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Addiction Genetics and Pleiotropic Effects of Common Haplotypes that Make Polygenic Contributions to Vulnerability to Substance Dependence

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Abstract

Abundant evidence from family, adoption, and twin studies point to large genetic contributions to individual differences in vulnerability to develop dependence on one or more addictive substances. Twin data suggest that most of this genetic vulnerability is shared by individuals who are dependent on a variety of addictive substances. Molecular genetic studies, especially genomewide and candidate gene association studies, have elucidated common haplotypes in dozens of genes that appear to make polygenic contributions to vulnerability to developing dependence. Most genes that harbor currently identified addiction-associated haplotypes are expressed in the brain. Haplotypes in many of the same genes are identified in genomewide association studies that compare allele frequencies in substance dependent *vs.* control individuals from European, African, and Asian racial/ethnic backgrounds. Many of these addiction-associated haplotypes display pleiotropic influences on a variety of related brain-based phenotypes that display 1) substantial heritability and 2) clinical cooccurence with substance dependence.

Keywords

addiction; psychiatric genetics; complex genetics; genomewide association

Current models for the genetic architecture for substance dependence in the population are based on information from: 1) family, adoption, and twin data that each support substantial heritability for addictions, 2) twin data (in which concordance in genetically identical monozygotic and genetically half-identical dizygotic twins are compared) that document that most of this heritable influence is not substance specific, 3) linkage-based (and genome-wide association) studies that fail to provide evidence for genes of major effect (e.g., for any single gene whose variants produce substantial reproducible differences in addiction vulnerability) for substance dependence.

Support for the idea that vulnerability to addictions is a complex trait with strong genetic influences that are largely shared by abusers of different legal and illegal addictive

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substances (Uhl et al., 1995; Tsuang et al., 1998; Karkowski et al., 2000; True et al., 1999) comes from classical genetic studies. Family studies document that first-degree relatives (e.g., sibs) of addicts display greater risk for developing substance dependence than more distant relatives (Uhl et al., 1995; Merikangas et al., 1998). Adoption studies find greater similarities between levels of substance abuse between adoptees *vs.* biological relatives than adoptees vs. members of the adoptive families (Uhl et al., 1995). In twin studies, differences in concordance between genetically identical and fraternal twins also support substantial heritability for vulnerability to addictions (Karkowski et al., 2000; Woodward et al., 1996; Tsuang et al., 1996; Kendler & Prescott, 1998; Kendler et al., 2006; Agrawal et al., 2004; Grove et al, 1990; Gynther et al., 1995). Twin data also allow quantitation of the amount, about half, of addiction vulnerability that is heritable. Twin data support the idea that the environmental influences on addiction vulnerability that are not shared among members of twin pairs are much larger than those that are shared by members of twin pairs (e.g., $e^2 > > c^2$ in virtually every such study). Many of the environmental influences on human addiction vulnerability are thus likely to come from outside of the immediate family environment.

TWIN DATA DOCUMENT THAT MOST OF THIS HERITABLE INFLUENCE IS NOT SUBSTANCE SPECIFIC, BUT PROVIDES “HIGHER ORDER” PHARMACOGENOMICS

We are fortunate to have data from studies of identical vs. fraternal twin pairs that evaluate the degree to which one twin’s dependence on a substance enhances the chance that his or her cotwin will become dependent on a substance of a different class. Results of these analyses document that most of the genetic influences on addiction vulnerability are common to dependence on multiple different substances, though others do appear to be substance specific (Tsuang et al., 1998; Kendler et al., 2006; Agrawal et al., 2004).

Elsewhere (Uhl et al., 2008c) we have suggested levels of analysis for pharmacogenomics and pharmaco-genetics: 1) *“primary” pharmacogenomics* that describe the genetics of individual differences in the adsorption, distribution, metabolism, and/or excretion of a drug; 2) *“secondary” pharmacogenomics* that describe individual differences in drug targets (e.g., G-protein–coupled receptors) that are the primary targets of drugs of abuse; and 3) *“higher order” pharmacogenomics* that provide individual differences in postreceptor drug responses. Such postreceptor drug responses are more likely to be common to actions of abused substances that come from several different chemical classes and act at distinct primary receptor or transporter sites in the brain. Based on the twin data that are currently available, we thus postulate that much of the human genetics of addition vulnerability is likely to represent “higher order” pharmacogenomics.

FAILURE TO DOCUMENT EVIDENCE FOR SUBSTANCE-DEPENDENCE GENES OF MAJOR EFFECT IN MOST POPULATIONS

There are few careful studies of the ways in which most human addiction vulnerabilities move through families (e.g., segregation analyses). No such study indicates a “major” gene effect on addiction vulnerability in most current populations. There is an exception: the

"flushing syndrome" variants at the aldehyde (ALDH) and alcohol (ADH) dehydrogenase loci in Asian individuals do provide genes of major effect in this population. Individuals with these gene variants are at lower risk for becoming dependent on alcohol than individuals with other genotypes (Chen et al., 1999) in Chinese (Thomasson et al., 1991; Chen et al., 1996), Korean (Shen et al., 1997), Japanese (Higuchi, 1994; Higuchi et al., 1994, 1995; Maezawa et al., 1995; Nakamura et al., 1996; Tanaka et al., 1997), and other populations (Luczak et al., 2002; Schuckit & Duby, 1982). Homozygous ALDH2*2 individuals are strongly protected from alcohol dependence (Higuchi, 1994; Higuchi et al., 1994). This locus thus provides a good example of "primary" pharmaco-genomics, though in a restricted population.

Quantity-frequency data for smoking also provide evidence for a replicable "secondary" pharmacogenomic effect of moderate magnitude. Markers in the chromosome 15 gene cluster that encodes the α3, α5, and β4 nicotinic acetylcholine receptors display different allelic frequencies in heavy vs. light smokers in each of several studies (Bierut et al., 2007; S. F. Saccone et al., 2007b; Berrettini et al., 2008]. This chromosome 15 locus is likely to provide a good example of "secondary" pharmacogenomics, since it has not been associated as reproducibly with dependence on other substances.

Linkage-based analyses for addiction vulnerabilities would be expected to reproducibly identify many of the genes whose variants exerted major influences on human addiction vulnerability. However, existing linkage data for human dependence on alcohol, nicotine, and a number of other substances fails to provide any highly reproducible results that would support any major gene locus (Uhl et al., 2008c; Guerrini et al., 2005; Zhong & Zhang, 2005; Clarimon et al., 2007; Gelernter et al., 2007; Hopfer et al., 2007; Kuo et al., 2006; Li et al., 2007; Loh et al., 2007; Pomerleau et al., 2007; S. F. Saccone et al., 2007a). These results add to the conclusion that no individual locus appears to make "oligogenic" contributions (e.g., to contribute a large fraction of the vulnerability) to dependence on any of the commonly abused addictive substances whose genetics have been studied, to date (Guerrini et al., 2005; Zhong & Zhang, 2005; Porjesz et al., 1998; Dick et al., 2004; Gelernter et al., 2004; N. L. Saccone et al., 2000; Schuckit et al., 2001; Bergen et al., 2003; Bierut et al., 2004; Dick et al., 2006b, 2002, 2006a; Edenburg & Foroud, 2006; Pinnaduwage & Briollais, 2005; Porjesz et al., 2002; Reck et al., 2005; Yang et al., 2005). As with many complex human disorders in which initial hopes for a tractable (e.g., oligogenic) underlying genetic architecture supported the use of linkage approaches, the linkage peaks that are identified in each individual study may be more likely to arise on other bases when the underlying architecture is, in fact, polygenic. Apparent linkage signals identified in single studies might result from a number of sources, including polygenic influences from several genes that each happen to lie near each other on human chromosomes or to be found on stochastic bases when there is no true major effect from any single gene variant (Gudmundsson et al., 2007).

CURRENT MODELS FOR THE GENETIC ARCHITECTURE OF HUMAN DEPENDENCE

Current models for the genetic architecture of human dependence on legal and illegal addictive substances in the population thus postulate that each is influenced roughly 50% by polygenic genetic influences, that is, by variants in individual genes that each contribute modest amounts to this overall genetic vulnerability. These models for underlying genetic architecture posit that many of these genetic vulnerabilities increase risk for addiction to several pharmacologic classes of abused substances, but that some of these genetic influences are specific to drugs of one class (Uhl et al., 2008c).

Analyses of twin data for vulnerability to develop dependence on a substance fit with large additive genetic components (a^2), large components for nonshared environmental influences (e^2), and small components for the c^2 terms that represent familial or other environmental influences that are shared between members of each twin pair (Karkowski et al., 2000; Woodward et al., 1996; Tsuang et al., 1996; Kendler & Prescott, 1998; Kendler et al., 2006; Agrawal et al., 2004; Grove et al., 1990; Gynther et al., 1995). If there were large interactions between genetic and environmental terms (G × E interactions), additive models for genetic and environmental contributions would be threatened, however. G × E correlations of three types have been described (Plomin et al., 1977; Scarr & McCartney, 1983). A “passive” G × E correlation has been invoked when parents transmit both genes and environmental influences that are relevant for a trait (Posthuma et al., 2003; Lytton et al., 1977). An “active” G × E correlation is found when subjects of a certain genotype actively select environments that are correlated with that genotype. A “reactive” G × E correlation occurs when consequences of an individual’s genotype incite different reactions from the environment. Small values for c^2 influences of common environments shared by members of sibpairs may provide some evidence against “passive” G × E correlations. On these bases, “active” and “reactive” G × E correlations remain of theoretical interest. One influential train of thought [Posthuma et al., 2003; Falconer & MacKay, 1996) does suggest that G × E correlations should be regarded as parts of the genetic variance because “. . . the non-random aspects of the environment are. . . consequence(s) of the genotype(es). . .”.

Large interactions between genetic and environmental components would also be likely to lead to 1) differences in estimates of heritability from samples obtained in different environments and 2) differences in molecular genetic findings in individuals sampled from different environments. Data from studies of twins who were sampled from a number of different environments are, nevertheless, largely convergent. Such convergence supports relatively modest upper limits on (G × E) interactions between genetic and environmental influences on addiction vulnerability. Modest G × E influences are also consistent with molecular genetic results that identify substantial overlaps between molecular genetics of vulnerability to dependence on illegal substances in samples from substantially different environments, such as the United States and Asia (see below).

Gene-gene interactions (G × G) of some magnitude appear likely, *a priori,* to make at least some contributions to addiction vulnerability. However, if there were large amounts of epistasis, G × G interactions in which specific alleles at one gene locus are required for

expression of the effects of allelic variants at a second gene locus, segregation analysis data might provide uneven patterns of familiality. With large amounts of epistasis, second-degree relatives (e.g., cousins) of addicts would be much less likely to display specific combinations of G × G alleles than anticipated, based on results from first-degree relatives (e.g., sibs). Substance-dependence rates would thus drop more precipitously between first- and second-degree relatives of addicts than they would if most risk alleles exerted largely independent effects on addiction vulnerability.

There are only a modest amount of family data that allow us to compare concordance in first- vs. second-degree relatives. However, the existing evidence does not support less concordance in second-degree relatives than we would anticipate, based on the observed concordance in first-degree relatives and the assumption that most risk alleles produce largely independent effects (Buster & Rodgers, 2000).

THE GENETIC ARCHITECTURE FOR SUBSTANCE DEPENDENCE IN INDIVIDUALS

What about the genetic architecture for substance dependence in individuals? Both *"between locus" heterogeneity* and *"within locus" heterogeneity* are likely. If we follow the implications of polygenic genetic models for addiction vulnerability, we can infer that each dependent individual might even display a nearly distinct set of risk-elevating or reducing allelic variants. As an illustrative example, we might postulate that 1) an individual must display at least 50 risk alleles to robustly elevate his or her likelihood of acquiring a substance-dependence disorder and 2) there are 200 genes that contain common allelic variants that can augment addiction risk. Under such circumstances, it is easy to see that the exact genetic recipe for addiction vulnerability found in one addicted individual might be replicated in only a relatively few other addicted individuals. Such an underlying genetic architecture would be consistent with the failure of linkage-based methods to provide reproducible results in addictions, since linkage relies on the identification of consistent patterns in the ways that specific DNA markers and phenotypes move through families that display high densities of the disorder.

As noted above, the best documented genetic heterogeneity for addictions comes from the chromosome four major gene effects found in poorly alcohol–metabolizing ("flushing") Asian individuals (Higuchi, 2004; Higuchi et al., 1994, 1995; Luczak et al., 2002). The best documented substance-specific influence comes from the chromosome 15 nicotinic acetylcholinergic receptor gene cluster. There are likely to be other examples of between-locus genetic heterogeneity and of genes whose variants exert substance-specific effects on use and/or dependence that have yet to be elucidated.

We also postulate that *within locus heterogeneity* is likely, though, to our knowledge, not yet clearly documented in addiction. Many common Mendelian disorders and rarer Mendelian phenocopies of common disorders display substantial heterogeneity within their pathogenic loci. A number of variants in the same CFTR gene produce cystic fibrosis disorders (Stanke et al., 2008). α synuclein missense variants and copy number variants can each provide phenocopies of idiopathic Parkinson's disease (Douglas et al., 2007). Evidence for within-

locus heterogeneity in complex disorders, including data from neurexin gene family variants in autism, is just beginning to be accrued, however (Stephan, 2008; Alarcon et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008).

POSSIBLE BASES OF BALANCING SELECTION IN EARLY EVOLUTIONARY ENVIROMENTS WITH LITTLE EVIDENCE FOR POTENT ADDICTIVE SUBSTANCES

A number of candidate or reproducible addiction-associated haplotypes lie within genes with little brain expression, including the ADH/ALDH variants that produce flushing in Asian individuals. While most genes that are likely to contain addiction-associated haplotypes display substantial levels of brain expression, few display expression that is limited only to the brain. It is easy to imagine how haplotypes in genes that are expressed at high levels, for example, in brain and heart could lead to balancing selection based on favorable haplotype effects in brain and unfavorable effects in heart or *vice versa*.

We focus here, however, on the likelihood that many of the common addiction-associated allelic variants have been maintained via balancing selection due to actions in the brain.

If many common haplotypes that are associated with individual differences in vulnerability to substance dependence in members of current populations were subjected to balancing selection based on their influences on other brain-based phenotypes, how might we identify such phenotypes? Some of the criteria that we might apply for identification of other phenotypes that might provide the bases for such balancing, brain-based selection include:

1. The other (i.e., nonaddiction) phenotypes should display significant degrees of heritability.
2. The other (i.e., nonaddiction) phenotypes should co-occur with substance dependence at rates significantly higher than those that would be expected by chance, based on the frequencies of occurance of addiction and othe other phenotypes in the general population.
3. There might be a plausible rationale for enhanced group survival, based on the existence of a range of values for the phenotype within small groups of humans in the environments likely to have been experienced during the course of most of the time that ancestral human populations accumulated and maintained the common allelic variants that make major contributions to addiction vulnerabilities in current human populations.

Initial genomewide association studies for several phenotypes that satisfy these three criteria now provide opportunities to assess overlaps with addiction genetics. We have recently reviewed evidence from genomewide association datasets that a number of phenotypes that might well provide opportunities for balancing selection share genetic overlaps with addiction-associated haplotypes. We review these data below briefly, and please see the summary of sources in Table 1 and (Uhl et al., 2008a) for more details.

Cognitive Abilities

Availability of data from genomewide association studies that correlated single-nucleotide polymorphism (SNP) allele frequencies with measures of cognitive function in several groups of indivudals identified substantial overlaps between the results from these samples. Thus, the SNPs that display nominally significant correlations between allele frequency differences with a measure of cognitive abilities in multiple samples cluster in genomic regions shared between these samples to extents much greater than those identified by chance. Further, the genomic regions that contain clusters of such nominally positive SNPs from these samples overlap at much greater than chance levels with those identified in comparisons between substance-dependent and control indivduals from multiple samples from differing racial/ethnic groups.

In current environments, individuals with greater vs. lesser cognitive abilities display features that might suggest balancing selection, as noted above, based on greater cognitive executive functions vs. less opportunity for maternal and fetal deaths based on cephalopelvic disproportion during parturition. It is thus conceivable that balancing selection based on at least some of the genetically determined features displayed by individuals with differences in cognitive abilities might have provided some of the balancing selection that appears to have been manifest in individuals with vulnerabilities to addiction.

Brain Volume (Frontal Lobe)

The availability of data from two genomewide association studies that compared indivudals with greater to those with smaller volumes of the frontal lobes have identified substantial overlaps between the results from these two samples. Thus, the SNPs that display nominally significant allele frequency differences between individuals with greater vs. less frontal lobe volume cluster in genomic regions shared between these two samples to extents much greater than those identified by chance. Further, the genomic regions that contain clusters of such nominally positive SNPs from these samples overlap at much greater than chance levels with those identified in comparisons between substance-dependent and control indivduals from multiple samples from differing racial/ethnic groups.

In current environments, individuals with greater vs. lesser frontal lobe volumes display features that might suggest balancing selection, as noted above, based on greater cognitive and executive functions vs. less opportunity for maternal and fetal deaths based on cephalopelvic disproportion during parturition. It is thus conceivable that balancing selection based on at least some of the genetically determined features displayed by individuals with differences in cerebral volumes might have provided some of the balancing selection that appears to have been manifest in individuals with vulnerabilities to addiction.

Personality Features (Neuroticism)

Availability of data from a genomewide association study of individuals with differing levels of the personality feature, neuroticism, has also identified nominally significant SNP allele frequencies, the genomic regions that contain clusters of such nominally positive SNPs from these samples that overlap at much greater than chance levels with those identified in

comparisons between substance-dependent and control indivduals from multiple samples from differing racial/ethnic groups.

In current environments, individuals with differing scores on tests of personality display features that might suggest balancing selection. Individuals with a range of personality features may be likely to display greater adaptive responses and interactions, as a group, than groups of individuals who display no differences in such measures.

CLASSES OF GENES THAT ARE IDENTIFIED IN GWA SAMPLES FOR ADDICTION AND CO-OCCURRING PHENOTYPES THAT MAY PROVIDE BASES FOR BALANCING SELECTION IN ANCESTRAL HUMAN GROUPS: FOCUS ON CELL-ADHESION–RELATED GENES

One way of thinking about the potential for balancing selection in the sorts of environments and small groups noted above is to focus on the specific genes and classes of genes that are identified in genomewide association studies for addictions and related heritable phenotypes. When we have made these comparisons, it is comforting to find that most of these genes, in fact, are expressed in the brain and in specific brain regions associated with memory and other cognitive abilities, especially the hippocampus. Further, many of the genes that we have identified in these analyses of convergent genomewide association findings are involved in “cell adhesion” processes (Table 2), whereby neurons recognize and respond to features of their environments that are important for establishing and maintaining proper connections. While other genes are involved in enzymatic activities, protein translation, trafficking and degradation, transcriptional regulation, receptor, ion-channel and transport processes, disease processes, cell structures, and unknown functions (summarized in Table 3), we focus here on the genes related to “cell adhesion” processes (Table 2), since we have documented that these genes are over-represented in lists of genes associated with vulnerabilities to substance dependence, those associated with cognitive abilities, those associated with differences in brain volumes, and those associated with the addiction-associated personality trait, neuroticism.

Cell-Adhesion–Related Genes

Cell-adhesion mechanisms are central for properly establishing and regulating neuronal connections during development. Cell-adhesion mechanisms can play major roles in mnemonic and other neuroadaptive processes in adults (Welzl & Stork, 2003; Benson et al., 2000). It is interesting to note that most of the cell-adhesion–related genes that we identify in these genomewide association studies (Table 2) are expressed in developing and adult brains. Altered expression of several of these genes can alter neurite extension (Fredette et al., 1996; Chen et al., 2006; Keene et al., 2006), activate signaling pathways (Kipmen-Korgun et al., 2005; Philippova et al., 2005; Hug et al., 2004; Ivanov et al., 2001; Dean et al., 2003; Yamakawa et al., 1998), and alter mnemonic processes (Keene et al., 2006). Almost all of these cell-adhesion–related genes are expressed in memory-associated brain regions that include the hippocampus and cerebral cortex (http://brain-map.org) (Kraus et al., 2006; Takeuchi et al., 2000; Lein et al., 2007; Kim et al., 2003). By contrast, substantial expression

in mesolimbic/mesocortical dopamine “reward system” neurons is not documented for many of them.

“Cell adhesion” related genes identified by these genomewide association studies encode members of several structural cell-adhesion-molecule subfamilies. Those that are anchored to cell membranes by glycophosphoinositol (GPI) anchors, those that display apparent single-transmembrane topologies, those that display apparent seven-transmembrane topologies, and those that produce soluble products are each represented.

Cell-Adhesion Molecules with the Strongest Levels of Cumulative Support from Studies of Vulnerability to Substance Dependence and Related Heritable Phenotypes

One of the cell-adhesion molecules that achieves the most striking nominal *P*-values in these analyses is an “atypical” member of the cadherin gene family, CDH13. Cadherin 13 is a GPI-anchored cell-adhesion molecule. CDH13 is expressed in neurons in brain regions that are likely to play roles in addiction, including the hippocampus, frontal cortex, and ventral midbrain (Takeuchi et al., 2000). CDH13 can inhibit neurite extension from select neuron populations (Fredette et al., 1996; Takeuchi et al., 2000) and activate a number of signaling pathways (Kipmen-Korgun et al., 2005; Philippova et al., 2005; Hug et al., 2004; Ivanov et al., 2001). It is thus a strong candidate for roles in brain mechanisms important for both developing and quitting addictions.

DSCAM is a single-transmembrane-domain cell-adhesion molecule with immunoglobulin and fibronectin domains that is expressed strongly in the brain (Yamakawa et al., 1998; Barlow et al., 2001) and in the hippocampus in ways that are required for appropriate neuronal connections to form in memory-associated circuits in model organisms (Chen et al., 2006; Keene et al., 2006). Different dendritic processes of the same neuron do not often cross each other; this self-avoidance mechanism depends on the expression of a large array of tightly regulated DSCAM isoforms (Wojtowicz et al., 2007; Gao, 2007). Simplifying this repertoire substantially disrupts the appropriate formation of neuronal networks *in vivo* (Hattori et al., 2007). Indeed, flies with altered DSCAM expression display altered memories for both rewarded and punished behaviors (Keene et al., 2006).

DAB1 interacts with, and participates in, signaling from several cell-adhesion molecules. DAB1 has long been identified with signaling through the cell-adhesion molecule, reelin, in ways that alter the formation and maintenance of neuronal processes (MacLaurin et al., 2007). More recent evidence also supports roles for DAB1 in signaling through other cell-adhesion or -regulatory mechanisms, including those that utilize the amyloid precursor protein cell-adhesion molecule (Young-Pearse et al., 2007). DAB1 expression in many brain neurons includes those in the hippocampus and mid- to deep cerebral cortical layers (Lein et al., 2007) (http://brain-map.org). Mice with DAB1 disruption display substantial alterations in cerebral cortical development accompanied by gross motor and other behavioral phenotypes (Sheldon et al., 1997).

CSMD1 is substantially expressed in adult brain regions that include the hippocampus (Kraus et al., 2006). High levels of CSMD1 expression in the growth cones of neurons cultured from developing brain support substantial roles in development as well (Kraus et

al., 2006). Less striking levels of evidence implicate variants in CSMD family members CSMD2 and CSMD3 in several of these brain-related phenotypes (Lau & Scholnick, 2003).

Potential Roles for Cell-Adhesion–Related Genes—The cell-adhesion genes identified here provide an attractive way to bridge the gap between 1) the remarkable observed overlap between the molecular genetics of the clinical and cognitive phenotypes reviewed here and 2) the brain differences, especially those that might manifest in the quantity and/or quality of neuronal connections, which might underlie these shared heritable influences.

DIRECTIONS, SUMMARY, AND CONCLUSIONS

It is an exciting time to be able to summarize and review the rapidly emerging data on the complex genetics of human addiction vulnerability and of related phenotypes. Genomewide association results for dependence on several different classes of addictive substances converge with each other in striking fashion that is highly unlikely to be due to chance (summarized in Table 1). Studies of dependence phenotypes in samples of individuals from several different racial and ethnic backgrounds support the idea that many of the allelic variants that predispose to these common disorders are so evolutionarily old that they are present in members of each major current human population. These data, combined with the varying results from linkage-based studies, fit a genetic architecture for addiction that is based on polygenic contributions from common allelic variants. Such a genetic architecture is quite consistent with data from family, adoption, and twin classical genetic studies.

The identification of genes with markers whose allelic frequencies distinguish addicts of several different ethnicities from matched controls supports “common disease/common allele” genetic architecture (Miller & Marshall, 2005) for much of addiction vulnerability. The convergent data derived from studies of individuals with addictions to substances in several different pharmacological classes support the idea that “higher order pharmacogenomic/pharmacogenetic” variations enhance vulnerability to many addictions. These results do not exclude additional contributions to addiction vulnerability from genomic variants that influence vulnerability to specific substances or variants that are found only in specific populations. Nevertheless, the findings presented here provide promise for enhancing the understanding of features that are common to human addictions in ways that could facilitate efforts to personalize prevention and treatment strategies for debilitating addictive disorders.

Identification of addiction-associated variants in genes that are likely to alter the quality of brain connections provides a first step toward defining a new neurobiology for the underpinnings of specific diseases and phenotypes. For many of these diseases and phenotypes, only little current research focuses on the direct study of brain connections. The “connectivity constellation” concepts that we introduce here support studies that develop and use current and novel means for assessing the qualities and quantities of brain connections, especially in contexts in which they assess their functional properties. We have identified contributions of connectivity constellation genes to volumes of the same brain regions in which many of these genes are expressed. This convergence may provide new insights into

data that document individual differences in frontal lobe volume and/or in function, detected by volumetric, deoxyglucose PET and/or fMRI imaging, for virtually all of the “connectivity constellation” phenotypes or disorders noted here (Seshadri et al., 2007; Carmelli et al., 2002).

This work, taken together, supports the idea that the heritable brain bases for individual differences in addiction vulnerability lie squarely in the midst of the repertoire of common complex determinants of individual differences that are manifest in many heritable complex brain disorders and phenotypes. Such conclusions place the biology of addictions squarely in the midst of important biologies of a number of brain phenotypes and disorders, hopefully in ways that will benefit them all.

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Table 1

Summary of Source Data[a]

Sample	Description	References
1	European-American polysubstance abusers and controls	(Smith et al., 1992; Persico et al., 1996; Uhl et al., 2001; Liu et al., 2006, 2005)
2	African-American polysubstance abusers and controls	(Smith et al., 1992; Persico et al., 1996; Uhl et al., 2001; Liu et al., 2006, 2005)
3	European-American alcohol dependent and control (COGA)	(Johnson et al., 2006)
4	Taiwanese methamphetamine dependent vs. control	(Uhl et al., 2008b)
5	JGIDA Japanese methamphetamine dependent vs. control	(Uhl et al., 2008b)
6	Australian-European and U.S. dependent vs. nondependent smokers	(Bierut et al., 2007)
7	WTCCC bipolar disease vs. control	(WellcomeTrustConsortium, 2007)
8	Bipolar vs. control: NIMH Genetics Initiative (http://nimhgenetics.org)	(Baum et al., 2007)
9	German bipolar vs. control	(Baum et al., 2007)
10	U.S. and UK bipolar vs. control	(Sklar et al., 2008)
11	Unrelated members of NHLBI twin pairs—frontal brain volume	(Uhl et al., 2008, in review)
12	Framingham study participants for assessment of frontal brain volume	(Seshadri et al., 2007)
13	European-American smokers who successfully vs. unsuccessfully quit smoking in trials in Philadelphia, Washington, DC, and Buffalo, New York	(Lerman et al., 2006; David et al., 2007)
14	European-American smokers who successfully vs. unsuccessfully quit smoking in trials in North Carolina	(Rose et al., 1998)
15	European-American smokers who successfully vs. unsuccessfully quit smoking in trials in Rhode Island	(David et al., 2005)
16	African-American individuals with levels of general cognitive ability as assessed by the Shipley Institute of Living scale	(Uhl et al., 2008, in press)
17	Replicate of sample 15	
18	Alzheimer's disease vs. control: brain donors	(Coon et al., 2007)
19	Alzheimer's disease vs. control: memory clinic participants	(Li et al., 2007)
20	Individuals with scores on tests of neuroticism	(Shifman et al., 2008)

[a] From Uhl et al., 2008a.

Table 2

"Cell-Adhesion–Related" Genes Identified in Multiple Genomewide Association Studies of Addiction and Related Disorders[a]

Gene	Description	Chr	bp	*P*-value
BAI3	Brain-specific angiogenesis inhibitor 3	6	69404158	<0.00001
CDH13	Cadherin 13	16	81218079	<0.00001
CLSTN2	Calsyntenin 2	3	141136897	<0.00001
CNTNAP2	Contactin-associated protein-like 2	7	145444386	<0.00001
CSMD1	CUB and Sushi multiple domains 1	8	2782789	<0.00001
CTNNA2	Catenin α 2	2	79593634	<0.00001
DAB1	Disabled homolog 1	1	57236167	<0.00001
DSCAM	Down syndrome cell-adhesion molecule	21	40306213	<0.00001
NRXN1	Neurexin 1	2	50000992	<0.00001
PTPRD	Receptor protein tyrosine phosphatase D	9	8307268	<0.00001
SGCZ	Sarcoglycan zeta	8	13991744	<0.00001
ASTN2	Astrotactin 2	9	118227328	0.000070
CNTN4	Contactin 4	3	2117247	0.000110
CNTN6	Contactin 6	3	1109629	0.000120
LRP1B	Low-density lipoprotein-related protein 1B	2	140705466	0.000150
NRG1	Neuregulin 1	8	32525295	0.000240
ITGB8	Integrin β 8	7	20337250	0.000260
PTPRM	Receptor protein tyrosine phosphatase M	18	7557817	0.000290
ROR1	Receptor tyrosine kinase-like orphan rec 1	1	64012302	0.000290
TRIO	Triple functional domain/PTPRF interact	5	14196829	0.000690
CSMD2	CUB and Sushi multiple domains 2	1	33752196	0.000830
CNTN5	Contactin 5	11	98397081	0.000980
CTNNA3	Catenin α 3	10	67349937	0.001090
LRRN6C	Leucine-rich repeat neuronal 6C	9	27938528	0.001340
CTNND2	Catenin δ 2	5	11024952	0.003270
ANKS1B	Ankyrin repeat sterile α domain 1B	12	97653202	0.003410
SEMA3C	Semaphorin 3C	7	80209790	0.006310

Columns list gene symbol, gene description, chromosome, base pair of gene start, and overall *P*-value for this gene in this entire dataset (described in Uhl et al., 2008a), based on 100,000 Monte Carlo simulation trials.

[a]Modified from Uhl et al., 2008a.

Table 3

Summary of Gene Classes[a]

Functional gene class	Genes identified
Cell-adhesion related	13
DNA/RNA handling	7
Enzyme	15
Ligand	1
Protein handling/modification	10
Receptor	10
Signaling	4
Structure	15
Transcription regulation	9
Transport	7
Unknown	13

[a]Identified in Uhl et al., 2008a and Drgon et al., 2008, manuscript in preparation.