Universität Basel

Research Project

Comprehensive genetic analysis of a series of large families affected with bipolar disorder

Third-party funded project

Project title Comprehensive genetic analysis of a series of large families affected with bipolar disorder
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Organisation / Research unit
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Department
Project start 01.06.2015
Probable end 31.05.2019
Status Completed
Aim of the project:
The aim of the proposed project is to improve understanding of the complex genetic causes of bipolar affective disorder by identifying highly penetrant risk genes or combinations of risk variants in a unique set of 20 extended and multiply affected families with bipolar disorder originating from Andalusia in Southern Spain. To reach this aim, we propose a combination of whole exome sequencing in several affected individuals as well as selected unaffected individualsă and high-density SNP arrays to enable a comprehensive bioinformatic and statistical analysis. The most promising 40 risk genes will be followed-up by next-generation resequencing in a series of 1260 unrelated patients with bipolar disorder, comprising 300 patients from Spain and 960 patients from Germany.

Background and rationale:
Bipolar disorder is a common neuropsychiatric disorder with a life-time prevalence of 0.5 – 1.5% in all populations worldwide and an estimated heritability of 60-80%. Previous work, including our own, provides evidence that the heritable part of bipolar disorder is comprised of a mutational spectrum ranging from “common low-penetrance” to “rare high-penetrance”. In the psychiatric genetics field the identification of rare variants with higher penetrance is considered a particularly promising area of research since they would allow insights into a so far less well studied portion of the heritability, and they could prove more amenable to subsequent biological investigation.
Systematic, exome-wide sequencing efforts in bipolar disorder using next-generation sequencing technology have only recently been launched by different international groups. Studies in unrelated (and often sporadic) cases are complicated by substantial locus and allelic heterogeneity. For the proposed project, we have favoured the analysis of multiply affected families as an alternative approach. Monitoring of co-segregation with disease in each family provides a useful tool for distinguishing disease-related from rare neutral variation. In particular, we will comprehensively exploit the exceptional genetic information content of a series of large families with bipolar disorder from a confined region in Andalusia/Spain. We propose to sequence on average 10 individuals per family which is more than in many other “standard” family-based exome-sequencing projects. We argue that this strategy will strongly increase the power to detect individual gene variants of higher penetrance as well as di- and multigenic effects because it is less hampered by the presence of phenocopies. In sequencing studies looking at few individuals per family (e.g. 3 affecteds), true risk variants are likely to be missed if one of the sequenced individuals is not a carrier of that variant. Apart from this, it will also allow us to compare the

genome-wide load of rare coding variants between affected and unaffected family members and how rare variants interact with each other. Genome-wide SNP data will provide opportunities to investigate the influence of copy number variants (CNVs) as well as polygenic risk scores on the penetrance of rare risk variants segregating in the families.

Relevance and impact:
In view of the large impact of bipolar disorder on the global burden of disease, it is important that basic research into this disorder will be performed. The identification of risk genes with large effects has now become feasible through next-generation sequencing technology and the use of suitable, large and multiply affected families. We anticipate that the results of our study will make an important contribution to understanding the biological foundations of bipolar disorder which is generally seen as a first step to developing new therapies.

Keywords rare risk variants; bipolar disorder; whole exome sequencing; next-generation resequencing; di-genic and multi-genic effects
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