NEW HOT PAPERS - 2009

May 2009

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Francis J. McMahon talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Neuroscience & Behavior.

Article Title: A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder

Authors: Baum, AE, et al.

Journal: MOL PSYCHIATR, Volume: 13, Issue: 2, Page: 197-207, Year: FEB 2008

* NIMH, Unit Genet Basis Mood & Anxiety Disorders, Mood & Anxiety Disorders Program, US Dept HHS,NIH, 35 Convent Dr,1A-202, Bethesda, MD 20892 USA.
* NIMH, Unit Genet Basis Mood & Anxiety Disorders, Mood & Anxiety Disorders Program, US Dept HHS,NIH, Bethesda, MD 20892 USA.
(addresses have been truncated)

SW: Why do you think your paper is highly cited?

This is the first genome-wide association study (GWAS) published on bipolar disorder, a common mental illness of unknown etiology. GWASs command attention due to the relatively comprehensive picture they can give of the genetic architecture of a trait.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

We used a relatively novel DNA pooling strategy that cut the costs of the study about 30-fold, compared to individually genotyping each sample on a genome-wide array. While it has limitations, this may be a promising approach for initial genome-wide screening to see whether a trait is worth the significant investment of individually genotyping thousands of subjects on genome-wide arrays.

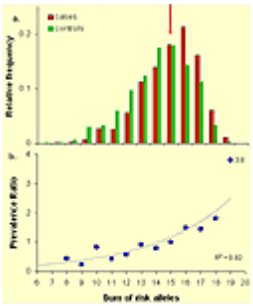
Figure 1: +details

Figure 2:

SW: Would you summarize the significance of your paper in layman's terms?

There are three main points. These are: 1) Even though bipolar disorder is inherited, there seem to be no common gene forms (alleles) that have a big impact on the risk for this condition. 2) One gene, DGKH, seems to play a role. This gene participates in a biochemical pathway that is known to be affected by lithium, a key medication for bipolar disorder (Figure 1). 3) Many genes seem to play a role in disease risk, and only people who have inherited a lot of these genes have a high risk of bipolar disorder (Figure 2). The "tipping point" at which someone was equally likely to have bipolar disorder or not, occurred at about 15 risk alleles in our study, but since we did not detect

all relevant genes, this is probably an underestimate.



SW: How did you become involved in this research, and were there any problems along the way?

I have been studying bipolar disorder for over 15 years. I have always found it intriguing that a disorder that manifests itself only in the mind can nevertheless be so strongly inherited. Despite this fact, progress in identifying the actual genes involved has been very slow. We now recognize that this probably reflects the role of many different genes in determining disease risk.

SW: Where do you see your research leading in the future?

We hope that studies like ours will lead to a better understanding of the biological basis of bipolar disorder—which is still largely mysterious—so that better methods of diagnosis and treatment can be developed.

SW: Do you foresee any social or political implications for your research?

Our research implies that genetic tests will have little or no role in the diagnosis of bipolar disorder for the foreseeable future. There are just too many genes involved, and the magnitude of risk conferred by any one gene is just too small.

Francis J. McMahon, MD
Chief, Genetic Basis of Mood and Anxiety Disorders
National Institute of Mental Health
National Institutes of Health
Bethesda, MD, USA
Web

KEYWORDS: LARGE-SCALE ASSOCIATION; USHERS SYNDROME; COMPLEX TRAITS; LINKAGE; SCHIZOPHRENIA; POPULATION; IDENTIFICATION; POLYMORPHISM; METAANALYSIS; POWER.

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Figures and descriptions:

Figure 1:

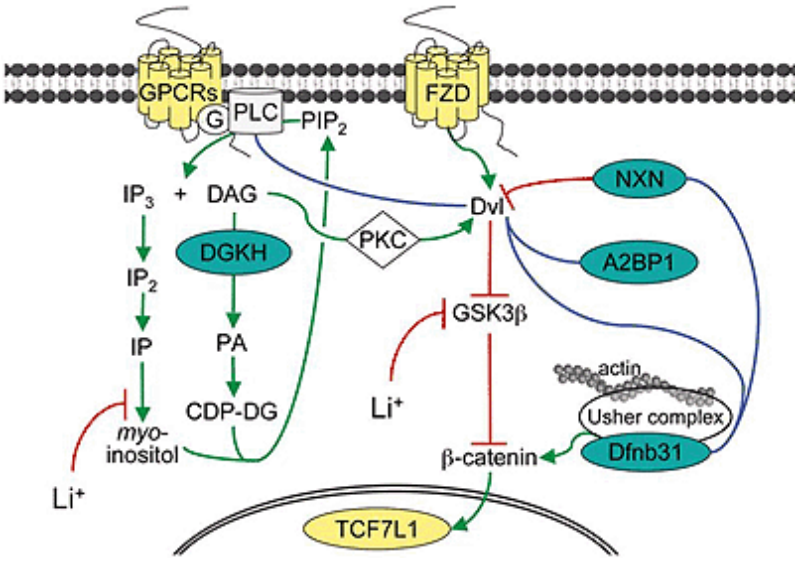

Figure 1:

Eight genes implicated in our study that play a role in lithium (Li+)-sensitive signaling pathways. Green lines denote enzymatic transformations or cofactor activations, red lines confirmed inhibitory actions, blue lines protein interactions of unknown nature from Lim J, *et al.* (2006), or hypothetical interactions. All colored genes contain at least one replicated SNP based on individual genotyping (teal) or pooled (yellow) data.

Reference

Lim J, *et al*., "A protein-protein interaction network for human inherited ataxias and disorders of Purkinje cell degeneration," *Cell* 125:801, 2006

Figure 2:

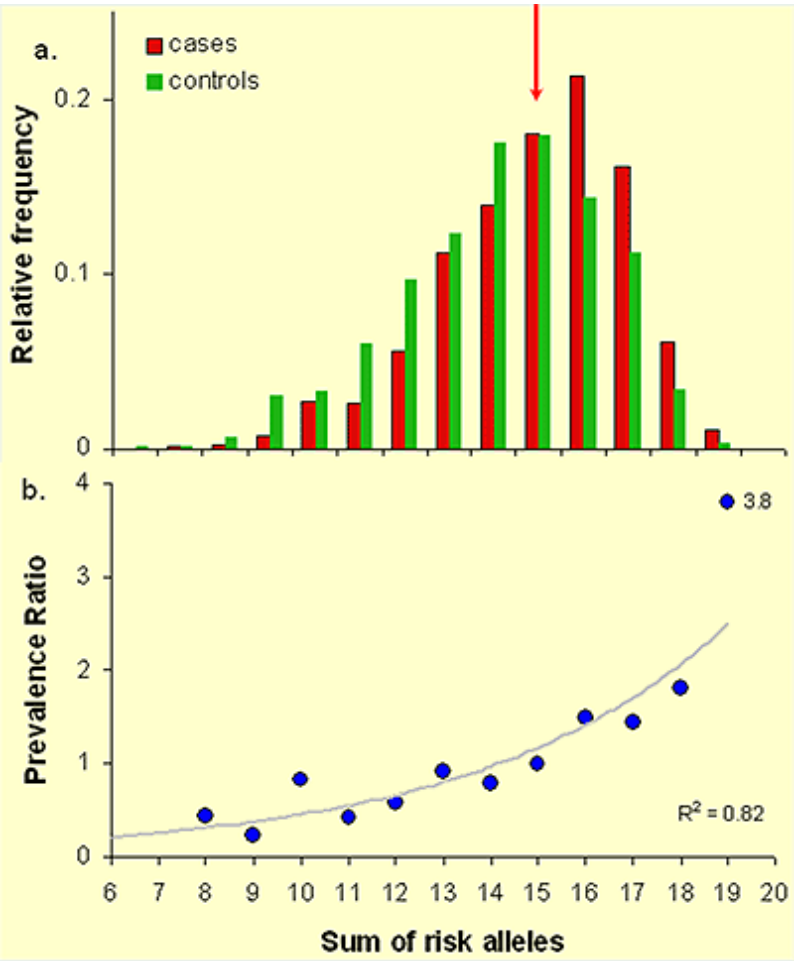

Figure 2:

Distribution of risk alleles among cases and controls (a), and relationship of prevalence ratio (cases: controls) to total burden of risk alleles (b). Data from ten individually genotyped SNPs (rs4411993, rs7683874, rs10937823, rs942518, rs11021955, rs10120953, rs1170191, rs9315885, rs9513877, rs2360111) are plotted. The "tipping point" is indicated by the red arrow. Cases are indicated in red, controls in green.

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