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REVIEW

The genetics of addiction—a translational perspective

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Addictions are serious and common psychiatric disorders, and are among the leading contributors to preventable death. This selective review outlines and highlights the need for a multi-method translational approach to genetic studies of these important conditions, including both licit (alcohol, nicotine) and illicit (cannabis, cocaine, opiates) drug addictions and the behavioral addiction of disordered gambling. First, we review existing knowledge from twin studies that indicates both the substantial heritability of substance-specific addictions and the genetic overlap across addiction to different substances. Next, we discuss the limited number of candidate genes which have shown consistent replication, and the implications of emerging genomewide association findings for the genetic architecture of addictions. Finally, we review the utility of extensions to existing methods such as novel phenotyping, including the use of endophenotypes, biomarkers and neuroimaging outcomes; emerging methods for identifying alternative sources of genetic variation and accompanying statistical methodologies to interpret them; the role of gene–environment interplay; and importantly, the potential role of genetic variation in suggesting new alternatives for treatment of addictions.

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Introduction

The term ‘addiction’ covers a broad range of maladaptive aspects of drug use or other behaviors leading to clinically significant impairment or distress.¹ Addiction includes alcohol use disorders, nicotine dependence, cannabis and cocaine use disorders as well as non-substance-related behaviors. These serious but common psychiatric disorders are among the leading contributors to morbidity and mortality worldwide.^{2,3}

This review discusses: (a) classification and diagnosis of addictions; (b) studies demonstrating the role of heritable variation in addiction and the overlap of heritable influences across drug classes; (c) putative candidate genes and emerging results from genomewide association studies; and (d) novel research methods to advance phenotyping of addictions, including the use of endophenotypes, biomarkers and imaging technology; (e) the role of alternative sources of genetic variants and bioinformatics; (f) gene–environment interplay; and (g) the emergence of pharmacogenomics. Finally, we discuss how the application of these various methods has begun to elucidate processes underlying nicotine addiction and the strategies this enables for new treatments.

Classification and diagnostic criteria

Addictions are primarily diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM, currently

DSM-IV)¹ according to which substance abuse and dependence are distinct categories—*throughout this review, we use the term ‘addiction’ to refer to substance abuse or dependence*. Proposed changes to the DSM system of nomenclature (DSM-5, <http://www.dsm5.org/Pages/Default.aspx>) may eliminate the distinction between abuse and dependence, replacing it with a single category of substance use disorder (see Box 1 for diagnostic criteria).⁴ Also proposed for DSM-5 is the addition of ‘behavioral addictions’.⁵ A number of candidate behavioral addictions were considered, such as compulsive internet use (for example, gaming), sexual activity or shopping, but the only behavioral addiction that is currently formally codified is disordered gambling. This decision was based, in part, on symptomatic and neurobiological similarities between disordered gambling and substance use disorders⁶ and the more developed research base for disordered gambling than for the other behavioral addictions.

Given the enormous public health burden of addictions, the delineation of their etiology has been of paramount importance. The next sections detail research findings outlining the magnitude of heritable influences on addictions.

Heritable influences on addiction

Numerous family, adoption and twin studies have identified the significant role of heritable influences on individual differences in addiction. Results from twin studies suggest that 33–71% of the variation in liability to **nicotine** depen-

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Box 1 Criteria for diagnosing addiction (abuse/dependence)

	DSM-5	DSM-IV
Failure to fulfill major role obligations	✓	✓ (abuse)
Recurring use in hazardous situations	✓	✓ (abuse)
Use despite interpersonal problems	✓	✓ (abuse)
Use despite recurring legal problems	x	✓ (abuse)
Tolerance		✓ (dependence)
Withdrawal		✓ (dependence)
Using more or longer than intended	✓	✓ (dependence)
Giving up important activities to use	✓	✓ (dependence)
Spending a lot of time using	✓	✓ (dependence)
Use despite recurring physical/psychological problems	✓	✓ (dependence)
Persistent, failed quit attempts	✓	✓ (dependence)
Craving—strong urge or desire to use drug	✓	x

Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV:

Abuse—1 or more of 4 criteria.

Dependence—3 or more of 7 criteria occurring in the same 12-month period.

DSM-5 (proposed: dsm5.org)

Substance use disorder:

Unaffected—0 or 1 of 11 criteria.

Moderately affected—2 to 3 of 11 criteria occurring in the same 12-month period.

Severely affected—4 or more of 11 criteria occurring in the same 12-month period.

dence^{7–10} can be attributed to heritable influences, while 48–66% of the variation in **alcohol** dependence^{11–14} is heritable. Similarly, a recent meta-analysis of eight twin studies reported heritability estimates of 51–59% for cannabis addiction.¹⁵ Heritability estimates for **cocaine** use disorders range from 42 to 79%, with the lower estimates reported for females.^{16–18} Two large-scale studies have examined **opioid** addiction. Kendler *et al.*¹⁶ reported that 23% of the variation in opioid addiction in men was attributable to genetic factors, whereas Tsuang *et al.*¹⁹ reported a considerably higher estimate of 54% in male Vietnam Era twins. There have also been two major twin studies of **disordered gambling**, with consistent evidence for heritable (49%) variation.^{20,21} Across these studies, there has been no consistent evidence for differences in the magnitude or nature of heritable influences on addiction in men and women. However, two important factors have been found to contribute to variation in heritability:

(a) *Stages of addiction*: Despite the typical clinical characterization of individuals as *affected* versus *unaffected* for addiction, research has shown that liability to addiction is a multi-stage process.^{7,22,23} The process of addiction begins with early stages of initiation of use, followed by escalation to regular and chronic use, which can become problematic and develop into addiction. Early stages are less heritable and more greatly influenced by familial environmental factors, whereas later stages, such as problem use and dependence are more strongly influenced by heritable factors. Multiple twin studies have examined the extent to which genetic influences on these later stages overlap with those influencing initiation and non-problem use.²⁴ Although a significant proportion of genetic factors influencing problem use also influence earlier stages, there is also support for genetic factors that are specific to problem use and contribute to its increased heritability.

(b) *Developmental course*: Due to the natural course of addiction, studying the role of developmental stage on addiction is challenging. Initiation of drug use typically occurs during adolescence, whereas disorders emerge during early adulthood. Even within these stages, there is considerable variation in etiology, depending on whether adolescents or adults are being studied.^{25,26} For instance, for a history of any alcohol use, heritability declines rapidly during emerging adulthood, likely due to the ubiquity of normative alcohol consumption. By contrast, for measures of quantity/frequency of use (for example, drinks/day),²⁷ and the number of substances used,^{28,29} heritable factors appear to have a stronger influence during adulthood. During adolescence, shared environmental factors contribute maximally to familial resemblance, but with the emergence of adulthood, genetic influences are unveiled and heritable variation explains up to 75% of individual differences.²⁷ For problem use, however, there has been consistent evidence for heritable influences, even during adolescence.³⁰

Drug-specific genetic influences. There is significant overlap in genetic influences on alcohol, nicotine and illicit drug addictions, as well as across addiction and other externalizing disorders. Particularly for illicit drugs, with the possible exception of opioids, twin studies have found only modest support for specific genetic factors,^{17,31} supporting the possible role of common pathways (for example, via dopaminergic neurotransmission) that connect problem use of multiple drugs. However, for nicotine dependence, genetic factors shared with alcohol and illicit drugs are responsible for only 37% of heritable variation, indicating a considerable degree of genetic specificity.³² Given their very different pharmacologies, the reason as to why greater genetic specificity is not observed among illicit substances in twin designs may be attributable to several factors. Most

Table 1 Association results with multiple replications or genomewide significance and biological plausibility

Gene	Summary
<i>Alcohol</i>	
<i>ALDH2</i> Glu504Lys (rs671)	Decreased capacity to metabolize acetaldehyde to acetate leads to high concentrations of acetaldehyde, and the ‘alcohol flush reaction’, ³³ which decreases alcohol use and the risk of alcohol dependence (e.g. ^{187–189})
<i>ADH1B</i> Arg48His (rs1229984)	Increased rate of conversion of ethanol to acetaldehyde leads to slightly higher concentrations of acetaldehyde, with similar deterrent effects on alcohol use and alcohol dependence risk (e.g. ^{188–190}).
<i>GABRA2</i> (rs279858, rs279826, rs279871)	Repeatedly associated with alcoholism (e.g. ³⁶) although non-replications also exist (e.g. ^{39,191}). Also associated with impulsivity and alcohol-related endophenotypes. SNPs are not functional but $\alpha 2$ subunit expression has been associated with binge drinking. ¹³⁸
<i>DRD2/ANKK1</i> (Taq1A, rs1800497)	Recognized as a risk factor for alcoholism. ¹⁹² Meta-analyses find odds ratios ≈ 1.2 ($P < 0.001$) ¹⁹³ – 1.4, ($P < 0.00001$), ¹⁹⁴ for the A1 allele. Considerable across-study heterogeneity exists.
<i>Nicotine</i>	
<i>CHRNA5/A3/B4</i> (rs16969968/rs1051780)	Meta-analyses of GWAS ^{88–90} and candidate gene ^{91,177} data show replicated association with cigarettes/day. Involved with receptor modification, ¹⁹⁵ sensitization and desensitization. ¹⁹⁶ Additional evidence for rs578776 as an independent signal ¹⁷⁷
<i>CHRN3-CHRNA6</i> (rs6474412)	Evidence from a large GWAS but not as widely replicated. ⁸⁹
<i>CYP2A6</i> (rs1801272)	Impairs metabolism of nicotine to cotinine. ¹⁹⁷ Associated with cotinine levels and associated at genomewide significance with smoking in one study, with other studies yielding inconsistent results (e.g. ⁸⁹).

Abbreviations: GWAS, genomewide association study; SNP, single nucleotide polymorphism.

notably, the high degree of comorbidity across addictions may amplify genetic overlap, and second, the power required to detect substance-specific genetic influences may be limited.

Decades of genetic epidemiological research have documented the importance of heritable influences on addiction. Multiple genetic variants of modest effect size contribute to this genetic architecture. The next section identifies genes that have been widely studied in the context of addictions.

Genes for addiction—candidate gene searches

Despite numerous studies examining putative candidate genes for addiction-related phenotypes, the field has been characterized by lack of replication and there are remarkably few genes that we can say with confidence are associated with addiction. Those genes with the strongest evidence for association are summarized in Table 1. In addition to these, there are a number of biologically plausible candidates for addiction for which there is some evidence for association (albeit without consistent replication).

Alcohol. In addition to widely studied variants in *ADH1B* and *ALDH2*, two functional polymorphisms (rs1693482 and rs698) in *ADH1C* are known to regulate alcohol metabolism and have been found to have a protective influence on alcohol consumption.³³ Unlike rs1229984 in *ADH1B* and rs671 in *ALDH2*, which are uncommon and absent respectively, in non-Asian populations, the *ADH1C* polymorphisms are common. In addition to metabolism genes, serotonergic variants have also been implicated in the etiology of alcoholism.³⁴ However, a meta-analysis of the commonly studied serotonin transporter gene (*SLC6A4*) polymorphism

found only weak association (odds ratio (OR) = 1.2, $P < 0.05$) with alcoholism.^{35–41}

Nicotine. Variants in the chromosome 15 cluster of genes encoding subunits of the nicotinic acetylcholine receptor, including *CHRNA5/CHRNA3/CHRNA4*, are among the most robustly replicated association signals for nicotine addiction. In addition, variants in *CHRNA4* (encoding the $\alpha 4$ subunit of the neuronal nicotinic acetylcholine receptor) have also been suggested to influence various aspects of nicotine addiction,^{42–44} albeit inconsistently. A recent meta-analysis of linkage studies identified the *CHRNA4* region on 20q13.2–q13.3 for maximum cigarettes smoked in a 24-h period. The *DRD2/ANKK1* Taq1A allele, the subject of many studies on alcohol, has been studied in the context of nicotine addiction—a meta-analysis found support for an association for smoking initiation and current smoking but not for cigarettes/day.⁴⁵

Cannabis. Inconsistent associations have been reported between variants in the cannabinoid receptor 1 gene (*CNR1*), to which cannabinoids putatively bind, and the fatty acid amide hydrolase gene (*FAAH*) and cannabis dependence symptoms (see Agrawal and Lynskey⁴⁶ for a review). As with alcoholism, *GABRA2* (encoding the $\alpha 2$ subunit of the GABA (gamma-amino-butyric acid) receptor) has been examined for cannabis dependence but with limited success.^{39,47,48}

Cocaine. Several genes have been implicated in various aspects of cocaine addiction. These include dopaminergic single nucleotide polymorphisms (SNPs) in *DRD2/ANKK1*⁴⁹ as well as neighboring *NCAM1* and *TTC12*, *CALCYON*,⁵⁰

dopamine beta-hydroxylase (*DBH*)⁵¹ and catechol-O-methyltransferase (*COMT*),⁵² opioidergic genes such as *POMC*,⁵³ *CNR1*,⁵⁴ orthologs of genes regulating circadian rhythms (*CLOCK*, *PER1*, and *PER2*),⁵⁵ tryptophan hydroxylase 2 (*TPH2*)⁵⁶ and others gleaned from linkage studies (for example, alpha-endomannosidase (*MANEA*))⁵⁷—a majority of these await replication. Of particular interest, the functional SNP in the *CHRNA5/A3/B4* cluster on chromosome 15, rs16969968, (extensively discussed in later sections and in Table 1 with reference to nicotine dependence) has been found to be associated with cocaine dependence in two independent studies—paradoxically, the allelic variant of this marker that confers risk for nicotine dependence appears to afford protection from cocaine addiction.^{58,59}

Opioids. The gene encoding the mu-opioid receptor (*OPRM1*) to which opioids bind to produce their analgesic and rewarding effects is the most widely studied candidate gene for heroin and other opioid addictions.⁶⁰ Functional *OPRM1* polymorphisms identified in humans include the extensively-studied rs1799971 (A118G),^{61–64} but a meta-analysis⁶⁵ did not support its significant role in opioid addictions. Other aspects of the opioidergic system have also been queried. However, analyses involving prodynorphin (*PDYN*),⁶⁶ proenkephalin (*PENK*),⁶⁷ and the kappa (*OPRK1*)^{68,69} and delta opioid receptors (*OPRD1*)^{69–71} have not produced consistent results.

Disordered gambling. A relatively novel subject of genetic enquiry, there have been only 10 candidate gene studies of disordered gambling.⁷² Two correlated variants in the gene encoding the dopamine receptor 1 (*DRD1*) have been reported to be associated with disordered gambling—rs4532 (-48G>A or -48Ddel)⁷³ and rs265981 (5262T>C, -800HaellI).⁷⁴ However, a recent study by Lobo *et al.*⁷⁵ did not replicate this association.

Putative mechanisms of action

The candidate genes described above can be broadly categorized into those with substance-specific influences (for example, *ALDH2* and *ADH1B* for alcohol) and those that likely influence addiction liability via their relationship with a general predisposition to externalizing behaviors, including disinhibition, impulsivity and addiction (for example, *DRD2/ANKK1*).

Drug-specific effects. Genes associated with metabolism of psychoactive substances are anticipated to exert drug-specific effects. For instance, the association between variants in *ADH1B* (rs1229984) and *ALDH2* (rs671) and alcohol consumption can be directly attributed to the effect of these SNPs on alcohol metabolism. rs1229984 affects the rate of conversion of alcohol to acetaldehyde, whereas rs671 substantially reduces conversion of this aversive acetaldehyde to acetate.^{33,76} The accumulation of acetaldehyde is well recognized in the development of the flushing syndrome. The alcohol flush reaction is common in Asians, and involves facial reddening, accompanied by nausea, dizziness and headaches; and these experiences result in

reduced alcohol intake. What is quite remarkable is that with increasing social pressures on Japanese and Koreans to consume alcohol, even individuals with protective *ADH1B* and *ALDH2* alleles continue to drink.^{77,78}

General effects. Based on extensive twin studies, there is clear evidence that a large proportion of genetic factors influencing multiple drugs of addiction are shared. For example, two independent twin studies reported that significant proportions of genetic influence on addiction to a variety of illicit substances could be attributed to a common genetic vulnerability.^{19,31} Liability to alcohol and nicotine (although, less so) also overlaps with this shared genetic influence.³² These shared genetic pathways likely reflect multiple processes. Koob and Volkow⁷⁹ attribute addiction to cycles of impulsivity and compulsivity. Initial experimentation with drugs or escalation to chronic use at a young age has been found to accompany other behavioral indices of impulsivity (for example, conduct problems), and thus genes influencing impulsivity will likely have a general effect on multiple addictions. Multiple genes, including those in the dopamine reward circuits, have been widely studied in this regard.⁸⁰ These reward circuits participate independently, and interactively with glutamatergic and GABA-ergic signaling, in the persistence of drug use and the development and maintenance of addiction. However, although there is clear evidence of central nervous system changes in these circuits related to impulsivity, disinhibition and drug use, the molecular mechanism of the action of gene variants in these pathways on specific drugs of addiction requires further consideration.

Candidate gene studies capitalize on *a priori* knowledge regarding the biological underpinnings of addiction. The next section summarizes the contributions of the more agnostic genomewide association study (GWAS) approach to the genetic study of addiction.

Genes for addiction—exploring the human genome

The challenge of non-replication in candidate gene studies, the desire for identification of novel variants for addiction and the decreasing costs and increasing efficiency of large-scale, high-density genotyping has led to the increasing use of GWAS to study addiction. The primary challenge in these studies is the profound burden of multiple testing, which requires gene variants to exceed a threshold *P*-value of 5×10^{-8} for statistical significance. Initial GWAS of smoking (for example, $N = 2000$),⁸¹ alcohol dependence ($N = 1884–3865$)^{82–85} (and heavy consumption, for example, $N = 3400–4000$)⁸⁶ and cannabis dependence (for example, $N = 3054$)⁸⁷ failed to find any statistically significant associations. Immediately recognizing the need for considerably larger samples, multiple research groups combined GWAS data to produce large meta-analyses. Studying cigarettes smoked per day (an indicator of liability to nicotine dependence), the Tobacco and Genetics Consortium ($N = 74,053$),⁸⁸ Thorgeirsson *et al.* ($N = 10,995$)⁸⁹ and Liu *et al.* ($N = 41,150$)⁹⁰ simultaneously identified rs1051730, which is highly correlated with a functional missense polymorphism (rs16969968) in the nicotinic acetylcholine

receptor gene cluster (*CHRNA5/A3/B4*) on 15q25. It is worth noting that although the first study to identify the role of rs16969968 on smoking behaviors was a study of nicotine dependence,⁹¹ these large meta-analyses have focused on cigarettes smoked per day as it is frequently assessed in a variety of genetic studies. Whether this SNP exerts as strong an effect on nicotine addiction as it does on smoking quantity/frequency is being investigated. Nonetheless, even the effect of this functional variant is modest and multiple other, as yet unidentified variants, are likely to be associated with smoking behavior and nicotine dependence.

Following this trend, a recent meta-analysis of alcohol consumption ($N=47,500$) identified a variant, rs6943555, in autism susceptibility candidate 2 (*AUTS2*) gene.⁹² Follow-up analyses found expression changes in *AUTS2* in mice bred for alcohol preference.⁹² For alcohol dependence, although similar meta-analytic efforts are ongoing, Frank *et al.*⁸³ recently identified rs1789891, which is a proxy for the functional Arg272Gln variant in *ADH1C*, to be associated with alcohol dependence at $P=1.27 \times 10^{-8}$. Given the clear biological significance of this variant, this finding is particularly encouraging.

Despite growing sample sizes and our ability to capture over 2.5 million SNPs across the genome, SNPs reaching formal significance levels in association studies typically explain <2% of the variance in addiction-related phenotypes. For instance, the effect associated with rs1051730 and liability for smoking was a β of 1.03. Thus, it was first thought, as has been suggested for other complex multifactorial traits, that most of the heritability of addiction is 'missing'.^{93,94} However, Visscher and colleagues⁹⁵ point out that the emphasis on SNPs reaching only formal significance at 5×10^{-8} overlooks the evidence for polygenic association in the remainder of the GWAS data. For instance, studies of smoking and substance-related phenotypes have identified cell-adhesion genes as contributors although no signal has attained genome-wide significance (for example, Bierut *et al.*⁸¹ and Johnson *et al.*⁹⁶). In addition, recent studies have found that sets of SNPs of nominal significance might be used to identify genomic regions that are over-represented across independent GWAS^{97,98}—here as well, cell-adhesion genes, such as cadherins, are prominent, although only nominally significant in the individual studies. Although it is not possible to distinguish true signals from false positives with current sample sizes, we can be certain that even among SNPs that are less significantly associated, there are many SNPs that do influence the traits under study. Using a regression approach that simultaneously examines the contribution of all GWAS variants, Visscher and colleagues⁹⁵ have shown that 43, 17 and 54% of total phenotypic variance in height, body mass index⁹⁹ and intelligence quotient¹⁰⁰ respectively, is due to causal variants in linkage disequilibrium with SNPs on commercial GWAS arrays. For height, they further showed that adjusting for imperfect linkage disequilibrium between typed SNPs and causal SNPs raised the estimate to 54%, and further adjustment for the gross under-representation of rare SNPs on commercial chips, raised the estimate to 70–80%, close to estimates of heritability of height from conventional twin and family studies. Such efforts are currently under way for studies of addiction.

A second, and perhaps more perplexing outcome of GWAS is the relative lack of findings that are biologically plausible. This has led investigators to question the content of current GWAS arrays which, despite their high density, can provide inadequate coverage of certain genomic regions, owing to fewer SNPs and absence of adequate linkage disequilibrium required to impute such variants. The *ADH1B* polymorphism, rs1229984, serves as an example: this functional variant is neither included on commercial GWAS arrays nor reliably imputed owing to its low allele frequency in non-Asian populations. However, by genotyping it in multiple large samples, Bierut *et al.*¹⁰¹ recently revealed a genome-wide significant association finding for rs1229984 with alcohol dependence.

Both candidate gene studies and GWAS continue to provide important clues regarding the sources of genetic variation in addictions. However, unless a variant is functional, considerably more research is required to understand how a signal from one of these gene-finding methods actually affects the liability to addiction at a biological level. Even for missense mutations, further work is often required to quantify expression changes. Thus, genetic epidemiological studies, such as gene association, are only the beginning. Using select examples, the next sections illustrate the utility of novel approaches that extend the search for the genetic basis of addictions.

Phenotyping

The first major area of growth for research into addictions has been the systematic transition from diagnostic classification of affected versus unaffected to a dimensional conceptualization, such as measures of quantity/frequency (for example, cigarettes smoked per day), symptom counts, factor scores extracted from multiple indices of problem use and other latent variables representing continuously distributed quantitative measures of addiction vulnerability. Such continuous measures are gaining popularity in genetic studies^{102–104} as they are heritable and this heritability overlaps considerably with genetic influences on addiction.^{103,105,106} An additional advantage of such continuous phenotypes is that they are not limited by heterogeneity in those who are unaffected (for example, assigning the same unaffected value to those who have never had a drink of alcohol, those who are light drinkers and those who endorse 1–2 criteria for alcohol dependence but do not receive a diagnosis) or affected but at varying levels of severity, which can significantly reduce power for genetic association studies. This research is also encouraged by DSM-5, which proposes to define addiction as a multi-level disorder (absent, mild/moderate and severe).

Variations in assessments. Although addiction is clinically diagnosed using the DSM, genetic research has relied on additional assessment strategies that can yield higher heritability and reduce measurement heterogeneity. For instance, nicotine dependence can be diagnosed using the DSM but, for research purposes, quantitative indices (which can also be used to define *affecteds* and *unaffecteds*) such as the Heaviness of Smoking Index¹⁰⁷ and the Fagerstrom Test for Nicotine Dependence (FTND)¹⁰⁸ are frequently

used. Interestingly, the overlap between FTND and DSM-diagnosed individuals is modest ($\kappa \approx 0.3$)¹⁰⁹ and one study found FTND-based nicotine dependence to be more heritable than DSM-based nicotine dependence.⁸

Challenge studies. Typically, for genetic research, addiction is assessed via self-report interviews and questionnaires and via clinical interview. However, laboratory-based measures can also be used to provide detailed assessments of individual differences in addiction using challenge paradigms in which acute doses of a drug are administered to participants in a controlled setting. Using this paradigm, Schuckit and Gold¹¹⁰ have developed the level of response phenotype for oral alcohol challenges—outcomes including positive (for example, high) and negative (for example, nausea) subjective feelings, body sway and various physiological and biomarker changes were used to identify low level of response individuals who are at increased risk for alcoholism^{111,112} (although, in some studies, high level of response associates with alcoholism^{113,114}). These subjective responses to alcohol have been found to be associated with variation in *GABRA2*^{115,116} (Table 1) and in *SLC6A4*.¹¹⁷

Endophenotypes. Level of response is considered by some to be an *endophenotype*. Defined by Gottesman and Gould¹¹⁸ as measurable indices of liability to a phenotype, these measures have gained popularity in genomic studies as they are heritable and assumed to be more proximal to the biological underpinnings of the behavior being studied.¹¹⁹ Although they may co-segregate with disease, they are more closely related to the causes than the consequence of disorder.¹²⁰ There have been multiple putative endophenotypes proposed for addiction, including alcohol and drug-related attentional bias, frequently assessed using a modified version of the traditional Stroop task,¹²¹ and electroencephalogram activity (for example, beta wave patterns, P300 amplitude).^{122–124} A number of these endophenotypes have been used in candidate gene efforts—for instance, SNPs in *GABRA2* (Table 1) have been found to associate with resting electro-encephalogram beta waves.^{36,125}

Biomarkers. Similarly, biomarkers are intermediate phenotypes that are related to disorder and can be a consequence of it. For instance, liver function tests (for example, gamma-glutamyl transferase) or carbohydrate-deficient transferrin are commonly used to examine the impact of prolonged alcohol use. Unlike endophenotypes, which can be used to putatively predict likelihood of disorder, these biomarkers are diagnostic aids that facilitate clinical management of addictions. They are also promising targets for gene association studies. Using various carbohydrate-deficient transferrin indices, and adjusting for alcohol intake, a recent GWAS isolated the highly significant independent effects of variants in the transferrin (*TF*, $P = 5.5 \times 10^{-43}$), and phosphoglucomutase 1 (*PGM1*, $P = 2 \times 10^{-9}$) genes on carbohydrate-deficient transferrin.¹²⁶

Neuroimaging phenotypes. Neuroimaging outcomes are promising new endophenotypes for addiction. Although

current sample sizes are modest, primarily due to costs and burden of imaging technology, promising results have begun to emerge. For example, although not directly addressing functionality, Villafuerte *et al.*¹²⁷ recently found that in families of alcoholics, rs279826 and rs279858 in the *GABRA2* gene, previously associated with alcohol dependence (Table 1), were associated, not only with alcoholism and self-reported impulsivity but also with insula cortex activation in women during anticipation of monetary reward. The insula cortex has been implicated in cue-induced drug craving and addiction and thus, this study provides a potential neurobiological perspective on the link between *GABRA2* and alcoholism. Capitalizing on polygenic variation in addiction, another recent study used a sum score created from frequently studied variants in dopamine pathways genes (*DAT1* 9-repeat, *DRD4* 7-repeat, *DRD2* -141C Del, *DRD2* Taq1A C (A2), and *COMT* Val(158)Met). Although no variant was statistically significant on its own, the sum score was associated with monetary reward-related activation in the ventral striatum, explaining 10.9% of variance.¹²⁸

Summary. How we measure addiction is likely to have a strong effect on the genes and genetic pathways that we identify. A multi-pronged approach to measurement, including multiple self-report assessments, laboratory-based measures and the collection of data on neurophysiological and neuroimaging endophenotypes and examining their correlations with each other, provide avenues for linking genes to behavior. To this end, resources such as the PhenX toolkit (Research Triangle Park, NC, USA),¹²⁹ which provides unrestricted access to state-of-the-art assessments for research, are invaluable. Not only does the toolkit provide protocols for such multi-pronged measurement but the systematic use of identical protocols by multiple investigators will ultimately result in sample sizes large enough to detect even modest genetic effects.

Advances in genomics

Until recently, candidate gene studies and GWAS focused on common variation. However, three additional sources of genomic variation have the potential to further explain heritability in addiction. First, copy number variants—large segments of DNA that are deleted or duplicated producing considerable structural instability—need to be explored for addictions. Recent research has shown associations between rare copy number variants (mostly deletions) and several psychiatric disorders, including schizophrenia, autism and Parkinson disease (see Stankiewicz and Lupski¹³⁰ for a review). Second, as discussed above, rare variants are inadequately captured on commercial GWAS arrays. Deeper sequencing of the human genome presents the opportunity to identify such rare SNPs (<1% minor allele frequency). Although this is being facilitated by the 1000 Genomes Project,¹³¹ the identification of disease-specific rare variants requires next-generation sequencing in samples ascertained for addiction. Finally, epigenetic modifications are implicated as contributors to and consequence of chronic substance use. Animal research shows that repeated drug use alters gene

expression profiles in the brain reward system, through epigenetic mechanisms such as histone acetylation and methylation change (see Renthal and Nestler,¹³² Maze and Nestler,¹³³ and Wong *et al.*¹³⁴ for reviews) and there is no doubt that epigenetic variation is an integral component of the biology of addiction. Although epigenomic methodologies (for example, whole genome methylation) grow increasingly accessible, the primary challenge remains tissue-specificity: epigenetic signatures in peripheral tissues (for example, leukocytes) may not correlate with those in the central nervous system. This has led to increasing investment in the NIH Roadmap Epigenomics Project,¹³⁵ which aims to develop databases of human epigenomic maps (epigenome atlas) in a variety of healthy and tumor tissue and eventually, to provide a degree of cross-tissue correspondence in epigenomic profiles. Even in the absence of direct epigenomic typing, resources such as the Encyclopedia of DNA Elements¹³⁶ allow flexible annotation of the functional landscape of the human genome, such as regions of potential epigenomic modification.

Summary. Despite some current disenchantment with studies of common variants, there is much work that is needed to understand the precise mechanisms by which candidate genes and their common SNPs influence addiction. Animal studies of gene manipulation afford opportunities to investigate this—for example, both *Xenopus* oocytes¹³⁷ and rodents¹³⁸ have been used to investigate the role of *GABRA2* in alcohol intake (Table 1). An alternative method involves the use of annotation algorithms to identify the potential correspondence between variants and gene activity and to further enmesh these variants in biological pathways. These approaches are briefly reviewed next.

Advanced biostatistics and bioinformatics

All of the above phenotypic and genotypic approaches rely heavily on biostatistical advances and innovation in statistical methods. Biostatistics and computational biology have rapidly become the foundation of post-GWAS interpretation of results. Relying primarily on existing curated databases, these methods attempt to model the inherent and often non-linear complexity in biological processes. For instance, gene-based association studies (for example, PLINK set-based test,¹³⁹ VEGAS,¹⁴⁰ GRAIL¹⁴¹ and GATES¹⁴²) combine information from several SNPs within each gene, identifying genes that show more signals of association than expected by chance. Pathway analysis also examines the combined effects of multiple genetic variants (that could be of small effect). By means of exploratory pathway analysis, it is possible to test whether associated genetic variants are more prevalent in any known biological pathway (see for example, IPA (Ingenuity Pathway Analysis; Ingenuity Systems, www.ingenuity.com)), or any known functional gene group.¹⁴³ In a recent study, Reimers *et al.*¹⁴⁴ performed a pathway analysis using SNPs within 48 addiction candidate genes in alcohol-dependent cases and controls. They tested seven gene sets (pathways), including various neurotransmitter systems. In line with previous findings, their results showed that four of the neurotransmitter pathways (corticotropin-releasing hormone, GABA, glutamate and norepinephrine) significantly contrib-

uted to alcohol-dependence risk. A number of these methods rely on the Gene Ontology project—a large bioinformatics project that combines the representation of genes and gene products across species as well as across different databases.¹⁴⁵

Summary. There is a considerable need for computational approaches to generate and interpret results from genetic studies for addiction. Although several groups have attempted to model the complex pathways underlying addictions, there has been little consistency across studies, which is likely due to the inherent lack of replication for the individual genetic findings. One possible reason for this lack of consistency across studies, at individual SNP and pathway levels, might be the moderating role of environment.

Gene–environment interplay

Moderation of genetics by environment. Genetic studies typically assume homogeneity of effect size. However, for addiction, the relevance of genetic influences may depend on environmental contexts. This has resulted in recognition of the importance of gene–environment interplay (including both gene–environment (GE) correlation and gene–environment ($G \times E$) interaction) in the etiology of addictions. GE correlation¹⁴⁶ refers to genetic predispositions that influence the likelihood of being exposed to a certain environment (for example, heritable influences have been found to influence affiliations with delinquent or substance-using peers). Gene–environment interaction ($G \times E$)¹⁴⁷ refers to moderation of genetic predisposition as a consequence of environmental exposure—for example, studies of adolescent Finnish twins indicated that in less stable neighborhoods, there was greater evidence of genetic influence on alcohol use.^{148,149} Conversely, in more supervised and restricted environments, there was less opportunity to express genetic predispositions to alcohol use and greater influence of environmental effects. Additionally, both low levels of parental monitoring¹⁵⁰ and increasing affiliations with substance-using peers^{151,152} have been found to augment the importance of genetic influences on drug use.

Studies examining potential interactions between *measured* genes and environment^{153,154} are also becoming more common. For example, Dick *et al.*^{155,156} reported that the association of *GABRA2* and *CHRM2* variants with externalizing trajectories diminished with high levels of parental monitoring. In addition to environment exacerbating genetic vulnerability, there is also evidence for the stress-buffering effects of genotype. Nelson *et al.*¹⁵⁷ found that the effect of childhood sexual abuse on alcoholism was buffered in those carrying the H2 haplotype of the gene encoding the corticotrophin-releasing factor (*CRHR1*).

The role of environment after accounting for genetics. Although the previous section presents the notion of environmental moderation of genetic vulnerability, whether environmental and other risk factors (for example, comorbid psychiatric problems) continue to exert an influence on addiction after overlapping genetic risk factors are partialled

out is of utmost interest to the prevention and treatment community. Twins, particularly MZ pairs discordant for environmental exposure, provide a fascinating demonstration of the constant interplay between genetic background and environmental exposures. For instance, examining pairs of twins discordant for exposure to childhood sexual abuse, Nelson *et al.*¹⁵⁸ reported that the twin who had experienced abuse was considerably more likely to also report a lifetime history of addiction, even when compared with their genetically identical but unexposed co-twin. Interestingly, these genetically identical twin pairs can even have differing epigenetic profiles, with within-pair differences becoming more pronounced with increasing age.¹⁵⁹ The informativeness of discordant MZ pairs applies to every research methodology described above and is only just being harnessed in genetic studies of addiction.

Summary. Recently, there have been several published critiques of the genotype–environment interplay methodology^{160,161} and it is likely that some of the limitations noted by these investigators apply to studies of addiction. However, addiction is the most obvious example of a process that is subject to gene–environment interplay—even individuals with a family history of addiction may circumvent their genetic vulnerability by limiting drug exposure. There is now even emerging evidence that the efficacy of behavioral treatments may interact with genotype to predict outcomes, such as disruptive childhood behaviors,¹⁶² and the next section briefly reviews genotypic modification of drug therapies. Thus, although it is important to recognize the importance of the statistical caveats to modeling gene–environment interplay, it is necessary to continue conducting such studies on addiction.

Pharmacogenomics

The extent to which drug therapy, such as acamprosate and naltrexone for alcohol dependence and nicotine replacement therapy and other medications (for example, bupropion and varenicline) for nicotine dependence, may be more successful in individuals with certain genetic profiles is of considerable interest.¹⁶³ These drugs target receptors encoded by genes of interest—for instance, baclofen (for alcohol) acts as an agonist at pre-synaptic GABA-B receptors, while varenicline (for nicotine) is a partial agonist of the $\alpha 4\beta 2$ nicotinic receptors. Although these drugs have shown promise in increasing rates of abstinence, typically only a minority of treated individuals discontinue drug use. For example, 12 months post-treatment, typically only 1 in 10 smokers treated with pharmacotherapies remain abstinent.¹⁶⁴ Although such findings suggest that pharmacotherapy may be a promising avenue for treatment development, given the typically low rate of success for existing approaches to treating addictions, individual differences in the apparent effectiveness of these drug treatments has led to increasing interest in *pharmacogenetics*, the study of genetic variation underlying individual differences in both drug metabolism and response to the effects of drugs.¹⁶⁵ Despite some non-replications, three independent studies have reported that carriers of the A118G polymorphism (rs1799971) in *OPRM1* respond more positively to naltrexone treatment for alcohol dependence.^{166–168}

Another promising treatment for alcoholism, ondansetron, a 5-HT₃ (5-hydroxytryptamine (serotonergic) receptor 3) antagonist has been found to be a particularly useful treatment in early-onset (Type II) alcoholics, while the selective serotonin reuptake inhibitor (SSRI) sertraline has been found to be more efficacious in later-onset (Type I) alcoholics.^{169,170}

Summary. Whether treatment effects vary by genotype is an important area of further study. Growth in this area relies heavily on discoveries of common and rare variants and a continued effort to outline their biological function.

Genetics of addiction and related illness

Thus far, we have discussed genetic influences underlying addictions. However, some of these genes are responsible for the links between addictive behaviors and other forms of illness, particular cancer. For instance, rs1229984 in *ADH1B* and rs671 in *ALDH2* have been implicated in the etiology of esophageal cancer.¹⁷¹ By modifying acetaldehyde accumulation and clearance, the enzymatic consequences of these variants result in increased exposure to ethanol and acetaldehyde, an effect that is exacerbated in individuals who drink alcohol despite carrying these protective variants.^{172,173} Likewise, rs16969968 (and other variants) in the chromosome 15 gene cluster that is now widely recognized as a risk factor for nicotine addiction has also been found to confer risk for lung cancer,^{174–176} peripheral artery disease¹⁷⁵ and chronic obstructive pulmonary disease.¹⁷⁷ Whether this missense mutation has an independent effect on these diseases or whether its effect is mediated by its modulation of exposure to smoking continues to be explored.¹⁷⁸ Finally, there appears to be an emergence of disordered gambling in patients receiving dopamine replacement therapy for Parkinson's disease—there is some evidence that dopaminergic stimulation interacts with variants in dopamine genes (for example, *DAT*, *DRD3* and *DRD4*) to induce reward-seeking behaviors, particularly pathological gambling, but these genetic connections are speculative.¹⁷⁹

Summary. Addictions, serious illnesses themselves, are linked with other diseases that may be consequences, and in rare instances, a potential cause, of the addictive behavior. Interplay between the addictive behavior and genetic predisposition (for example, increased risk of esophageal cancer in those who carry one copy of rs671 in *ALDH2* and also continue to drink alcohol) is likely responsible for a majority of these relationships.

Can animal models inform human genetic studies of addiction?

Throughout this review, where possible, experimental manipulation in animals is used to highlight progress made in understanding the functional significance of genetic systems. There is also a long and distinguished tradition of animal models for addiction. A detailed discussion of these methods is beyond the scope of this review. Both rats and mice, for instance, can be selectively bred for alcohol preference (for example, alcohol-preferring,¹⁸⁰ alko-alcohol¹⁸¹) and these

Table 2 Multi-method progress made in studying the genetic underpinnings of nicotine addiction

Stage of enquiry*	Method	Example
Phenotyping		Nicotine addiction is a multistage process, with exposure, initiation, regular smoking, heavy smoking, nicotine dependence and persistence. ¹⁹⁸ Nicotine dependence can be measured using various psychometrically valid assessments (e.g. DSM-IV, FTND, HSI). ¹⁹⁹ Aspects of nicotine dependence (e.g. FTND—time to first cigarette, DSM-IV withdrawal) contribute to the dependence syndrome while also having features unique to them. ^{200,201}
Studies of related individuals	Family Studies Twin Studies	1.77 increased hazards of habitual smoking in relatives of smokers. ²⁰² Cigarette smoking is heritable. ²⁰³ Genetic factors influence smoking initiation (75%), quantity smoked (57%), nicotine dependence (60%), persistence (40–50%) and nicotine withdrawal (40%). There is significant overlap of genetic influences between smoking initiation and nicotine dependence as well as persistence. ⁷ Dependence measures using HSI/FTND are more heritable than DSM-IV. ⁸ 19% of genetic influences on DSM-IV withdrawal do not overlap with other aspects of smoking. ²⁰⁴
Gene finding	Linkage Candidate genes GWAS	Several linkage studies of smoking behaviors. A recent meta-analysis implicates 17q24.3–q25.3 with regions on 17q24.3–q25.3, 20p12.1–q13.12, 20q13.12–q13.32 and 22q12.3–q13.32 significant or suggestive for maximum cigarettes smoked in a 24-h period. ²⁰⁵ The nicotinic acetylcholine receptor subunit genes, including <i>CHRNA5/A3/B4</i> (chr 15), <i>CHRNA4</i> (chr 20), <i>CHRNB2</i> (chr 1), as well as <i>CYP2A6</i> (chr 19), <i>OPRM1</i> (chr 6) and <i>DRD2/ANKK1</i> (chr 11) have been actively studied. Most widely replicated GWAS signal, first identified via candidate gene analysis, ⁹¹ is a missense mutation, rs16969968 (D398N, or proxy, rs1051730) in the <i>CHRNA5/A3/B4</i> cluster. Subsequent meta-analysis identified it at $P < 10^{-70}$. ^{88–90}
Gene–environment interplay	Latent genetic/twin Measured genetic/SNP	Heritable influences on adolescent smoking increase with decreasing parental monitoring. ¹⁵⁰ Heritable influences on onset and daily smoking decrease with increasing state-level taxation, control and policy stringency. ²⁰⁶ Those with high-risk genotype of rs16969968 are less sensitive to peer influences ²⁰⁷ although the effect of the risk variant is most pronounced in those exposed to low parental monitoring. ²⁰⁸ Age at onset of smoking behaviors interacts with rs16969968 to predict continued smoking, although studies diverge on whether the variant exerts greater influence in early or late onset smokers. ^{209,210}
Biological relevance	Bioinformatics Biological function via experiments Neuroimaging	Pathway analyses reveal that genes in glutamatergic, tyrosine kinase signaling, transporter, cell adhesion and opioidergic systems influence smoking. ²¹¹ Mice homozygous for absence of $\alpha 5$ subunit (–/–) show reduced sensitivity to a variety of physiological outcomes associated with nicotine or its agonists. ²¹² Increased nicotine intake in $\alpha 5$ knock-out mice, which is rescued by re-expressing $\alpha 5$ in the medial habenula. ²¹³ Epibatidine response is nearly twice as high for cells transfected with wild-type (D398) relative to the N398 variant but there were no differences in receptor expression. ¹⁹⁵ Greater short-term desensitization of N398-containing receptors has been noted but only when coupled with $\alpha 4\beta 2$ subunits. ¹⁹⁶ rs16969968 associated with reduced functional connectivity between dorsal anterior cingulate cortex ventral striatum and extended amygdala. Those with low risk variant show increased response to smoking cues in the brain regions linked to memory and habitual behaviors. ²¹⁴
Treatment	Pharmacogenomics	Minor allele carriers of <i>CHRNB2</i> variants experience greater nausea and dizziness upon use of varencline. ²¹⁵ High (42 mg) nicotine dose more efficacious in highly dependent smokers with a low quit-success genotype score based on 12,508 SNPs ²¹⁶

Abbreviations; DSM, Diagnostic and Statistical Manual of Mental Disorders; FTND, Fagerstrom Test for Nicotine Dependence; GWAS, genomewide association study; HSI, Heaviness of Smoking Index; SNP, single nucleotide polymorphism.

animals can be trained to approximate aspects of addiction, such as binge drinking (for example, using the drinking-in-the-dark paradigm).¹⁸² Mutagenesis has been used to produce fruit flies (*Drosophila melanogaster*) that vary on their alcohol consumption and response to alcohol (for example, cheap-date, tipsy).¹⁸³ For addiction research, the issue of consistency, or the relative similarities and differences between human behavior and animal phenotypes devised to study these behaviors, continues to be a challenge. Highlighting the need to reconcile these differences, Crabbe,¹⁸⁴ for instance, notes that while rodents, even those with high alcohol

preference, self-limit their alcohol ingestion and rarely induce intoxication, loss of control over alcohol intake is the cornerstone of alcoholism producing conceptual discrepancies across rodent and human behaviors.

Genetic studies of nicotine addiction

Genetic studies of addiction are at a watershed—we have clearly identified some genetic contributors to addiction and we continue to explore the role of others using multiple methods and considering the pivotal role of environmental

variation. The research described so far is made possible by growing collaboration and intellectual sharing across investigators from varying disciplines—such collaboration is critical now as technological advances allow us to study addiction from multiple integrated perspectives. To highlight the enormous potential of using multiple translational methods, Table 2 summarizes the application of a number of approaches outlined above to the study of nicotine addiction.

Addiction, genetics and public health

Why study the genetics of addiction? Critics argue that it has modest benefit from a public health standpoint (e.g., ref. 185). They posit that (a) genetic variants, when and if they are discovered, have small effect sizes; (b) comparable environmental factors are easier to delineate and have stronger influence; and arguably (c) are more amenable to modification. These criticisms, by taking a short-sighted view, often obfuscate the true goal of genetic research—to provide improved therapeutic alternatives for individuals who, despite rigorous environmental modification (for example, increased taxation, reduced availability and even treatment) remain addicted to drugs. It is worth reiterating that the goal of genetic research into addiction is no different from that for Type 2 diabetes or cardiovascular disease and that addictions are also among the top contributors to preventable death worldwide. Perhaps this argues for an even more concentrated effort to understand the etiology of addiction.

In his commentary on genomic studies of complex traits, Hirschhorn¹⁸⁶ notes that ‘The difficulty in translation is not unique to genetic discoveries: nearly a century and three Nobel Prizes separate the determination of the chemical composition of cholesterol from the development of statins. Each discovery of a biologically relevant locus is a potential first step in a translational journey, and some journeys will be shorter than others.’ Genetic factors are partly responsible for, not only, the comorbidity across addictions but also between addictions and other mental illness (for example, autism and bipolar disorder). The growth of these existing findings from genetic epidemiological studies into promising leads for treatment is necessary and with time, sustained funding and translational collaborations, this goal of a clear impact of genetic research on public health can and will be achieved.

Conflict of interest

The authors declare no conflict of interest.

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