree, unaffected family members vs. healthy

controls) [18]. Endophenotypes have many applications besides advancing genetic association research: they can also be used to clarify classification and diagnosis, and to foster the development of animal models [17].

Putative endophenotypes of BPD [3,19] include specific behavioral traits (e.g., stress-potentiated impulsivity [20], impulsive aggression [21,22,23], and affective instability), cognitive impairments (e.g., deficits in executive functions, response inhibition, attention and cognitive control [24,25,26] and abnormal social cognition [27,28,29], abnormalities in somatosensory processing [30], sensory integration and motor coordination [31], and alterations in brain structure and neural circuits [32,33,34,35], and molecular pathways [36,37].

Applying the endophenotype approach can address the challenges of high heterogeneity within BPD. Specifically, the power to detect significant associations could theoretically be substantially increased by selecting samples for genetic studies based on the presence or absence of a specific endophenotype, rather than on the presence of the DSM-based categorical disorder. This approach is aligned with the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health, which aims to to develop novel classifications of patients based on dimensions that cut across traditional diagnostic boundaries, and with the Alternative Model for Personality Disorders, described in Section III of the Diagnostic and statistical manual of mental disorders, 5th Edition (DSM-5) [38]. The personality dimensions included in the alternative model for personality disorder are based on well-validated models of personality, and are hypothesized to span the full spectrum of the population, from normal to abnormal. Given the substantial heritability of these personality traits, they may be valuable targets for investigating the genetic underpinnings of personality disorders such as BPD [39].

Genome wide association studies (GWAS)

Genome wide association studies (GWAS) have been a pivotal approach in identifying certain risk alleles of many complex disorders. Importantly, in recent years, these studies have identified risk variants that may increase the risk of psychiatric disorders, such as schizophrenia [40].

GWAS in BPD is only in its infancy; there have only been two GWAS on BPD, one of which did not focus on patients with the full BPD diagnosis, but on self-reported BPD traits [11]. More research is needed in order to discover genetic variants significantly associated with BPD, which could help determine underlying mechanisms and thus future treatments.

Lubke et al. performed the first GWAS on BPD traits using three cohorts of data and determining the phenotype of BPD based on the Personality Assessment Inventory Borderline Scale (PAI-BOR) [11]. The PAI-BOR contains 24 items grouped into symptom domains of BPD, including affect instability, identity problems, negative relations, and self-harm. Even though a relatively modest sample size for a GWAS was used (8,426 patients), the study does measure the phenotype using the same scale for all patients. Approximately 6.6 million SNPs were analyzed throughout the three cohorts of patients, and 7 SNPs, all of

which were located in a small region on chromosome 5, showed significant association. All of these SNPs were within the serine incorporator 5 gene (SERINC5), which facilitates synthesis of lipids, particularly relevant for the incorporation of serine in lipids of cells of the nervous system.

While distinct disorders, borderline personality disorder (BPD) and bipolar disorder (BD) both share some phenotypic overlap, suggesting a common genetic background [41]. Witt et al (2014) performed an association study of 5 SNP variants significantly associated with BD in previous GWAS, to examine whether they were also associated with BPD [42]. The 5 SNPs were located in the genes CACNA1C (2 SNPs), ANK3 (2 SNPs), and ODZ4 (1 SNP). Their sample included 673 BPD patients and 748 controls. The only SNP that showed nominal significance was one in CACNA1C, Rs1006737. However, after correction for multiple testing, the SNP no longer showed any significant association. Interestingly, this SNP did show a sex-specific association in the female subsample only. CACNA1C has been implicated in many psychiatric diseases, including major depression and schizophrenia [43]. Elucidation of a role for CACNA1C in BPD may reveal a common mechanism across the disorders. Further testing must be done as the authors themselves noted that although this was the largest BPD cohort to date, their sample size was still a limiting factor.

Lastly, Witt et al. performed the first GWAS on BPD patients to date, with a total of 998 BPD patients and 1,545 controls [44]. It is important to note that this is still a limited sample size compared with GWAS in other psychiatric disorders. Single marker analysis showed no significant associations after correcting for multiple testing. Gene-based analysis yielded two significant genes: dihydropyrimidine dehydrogenase (DPYD) on chromosome 1, and Plakophilin-4 (PKP4) on chromosome 2. Furthermore, a gene set involved in exocytosis showed significant association with BPD. Interestingly, the study also found significant genetic overlap with bipolar disorder, major depressive disorder, and schizophrenia. This finding can help direct future research on genes involved in BPD. These important findings warrant follow-up and replication in larger samples.

Gene-environment studies of Borderline Personality Disorder

Given that BPD most likely arises from the combination of a genetic predisposition and environmental factors, and that traumatic events may be more common among BPD patients [29], it is surprising that there are very few studies examining gene-environment interactions in BPD patients [45]. Moreover, many of these studies, like most related to BPD, are limited by small sample sizes and a lack of replicated results. Only two studies have assessed gene-environment interactions as predictors of BPD diagnosis; rather, most studies have focused on investigating individual traits characteristic of BPD, such as suicidal behavior, aggression, anger and impulsivity.

Many studies have examined the role of gene-environment interactions in BPD-like traits in populations of subjects without a diagnosis of BPD (see [45] for a review). For example, Ben-Efraim et al. studied the role of interactions between SNPs within the corticotropin-releasing hormone receptor-1 (CRHR1) gene and stressful life events in family-based samples of suicide attempters [46]. Other studies have focused on anger/aggression, finding

gene-environment interactions between dopaminergic and serotonergic gene variants (Dopamine receptor 4, DRD4 and serotonin transporter propmoter 5-HTTLPR polymorphism) and aggression outcomes depending on the social environment [47]. Those with the “risk” variants had higher aggression when raised in unsupportive and stressful environments, but had lower aggression levels than other genotypes when raised in supportive environments.

Distel et al. performed the largest study to date exploring gene x environment interactions and gene x environment correlations in relation to the risk of developing BPD. The degree to which an individual was at risk to develop BPD was estimated through the score on the Personality Assessment Inventory – Borderline features scale (PAI-BOR) scale. The study used self-reported PAI-BOR data from 5083 twin pairs and 1285 non-twin siblings from the general population. The study results support the previously reported relationship between having experienced traumatic life events and the severity of BPD traits. Moreover, the authors identified a gene x environment correlation effect for certain life events; i.e. genes that may confer risk for the development of BPD traits also increase the likelihood of being exposed to some types of life events [48].

In the only study to date examining gene-environment interactions as a predictor of the risk to develop the categorical, clinical diagnosis of BPD, Wilson et al. [49] found that risk alleles in the Tryptophan Hydroxylase I (TPH1) gene moderated the association between childhood abuse and risk of developing BPD in adulthood, such that risk allele carriers with a history of abuse had higher risk of developing BPD.

Additional studies have focused on the gene-environment underpinnings of individual BPD traits in patients diagnosed with BPD (see [45] for a review). For example, studies have found that the catechol o-methyltransferase (COMT) val158met polymorphism and the 5-HTTPLR ss/sl polymorphism modulated the effect of stressful life events on impulsivity and aggression [50,51].

In summary, several -mostly small- studies have identified gene-environment interactions that have not been replicated. While animal models of the interaction between genetic factors and early life experience can provide valuable information, they do not make up for the need for larger, longitudinal studies in humans. More research is needed, ideally in large, prospective children cohorts, to elucidate the gene-environment interplay leading to BPD.

Epigenetics

Epigenetic modifications alter gene expression and include DNA methylation, histone remodeling, and non-coding RNA silencing. Of all genes, about 70% contain methylation sites known as CpG island promoters, named for their characteristic GC and CpG-rich DNA sequences [52,53]. These DNA CpG regions can be unmethylated or hypermethylated, which respectively correlate to active genes with open chromatin structures and silenced genes with closed chromatin structures [54]. Recently, it has been shown that environmental conditions can alter epigenetic states that may affect the development of complex diseases, including psychiatric illnesses. Post-traumatic stress disorder (PTSD), major depressive

disorder (MDD), schizophrenia, bipolar disorder, and borderline personality disorder (BPD) have all been shown to have aberrant epigenetic modifications [55,56,57]. In particular, there is a growing body of research surrounding epigenetic modifications associated with BPD.

In general, environmental conditions can cause epigenetic shifts [58,59]. For BPD, numerous abnormal patterns of epigenetic modification have been discovered. In particular, childhood trauma, a known risk factor for BPD, may be an important environmental condition that causes epigenetic changes. In 2014, Martin-Blanco et al. revealed that the severity of both childhood trauma and BPD were associated with higher methylation for a key stress related gene, glucocorticoid receptor NR3C1, supporting a prior finding by Dammann et al. that BPD patients had higher NR3C1 methylation levels [60]. What remains to be determined is whether BPD causes or is a result of NR3C1 methylation. In addition to NR3C1, the 2011 Dammann et al. study analyzed the methylation patterns of 14 neuropsychiatric candidate genes and also found increased methylation patterns in the serotonin receptor 2A (HTRA2A), monoamine oxidase A and B (MAOA and MOAB) and catechol O-methyltransferase (S-COMT) genes for patients with BPD compared to controls [61]. In 2013, Perroud et al. showed BPD patients had higher methylation rates for brain-derived neurotrophic factor (BDNF), which—due of its role neurodevelopment—may serve as a marker for childhood stress. Moreover, the data revealed that increased childhood trauma directly correlated with increased methylation levels of BDNF [62]. In 2015, Teschler et al. found aberrant methylation patterns for patients with BPD in the ribosomal rRNA gene (rDNA) and the proline rich membrane anchor 1 gene (PRIMA1). For PRIMA1, methylation levels were 1.5-fold higher in BPD patients compared to controls and for rDNA, methylation levels were 0.9-fold lower. Notably, PRIMA1 assembles acetylcholinesterases into tetramers by anchoring them at neural cell membranes [63]. Therefore, an increase in PRIMA1 methylation causes decreased enzyme function and increased cholinergic activity, which has been reported in BPD patients [64]. In 2013, Teschler et al. found increased methylation in APBA2, APBA3, GATA4, KCNQ1, MCF2, NINJ2 and TAAR5 in female BPD patient blood samples compared to controls [65]. APBA2 and APBA3 are neuronal proteins with aberrant methylation previously found in cancer, but not in psychiatric disorders [66].

In summary, several small studies suggest that BPD patients may have abnormal epigenetic modification patterns in genes related to stress, neurodevelopment and neuropsychiatric conditions. However, it is not yet clear how these epigenetic modifications result in the BPD phenotype. More research is needed, and in larger samples, to clarify the role of genetic and epigenetic variation and elucidate the neurobiological and molecular mechanisms leading to BPD.

Imaging Genetics

A wealth of studies and meta-analyses have found abnormalities in brain structure and function in BPD patients compared to healthy controls [67–70]. Theoretically, changes in neural activity and structure can be linked to specific genes. “Imaging genetics” is a research approach in which genetic information and functional neuroimaging data are obtained and linked in the same subjects to characterize genetic modulation of neural circuit activity or

structure [71,72]. Surprisingly, there has been very little research applying the imaging-genetics approach in BPD. Conversely, in other psychiatric disorders such as Attention Deficit and Hyperactivity Disorder (ADHD), imaging genetics-based approaches have provided valuable insights for clinical diagnoses [73], understanding of disorders [74], and targeted therapy [75]. As imaging technology improves, it is becoming more feasible to look for and analyze abnormalities in neural structure and function, and imaging genetics has been an important area of psychiatric research since the turn of the century [76].

A recent study by Perez-Rodriguez et al. applied the imaging-genetics approach to elucidate the role of Brain Derived Neurotrophic Factor (BDNF) genetic variants in modulating amygdala habituation [77]. Deficient amygdala habituation has been hypothesized to be a potential endophenotype for BPD [78]. BDNF genotypes are known to modulate amygdala reactivity to emotional stimuli, which is a putative neural substrate of the emotional dysregulation which characterizes BPD [79–81]. The authors sought to determine whether amygdala habituation is also influenced by BDNF genotypes. During a functional magnetic resonance imaging (fMRI) scan, 57 subjects including BPD patients, psychiatric controls with other personality disorders, and healthy controls were twice presented with a mix of unpleasant, neutral, and pleasant pictures to determine amygdala habituation. The results support the hypothesis that the BDNF 66Met allele was associated with impaired amygdala habituation. The researchers hypothesize that this impairment in amygdala habituation may be an endophenotype of disorders involving emotional dysregulation, such as BPD.

Animal Models in the Study of BPD

Animal models play an important role in the development of pharmaceuticals and provide a valuable framework from which to address research questions that cannot be easily answered in human subjects. However, finding suitable models for complex psychiatric disorders such as BPD can be difficult [82]. Although modeling a disorder so heavily rooted in human perception and social concepts can be challenging with our limited current understanding of the underlying neurobiology of BPD, many animal models are available for domains extremely relevant to BPD, such as aggression [83], social withdrawal and abnormal pain perception [84], and social defeat [85]. These models are often rodents, chosen for their social nature with very complex and distinct patterns of social behavior [86].

Social rejection is one such relevant domain, as BPD patients tend to be unusually averse to and sensitive towards social rejection and exclusion [87]. It is hypothesized that in BPD, patients may be unusually vulnerable to harmfully inadequate social interactions during childhood and adolescence [88]. Rats have been used to model similar social rejection; developing rats of the playful Wistar strain were exposed to either other Wistar rats (adequate partners), or less playful Fischer344 rats (inadequate partners). Wistar rats exposed to inadequate partners were less likely to have adequate interactions with other Wistar rats when fully developed, had higher pain thresholds, and had higher emotional sensitivity than rats exposed to adequate partners throughout development. Long-term changes in corticosterone release and the endocannabinoid system were also observed [84]. Importantly, animal models allow the study of “multiple hits,” where early developmental stress is followed by further stress at a later age, a pattern that matches the history of many

sufferers of BPD. This is of high clinical relevance, as it enables experiments allowing researchers to discover risk, resilience, and plasticity genes, as well as endophenotypes predictive of the disease.

Several human genetic variants implicated in anxiety-related traits, such as brain-derived neurotrophic factor (BDNF) and fatty acid amide hydrolase (FAAH), have been knocked into mice. Casey et al. [89] found these knock-in mice to "recapitulate human phenotypes at complex levels of biology and behavior." These mouse models and others provide the framework for systematic studies of gene x environment interactions that might otherwise be impractical or impossible.

Animal models can also provide the means to mechanistically study the neurobiology of some hypotheses. For example, there is a great deal of evidence suggesting that serotonin systems play a tremendous role in BPD [90,91]. Rodent models have allowed researchers to directly manipulate the cellular underpinnings of these neurobiological systems. For example, recently Challis and Berton manipulated vmPFC synaptic inputs to the dorsal raphae nuclei of mouse models through direct monosynaptic excitation and indirect disynaptic inhibition of 5HT neurons to reveal bidirectional influences on socioaffective behaviors such as social avoidance [92]. Despite these promising advances in animal models mimicking BPD-relevant domains, animal model research in BPD is still in its very early phases. Since animal models are almost always a prerequisite for drug development, it is of critical importance to increase research focused on developing and testing animal models related to BPD.

Future Directions

Future research studies must include larger sample sizes similar to studies done for other psychiatric disorders, such as schizophrenia. The small sample sizes have decreased the power of many studies, making findings difficult to confirm. For example, there have only been a few GWAS on BPD or BPD traits, and all have had small sample sizes compared to GWAS on disorders such as schizophrenia, which have sample sizes upwards of 10,000 cases [93]. This sample size issue is exacerbated by a lack of a holistic animal model for borderline personality disorder. Other common problems in research studies have been high heterogeneity and population stratification effects. A combination of large, mixed ethnic populations and BPD's wide phenotypic heterogeneity may be masking significant effects for specific populations or presentations. Furthermore, males and females tend to present differently [94], and many studies tend to look at only one sex or intermix the two, both of which may cause difficulties in interpreting their results. Another area of genetic research that is currently being explored for the first time in BPD is exome sequencing, which is currently being completed on a cohort of BPD patients and matched controls. The goal is to identify genes or pathways in which functional coding variants are overrepresented in BPD patients compared to healthy controls [95].

Another area of research that needs to be expanded is the identification and characterization of endophenotypes for BPD. Identification of these markers will be relevant for early

detection of BPD before the onset of outward phenotypic symptoms and can be useful for genetic association studies and development of animal models.

Though the etiology of borderline personality disorder is still unknown, the currently available data suggest that it is the result of the interaction between multiple genetic risk factors and environmental effects, likely mediated by specific epigenetic modifications, particularly those associated with early childhood trauma. Current work in this field is promising, linking increased aberrant methylation of multiple genes to BPD. However, in the future it will be important for research in this area to include larger patient sample sizes to more definitively understand these associations. Additionally, because epigenetic shifts are detected with peripheral blood samples, they are not a direct measure of the epigenetic patterns in the brain. It will be important to examine correlations of epigenetic changes in peripheral blood compared to those in the central nervous system (CNS) (e.g., cerebrospinal fluid, CSF). Moreover, it will be important to analyze how variations in blood samples due to exercise or lifestyle impact DNA methylation levels [96].

Conclusion and Critical Comment

Genetic research in BPD is still in its very early stages compared to other major psychiatric disorders. To illustrate this point, a PubMed search for genetic studies in BPD yielded only 156 publications, while a similar search in schizophrenia yielded over 13,000 publications.[1] The only GWAS published in BPD patients was severely underpowered, including only 998 patients. For comparison purposes, the consensus in the genetic literature is that tens of thousands of patients are needed to identify genetic variants associated with complex diseases such as psychiatric disorders [97]. For comparison purposes, a recent GWAS study in schizophrenia included a sample of over 30,000 subjects and 100,000 controls [40]. Moreover, despite causing significant disability, morbidity and mortality comparable to other serious mental illnesses such as schizophrenia and bipolar disorder, BPD has not received the attention and funding it deserves by the biomedical research community and funding agencies. An example of the neglect surrounding BPD is that, despite causing significant disability, BPD is not included among the disorders selected by the World Health Organization to calculate Global Burden of Diseases [98].

The number of clinical trials targeting BPD (only 36 in the US -including completed trials- are listed in ClinicalTrials.gov) is also concerningly low, compared to over 2,000 listed for depression. It is thus unfortunately not surprising that BPD remains one of the few major psychiatric disorders without any FDA-approved medications. Despite the challenges and limitations described above, the future of genetic research in BPD holds promise that it will point to new therapeutic targets to develop new medications, and will help elucidate the underlying pathophysiological mechanisms behind the disorder. It is thus critical to advance genetic research in BPD since it can allow the identification of new drug targets and the

[1]The search was performed on https://www.ncbi.nlm.nih.gov/pubmed on 8/14/2017, using the following search terms: “(gene) OR (epigenetic) OR(methylation)OR (RNA) OR(DNA) OR (histone) OR (polymorphism) OR(haplotype) OR (heritability)OR(sequencing)) AND (“borderline personality”)” for the BPD-related search, and “(gene) OR (epigenetic) OR(methylation)OR (RNA) OR(DNA) OR (histone) OR (polymorphism) OR(haplotype) OR (heritability)OR(sequencing)) AND (schizophrenia)” for the schizophrenia-related search.

development of disease-modifying therapies against the core pathophysiological features of BPD, beyond mere symptomatic improvement. Animal models, GWAS and deep-sequencing approaches are of particular interest because of their potential to uncover and/or test new drug targets and should be prioritized in future studies in BPD.

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dehydrogenase showed significant association with BPD. Gene-set analysis showed that the gene set of exocytosis was significantly associated with BPD. This study was very significant in that it was the first GWAS of patients diagnosed with BPD. Its results need to replicated in larger samples but hold promise for future genetic studies elucidating the mechanism underlying BPD. [PubMed: 28632202]

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