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

Analytical methods to systematically identify genotype-phenotype associations in psychiatric disorders

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Psychiatric disorders are common mostly chronic disorders and like other common disorders they are complex in their etiology. Their clinical presentation is diverse, and different courses and outcomes are observed within diagnostic categories. In contrast to somatic disorders, no objective laboratory measures are available to refine diagnoses, which rely entirely upon clinical symptoms. Although there is high reliability between psychiatrists in terms of the assignment of categorical diagnoses on the basis of clinical symptoms, considerable clinical heterogeneity exists within disorders. To establish diagnostic systems that define more homogeneous groups of patients in terms of biological factors, a more comprehensive knowledge of the etiology and pathophysiology of psychiatric disorders is required. Despite extensive research aimed at disentangling these factors, they remain poorly understood.

Conclusive evidence has been obtained from formal genetic studies of twins and extended families for the contribution of genetic factors to the susceptibility to psychiatric disorders. Studies of twins have estimated a heritability of at least 80% for both SZ and BD, and around 33-77% for MDD. To identify genetic vulnerability factors, linkage candidate and genome-wide analysis studies (GWAS) have been performed. The latter normally analyse between 500k and 1 million single nucleotide polymorphisms (SNPs) for a significant association with a particular disease. Although GWAS have led to the identification of the first genome-wide significant association findings many more variants (each making only a small contribution to the susceptibility of psychiatric disorders) are expected and around 50% of the estimated heritability can be captured by all SNPs of a GWAS. But only very few such variants can be detected at the moment.

The goal of this thesis is to systematically explore which phenotypic traits (e.g. clinical characteristics, sociodemograpic or environmental variables) or phenotype clusters show the strongest relationships with genotypic clusters in psychiatric disorders by focusing on stratification and interaction analysis. Thus, particularly the ability of applying methods that have been successfully used in other fields has been investigated. Finally 4 methods, a) set-based analysis, b) association rule mining, c) biclustering, and d) analysis of latent genotype structures, have been applied to GWAS data of patients with bipolar disorder and schizophrenia.

The basic prerequisite to apply the methods used in this thesis is an appropriately sized dataset of patients and controls. For both groups genetic data and particularly in case of the patients a variety of phenotype information (e.g. clinical data) are required. A substantial part of this thesis included the collection of patients and the related available phenotype information and there consolidation into a unique database, referred as MooDS Phenome Database (MPDB). As a result the MPDB represents the largest collection of BD samples in Europe at the present time.

Applying the four methods two, the set-based approach and the rule mining approach, led to the identification of new genotype-phenotype association findings. Regarding the latter, a novel software tool, called RUDI, has been established and made publicly available to the genetic community. Performing biclustering and analysis on latent genotype structures did not led to new findings here but showed potential for usage in upcoming studies.

In summary, this thesis shows that alternative methods to default GWAS analysis can be used to gain new association findings. Looking at the large amount of available data, more and more becoming available through public databases, it seems indispensable to develop such methods in order to cover the theories that try to unveil more details on the expected heritabilities. Furthermore it may be required to build more comprehensive analytical tools instead of single algorithms that not only use genotype and phenotype data as in GWAS but further biological knowledge. The results further stress the importance of careful phenotyping, particularly with regard to comorbidity.