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DNA methylation of *APBA3* and *MCF2* in borderline personality disorder: Potential biomarkers for response to psychotherapy

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Abstract
Borderline personality disorder (BPD) is a severe and complex mental disease associated with high suicidal tendencies and hospitalization rates. Accumulating evidence suggests that epigenetic mechanisms are implicated in the etiology of BPD. A recent epigenome-wide study identified several novel genes which are epigenetically dysregulated in BPD. Those genes include *APBA3* and *MCF2*. Psychotherapy such as Dialectical Behavior Therapy (DBT), an established treatment for BPD, provides an excellent setting to investigate environmental influences on epigenetic mechanisms in order to identify biomarkers for disease status and therapy success. However, the effects of DBT on epigenetic regulation has only been researched in one previous study analyzing *BDNF*. In the present study, we aimed to investigate the role of DNA methylation of *APBA3* and *MCF2* as possible biomarkers for treatment outcome in BPD, whilst validating the previous findings of differential DNA methylation in a cohort of 44 BPD patients and 44 well-matched healthy control individuals. Unexpectedly, we did not detect significant DNA methylation differences between patients and control individuals. However, we found a high correlation between the methylation status of *APBA3* and *MCF2* and therapy outcome: before DBT treatment, both genes were significantly higher methylated in patients responding to therapy compared to patients that did not respond. Our study is the first to report results pointing to possible predictive epigenetic biomarkers of DBT outcome in BPD patients. Following replication in independent cohorts, our finding could facilitate the development of more personalized therapy concepts for BPD patients by including epigenetic information.

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1. Introduction

With a prevalence of up to 2% in the general population and up to 25% in clinical settings, borderline personality disorder (BPD) is one of the most frequent personality disorders (Gunderson, 2009; Torgersen et al., 2001). A high rate of committed suicides (about 10% of the patients) characterizes the severity of this disease. In addition to the high rate of completed suicides, more than 70% of patients suffering from BPD had at least one suicide attempt in their medical history (Oldham, 2006). BPD is characterized by impairments in emotion and affect regulation, self-perception and interpersonal relationships. The severity of BPD is further emphasized by the high rates of relapse after initial successful therapy (Gunderson, 2009; Leichsenring et al., 2011; Zanarini et al., 2006). This renders a sustainable therapy even more essential for a good prognosis.

Dialectical behavior therapy (DBT) established by M. Linehan, is a widely used psychotherapeutic treatment for BPD, whose efficacy has been shown in many studies (Bohus et al., 2004, 2000; Linehan, 1993; Barley et al., 1993). Designed for suicidal patients meeting the BPD criteria, the main aim of the therapy is to reduce suicidal tendencies, including self-harmful behavior, as well as behavior preventing therapy or prolonging inpatient treatment (Bohus et al., 2004; Fleischhaker et al., 2011). Initially designed as outpatient treatment, the DBT was recently modified for inpatient settings, now typically lasting 12 weeks in European psychiatric institutions (Bohus et al., 2004).

The pathomechanism of BPD is not completely understood to date. M. Linehans' model of a biosocial development suggests that BPD is a disorder resulting from biological vulnerability combined with harming environmental influences. A depreciating and emotionally unstable environment during childhood together with genetic vulnerability could result in the disturbances of emotion regulation which is typical for BPD (Crowell et al., 2009; Linehan, 1993). Whereas twin and family studies suggest a heritability of BPD between 35% and 65% (Distel et al., 2009; Torgersen et al., 2000), individual risk genes could not be identified for BPD thus far (Calati et al., 2013; Gunderson, 2009). Over the past years, evidence emerged that epigenetic mechanism play a major role in the mediation of genome-environment-interactions. Alterations in epigenetic regulation have been described for several psychiatric disorders e.g. major depression, schizophrenia and BPD (Januar et al., 2015; Perroud et al., 2016; Rivollier et al., 2014; Teschler et al., 2016). Epigenetics include posttranslational histone modifications, DNA methylation and the activity of non-coding RNAs (Hashimoto et al., 2010). DNA methylation is catalyzed by methyltransferases (DNMTs) (Egger et al., 2004; Jones and Takai, 2001), which transfer a methyl group from S-adenosyl-methionine to cytosine creating 5-methyl-cytosine (Sutherland and Costa, 2003). Regulatory DNA methylation mainly occurs at the cytosine of a CpG dinucleotide. Whereas CpG sites are underrepresented throughout the genome, they are enriched in so called CpG islands (Jones and Takai, 2001), areas containing more than 50% of cytosine and guanine (Egger et al., 2004; Sutherland and Costa, 2003). CpG islands overlap with the promoter regions of 50–60% of human genes and are typically less methylated than CpG sites outside of CpG islands (Wang and Leung, 2004). Hypermethylation of CpG sites in promoter regions typically inhibits transcription through several mechanisms (Sutherland and Costa, 2003), whereas hypermethylation in the gene body usually results in increased expression (Jones, 2012). The epigenome was formerly believed to be stable after the embryonal development (Razin and Riggs, 1980). However, current studies imply that epigenetic regulation is a more dynamic process that is influenced by pre- and postnatal environmental factors (e.g. Nieratschker et al., 2014).

Epigenetic research in BPD thus far has mainly focused on candidate genes of other psychiatric disorders e.g. *BDNF, COMT, 5-HTT* and *MAOA* (Dammann et al., 2011; Perroud et al., 2013; Teschler et al., 2013, 2016). However, Teschler et al. investigated DNA methylation in BDP using a systematic epigenome-wide approach. In this previous study, 259 significantly differentially methylated CpG sites were discovered. The authors selected several of those sites for validation and where able to confirm their findings for two CpG sites located in *APBA3* and one site in *MCF2* and *NINJ2*, respectively (Teschler et al., 2013). An association with BPD has not been described for any of those genes before.

An influence of psychotherapy on DNA methylation levels has been described recently. Roberts et al. (2014) found significant alterations in DNA methylation levels of the serotonin transporter gene (*5-HTT*) in the course of anxiety treatment in children: Those who responded to cognitive behavior therapy (CBT) showed increased methylation levels at a specific CpG site after treatment, whereas the levels of non-responders decreased significantly. A second study reported similar results for *FKBP5:* Here, a decrease in DNA methylation during therapy was associated with a strong reduction in symptom severity, whereas an increase in DNA methylation was associated with a weaker response to treatment (Roberts et al., 2015). In addition to the findings in children suffering from anxiety disorder, an epigenetic effect of CBT has also been described in adult anxiety patients: Ziegler et al. (2016) detected epigenetic alterations in *MAOA* associated with response to CBT in adult panic disorder patients. Prior to therapy the DNA methylation levels of *MAOA* were significantly reduced in patients compared to healthy controls. While the DNA methylation levels of responders increased and where no longer significantly different from those of control individuals, the DNA methylation levels of non-responders decreased even further during the course of the CBT (Ziegler et al., 2016). A similar correlation has been described for *FKBP5* in the context of PTSD: While therapy responders showed a decrease, non-responders showed an increase in DNA methylation over time (Yehuda et al., 2013). In contrast to those findings, DNA methylation of the *GR* was not significantly different in responders and non-responders post-treatment, but the pre-treatment DNA methylation levels predicted treatment response to the extent that responders showed higher levels compared to non-responders (Yehuda et al., 2013). Only one study thus far investigated the epigenetic effects of DBT in BPD: Perroud et al. (2013) showed that *BDNF* DNA methylation

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