

THE GENETICS OF ADDICTIONS: UNCOVERING THE GENES

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Abstract | The addictions are common chronic psychiatric diseases that today are prevented and treated using relatively untargeted and only partially effective methods. The addictions are moderately to highly heritable, which is paradoxical because these disorders require use; a choice that is itself modulated by both genes and environment. The addictions are interrelated and related to other psychiatric diseases by common neurobiological pathways, including those that modulate reward, behavioural control and the anxiety or stress response. Our future understanding of addictions will be enhanced by the identification of genes that have a role in altered substance-specific vulnerabilities such as variation in drug metabolism or drug receptors and a role in shared vulnerabilities such as variation in reward or stress resiliency.

AFFECTIVE DISTURBANCE

An abnormal or inappropriate emotion or mood.

POINT PREVALENCE

The proportion of individuals who have a phenotype at a specified point in time or within a defined timeframe (for example, 1 year).

DISABILITY ADJUSTED LIFE YEAR

The years of life that are lost due to premature mortality or disability.

PSYCHOPATHOLOGY

A psychiatric disease, or the manifestation of a psychiatric disease.

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Addictions are psychiatric disorders that are associated with maladaptive and destructive behaviours, and that have in common the persistent, compulsive and uncontrolled use of a drug or an activity. Addictive agents induce adaptive changes in brain function; these changes are the bases for tolerance and for the establishment of craving, withdrawal and AFFECTIVE DISTURBANCE, which persist long after consumption ceases¹. This self-maintaining and progressive neurobiology of addictions makes them chronic and relapsing disorders.

The addictions are a worldwide public-health crisis, and exert corrosive effects at family and societal levels, leading even to the narco-political and narco-economic domination of countries and regions. The World Health Organization (WHO) estimated that there are 2 billion alcohol users, 1.3 billion tobacco users, and 185 million users of illicit drugs (see the WHO reports in the Online links box). In 2001, these three categories together contributed to 12.4% of deaths worldwide (see the WHO reports in the Online links box). According to the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)², the one-year POINT PREVALENCE of DSM-IV (the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders issued by the American Psychiatric Association) substance-use disorders (excluding nicotine) is 9.35% in

the United States, representing 19.4 million adults (BOX 1). As well as causing ~590,000 deaths per year in the United States, addictive drugs also cause injury or illness to almost 40 million individuals³. On a population basis, alcoholism alone subtracts an average of 4.2 DISABILITY ADJUSTED LIFE YEARS (DALYs) per person, tobacco subtracts 4.1 DALYs and illicit drugs subtract 0.8 DALYs. For comparison, AIDS subtracts 6.0 DALYs and **type 1 diabetes** subtracts 0.1 DALYs⁴. The addiction disease burden is unequally distributed across countries; drugs have a higher impact in the United States and Europe than in developing countries where life expectancies are shorter (see the WHO reports in the Online links box).

Environmental and genetic factors contribute to individual differences in vulnerability to initiating use of addictive agents and in vulnerability to the shift from use to addiction. Cross-sectional studies on large twin samples also indicate that a mixture of environmental and genetic influences are shared between diseases⁵ and provide a link between the normal range of behavioural variation and PSYCHOPATHOLOGY^{6,7}. However, because addictions are in theory entirely preventable by law or individual choice, it has been argued that addictions are a low priority for genomic research⁴. Substance use shapes patterns of abuse and dependence, and conversely, addictive drugs are largely consumed by

POLYGENICITY

A model of genetic determinism in which many alleles function in combination to produce a phenotype.

HETEROGENEITY

A model of genetic determinism in which different alleles lead to the same phenotype in different individuals, but an individual allele can suffice to produce the phenotype.

HERITABILITY

An estimate of the genetic component of liability, which ranges from zero to one.

ADDICTION LIABILITY

The relative potential of an agent to lead to addiction.

ABUSE

Substance abuse is a disease that is operationally defined using objective criteria such as those issued by the American Psychiatric Association and the World Health Organization.

addicted individuals⁸. Addictive substances are widely used worldwide⁹ (FIG. 1). However, voluntary or enforced choice has met with partial success. Restrictions generally reduce addictions but are variably applied. Furthermore, the addictions encompass non-substance related behaviours that are widespread and that might access the same neurobiological pathways that modulate reward¹⁰, impulsive and compulsive behaviour, and mood. These diverse behaviours, including binge eating, compulsive gambling and playing video games, resemble the substance addictions in their clinical course and harmful effect. Therefore, the public-health impact of gene discovery for the addictions is potentially very large, as Merikangas and Risch⁴ noted. The origins of addiction vulnerability are complex and wide-ranging; the underlying genetic factors need to be identified to solve the puzzle of what causes these pervasive and relatively intractable disorders. Fortunately, the establishment of widely accepted definitions has created a unifying framework for research and for the clinical treatment of disorders that frequently share neurobiological and clinical course¹¹ (BOXES 1,2).

In this review, we describe our current understanding of addictions. We begin by comparing their mode of inheritance and then discuss the nature of inherited factors, including the genetic risk factors that are shared across diseases versus disease-specific factors, and evidence for POLYGENICITY and HETEROGENEITY. We describe the progress that has been made in gene mapping, including recent work that has used intermediate phenotypes as predictors of vulnerability, and studies of candidate addiction-predisposing genes in animal

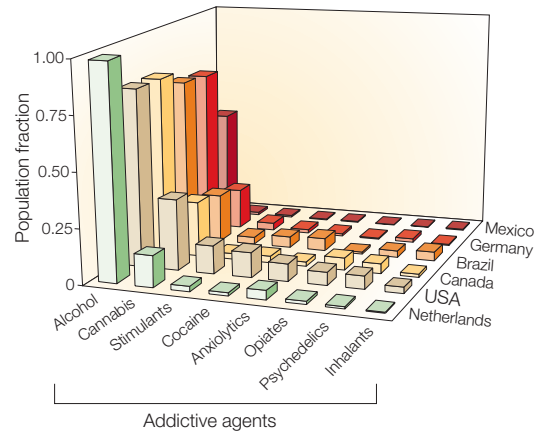


Figure 1 | **Lifetime prevalence of substance use in 6 countries.** Alcohol use is defined as having consumed 12 or more drinks in at least 1 year. Other drug use is defined as reporting use of the drug more than five times ever. Data are from Vega *et al.*⁹

models. We conclude by discussing the integration of genotypes into diagnosis; this goal is particularly timely given the enormous public-health impact of addictions and the potential power of precisely and inexpensively defined genotypes associated with these heritable diseases.

Inheritance of addictions

The inheritance of addictions has been evaluated in many ways, including studies on families and adoptees, but the cornerstone of our knowledge comes from the patterns of correlations in monozygotic (MZ) and dizygotic (DZ) twins.

Addictions are among the most heritable of psychiatric disorders, as shown in studies of large, carefully characterized cohorts of twins (TABLE 1), including epidemiologically ascertained cohorts from Virginia, USA, and Australia. HERITABILITIES range from 0.39 (for hallucinogens) to 0.72 (for cocaine) (FIG. 2a). These moderate to high heritabilities are seemingly paradoxical: addiction depends initially on individual choice to use an addictive agent (so, if a person chooses to use a drug, how can addiction to the drug be heritable?) and wide variations in ADDICTION LIABILITY are observed across time and space. However, heritability studies are generally carried out within populations and age-cohorts that share a substantial likelihood of exposure. Furthermore, it is becoming clear that susceptibility to several complex diseases — coronary artery disease, obesity, cancer and AIDS — is genetically influenced, but also depends profoundly on lifestyle choices. It should also be emphasized that, within populations, exposures are frequently pervasive (for example, exposure to nicotine, alcohol, gambling and caffeine in the United States) and that twin studies therefore cannot expose the full range of genotypes that underlie addiction. In addition, certain individuals are predisposed to initiate use. Heritabilities for initiation and use are generally lower than for dependence, but are still significant^{12,13}. Finally, heritabilities should not be overinterpreted as

Box 1 | Definition and classification of addictions

Clinical addictions are generally diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) issued by the American Psychiatric Association (APA), or using the International Classification of Disease (ICD) of the World Health Organization (WHO). These manuals are also used in research. The most recent versions of both systems (DSM-IV and ICD-10) recognize two categories: ABUSE (DSM-IV) or harmful use (ICD-10) and dependence. DSM-IV definitions of abuse and dependence are shown in BOX 2. Diagnoses can be made with high reliability; κ -values (a widely used coefficient of reliability that ranges from -1.0 to +1.0) are more than 0.70 for both DSM-IV and ICD-10 current alcohol dependence diagnoses¹¹. Addiction diagnoses are not aetiologically based, but are descriptive and syndromic, based on clusters of symptoms and clinical course¹⁰⁴. This issue limits their usefulness for research into the causes of addictions and is failing to promote individualized treatment and prevention.

The clinically heterogeneous nature of addictions led to sub-classifications, usually A versus B^{54,105}. More complex subdivisions are sometimes made¹⁰⁶⁻¹⁰⁹ that take into account age, age at onset, gender, psychiatric comorbidity and clinical course^{105,107}. For alcoholism, type A (for example, Cloninger type I) comprises approximately two-thirds of alcoholics and is characterized by later onset, slower course and better prognosis. Type B (for example, Cloninger type II) is characterized by stronger familial clustering, antisocial behaviour, earlier onset, rapid course and poorer prognosis. A frequently identified subtype is that of the negative affect or internalizing alcoholic, who is characterized by high levels of anxiety and depression^{106,107}. A and B distinctions are largely extendable to other addictions^{110,111}. Future versions of the DSM will probably incorporate dimensional indices such as age at onset, years of drug use, frequency and quantity of use. Future categorizations might also handle better the cross-connections between addictions and other psychopathologies.

Box 2 | Formal criteria for diagnosing substance-use disorders

Substance-use disorders, including abuse and dependence, are maladaptive patterns of use that lead to clinically significant impairment or distress. According to the definition that is included in the frequently used Diagnostic and Statistical Manual of Mental Disorders (DSM, issued by the American Psychiatric Association), the diagnosis of substance dependence requires at least three of seven criteria and the diagnosis of substance abuse requires one of four criteria. The criteria listed below are those described in the fourth edition of DSM (DSM-IV), published in 1994.

The seven criteria for substance dependence

- The need for markedly increased amounts of the substance to achieve intoxication or desired effect, or diminished effect with continued use of the same amount (tolerance).
- Withdrawal syndrome or use of the substance to relieve or avoid withdrawal symptoms.
- One or more unsuccessful efforts to cut down or control use.
- Use in larger amounts or over a longer period than intended.
- Important social, occupational or recreational activities are given up or reduced because of substance use.
- A large amount of time is spent in activities that are necessary to obtain, to use or to recover from the effects of the substance.
- Continued use despite knowledge of having persistent or recurrent physical or psychological problems that are caused or exacerbated by the substance.

The four criteria for substance abuse

- Recurrent use resulting in a failure to fulfil the main obligations at work, school or home.
- Recurrent use in physically hazardous situations.
- Recurrent substance-related legal problems.
- Continued use despite persistent or recurrent social or interpersonal problems that are caused or exacerbated by the substance.

For both disorders, symptoms must occur within the same 12-month period. The abuse diagnosis is excluded in patients who have ever been dependent.

absolute levels of genetic influence. Heritabilities are estimates that are based on correlations, and are subject to sampling and methodological errors, so the accuracy of diagnosis or the measurement error places a limit on the strength of correlations. Because the total variance includes measurement error and gene–environment covariance, the role of unshared environmental factors cannot be calculated by subtracting heritable variance in liability from total variance.

Addiction liability and heritability. Drugs differ in their addiction liability. Addictive liability should correlate with heritability of addiction if variation in the neurobiological basis of addiction is what is being inherited. Although addiction liability is difficult to quantify, Goldstein and Kalant ranked relative risks of addiction to different classes of substances¹⁴. Using those risk rankings as crude indicators, it seems that addiction liability predicts heritability moderately well, as shown in FIG. 2b. Cocaine and opiates, among the most addictive of substances, are among the most heritable. On the other hand, hallucinogens are among the least addictive, and are also the least heritable. These data seem to point towards an inheritance of variation in the core neurobiological basis of addiction, such as

the pathways that mediate reward, behavioural control, obsessiveness, compulsivity, or stress and anxiety response. If genes that underlie such variation are detected, they might be informative across addiction disorders and for other behavioural differences that are determined by the same neurobiological processes.

Mode of inheritance. The addictions are inherited as common, complex diseases that show no obvious pattern of Mendelian transmission¹⁵. However, beyond the importance of environmental interactions, the origin of the complexity is poorly understood. It is tempting to imagine that addictions are polygenic, with vulnerability arising from the simultaneous impact of functional variations at several genes. This model of composite, vulnerable neurobiological processes is consistent with the variety of pathways involved, and the numerous genes involved in these pathways, any one of which could have functional genetic variants. Under a polygenic model, the simultaneous inheritance of many genetic variants (shown as a combination of puzzle pieces in FIG. 3a) is necessary for expression of the disease. However, the molecular complexity of the neural systems can also lead to genetic heterogeneity: a single genetic variation determines vulnerability and RESILIENCY, but different variants (FIG. 3a) can suffice for expression of the disease in different individuals and families. Polygenicity and heterogeneity have a different effect on MZ:DZ twin concordance ratios (FIG. 3b). These ratios can thereby provide a test to investigate whether a disease is polygenic. This is because MZ twins share all alleles but DZ twins are unlikely to share a combination of alleles. Certain psychiatric diseases (for example, autism and schizophrenia) have high or moderately high MZ:DZ ratios, indicating they might be polygenic or at least oligogenic. The MZ:DZ twin concordance ratios (FIG. 4) reveal no powerful imprint of polygenicity on the inheritance of most addictions, although modest polygenic effects are sometimes seen. For example, the ratio for cocaine is almost 4:1, invoking OLIGOGENICITY or perhaps the effect of a single recessive allele. In most other cases, the MZ:DZ ratios converge to 2:1, which is consistent with alleles of individual effect, and the genetic heterogeneity model. The relative importance of polygenicity versus heterogeneity has implications for the potential diagnostic use of genetic markers and for strategies to identify gene effects. High within-gene heterogeneity (for example, of the breast cancer 1, early onset (*BRCA1*) gene in certain cancers) can cause the failure of case–control association analysis using HAPLOTYPES, because different risk alleles will often reside on different haplotypes. By contrast, individual families and isolated populations could be more useful under a model of high genetic heterogeneity. Under a model of polygenicity and strong epistatic effects, some loci might be undetectable except by two-locus analysis, which should be used with trepidation because of the geometric increase in the number of tests carried out, and the consequent loss of power.

RESILIENCY

The ability to withstand mental or physical stress.

OLIGOGENICITY

A model of genetic determinism in which a few alleles function in combination to produce a phenotype.

HAPLOTYPE

A combination of alleles at different loci on the same chromosome.

Table 1 | National surveys of addictive agents in adult twin pairs

Addictive agents	MZ pairs	DZ pairs	Surveys	References
Cannabis	4,348	3,311	VTR, MTRS, ATR, VETR	13,128–131
Sedatives	2,676	2,082	VTR, MTRS, VETR	13,128,131
Stimulants	1,302	910	VTR, MTRS	13,128,132
Cocaine	1,287	919	VTR, MTRS	13,128,133
Hallucinogens	2,582	1,988	VTR, VETR	13,131
Opiates	1,930	1,564	MTRS, VETR	128,131
Smoking	5,664	4,956	VETR, STR, NAS-NRCTR, VTR	18,134–137
Alcohol*	5,682	4,215	ATR, VTR, VETR, NAS-NRCTR	134,138–141
Caffeine†	3,480	3,517	NAS-NRCTR, VTR	18,142,143
Gambling	1,869	1,490	VETR	144

*Studies measuring the heritability of alcohol dependence were used to compute the mean heritability estimate for alcoholism. The US National Academy of Sciences-National Research Council (NAS-NRC)¹⁴¹ study, which measured the heritability of the volume of alcohol consumed, was used only for computing the monozygotic (MZ):dizygotic (DZ) twin ratio. †The Hettema and Corey¹⁴² study was used for caffeine consumption weighted heritability estimates, but not for MZ:DZ ratios because MZ and DZ tetrachoric correlations were not reported. ATR, Australian Twin Registry; MTRS, Minnesota Twin Registry; NAS-NRCTR, NAS-NRC Twin Registry of World War II Veterans; STR, Swedish Twin Registry; VETR, Vietnam Era Twin Registry; VTR, Virginia Twin Registry.

Shared and unshared inheritance. The abuse of drugs is frequently associated with the abuse of other drugs¹⁶. COMORBIDITY between disorders poses the question of shared causation, which is being answered by genetic transmission and linkage studies and studies of the neurobiological basis of addiction. The genetic studies address the extent to which variation in liability of different diseases is shared or unshared. Briefly, this is done by evaluating whether the disease status of a proband is predictive of the risk of developing a different disease in a relative; for example, a twin. Genetic studies that cross-compare risks for two phenotypes in twins and other relative pairs indicate that some risk factors are substance-specific whereas others are shared between different substances (reviewed by Goldman and Bergen¹⁷). Alcoholism and nicotine addiction, for example, are both comorbid and cross-transmitted. Approximately 85% of alcoholics smoke. Some 50% of the genetic liability to nicotine dependence is shared with alcoholism, and 15% of the genetic liability to alcoholism is shared with nicotine dependence¹⁸. These findings are guiding investigators to study genes involved in neurobiologies that are common to diverse addictive agents; for example, the nicotinic receptor subunit genes that are gatekeepers for nicotine action¹⁹ are also modulated by ethanol²⁰.

Although such cross-transmission studies have a unique ability to detect the effects of common aetiology, they have important limitations. For example, the within-family shared environment might be more important in influencing which drug is used compared with whether a person becomes addicted to the drug. It is also more difficult to detect cross-transmission of the rarer addictions than it is for

common addictions such as alcoholism and nicotine dependence^{2,8}. These observations could help to explain the high substance-specific heritability (0.70) for heroin among Vietnam veterans²¹ compared with the Virginia registry, where rates of exposure were lower and heroin-specific heritability was not detected²².

Gene identification: positional cloning

Because addictions are common, it is possible to assemble large family and population datasets. The US National Institute on Drug Abuse (NIDA) Genetics Consortium is assembling datasets that consist of DNA, clinical diagnoses and other information relevant to drug addictions, and will be made available in 2006. Part of the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) Collaborative Study on the Genetics of Alcoholism (COGA) dataset is available. Because addictions are common, the relative risk (λ , which is the ratio of familial risk to population risk) is not high for any of them and large datasets are therefore required. PHENOCOPIES and GENOCOPIES, as well as non-PENETRANCE, are important problems for these diseases, and the role of protective alleles is significant. Therefore, it is generally as informative to evaluate phenotypically unaffected and discordant relative pairs as it is to study affected relative pairs. The high population prevalences have also made it relatively easier to carry out linkage analysis in environmentally and genetically homogeneous population isolates such as southwestern Native Americans²³ and Finns²⁴. Such studies can be extended to larger population-based datasets, such as the Icelandic population²⁵, which has proved powerful for the genetic analysis of complex diseases²⁶.

Whole-genome linkage analysis using moderately sized marker panels and LOCUS-BASED LINKAGE on families that are derived from the cosmopolitan population of the United States and from population isolates has yielded replicated linkages to chromosomal regions²⁷, even when these studies have used heterogeneous definitions such as alcohol dependence^{23,28}, antisocial alcoholism²⁴ or alcoholism with depressive syndrome²⁹. Whole-genome scans using the allele-based LINKAGE DISEQUILIBRIUM approach have been carried out for addictions³⁰ using a relatively small panel of SNP markers. These studies will be further facilitated by the large arrays of markers that are available through the International HapMap Project. Around 1,000,000 SNPs and their linkage disequilibrium relationships and allele frequencies in four populations are recorded in the HapMap database. This project allows the selection of informative panels of marker loci, as well as known and potential functional loci, for almost any gene. Various methods for large-scale genotyping, including array methods, allow marker-intensive gene, region-based and whole-genome linkage disequilibrium studies to be carried out. In this regard, NIDA recently announced its sponsorship of a whole-genome linkage disequilibrium scan for addictions.

COMORBIDITY

The co-occurrence of two or more diseases in an individual or an excess of disease co-occurrence in a population.

PHENOCOPIE

Describes the situation in which a phenotype of an environmental origin mimics a phenotype of a genetic origin.

GENOCOPIE

Describes the situation in which a phenotype of a genetic origin mimics a phenotype of a different genetic origin.

PENETRANCE

The probability of expressing a phenotype that is determined by a genotype.

LOCUS-BASED LINKAGE

The detection of locus-to-locus or locus-to-phenotype genetic linkage. This is generally accomplished by detecting a lack of meiotic recombination in families in which alleles at one locus are observed to be in coupling (co-transmitted) or repulsion (not co-transmitted) with alleles at a second locus.

A non-exhaustive list of convergences across studies includes the telomere of chromosome 11p, which contains the dopamine receptor D4 (*DRD4*) gene and several other neurogenetic candidate genes. Another region, on chromosome 4q, contains the alcohol dehydrogenase (ADH) gene cluster, whereas a chromosome 4p region near the centromere contains a γ -aminobutyric acid receptor A (*GABA_A*) gene cluster.

The GABA receptor. GABA is the principal inhibitory neurotransmitter in the brain and *GABA_A* receptor-mediated chloride currents into neurons are facilitated by alcohol and by BENZODIAZEPINE DRUGS, with which alcohol shows cross-tolerance. A series of mouse ethanol-related behaviours, including preference, withdrawal severity and sedation sensitivity, map to four QUANTITATIVE TRAIT LOCUS (QTL) regions at which *GABA_A* receptor-gene complexes are located³¹. These gene complexes apparently originated from ancient duplications of chromosomes or chromosomal regions, because the order and orientation of subunit gene types are conserved. In the rat, the *GABA_A* $\alpha 6$ subunit gene Arg100Gln missense variant is associated with variation in ethanol and benzodiazepine sensitivity³². A human variant of *GABA_A* $\alpha 6$ (Pro385Ser), which is located in the chromosome 5 cluster, is also linked to sensitivity to alcohol^{33,34} and benzodiazepine³⁵ in relatively small datasets. Low alcohol response or sensitivity is a heritable intermediate phenotype that is predictive of increased alcohol preference in rodents³⁶ and alcoholism in humans³⁷. Variation in human alcohol response and mouse alcohol sensitivity is mainly PHARMACODYNAMIC in origin, rather than metabolic (PHARMACOKINETIC), pointing to potential differences in receptors or signalling molecules that might function as gatekeepers. In humans, both the chromosome 4 (REFS 23,38) and chromosome 5 (REF. 39) clusters are implicated. Linkage disequilibrium mapping has refined the localization to the *GABA_A* $\alpha 6$ region³⁹ on chromosome 5 and the *GABA_A* $\alpha 2$ gene region³⁸ on chromosome 4 (FIG. 5).

Alcohol dehydrogenase genes. The two outstanding examples of verified human ‘addiction genes’ encode for enzymes that catalyse consecutive steps in alcohol metabolism: alcohol dehydrogenase IB (*ADH1B*) and aldehyde dehydrogenase 2 (*ALDH2*). ADH metabolizes ethanol to acetaldehyde, a toxic intermediate, which is in turn converted to acetate by ALDH. The most important functional loci at these genes are His47Arg in the *ADH1B* gene and Glu487Lys in the *ALDH2* gene. Either higher activity of *ADH1B* (conferred by the His47 allele) or lower activity of *ALDH2* (conferred by the Lys487 allele) leads to accumulation of acetaldehyde following an alcohol load. Acetaldehyde accumulation causes the aversive flushing reaction that discourages further alcohol intake. The genotype-associated flushing that is attributable to the higher activity codominant His47 allele and the lower activity dominant Lys487 allele is equivalent to

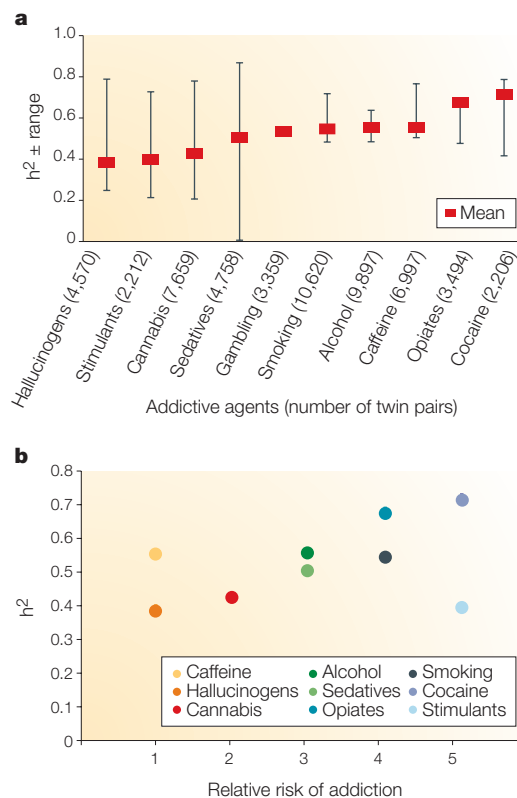


Figure 2 | Heritability of addictive disorders. **a** | The heritability (weighted mean and range) of 10 addictive disorders. These include hallucinogens, stimulants, cannabis, sedatives, gambling, smoking persistence, alcohol dependence, caffeine consumption or heavy use, cocaine dependence or abuse, and opiates. **b** | Weighted heritability (h^2) is plotted against the approximate ranking for relative risk of addiction. Relative risk of addiction is expressed on a five-point scale¹⁴, one indicates the lowest risk and five denotes the highest risk. In parts **a** and **b**, h^2 means were calculated using data from the national surveys of adult twins listed in TABLE 1.

the effects of disulfiram (a drug that is used to prevent relapse), and to certain antiprotozoal drugs, such as metronidazole, that inhibit ALDH. In several eastern Asian countries, such as Japan, where both His47 and Lys487 are highly abundant, most of the population carries a heterozygous or homozygous genotype that is protective against alcoholism. The protective effect seems to vary across environments⁴⁰ and the effects of genotypes are additive⁴¹. Each of these protective alleles apparently represents a single ancient mutation^{42–45}, based on the highly diverged haplotypes on which they reside, and there is some haplotype-based evidence for maintenance by selection⁴². It is improbable that these gene variants have evolved to protect against alcoholism. It is more plausible that these common gene variants might have conferred some other effect on fitness, such as protection against severe infectious diseases by protozoans that are sensitive to inhibition of alcohol metabolism, either because of their localization in the gut or because of their lack of intrinsic aldehyde dehydrogenase⁴⁶.

LINKAGE DISEQUILIBRIUM

The excess and complementary deficit of combinations of alleles at two different loci, which is based on rarity of meiotic recombination between loci on the same chromosome.

BENZODIAZEPINE DRUGS

Structurally similar selective *GABA_A* receptor agonists that have potent anxiolytic, sedative, central muscle relaxant and anti-epileptic properties.

QUANTITATIVE TRAIT LOCUS

A genetic locus that is identified through the statistical analysis of complex traits (such as body weight). These traits are typically affected by more than one gene and by the environment.

PHARMACODYNAMIC

Relating to the response of cells and tissues to drugs.

PHARMACOKINETIC

Relating to drug absorption, distribution or metabolism.

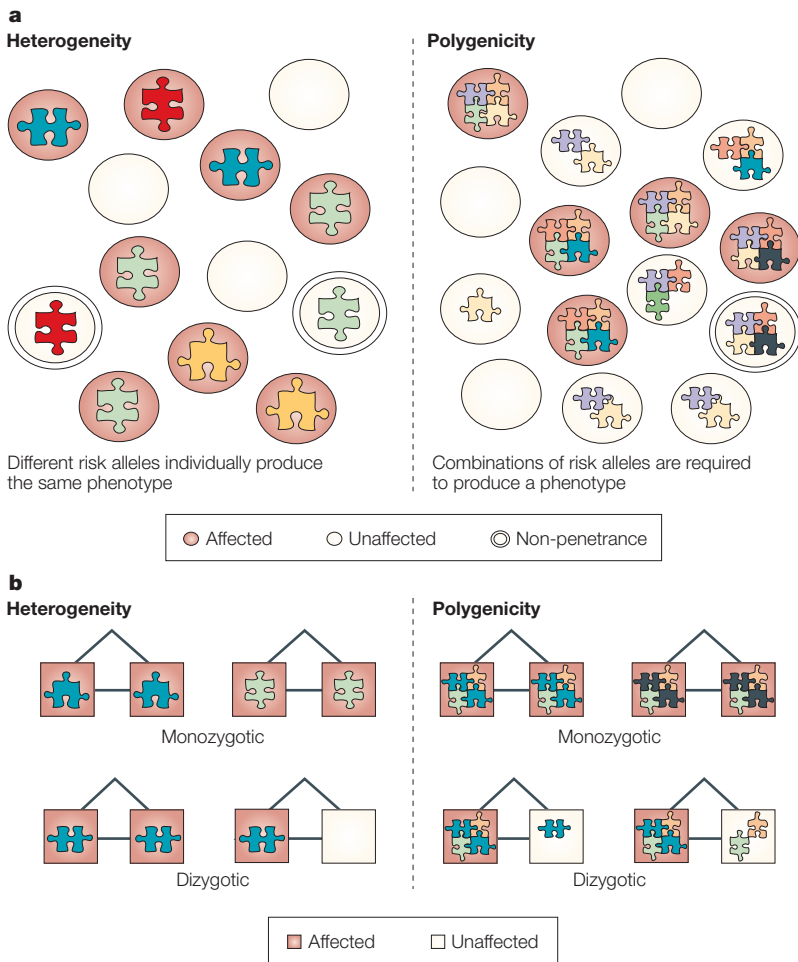


Figure 3 | **Genetic complexity in unrelated individuals and its effect on twin concordance.** **a** | Genetic complexity in unrelated individuals. **b** | Genetic complexity in twin pairs. Each risk allele is represented as a puzzle piece of a different colour or shape.

Our understanding of the neurobiological basis of addiction has evolved mainly from studies in animal models (BOX 3). The potential uses of animal models are almost limitless owing to the ability to directly access addiction neurobiology and the new and emerging tools to selectively express and downregulate genes in different regions of the brain. As genetic variants that are orthologous to human polymorphisms are discovered, sequencing of mouse, rat and non-human primate genomes is allowing these species to be better exploited.

Progress through intermediate phenotypes

The neurobiological processes that are involved in addiction, including reward, executive cognitive function and stress or anxiety, substantially overlap with those that underlie other psychiatric disorders, leading to the expectation that shared genetic factors are involved. Therefore, it is crucial to determine whether common disease origins determine the excess aggregation of these disorders observed in populations and in families^{2,16,47,48}. Such aggregation can be due to the natural course of one disease increasing the risk of developing a second disease or because individuals

who are chronic, treatment resistant or psychosocially impaired are more likely to be ascertained⁴⁹. Several loci that alter intermediate phenotypes that are important in shared risk have been found (see below). Intermediate phenotypes that reflect substance-specific neurobiology have been identified — for example, variation in alcohol-induced sedation and euphoria — and are also being used to identify genes that might be substance-specific in their action³⁴.

Impulsivity and externalizing behaviours. Behavioural control is fundamental for the ability to inhibit the immediate pursuit of pleasurable stimuli and for the development of structured patterns of behaviour that produce long-term rewards. In children, deficits in the development of behavioural control lead to various problems, including substance use^{50,51}. In the Virginia Twin cohort, a common factor encompassing externalizing disorders such as antisocial personality disorder (ASPD) and conduct disorder (CD) accounted for 71% of the genetic liability to alcoholism and 67% of the inheritance of vulnerability to illicit drug abuse or dependence⁵. Data from other twin studies, including a large community sample⁵² and a small sample of MZ twins that were reared apart⁵³, also revealed the connection between ASPD, CD and alcoholism. In a seminal adoption study, antisocial personality and alcoholism were observed to be cross-inherited⁵⁴. The temporal sequence is consistent with the hypothesis that antisocial behaviours and CD are causal factors for alcoholism and other substance dependencies, because CD usually occurs before alcohol dependence. However, alcohol and other drugs are disinhibiting, leading to antisocial behaviours⁵⁵. In adolescence, the likelihood of alcoholism and drug abuse is diminished by 4–5% for each year that onset of drug use is delayed⁵⁶.

Several genes that influence impulsivity and externalization have been found. Polymorphisms in both the *DRD4* gene and the dopamine transporter *SLC6A3* (solute carrier family 6, member 3) have been linked to attention deficit hyperactivity disorder (ADHD) and CD, with linkage to *DRD4* long-repeat alleles being more replicable⁵⁷. Monoamine oxidase A (*MAOA*) metabolizes dopamine and a rare stop-codon variant of this gene was linked to impulsive behaviour among males in a Dutch family⁵⁸. An abundant *MAOA* variable number tandem repeat locus is linked to antisocial behaviour in children, in an environment-specific fashion⁵⁹. Serotonin is the neurotransmitter that is most consistently implicated in aggression and impulsivity by neurochemical and neurobehavioural studies in humans and other species⁵⁵. The 5-hydroxytryptamine (serotonin) receptor 1B (*HTR1B*) gene is located at the site of several mouse alcohol QTLs on chromosome 9, and mice in which this gene has been knocked out were more aggressive and had a preference for alcohol⁶⁰. *HTR1B* was linked to ‘antisocial alcoholism’ in a Finnish family sample that was ascertained through criminal alcoholic probands, and in a southwestern Native American community sample²⁴. However, replication of the association of *HTR1B* with impulsivity

MANIA

A pathological elevated mood-state that is associated with mental and physical hyperactivity.

PANIC DISORDER

An anxiety disorder characterized by paroxysms of overwhelming fear with associated somatic, behavioural and cognitive symptoms.

AGORAPHOBIA

An anxiety disorder that is characterized by fear and avoidance of places from which escape might be difficult.

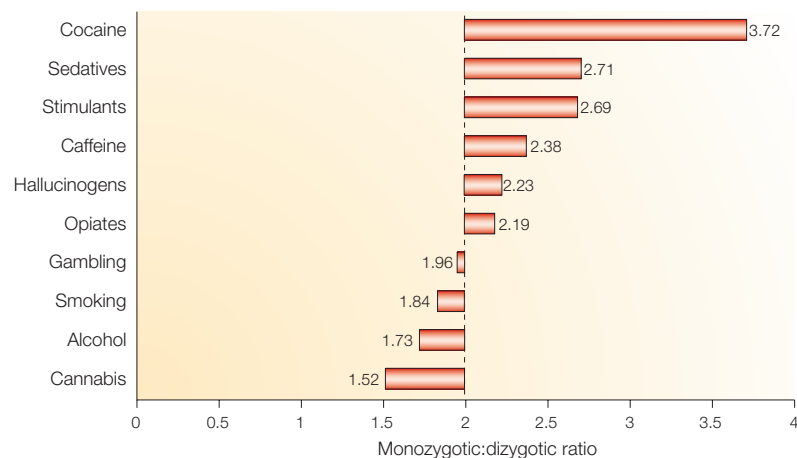


Figure 4 | Weighted means of monozygotic and dizygotic tetrachoric correlation ratios for 10 addictive disorders. Weighted means of monozygotic to dizygotic ratios were calculated using monozygotic and dizygotic tetrachoric correlations that were estimated from the national surveys of adult twins listed in TABLE 1. The dashed line indicates the 2:1 ratio that is expected for a monogenic dominantly inherited phenotype.

BULIMIA

An eating disorder that is characterized by recurrent binge eating, which is accompanied by self-induced purging and/or other inappropriate compensatory behaviours.

ALLOSTASIS

A new homeostatic (maintained) equilibrium that lies outside the normal range and is characterized by long-lasting adaptational mechanisms that are activated in response to a stressor.

CATECHOLAMINES

A class of structurally similar amine neurotransmitters, including dopamine, noradrenaline and adrenaline, that are derived from the amino acid tyrosine.

WISCONSIN CARD-SORT TEST

A neurocognitive test of frontal lobe function that requires the subject to switch strategies that are needed to match cards to a target.

N-BACK TEST

A neurocognitive test of frontal lobe function and working memory that requires the recall of an earlier stimulus after a new stimulus (or stimuli) has been presented.

WORKING MEMORY

A memory system that is activated for temporary storage and manipulation of information while a mental task is carried out.

or aggression has been variable^{61,62} and no functional locus polymorphism is known.

Intermediate phenotypes in impulsivity and externalization have been linked to certain gene regions, and to specific loci. Disturbed attention processes, as assessed by electrophysiological responses to unexpected stimuli, are more common in drug-naïve offspring of alcoholics. The use of this phenotype in a whole-genome linkage scan led to the identification of several linkage regions⁶³. The chromosome 11p telomere region has been linked to addictions³⁶. *DRD4* lies on chromosome 11p, and a 16 amino-acid repeat polymorphism in *DRD4* has variably been associated with novelty seeking^{64,65}.

The anxiety or dysphoria domain. In the NESARC national epidemiologic survey, all mood and anxiety disorders were comorbid with alcohol and drug-use disorders (odds range from 1.6 to 13.9), the strongest correlation being between *MANIA* and *PANIC DISORDER*, and *AGORAPHOBIA*². The magnitude of anxiety and addiction comorbidity is greater in women⁴⁸. Large twin studies^{5,66} provide only weak support for a shared genetic predisposition to substance-use disorders and the mood and anxiety disorders. In a study on females, more than three-quarters of the genetic liability to alcoholism was not shared with major depression, anxiety disorders and *BULIMIA*⁶⁶. In both men and women, alcoholism and other drug disorders are genetically largely independent from major depression, generalized anxiety and phobic disorders⁵. However, fundamental to the process of addiction is a drug exposure-induced shift to a long-lasting *ALLOSTATIC* state such that many drug-free addicts show persistent affective disturbances and are vulnerable to craving. This means that they are liable to rapid relapse when triggered by stressful life events or re-exposure to the drug. When re-administered, the drug might elevate mood, but not to the level experienced before addiction⁶⁷. Studies on drug-exposed

animals indicate that long-lasting physiological changes take place that are associated with changes in the expression of stress-related genes^{68,69}. It is likely that individuals are predisposed to addiction, based on diminished stress resiliency⁶⁹. Indeed, acute and early-life stress exposures have the effect of increasing the risk of addictions and other psychiatric diseases⁷⁰ and of increasing the intake of alcohol and drugs in animal models⁷¹.

Genes and neurobiologies

Vulnerabilities to substance use diverge diametrically between individuals; this fact provides an opportunity and a challenge for gene mapping. The catechol-*O*-methyltransferase (*COMT*) gene provides a powerful example. *COMT* is an enzyme that metabolizes *CATECHOLAMINES*, terminating the action of these neurotransmitters in the synapse, particularly in regions of the brain where levels of the relevant monoamine transporters are low. A common polymorphism that exerts an effect on *COMT* function is Val158Met. The Val158 allele is approximately three times more thermostable than Met158 at normal body temperature, and has 40% higher activity⁷². Furthermore, Val158 and Met158 are found on differentially expressed haplotype backgrounds⁷³ of ancient origin, as indicated by their opposite (yin–yang) allelic configurations (a 5-locus haplotype pattern of 1122Val versus 2211Met) that are both abundant in populations worldwide⁷⁴. The haplotype analyses predict variation in *COMT* expression, and it is likely that *COMT* linkage studies will incorporate haplotype information to capture more details on the functional genetic variation of this gene. For example, linkage of a Val158-containing haplotype to *schizophrenia* was more robust than the Val158 allele itself⁷⁵, and haplotype analysis was also used in a replication study of linkage of *COMT* to pain threshold⁷⁶.

The higher activity Val158 allele is predicted to reduce dopamine levels in the frontal cortex because levels of the dopamine transporter are low in this region. Consistent with the role of dopamine in the tuning of frontal cortical function, the Val158 allele and Val158 haplotypes have replicably been linked to frontal lobe function, as assessed by measures such as the *WISCONSIN CARD-SORT TEST* and the *N-BACK TEST*^{77–79}, and by the metabolic activity of the frontal cortex during a *WORKING-MEMORY* task⁷⁷. In certain populations, including polysubstance abusers that were ascertained in Baltimore, USA⁸⁰, the Val158 allele is associated with vulnerability to addiction through impulsivity or dyscontrol. By contrast, in populations of addicts in whom anxiety is a more salient predisposing cause — for example, in late-onset alcoholics⁸¹ and social drinkers⁸² — the Met158 allele is more common. The counterbalancing disadvantage (in fitness terms) of the Met158 allele seems to be the enhanced vulnerability of Met158 genotypes to stress and anxiety. Met158 homozygous women in two different populations were more anxious⁸³. This balance of advantages in stress resiliency (Val158 allele) versus

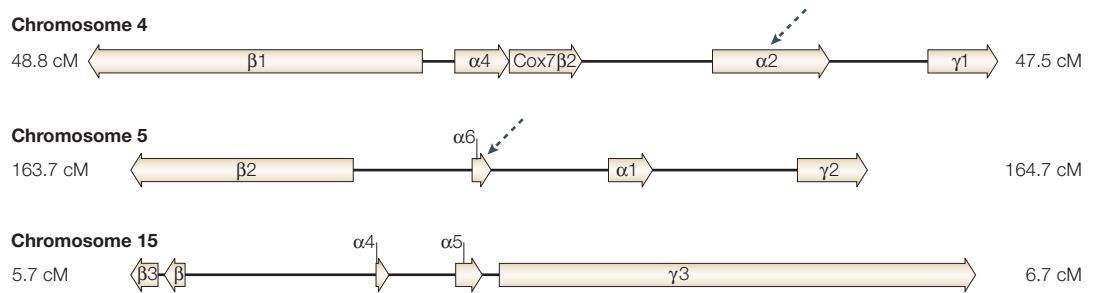


Figure 5 | Clusters of the γ -aminobutyric acid (GABA) subunit genes in humans. Arrows indicate chromosome regions that have been shown to influence vulnerability to alcoholism in the pharmacodynamic domain.

cognitive function (Met158 allele) forms the basis for the *WARRIOR/WORRIER MODEL*. This model invokes frequency-dependent selection or balancing selection to conserve both ancient *COMT* functional alleles across human populations. The warrior haplotype (Val158) leads to better stress resiliency, but also to modest diminution of executive cognitive performance under most conditions. On the other hand, following a pain or stress challenge, the worrier (Met158) allele dosage predicted a progressively lower pain threshold, stronger affective response to pain and inability of the endogenous brain opioid system to become activated following pain⁸⁴. As already mentioned, linkage of Met haplotypes to a lower threshold to experimentally administered painful stimuli was recently replicated in a large cohort of women⁷⁶.

Linkage studies of the serotonin transporter gene underline the power of neuroimaging studies and the usefulness of approaches that consider the interaction of environmental and gene effects. Two main alleles of the serotonin transporter polymorphism (*HTTLPR*) that lie in the promoter of this gene have either 14 (short (S)) or 16 (long (L)) copies of a 22-bp imperfect repeat⁸⁵. The lower transcribing S allele contributes significantly to risk for alcohol dependence, with the greatest effect observed among individuals with more severe alcohol dependence, antisocial behaviour or suicide attempt⁸⁶. However, this locus only has a modest effect on complex behaviour. The S allele has been linked to anxiety, but in a meta-analysis of 23 association studies, each copy of the S allele contributed only a 0.106 standard deviation increment in anxiety that was measured on personality scales⁸⁷. Furthermore, without objectively discarding certain studies there was no significant effect overall⁸⁷.

The role of the serotonin transporter in behaviour has been clarified by studies showing that the effect of the S allele in dysphoria and drug consumption might be dependent on exposure to stress^{71,88}. The effects of this locus are clearest at the neurobiological level. The polymorphism alters transporter expression in the brain^{89,90} and in the *AMYGDALA*, and changes the metabolic response to emotional stimuli⁹¹ and the volume of the amygdala⁹². Recently, the additive effects of *HTTLPR* alleles and *COMT* Val158Met allele were observed in the metabolic response of the amygdala to emotional stimuli⁹³. A further functional

allele was also discovered at the *HTTLPR* locus (an A to G substitution in the first of the two extra repeats defining the L allele)⁹⁴, which accounts for even more variation in serotonin transporter expression, and improves the ability to predict both complex behaviours and intermediate phenotypes⁹⁵.

From genotype to medical management

The treatment and prevention of addictions are only partially successful. Prevention strategies could focus on children and adults who are vulnerable due to variations in particular neurobiological domains, for example, behavioural dyscontrol versus stress or anxiety. It is still unclear whether such targeting of prevention would be essential or even appropriate. The high rates of addictions and the economics of the problem make it worthwhile to apply many prevention strategies across entire population cohorts without identifying particular vulnerability alleles. However, it would be important to know the efficacy (or lack of effect) of untargeted prevention strategies on individuals with particular vulnerabilities.

Individualization of therapy and the identification of new therapeutic targets are required for the large number of individuals who are already ill, and for the newly incident cases each year. One-year relapse rates for alcoholism and cocaine range from 20 to 60%, depending on the clinical study^{96,97}. Medications for treatment of addictions include *AGONISTS* (methadone), *ANTAGONISTS* (naltrexone), anticraving medications and drugs that block the metabolism⁹⁸. Except for the management of the acute phase, addictions remain largely under-treated diseases. Although addictions are chronic and relapsing or remitting, medical management has focused on the acute phase (intoxication and withdrawal) because treatment occurs within a socio-medical matrix in which long-term benefits of prevention and follow-up care are not encouraged by adequate reimbursement⁹⁸. This is despite the efficacy of treatment, which is comparable to that of treatment for other chronic disorders such as diabetes and asthma⁹⁸. For such illnesses, incremental improvements in management that are applied conscientiously have extended life expectancies from less than 20 years to more than 50 years. Improvements in the targeting of addiction treatment and availability of new treatment methods (including new approaches to cognitive and behavioural therapy) could also drive

WARRIOR/WORRIER MODEL
A selectionist explanation for the maintenance of *COMT* alleles that have counterbalancing effects in cognition versus resilience to stress and anxiety.

AMYGDALA
A complex region of the brain temporal lobe that is important in modulating emotional states.

AGONISTS
Molecules that bind to receptors and elicit signal transduction.

ANTAGONISTS
Molecules that bind to receptors and, although they do not have intrinsic action, inhibit signal transduction.

Box 3 | **Animal models of addiction neurobiology and genetics**

Studies in rodents have identified both neuroanatomical circuits¹¹² (such as limbic reward and emotionality circuits) and cellular molecular networks that are crucial in addiction^{113,114}. Several of the genes that are central to drug response and neuroadaptation have already been tested as leading candidates in genetic studies in humans. So far, the brain-derived neurotrophic factor (*BDNF*)¹¹⁵, the 5-hydroxytryptamine (serotonin) receptor 1B (*HTR1B*)²⁴, the γ -aminobutyric acid receptor A (*GABA_A*) receptor³⁸, neuropeptide Y (*NPY*)¹¹⁶, and the dopamine D2 receptor (*DRD2*)¹¹⁷ genes have been implicated in animal studies and evaluated in humans, with promising results. However, most of the strong candidate genes to emerge from animal neurobiological studies of addiction have yet to be evaluated for sequence variation and linkage to human addictive behaviour. These include *deltaFosB*, and the genes that encode the proline–cysteine transporter, the cyclic-AMP-response element binding protein (*CREB*), and various glutamate receptors^{113,114}.

Animal models allow genes to be associated with neurobiological phenotypes that are not accessible in humans, and with various addiction-related behaviours that are studied under highly controlled conditions. In rodents, genes that are implicated by QTL studies include the μ -opioid receptor 1 (*OPRM1*) in morphine preference^{118,119}, the multiple PDZ-binding domain protein (*MPDZ*) in acute pentobarbital and ethanol withdrawal¹²⁰, *NPY* in ethanol preference¹²¹, glutamic acid decarboxylase (*GAD1*), a GABA biosynthetic enzyme, in ethanol-induced locomotion¹²², and *DRD2* and *HTR1B* in ethanol preference³¹. The functional allele has not been verified in any of these cases, but in other examples, effects of alleles, including artificial gene knockouts, are directly known. *Cheapdate*, a mutation that leads to enhanced sensitivity to ethanol in *Drosophila melanogaster*, is an allele of the memory mutant *Amnesiac* and results in diminished activation of the cAMP pathway¹²³. In primates, a serotonin transporter promoter locus that is orthologous to a functional polymorphism in the promoter of a human serotonin transporter alters ethanol preference, and this effect can be modified by stress in early life⁷¹. More than 100 mouse gene knockouts and transgenics alter addiction-related behaviours, reflecting the diversity of pathways that can lead to addiction, and the potential for heterogeneity or polygenicity discussed earlier. *OPRM1* mouse knockouts are characterized by reduced opioid-mediated analgesia, reward and physical dependence¹²⁴. The knockout for the nicotinic acetylcholine receptor β 2 gene blocks nicotine self-administration, reflecting the gatekeeper role of the nicotinic receptor in influencing the self-administration of this drug¹²⁵. Knockouts in signalling genes such as protein kinase C (*PKC*)¹²⁶ or genes that modulate stress response, such as *NPY*¹²⁷, could be predicted to influence diverse addictive behaviours.

changes in the clinical management of these diseases, leading to a more multidimensional level of care. The clinical subclassifications of addictive disorders are a first systematic effort to create more homogeneous categories to individualize treatment and prevention, and to identify new therapeutic targets. It is precisely at this point that progress has stalled. Although some drugs (for example, naltrexone and acamprosate) have efficacy for the treatment of heterogeneous populations of alcoholics, others (for example, ondansetron and selective serotonin reuptake inhibitors) seem to be differentially effective in subgroups^{99–101}. However, although efforts to clinically subclassify addictions are likely to continue, it is improbable that future meta-groupings of addictions and other psychiatric diseases will advance until neurobiological indicators, including genotypes, are integrated.

Conclusions

Liability to addictions is widespread, but individuals with addicted first-degree relatives are at greater risk. The correlation between the heritability of different addictions and the relatively simple estimates of addiction liability for particular agents indicates that a large component of what is inherited is interindividual variation in the fundamental neurobiological basis of addiction. Advances in the neurobiology of addiction have led to the identification of some underlying genes and have allowed the actions of certain risk loci to be understood. Genetic loci that have defined roles in addictions include substance-specific genes, such

as the alcohol metabolic genes, and loci, such as the serotonin transporter and *COMT*, that alter liability to different addictions and other psychiatric illnesses. Evidence from twin studies indicates that further loci in both addiction substance-specific and addiction substance-nonspecific categories will be discovered. The twin concordance ratio data predict that many of the addiction loci will have an individual effect whenever the functional allele is actually found in a person. This information helps us to postulate that genetic markers with significant predictive value will be discovered and serve as guides to new molecular mechanisms and targets for medicine.

Large datasets and new tools in genetics and molecular neurobiology have facilitated various genetic approaches in humans and other species. These approaches have allowed the detection of gene effects on the clinical phenotypes of addictions that are small on a population basis and that, because of causal heterogeneity, are sometimes inconsistent across different types of addicted patient. Larger and apparently more consistent gene effects are being observed at the levels of neurobiology and of intermediate phenotypes, and owing to the improved understanding of the influence of environmental exposures, particularly stress. Indeed, identifying gene–environment interactions is a crucial issue in the study of addictions, which by definition depend on exposure to an addictive agent and are strongly modulated by other environmental factors. The story of genes in addictions and other complex behavioural

diseases seems to be one of incremental progress as the functional significance of sequence variations is discovered and then related both to intermediate phenotypes and to the complex diseases that are emergent from an intermediate neurobiology.

The high population prevalences of addictions and the relative crudity and ineffectiveness of addiction treatment and management constitute a public-health crisis. Through intensive clinical management and the application of new strategies, the outcomes of other chronic medical diseases such as cystic fibrosis¹⁰² and juvenile-onset diabetes¹⁰³ have been markedly improved. There is no indication that such comprehensive approaches are on the verge of being developed and applied to the addictions without significant breakthroughs in genetics and neurobiology. It is a sobering reality that genetic findings have so far not

led to the creation or targeting of addiction treatment or prevention. Future research is likely to integrate genetic variation ever more closely, with effects on intermediate neurobiological processes such as reward, behavioural control and anxiety response that are now understood to underlie addiction vulnerability and recovery. Such studies will frequently be fine-grained and take advantage of powerful methods that capture neurobiology, including neuroimaging, and direct interventional studies in animals that are not feasible, or ethical, in humans. Future research must also find a role for genotypes, either as guides to new therapeutic targets or as predictors for treatment and prevention, in natural populations of patients and individuals at risk where the efficacy of new tools can objectively be defined and integrated into multidimensional management.

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Competing interests statement

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