Published in final edited form as:
*Nat Rev Genet*. 2009 April ; 10(4): 225–231. doi:10.1038/nrg2536.

# New insights into the genetics of addiction

**Ming D. Li**[1),*] and **Margit Burmeister**[2)]

[1)]Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, 1670 Discovery Drive, Suite 110, Charlottesville, Virginia 22911, USA

[2)]Molecular & Behavioral Neuroscience Institute, Departments of Psychiatry and Human Genetics, University of Michigan, M4140 SPH II, 109 South Observatory Street, Ann Arbor, Michigan, 48019, USA

## Abstract

Drug addiction is a common brain disorder that is extremely costly to the individual and to society. Genetics contributes significantly to vulnerability to this disorder, but identification of susceptibility genes has been slow. Recent genome-wide linkage and association studies have implicated several regions and genes in addiction to various substances, including alcohol and, more recently, tobacco. Current efforts aim not only to replicate these findings in independent samples but also to determine the functional mechanisms of these genes and variants.

Addictions are chronic, often relapsing disorders characterized by obsession, compulsion, or physical or psychological dependence. The World Health Organization estimates that there are 2 billion alcohol users, 1.3 billion tobacco users, and 185 million illicit-drug users worldwide. Twin and family studies provide strong evidence that addictions involve the interplay of genetic and environmental factors.[1–5] Greater knowledge of the genetics underlying addiction therefore is crucial for the development of more effective interventions. For example, after attempting to quit, smokers of European ancestry with the CYP2B6*6 genotype are more likely to relapse than those with other genotypes when on placebo but can be helped by bupropion treatment.[6]

In recent years, significant progress has been made in identifying susceptibility genes for addictions. Given that most of this progress primarily on a specific substance has been covered in other reviews,[1–5,7] we focus here on the most recent advances made through the use of linkage and association approaches, especially with genome-wide association study (GWAS); our goal is to provide an updated summary of identified susceptibility loci/genes for multiple substances. Regions on human chromosomes 4, 5, 9–11, and 17 are more likely to harbor susceptibility genes for multiple substances. Among the susceptibility genes for addiction identified from candidate gene-based or GWAS approaches, we limit our focus to representative genes that encode aldehyde dehydrogenase (*ADH*), nicotinic acetylcholine receptor (nAChR) subunits, $GABA_A$ (gamma-aminobutyric acid A) receptor subunit 2 (*GABRA2*), ankyrin repeat and kinase domain containing 1 (*ANKK1*), and neurexins, because of their influence on susceptibility to addiction to multiple substances, the strong statistical evidence to support their roles, or the importance of their biological functions in addiction. We first focus on evidence for the contribution of genetics to addiction, then on the recently identified loci/gene that confer susceptibility to multiple substances, and finally on the knowledge gained from engineered mice.

[*]**Correspondence to:** Ming D. Li, Ph.D. University of Virginia Department of Psychiatry and Neurobehavioral Sciences Section of Neurobiology 1670 Discovery Drive, Suite 110 Charlottesville, VA 22911 Tel: (434) 243-0566 Fax: (434) 973-7031 Ming_Li@virginia.edu.

## Genetic contribution to addictions

Epidemiological studies strongly suggest that genetic factors operate at all steps of addiction, including vulnerability to initiation, continued use, and propensity to become dependent (**Box 1**). Twin studies have been popular to investigate the relative contributions of genetic and environmental factors. In addition to estimating genetic liability, twin studies provide information about environmental contributions, including the availability of and exposure to a substance, and shared and unique environments. The genetic influence on addiction has proved to be substantial, and HERITABILITIES for most addictive disorders are moderate to high.

Numerous large twin studies for alcohol-related behaviors have consistently shown that heritability of alcohol abuse and dependence ranges from 50% to 70%.[8] A similarly high heritability also is seen across other alcohol-related behaviors, including heavy consumption and `problem' drinking.[8] Meta-analysis of the twin studies shows that both genes and environment are important in smoking-related behaviors, with an estimated mean heritability of 0.50 for smoking initiation and 0.59 for nicotine dependence (ND).[4] Genetic factors have a larger role in initiation than in persistence in women, whereas the opposite is observed in men.[4,9]

Fewer studies have examined genetic influences on illicit drug addiction. Heritability of the use/dependence on stimulants, sedatives, and heroin in males is 0.33, 0.27, and 0.54, respectively.[10] These values are similar to those seen in females, although such studies are rarer.[11] Moreover, twin studies indicate a large overlap between the genetic predispositions to dependence and that to most classes of substances. For example, twin studies suggest that nicotine and alcohol dependencies share more than 60% of their genetic vulnerabilities.[12]

Finally, we point out that heritability is specific to the sample under study. Thus, the role of genetic influences may differ across samples, and heritability may be affected by many factors, such as sex, age, education, socioeconomic status, and cultural background.

## Identifying susceptibility loci for addiction

Both LINKAGE and association mapping have identified susceptibility loci for addiction-related phenotypes, especially for alcohol dependence (AD) and ND. However, few putative genome linkages have been replicated in independent studies, probably because of GENETIC HETEROGENEITY.

Despite these limitations, significant progress has been made, especially for AD and ND. Linkage studies have identified a locus on chromosome 4q near the *ADH* gene cluster as a major locus for alcoholism in American Indians and Caucasians,[13–15] in addition to the known *ADH2* and aldehyde dehydrogenase 2 (*ALDH2*) variants in Asians and Jewish Americans.[16–18] The *ADH* locus contains a cluster of seven genes, of which *ADH2* is the most important across populations,[19] although functional variants in *ADH4* and *ADH7* might also be involved.[16,20,21]

One of the most successful examples of the POSITIONAL CANDIDATE GENE APPROACH in addiction research has been the identification of *GABRA2* as a susceptibility factor for alcoholism. Early linkage studies in Southwest American Indians[13] implicated chromosome 4p near the *GABRA2/B1* cluster; these results were confirmed in some Caucasian studies,[22] and became particularly convincing when linkage of alcohol-related phenotypes was combined with QUANTITATIVE TRAIT LOCUS (QTL) MAPPING of electroencephalographic quantitative trait data.[23] Initial association findings of *GABRA2*[24] in that linkage region were replicated in multiple studies,[25–27] so that *GABRA2* is now considered a confirmed risk locus for AD.

Similarly, variants in *GABBR2* (on chromosome 9q22), which encodes the $GABA_B$ receptor subunit 2, have been associated with ND.[28] Linkage of chromosome 9 with smoking behavior has been reported in several independent studies,[29–32] and *GABBR2* contributes 28%–38% to this linkage signal.[33] The involvement of GABA signaling across addictions has been confirmed in animal models (see below).

Although many linkage scans have been reported for addiction to a specific drug, only few have investigated the convergence of linkage peaks across drug addictions. Toward this objective, we searched for linkage peaks among multiple abused substances, according to the criteria proposed by Lander and Kruglyak.[34] We found that regions on chromosomes 2–5, 7, 9–11, 13, 14, and 17 have independent evidence of "suggestive" or "significant" linkage, with regions on chromosomes 4, 5, 9, 10, 11, and 17 receiving the strongest support for harboring susceptibility genes for addictions to multiple drugs (Figure 1).

Although many candidate genes have been investigated for associations with addiction, only a few findings have been replicated in independent studies for multiple addictions. Instead of giving a detailed review of these candidates individually, our discussion focuses on representative genes that have recently received much attention or are associated with addictions to multiple substances.

## Susceptibility genes for substance addiction

In the past two years, the most significant findings in addiction genetics have been the involvement of a few nAChR subunit genes specifically in ND and more generally in substance abuse. As illustrated in **Box 2**, nicotine exerts its biological function by binding to nAChRs, which are composed of five subunits. There are 12 nAChR subunit genes: nine alpha (α2–α10) and three beta (β2–β4) subunits. Variants have been associated with dependence on nicotine, alcohol, and cocaine and with lung cancer susceptibility, as explained below.

### nAChR α4 subunit gene

A significant association of variants in *CHRNA4*, which encodes the α4 subunit, with ND has been detected in three independent studies. The first study revealed significant protective effects of two SNPs against ND in Chinese men.[35] A second study showed that four SNPs and HAPLOTYPEs that consisted of these SNPs are significantly associated with ND in European and African Americans, but the effects differed as a function of ethnicity or sex.[36] A third study reported that two SNPs are significantly associated with the subjective response to smoking.[37] Although not all associations have been replicated, two SNPs (rs1044396 and rs2236196) are consistent in two of the three studies. Together, these studies provide evidence that variations in *CHRNA4* influence ND.

### Association and interaction analysis of CHRNB2

By contrast, no significant association of *CHRNB2*, which encodes the β2 subunit, with ND was reported in four independent studies (e.g., see [35,36]), except for a significant association of rs2072661 in the 3′-UTR of the gene with ability to quit smoking.[38] However, epistatic analysis using a generalized MULTIFACTOR DIMENSIONALITY REDUCTION METHOD[39] revealed that *CHRNB2* has a significant effect on ND when analyzed with *CHRNA4* together.[40] The failure to detect significant association of *CHRNB2* with ND by itself may thus be attributable to the relatively small effect of *CHRNB2* or strong dependency of *CHRNB2* effects on specific *CHRNA4* variants. More importantly, detection of significant interaction of *CHRNB2* with *CHRNA4* in humans is consistent with the formation of functional nAChRs with these two subunits.[41,42] A moderate association of *CHRNB2* with early response to alcoholism has also been reported.[43]

Recent development of selective partial agonists of α4β2 nAChRs as effective smoking-cessation agents further supports the role of α4β2 nAChRs in ND. For example, the partial α4β2 nAChR agonist vareniclinie was approved by the US Food and Drug Administration as an aid to smoking cessation. It produces significantly higher quit rates (2–3×) than do other treatments.[44] Vareniclinie can selectively decrease ethanol consumption and seeking in animals, implying it may be valuable also for the treatment of alcoholism.[45]

## Association of CHRNA5/A3/B4 with ND and lung cancer

Three recent GWASs suggested a strong association between variants of *CHRNA5/A3/B4* (encoding subunits α5, α3, and β4) at 15q24 and lung cancer.[46–48] However, although one study revealed a significant association of a *CHRNA3* SNP with ND,[48] the other two studies suggested association of this and other variants with lung cancer independent of their association with smoking.[46,47] Several other studies provide independent verification of the association between this gene cluster and ND,[49–51] and suggest that power, precision of phenotyping, or severity may explain the apparent association with lung cancer rather than a direct, smoking-independent association. We feel that a biological link between variants in the *CHRNA5/A3/B4* cluster and ND is more plausible than a direct effect of these variants on lung cancer.

## Association of CHRNA5/A3/B4 with alcohol and cocaine dependence

Association of the *CHRNA5/A3/B4* gene cluster with alcohol and cocaine addictions has been reported. Wang et al.[52] identified a group of SNPs across *CHRNA5/A3* associated with AD. Because these variants are in low linkage disequilibrium (LD) with the SNPs associated with ND and lung cancer, the authors concluded that *CHRNA5/A3* variants are associated with AD but through different SNPs and mechanisms from those identified in ND and lung cancer. Moreover, Grucza et al.[53] found that a nonsynonymous polymorphism in *CHRNA5* has the opposite effect on cocaine dependence (CD) than is associated with ND. Such contradictions in allelic associations are found in other psychiatric disorders also.[54] It remains to be seen whether there is true heterogeneity of association (in this case, between ND and CD), or whether some findings will turn out to be false positives.

## Future research on the CHRNA5/A3/B4 cluster

Further steps are required to characterize the *CHRNA5/A3/B4* cluster as a susceptibility locus for addictions and lung cancer. First, it is important to determine which variant(s) cause such significant associations. Resequencing might identify additional variants that explain the complex patterns, but functional analysis also will be necessary. The nonsynomous variant rs16969968 (Asp398Asn) causes the substitution of a negatively charged residue within the M3–M4 intracellular loop of *CHRNA*3 (**Box 2**), a region thought to be involved with receptor trafficking. Indeed, the variant form of *CHRNA5* alters receptor function without affecting expression.[55] Second, it is important to determine whether the *CHRNA5/A3/B4* cluster also has a significant role in non-European populations. Third, more research is needed to determine which smoking-related behavior drives the association with this cluster. For example, ND was measured by smoking quantity in two studies,[48,50] whereas another focused on searching for susceptibility genes underlying the transition from regular non-dependent to dependent smokers.[49] Weiss et al.[51] found a significant association of the cluster with ND only in early-onset smokers. Fourth, other genes in the region, such as a hypothetical locus LOC123688, cannot be excluded because of the association with other SNPs within this cluster.[47] However, this issue may be difficult to solve genetically because of the extensive LD structure.

### Associations of other genes with addictions

Although many candidate genes have been associated with addiction (see Table 1 for verified and Supplementary Table 1 for non-verified genes associated with multiple substances and Supplementary Table 2 for genes associated with only one substance), few findings have been replicated. Given the controversial association reports for many genes, we focus on genes that have not only received strong statistical support for association with multiple substances of abuse but also have greater biological support.

Variants in *GABRA2* are strongly associated with alcoholism,[24–27] but an association has been reported between *GABRA2* variants and addiction to nicotine and polysubstance abuse.[56,57] Furthermore, a linkage study has implicated the region near *GABRA2* in the etiology of cannabis use.[58] Variants in *ANKK1*, a protein kinase involved in signal transduction,[59] have also been associated with susceptibility to ND,[60,61] AD, [62,63] and comorbid alcohol and drug dependence.[64] Finally, several GWASs provide evidence for the involvement of cell adhesion-related genes in vulnerability to addiction and other psychiatric disorders.[65] Representative members of this category include neurexin 1 for ND[66,67] and neurexin 3 for polysubstance, [65] alcohol,[68] and opioid abuse.[69] Rare mutations in several members of this gene family, including neurexin 1, also have been associated with autism[54,70] and schizophrenia,[71] implying the members of this family are important in many psychiatric disorders.

## Murine behavioral studies

### Knockout (KO) models of nAChR subunit genes

Genes encoding nAChRs mediate variability in many of the behavioral effects of nicotine. KO mice for nAChR subunits α3–α9 and β2–β4 have shown that the deletion of these genes alters many effects of nicotine. Unlike wild-type animals, mice lacking the α4 and β2 subunits do not self-administer nicotine and do not show nicotine-induced increases of dopamine in the ventral stratum.[72,73] In addition, β2 KO mice self-administer cocaine but fail to maintain self-administration when cocaine is switched to nicotine,[72] whereas α4 KO mice exhibit a prolonged motor response to cocaine.[73] Together, the findings from α4 and β2 KO mice provide evidence that α4β2* (* indicates another undetermined subunit) nAChRs are required for proper regulation of dopamine release and maintenance of self-administration and reinforcement.

KO mice of α5[74] and β4[75], as well as α3 KO heterozygous mice,[76] show that each of the three genes in a cluster on chromosome 15 mediates similar effects of nicotine; i.e., the animals show resistance to nicotine-induced seizures, whereas the α5 and α3 subunits mediate both the locomotion-suppressant effects of nicotine and somatic signs of nicotine withdrawal.

### Knockin (KI) model of α4 nAChR subunit in nicotine

To better understand the roles of α4-containing nAChRs, a KI approach was adopted with the goal of making a hypersensitive nAChR that might generate more noticeable phenotypes. One of the most successful examples of this approach was the generation of two lines of α4 KI mice by introducing a point mutation into the M2 transmembrane region of the α4 subunit.[77,78] In Leu9′Ser KI mice, this mutation produces α4-containing nAChRs with a ~30-fold increase in sensitivity to acetylcholine and nicotine. Heterozygous KI mice exhibit greater anxiety, impaired motor learning, excessive ambulation that is eliminated by small amounts of nicotine, and reduction of dopaminergic function on aging.[78] In contrast, both homozygous and heterozygous Leu9′Ala KI mice are exceptionally sensitive to nicotine and ND-related behaviors, including reward, tolerance, and sensitization.[77] These findings suggest that genetic variability in the α4 subunit can produce dramatic changes in nicotine sensitivity, implying that a variant(s) in the human *CHRNA4* gene alters sensitivity to nicotine and vulnerability to ND.

### Mouse models of GABA genes in alcohol and other addictions

Rodent models of addiction have been studied for decades.[79] QTL mapping of alcohol withdrawal identified several loci reproducibly: for example, one replicated locus involves nonsynonymous variants in *GABRA2*.[80] Deletion of $GABA_A$ receptor α1 or β2 subunits leads to reduced loss of the righting reflex in response to alcohol, as well as reduced consequences in response to other drugs.[81] Conversely, sensitivity to alcohol can be manipulated by overexpression or reduction of the activity of the GABA transporter.[82]

Overall, many other mutants, KI, KO, and transgenic mice of various GABA subunit genes have convincingly established a role for GABA in mediating the behavioral consequences of alcohol[79] and other drugs.[83] The specific genes and alleles may differ from those associated in humans, but overall, animal models have confirmed and extended findings of GABA's involvement in AD and other addictions.[79,83] The molecular mechanism of the effects of GABA are being established by microarray analysis.[79,84]

## Conclusions

Significant progress has been made in identifying susceptibility loci and genes for addictions. Comparison of linkage peaks for addictions to various substances confirms what we have learned from genetic epidemiological studies, namely that genetic vulnerability to different substances in part overlaps. Variants in several genes, including aldehyde dehydrogenases, *GABRA2*, *ANKK1*, and neurexins 1 and 3, have been associated with addictions to multiple drugs. Most recently, variants of the *CHRNA5/A3/B4* cluster on chromosome 15 were found by GWAS, as well as by targeted studies, to be associated not only with addictions to tobacco, alcohol, and cocaine, but with lung cancer as well. These genes have effects on nicotine responses in animal models and can thus be considered established targets for these studies. Nevertheless, the exact nature of the variants and their functions are still unknown. Functional studies as well as studies in other ethnic populations with different LD structure may be revealing. GWAS confirmation of candidate gene findings is reassuring, and similar to the robust findings in type II diabetes[85] but in sharp contrast to GWAS results in other psychiatric disorders, which so far have failed to replicate any candidate findings.[54] Such candidate genes with prior biochemical evidence and animal models allow a quicker move to functional studies. Well-designed GWASs with large samples should help to identify additional genes, including genes that implicate novel biological pathways involved in addiction.

### Box 1: Definition of addiction and challenges in addiction genetics research

**Diagnostic assessment of addiction: nicotine dependence as an example**

Drug addiction is characterized by a compulsion to take a substance, with goal-directed behavior toward excessive substance intake and a loss of control in limiting intake. Clinical addictions generally are diagnosed using the Diagnostic and Statistical Manual IV (DSM-IV)[86] and the International Classification of Disease, 10th Revision (ICD-10) of the World Health Organization (WHO).[87] The most recent versions of DSM-IV and ICD-10 recognize two categorizes of addiction: *abuse* or *harmful use*, characterized by regular and increasing intake despite adverse consequences, and *dependence*, which in addition requires symptoms of withdrawal and/or tolerance.

Although there is significant comorbidity among addiction to different drugs, the measurement of various addictions differs greatly. Here, we use nicotine dependence (ND) to illustrate the complexity of this behavior. Historically, the assessment of ND has relied largely on the use of the Fagerström Tolerance Questionnaire[88] or a shorter version, the FTND.[89] Since they were introduced, these two scales have been used frequently in both clinical and research settings, partly because of their relation to treatment outcome.

However, the Fagerström scales were developed as unidimensional measures of physical tolerance[88] and thus do not assess some important aspects of ND, such as craving, subjective compulsion to smoke, nicotine withdrawal symptoms, BEHAVIORAL SALIENCY, or BEHAVIORAL AUTOMATICITY, which often are regarded as core constructs of ND.[90]

ND also can be assessed by diagnostic criteria based on the DSM-IV.[86] However, these symptoms are ultimately aggregated into a dichotomous classification as "dependent" or "not dependent," which limits its usefulness for research into the causes of addiction. Given that a diagnosis of dependence can be assigned by meeting various combinations of criteria, the diagnosis is conceptually heterogeneous. To expand the breadth of the diagnosis criteria and thereby improve the self-reported assessment of ND, new scales such as the Wisconsin Inventory of Smoking Dependence Motives[91] and the Nicotine Dependence Syndrome Scale[92] were developed. Whether these new scales can capture different aspects underlying ND and reduce the phenotypic heterogeneity among smokers remains to be investigated, especially in non-Caucasian smokers.

**Genetic and phenotypic heterogeneity**

One of the most significant challenges in genetic research on addiction concerns heterogeneity at both the phenotypic and genetic levels. Phenotypic heterogeneity is extensive in the manifestation of addiction, with users differing in magnitudes such as age of onset of problems, drug symptoms, abusing history, and comorbid disorders. One means to reduce phenotypic heterogeneity is to classify more genetically or neurobiological homogeneous phenotypes or use ENDOPHENOTYPES as an intermediate phenotype between an addicted phenotype and the biological processes responsible for the manifestation of that disorder. GENETIC HETEROGENEITY is another major concern in genetic studies on addiction. Genetic differences exist between different ethnic groups or samples from different geographic locations. One way to minimize the impact on final genetics findings is to increase sample size and use more homogeneous samples.

## Box 2: Composition and function of neuronal nicotinic acetylcholine receptors (nAChRs) in the brain [contains figure]

Neuronal nicotinic acetylcholine receptors belong to a super-family of ligand-gated ion channels that also includes receptors for GABA, glutamate, glycine, and serotonin. nAChRs are pentameric complexes assembled from an extensive family of subunits. In vertebrates, 12 nAChR subunit genes with a common ancestor have been cloned and classified into two subfamilies of nine alpha (α2–α10) and three beta subunits (β2–β4). There is considerable subunit diversity amongst nAChR subtypes and, consequently, receptor subtypes are commonly referred to by their subunit composition.

nAChRs are widely distributed in the brain, and their subunit composition is cell and region specific. Most nAChRs in the nervous system contain one type of α and one type of β subunit, with α4β2 receptors accounting for 90% of the high-affinity nAChRs in the brain; α3β4 receptors are the main subtype in the autonomic ganglia and adrenal medulla as well as in subsets of central nervous system neurons. The α4β2 and α3β4 subtypes also can contain the α5 subunit, which is believed to increase the rate of channel desensitization and calcium permeability.

Because nAChRs are the primary site of action for nicotine in the brain, they are important targets for the development of therapeutic agents that facilitate smoking cessation efforts. nAChRs are composed of five subunits that combine to form a functional receptor (Panel ***a***). Each subunit comprises four membrane-spanning domains, which are arranged in concentric layers around a central aqueous pore with the M2 domain lining the pore. On nAChR activation by an endogenous agonist (acetylcholine, for example) or exogenous

agonist (such as nicotine), the domains of each of the five nAChR subunits rearrange such that the central pore opens and permits cationic trafficking (Panel ***b***). Nicotine binds at the interface between the α and β subunits in heteromeric nAChRs to activate the receptor (Panel ***c***). Activation of nAChRs can potentiate neurotransmitter release (when expressed at presynaptic terminals) and neuronal excitability (when expressed at postsynaptic terminals) throughout the brain. As a result, nAChRs contribute to a wide range of brain activities that include cognitive functions and neuronal development and degeneration. Nicotine dependence is initiated through the activation of nAChRs. Chronic nicotine exposure produces the long-lasting physiological and behavioral changes associated with addiction, including nAChR up-regulation, gene expression alteration, and long-term potentiation and depression induction at glutamatergic synapses.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

The authors are supported by grants from the National Institutes of Health (DA12844, DA-13783, DA15462S1, AA012217, and AA016104). The authors thank Chamindi Seneviratne, Ju Wang, and Jennie Z. Ma of the University of Virginia for assistance in the preparation of tables and figures.

## Short Biographies

Ming D. Li is the Jean and Ronald Butcher Professor of Genetics in Psychiatry and Neuroscience and Head of the Section of Neurobiology in the Department of Psychiatry and Neurobehavioral Sciences at the University of Virginia in Charlottesville. Dr Li received his MS in statistical genetics and PhD in molecular genetics/biology at the University of Minnesota in Minneapolis. After carrying out postdoctoral research in genetics and neuropharmacology, he has served on the faculties of three institutions. Dr Li's research focuses on the identification and characterization of genes underlying drug addiction in both humans and animals, with a focus on nicotine dependence, using genomics, functional genomics, and bioinformatics approaches.

Margit Burmeister received a Diplom (M.S.) in biochemistry from the Free University of Berlin, Germany with thesis work at the Weizmann Institute of Science in Rehovot, Israel and a Dr. rer. nat. (a Ph.D. equivalent) in biology from the Ruprecht-Karls University in Heidelberg, Germany, for work performed with Hans Lehrach at the European Molecular Biology Laboratory. After carrying out postdoctoral research at the University of California in San Francisco, with Richard M. Myers and David R. Cox, she joined the faculty of the Molecular & Behavioral Neuroscience Institute and Departments of Psychiatry and Human Genetics at the University of Michigan, where she now also serves as the Director of the Bioinformatics Graduate Program in the Center for Computational Medicine and Bioinformatics.

## Glossary

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| Behavioral automaticity | Control of behavior by external stimuli and events in the immediate environment, often without knowledge or awareness of such control. |
| Behavioral saliency | In the context of this article, the likelihood and the degree to which a stimulus elicits a reaction or response. |
| Depression Induction | A procedure that induces a state of depression. |

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| Endophenotype | In psychiatry, a biomarker for a behavioral symptom that has a clear genetic connection. |
| Generalized Multifactor Dimensionality Reduction (GMDR) method | An extension of MDR applicable to different kinds of phenotypes that allows covariate adjustment on the basis of generalized linear models. |
| Genetic Heterogeneity | Causation of a disorder or trait by different genetic variants in different samples. This can arise when participants of different ethnic origins are included, genetic effects or samples are small, and marker density is low. |
| Haplotype | A combination of the alleles at different loci on the same chromosome. |
| Heritability | The proportion of phenotypic variance that can be attributed to variance of the genotype. |
| Linkage Mapping | Linkage refers to the tendency of two close loci on the same chromosome to co-segregate within a pedigree. Genome-wide linkage scanning can identify loci involved in conditions for which there is no *a priori* reason to suspect any contribution. |
| Long-term potentiation | The long-lasting improvement in communication between two neurons that results from stimulating them simultaneously. |
| Multifactor dimensionality reduction method (MDR) | A data reduction approach for detecting combinations of attributes or independent variables that interact to influence a binary outcome. |
| Positional Candidate Gene Approach | A candidate gene-based association study following a genome region identified from linkage analysis. |
| Quantitative Trait Locus (QTL) mapping | The statistical study of the genetic loci that contribute to variations in a quantitative trait or phenotype. |
| Tagging SNPs | An informative subset of SNPs that can explain the majority of the complex patterns of linkage disequilibrium between adjacent SNPs in a region of interest. |

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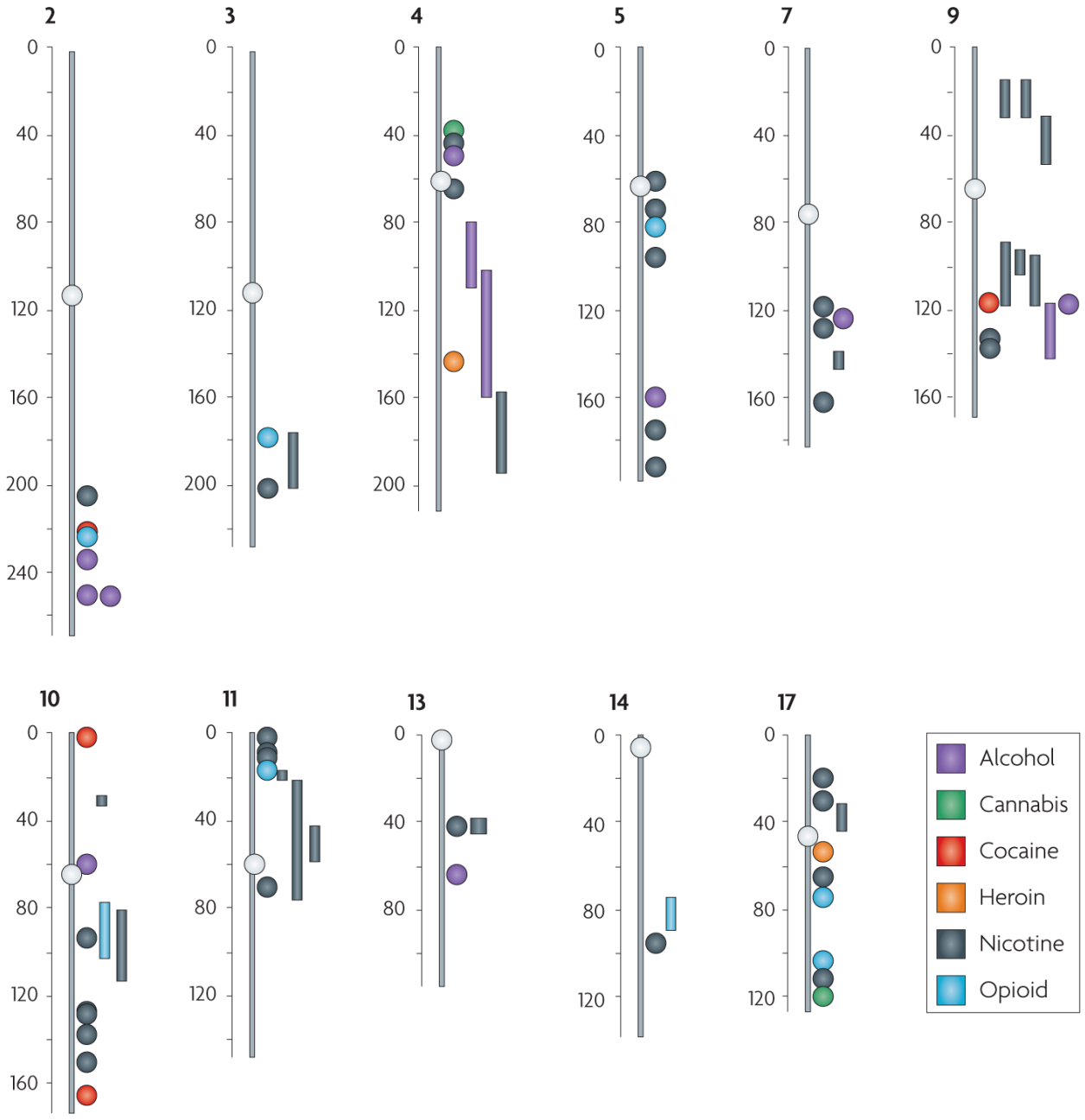

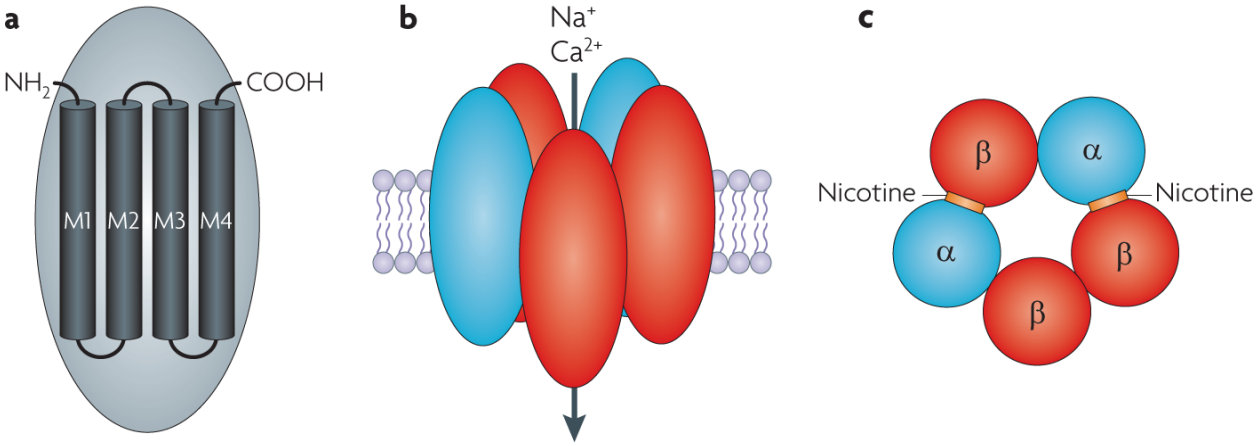


**Figure 1. Chromosomal locations of peaks or intervals for addiction to multiple substances**

Summary of chromosomal locations of nominated peaks or intervals for addictions to alcohol, cannabis, cocaine, heroin, nicotine, and opoids. Each linkage is given with either a color-filled circle or a rectangle, representing a reported linkage peak or region, respectively. "Significant" or "suggestive" linkage was determined by independent studies on at least two substances of abuse. The determination of "significant" or "suggestive linkage" at each linkage peak/interval was based on the rigorous criteria proposed by Lander and Kruglyak,[34] which define an LOD of >3.6 or a P value of $<2.2 \times 10^{-5}$ as a "significant linkage" and an LOD of >2.2 but <3.6 or a P value of $7.4 \times 10^{-4}$ as a "suggestive linkage." Each color represents a type of abused substance. The "unit" for each chromosome is "cM."

**Table 1**

Candidate genes associated with at least one drug addiction that are verified by meta-analysis*

| Gene Symbol | Gene Name | Biological System and Function | Chrom. Location | Drug (phenotype#) | Evidence from KO animal model | References for meta-analysis |
|---|---|---|---|---|---|---|
| 5HTT/ SERT | 5-Hydroxytryptamine transporter | Neurotransmitter transport | 17q11.1-q12 | Alcohol (i, d, c); Cocaine (d, c); Heroin (d); Methamphetamine (d); Nicotine (d) | Increased sensitivity to alcohol-induced sedation/ hypnosis; Motor-coordination deficits in response to alcohol; Reduced gross alcohol intake; Altered behavioral responses to cocaine and alcohol | 93,94 |
| CYP2A6 | Cytochrome P450, family 2, subfamily A, polypeptide 6 | Oxidation reduction | 19q13.2 | Alcohol (d); Nicotine (i, d, c) | | 94 |
| DAT1 | Dopamine transporter | Neurotransmitter transport | 5p15.3 | Alcohol (d, c); Cocaine (d); Heroin (d); Methamphetamine (d); Nicotine (i, d, c) | Reduces alcohol preference in female mice; Cocaine-induced stereotypy | 94,95 |
| DRD2 | Dopamine receptor 2 | Synaptic transmission, dopaminergic | 11q23.1-q23.2 | Alcohol (d, c); Cocaine (d); Heroin (d); Nicotine (i, d, c) | Alcohol preference and alcohol-induced ataxia; limit rates of high-dose cocaine self-administration | 96 – 99 |
| IL10 | Interleukin -10 | Cytokine activity | 1q31-q32 | Alcohol (d) | | 100 |
| BDNF | Brain-derived neurotropic factor | Regulation of synaptic plasticity | 11p13 | Alcohol (i, d, c); Nicotine (d); Cocaine (d); Methamphetamine (d) | Increased alcohol intake; Increased preference for cocaine | 101 |

Notes:

*: The genes reported here have one or more variants that have been associated with more than one addiction.

#: d – Abuse/Dependence; i - initiation; c - cessation/withdrawal. This table may only represent a partial list of genes that have been investigated for association with addictions.