Published in final edited form as:
Nat Med. 2009 May ; 15(5): 488–490. doi:10.1038/nm0509-488.

Breaking the gene barrier in schizophrenia

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Abstract

Studies of schizophrenia have been plagued by shortcomings such as weak genetic association with disease, inadequate animal models and limited replication of gene expression findings. Future success may lie not in overcoming any one of these limitations but in a broad approach strengthening the evidence in each area. Using such an approach, neuroscientists have uncovered a new gene behind the disease (pages 509–518).

What does it take to identify a gene that is crucial for the pathophysiology of schizophrenia? A genetic association replicated across several cohorts? Postmortem changes in the brains of diseased individuals? Gene effects on brain structure and cognitive processing? All of above, and some more.

The study by Huffaker *et al.*[1] in this issue of *Nature Medicine* has it all, providing compelling evidence that the *KCNH2* gene, which encodes a membrane-spanning potassium channel, may be a strong contributor to the disease phenotype. Additionally, the authors show that KCNH2 has a role in cortical phys iology, cognition and psychosis.

Schizophrenia is a devastating brain disorder characterized by abnormal mental functions and disturbed behavior[2] (**Fig. 1**). Vulnerability to schizophrenia is clearly related to genetic factors. Yet, the inheritance of this complicated disease is nonmendelian, as alleles in multiple genes carry moderate to small effects in predisposing to the disease[3]. The genetic and genome-wide association studies in the last few decades have identified several promising schizophrenia susceptibility genes (for example, disrupted in schizophrenia-1 (*DISC1*), neuregulin-1 (*NRG1*), regulator of G protein signaling-4 (*RGS4*) and dystrobrevin-binding protein-1 (*DTNBP1*)). It has been postulated that risk-associated polymorphisms interact with a wide range of environmental factors during a developmental time line[2].

So, where do we stand today? Unfortunately, our understanding of the disease is still limited. Genetic studies of schizophrenia rarely show irrefutable disease association, are not easily replicated and are unable to provide mechanistic insight into the disease process[4,5]. Postmortem studies are under-powered, complicated by the presence of other conditions,

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progression of pathology over time, treatment effects and postmortem changes in the brain tissue[6]. Animal models cannot recapitulate the complex genetics and environmental influences that are the core feature of the disorder[7], whereas cognitive assessments and functional imaging studies fail to address the molecular mechanisms at work. In light of these serious limitations, what is the right strategy to arrive at the answers we seek?

The most promising (and perhaps only) strategy is to accept the limitations of each individual method and to seek convergence among various findings[5]. A weak genetic association is meaningless on its own, yet it becomes intriguing if the identified single nucleotide polymorphism (SNP) is associated with altered cognitive performance, brain structure or postmortem gene expression. This is the arena where the work of Huffaker *et al.*[1] excels, as it provides a road map for how we should perform future studies.

The authors initially observed a disease-associated SNP near the *KCNH2* gene transcription start site, located in the 7q36.1 chromosomal region. This was an intriguing but inconclusive observation on its own, and it had to be replicated, expanded and put into a pathophysiological context of the investigated disease.

To achieve this, the authors tested whether risk-associated SNPs affected the biology of the brain regions affected in schizophrenia[1]. First, they found that a particular variant of KCNH2, isoform 3.1, which arises from an alternate transcription start site near the risk-associated SNPs, was a primate-specific transcript not expressed in rodents[1]. Second, structural brain imaging studies revealed a notable volume decrease in the hippocampus of the individuals carrying the minor risk-associated alleles. Third, functional imaging studies discovered inefficient information processing in unaffected individuals carrying the risk-associated alleles. Fourth, risk-associated SNPs also predicted increased expression of the *KCNH2* isoform 3.1 mRNA in the postmortem human hippocampus. Fifth, electrophysiological characterization of primary cortical neurons showed that overexpression of KCNH2 isoform 3.1 leads to profound changes in neuronal firing pattern.

There are potentially important clinical implications to these findings. Although the genetic association of *KCNH2* with schizophrenia is only modest (and comparable to that observed for other putative schizophrenia susceptibility genes), *KCNH2* still deserves our full attention. We know that a good drug target does not have to show an exceptionally strong genetic signal: thiazolidinediones are potent type 2 diabetes treatment agents that target the gene encoding peroxisome proliferator-activated receptor gamma (*PPARG*), a gene that showed a less than impressive genetic association with diabetes[8]. Furthermore, it is also important to remember that the currently available antipsychotic treatments do not directly target genes that were identified by genetic observations. Consequently, we must not judge schizophrenia drug targets on the basis of the strength they show in genetic association studies—rather, we should use a ‘converging evidence strategy’ to prioritize them. It is also important to point out that KCNH2 is a membrane-inserted potassium ion channel and, owing to its expression on the cell surface, represents a more accessible drug target than the intracellular proteins[9].

What is the natural continuation of these studies? The need for replication of the findings by other researchers is obvious, and there is also an apparent need for the expansion of the mechanistic studies related to KCNH2 regulation and function in the brain. Intriguingly, one might hypothesize that antipsychotic medications, directly or indirectly, can regulate the function of the *KCNH2* gene. This hypothesis is based on the converging observations that *KCNH2* is also expressed in heart muscle, mutations of the *KCNH2* gene cause long QT syndrome type 2 (ref. 10) and 3 and that patients with schizophrenia who receive antipsychotic medication show increased QT interval on EKG[11].

The pessimist can point out that this is a half-empty glass and that we are only at the initial stages of understanding the relationship of KCNH2 to schizophrenia. One might also argue that, despite the very promising initial observations, the road to drug development is always paved with numerous uncertainties[12]. However, there is also reason for optimism. The findings that *KCNH2* has a prominent role in cortical physiology, cognition and psychosis suggest that this gene is a key piece of the schizophrenia puzzle and that this converging evidence strategy is promising for new drug target identification. After all, single-method discoveries did not deliver promising schizophrenia treatment candidates to date, and we must explore conceptually new approaches.

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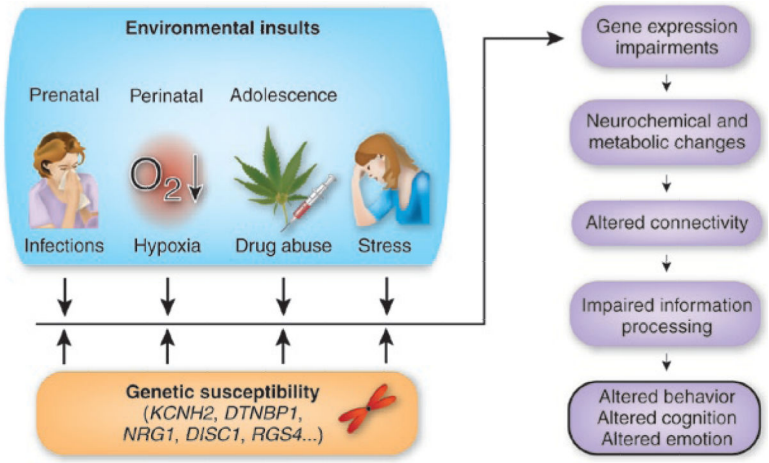

Figure 1.

Schizophrenia is a multifaceted disturbance. Predisposing genetic factors (such as SNPs or copy number variations) interact with a wide range of environmental factors, and their combined effects trigger a complex cascade of pathophysiological processes in the developing brain. The first changes most likely include gene expression alterations and a variety of neurochemical-metabolic disturbances. The altered brain homeostasis affects the normal wiring of the brain, resulting in inefficient information processing in the affected individuals. The combined changes ultimately lead to behavioral, cognitive and emotional deficits, which are the clinical hallmarks of the disease.