

# Chapter 9

## Epigenetic Modifications in Borderline Personality Disorder

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**Abstract** Borderline personality disorder (BPD) is a complex psychic disease with an increased importance in the last years. While the diagnosis and therapy are well established, little is known on the pathogenesis of BPD. Epigenetic alterations are a hallmark for abnormal gene expression and could be involved in the etiology of BPD. These epigenetic changes are mainly classified into altered histone modifications and DNA methylation. Here, we summarize recent findings on epigenetic alterations in BPD. Significant aberrant DNA methylation of serotonin receptor 2A (HTR2A), monoamine oxidase A and B (MAOA and MAOB), glucocorticoid receptor (GR/NR3C1), brain derived neurotrophic factor (BDNF), amyloid beta precursor protein-binding family A member 2 and 3 (APBA2 and APBA3), KCNQ1, MCF2, and ninjurin 2 (NINJ2) has been reported. DNA methylation changes range between 1.1- and 1.5-fold increased methylation in the blood of BPD subjects. Especially, GR/NR3C1 methylation was positively associated with childhood maltreatment and clinical severity in BPD. These data may provide new insights into epigenetic mechanisms underlying the pathogenesis of borderline personality disorder.

**Keywords** Borderline personality disorder • Epigenetics • DNA methylation

### 9.1 Borderline Personality Disorder

Borderline personality disorder (BPD) is a serious mental disorder characterized by a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self-image. BPD is discussed to be part of the bipolar (Agius et al. 2012)

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or of the atypical depressive spectrum (Gremaud-Heitz et al. 2014) but less of the schizophrenia spectrum (Dammann 2004).

Clinical signs of BPD include emotional dysregulation, impulsive aggression, repeated self-injury, and chronic suicidal tendencies, which make these patients frequent users of mental health resources (Lieb et al. 2004; Leichsenring et al. 2011). The nine criteria for borderline personality (Diagnostic and Statistical Manual of Mental Disorders: DSM-IV) (APA 1994) can be organized into four sectors of psychopathology: (a) affective disturbance (a range of intense dysphoric affects, sometimes experienced as aversive tension or tremendous mood reactivity), (b) disturbed cognition (overvalued ideas of being bad, experiences of dissociation in terms of depersonalization and derealization, and nondelusional suspiciousness and ideas of reference), (c) impulsivity (e.g., deliberately physically self-destructive and more general forms of impulsivity, disordered eating), and (d) intense unstable relationships (e.g., profound fear of abandonment or tumultuous quality to close relationships). The lifetime prevalence has been estimated to be about 5.9% (Grant et al. 2008). The point prevalence rates are estimated to be about 0.7% in European national community samples (Torgersen et al. 2001). Additionally, findings showed that BPD was more common in women than in men (about 70% and 30%, respectively) (Widiger and Weissman 1991). The disorder often co-occurs with mood, anxiety, and substance use disorders and is also associated with other personality disorders. The disorder is characterized by severe psychosocial impairment (Skodol et al. 2002a) and a high mortality rate due to suicide – up to 10% of patients commit suicide, a rate almost 50 times higher than in the general population. Several measures (semi-structural interviews) are highly reliable in the care of these patients (Zimmerman 1994). Borderline personality seems to be less stable over time than expected for personality disorders (Zanarini et al. 2006). Causal factors are only partly known, but genetic factors (Siever et al. 2002; Skodol et al. 2002b; Torgersen et al. 2008) and adverse events during childhood, such as physical and sexual abuse (Soloff et al. 2002), contribute to the development of the disorder.

Etiologies such as trauma, abuse, childhood adversity, and exposure to war appear to influence posttraumatic stress disorder, BPD, emotional dysregulation, empathy, and impulsivity via epigenetic mechanisms (Ripoll et al. 2013). Accumulating evidence points to severe emotional and relationship dysfunction as the core epigenetic expressions of BPD (Steele and Siever 2010). In adulthood, BPD is typified by disorganization within and across interpersonal domains of functioning (Clarkin et al. 2004). When interacting with their infants, mothers with BPD show marked withdrawal and frightening or frightened behavior, leading to disorganized infant-mother attachments. Linked to both infant disorganization and BPD is a maternal state of mind typified by unresolved mourning regarding past loss or trauma. Early risk factors for BPD in adulthood include maternal withdrawal in infancy and separation of 1 month or more from mother in the first 5 years of life (Steele and Siever 2010). The evolutionary based complex gene-environment picture emerging confers risk or protection against BPD pathology in ways consistent with infants varying biological sensitivity to context (Dammann 2003). Maternal separation is influencing epigenetic regulation (Toda et al. 2014).

Epigenetic mechanisms are relevant for the description of the endogenous oxytocin system, playing a central role in social cognition, disturbed in BPD (Puglia et al. 2015). Various forms of epigenetic regulation at the levels of DNA methylation, histone modification, and noncoding RNAs (ncRNAs) can modulate transcriptional and translational events required for memory processes. By changing the cellular profile in the brain's emotional, reward, and memory circuits, these epigenetic modifications have also been linked to perseverant, pathogenic memories typical for posttraumatic stress disorder (PTSD) and BPD (Sullivan et al. 2015). Because epigenetic marks (e.g., DNA methylation) can be modulated by environmental stimuli, DNA methylation may be important in the development of anxiety (Alisch et al. 2014), suicidality (Turecki 2014), and vulnerability for stress (Tsuji et al. 2014) common in BPD.

## 9.2 Aberrant DNA Methylation in Borderline Personality Disorder

Aberrant epigenetic modifications are hallmarks of altered gene expression and contribute to several diseases including cancer and psychiatric illness (Dammann et al. 2000; Esteller 2007; Jones and Baylin 2007; Tsankova et al. 2007; van Vliet et al. 2007; Abdolmaleky et al. 2008). Epigenetic regulation is mediated through altered chromatin modifications, including changes in DNA methylation levels and aberrant histone marks. Gene promoters are often located in G/C- and CpG-rich DNA sequences which are termed CpG island promoters (Bird 1986). Active CpG island promoters are associated with unmethylated DNA sequences and open chromatin structures. In contrast, inactive promoters are in a repressed chromatin state: CpG sites are hypermethylated and histones are deacetylated. More than 70% of genes (e.g., housekeeping genes) are transcribed from unmethylated CpG island promoters (Saxonov et al. 2006; Weber et al. 2007). The other genes are transcribed from G/C- and CpG-poor and are rather methylated in the human genome.

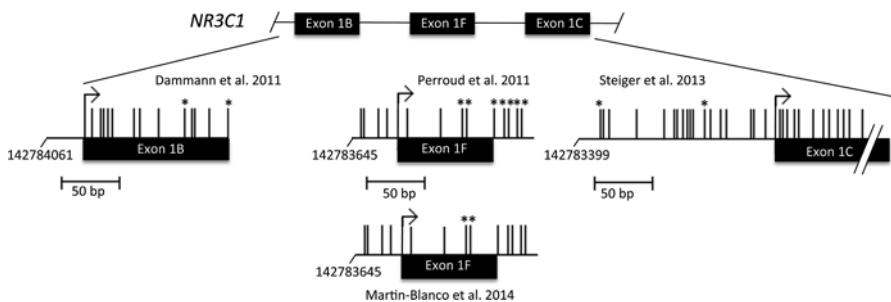
For borderline personality disorder, the epigenetic regulation of some disease-associated genes has been investigated in detail (Table 9.1). In a first study, we have analyzed the DNA methylation pattern of 14 neuropsychiatric genes: COMT, DAT1, GABRA1, GNB3, GRIN2B, HTR1B, *5-hydroxytryptamine (serotonin) receptor 2A* (HTR2A), 5-HTT, *monoamine oxidase A* (MAOA), *monoamine oxidase B* (MAOB), NOS1, *glucocorticoid receptor* (GR/NR3C1), TPH1, and TH (Dammann et al. 2011). DNA methylation was analyzed by bisulfite restriction analysis and pyrosequencing in whole blood samples of 26 patients diagnosed with BPD and 11 controls. Aberrant methylation was undetectable by bisulfite restriction analysis. By utilizing pyrosequencing, a significant hypermethylation of HTR2A (1.2-fold), GR/NR3C1 (1.2-fold), MAOB (1.1-fold), MAOB (1.1-fold), and soluble COMT (1.1-fold) was revealed for BPD patients (Table 9.1). Methylation of DAT1, GABRA1, GNB3, GRIN2B, HTR1B, 5-HTT, NOS1, TPH1, and TH was not yet analyzed by pyrosequencing in further details (Dammann et al. 2011).

**Table 9.1** Summary of DNA methylation analysis in borderline personality disorder (BPD)

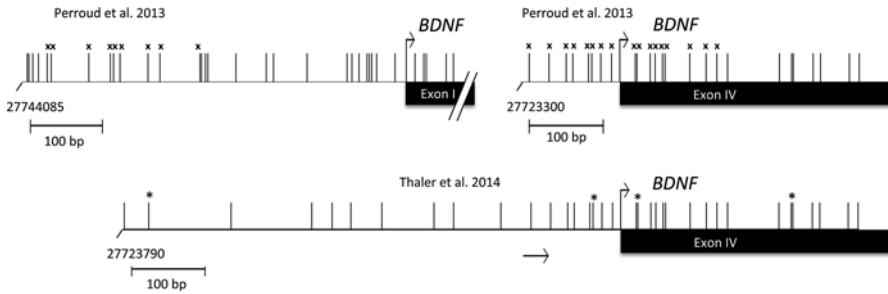
Gene	Methylation increase in BPD compared to controls	Tissue	Control subjects	Methods	References
ABPA3	1.1	Blood	Normal	27 K bead cheap/pyrosequencing	Teschler et al. (2013)
APBA2	1.1	Blood	Normal	27 K bead cheap/pyrosequencing	Teschler et al. (2013)
BDNF (exon I and IV)	2.2 and 3.3, respectively	Blood	52 controls	High resolution melt assay	Perroud et al. (2013)
BDNF (exon IV)	Increased in BPD and bulimia nervosa	Lymphocytes	Non-eating disordered women	Bisulfite and mass spectrometry	Thaler et al. (2014)
DRD2	1.1 in BPD and bulimia nervosa	Lymphocytes	Non-eating disordered women	Bisulfite pyrosequencing	Groleau et al. (2014)
GR/NR3C1 (exon 1 <sub>B</sub> )	1.2	Blood	Normal	Bisulfite pyrosequencing	Dammann et al. (2011)
GR/NR3C1 (exon 1 <sub>F</sub> )	1.3 in subjects with childhood maltreatment	Blood	Non-sexually abused	Bisulfite pyrosequencing	Perroud et al. (2011)
GR/NR3C1 (exon 1 <sub>C</sub> )	1.4-1.5 in BPD with bulimia nervosa	Lymphocytes	Non-eating disordered women or bulimia nervosa (no BPD)	Bisulfite and mass spectrometry	Steiger et al. (2013)
GR/NR3C1 (exon 1 <sub>F</sub> )	Positive association between methylation and childhood maltreatment	Blood	281 BPD sample	Bisulfite pyrosequencing	Martin-Blanco et al. (2014)
HTR2A	1.2	Blood	Normal	Bisulfite pyrosequencing	Dammann et al. (2011)
KCNQ1	1.5	Blood	Normal	27 K bead cheap/pyrosequencing	Teschler et al. (2013)
MAOA	1.1	Blood	Normal	Bisulfite pyrosequencing	Dammann et al. (2011)
MAOB	1.1	Blood	Normal	Bisulfite pyrosequencing	Dammann et al. (2011)
MCF2	1.1	Blood	Normal	27 K bead cheap/pyrosequencing	Teschler et al. (2013)
NIN2	1.2	Blood	Normal	27 K bead cheap/pyrosequencing	Teschler et al. (2013)
S-COMT	1.1	Blood	Normal	Bisulfite pyrosequencing	Dammann et al. (2011)

### 9.3 Aberrant DNA Methylation of GR/NR3C1 and BDNF in BPD

For the neuron-specific glucocorticoid receptor (GR/NR3C1), decreased levels of mRNA as well as increased methylation of the promoter were observed in hippocampus obtained from suicide victims with a history of childhood abuse (McGowan et al. 2009). We and others have reported increased methylation of GR/NR3C1 in borderline personality disorder (Dammann et al. 2011; Perroud et al. 2011; Steiger et al. 2013; Martin-Blanco et al. 2014). In Fig. 9.1, we have indicated CpG sites that exhibited significant changes in methylation levels in these studies. Perroud et al. have analyzed the methylation of exon 1F of GR/NR3C1 in 101 BPD and 99 major depressive disorder (MDD) subjects (Perroud et al. 2011). They report that childhood maltreatment and its severity (e.g., the number of maltreatments) positively correlated with increased NR3C1 methylation (Perroud et al. 2011). For example, they revealed a significant correlation between sexual abuse and GR/NR3C1 methylation showing a 1.34 higher methylation in sexually abused subjects than in nonsexually abused individuals (Table 9.1). These data suggest that early life events may permanently impact the hypothalamic-pituitary-adrenal axis through epigenetic alterations of the GR/NR3C1 (Perroud et al. 2011). Others have analyzed GR/NR3C1 methylation in lymphocytes of women with eating disorder, childhood abuse, or BPD (Steiger et al. 2013). They reported a significant 1.4- to 1.5-fold increased methylation at two out of 18 CpG sites adjacent to exon 1C in women with BPD and bulimia nervosa compared to subjects without BPD (Table 9.1 and Fig. 9.1). No parallel effects owing to childhood abuse were observed (Steiger et al. 2013). Martin-Blanco et al. have analyzed the methylation of GR/NR3C1 (exon 1F) in blood isolated from 281 BPD subjects (Martin-Blanco et al. 2014). They reported a significant positive correlation between GR/NR3C1 methylation and childhood maltreatment (e.g., physical abuse or emotional neglect) (Table 9.1 and Fig. 9.1). Absence of employment was also associated with increased GR/NR3C1 methylation (Martin-Blanco et al. 2014).



**Fig. 9.1** Genomic organization of the analyzed NR3C1/GR exons at chromosome 5q31.3. CpGs are shown as vertical lines and significant aberrantly methylated CpGs are marked with asterisks. Transcription start sites are depicted with arrows and genomic positions are indicated. Graphics were generated with the python.vs.cobra program (<https://launchpad.net/python.vs.cobra>)



**Fig. 9.2** Genomic organization of the analyzed *exon I* and *IV* of *BDNF* at chromosome 11p14.1. CpGs are shown as *vertical lines* and analyzed CpGs are marked with *x*. Thaler et al. (2014) observed that patients with BPD and bulimia nervosa had significant higher methylation levels at four (*asterisks*) out of 27 CpG sites compared to non-eating disorder women. Transcriptions start sites are depicted with *arrows* and genomic positions are indicated. Graphics were generated with the [python.vs.cobra](https://launchpad.net/python.vs.cobra) program (<https://launchpad.net/python.vs.cobra>)

Methylation of the brain derived neurotrophic factor (BDNF) gene has also been analyzed in psychiatric disorders, including BPD (Perroud et al. 2013; Mitchelmore and Gede 2014; Thaler et al. 2014). In Fig. 9.2, we have indicated genomic regions of BDNF that were investigated. In peripheral blood cells from 115 BPD subjects and 52 healthy controls, exon I and IV of BDNF were examined for DNA methylation (Perroud et al. 2013). Increased DNA methylation was observed in both exons of BDNF, compared to healthy controls (Table 9.1 and Fig. 9.2). In BPD individuals, a decrease in methylation levels was observed in responders to a 4-week psychotherapy course, whereas nonresponders showed increased methylation (Perroud et al. 2013). Thaler et al. have analyzed the methylation of BDNF in women with bulimic eating syndrome (Thaler et al. 2014). They report that subjects with BPD, eating disorder (bulimia nervosa), or childhood abuse exhibit increased level of methylation at specific CpGs of the exon IV promoter region (Table 9.1 and Fig. 9.2). They observed that patients with BPD and bulimia nervosa had significant higher methylation levels at four out of 27 CpG sites compared to 32 non-eating disorder women (Thaler et al. 2014). Methylation of the dopamine D2 receptor (DRD2) was also analyzed in women with BPD and eating disorder (Groleau et al. 2014). Increased methylation of DRD2 was revealed in eight subjects with BPD and compared to 19 women with no eating disorder and no BPD (Table 9.1). Subjects with eating disorder and without eating disorder did not differ in the mean methylation level of the DRD2 promoter (Groleau et al. 2014).

In summary, these data suggest that aberrant methylation of disease-relevant genes (e.g., GC/NR3C1 and BDNF) occurs in peripheral blood of BPD patients, and these methylation marks may serve as candidate tool to identify potentially affected BPD subjects.

## 9.4 Epigenetic Alterations Detected by High Throughput Technology in Borderline Personality Disorder

Microarray (chip) technology is a high throughput assay to identify disease-related candidate genes. For microarray-based methylation analysis, two different methylation specific-bead chips from Illumina are available: the HumanMethylation27k bead chip (>27,000 CpG sites) and the second generation HumanMethylation450k bead chip (>450,000 CpG sites) (Bibikova et al. 2006; Sandoval et al. 2011). We have performed 27k methylation bead chip assay with bisulfite converted DNA from blood of 26 BPD patients and 11 controls (Teschler et al. 2013). As expected, our results show that no huge difference in methylation levels between BPD patients and controls are found (Teschler et al. 2013). Genome wide methylation levels of blood samples of BPD patients and control samples are rather similar. However, on several gene-specific CpG sites, bead chip technology and quantitative bisulfite pyrosequencing showed a significantly increased methylation of amyloid beta (A4) precursor protein-binding family A member 2 and 3 (*APBA2*: 1.1-fold and *APBA3*: 1.1-fold), potassium voltage-gated channel KQT-like subfamily member 1 (*KCNQ1*: 1.5-fold), MCF.2 cell line derived transforming sequence (*MCF2*: 1.1-fold), and ninjurin 2 (*NINJ2*; 1.2-fold) in BPD patients (Table 9.1). For the CpG sites of *GATA4* and *HLCS*, an increase in DNA methylation was observed but was only significant in the bead chip assay (Teschler et al. 2013). These results show a significant 1.26-fold average increase in methylation at the analyzed gene-associated CpG sites in the blood of BPD patients compared to controls (Teschler et al. 2013). It is interesting to note that three of these genes (*APBA2*, *APBA3*, and *NINJ2*) are correlated with Alzheimer's disease.

Others have utilized the HumanMethylation450k bead chip to analyze methylation level in DNA isolated from peripheral blood leukocytes in 96 BPD subjects suffering from a high level of child adversity and 93 subjects with major depressive disorder (MDD) and a low rate of child maltreatment (Prados et al. 2015). They report significant differential methylation of *IL17RA*, *miR-124-3*, *KJCNQ2*, *EFNB1*, *OCA2*, *MFAP2*, *RPH3AL*, *WDR60*, *CST9L*, *EP400*, *A2ML1*, *NT5DC2*, *FAM163*, and *SPSB2* either in BPD compared with MDD or in relation to the severity of childhood maltreatment (Prados et al. 2015). Aberrant methylation of one CpG site of *miR124-3* was also analyzed by pyrosequencing in BPD and MDD subjects; however, differential methylation was insignificant by this assay (Prados et al. 2015). The microRNA *miR-124* promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing and could be involved in the regulation of *GR/NR3C1* (Makeyev et al. 2007; Prados et al. 2015).

## 9.5 Altered Histone Modifications in Borderline Personality Disorder

Aberrant histone modifications represent another important epigenetic alteration that may cause changes in expression pattern of disease-related genes in borderline personality disorder. However, histone modifications were not investigated in BPD up to now. The main method to analyze histone modifications or histone variants is cross-linking chromatin in tissue samples and to utilize specific antibodies to precipitate and to quantify chromatin changes. For obvious reasons, relevant fresh tissue samples are rather difficult to obtain from human subjects. Candidate genes to investigate of aberrant histone modification or variants are BDNF, HTR2A, and GR/NR3C1 (Perroud et al. 2011; Mitchelmore and Gede 2014; Paquette and Marsit 2014).

## 9.6 Conclusions

Increased DNA methylation of several neuropsychiatric genes occurred in blood of BPD patients and was also linked to child abuse or clinical severity (e.g., GR/NR3C1) (Perroud et al. 2011; Martin-Blanco et al. 2014). A number of studies have suggested a role for environmentally mediated aversive events in the development of BPD and have found an association between the diagnosis of BPD and psychotraumatization during childhood (Herman et al. 1989; Famularo et al. 1991; Goldman et al. 1992; Paris et al. 1994; Waller 1994; Silk et al. 1995). In a family environment, early maltreatment (childhood abuse and neglect) within a family environment may be particularly important in producing long-term epigenetic changes (Gunnar and Quevedo 2007). In animal models, postnatal maternal care has been linked to epigenetic alteration via DNA methylation (Kaffman and Meaney 2007; McGowan et al. 2011). In the blood of BPD subject, aberrant methylation of several neuropsychiatric genes was revealed, and these findings are summarized in Table 9.1. In future work, it will be interesting to verify this methylation changes in other tissues and to reveal novel BPD-specific biomarkers.

## References

- Abdolmaleky HM, Smith CL, Zhou JR, Thiagalingam S (2008) Epigenetic alterations of the dopaminergic system in major psychiatric disorders. *Methods Mol Biol* 448:187–212
- Agius M, Lee J, Gardner J, Wotherspoon D (2012) Bipolar II disorder and borderline personality disorder – co-morbidity or spectrum? *Psychiatr Danub* 24(Suppl 1):S197–S201
- Alishch RS, Chopra P, Fox AS et al (2014) Differentially methylated plasticity genes in the amygdala of young primates are linked to anxious temperament, an at risk phenotype for anxiety and depressive disorders. *J Neurosci* 34:15548–15556. doi:10.1523/JNEUROSCI.3338-14.2014



- APA (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington, DC
- Bibikova M, Lin Z, Zhou L et al (2006) High-throughput DNA methylation profiling using universal bead arrays. *Genome Res* 16:383–393
- Bird AP (1986) CpG-rich islands and the function of DNA methylation. *Nature* 321:209–213
- Clarkin JF, Levy KN, Dammann G (2004) An object-relations approach to the treatment of borderline patients. In: Kaslow FW, Magnavita JJ (eds) *Comprehensive handbook of psychotherapy*, vol 1, Psychodynamic/object relations. Wiley, New York, pp 239–252
- Dammann G (2003) Borderline personality disorder and theory of mind: an evolutionary perspective. In: Brüne M, Ribbert H, Schiefenhövel W (eds) *The social brain: evolution and pathology*. Wiley, Chichester, pp 373–417
- Dammann G (2004) Differential diagnosis between borderline personality disorder and schizophrenic illness in adolescents with psychotic symptoms. In: Bürgin D, Meng H (eds) *Childhood and adolescent psychosis*. Karger, Basel, pp 94–108
- Dammann R, Li C, Yoon JH, Chin PL, Bates S, Pfeifer GP (2000) Epigenetic inactivation of a RAS association domain family protein from the lung tumour suppressor locus 3p21.3. *Nat Genet* 25:315–319
- Dammann G, Teschler S, Haag T, Altmüller F, Tuzcek F, Dammann RH (2011) Increased DNA methylation of neuropsychiatric genes occurs in borderline personality disorder. *Epigenetics* 6:1454–1462. doi:[10.4161/Epi.6.12.18363](https://doi.org/10.4161/Epi.6.12.18363)
- Esteller M (2007) Cancer epigenomics: DNA methylomes and histone-modification maps. *Nat Rev Genet* 8:286–298
- Famularo R, Kinscherff R, Fenton T (1991) Posttraumatic stress disorder among children clinically diagnosed as borderline personality disorder. *J Nerv Ment Dis* 179:428–431
- Goldman SJ, D'Angelo EJ, DeMaso DR, Mezzacappa E (1992) Physical and sexual abuse histories among children with borderline personality disorder. *Am J Psychiatry* 149:1723–1726
- Grant BF, Chou SP, Goldstein RB et al (2008) Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the wave 2 national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry* 69:533–545
- Gremaud-Heitz D, Riemenschneider A, Walter M, Sollberger D, Kuchenhoff J, Dammann G (2014) Comorbid atypical depression in borderline personality disorder is common and correlated with anxiety-related psychopathology. *Compr Psychiatry* 55:650–656. doi:[10.1016/j.comppsy.2013.11.021](https://doi.org/10.1016/j.comppsy.2013.11.021)
- Groleau P, Joobar R, Israel M, Zeramini N, DeGuzman R, Steiger H (2014) Methylation of the dopamine D2 receptor (DRD2) gene promoter in women with a bulimia-spectrum disorder: associations with borderline personality disorder and exposure to childhood abuse. *J Psychiatr Res* 48:121–127. doi:[10.1016/j.jpsychires.2013.10.003](https://doi.org/10.1016/j.jpsychires.2013.10.003)
- Gunnar M, Quevedo K (2007) The neurobiology of stress and development. *Annu Rev Psychol* 58:145–173
- Herman JL, Perry JC, van der Kolk BA (1989) Childhood trauma in borderline personality disorder. *Am J Psychiatry* 146:490–495
- Jones PA, Baylin SB (2007) The epigenomics of cancer. *Cell* 128:683–692
- Kaffman A, Meaney MJ (2007) Neurodevelopmental sequelae of postnatal maternal care in rodents: clinical and research implications of molecular insights. *J Child Psychol Psychiatry* 48:224–244
- Leichsenring F, Leibling E, Kruse J, New AS, Leweke F (2011) Borderline personality disorder. *Lancet* 377:74–84
- Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M (2004) Borderline personality disorder. *Lancet* 364:453–461
- Makeyev EV, Zhang J, Carrasco MA, Maniatis T (2007) The MicroRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing. *Mol Cell* 27:435–448. doi:[10.1016/j.molcel.2007.07.015](https://doi.org/10.1016/j.molcel.2007.07.015)

- Martin-Blanco A, Ferrer M, Soler J et al (2014) Association between methylation of the glucocorticoid receptor gene, childhood maltreatment, and clinical severity in borderline personality disorder. *J Psychiatr Res* 57:34–40. doi:[10.1016/j.jpsychires.2014.06.011](https://doi.org/10.1016/j.jpsychires.2014.06.011)
- McGowan PO, Sasaki A, D'Alessio AC et al (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 12:342–348
- McGowan PO, Suderman M, Sasaki A, Huang TC, Hallett M, Meaney MJ, Szyf M (2011) Broad epigenetic signature of maternal care in the brain of adult rats. *PLoS One* 6:e14739
- Mitchelmore C, Gede L (2014) Brain derived neurotrophic factor: epigenetic regulation in psychiatric disorders. *Brain Res* 1586:162–172. doi:[10.1016/j.brainres.2014.06.037](https://doi.org/10.1016/j.brainres.2014.06.037)
- Paquette AG, Marsit CJ (2014) The developmental basis of epigenetic regulation of HTR2A and psychiatric outcomes. *J Cell Biochem* 115:2065–2072. doi:[10.1002/jcb.24883](https://doi.org/10.1002/jcb.24883)
- Paris J, Zweig-Frank H, Guzder J (1994) Risk factors for borderline personality in male outpatients. *J Nerv Ment Dis* 182:375–380
- Perroud N, Paoloni-Giacobino A, Prada P et al (2011) Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. *Transl Psychiatry* 1:e59. doi:[10.1038/tp.2011.60](https://doi.org/10.1038/tp.2011.60)
- Perroud N, Salzmann A, Prada P et al (2013) Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. *Transl Psychiatry* 3:e207. doi:[10.1038/tp.2012.140](https://doi.org/10.1038/tp.2012.140)
- Prados J, Stenz L, Courtet P et al (2015) Borderline personality disorder and childhood maltreatment: a genome-wide methylation analysis. *Genes Brain Behav*. doi:[10.1111/gbb.12197](https://doi.org/10.1111/gbb.12197)
- Puglia MH, Lillard TS, Morris JP, Connelly JJ (2015) Epigenetic modification of the oxytocin receptor gene influences the perception of anger and fear in the human brain. *Proc Natl Acad Sci USA* 112:3308–3313. doi:[10.1073/pnas.1422096112](https://doi.org/10.1073/pnas.1422096112)
- Ripoll LH, Snyder R, Steele H, Siever LJ (2013) The neurobiology of empathy in borderline personality disorder. *Curr Psychiatry Rep* 15:344. doi:[10.1007/s11920-012-0344-1](https://doi.org/10.1007/s11920-012-0344-1)
- Sandoval J, Heyn HA, Moran S, Serra-Musach J, Pujana MA, Bibikova M, Esteller M (2011) Validation of a DNA methylation microarray for 450,000 CpG sites in the human genome. *Epigenetics* 6:692–702
- Saxonov S, Berg P, Brutlag DL (2006) A genome-wide analysis of CpG dinucleotides in the human genome distinguishes two distinct classes of promoters. *Proc Natl Acad Sci USA* 103:1412–1417
- Siever LJ, Torgersen S, Gunderson JG, Livesley WJ, Kendler KS (2002) The borderline diagnosis III: identifying endophenotypes for genetic studies. *Biol Psychiatry* 51:964–968
- Silk KR, Lee S, Hill EM, Lohr NE (1995) Borderline personality disorder symptoms and severity of sexual abuse. *Am J Psychiatry* 152:1059–1064
- Sullivan SE, Vaissiere T, Miller CA (2015) Neuroepigenetic regulation of pathogenic memories. *Neuroepigenetics* 1:28–33. doi:[10.1016/j.nepig.2014.10.003](https://doi.org/10.1016/j.nepig.2014.10.003)
- Skodol AE, Gunderson JG, McGlashan TH et al (2002a) Functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder. *Am J Psychiatry* 159:276–283
- Skodol AE, Siever LJ, Livesley WJ, Gunderson JG, Pfohl B, Widiger TA (2002b) The borderline diagnosis II: biology, genetics, and clinical course. *Biol Psychiatry* 51:951–963
- Soloff PH, Lynch KG, Kelly TM (2002) Childhood abuse as a risk factor for suicidal behavior in borderline personality disorder. *J Pers Disord* 16:201–214
- Steele H, Siever L (2010) An attachment perspective on borderline personality disorder: advances in gene-environment considerations. *Curr Psychiatry Rep* 12:61–67. doi:[10.1007/s11920-009-0091-0](https://doi.org/10.1007/s11920-009-0091-0)
- Steiger H, Labonte B, Groleau P, Turecki G, Israel M (2013) Methylation of the glucocorticoid receptor gene promoter in bulimic women: associations with borderline personality disorder, suicidality, and exposure to childhood abuse. *Int J Eat Disord* 46:246–255. doi:[10.1002/eat.22113](https://doi.org/10.1002/eat.22113)
- Teschler S, Bartkuhn M, Kunzel N, Schmidt C, Kiehl S, Dammann G, Dammann R (2013) Aberrant methylation of gene associated CpG sites occurs in borderline personality disorder. *PLoS ONE* 8:e84180. doi:[10.1371/journal.pone.0084180](https://doi.org/10.1371/journal.pone.0084180)

- Thaler L, Gauvin L, Jooper R et al (2014) Methylation of BDNF in women with bulimic eating syndromes: associations with childhood abuse and borderline personality disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 54:43–49. doi:[10.1016/j.pnpbp.2014.04.010](https://doi.org/10.1016/j.pnpbp.2014.04.010)
- Toda H, Boku S, Nakagawa S et al (2014) Maternal separation enhances conditioned fear and decreases the mRNA levels of the neurotensin receptor 1 gene with hypermethylation of this gene in the rat amygdala. *PLoS ONE* 9:e97421. doi:[10.1371/journal.pone.0097421](https://doi.org/10.1371/journal.pone.0097421)
- Torgersen S, Kringlen E, Cramer V (2001) The prevalence of personality disorders in a community sample. *Arch Gen Psychiatry* 58:590–596
- Torgersen S, Czajkowski N, Jacobson K, Reichborn-Kjennerud T, Roysamb E, Neale MC, Kendler KS (2008) Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: a multivariate study. *Psychol Med* 38:1617–1625
- Tsankova N, Renthal W, Kumar A, Nestler EJ (2007) Epigenetic regulation in psychiatric disorders. *Nat Rev Neurosci* 8:355–367
- Tsuji M, Miyagawa K, Takeda H (2014) Epigenetic regulation of resistance to emotional stress: possible involvement of 5-HT1A receptor-mediated histone acetylation. *J Pharmacol Sci* 125:347–354
- Turecki G (2014) The molecular bases of the suicidal brain. *Nat Rev Neurosci* 15:802–816. doi:[10.1038/nrn3839](https://doi.org/10.1038/nrn3839)
- van Vliet J, Oates NA, Whitelaw E (2007) Epigenetic mechanisms in the context of complex diseases. *Cell Mol Life Sci* 64:1531–1538
- Waller G (1994) Childhood sexual abuse and borderline personality disorder in the eating disorders. *Child Abuse Negl* 18:97–101
- Weber M, Hellmann I, Stadler MB, Ramos L, Paabo S, Rebhan M, Schubeler D (2007) Distribution, silencing potential and evolutionary impact of promoter DNA methylation in the human genome. *Nat Genet* 39:457–466
- Widiger TA, Weissman MM (1991) Epidemiology of borderline personality disorder. *Hosp Community Psychiatry* 42:1015–1021
- Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR (2006) Prediction of the 10-year course of borderline personality disorder. *Am J Psychiatry* 163:827–832
- Zimmerman M (1994) Diagnosing personality disorders. A review of issues and research methods. *Arch Gen Psychiatry* 51:225–245