FINDING GENES FOR COMPLEX BEHAVIORS : PROGRESS IN MOUSE MODELS OF THE ADDICTIONS JOHN C. CRABBE pdf

1: Behavioral Genetics in the Postgenomic Era : Robert Plomin :

Finding Genes for Complex Behaviors: Progress in Mouse Models of the Addictions â€"John C. Crabbe Genetic and Environment Risks of Dependence on Alcohol, Tobacco, and Other Drugs.

A highresolution single nucleotide polymorphism genetic map of the mouse genome. Williams, Richard Mott, Jonathan Flint , " High-resolution genetic maps are required for mapping complex traits and for the study of recombination. We report the highest density genetic map yet created for any organism, except humans. Using more than 10, single nucleotide polymorphisms evenly spaced across the mouse genome, we have constr Using more than 10, single nucleotide polymorphisms evenly spaced across the mouse genome, we have constructed genetic maps for both outbred and inbred mice, and separately for males and females. Recombination rates are highly correlated in outbred and inbred mice, but show relatively low correlation between males and females. Differences between male and female recombination maps and the sequence features associated with recombination are strikingly similar to those observed in humans. Genetic maps are available from Show Context Citation Context The accuracy of these methods depends on the accuracy of the genetic map. Additionally, as in human linkage m Behavioral differences between inbred strains of mice and rats have a genetic basis that can now be dissected using quantitative trait locus QTL analysis. Over the last 10 years, a large number of genetic loci that influence behavior have been mapped. In this article I review what that information In this article I review what that information has revealed about the genetic architecture of behavior. The small effect of each QTL on behavioral variation suggests that the mutational spectrum is different from that which results in Mendelian disorders. Regions of DNA should be appropriately prioritized to find the molecular variants, for instance by looking at sequences that control the level of gene expression rather than variants in coding regions. While the number of allelic loci that can contribute to a trait is large, this is not necessarily the case: I conclude by arguing that genetic mapping has more to offer than a starting point for positional cloning projects. With advances in multivariate analyses, mapping can also test hypotheses about the psychological processes that give rise to behavioral variation. Cookson, Youming Zhang, Robert M. Rawlins, Richard Mott, Jonathan Flint , " Behav Genet ; 31 by John K. Belknap, Robert Hitzemann, John C. Quantitative genetics and QTL mapping have undergone a revolution in the last decade. Progress in the next decade promises to be at least as rapid, and strategies for fine mapping QTLs and identifying underlying genes will be radically revised. In this commentary we address several key issues: We compare current practice and procedures in QTL analysis with novel methods and resources that are just now being introduced. Second, we compare QTL analysis with whole genome mutagenesis in mice and point out some of the strengths and weakness of both of these phenotype-driven methods. Finally, we explore the advantages and disadvantages of naturally occurring vs mutageninduced polymorphisms. We argue that these two complementary genetic methods have much to offer in efforts to highlight genes and pathways most likely to influence the susceptibility and progression of common diseases in human populations. Show Context Citation Context We assume that the cells and tissue types related to the phenotype aresBelknap et al. This will almost always be the case for morphometric t Quantitative trait locus QTL analysis is a powerful tool for mapping genes for complex traits in mice, but its utility is limited by poor resolution. A promising mapping approach is association analysis in outbred stocks or different inbred strains. As a proof of concept for the association approa As a proof of concept for the association approach, we applied whole-genome association analysis to hepatic gene expression traits in an outbred mouse population, the MF1 stock, and replicated expression QTL eQTL identified in previous studies of F2 intercross mice. We found that the mapping resolution of these eQTL was significantly greater in the outbred population. Our results also highlight the importance of correcting for population structure in whole-genome association studies in the Show Context Citation Context The presence of common local eQTL, where one can assume, with high confidence, that the causal genetic variant lies within or PLoS Genetics www. We detail how these data were used to select families for the QTL

FINDING GENES FOR COMPLEX BEHAVIORS : PROGRESS IN MOUSE MODELS OF THE ADDICTIONS JOHN C. CRABBE pdf

study and discuss strategies that may help elucidate the molecular pathways leading from gene We detail how these data were used to select families for the QTL study and discuss strategies that may help elucidate the molecular pathways leading from genes to anxious depression. Twin Research 3, by Valerie J. Cook, Lorraine Flaherty, Valerie J. Cook, Lorraine Flaherty - Genome Research , "

FINDING GENES FOR COMPLEX BEHAVIORS : PROGRESS IN MOUSE MODELS OF THE ADDICTIONS JOHN C. CRABBE pdf

2: Animal Models for the Genetic Study of Human Alcohol Phenotypes

Although attention is now focused on finding genes for complex quantitative traits, the greatest impact on individual differences research will come after genes have been identified. The future of genetic research on individual differences lies in moving from finding genes (genomics) to finding out how genes work (functional genomics).

Mouse mutagenesis-systematic studies of mammalian gene function by Steve D. Nolan - Hum Mol Genet , " The mouse will play a pivotal role in mammalian gene function studies as we enter the post-genomics era. The challenge is to develop systematic, genome-wide mutagenesis approaches to the study of gene function. The current mouse mutant resource has been an important source of human genetic disease m The current mouse mutant resource has been an important source of human genetic disease models. However, despite an apparently large catalogue of mouse mutations, we have access to mutations at only a small fraction of the likely total number of mammalian genesâ€”there is a phenotype gap that needs to be filled by the establishment of new mutagenesis programmes. Two routes, genotype- and phenotype-driven, can be used for the recovery of novel mouse mutations. For the former, gene trap embryonic stem cell libraries appear set to deliver a large number of mutations around the mouse genome. The advantage of genotype-driven approaches is the ease of identification of the mutated locus; the disadvantage that a priori assumptions have to be made concerning the function and likely phenotype of the mutated gene. In contrast, phenotype-driven mutagenesis emphasizes the recovery of novel phenotypes. One phenotype-driven approach that will play an important role in expanding the mouse mutant resource employs the mutagen N-ethyl-N-nitrosourea ENU. The phenotype-driven route makes no assumptions about the underlying genes involved, and ENU mutagenesis programmes can be expected to play a significant role in uncovering novel pathways and genes; the disadvantage is that the identification of the mutant gene is still not trivial. Together, the complementary routes of genotype- and phenotype-driven mutagenesis will provide a much enlarged catalogue of mouse mutations and phenotypes for future gene function studies. Show Context Citation Context Tim 38 and Frq 39 loci were characterized successfully. Phenotypically, Clock is a specific circadian rhythm mutation, with a lengthening of the circadian period of locomotor activity by 1 h in heterozygotes and by longer in homozygotes see, for example QTL analysis and genomewide mutagenesis in mice: Behav Genet ; 31 by John K. Belknap, Robert Hitzemann, John C. Quantitative genetics and QTL mapping have undergone a revolution in the last decade. Progress in the next decade promises to be at least as rapid, and strategies for fine mapping QTLs and identifying underlying genes will be radically revised. In this commentary we address several key issues: We compare current practice and procedures in QTL analysis with novel methods and resources that are just now being introduced. Second, we compare QTL analysis with whole genome mutagenesis in mice and point out some of the strengths and weakness of both of these phenotype-driven methods. Finally, we explore the advantages and disadvantages of naturally occurring vs mutageninduced polymorphisms. We argue that these two complementary genetic methods have much to offer in efforts to highlight genes and pathways most likely to influence the susceptibility and progression of common diseases in human populations. The success of this experiment depended at least in part on the extremely small variability in circadian rhythm photoperiod in the background inbred strain. Thus, a single outlier mutant mouse coul Generalization and discovery by assuming conserved mechanisms: Cross species research on circadian oscillators by William Bechtel - Philosophy of Science , " In many domains of biology, explanation takes the form of characterizing the mechanism responsible for a particular phenomenon in a specific biological system. How are such explanations generalized? One important strategy assumes conservation of mechanisms through evolutionary descent. But conservation is seldom complete. In the case discussed, the central mechanism for circadian rhythms in animals was first identified in Drosophila and then extended to mammals. How do scientific explanations generalize? When explanation is viewed as the application of scientific laws to specific cases, generalization is relatively straightforward: It then applies to any condition in which the antecedent is

satisfied. The Downs and Ups of Mechanistic Research: In the context of mechanistic explanation, reductionistic research pursues a decomposition of complex systems into their component parts and operations. Using research on the mechanisms responsible for circadian rhythms, I consider both the gains

FINDING GENES FOR COMPLEX BEHAVIORS : PROGRESS IN MOUSE MODELS OF THE ADDICTIONS JOHN C. CRABBE pdf

3: NIAAA Publications

Behavioral genetics in the postgenomic era. Finding genes for complex behaviors: progress in mouse models of the addictions / John C. Crabbe --Genetic and.

Researchers are increasingly using animal models to study the genetic basis of complex human behaviors, such as alcoholism. The most commonly used animal species are rodents, but other species, such as nonhuman primates, fruit flies, and zebrafish, can also provide important information. A variety of approaches are employed in these studies, particularly knockout and transgenic mice as well as specially bred animal lines that can be used for various genetic analyses, including quantitative trait locus mapping. Overall, the DNA sequences of humans and other organisms e. One example of how genetic discovery in human alcoholics can be translated to animal research involves the dopamine D2 receptor gene called DRD2 in humans and Drd2 in mice. Dopamine is a brain chemical i. Several genes encode dopamine receptors, including DRD2. Together with the clinical results obtained in humans, this finding led researchers to consider the mouse Drd2 gene as a good candidate for further study. Researchers also introduced a modified virus into a specific brain region of rats called the nucleus accumbens, which plays an important role in drug reward. The modified virus produced excessive amounts of the D2 receptor and resulted in reduced alcohol consumption and preference in the animals Thanos et al. The prediction is not that straightforward, however. The animals with the excessive receptor levels, in contrast, receive a stronger rewarding effect after consuming alcohol. As a result, they will consume less alcohol to get the same rewarding effect as rats with normal receptor levels. Although these findings do not prove that the gene identified by QTL mapping on mouse chromosome 9 is Drd2, they do provide justification for continued studies of the role of this gene and its product in alcohol consumption. This article describes several of the genetic methods that have been used in various animal models of alcohol research, including rodents and other species. It is important to realize, however, that for such complex diseases as alcoholism, animal models cannot prove genetic associations in humans. Human alcoholism cannot be exactly replicated in animals, even though some external factors thought to influence human alcohol consumption, such as physiological and social stress, can be modeled in animals. Despite these limitations, the ability to precisely control environmental and genetic characteristics of animal models allows researchers to identify important avenues of investigation that can then be translated to research in humans. Ultimately, careful investigation of geneâ€"gene interactions in human populations will contribute to a more complete understanding of the coordinated biological systems that influence the susceptibility to and progression of alcoholism as well as the effectiveness of alcoholism treatment. For example, mice in which the function of a particular gene has been disruptedâ€"called knockout miceâ€"are increasingly being used in research Anagnostopoulos et al. In many cases, a particular transgenic or knockout animal is studied because pharmacological or electrophysiological evidence implicated the gene product that is altered in that animal. Evidence from human linkage studiesâ€"studies in which researchers analyze whether people with a certain trait e. Certain difficulties, however, are associated with interpretation of data generated using transgenic or knockout animals e. In particular, any interpretation must take into consideration the difference between variation in gene function associated with different variants i. In some instances, a disease develops when the function of a specific gene is completely absent. In other cases, variation in disease susceptibility appears to be associated with altered, rather than absent, gene function. In these instances, when elimination of gene function affects a trait e. Quantitative Trait Locus QTL Mapping Quantitative traits are genetically influenced characteristics that differ in the extent to which each individual in a population possesses that characteristic e. Quantitative traits are generally determined by more than one gene, each of which can exist in several forms i. Thus, differences in the trait among the individuals in a population most commonly result from variations in gene function rather than from the presence versus absence of gene function. The DNA regions that influence quantitative traits i. QTL mapping takes advantage of naturally occurring genetic variation to determine the

regions of specific chromosomes that harbor genes influencing quantitative traits. For QTL mapping analyses, researchers can use different types of genetically defined animal populations, including the following Palmer and Phillips Recombinant inbred RI strains. Because of genetic recombination of the DNA from the parent strains that occurs during the production of sperm and egg cells, each F2 animal has a slightly different combination of genes from the parent strains. By repeated inbreeding, animal strains are generated in which all the animals within a strain are genetically identical, but each strain differs in the specific combination of parental genes. For more information on this approach, also see the article by Dick and Foroud, pp. Chromosome substitution strains CSS. To create a CSS, an entire chromosome of one inbred strain is replaced with that of another strain. Intercross and backcross populations. An intercross population is the F2 offspring of two genetically distinct inbred strains. A backcross population is produced by mating two genetically distinct inbred strains to produce the first generation F1 and then breeding the F1 offspring back to one of the parent inbred strains. These lines are discussed in the next section. Individuals within these populations have diverse genetic backgrounds. The most commonly used heterogeneous mouse stock was produced by interbreeding eight genetically diverse inbred strains. Finer mapping of a QTL to the smallest possible genetic segment may involve the use of specialized genetic models e. To identify specific genetic variants associated with a particular alcohol effect, it is important to narrow the DNA region possessing a QTL down to one that is likely to contain only a few genes see Palmer and Phillips Any genes that are identified in such a mouse model of alcohol sensitivity may prove important for investigations in human populations, because relative insensitivity to alcohol may be related to increased alcoholism risk e. Selected Lines Selected lines are generated by selectively breeding animals within a population that have either very high or very low levels of the desired trait e. When the selective breeding is conducted over several generations, the selected lines often show progressively greater differences from each other with respect to the trait under investigation and with respect to the gene variants that influence the trait. The lines should remain similar, however, with respect to traits not influenced by those genes. Selective breeding approaches have resulted in several rat and mouse lines that have extremely high or low sensitivity, preference, or aversion to alcohol. Some of these lines have also been shown to exhibit different types of adaptation in brain function i. Selected lines are frequently used to identify traits that are influenced by common underlying genetic factors. Selected lines also are being used in QTL mapping studies to locate the genes that influence the selected trait. For example, a study comparing rats that were selectively bred to consume either large amounts of alcohol i. NPY is a small protein molecule i. Studies in other genetic models e. These contradictory findings may result from differences in the genetic backgrounds of the rats used in the two studies. Similarly discrepant results regarding the role of NPY have been found in humans. Thus, one study in humans found that a certain NPY gene variant was associated with increased alcohol consumption Kauhanen et al. This discrepancy may result from differences in the phenotypes that were examined in the two studies. Future research needs to clarify the exact role of the NPY gene in influencing alcohol consumption and alcoholism risk as well as the exact sources of the discrepancies in the existing findings. Random Mutagenesis Researchers use transgenic or knockout mice to study the specific effects of a known gene. To identify new genes that might affect a trait of interest, however, they may use an approach called random mutagenesis. With this approach, the animals e. Consequently, every gene becomes a potential target for study. In , seven institutes of the National Institutes of Health NIH , including the National Institute on Alcohol Abuse and Alcoholism NIAAA , initiated a mouse genetics research program to launch genomewide mutagenesis projects in mice and develop methods allowing rapid screening of large numbers of phenotypes resulting from such random mutagenesis Moldin et al. The hope is that these genetic tools will lead to broad insights in the study of complex behaviors, such as alcohol consumption. However, researchers will be facing significant hurdles in achieving this goal. For example, phenotypic screening of animals with such mutations is most likely to detect major gene effects and may miss more subtle effects. Furthermore, the identification of specific mutation s associated with a complex trait will require extensive mapping like that used in QTL analyses Belknap et al. The fruits of this approach in addiction research await

harvesting. One way to transfer the gene is to insert it into a modified virus that can then be used to infect a specific cell type but is not harmful to the animal or human being studied. Using technologies called gene chip or microarray analyses, these investigators examine the expression of thousands of genes simultaneously from a single DNA sample. This approach is also called gene expression profiling. It allows researchers to collect information about genetic changes that occur together in a coordinated fashion to affect a given phenotype, rather than being limited to the examination of one gene at a time. For example, alcoholics often exhibit loss of white matter in various brain regions. This white matter is composed of the extensions of nerve cells that are normally covered by an insulating substance called myelin. This gene was further studied by injecting a fragment of the CART gene product into the ventral tegmental area of rats, a brain region thought to influence the experience of drug reward. Injection of this fragment induced behaviors virtually identical to those seen after cocaine administration Kimmel et al. Similar work is being conducted to study other genes whose expression is found to be changed in response to alcohol. For example, changes in gene expression in response to chronic cocaine treatment have been described in certain brain areas of nonhuman primates Freeman et al. Another commonly used animal model is the fruit fly Drosophila melanogaster, which has a long and rich history in genetic research. The entire Drosophila DNA sequence has been deciphered and has shown considerable similarity i. Several laboratories have studied Drosophila genes that influence sensitivity or tolerance to alcohol see Heberlein The mutation in this strain affects a signaling system called the cAMP pathway, which is important for many regulatory processes in the cell. The cAMP signaling pathway also has been implicated in determining alcohol consumption and sensitivity to alcohol in studies of a mouse knockout model Thiele et al. Studies in various animal models sometimes also complement or inform each other. For example, the findings regarding the role of the cAMP signaling pathway just described are supported by studies in the round worm i. Analyses in that organism identified a gene that is also part of the cAMP pathway and which influences adaptation to another addictive substance, nicotine Waggoner et al. Another organism that is increasingly used in research on alcoholism and other addictions is the zebrafish Danio rerio. The embryos of these fish are transparent, allowing easy anatomical characterization that facilitates genetic analysis. Furthermore, for many zebrafish genes, corresponding genes exist in mammals. For example, researchers have cloned a zebrafish gene that corresponds to a mammalian receptor for opioid drugs e. This research may have implications for alcohol research in humans because drugs that interfere with the activity of opiates and their receptors i. Researchers also have recently cloned the zebrafish gene for alcohol dehydrogenase ADH , the primary enzyme responsible for the degradation of alcohol in the body Dasmahapatra et al. This gene also exhibits substantial genetic similarity to a human ADH gene. Finally, zebrafish exhibit behavioral responses to alcohol that are reminiscent of those seen in other model organisms Gerlai et al.

FINDING GENES FOR COMPLEX BEHAVIORS : PROGRESS IN MOUSE MODELS OF THE ADDICTIONS JOHN C. CRABBE pdf

4: results in SearchWorks catalog

Behavioral genetics in the postgenomic era. Pericak-Vance --Finding genes for complex behaviors: progress in mouse models of the addictions / John C. Crabbe.

For example, researchers consistently have observed low levels of the neurotransmitter serotonin in certain brain areas i. Other studies with selected lines have shown dysregulation of the GABA and glutamate systems in animals bred to exhibit severe withdrawal. By acting on all these signaling systems, alcohol ultimately exerts its effects through modulation of intracellular signaling cascades Newton and Messing These gene-mapping studies, which commenced in the early s, have used methods similar to those described above for human studies e. They primarily have sought to identify quantitative trait loci QTLs â€”DNA regions that are associated with characteristics i. Such traits typically are determined by multiple genes and each QTL may contain one or more of these genes. Compared with humans, studies with rats and mice have the distinct advantage that researchers can use individuals with defined genotypes and control patterns of mating, making it much easier to localize the chromosome region of interest i. The most recent systematic review Crabbe et al. The greatest success story for alcohol-related QTL mapping in rodents has been the discovery of a quantitative trait gene QTG 9 [9In contrast to a QTL, which only identifies a DNA region that is likely to contain a gene contributing to a quantitative trait but also may contain other, unrelated DNA sequences , a QTG represents the actual gene. Originally, investigators mapped several QTLs contributing to this trait to locations on various mouse chromosomes Buck et al. Subsequent studies with a variety of specifically created genetic animal models gradually narrowed down the size of the DNA region i. Functional studies then demonstrated that the most likely gene contributing to the trait was Mpdz, which encodes a protein containing multiple structural components known as PDZ-domains Shirley et al. Additional mapping studies aim to narrow other QTLs for alcohol responses, both in animals Bennett et al. A recent comparison of data from mouse and human QTL mapping identified a promising region of human chromosome 1 that was linked to alcohol dependence and which overlapped with an area of mouse chromosome 1 that has been linked to an alcohol withdrawal QTL Ehlers et al. Thus, about 80 percent of genes that are located closely together on a human chromosome also tend to be located in a cluster on a mouse chromosome. Nevertheless, some promising results of cross-species consistency exist, which likely will increase in number as the details of both rodent and human genetic maps improve. Classical QTL analysis has associated individual differences in gene sequence or in other genetic markers, such as microsatellites with differences in the phenotype being mapped. This information can be gathered from microarray experiments that measure the levels of individual mRNAs. These additional eQTLs greatly expand the pool of potentially informative genes. The eQTL approach has been used to compare gene expression in brain tissue from several rodent lines and strains genetically predisposed to drink alcohol with control tissue from low-drinking animals. The chromosomal location of differentially expressed genes then was compared with QTL data based on genetic sequence variations i. This combination of information suggested several candidate genes that may influence alcohol drinking Mulligan et al. An additional refinement to the gene-finding efforts has been the study of networks of proteins or the genes that encode them. Candidate Gene Studies and Gene Targeting Another important development enhancing the possibilities of genetic animal models of alcoholism was the development of transgenic animals in the late s. These are animals that have been genetically modified so that the expression of a single candidate gene has been selectively inactivated or augmented compared with the parent strain. This approach allows researchers to study the influence of individual genes on risk for alcoholism or many other diseases or behaviors. As reviewed by Crabbe and colleagues , most of the genes thus studied were found to influence some aspect of alcohol sensitivity. For example, of 84 different transgenic animals tested for effects on alcohol self-administration, one-quarter exhibited increased drinking, one-third exhibited decreased drinking, and 40 percent did not differ from control animals Crabbe et al. This finding clearly demonstrates the multiplicity of

genetic influences on alcohol responses. As gene-targeting technologies allow more specific experimental regulation of genes than simple deactivation or overexpression, these approaches will continue to provide important data. For example, researchers now can manipulate genes so that they are expressed only in certain cell types or during particular developmental periods. Candidate gene studies also have been valuable in looking for consistency across species in the impact of certain genes or gene variants. However, to be able to use such models, researchers first need to demonstrate that corresponding genes exist in these organisms and that they actually have similar functions. One example of such convergence of evidence is the finding that a small signaling molecule called neuropeptide Y NPY and its receptors play a role in alcohol intoxication in mice, rats, and Drosophila Chen et al. A meta-analysis of human association data, in contrast, found no clear evidence that polymorphisms in the gene encoding a precursor of NPY are associated with alcohol dependence Zhu et al. However, some genes encoding NPY receptors may play a role in alcohol dependence and withdrawal Wetherill et al. Finally, certain signaling proteins e. Advances in genetic technologies already have allowed researchers to explore the genome in ever greater detail, and with the advent of whole-genome sequencing, complete delineation of genetic variation soon will be available. In contrast, our understanding of the critical environmental factors influencing alcohol use disorders remains inadequate and is an area of active research. One of the challenges is how to define the environment, which may include family, peer, and societal influences; other exposures; personality or psychiatric factors which also have genetic components ; and many more, most of which change over time. Furthermore, the influence of these factors on the risk of alcohol use disorders varies within the lifespan Sher et al. Given their methodological power, it is surprising how little research into this area has been done using genetic animal models. One trait that has been found to be genetically determined is alcohol preference of inbred mouse strains. Thus, specific mouse strains have displayed their tendencies to drink more or less alcohol by choice repeatedly across 50 years of studies. In fact, alcohol preference in these animals is even more replicable across studies and therefore, across environments than brain weight Wahlsten et al. Not all alcohol traits are so stable, however, and the combined effects of genetic and environmental manipulations could be exploited more fully using genetic animal models. A recent review has discussed several important features of geneâ€”environment interaction research Sher et al. For example, the social environment plays such a crucial role in shaping drinking behaviors in humans, but it is difficult to identify corresponding rat and mouse behaviors and environmental factors. One example of a study analyzing geneâ€”environment interactions in animals Hansson et al. Thus, this study demonstrated an interaction between a specific genotype and an environmental factor i. Analysis of human geneâ€”environment interactions also are complicated by the fact that these interactions are important from adolescent exposure to alcohol and then throughout life. Accordingly, from a developmental perspective, the critical environmental influences are likely to change over time e. Studies that follow genetically specified animals prospectively while extracting biological information at different times along the way are a promising area for future research that has not been sufficiently exploited thus far. One such factor that can impact gene expression is methylation of the DNA. Other epigenetic changes alter the packaging of DNA into chromatin. For example, two enzyme families called histone acetyltransferases and deacetylases can be used to alter chromatin structure experimentally, and studies found that when such changes accompany chronic drug administration, they can modify cocaine-related behaviors in rats Renthal and Nestler Although similar research on alcohol-related traits still is in its infancy, some studies have found that alcoholic patients exhibited greater levels of DNA methylation of two different genes than nonalcoholics and, consequently, greater reduction in the expression of those genes Bleich et al. These microRNAs also offer a new experimental method for silencing the expression of specifically targeted genes. The expression of microRNAs is sensitive to epigenetic modulation, and turning microRNAs on or off has become feasible in rodent models. Modification of microRNAs may offer a new pathway for identifying critical genes that can then serve as target for new therapeutic drugs for alcoholism treatment. In summary, the genetics field has undergone a technological revolution, particularly in the past decade, allowing researchers to process large

numbers of samples for their genetic studies and to efficiently interrogate the entire genome. Using these strategies, researchers have been able to identify a number of genes in which variations appear to contribute to the susceptibility to alcohol dependence. It is important to note, however, that the individual role of each of these genes, and the SNPs within them, is quite modest. This means that a given allele or SNP that has been found to be associated with alcohol dependence may increase the risk of alcoholism only incrementally. As a result, it would be a gross overinterpretation of the results obtained in human association studies to date to suggest that we currently have a means to identify people at greatest risk for alcohol dependence. With the exception of the strong protective effects of certain ADH and ALDH variants, each gene variant identified to date has a much smaller individual effect on alcoholism risk than, for example, a family history of alcoholism. Another challenge is to relate the complex human behavioral phenotypes to specific variations in the sequence and expression of specific genes and, perhaps more importantly, to the function of the proteins encoded by these genes. The answers may come from networks of genes that encode proteins of similar function, rather than from specific genes individually. Examining such networks represents another level of complexity that poses a huge quantitative challenge, computationally and statistically. However, researchers also are making substantial progress on this bioinformatics front, and the continuing development of greatly enhanced bioinformatics capacity is increasing the power of studies in both rodent models and humans. It also may yield important insights that will allow the development of better pharmacological treatments to help those who wish to reduce their alcohol consumption. All such potential new therapies will of course be tested first in animal models Egli , and the coordination of animal model and human research therefore will continue to be an important theme for alcohol research for many years to come. Are there genetic influences on addiction: Evidence from family, adoption and twin studies. Association of GABRA2 with drug dependence in the collaborative study of the genetics of alcoholism sample. American Psychiatric Association, Begleiter, H; Reich, T. The Collaborative Study on the Genetics of Alcoholism. Bennett, B; Carosone-Link, P. Genetic dissection of quantitative trait locus for ethanol sensitivity in long- and short-sleep mice. Genes, Brain, and Behavior 7: Quantitative trait locus mapping for acute functional tolerance to ethanol in the L x S recombinant inbred panel. Clinical and Experimental Research A genome-wide association study of alcohol dependence. Proceedings of the National Academy of Sciences of the U. Defining alcohol-related phenotypes in humans. DNA hypermethylation of the alpha synuclein promoter in patients with alcoholism. Quantitative trait loci involved in genetic predisposition to acute alcohol withdrawal in mice. Journal of Neuroscience Involvement of the limbic basal ganglia in ethanol withdrawal convulsivity in mice is influenced by a chromosome 4 locus. A protein kinase C activity localized to neuropeptide Y-like neurons mediates ethanol intoxication in Drosophila melanogaster. Genotypes for aldehyde dehydrogenase deficiency and alcohol sensitivity. The inactive ALDH2 2 allele is dominant. Journal of Clinical Investigation A line of mice selected for high blood ethanol concentrations shows drinking in the dark to intoxication. The complexity of alcohol drinking: Studies in rodent genetic models. Behavior Genetics, , In press. Identifying genes for alcohol and drug sensitivity:

FINDING GENES FOR COMPLEX BEHAVIORS : PROGRESS IN MOUSE MODELS OF THE ADDICTIONS JOHN C. CRABBE pdf

Pimsleur Language Program German Intermediate (Pimsleur Language Program) Select bibliography (p. [ix]-xii) V. 5. Cundurango-Helonias Dioica Stress Management and Counselling Clockwork by philip pullman In far north-east Siberia The eagle and the hunter. Enders game book 2 RGT Classical Guitar Playing Step 1 Rosenzweig Lehrhaus Banning landmines A learners guide to Pintupi-Luritja Return to the center College applications step by step Agricultures import saving role Reflections on Beckett Hydrocarbon processing petrochemical processes 2010 handbook The Flyer (The Lighthorseman series) The nature of copyright The Invention of Infinity World list of serials in agricultural biotechnology Paul lawrence guthrie making of the white man Learn to play bluegrass bass Institutional suspicion : the management and governance challenge in user-owned microfinance groups Susan Transformation of Miss Mavis Ming Leaves from a Childs Garden of Verses The story of stuff Executive development and organizational learning for global business The environment of industrial marketing Conquest of Jerusalem and the Third Crusade Italy in the European Monetary Union Rhymin and designin : hip-hop and the art of the album cover Carlo McCormick California mechanics lien law handbook On the Case With Inspector Poirot Ritz Address Book Glencoe vocabulary power grade 5 Mahabharata ebook The hobbit the desolation of smaug Munkres topology solutions chapter 2 section 20 The Lincoln bulletin