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Polygenicity of Bipolar Disorders and Genetic Job Discrimination

Preface

Some significant recent studies and publications (Ketter, 2010; Young, 2010; Parker, 2008) challenge the established views and classifications of Bipolar Depression. Gordon Parker, executive director of the Black Dog Institute in Sydney, underlines that Bipolar Disorder is now more commonly viewed as a spectrum of conditions rather than a single disease entity. He also stresses that only Bipolar II disorder affects up to 6 % of the population.

Terence A. Ketter, Chief of Bipolar Disorders Clinic at the Stanford University, titles his recent Handbook in plural as “Bipolar Disorders” corresponding to the name of his Clinic. Ketter and his colleague Wang call for prudent use of the diagnosis Bipolar Disorder NOS (NOS stands for “not otherwise specified”) as a helpful way to indicate a degree of lack of diagnostic certainty if the careful assessment is inconclusive and, therefore, the three specific bipolar disorder constructs (Bipolar I Disorder, Bipolar II Disorder, and Cyclothymic Disorder) should not be used. The Bipolar Disorder Not Otherwise Specified (BD NOS) can acknowledge the evidence of bipolarity in certain cases yet preserve the integrity of the three specific bipolar disorder constructs.

James Phelps (PsychEducation.org; Co-Psych.com) was invited to submit a contribution to the recent book on Bipolar II Disorder edited by Gordon Parker and he came with an idea which he himself calls “dangerously premature and far overreaching” but this idea, if supported by others, could lead to a diagnostic paradigm shift. Whereas the current default assumptions are ‘unipolar unless proven bipolar’ and ‘antidepressant unless proven to need a mood stabiliser’, the (Parker’s) spectrum perspective suggests that the two assumptions may need to be completely reversed. In practice it means that patients showing symptoms of

depression (more than 12.5% of men and more than 25% of women at least ones in their life time) should be presumed to be bipolar unless a Bipolarity Index (diagnostic system devised in 2004 by Gary Sachs and his colleagues at the Bipolar Clinic and Research Program at the Massachusetts General Hospital in Boston and Harvard Medical School) or equivalent analyses including not just manic features but also family history, course of illness and response to treatment is nearly or completely negative.

Many candidate genes of individually quite small effect

Linking the abovementioned preface statements to the topic of this paper, it needs to be said that there is no polygenicity of Bipolar Disorder as such but polygenicity of the whole spectrum of Bipolar Disorders including Bipolar Disorders Not Otherwise Specified (NOS) which makes it even more complicated as many more genes may be involved, different genes for different parts of the spectrum may be relevant and even more overlapping with other health conditions may exist than previously assumed.

Barnett and Smoller, experts from Center for Human Genetic Research, Department of Psychiatry at the Massachusetts General Hospital in Boston, state that the search for genes influencing bipolar disorder has been complicated not only by the paucity of animal models, but especially also by the limited understanding of pathogenesis, and the genetic and phenotypic complexity of the syndrome.

Linkage studies have implicated several chromosomal regions as harboring relevant genes, but results have been inconsistent. It is now widely accepted that the genetic liability to bipolar disorder reflects the action of many genes of individually small effect, a scenario for which linkage studies are poorly suited. Thus, association studies, which are more powerful for the detection of modest effect loci, have become the focus of gene-finding research.

A large number of “candidate genes”, including biological candidates derived from hypotheses about the pathogenesis of the disorder and positional candidates derived from linkage and cytogenetic studies, have been evaluated. Several of these genes have been associated with the disorder in independent studies (including BDNF, DAOA, DISC1, GRIK4, SLC6A4, and TPH2), but none has been established (Barnett, Smoler, 2009).

Ones more, the clinical heterogeneity of bipolar disorder and its phenotypic and genetic overlap with other disorders (especially schizophrenia, schizoaffective disorder, and major depressive disorder) have raised questions about the optimal phenotype definition for genetic studies. Nevertheless, genomewide association analysis, which has successfully identified susceptibility genes for a variety of complex disorders, has begun to implicate specific genes for bipolar disorder (DGKH, CACNA1C, ANK3).

Craddock, O'Donovan and Owe stated already in 2005 that genomic regions of interest in bipolar disorder include 6q16–q22, 12q23–q24, and regions of 9p22–p21, 10q21–q22, 14q24–q32, 13q32–q34, 22q11–q22, and chromosome 18. The strongest evidence supports DAOA(G72) and BDNF as Bipolar Disorder susceptibility loci.

David J. Miklowitz, Professor of Psychiatry at the University of California and researcher at the Oxford University, also calls the genes suspected to contribute to genetic vulnerability to Bipolar Disorders “candidate genes” and he gives examples: Genes for brain-derived neurotrophic factor (BDNF), which is involved in the stress response; genes for the serotonin transporter (SLC6A4) and the NMDA (N-methyl-D-aspartate) glutamate receptor; the monoamine oxidase A (MAOA) gene and “clock” genes that control circadian rhythms.

Genetic job discrimination of people suffering under all forms of bipolar disorders

The federal Genetic Information Nondiscrimination Act (GINA) of 2008 prohibits US employers from using genetic information for any employment decisions and also restricts their acquisition of such information. "Genetic information" as defined by the law is not limited to clinical lab data, but includes any information that may lead an employer to conclude certain predispositions. In addition to actual genetic data, this may include basic information about family history.

It is not difficult to assume that bipolar disorders will rank (if not already ranks) among the top causes of genetic job discrimination, a serious form of discrimination which is illegal not only in the United States but also in the European Union. Given how quick, cheap and accurate genetic tests will become in the years to come and how difficult it is to detect this criminal activity, it can be assumed that the temptation to genetically test the job applicants and current employees will grow.

Bipolar Disorders are undoubtedly one of the illnesses the employers around the world fear the most. If the job applicant is stabilized, it is almost impossible to detect this latent sickness during a job interview or even assessment centre. In majority of the cases an applicant will even be undiagnosed or misdiagnosed (see the above mentioned statement of Parker on prevalence of Bipolar II Disorder in 6% of the population – most of them have never been diagnosed) so the applicant himself don't know that he suffers under one of the bipolar disorders and, therefore, receives none or wrong treatment. This employee can deliver excellent performance for years but than suddenly make a (very) serious mistake(s) causing (potentially large) damage for the company and his own carrier in the manic or hypomanic phase or display a serious drop in performance or extended absence for medical reason in the depressive phase.

Many genetic testing services already test for bipolar disorder, despite the fact, as described above, that only “candidate genes” are known. Most of the companies do it legally. People want and are willing to pay for being tested. As an example, the Californian company 23andMe tests already for bipolar disorder. It tests gene/gene region 10q21 and SNP rs4948418. 23andMe underlines on their webpage that finding variations associated with bipolar disorder has been difficult. The SNPs that have been identified, including the abovementioned one, explain only a fraction of the genetic contribution to the disease. The SNP that 23andMe reports data for here is a proxy for another one also located in the ANK3 gene. The protein encoded by this gene is involved in the structure and function of nerve cells. It is not yet known how SNPs in this gene might be involved in bipolar disorder.

As reported by popular media, some employers in the EU, US and Asia have already been under suspicion or even accused of testing their job candidates and employees illegally. It can be assumed that significant criminal and litigation cases are yet to come. It is a new type of criminal activity also for the law enforcement which causes delays in detection, investigation and prosecution.

Conclusion

The polygenicity of the whole bipolar disorders spectrum means also that very large samples will be needed to detect the modest effect loci that likely contribute to bipolar disorder (Barnett, Smoler, 2009). As a matter of fact, the statement of Leboyer and Henry from 2005 still stands that genes predisposing for the disease are not known, in part because bipolar disorders are very heterogeneous. The current testing for bipolar disorder is based on a limited number of “candidates”, not more, and can, therefore, be highly inaccurate. People with no genetic predisposition to any form of bipolar disorder what so ever can be currently tested positively. This could not only cause large distress for the person affected but the very same person could end up being genetically discriminated by his employer.

Detailed genetic dissection of the bipolar disorders may in future largely or even completely change pharmacologic treatment of people suffering under this serious illness and open the way for personalized treatment. It can also reduce the risk of misdiagnoses and help to better target psychotherapeutic treatment. It can, however, potentially lead also to discrimination in the workplace of up to 10 % of the population if we count together Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder and the Bipolar Disorder Not Otherwise Specified (BD NOS).