Massive schizophrenia genomics study offers new drug directions

But much more basic research on disease pathways is needed to entice more pharmaceutical companies back to the field.

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It was an affirmation of sorts. Although the dopamine type 2 (D_2) receptor is a target of all marketed antipsychotic drugs, and although focused genetic studies have tied the gene encoding the D_2 receptor, *DRD2*, to schizophrenia, none of two dozen or more unbiased genome-wide analyses had previously found *DRD2* to be a significant genetic risk factor for the mental illness. So, when Patrick Sullivan and his colleagues from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) conducted the largest genome-wide association study (GWAS) to date for the disease, involving around 37,000 individuals with schizophrenia and 113,000 controls, they were pleased to see *DRD2* as a top hit.

"It was really quite vindicating and intellectually fascinating that *DRD2* popped up given its critical importance for drug development," says Sullivan, a psychiatrist and geneticist at the University of North Carolina (UNC) at Chapel Hill School of Medicine and the principal investigator of the PGC, a massive gene-finding effort that includes more than 500 scientists from some 80 institutions around the globe.

DRD2 was far from the sole genetic contributor. The new analysis — published recently by Sullivan and his 300-plus co-authors in *Nature* (**511**, 421–427; 2014) — linked 108 regions of the genome to schizophrenia, 83 of which had not been flagged in any previous GWAS (TABLE 1). "It's increasingly clear that the genetic architecture of schizophrenia is complicated," says Sullivan, who expects to find even more common genetic variants as his team expands the analysis to include at least 60,000 people with schizophrenia. "This is a disease that is dominated by common genetic variation," Sullivan continues. "There are just a lot of things of small effect."

With each gene making only a minor contribution to disease risk, it remains unclear which if any of the newly implicated targets will make good starting points for drug development in schizophrenia, a disease that has not seen a new class of medications since the advent of second-generation or 'atypical' antipsychotics a quarter-century ago. Experts predict that sophisticated pathway modulation will be needed to make a therapeutic impact. "It's unlikely that targeting any one of those [genes identified in the GWAS] alone will be successful in the population at large," says Bryan Roth, a UNC expert on polypharmacology who consults for many companies working in the schizophrenia drug space but was not involved in the GWAS paper. "We'll likely need compounds that hit multiple molecular targets."

Following up

Despite the genetic complexity, the new mega-GWAS provides fodder for companies already engaged in schizophrenia drug development.

Jens Wendland, head of neuroscience genetics at Pfizer and a co-author of the recent study, says his company has already systematically gone through the list of 108 gene candidates to find those loci that might provide "quick wins". Among other yardsticks, Wendland and his team crosschecked the GWAS findings against an independent data set of RNA expression levels taken from post-mortem brain samples; this was made possible through a consortium launched in March by the Lieber Institute for Brain Development in Baltimore, Maryland, and five drug companies, including Pfizer and Roche. Importantly, these transcriptomic data provide insight into whether the genes docketed by the GWAS are up- or downregulated in schizophrenia.

Wendland says his group narrowed the list down to a "handful" of the most promising gene regions. Now, he says, "we are investing a number of resources into following up on those with the aim being that we develop a path towards a preclinical data package".

For Janssen and its collaborators at Addex Therapeutics, the new study de-risks ongoing development work. The firms have advanced a positive allosteric modulator of the metabotropic glutamate receptor 2 (called JNJ-40411813) into Phase II trials, and several relevant genes involved in glutamatergic neurotransmission and synaptic plasticity were newly implicated in the GWAS.

"It gives you a lot of confidence in new pathways associated with the disease," adds Anirvan Ghosh, global head of neuroscience discovery at Roche. Roche recently had a series of Phase III trial failures with its schizophrenia candidate bitopertin (*Nature Rev. Drug Discov.* **13**, 244–245; 2014), but remains actively involved in the field. Ghosh points in particular to the discovery that several genes involved in neuronal calcium signalling are linked to the disease. "This justifies paying additional attention to

Table 1 | **Selected genes within newly implicated genome-wide significant loci***

Genes	Properties
G protein-coupled receptor signalling	
DRD2	Dopamine type 2 (D_2) receptor subtype blockade remains a necessary and sufficient condition for antipsychotic activity, despite attempts to develop alternatives
GRM3	Encodes metabotropic glutamate receptor 3 (mGluR3), a receptor that is predominantly expressed in astrocytes and that has been extensively explored as a potential therapeutic target in schizophrenia
Glutamatergic neurotransmission	
GRIN2A	Encodes the NMDA (*N*-methyl-D-aspartate) receptor subunit NR2A, a key mediator of synaptic plasticity. NMDA receptor channel blockers such as ketamine and NMDA autoantibodies mimic some of the symptomatology of schizophrenia in humans
GRIA1	Encodes glutamate receptor 1 (GluR1; also known as GluA1), a subunit of an AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; non-NMDA) receptor that mediates fast synaptic transmission
SRR	Serine racemase (SRR) catalyses L-serine racemization to D-serine, and is an essential co-agonist and activator of NMDA receptors
CLCN3	Encodes CLC3, a voltage-gated chloride channel localized to glutamatergic synapses in the hippocampus, where it modulates plasticity
Neuronal calcium signalling	
CACNA1I	Encodes the pore-forming alpha subunit of the Cav3.3 T-type calcium channel. Involved in synaptic plasticity and long-term potentiation
RIMS1	Regulating synaptic membrane exocytosis proteins (RIMs) are multi-domain proteins that tether calcium channels to synaptic active zones, dock and prime synaptic vesicles for release, mediate presynaptic plasticity and facilitate neurotransmitter release
Synaptic function and plasticity	
KCTD13	Encodes polymerase delta-interacting protein 1 (POLDIP1), a substrate-specific adapter of an E3 ubiquitin protein ligase complex involved in the regulation of cytoskeleton structure
NLGN4X	Neuroligins induce localized formation of functional neurotransmitter release sites in axons by aggregating neurexins and inducing the formation of glutamatergic and GABA (γ-aminobutyric acid)-ergic presynapses. Neuroligin 4 (NLGN4) may modulate the pre-synaptic calcium channel population through its interaction with neurexins
IGSF9B	Immunoglobulin superfamily member 9B (IGSF9B) is a brain-specific adhesion molecule that is strongly expressed in GABAergic interneurons, and localized to hippocampal and cortical inhibitory synapses where it is required for their development into interneurons
CNTN4	Contactins (CNTNs) are axon-associated cell adhesion molecules that function in neuronal network formation and plasticity
MEF2C	Myocyte enhancer factor 2C (MEF2C) is a transcription factor that regulates neurogenesis, excitatory synapse number, dendrite morphogenesis and differentiation of post-synaptic structures
PTN	Pleiotrophin (PTN) is a developmentally regulated neurite growth-promoting factor (NEGF) family cytokine/growth factor
CNKSR2	Connector enhancer of kinase suppressor of RAS 2 (CNKSR2) is a scaffold/adaptor protein that mediates the mitogen-activated protein kinase (MAPK) pathway downstream from RAS
PAK6	p21-activated kinase 6 (PAK6) is a serine/threonine protein kinase that is highly expressed in the brain and associated with neurite outgrowth, filopodia formation and cell survival
SNAP91	Synaptosomal-associated protein, 91kDa (SNAP91) is enriched in the presynaptic terminal of mammalian neurons where it regulates synaptic vesicle endocytosis through a clathrin-dependent reassembly process
Other neuronal ion channels	
KCNB1	Encodes Kv2.1, a delayed rectifier voltage-gated potassium channel in the *Drosophila* Shab-related subfamily
HCN1	HCN1 is a potassium channel pore-forming subunit and a major contributor to the inward hyperpolarization-activated cation current (I_h) current in the brain, which regulates neuronal excitability, rhythmic activity and synaptic plasticity
CHRNA3, *CHRNA5* and *CHRNB4*	*CHRNA* genes encode nicotinic acetylcholine receptors (nAChRs), which form ligand-gated ion channels in certain neurons and also on the presynaptic and postsynaptic sides of the neuromuscular junction
Neurodevelopment	
FXR1	Fragile X mental retardation syndrome-related protein 1 (FXR1) is a member of the family of RNA-binding proteins that includes FMRP, mutations in which cause fragile X syndrome
SATB2	Encodes a DNA-binding protein that binds nuclear matrix attachment regions, regulating transcription and chromatin remodelling

*Modified from supplementary information in *Nature* **511**, 421–427; 2014.

really understanding how calcium channels contribute to the disorder," he says.

This study also highlights the importance of genes involved in immune dysregulation, a therapeutic strategy that is not currently being investigated in any publicly disclosed industry-led schizophrenia research and development (R&D) programmes today.

Ultimately, the GWAS paper "has to be viewed as a long-term investment", argues Jeffrey Conn, director of the Vanderbilt Center for Neuroscience Drug Discovery in Nashville, Tennessee. "If we don't follow these genetic studies with very focused, intense neuroscience efforts aimed at understanding what it all means, the genetics in and of itself is not going to take us very far," Conn says. "That's what's needed now."

To enable that line of investigation, Ted Stanley, a philanthropist who made his fortune in the collectibles business, committed US$650 million in July to the Broad Institute of MIT and Harvard in Cambridge, Massachusetts, specifically to support basic research into the biological basis of schizophrenia and other mental illnesses. The donation, which comes on top of $175 million already bequeathed by Stanley to the Broad Institute, is the largest ever in psychiatric research.

Additional funding could come from venture capital firms and other types of R&D investors, notes Harry Tracy, editor and publisher of *NeuroPerspective*, a monthly publication geared at drug developers working in the neurotherapeutic field. The GWAS could "bring a modest increase in seed money to academic programmes working on targets relevant to the relatively more novel, potential genetic pathways highlighted in the paper," he says.

Still, according to Tracy, "this paper does nothing to entice the majority of large and mid-size pharma companies that eschew schizophrenia drug R&D back into the area".

Absentee targets

Noticeably absent from the list of candidate schizophrenia-associated genes were *CHRNA7*, which encodes the α7 nicotinic acetylcholine receptor (AChR), and *PDE10*, which encodes the enzyme phosphodiesterase 10. At least five companies have α7 AChR agonists in clinical development for schizophrenia, mostly for the treatment of cognitive symptoms, and another handful are pursuing inhibitors of PDE10 to alleviate the psychosis and hallucinations common in people with the disease.

The non-appearance of *CHRNA7* and *PDE10* doesn't concern Gerhard Koenig, chief scientific officer at FORUM Pharmaceuticals (formerly EnVivo Pharmaceuticals), which has clinical-stage programmes aimed at modulating each of these two targets.

For one thing, previous smaller studies have connected schizophrenia to both single nucleotide polymorphisms and DNA copy number variations in the vicinity of *CHRNA7*. For another, PDE10 inhibition helps alleviate dopaminergic and glutamatergic dysfunction — processes that are implicated by candidate genes in the GWAS paper. Even without a concrete genetic association, however, Koenig says his company is set to forge ahead with its development plans for encenicline, its α7 AChR potentiator, and FRM-6308, its PDE10 inhibitor.

"Genetics is important for us in the drug industry, but it's not sufficient to justify a drug development programme," he says. "You can affect the disease pathway even if you don't have genetic linkage."