New genes linked to schizophrenia

Joanna Owens, Joanna.Owens@current-trends.com

Several genes associated with schizophrenia have recently been discovered, which could speed up the search for effective drugs, diagnostics and markers of treatment safety and efficacy for the disease. Researchers at deCODE genetics (Reykjavik, Iceland) have identified a schizophrenia-associated gene that encodes a protein that is expressed at the synapses of neurons in the CNS. Studies are now under way by deCODE to further dissect the molecular pathway of schizophrenia; indeed, the experimental examination of the identified disease gene in a two-hybrid yeast system has already revealed several other genes that are expressed at synapses, thus leading to the elucidation of a novel signaling pathway.

A difficult disease

Schizophrenia is a complex, debilitating illness that affects 0.5–1.0% of the worldwide population, starting most commonly in early adulthood, and acute exacerbations of the disease are typified by psychosis, hallucinations, thought disorder, delusions and disturbed body movements. There is currently no effective causative therapy for schizophrenia because little is known about the molecular pathology of the disease. However, it has long been speculated that the disease has a genetic component, because of the substantial degree of inheritability of the disease, as indicated by familial clustering.

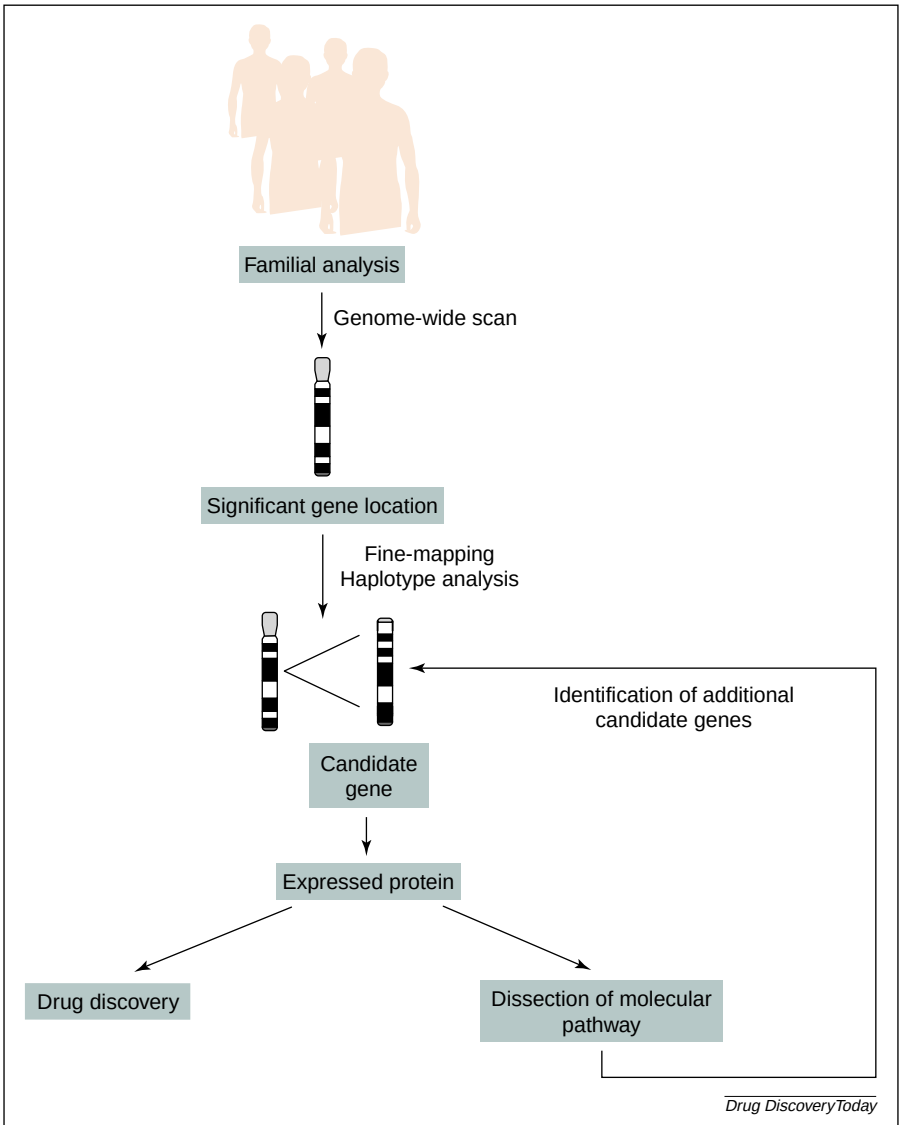

Figure 1. The deCODE research process. Using DNA samples from large Icelandic families, genome-wide scans are carried out to identify significant gene linkages. Disease-associated genes are then localized by further scrutiny of a specific region on the chromosome by fine-mapping and haplotype analysis. The candidate genes and their product(s) can then used as putative therapeutic targets and will help to elucidate the molecular pathogenesis of diseases such as schizophrenia.

The population-driven approach

As part of its population-based genetic research, deCODE has conducted genome-wide scans of DNA samples from large families in Iceland in which several family members are afflicted with schizophrenia. Strong population-wide linkages were observed and the disease gene was subsequently identified by fine mapping and haplotype analysis (Fig. 1). Despite studying a discrete population for disease genotypes, Kari Stefansson, CEO of deCODE, is optimistic that the results will be relevant to other populations: 'Icelandic models of human disease are valid, and prevalent diseases in Iceland are prevalent elsewhere. The opinion that disease differs regionally is naïve.' However, he adds that variation

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in the frequency or prevalence of a disease gene within a population might be a factor to consider in the development of diagnostics for diseases such as schizophrenia. deCODE is working with groups of patients in the USA and Europe in their quest to study the genetic basis of ~60 diseases. These include Alzheimer's disease, type 1 and type 2 diabetes mellitus, osteoarthritis, osteoporosis, stroke, manic depression, anxiety, rheumatoid arthritis, inflammatory diseases, hypertension and a variety of cancers, in addition to aging.

The contribution of gene variants

Although several gene localizations have been linked to schizophrenia (reviewed in Ref. 1), these data represent the first time that a single gene has been identified as contributing to the disease. However, Stefansson stresses that although deCODE has demonstrated a direct link between this gene and the disease, it does not eliminate the role of other genetic and environmental factors: 'All of the common diseases are complex, and it is this complexity that makes them common.' He continues, 'For example, in Iceland, no non-smokers develop emphysema; however, only 15% of those who do smoke develop the disease. In these people there is a genetic component, but without the environmental factor (i.e. smoking) there would be no cases of emphysema.' Stefansson believes that locating the genetic components of a disease could teach us more about the environmental factors that are involved.

Hot on the heels of this discovery by deCODE is the identification of another schizophrenia-associated gene, *WKI1*, by Klaus Peter Lesch and colleagues at Julius Maximilian-University of Würzberg (Germany)[2]. From a study of three generations of an extended German family, of which eight members had schizophrenia, a gene on chromosome 22 was identified by linkage analysis. Further investigation has revealed that the gene encodes a protein that is similar to known ion channels and might be involved in the transport of nerve impulses in the CNS. It is thought that a mutated form of the protein, in which a leucine residue is replaced with a methionine residue in one of the seven transmembrane domains, might cause abnormal transmission of electrical impulses in the brain.

Validated targets

A major advantage of genetic studies, such as those carried out by deCODE and the University of Würzburg, is the validation of targets at an early stage in drug discovery. As Stefansson highlighted, 'The pharmaceutical industry agrees that it is overburdened with targets from genomics and can't prioritize'; the targets are plentiful, but hypothetical, as they are derived mostly from looking at differences in gene expression between diseased and healthy tissue. Stefansson points out the limitation of this: 'If you hit a pancreas with a hammer, you will change the expression of many genes, but this won't lead you to the hammer as the cause, that is, 99% of this change will be reactive not causative'. Stefansson believes that drug discovery is better when based on deductive reasoning from what is already known about a disease. Therefore, even if the disease gene associated with schizophrenia proves to be inappropriate as a target for drug discovery, it will have provided essential new insights to our understanding of the complex schizophrenia pathogenesis.

Future drug discovery

The schizophrenia-associated gene discovered by deCODE, and its protein product, are now being studied by researchers at F. Hoffmann-La Roche Pharmaceuticals (Basel, Switzerland), as part of its drug discovery collaboration with deCODE. 'Only a more specific understanding of the pathological processes on the molecular level – where disease first happens – will ultimately allow continued progress in medicine,' commented Jonathan Knowles, Global Head of Research at F. Hoffmann-La Roche. 'Genetic research is one of the most powerful approaches to gather this knowledge and has become an essential component of biomedical research,' he continued. The aim is to use these putative targets, and others that are revealed from further dissection of the schizophrenia pathway, in the search for conventional small-molecule therapeutics. 'It will still be a long way to go from target to a new medicine that is approved by the regulatory authorities and can be given to patients suffering from schizophrenia', Knowles points out, 'but using targets that we know are truly involved in the causation of the disease should make such new medicines overall more successful, and particularly in those zpatients in whom the particular mechanism linked to the gene targeted by the new drug contributes importantly.' Klaus Lindpaintner (Head of Roche Genetics, Europe) also commented that, 'As we move forward, more of the genetic factors predisposing or contributing to various diseases are discovered and, in due course, new drugs are developed, It will become increasingly important to understand better the presence or absence of any of these genetic factors in a given patient, to provide the "custom-tailored" medical regimen that promises the greatest likelihood of being successful.'

The ultimate prize for population-based genomics will be the development of efficient and effective diagnostics for genetically based diseases such as schizophrenia, which will enable the early identification of individuals who are predisposed to the disease and thus offer the opportunity for lifestyle changes, in addition to effective personalized treatments.

In keeping with this logic, Roche Diagnostics has recently announced its intention to enter into a 5-year

collaboration with deCODE to develop DNA-based diagnostics from the results of deCODE's genetic studies. This alliance will complement the existing drug discovery partnership between the two companies, and involves Roche providing research funding, milestone payments and product royalties to deCODE.

References

1 Bray, N.J. and Owen, M.J. (2001) Searching for schizophrenia genes. *Trends Mol. Med.* 7, 169–174

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Intelligent inhalers for systemic administration?

Rebecca N. Lawrence, News & Features Editor

Promising results from a study with a new intelligent inhalation technology in asthmatic children has prompted the development of the technology for use in a variety of other conditions, including the administration of systemic drugs. The six-month study using the Adaptive Aerosol Delivery (AAD™) system from Profile Therapeutics (Bognor Regis, West Sussex, UK) was shown to improve accuracy of dose delivery, decrease the quantity of drug required and improve compliance compared with conventional nebulizers.

One of the problems found with many nebulizer systems is that they are dependent on the breathing pattern of the patient, the way the nebulizer system is used (which can cause variability of sometimes >60%)[1] and the drug output characteristics of the nebulizer[2]. Every patient breathes differently, especially in relation to flow, volume and frequency[3]. If the patients' inhalation flow rate does not exceed the nebulizer flow rate, then more of the nebulizer output is wasted and this is particularly important in dosing for the paediatric population[4]. Using nebulizers has been found to waste up to 60–70% of the drug as only 30–40% of the respiratory cycle is accounted for by inspiration[5,6]. The quantity of drug actually inhaled by the patient is especially important for the administration of drugs with a narrow therapeutic window.

The system

The AAD technology was designed to try to avoid these problems by delivering the drug only during the optimal phase of inspiration (i.e. the first 50% of each breath). Sensors in the system monitor the flow rate and the length of the first three breaths of the patient before starting the dose. The results are then averaged and used to calculate the correct quantity of drug to be delivered into each breath. The patient's breathing is then monitored every 30 msec during dosing to enable the device to adapt the release of aerosol to changes in the

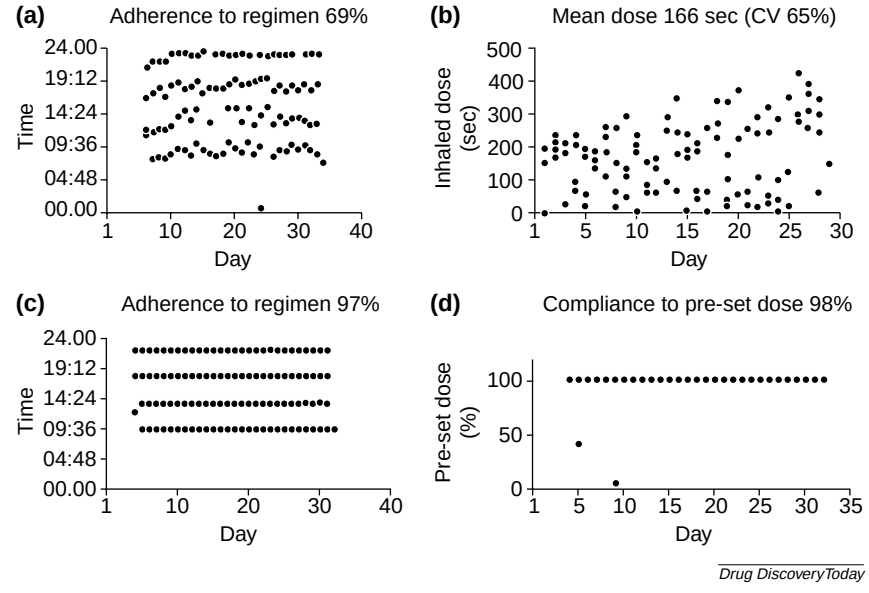

Figure 1. Patient adherence with four-week domiciliary use of conventional nebulizers (a) and (b) compared with using the AAD system (c) and (d) for the treatment of COPD. All patents were aged over 65 years. In (a) and (b), the regimen consisted of 2.5 mg salbutamol four times daily. In (c) and (d), the regimen consisted of 2.5 mg salbutamol plus 500 μg ipatropium bromide four times daily.

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