Exact phenotype definition for complex genetic traits: Novel strategies to establish valid diagnostic entities in psychiatric genetics in the age of high-throughput genotyping and brain imaging.

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Introduction Psychiatric disorders, such as schizophrenia and bipolar disorder (manic-depressive illness) can be viewed as paradigmatic examples of complex genetic traits, with genetic and environmental factors contributing to disease etiopathology. In contrast to somatic complex diseases such as asthma, diabetes, or cardiovascular disease, however, psychiatric disorders pose a specific challenge to the identification of vulnerability genes, given that psychiatric diagnoses cannot yet be guided by biological markers (e.g. a blood test). Thus, exact phenotype characterization is the key step in any psychiatric genetic study. The recent success in the identification of vulnerability genes for schizophrenia and bipolar disorder is largely owed to the application of reliable methods for phenotype characterization (such as the DSM-IV system), genotyping, and statistical analysis. However, recent findings do not necessarily fit the current diagnostic categories: the same genes are proving to be associated with different disorders, and single disorders are not associated with single genes. The challenge that lies ahead is to define genotype-phenotype relationships that have validity at the molecular level [1,2,3].

Methods After an introduction to the development of modern diagnostic assessment tools in psychiatry, we will present data to demonstrate novel approaches in defining complex genotype-phenotype relationships. Using large data sets on bipolar disorder from Germany (300 cases and 300 controls) and the USA (1246 individuals in 172 families), we will present different strategies for systematic genotype-phenotype studies. First, we have developed an approach we call "reverse–phenotyping", which uses genetic marker data to drive new phenotype definitions. Second, we use the results from our reverse-phenotyping approach to define target phenotypes in structural magnetic resonance imaging (MRI) of the brain in a sample of 40 cases with bipolar disorder and 40 controls. Finally, we explore the feasibility of using familial phenotypic characteristics to define subsets of bipolar disorder that are more genetically homogeneous than traditional diagnostic systems.

Results Using reverse-phenotyping, we demonstrate that an established genetic association between bipolar disorder and the G72/G30 locus on chromosome 13q, which was originally identified as a vulnerability gene for schizophrenia, is driven by cases with a life-time history of persecutory delusions [4]. In the MRI study, bipolar disorder patients showed a decrease in the fronto-temporal regions of the brain compared to controls. A grey matter decrease in these areas has previously only been shown in patients with schizophrenia. Moreover, the decrease was even more prominent when only bipolar disorder cases with a life-time history of persecutory delusions were compared to controls. Finally, our study on the familiality of phenotypic characteristics in bipolar disorder revealed substance abuse, alcoholism, psychosis, history of suicide attempt, episode frequency, and the level of social functioning to be strongly familial [5].

Discussion Our finding that the genetic association between markers at the G72/G30 locus gene locus and bipolar disorder is mainly due to those cases with a life-time history of persecutory delusions hints to a molecular genetic overlap in the etiology of bipolar disorder and schizophrenia, given that persecutory delusions, or paranoia, is considered a key feature of schizophrenia. Reverse-phenotyping may prove to be a valuable approach to genome-wide association data.; marker alleles from the entire genome can be assessed against phenotypic characteristics of cases that have been genotyped. Furthermore, the sub-phenotype "life-time history of persecutory delusions" may be considered an important clinical feature in the quest for homogenizing the phenotype of bipolar disorder, thus adding to a high validity at the molecular level. The results from our MRI study already point to a potential biological validity (i.e. in terms of a correlate in brain morphology) of the sub-phenotype "life-time history of persecutory delusions". Finally, we systematically studied the familiality of phenotypic characteristics in bipolar disorder and demonstrated that comorbid conditions and social functioning along with selected other phenotypic characteristics may prove to be valuable in formulating BD subtypes suitable for genetic and other biological studies. Consequently, we are conducting refined linkage and association studies with those phenotypic characteristics that proved to be familial

Outlook Modern operationalized diagnostic criteria, such as DSM-IV, have allowed us to reach reliable and valid diagnoses in psychiatry. With the help of these instruments, first susceptibility genes for psychiatric disorders have been identified. The challenge that now lies ahead of us is to further refine the process of phenotype characterization by incorporating biological information such as (genome-wide) genotype data and brain imaging. On this path, the interaction of clinical expertise, state-of-the art biological techniques, and robust statistical approaches is of utmost importance. Such framework will by no means benefit only psychiatric phenotypes but will prove successful in any complex genetic trait.

Literature

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