Genetic Dissection of Motor Activity Levels and Avoidance Behavior in The Home Cage; Translational Phenotypes for Mood Disorders

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ABSTRACT

Identifying susceptibility genes for endophenotypes by studying analogous behaviors across species is an important strategy for understanding the pathophysiology underlying psychiatric disorders. This approach provides novel biological pathways plus validated animal models critical for selective drug development. One such endophenotype is avoidance behavior. In the present study, novel automated registration methods for longitudinal behavioral assessment in home cages are used to screen a panel of recently generated mouse chromosome substitution strains that are very powerful in quantitative trait loci (QTL) detection of complex traits. In this way, we identified chromosomes regulating avoidance behavior (increased sheltering preference) independent of motor activity levels (horizontal distance moved). Genetic information from the mouse QTL-interval was integrated with that from the homologous human linkage region for a mood disorder.

We genetically mapped a QTL for avoidance behavior on mouse chromosome 15, homologous with a human genome region (8q24) linked to bipolar disorder. Integrating the syntenic mouse QTL-interval with genotypes of 1868 BPD cases versus 14,311 control subjects revealed two associated genes (***ADCY8*** and ***KCNQ3***). Adenylyl cyclase 8 (***Adcy8***) was differentially expressed in specific brain regions of mouse strains that differ in avoidance behavior levels. Finally, we showed that chronic infusion of the human mood stabilizer carbamazepine (that acts via adenylyl cyclase activity) significantly reduced mouse avoidance behavior, providing a further link between human mood disorders and this mouse home cage behavior. Our data suggest that ***Adcy8*** might encode a translational behavioral endophenotype of bipolar disorder [1].

Author Keywords

Animal model, chromosome substitution strains, endophenotype, home cage environment, mood disorder, psychiatric disorders.

INTRODUCTION

Family and twin studies have revealed that genetic factors play a major role in psychiatric disorders, however, attempts to find susceptibility genes for these complex disorders have been largely unsuccessful. Therefore, new research strategies are required to tackle the complex interactions of genes, developmental, and environmental events. Recently, we have proposed a behavioral domain concept that focuses on the genetics of behavioral domains relevant to both animal behavior and across human psychiatric disorders [2]. We believe that interspecies trait genetics rather than complex syndrome genetics will optimize genotype–phenotype relationships for psychiatric disorders and facilitate the identification of biological substrates underlying these disorders. The development of automated paradigms that address these behavioral domains is a crucial step in this translational research field.

NOVEL VIEWS AND METHODOLOGIES

Identification of novel genetic loci in animal models for neurobehavioral traits relevant to psychiatric disorders relies on the fact that these traits are truly translatable across species. Once found, one can apply sensitive genetic strategies to these traits in order to unravel the underlying mechanisms. With the availability of a large variety of inbred mouse strains and their recently known genome sequences, mouse genetics offer a challenging way to study complex behavioural traits. For example, in contrast to patient populations, mouse strains can be used to control for phenotypic and genetic heterogeneity as well as for complex gene-environment interactions. Interestingly,

recent studies have shown that genetic variation associated with psychiatric disorders affect analogous neural circuits and behavioural traits in mice and men, demonstrating that mouse models can contribute to systematic searches for genetic determinants of psychiatric disorders [3].

In general, rodent species have an innate preference for sheltered places that have lower light intensities than the outside-world and that provide a sense of safety via body contact with the shelter area surface (thigmotaxis). The assessment of this anxiety-related behavior is generally measured in relative short-lasting laboratory tasks and is highly dependent on strain differences in motor activity levels. In light of this, we have recently designed an automated home cage environment to assess separate behavioral domains over the 24-h day [4, 5, 6]. For instance, a hungry organism searching for food depends on an efficient exploration strategy in which finding the food resource in an appropriate period of time needs to be balanced against the risk of being exposed to potentially threats, such as predators. Thus, exploration for food relies on a balance between movement throughout the environment and avoidance behavior. To assess these behavioral domains as a function of time of day, a home cage environment for mice was designed with a sheltered and a non-sheltered feeding platform that would allow dissociation of the preference for shelter during feeding and for motor activity levels over several days and with minimal human disturbance [6].

For mouse genetics of these behavioral domains, there is an increasing appreciation of the properties of the set of mouse inbred strains which have been established over the last century of mouse genetics. Data are accumulating on each of this diverse collection of over 500 strains allowing strains to be chosen that cover a range of phenotypic variation in whatever phenotype is of interest. Traditionally, such strain combinations would be used to set up a cross or segregating population for genetic mapping purposes. More recently, Genetic Reference Populations (GRPs) with more optimal genetic properties are available or under construction. The prototype is the Recombinant Inbred (RI) panel which is generated from a cross between two inbred strains followed by an F1 intercross and 20 generations of inbreeding. The best characterized mouse RI panel, derived from C57BL/6J and DBA/2J (BXD) strains, has been a workhorse of behaviour genetics since the early 1990s. The BXD panel, of (until recently) 35 lines, gives only a coarse genetic resolution. However, several aspects of this picture have recently changed. One is the idea of treating transcript abundance and protein abundance or modification as phenotypes in their own right. This kind of genetical-genomics is an extremely promising way of examining networks of function. Although it is possible with conventional genetic crosses or outbred populations, using (effectively immortal) inbred GRPs allows much more value to be extracted from each data set. This is also true of other phenotypic data, and there is a renewed interest in the importance of accumulating data from many investigators. It is now possible to not only genetically map Quantitative Trait Loci (QTLs) on the BXD RI panel (recently expanded to 80 lines), but also to correlate new data with a large database of phenotypic data including gene expression data on several tissues. This is a major aid to positional cloning projects and multivariate analysis approaches currently being explored offer a way to assign some idea of function to many of the genes whose function is currently unknown. Other genetic reference populations have been developed. For example, chromosome substitution (consomic) panels have been generated for two strain combinations. This is done by repeated backcrossing to produce strains each with a single chromosome of one strain on the background of another. This is attractively simple to analyze and offers the simplification of multi-locus traits with only a single chromosome segregating [7].

RESULTS AND CONCLUSIONS

By testing a panel of 21 chromosome substitution strains in a wide variety of traditional and in an automated home cage environment, we have shown that behavioral components can be genetically dissociated. For example, we have shown that motor activity levels are under different genetic control than the preference to shelter by using a novel automated home cage task [6]. Further genetic mapping of these chromosomal regions revealed genetic loci that are syntenic with human linkage regions for mood disorders. Candidate gene selection within the QTL-intervals can nowadays be facilitated by combining quantitative phenotypic data from inbred mouse strains with their online available genome sequences. Single Nucleotide Polymorphism (SNP) databases provides gene-by-gene, SNP-by-SNP distribution patterns for various inbred lines and allow pinpointing SNP's in the QTL-regions that are associated with the behavioral trait of interest. Furthermore, biological pathway analysis can further be applied to provide additional candidate gene information. Subsequently, homologous candidate genes can then be tested in DNA samples from well-characterized psychiatric patient populations. In this way, interspecies genetics offers a great opportunity to translate essential behavioral traits in animals to human psychiatric disorders and to further understand the mechanisms underlying these traits. The automated home cage environments provides a modular system for the development of new longitudinal behavioral paradigms with translational value to disease.

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