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GENOMEWIDE-ASSCOCIATION STUDIES OF PSYCHIATRIC PHENOTYPES: WHAT THEY HAVE TOLD US AND WHAT TO DO NEXT

T.G. Schulze[1,2]
[1]Section on Psychiatric Genetics, Department of Psychiatry & Psychotherapy, University Medical Center Göttingen, Göttingen, Germany, [2]Department of Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA

Genome-wide association studies of psychiatric disorders have highlighted several novel susceptibility genes and taught us several importnat lessons.

1)Psychiatric disorders are polygenic disorders. The contribution of each locus to risk of disease is modest and disease risk increases substantially with the total burden of risk alleles carried.

2) The best findings from GWAS do not necessarily fall within those genes that have previously been widely studied.

3) Pursuing a “top-hits-only” strategy may prevent us from understanding the genetic complexity of psychiatric disorders and polygenic disorders in general. A detailed consideration of the wider distribution of association signals across studies may prove to be a valuable strategy in complex genetics.

4) Allelic heterogeneity may be an important factor in psychiatric disorders. Allelic heterogeneity means that a phenotype can be caused by different alleles within a gene; this phenomenon has been extensively observed in monogenic disorders such as cystic fibrosis as well as in BRCA1/2-associated breast cancer.

5) Finally, as with other complex phenotypes, GWAS in psychiatric disorders demonstrate that the variants identified so far only account for a small fraction of genetic variability.

Future research will need to embark on several complementary approaches in order to fill the yet “unexplained” part of the variance. These will among others include sequencing projects, pharmacogenetic studies, detailed genotype-phenotype dissection approaches, and the study of prospectively assessed phenotypes.

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