Pursuit of the "truth" about mental illness: the significance of findings in neuropsychiatric research, and lessons from the past

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Abstract

Technology in genetics and brain imaging has advanced so rapidly that it is difficult to be knowledgeable about all the new tools being used in the pursuit of progress toward understanding and treating mental illness. While findings from new studies remain promising, caution is needed with regard to their current applicability to clinical use, both to predict who is likely to become ill and who is likely to respond to medication. A perspective on the past, using schizophrenia as an example, illustrates important findings that were published, had much visibility, and caused a flurry of new related studies, but then slowly disappeared, either to be abandoned as an artifact of the assay or study design, an epiphenomenon, or as simply nonreplicated findings not leading to further progress. Remembering that good science is "the pursuit of the truth" and not joining the latest "bandwagon fad" of "believers" is an important principle to adhere to when participating in the politics of science.

Keywords: *GWAS; PGC; pharmacogenetics; genetic risk; ethical issues in genetics*

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The latest findings in psychiatric genetics

Genetic technology has advanced at such a rapid pace that it is even difficult for those of us in the field of genetics to keep up with the latest techniques and methods for analyses. Psychiatry in particular has a history of taking advantage of new advances in the field to explore differences that occur in people with mental illness. Essentially, this has occurred because hypothesis pursuit in the field has continually led to failure over the years. Thus, the underlying neural mechanisms for major mental disorders, such as schizophrenia, bipolar disorder, and autism remain mysteries, and preventive measures are nowhere in sight. The current thinking is that psychiatry will not be ready for hypothesis-driven research until searches of large genetic datasets produce consistent findings that then can lead to construction of new proposed pathways or mechanisms for disease. Pharmaceutical companies have thus been liaising with current researchers in order to find clues from this work to target new drug development.

It was therefore with great interest that it was heard and read that the most important research result in psychiatry has finally been published.[1] One hundred and eight independent loci conferring elevated risk for schizophrenia have been found by an unusually large combination of case-control samples collected worldwide. Questions asked are: (i) how elevated is the risk for each variant? and (ii) are these additive, conferring higher risk? Creative statistical geneticists have been able to calculate a Polygenic Risk Score[2] that is valuable for correlational analyses in research studies, but is not likely to be of value for clinical prediction, given its likelihood of both false-positives and false-negatives. It has not yet been shown to be valid and reliable, nor do we understand the genetic architecture of the illness enough to be able to say how it is related to true risk. This fact, however, is not likely to be perceived that way by the public, and may unfortunately be taken up in the clinic as a new predictive tool.

These data came about because of a new approach that was championed by the Broad Institute in Boston, USA. It is paralleled by other collaborations in other complex genetic disorders such as Alzheimer's disease or colon cancer. "More is better" has been the focus. Thus, the larger the number of subjects, the more likely a significant result or set of results will emerge. This concept for psychiatry was first publicly proposed by Dr Edward Scolnick of the Broad Institute in a closing session of The World Congress of Psychiatric Genet-

ics in New York City in 2007.[3] It developed into one of the largest-ever psychiatric collaborations, called the PGC (Psychiatric Genomics Consortium), now based at the Broad Institute for worldwide organization and analyses. One does not need a hypothesis with this design; it just compares thousands of people and looks for any differences between patients and controls. It has worked most robustly for schizophrenia,[1] but now what is the next step? Some research groups are sequencing large cohorts of patients and controls, while others are going back to examining individual families—those with multiple ill members—to note patterns of inherited sequenced segments and how they segregate with illness, a method used long ago when technology was not so advanced. Yet these findings from families can lead to clues for pathways involved that will generalize to the larger population of people with illness, and hopefully lead to new targets for drug development.

The significance of genome-wide association studies

The findings from genome-wide association studies (GWAS) consist of common variations in genes that by themselves may mean little. What is important is that they may form the basis for future studies of their mechanisms, how they relate to each other, and the pathways they involve, which may suggest targets for drug development. GWAS are clearly not family-based, and thus it has not yet been determined whether the risk variants are associated with illness within families or are sufficient and/or necessary to lead to illness, nor whether they can be used to predict future illness within families.

The most hopeful findings thus so far have come from the schizophrenia GWAS, and not those in affective disorder. Despite most of the elevated risk single-nucleotide polymorphisms appearing in noncoding regions of the genome, some promising pathways have evolved as candidates from these results, and these not surprisingly can be divided into those that affect NMDA receptor modulation and related pathways, muscarinic acetylcholine receptors, γ-aminobutyric acid pathways, nicotinic-7 receptors, oxidative stress, and the immune system.[1]

The problem with large GWAS collaborations is that the sample characteristics are lost. Given that the illnesses screened are so very heterogeneous clinically, as well as demographically, it may not be realistic that the obtained polygenic risk factor identifies any one clear biological mechanism for a specific clinical disorder. The strategy used for such large GWAS samples precludes carefully structured systematic ascertainment of samples with good diagnostic reliability across populations to be able to know whether a diagnosis in one center is the same as one in another. Each cohort contributing to the larger one was collected, ascertained, and evaluated in different ways, and thus may have picked up different psychopathologies. Redissecting each may be difficult. This is what is sacrificed in the ability to produce such large samples. There is certainly much that can be said for systematically collecting cohorts and obtaining reliability across them. Unfortunately, in these times of the popularity of "big data" collecting, these principles and the quality of the work going into the sample collection is often lost.

Pharmacogenetics

Understanding how to predict response to medication makes up a major portion of this issue of *Dialogues in Clinical Neuroscience.* Perhaps the most successful use of new genetic technology will not come from GWAS, but rather from the development of specific hypothesis-driven DNA markers that predict response to medications and also the risk of some dangerous side effects. The cytochrome P450 metabolic enzymes, important in drug metabolism, can be genotyped (CYP2D6 and CYP2C19) to determine slow- and fast-metabolizing variants, thus enabling the prediction of side effects in individuals at particular doses of antidepressants, antipsychotics, and other medications. HLA-B15:02 has also been useful in predicting carbamazepine side effects. Moreover, these are established enough that the USA FDA has issued warnings about genotypes for certain medication usage (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm). Studies still in progress, but of high interest, are those using genomics to determine prediction of antipsychotic weight gain and clozapine-induced agranulocytosis.

Pharmacogenetics will also be useful in determining outcome, with the most frequently used genes such as those encoding the serotonin transporter (SLC6A4), the serotonin-2A receptor (HTR2A), and p-glycoprotein (ABCB11) and others that may be associated with lithium response.[4,5]

Ethical issues in the use of psychiatric research data

Should scientists be concerned about the use of their data by the public and the implications drawn from them? This is a much-debated question, leading to science, unfortunately, becoming entangled in politics, particularly when there is a clear gap between the knowledge that researchers have and the perceptions of the research by the public.[6] An extreme example of the misuse of genetic information is the way the Nazi era brought a pseudoscientific thinking that, given mental illness was genetic, cleansing the population of people carrying the genes would eradicate it worldwide. Not only is this scientifically erroneous, but profoundly unethical. Unfortunately, thousands of psychiatric patients were exterminated in Germany in the late 1930s because of this notion.[7]

Currently, sequencing an individual's genome carries the risk of stigmatizing that person and placing him/her under unnecessary scrutiny when applying for employment and in the social scene. The privacy of this information can only be maintained with proper government regulations and the stigma reduced by continual public education. If there is a gap between what researchers know and public knowledge, then misunderstandings, panic, and misuse of the information occur.

In the research itself, ethical issues are debated and are difficult to deal with when attempts are made to combine samples collected worldwide in many ways. Was informed consent obtained from each individual, and what really was their understanding of how their DNA would be used? Some countries and ethical review boards have strict regulations about human DNA being transported out of their respective countries. Who owns these samples and has the rights to them? At some point in the near future these questions will be debated. Is it each individual who contributed DNA, is it the funding agency who made the project possible, the researchers who worked hard on obtaining each sample, the researchers in the laboratory who processed it, or the institutions who administered and oversaw the work? The answer is far from clear.

Lessons from the past: hypotheses gone wrong

Biological psychiatry is replete with old findings of factors present in blood, urine, and even cerebrospinal fluid that were supposed clues to the cause of illness, predictive of it, or predictive of its outcome.[8-11] A low platelet monoamine oxidase enzyme level was hypothesized in the 1970s to be causative of schizophrenia and also affective disorders, as was the endogenous hallucinogen, phenylethylamine. Some of these were found to be artifacts of environmental and iatrogenic variables including general effects of long-term medication, and some were never replicated.[12-15]

When brain imaging was introduced into psychiatry, various indices, such as ventricular enlargement, were used to predict outcome,[16,17] but none of these ever made it to clinical utility. Nor has any brain imaging measurement been found to be predictive of a specific disorder. Nevertheless, PET scanning, which is a difficult and expensive procedure to have patients undergo, does have promise for predicting receptor occupancy that will lead to response to specific medications that effect those receptors. It does not have predictive value for diagnosis of mental disorders, such as schizophrenia, despite its usefulness in Alzheimer's disease.[18]

Psychodynamic issues were also raised, and at one time seemed popular candidates for the cause of schizophrenia, and other major psychiatric disorders leading to the family therapies of the 1960s and 1970s.[19] A measles vaccine scare resulted from erroneously attributing autism to a vaccine side effect.[20] At one time cooking in aluminum pots was thought to cause Alzheimer's dementia.[21] Lastly, birth complications and flu during pregnancy as potential causative factors for later mental illness have caused scares among the patients of obstetricians, but have never found to be clearly causative in the majority of individuals who have these complications during pregnancy.[22,23] Even today, there is much debate about whether cannabis by itself can cause a psychotic illness.[24,25]

In genetics as well, findings have come and gone, and some are long forgotten. For example, there was much excitement in the late 1980s about a finding on the long arm of chromosome 5 that was linked to schizophrenia.[26] This was followed in the 1990s by linkage to chromosomes 6p and 8p,[27] which led to the candidate genes of dysbindin[28] and neuregulin,[29] respectively. But what has become of them in the new GWAS era?

Conclusions

Sophisticated new technology has provided the medical profession with tools for diagnosis, prediction of ill-

ness, new medications, and personalized pharmacologic treatments. But with these come new problems for data interpretation, validity, and ethical use of the information generated. In general, it makes sense to adopt a cautiously optimistic approach to new findings generating excitement in psychiatric research, given that so many in the past are buried in the literature and forgotten, for good reason. ❑

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