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LETTERS TO THE EDITOR

GWAS for psychiatric disease: is the framework built on a solid foundation?

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In setting out their framework for interpreting genome-wide association studies of psychiatric disorders,[1] the Psychiatric GWAS Consortium Steering Committee considers all possible outcomes ranging from the most favorable ('psychiatric' equivalents to association between fat mass and obesity associated (*FTO*) variants and body mass index), through to the least, that the common disease/common variants (CDCV) hypothesis predicated by the GWAS-study design is flawed. This laudable and transparent synopsis of what may or may not emerge from costly GWAS mega-analyses raises conceptual and practical issues that bear comment.

The CDCV model of psychiatric disease is founded on the multifactorial threshold model of risk for disease[2] and assumes that disease arises from the co-inheritance of multiple risk variants, each of small individual effect. To explain the population prevalence, such variants must themselves be common and should therefore be detectable by GWAS.[3] This model assumes that liability is normally distributed in the population. To explain how a discontinuous trait such as a psychiatric diagnosis can emerge from such a distribution, a threshold of liability (of unspecified origin) is invoked, with those individuals above being at high and those below at low risk of the disease. This statistical sleight of hand allows the powerful statistics of normal distributions to be applied, but how strong is this conceptual foundation?

The polygenic CDCV model in psychiatry was latched onto in the wake of the failure to detect single genes of common and major effect in sib pair and small-family linkage studies.[3] But those studies did not protect against modest levels of locus heterogeneity and variable penetrance, which, along with an appreciable contribution from *de novo* mutation,[4,5] can easily explain observed familial recurrence risks. Familiality and twin concordance data are the bedrock on which all psychiatric genetics, including GWAS, is based and justified. Occam's razor and statistical probability both argue that the co-inheritance of one or just a few risk genes by any individual case is the more likely explanation for the majority of incidence. Indeed, the accumulating evidence points strongly in this direction.[6–8] It is thus highly plausible that psychiatric disorders are inherited in similar manner to deafness, epilepsy or retinitis pigmentosa, which all can be caused by dominant or recessive mutations (model heterogeneity) in any one of a large number of genes (locus heterogeneity) and by alternative mutations (allelic heterogeneity) in the same gene, but which importantly point collectively to shared pathway biology. Each is individually rare in the population, specific to one lineal descent and maintained at a low level by the mutation-selection balance.[9]

It is noted that the studies cited as successes in support of the Psychiatric GWAS Consortium framework are, in the main, studies of recurrent copy-number variants (CNVs) of large effect in individuals, not single nucleotide polymorphism association studies for common effects, around which the CDCV GWAS argument is framed. Copy-number variant studies are in turn simple extensions of the molecular cytogenetics approach, which through comparatively modest investment has nominated well replicated loci for psychiatric disease, such as the VCFS region on 22q11 and multiple biologically plausible genes, such as *DISC1*, *PDE4B*, *GRIK4* and *NPAS3*.[6,7] Linkage studies have also been successful, for example, in identifying mutations in specific pedigrees that strongly predispose to autism. Although individually very rare, these discoveries have converged on a common biological pathway and thus provide invaluable insights into the pathogenic mechanisms.[8] This Multiple Rare Variants model, although discussed as a possibility by the Psychiatric GWAS Consortium, is in reality far better supported by the available data than the CDCV model. It does, nevertheless, leave room for effects of genetic background on the phenotypic expression of rare variants (epistasis), with possible contributions from common alleles as risk modifiers. But in doing so, it firmly predicts that common alleles will explain only a very small fraction of the heritability of psychiatric disorders,[10] and that strategies other than GWAS will be required to detect the primary (rare) causative variants.

A primary justification for any genetic study of a condition of uncertain etiology must surely be to shed light on the biological causes. Haven't we learnt more about disease mechanism and potential routes to the treatment of Alzheimer's disease from the rare variant examples of amyloid beta (A4) precursor protein (*APP*), presenilin-1 (*PS1*) and presenilin-2 (*PS2*) than from the archetypal common variant example of apolipoprotein E, isoform 4 (*ApoE4*)? And if there were an *ApoE4* equivalent for schizophrenia or bipolar affective disorder, Schizopherica (disorder) should it not have already been identified by the multiple GWAS forerunners to the Psychiatric GWAS Consortium?

It is important to contrast the relative value of identifying common variants that contribute statistically significant, but very modest population attributable risks (the most favorable possible outcome of mega-GWAS) with that of genes that in a subset of families and individuals have high predictive value. Focused studies on individual cases, single families or genetically homogenous populations do not currently attract the same cash or cachet as consortium-based GWAS studies, but promise greater returns in terms of biological insight and etiological understanding. In conclusion, from a starting point of those studies that have already identified genes that are both explanatory of risk in related individuals and are biologically plausible, a pathway biology approach from these seeds of certainty provides a logical antidote to the uncertainty of ever larger, more heterogenous and more costly GWAS.

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A 5′ promoter region SNP in NRG1 is associated with schizophrenia risk and type III isoform expression

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NRG1 is a schizophrenia candidate gene which regulates brain development and neural function. The minor allele of rs7014762 in the NRG1 5′ core promoter was associated with schizophrenia ($P = 0.031$), and it significantly predicted reduced NRG1 type III isoform expression in post-mortem human brain of schizophrenia cases ($P = 0.001$). Our results provide additional evidence for transcriptional dysregulation as a biological mechanism implicating NRG1 in schizophrenia risk.

Association between NRG1 and schizophrenia was originally discovered through haplotype analysis in an Icelandic sample (HAP_{ICE}) at the 5′ end of the gene[1] and further replicated in a Scottish population.[2] In this report, we examined association between schizophrenia and the NRG1 single nucleotide polymorphism (SNP) rs7014762 because it is situated within a core promoter region[3] and is physically proximal (87 bp) to a functional SNP, which has been shown to influence NRG1 type IV isoform expression.[4] In addition to clinical association analyses, we validated the functional effects of rs7014762 by testing for effects on mRNA expression in post-mortem human brain.

Cases ($N = 296$) and controls ($N = 365$) were ascertained as part of the Clinical Brain Disorders Branch Sibling Study. The probands met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria for a broad diagnosis category, including schizophrenia, schizoaffective disorder, psychosis NOS (not otherwise specified), delusional disorder, schizotypal, schizoid or paranoid personality disorder. Control individuals were screened to exclude individuals with psychiatric diagnoses. All participants gave informed consent and self-identified as Caucasian. Blood was collected and DNA was extracted using standard methods. Genotypes were obtained using the Taqman 5′-exonuclease allelic discrimination assay.

The post-mortem brain tissue was collected with informed consent from the legal next of kin. The sample was described earlier in detail along with the NRG1 primer and probe sets.[3,4] Briefly, hippocampi from 84 normal controls (22 females/62 males, 53 African American/25 American Caucasian/5 Hispanic and 1 Asian individual, mean age 40.5 ± 15.4 years (s.d.), post-mortem interval 30.7 ± 13.9 h, pH 6.59 ± 0.32); and 44 schizophrenic patients (15 females/29 males, 24 African Americans/20 Caucasians, mean age 49.7 ± 17.2 years, post-mortem interval 36.3 ± 17.7 h, pH 6.48 ± 0.28) were available for study. Diagnoses were determined by independent reviews of clinical records and family interviews by two psychiatrists using DSM-IV criteria. Macro- and microscopic neuropathological examinations and toxicology screening were performed prior to inclusion. No differences were observed for variables that potentially affect gene expression in human post-mortem brain (that is, age, post-mortem interval, pH and RIN, RNA integrity number) by rs7014762 genotype group. NRG1 (types I–IV) mRNA splice isoform expression was measured by real-time quantitative reverse transcriptase-PCR using an ABI Prism