Published in final edited form as:
Mol Psychiatry. 2012 January ; 17(1): 2–3. doi:10.1038/mp.2011.94.

DON'T GIVE UP ON GWAS

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Psychiatric diseases are of major public health importance owing to their enormous morbidity, mortality, and personal/societal cost. Little is known for certain about the etiology of these diseases, and treatment, detection, and prevention strategies are not directed by knowledge of pathophysiology. As family history is a major risk factor, genetic approaches are critically important for most psychiatric disorders.

The initial set of genome-wide association studies (GWAS) using microarrays to test for the role of common genetic variants for psychiatric disorders did not unambiguously identify risk or protective loci. This "disappointing" pattern of results was also seen in many other diseases to which GWAS was applied. It rapidly became apparent that many "failures" were merely due to low power.

The outcomes of GWAS cannot be declared until sample sizes are sufficiently large. If samples are sufficient, GWAS can deliver fundamental knowledge about genetic architecture, identify specific loci for biological follow-up, and localize pathways altered in disease. This technology has been spectacularly successful with the identification of candidate loci for over 100 complex diseases and 115 biometrical traits (1). Meta-analyses for height and body mass have revealed hundreds of new genes falling in pathways that confirm and substantially extend knowledge of the genetics of these traits (2–3). GWAS is arguably one of the more productive technologies in the history of medicine.

In psychiatry, multiple consortia have been formed so that sample sizes can be increased via collaborative analyses (4). For schizophrenia and bipolar disorder, GWAS meta-analyses identified ~15 loci meeting genome-wide significance, and yielded new hypotheses about etiology. In schizophrenia, the results implicate a micro-RNA important in neuronal development along with a network of its targets (5). In bipolar disorder, GWAS results implicate genes important to the control of axonal growth (6–7).

A recent review (8) compared schizophrenia GWAS with eight complex diseases and two anthropometric traits to evaluate the relation between the number of genome-wide significant regions and the number of cases studied. Crohn's disease and systemic lupus erythematosus had the strongest relation between these two variables (~3 genome-wide

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Signed by 96 Psychiatric Genetics Investigators (listed in Table S1)

significant regions per 1,000 cases), followed by type 1 diabetes mellitus and height (~1). Schizophrenia (0.4) was intermediate: slightly worse than multiple sclerosis and age-related macular degeneration (0.5), similar to lung cancer (0.4), and slightly better than type 2 diabetes mellitus (0.3), breast cancer (0.2), and body mass (0.1). The pace of gene discovery for schizophrenia is thus typical.

Empirical data from other complex traits can project what might be discovered if we had larger sample sizes for schizophrenia and bipolar disorder (9). With sample sizes four times larger than those currently available, 30–60 more loci might be identified for schizophrenia and bipolar disorder. This new knowledge would greatly improve pathway analyses to elucidate the fundamental biology of these diseases. With funding, this work could be completed by 2013.

Given the initial successes in the identification of loci for schizophrenia and bipolar disorder, we assert that GWAS will continue to be of great importance in the identification of novel biological candidates for psychiatric illness. GWAS has “worked” for psychiatric diseases, although our sample sizes are small in comparison to other diseases. GWAS technology is mature and relatively inexpensive.

Therefore, we urge the major funding bodies worldwide to continue to support GWAS as a major investigative tool for uncovering hard leads about the fundamental biology of psychiatric diseases. In conjunction with other genomic and phenomic approaches, these leads will be crucial for our understanding and treatment of psychiatric disorders in the 21st century.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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