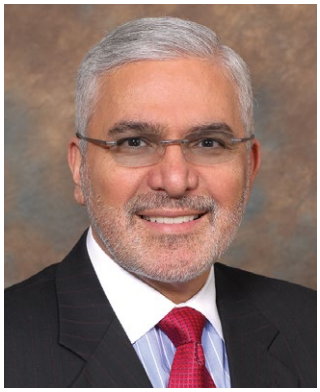
'Druggable' genes, promiscuous drugs, repurposed medications



Henry A. Nasrallah, MD
Editor-in-Chief

Thanks to disruptive genetic breakthroughs in psychiatry, there are glittering lights at the end of the psychopharmacotherapeutic discovery tunnel.

Unprecedented collaboration among 900 genetics investigators across 40 countries led to creation of the highly productive Psychiatric Genomics Consortium (PGC), which is analyzing 400,000 individual DNA samples.[1] The Consortium has an open-source approach, with data freely available to all who are interested.[a]

The PGC recently published the results of a large Genome Wide Association Study (GWAS) of 36,989 people with schizophrenia and 113,075 controls. Investigators discovered 108 genetic loci (each containing as many as 26 genes), adding up to 341 protein-coding risk genes for schizophrenia, distributed across all 23 chromosomes.[2] One of these risk genes, on chromosome 6, is in the major histocompatibility complex and has the strongest association with schizophrenia ($P = 10^{-31}$). This finding provides insight that schizophrenia might be related to immune dysfunction, supported by evidence for neuro-inflammation and elevated pro-inflammatory biomarkers in this syndrome.[3]

In addition to heritable risk genes, the PGC has found many copy number variants (CNVs) and rare *de novo* mutations that are found significantly more often (10-fold or greater) in schizophrenia. But, as reflected by the 50% concordance rate for schizophrenia in monozygotic twins, non-genetic pathways to schizophrenia obviously exist; this is especially so through adverse events during pregnancy, which can disrupt brain development in a manner similar to disruption caused by risk genes, CNVs, and mutations.

[a]Available at http://pgc.unc.edu/downloads.

The most exciting consequence of these breakthroughs?

These genetic discoveries have great implications for novel drug development for the hundreds of biological subtypes of schizophrenia. At latest count, 23,345 genes that code for proteins, the building blocks of the body, are found in the human set of 23 chromosomes.[2] Approximately 7,000 of those genes are *druggable* and can open the way to developing new agents. In fact, identifying potential targets for pharmacotherapeutic intervention is the major goal of conducting a GWAS.[4]

What it means to be 'druggable.' Two conditions must be met for a gene to be druggable: First, it must code for a protein with folds that can interact with chemical compounds; second, that protein must be associated with a human disease.[5] A drug that interacts with several target proteins (eg, kinases, proteases, transporters, enzymes) is

continued on page 41

An auspicious scientific journey, from genome to clinic, has begun in earnest

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continued from page 23

considered *promiscuous*. After such a drug is found to have efficacy in 1 disease, it can be repurposed for treating other diseases. Such repositioning of an already approved drug for other conditions could save the pharmaceutical industry an enormous amount of time and billions of research and development dollars in developing new drugs for psychiatric illnesses that might have been used to treat various other medical conditions.

To exploit the principle of repurposing, Lencz and Malhotra[2] examined the 341 coding genes associated with schizophrenia, to determine whether available drugs interact with the proteins produced by some of those genes. They identified 40 druggable genes (11.7% of the 341) and reported that:

- 27 coding genes (7.92% of the 341) are drug targets[6]
- 20 of the 40 druggable genes are already approved by the FDA to treat a range of medical disorders, including glaucoma, epilepsy, hypertension, angina, irritable bowel syndrome, incontinence, smoking cessation, nausea, hypertension, prostate cancer, type 2 diabetes mellitus, pulmonary fibrosis, and acute promyelocytic leukemia; in addition, some genes act as a diuretic or an nonsteroidal anti-inflammatory drug
- another 20 druggable genes are not approved for use but are in clinical trials for disorders such as Alzheimer's disease, heart failure, neuropathic pain, depression, cancer, immune-supported acne psoriasis, and myeloma.

The opportunity to repurpose some of those promiscuous drugs for various medical indications for the treatment of schizophrenia is exciting, and presents Pandora's box of new mechanisms of action.[7] It is intriguing how therapeutic mechanisms for a wide range of unrelated medical conditions may have commonality with the neurobiological underpinnings of a serious brain disorder such as schizophrenia.

Journey from genome to clinic

Psychiatrists should be heartened by this translational research into the pharmacotherapeutic promise of emerging genetic advances. The parched terrain of psychopharmacology—the result of a drought of truly innovative medications for serious psychiatric brain disorders—soon may be drenched by a shower of translational discoveries from druggable genes.[8] An auspicious scientific journey, from the genome to the clinic, has begun in earnest.

That is great news for our patients, and uplifting to us as well. Breakthroughs to cure intractable and persistent psychiatric brain disorders will not only vanquish disability and restore functioning, but also will be a powerful, long-awaited antidote to the virulent stigma of mental illness.

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