Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Longitudinal Investigation of Phenotypic, Genetic and Epigenetic Factors in Mood Disorders

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Mood disorders such as depression and bipolar disorders are leading causes of the global disease burden. They are characterized by severe changes in mood ranging from depression to mania. Despite decades of research, the etiology of mood disorders is not fully understood. Due to the lack of biomarkers, diagnosis and treatment protocols are still made on the basis of clinical interviews and the subjective description of symptoms by the patient, which are both prone to bias. At present, mood disorders are understood as multifactorial, where an interplay of environmental and genetic factors is causing the disorder. In search for the genetic underpinnings of mood disorders, formal genetic studies showed that mood disorders are heritable (depression ~40%, bipolar disorder ~80%). Genome-wide association studies revealed that many different genetic variants are associated with depression and bipolar disorders and that psychiatric disorders share partly common genetic roots. Also, environmental factors can act via epigenetic modifications, such as DNA methylation. Several studies found differentially methylated markers in individuals with mood disorders compared to healthy controls. In addition, response to antidepressant treatment is related to DNA methylation changes. The overall aim of the two studies was to investigate whether the characterization of mood disorder and treatment response groups is possible with genome-wide and epigenome-wide data. Implicated genes and pathways and their potential role in the development of mood disorders were further investigated.
In the first study, genome-wide data from depression, bipolar disorders (i.e., bipolar I disorder, bipolar II disorder), and biological rhythms were dissected by quantification of their genetic overlap. This was done with biostatistical methods to estimate the genetic correlations, calculate differences in correlations for the different mood disorder subtypes, and conduct gene-level analysis. The biological meaning of the overlapping genes was further researched using genetic databanks. In the second study, differential DNA methylation was analyzed to classify responders and non-responders to Electroconvulsive therapy and identify changes in DNA methylation over time. First, an epigenome-wide association study was conducted, looking at the interaction of treatment group and time, followed by differentially methylated regions and pathway analysis.
The results of study 1 show genetic associations of mood disorder subtypes with biological rhythms. Different and similar correlation patterns of mood disorders with biological rhythms were investigated; showing the strongest differences in correlations with biological rhythms between depression and bipolar I disorder, bipolar II disorder takes a position in between the two mood disorders. These findings show that the associations previously observed in clinical studies are already rooted in genetic differences between the mood disorder subtypes and are not solely due to the specific episode they are observed in. The predisposition for increased activity in bipolar I disorder and the weaker negative association with circadian rhythm implies that the genetic underpinnings of bipolar I disorder may be protective regarding disturbed biological rhythms compared to depression. Furthermore, we identified genes that were associated with both mood disorders and biological rhythms (i.e., *MEF2C*, *CCDC36*, *ERBB4*, *MSRA*, *CADM2*) previously implicated in cell differentiation, neurogenesis, meiosis, and neuropsychiatric disorders. Also, circadian genes such as *NR1D1*, *PER1,* and *ARNTL* were related to depression and bipolar disorder. Results of the second study included differential methylation associated with response groups located in *TNKS*, which is involved in cellular processes, and telomere length and has been found in previous genome-wide association studies of bipolar disorder and positive affect. Under the nominal significant hits, we found *FKBP5*, previously associated with stress and stress-related disorders, and *RAB21,* linked to response to antidepressants, suggesting that similar genes might be implicated in the epigenetic response to different antidepressant treatments. The two

differentially associated regions annotated to *LRATD2* (*FAM84B*) and *BLCAP* are involved in cancer, cellular processes, brain development, and neuronal differentiation.
In conclusion, these studies provide evidence that subgroups of mood disorders and treatment response of Electroconvulsive therapy can be characterized with genome-wide genetic and epigenetic data. Both studies identified genetic and epigenetic markers, which could be potential starting points for further research on the etiology and treatment of mood disorders.