



NEWS & VIEWS

Mouse models of madness

Psychiatric disorders have important genetic contributions, but it has been very difficult to identify the responsible genes using human populations. Recent developments in mouse genomics hold considerable promise of providing important insights into the genetics of these diseases.

The strong genetic component of many psychiatric disorders is clear. For example, schizophrenia has a heritability of about 50%,¹ higher than type I diabetes. However, it has been very difficult to identify the genes responsible for psychiatric disorders using linkage analysis, probably due to the obstacles that frequently hinder analysis of complex traits in humans. These impediments include genetic heterogeneity and the fact that many genes, each contributing a small effect, can conspire together in a combinatorial fashion to give rise to the final phenotype. For psychiatric disorders, perhaps some of the most promising avenues of investigation are those that circumvent these problems by using genetically isolated populations to decrease the effects of heterogeneity.² Another valuable approach is to identify genes responsible for behavioral deficits in the context of aneuploidy.³ Nevertheless, the identification of the genes underlying psychiatric disorders remains a formidable task. In this News & Views we will investigate the increasing promise of the mouse as an experimental system to understand the genetics and biology of psychiatric disorders.

The mouse offers well-known advantages compared to human populations, including facile genetics, well controlled behavioral experiments and the opportunities for precise genetic manipulation. Thus, the effects of a single mutation upon a final phenotype can be easily studied, permitting greater likelihood of success in identifying genes involved in complex traits. Such investigations will provide candidate genes that can be tested in human populations using the methods of statistical association, which are potentially more powerful than standard linkage studies.⁴

At first glance, the prospects for modeling a psychiatric illness such as schizophrenia in the mouse seem bleak, since these diagnoses in humans are usually made by talking with affected individuals. However, a surprisingly large number of phenotypes manifest in the psychiatric disorders can be modeled in the mouse.

In the case of schizophrenia, examples of these phenotypic investigations include sensorimotor gating, social interactions and detailed neuropathology to look for neuronal disorder and increased ventricular volume.

What are some of the genetic approaches being taken that employ the mouse to identify genes involved in psychiatric conditions? Perhaps one of the most exciting developments is a two-pronged attack on understanding the connection between brain and behavior using the mouse, one founded in behavior, the other in genomics. The behavioral approach employs large-scale mutagenesis, while the genomic approach relies upon the advent of serious efforts to sequence the mouse genome.

The utility of mutagenesis was highlighted by a landmark study that identified a gene involved in control of mammalian circadian rhythms.⁵ This investigation established that large-scale genetic screens in conjunction with a battery of high throughput phenotypic assays could be a useful tool to identify new dominant and recessive loci affecting behavior and morphology. Worldwide efforts are now being launched^{6,7} that should lead to the screening of more than 40 000 mice per year and allow the identification of more than 400 new mutants per year. The assays in these protocols seek behavioral abnormalities that can be related to schizophrenia, learning and memory, anxiety and drug addiction. Structural and functional imaging of mice is now technically feasible⁸ and is likely to play an increasingly important role in these screens. The identification of interesting loci will be profoundly simplified by the serious efforts now underway to initiate and complete a draft sequence of the entire mouse genome by 2003. In the early '80s the excitement underlying the development of complete physical maps led to the idea that the tedious process of molecular cloning would be replaced by a process in which one could 'clone by phone'. The production of the complete mouse genome sequence in combination with a comprehensive panel of mouse mutants will further this concept of consumer convenience, and permit gene identification by going with ease from genetic screen to computer screen.

Although these forward genetic techniques offer

Correspondence: Dr DJ Smith, Dept of Molecular and Medical Pharmacology, UCLA School of Medicine, 23-120 CHS, Box 951735, Los Angeles, CA 90095-1735, USA. E-mail: dsmith@mednet.ucla.edu

great power, there are other reverse genetic approaches to link genes identified through sequence to final phenotype. Gene trap techniques can be used to create large libraries of gene knockouts in embryonic stem cells which can be readily converted to living mice for phenotypic analysis.⁹ Undoubtedly, knockouts will reveal unexpected relationships between genes and psychiatric disorders. For example, a knockout of *Dvl 1*, a mouse *Dishevelled* homolog, results in defects in sensorimotor gating, social behavior, as well as other abnormalities. This constellation of defects suggests that the *Dishevelled* family of genes represents candidates for the genetic etiology of schizophrenia.¹⁰ The knockout approach allows evaluation of loss-of-function phenotypes, but analysis of behavior in knockouts may be prevented by homozygous inviability. This shortcoming could be addressed by a complementary global approach to gene function that uses systematic overexpression of genes. This approach has already been used to identify a novel secreted protein involved in bone remodeling.¹¹

Another way that mice can be usefully employed is as a bioassay tool to narrow regions of the human genome implicated in psychiatric disorders. One approach uses *in vivo* libraries of large insert transgenic mice to screen through lengthy regions of the human genome implicated in a complex trait. *In vivo* libraries were invaluable in assigning function to sequence in a 2 Mb region of chromosome 21q22.2 implicated in the causation of Down syndrome. Fine mapping of the 2 Mb region using an *in vivo* library identified a gene, that when overexpressed, produced learning and memory defects in the transgenic mice studied. The gene, *DYRK*, had already been identified as being involved in learning and memory on the basis of genetic screens in *Drosophila*. Thus, *in vivo* libraries allowed fine structure mapping and identification of a gene involved in learning and memory in mammals and fruit flies, and which may also be involved in Down syndrome. The approach could be useful in mapping genes involved in complex traits other than Down syndrome. A conceptually similar approach to screening large genomic regions of a genome is the creation and phenotypic analysis of targeted large deletions of the mouse genome.¹²⁻¹⁴ In addition, attractive candidate genes suggested by human studies can be formally tested using the mouse. In one example, proline dehydrogenase is a candidate for the increased risk of schizophrenia in humans with deletions of chromosome 22q11 associated with velocardiofacial syndrome (VCFs). A mutation of the proline dehydrogenase gene in mice was found to have some of the behavioral deficits associated with schizophrenia in humans.¹⁵ Thus, it seems clear that using the mouse and human systems together to provide synergy in discovery will allow a speedier unraveling of the complex etiology of psychiatric disorders.

Ultimately, we can anticipate the advent of enormous interlocking databases in which all mammalian genes are linked into the networks of their relevant biochemical activities and organismal function. The

beginnings of the process are already manifest in the model organisms yeast and *C. elegans* whose genome sequences have been completed. A full understanding of the function of all genes will allow a deeper understanding of how genes sculpt neural connections to construct the brain and how this process can go wrong in psychiatric disorders. This will provide the foundation for rational therapeutic intervention in these illnesses. Finally, the isolation of genes responsible for psychiatric disorders will allow a proper appreciation of the importance of environmental contributions to the disease which, of course, may represent some of the very best avenues for therapeutic and prophylactic intervention.

VM Brown and DJ Smith

Department of Molecular and Medical Pharmacology
UCLA School of Medicine
Los Angeles, California 90095, USA

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