Introduction: Addiction, genetics, and the disease model

Addiction is both economically costly and contributes significantly to excess morbidity and mortality (see e.g., Merikangas and Risch, 2003). Although estimates of the total costs of addictive behaviors are by necessity imprecise and subject to much debate, in the United States alone, estimates of economic costs of around half a trillion dollars a year are frequently cited (see Rice, 1999), along with more than half a million excess deaths in the United States per year (see, e.g., Minino and Smith, 2001; MMWR, 2008).

Given these high costs, and the difficulties in successfully treating addictions (see, e.g., Sellman, 2009 and citations therein), there is obvious interest in learning more about the etiology of addiction, with the aim of reducing the costs – both in terms of human suffering and financial costs – of addiction. Studies of the genetic contributions and/or susceptibility to addiction are usually framed as part of this project of ameliorating the costs of addiction. The idea is that if the underlying genetic factors associated with addictive behaviors can be elucidated, then targeted interventions (such as individually tailored pharmaceuticals and/or more focused psychological/therapeutic help) might provide a low(er) cost method of reducing the frequency and impact of addictive behaviors. Alternatively, broad population screening might permit people with particular susceptibilities to addictive behaviors or to particular kinds of addiction (e.g., alcohol) to be warned of their particular risk, and to change their behaviors accordingly. The following examples are illustrative of the tone of much published research on this topic.

Understanding the genetic basis of alcoholism is a crucial step for the development of efficient prevention strategies and personalized treatments. For this purpose, it is important to identify genes predisposing individuals to alcoholism, genes moderating consequences of alcohol exposure, clinical course and treatment response, mechanisms through which genes exert their effects on behavior and interactions of genes with other genes and with environmental factors. (Ducci and Goldman, 2008)

Employing the power of genetic studies … will enhance research on etiology, treatment, and prevention for these complex diseases. (Berrettini et al., 2004)

[The] public health impact of gene discovery for the addictions is potentially very large … this goal [the integration of genotypes into diagnosis] is particularly timely given the enormous public health impact of addictions and the potential power of precisely and inexpensively defined genotypes associated with these heritable diseases. (Goldman et al., 2005)
Of course, understanding vulnerability can lead to the best possible 'treatment', which is prevention of the development of addictive disorders... the role of genes is unfolding and should influence the development of more effective biological treatments... In the area of addiction we have already begun to knock on the door of genomic medicine... Systematic probing as discussed by Schumann using animal models, genetics, brain imaging and other measures may well allow us to predict in advance which patients are most likely to respond to which treatment. (O’Brien, 2007)

As the above suggest, much of the contemporary research into the genetics of addiction/addictive behaviors has focused on attempting to understand individual variation in addiction or susceptibility to addiction or addictive behaviors. That is, the research has focused on which distinct features of this person, or this person’s experiences, led him or her to become an addict. Why, in other words, did this person and not that person become addicted? What risk factors account for some people becoming addicts rather than others? What identifies people at high risk for being addicts? Research into the genetics of addiction generally attempts to answer this question by finding genetic correlates to addiction and/or addictive behaviors – that is, by finding alleles (variants of genes) that are more common in addicts than in nonaddicts, and, ideally, by finding plausible biochemical pathways that would result in these different alleles being associated with different risks of addiction.

While there are technical and ethical challenges to both conducting such research and interpreting the results of that research (for a discussion, see Kaplan, 2006; see Munafò, 2009b for discussion of addiction research in particular; see Ioannidis et al., 2001 for a review of the difficulties inherent in genetic association studies more generally), it is rather the stated goals of genomic approaches to understanding addiction, and the difficulties that these approaches have in achieving those goals, on which this chapter will focus. The difficulty is that there is a disconnection between studying the causes of individual variation in addiction (which particular risk factors are associated with this person and not that person becoming an addict) and working to reduce the harms associated with addiction. Seriously reducing the economic costs and human suffering associated with addiction probably requires more than an attention to the details of individual addicts or to those people particularly susceptible to addiction. Indeed, it is likely that an attention to this kind of individual variation – including genetic variation – can have at best a relatively minor impact on the overall costs, both economic and health-related, of addiction and addictive behaviors.

In fact, seriously reducing the costs associated with addiction probably requires attention to the broader social environment in which addiction takes place. Both rates of addiction and the harms associated with addiction vary significantly between social environments – for example, there is substantial variation in the rates of addiction and the associated harms between different countries, between locales within countries (including rural/urban divides), and between racial/ethnic groups. Rather than looking for the correlates to addiction within a particular social environment (within a particular country or locale, for example), looking toward the differences that emerge in different social environments – that is, the differences between populations – might well reveal the causes of the differences in rates and costs of addiction between those social environments. Often, this kind of analysis reveals that attempting to modify the broad social environment has more potential for harm and cost reduction than does a focus on high-risk individuals within a particular social environment (see below and Rose, 1985).

However, the difficulty with interventions aimed at population differences is that they require a kind of “political will” that is strikingly absent from current social and political
policymaking and discourse. The kinds of changes that a focus on between-population variation suggests often include public policies that influence the costs and availability of particular substances (e.g., cigarettes, alcohol), or activities (gambling); in many cases, entrenched industry interests and extant taxation schemes make serious changes to these policies difficult to implement. Perhaps even more problematically, between-population variation is often associated with such seemingly intractable social and political issues as poverty/deprivation, income distribution, and social opportunities. Although it might be true that one reason to oppose, for example, tax policies that result in more unequal distributions of income and wealth is that such unequal income and wealth distributions are associated with higher addiction rates and costs (see below), it would seem that in the United States the political will is missing even to think seriously about addressing these kinds of inequality.

Given this, there are reasons to worry that genetic research into addiction susceptibility might result in an increased focus on the individual as the proper locus of research, and that the “cause” of addiction might come to be increasingly seen as something internal to the individual addicts. Indeed, in this sense, the move toward explanations of addiction at the genetic level might be seen as an extension of the disease model of addiction and addictive behavior (see Edwards, 2010 for a discussion). While the disease model itself has had a tendency to shift the focus to the individual, the search for “susceptibility” genes suggests a move to treating addiction as a genetic disease, and hence a disease with roots internal to the individual and ever less connected to the social environment.

It is likely that researchers into the genetics of individual variations in addiction susceptibility are being sincere when they state that one of their goals is to find ways of ameliorating the suffering associated with addiction. But as a way of addressing that suffering, an approach that focuses on the causes of individual variation within a social environment is rather weak. More worrisome, such research is not only likely to fail to seriously reduce the harms associated with addiction, but it is likely to keep the focus of policy discussions and decision making on the individual addicts themselves. By focusing on the individual variations, these approaches provide a way of shifting blame back to the individual addicts. Even if the addicts’ genes make them more susceptible, by locating the causes of their addictions within the bodies of the addicts themselves, these approaches keep the focus on the individuals and away from the broader social environment. If the social environment is not a locus of explanation, changes in the social environment that might be efficacious will not even be considered: the focus will stay from the broad social and political policy choices that get made and create the environments in which addiction and its associated harms take place. Although it might, in the end, be politically impossible to shift US policy to one that favors more economic equality, for example, if the broad risks associated with the current policy remain hidden (behind discoveries centered on individual variation), the discussion itself becomes impossible.

**Explaining human behaviors: Addiction as an example**

There are multiple different questions that can be asked about any biological trait, including the behaviors of biological entities. If asked “what explains this trait?” the answer will depend on exactly what is about the trait one wants explained. The options include at least the following:

1. **Ontogeny:** How does the trait develop? That is: How does the trait in question arise in the development of the individual organism? Developmental accounts can include, for
example, analyses of cell differentiation and the genetic pathways employed, as well as following particular kinds of environmental inputs.

(2) Phylogeny: What explains the presence of the trait in the population (at whatever level it is present)? Historically, how did the trait first emerge, how and why did it spread in the population, and, if it is being actively maintained in population now, what is the mechanism that is maintaining it? These accounts are evolutionary in nature – they attempt to explain, from the perspective of the evolutionary history of the type of organisms, how the traits in question came to be. Sometimes this will involve selective accounts (fitness variations), sometimes it will involve “phylogenetic inertia,” sometimes drift, etc.

(3) Individual variation: If the trait varies between individuals within a population, what explains the variability of the trait in that population? Why do different individuals have different versions of the trait, or why do some individuals have the trait and not others? Generally speaking, many if – not most – analyses of individual variation within a population approach the question via an “analysis of variance” and attempt to partition the variation in the population between potential variables causally associated with that variation (often these causes are roughly divided into genetic, environmental, and interactive causes of various sorts). For example, in humans, most variation in eye color is the result of genetic variation, whereas most variation in finger number is the result of environmental variation (traumatic amputations account for most of the variation in finger number in humans!).

(4) Population variation: If the frequency or form of the trait varies between populations, what explains the variation of that trait between populations? Why do different populations, for example, have different proportions of individuals that have the trait in question, etc.? Here, the question is about why a particular trait is more common in one population than another. Again, this question is usually approached via an analysis of variance, but with the variance to be explained the variance between populations rather than individuals within a population.

Although these questions are not strictly independent of one another, each demands attention to a different (but not unique) set of variables, and to different sorts of details; in general each requires different kinds of evidence to answer. Understanding the “genetic contribution” to a trait may involve attempting to answer any (or all!) of the above questions, but what that “genetic contribution” involves, and how it can be tested or explored, is often very different. In Box 14.1, these four questions are explored for two different traits: lactase persistence and nicotine addiction. Lactase persistence is a fairly-well-understood trait – in some populations (those with a history of dairy farming), lactase continues to be produced after infancy, permitting the digestion of lactose (in milk). Most mammals cannot effectively digest milk after infancy, and the nonpersistence of lactase was the “original” state for humans; lactase persistence became prevalent in some populations because it is confers a strong selective advantage. The details in the case of nicotine addiction remain less well established, but nevertheless separating out the different questions provides a sense of the diversity of possible approaches to the seemingly straightforward question “What explains nicotine addiction?”

Much of the current genomic research into addictions has focused on individual variation (mainly trying to answer the third kind of question noted above). By contrast, much of the extensive work into the neurobiology of addiction and addictive behaviors has focused
## Box 14.1 Different questions, different fields, different evidence: Two examples

<table>
<thead>
<tr>
<th>Questions/cases</th>
<th>Field/evidence</th>
<th>Lactase persistence*</th>
<th>Nicotine addiction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontogeny: How does the trait develop?</td>
<td>Developmental biology, including molecular and cellular biology</td>
<td>Change in the promoter region associated with gene expression keeps lactase production high throughout life.</td>
<td>Nicotine addiction develops primarily with self-administration of nicotine, via the effects of nicotine on the (evolutionarily highly conserved) nicotinic acetylcholine receptors (nAChRs).</td>
</tr>
<tr>
<td>Phylogeny: What explains the presence of the trait in the population (at whatever level it is present)?</td>
<td>Evolutionary biology; analysis of related species, fitness consequences of the trait in various environments, etc.</td>
<td>History of dairy farming. Populations with a history of dairy farming acquired lactase persistence because of the adaptive advantages of being able to consume dairy foods. It is maintained in populations that consume dairy owing to its continued adaptive significance (different populations have different mutations associated with continued gene expression, revealing that the trait arose independently multiple times in different populations).</td>
<td>The nAChRs are part of a highly conserved (ancient) variant of receptors involved in neurotransmission. The nAChRs play functional roles in various tissues in organisms in the Bilateria phylum. Given this, addiction to nicotine can occur with exposure to (self-administered) nicotine, with tobacco use being the primary mechanism in humans.</td>
</tr>
<tr>
<td>Individual variation: If the trait varies between individuals within a population, what explains the variability of the trait in that population?</td>
<td>Analysis of variance, quantitative genetics, developmental biology, environmental field work (including, e.g., sociology in humans), ethology</td>
<td>Individual variation in lactose tolerance (lactase persistence) within populations tends to be the result of recent migration from other populations. There is some variation within populations due to mutation, etc., but it is not highly significant.</td>
<td>Within different populations, different factors are associated with the probability of an individual’s smoking and becoming addicted to nicotine; these include gender, socioeconomic status, etc. In addition to environmental influences, there is some evidence that different variants of the nAChRs may play a role, and there is the possibility of other sorts of genetic variations (say, those associated with impulse control in particular environments, etc.) playing a role as well.</td>
</tr>
</tbody>
</table>
Box 14.1 (cont.)

<table>
<thead>
<tr>
<th>Questions/cases</th>
<th>Field/evidence</th>
<th>Lactase persistencea</th>
<th>Nicotine addictionb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population variation: Why do different populations have different proportions of individuals that have the trait in question, for example?</td>
<td>Population genetics, environmental field work, ethology, evolutionary biology including fitness differences associated with different environments, etc.</td>
<td>Rates of lactase persistence vary substantially between populations, based on whether that population has an (evolutionary) history of dairy farming.</td>
<td>Broadly environmental/social factors, such as tobacco accessibility (including price), social acceptability of smoking, etc., account for much of the variation. Although it is possible that genetic differences between populations might contribute to the different rates of addiction, it seems unlikely that this is a major factor in the different population rates.</td>
</tr>
</tbody>
</table>

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*See, e.g., Ingram and Swallow, 2007; Ingram et al., 2009.  
b See, e.g., Mineur and Picciotto, 2008; Benowitz, 2010.

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Box 14.2 Epigenetic mechanisms and addiction/addictive behaviors

“Epigenetics,” in its most general sense, refers to heritable nongenetic variation; more often, it is used to refer to heritable changes in gene expression. The two most commonly cited examples are DNA methylation and changes in the chromatin structure. The addition (or removal) of methyl groups to DNA modifies gene expression (generally, but always, methylated genes are “downregulated” or silenced); these changes can be environmentally caused and are partially heritable. Similarly, modifications to the chromatin structure (the physical structure of the DNA and associated proteins) can influence which genes are accessible for transcription and are (partially) heritable. (See Rakyan and Beck, 2006 and citations therein for a review.)

Epigenetic changes can therefore be a part of answering questions about the ontogeny of traits (the first question noted above — how a particular trait develops in an individual organism) as well as the about the causes of individual variations in traits (the third question noted above); indeed, in some cases, epigenetic variation might even be part of addressing variation between populations (the fourth question noted above), and might be implicated in certain selective scenarios (and hence relevant to the phylogeny of traits!).

If addiction can modify gene expression, either through modifying methylation or chromatin structure, those changes might explain the stability of addiction (how difficult it is to change addiction/addictive behaviors; see, e.g., Holder, 2009; Sellman, 2009) and the heritability of addiction (see, e.g., Ball, 2007; Agrawal and Lynskey, 2008). There is some compelling evidence that epigenetic effects are implicated in the first of these, but evidence for the second remains merely suggestive. (See Renthal and Nestler, 2008 and citations therein for reviews.) Nevertheless, the possibility of epigenetic inheritance in the case of addiction should not be dismissed.
on the development of addiction (the first kind of question noted above). Although research into the neurobiology of addiction has led to fascinating insights, it is also, as Kalant notes, unlikely to be of much help elucidating the unique nature of addiction (as opposed to, e.g., nonaddictive drug dependence) (Kalant, 2010; see also Carter and Hall, 2010). The mechanisms underlying the neurobiology of addiction would seem to be diverse and ubiquitous, involved in many “normal” functions as well as addiction (Kalant, 2010; for a summary of some of the diverse functions of nicotinic acetylcholine receptors, see Egleton et al., 2008 and citations therein). Likewise, we should expect that the genes involved in those processes are similarly diverse in both their form and their expression. Although there are some promising early results on changes in gene expression associated with addiction/addictive behaviors (see Box 14.2), these have yet to garner significant public attention. In both cases, the failure of these research programs to capture the public attention probably emerges from their addressing a variant of the question “What explains addiction?,” which is perceived to be less exciting than explanations that address the causes of individual variation. They do not, in other words, address the kinds of individual risk factors that the public has some to expect from “explanations” of human behavior genetics, or from human epidemiology more generally.

Instead, significant public attention accrues primarily to research associated with explaining individual variations in addiction/addictive behavior; this is true both of genes that are supposed to predispose one to becoming addicted to particular substances and genes that are supposed to predispose one to addictions more generally. For example, consider the following newspaper and magazine headlines:

“Gene linked to addiction, cancer.” (Sydney Morning Herald, 2008)
“Gene glitch tied to youth smoking addiction.” (Fox News, 2004)
“Genes influence smoking addiction: study.” (ABC Science, 2010)
“Coffee addiction ‘in your genes.’” (Briggs, 2011)
“Addictive personality? You might be a leader.” (Linden, 2011)
“Marijuana, alcohol addiction may share genes” (Thomas, 2009)
“Drug addiction could be down to your genes.” (Highfield, 2007)
“Gene may protect against alcoholism” (Los Angeles Times, 2010)

In each case, the focus is on explaining why some individuals, but not others, are addicts. In some cases, the issue is a specific substance and a specific gene somehow associated with this substance. For example, the article “Gene glitch tied to youth smoking addiction” states that the risk of addiction was “especially high for those [seventh graders] with an inactive CYP2A6 gene” and that this may be because the inactive version of the gene makes “people more vulnerable to nicotine” (Fox News, 2004). The article claiming that coffee addiction is “in your genes” states that “genetic factors could explain why some people consume large amounts of coffee” and that the “two stretches of DNA linked with high caffeine consumption contain two genes thought highly likely to be involved in the way the body processes caffeine” (Briggs, 2011, reporting for the BBC). In other cases, the claims surround not genes specifically involved with particular substances, but rather with personality traits (or general biological pathways) that predispose one to addiction more generally. So for example, the article “Addictive personality? You might be a leader” posits that genetic factors are associated with being a “compulsive risk taker” and with “a high degree of novelty-seeking behavior” may partially account for both one’s risk of addiction and for behavioral traits
associated with engaging in successful high-risk work (Linden, 2011, reporting for the *New York Times*).

Of course, addiction to particular substances is impossible in the absence of the substance; addiction, by its very nature, depends on the environmental availability of the stimulus. But as Lachman (2006) notes, most people who try particular addictive substances or activities do not become dependent: “although initial use of an addictive substance is a necessary step in the development of dependence, clearly such use is not sufficient to cause it” (Lachman, 2006: 134). Lachman asks “what converts a casual drug or alcohol user into an addict, or an occasional gambler into a compulsive one?” This question might be about the mechanisms that underlie addiction in general – one might be asking which developmental processes are associated with people becoming addicts. The difference between addicts and nonaddicts would be cashed out in terms of the particular processes they have undergone, rather than in terms of their preexisting risks. This would focus attention on the first and second questions noted above – on ontogeny and phylogeny. But Lachman’s approach to this question instead moves in a very different direction; Lachman notes that a “substantial body of evidence from family, twin, and adoption studies indicates that a genetic component underlies all addiction disorders” (Lachman, 2006: 134), and proceeds to place his focus directly back on attempts to explain individual variations. This is the approach taken by most review articles on the genetics of addiction, as well: the focus is always on the question of individual variation (see, e.g., Agrawal and Lynskey, 2008; Ball, 2007). The interest is in individual variation within a particular social environment rather than on the way the trait develops or on the ways in which the trait varies between populations.

The focus on explanations for individual variations within particular (social) environments is hardly unique to research on addiction genetics, or addiction more generally. Indeed, the same pattern can be seen in research into other human behaviors generally seen as troublesome, or even as merely interesting. Longino, for example, has explored the different levels of “uptake,” in both the popular media and in further research publications that different kinds of explanatory projects wrapped up in human behavior receive. She notes that research privileging explanations that focus on *individual differences* (rather than *population differences*) tends to get more uptake in the media (Longino, in press; see also Longino, 2003), and further, that genetic research is seen as advancing the goal of explaining (and, eventually, manipulating) those differences. So for example, she writes that in the popular media “biologically/genetically oriented research [is] represented as eventually producing results, in contrast to environmental research [which is] represented as terminally inconclusive” and that any criticism of the claims made regarding genes “is presented as but a tempering of claims, rather than as representing an alternative framework for research” (Longino, in press). Longino argues that researchers interested in the genetics of behavior tend to conceptualized behavior “as individual behavior” and take “difference and variation among individuals” as their explanatory target, with “research focused on population/ecological issues” making “no appearance” (Longino, in press).

So for example, research into the biological and genetic correlates to individual variation in violence/violent behavior has historically had, and continues to have, more “uptake” in both the popular press and the academic literatures than has research into the broader social correlates to violent and violent behavior. Consider, for example, Caspi’s (2002) work on gene-by-environment interactions in the production of violent behavior. Famously, Caspi et al. found that male children born with one variant of the MAOA gene (more precisely, the shorter rather than longer promoter region) had a higher risk of committing violent crimes
as adults, but only if they also grew up in households with significant violence (households with serious domestic violence) (Caspi et al., 2002). Children with the short version of the promoter were not at higher risk if their households were not violent. Children with either version were at higher risk in violent households than in nonviolent households, but the risk was much greater for children with the short version. Headlines reporting this research ranged from the relatively cautious “Scientists identify gene that may trigger violence in abused children,” to the rather bolder “Genetic link to cycle of violence identified,” through to the rather absurd “Beware the aggression gene” (Milwaukee Journal Sentinel, 2002).

But while many of these sources dutifully reported that the small fraction (about 12%) of men in the study who had both the short MAOA gene variant and a history of abuse as children were responsible for almost half of the violent crimes, the disparity between the levels of violent crimes cross-culturally (and especially cross-nationally) was less well reported (see below for more on this issue). This is not surprising; Caspi et al. ended their article with the claim that their “findings could inform the development of future pharmacological treatments” (Caspi et al., 2002: 853). Whereas Caspi et al. were ostensibly focused on the ways that different genes interacted with different environments in the production of human behaviors, the focus shifts rapidly to biochemical intervention and away from environmental intervention. As Longino notes, despite Caspi et al.’s research’s supposed focus on “integrative” biology and the interaction between genes and environment, in fact the model they offer “is treated as an insight into how a specific gene works” rather than as the beginning of a truly integrative approach to the development of particular traits (Longino, in press).

**Changing behaviors: Individuals and populations in the modification of human behaviors**

For studies of human behaviors that are subject to social disapproval, the companion to explaining the behaviors in question is controlling them. And indeed, both research articles and media reports on the genetics of addictive behaviors follow this pattern; explaining addiction is seen as the first step in preventing or curing addiction. From research articles, claims like the following are common:

An increased understanding of the mechanisms of nicotine addiction has led to the development of novel medications (e.g., varenicline) that act on specific nicotinic receptor subtypes. The development of other drugs that act on nicotinic receptors and other mediators of nicotine addiction is likely to further enhance the effectiveness of smoking-cessation pharmacotherapy. (Benowitz, 2010)

Applied genomic research has a role to play in … [identifying] biologic targets for intervention such as drugs and vaccines. Although most clinical applications of genomics are not ready for widespread use, there is an increasing need to develop, evaluate, and integrate genomic tools into clinical and public health research. (Khoury et al., 2005)

Future [addiction] research must also find a role for genotypes, either as guides to new therapeutic targets or as predictors for treatment and prevention, in natural populations of patients and individuals at risk where the efficacy of new tools can objectively be defined and integrated into multidimensional management. (Goldman et al., 2005)

In these cases, the expressed hope is that research that attempts to explain the individual variations in addiction (why some people become addicts and not others) will also be useful for developing interventions that can be applied in individual cases. This line is followed in the news media as well. For example, in a 2007 article in *The Telegraph*, Highfield reports that Dalley said of his research into the genetics of traits that predispose one to addiction that
Section 3: Translating addiction research

it “may provide important new leads in the search for improved therapies for compulsive brain disorders” (Highfield, 2007). And, capitalizing on the idea that knowing one’s risk of acquiring an addiction might change one’s behaviors, Roan argued, in an article in the *Los Angeles Times*, that genes associated with variations in alcohol metabolism “might be used in the future to give people, especially young people who have not yet started to drink, an idea of their odds of developing alcohol problems” (Roan, 2010).

In “Do we need genomic research for the prevention of common diseases with environmental causes?” Khoury et al. (2005) argue that although population-based approaches aimed at modifying the environmental risk factors for common diseases might be effective, this focus should not detract from a focus on individual treatment. They write for example that “although we know that smoking and drugs cause disease, they also cause addiction, undermining interventions focused exclusively on the causative environmental agents … new knowledge derived from applied genomic research could lead to new pharmacologic and behavioral methods of combating addiction to tobacco and drugs” (Khoury et al., 2005: 800).

Over a quarter of a century ago, Rose argued that strategies to address population health were likely to be very different than those that addressed individual health, and that population-based approaches had the potential to impact population health in ways that individual approaches could not (Rose, 1985). Khoury et al acknowledge Rose’s basic point, but argue that “both high-risk approaches to prevention (those targeted toward high-risk subgroups) and population approaches to prevention will be needed” to address common diseases, and that since “individual” and “population” approaches are not in competition, “we should strive to develop, validate, and integrate applied genomic tools in our public health research agenda” (Khoury et al., 2005: 804). But this misses what Rose regarded as the “radical” aspect of a population focus – namely, that by focusing on between rather than within population variation, far more variability is revealed. Rose writes that:

> There is hardly a disease whose incidence rate does not vary widely, either over time or between populations at the same time. This means that these causes of incidence rates, unknown though they are, are not inevitable. It is possible to live without them, and if we knew what they were it might be possible to control them. (Rose, 1985: 34)

Although the ostensible focus of Khoury et al. is, again, the need for an integrative approach, the focus remains on variations within particular cultures, and on high-risk individuals and high-risk environments. There may be no in principle competition between those approaches focused on individual risk and those approaches focused on the variations in population-level incidence, but in practice the individual-based approach easily becomes the “default” in these cases.

Consider again the claim by Caspi et al. noted above, that their findings regarding the interaction between abusive home environments and particular alleles in the production of violent adults “could inform the development of future pharmacological treatments” (Caspi et al., 2002: 853). Perhaps it could. But the idea of identifying high-risk children – those with both the shorter MAOA promoter variant and who are exposed to serious domestic abuse in their homes – and addressing that risk by drugging the children seems, on the face of it, insane. Given that whichever gene variant the children had, being exposed to serious domestic abuse raised the probability of their becoming violent adults, ‘treating’ the problem by changing the MAOA levels would have less of an impact, ceteris paribus, than changing...
the level of violence in the household. And of course, preventing domestic violence is a worthy goal whatever effects it has on the children’s chances of becoming violent adults!

Even leaving aside Caspi et al.’s particular findings and recommendations, the focus on the individual as the locus of intervention would seem to be, in the case of violence, deeply and obviously misguided. The refrain from researchers into the biological correlates of violence is that, cross-cultural, a small fraction (6–12%) of the young men commit a large fraction (50–70%) of the violent crimes; but while that may be true, the rates of violent crime vary between cultures by more than an order of magnitude. (For a discussion, see Kaplan, 2007 and citations therein). Consider, for example, the difference in violent crime rate between the countries of southern Africa (with over 30 homicides per 100,000 per year) and those in western Europe (with less than 3 homicides per 100,000 per year) (see GBAV, 2008). Surely, if one is interested in ameliorating the burdens associated with violent crime, these profound differences in rates between cultures represents a greater potential source of change than does a focus on some large set of supposedly high-risk individuals (this, again, is what Rose refers to as the “radical” aspect of population health; Rose, 1985).

It is reasonable to suggest that the case is similar for addiction. For example, rates of nicotine addiction follow (roughly) the rates of smoking, and as the percentage of smokers in the population drops, so too do the number of addicted smokers. In the United States, the prevalence of smoking dropped from a high of over 40% in 1965 to around 20% in 2010 (see Levy et al., 2010: 1253), and the average number of cigarettes smoked per person per year dropped from a high of over 4300 per person in the mid-1960s to around 2300 per person by 1999 (Gale et al., 2010); it goes without saying, one hopes, that the distribution of genes associated with nicotine addiction did not change that rapidly in the United States. Higher cigarette prices (via taxation), changing media messages, and “clean air laws” (smoking ban in workplaces and other public areas), resulted in fewer people initiating smoking, more people trying to quit, and in smokers reducing the average number of cigarettes smoked per day. There are good reasons to think that further reductions in smoking (and nicotine addiction) rates could be achieved with further population-based policy changes along the same lines (see Levy et al., 2007 and citations therein), independently of the genetics involved in individual variation.

More generally, rates of addiction vary with socioeconomic status (within societies) and with the overall degree of social inequality within a society (between societies). People who are at the lower end of the socioeconomic scale are more likely to be addicts (more likely to be addicted smokers, illegal drug users, problem gamblers, etc.) than people at the upper ends of the socioeconomic scale, and people within societies that are more unequal are more likely to be addicts than people who live in societies that are more equal (see, e.g., Wilkinson and Marmot, 2003; Room, 2005; Baumann et al., 2007). There are two immediate lessons to be drawn from this. First, individual genotyping for addiction risk or tailored pharmaceutical intervention is unlikely to have a profound effect on addiction rates, given that the people most at risk are the least likely to be in a position to access new medical technologies. That is, as the poor within a society are generally the least likely to have access to the latest medical technologies, high-technology targeted approaches are most likely to miss the very people who suffer the most from addictive disorders. Second, approaches that treat the individual as the proper focus for addiction prevention and amelioration will miss those variables associated with the most dramatic differences in addiction rates. One is unlikely to pay attention to cross-cultural variability and the associated different levels of harm in different
cultures if one is focused on the causes of individual variation within particular cultures or social environments.

The individualization and internalization of addiction as disease

There is nothing inherently wrong with research that investigates individual variations in addiction; indeed, as Khoury et al. (2005) forcefully argue, research into individual variation in human behaviors can be a valuable research tool. But such research is not without its risks. A focus on what makes this individual more susceptible to addiction than that individual can make the individual out to be the (only) proper locus of explanation and intervention. If it is individuals who are at risk of addiction because of (in part) their particular genetic (and other) endowments, it is natural to focus on those “at-risk” individuals, rather than the broader social environment, when thinking about addiction.

That this kind of individualization of risk can be problematic with respect to public policy is perhaps most obviously seen in the case of gambling addiction/pathological gambling. Despite ongoing arguments regarding whether non-substance-abuse-based disorders should count as “addictions” (see, e.g., Petry, 2006; Potenza, 2008), studies of the genetics of gambling addiction make the same sorts of claims as studies of other addictive behaviors, both with respect to their findings and the reasons for pursuing the research. For example, Lobo and Kennedy state that “results from family and genetic investigations corroborate further the importance of understanding the biological underpinnings of PG [pathological gambling] in the development of more specific treatment and prevention strategies” (Lobo and Kennedy, 2009). Again, the focus is on individual variation – why some people but not others “exposed” to gambling develop problems (become addicted), with an emphasis on which factors internal to the person in question determine that person’s risk of being a pathological gambler.

The idea that the pathological gambler is a type of person – that one’s risk of becoming a pathological gambler is determined mainly or at least in large part by one’s particular circumstances, including one’s genetic endowments – feeds into the idea that pathological gamblers are simply an inevitable part of gambling’s existence. In an interview on 60 Minutes, Pennsylvania Governor Ed Rendell repeats the refrain that the proximity of gambling opportunities does not create new problem gamblers, and that given that problem gamblers will be problem gamblers (and lose their money) whatever Pennsylvania does, it is better that the money lost by Pennsylvanians stay in Pennsylvania. When Lesley Stahl asks him if he is concerned that the easy availability of gambling in Pennsylvania has resulted in more people becoming problem gamblers, he responds with visible annoyance that “You don’t listen. Anyone who has that bent would be doing it in other places had Pennsylvania not legalized gambling” (CBS News, 2011). This is essentially the line taken by the American Gaming Association (AGA); for example, Frank Fahrenkopf, the AGA’s President, argues that problem gamblers constitute “somewhere between 1–5% of the population” and that they are “people who can’t help themselves and will go in and gamble away their money” (Koughan, 1997). Later, Fahrenkopf takes the internalization route quite directly when he argues that “despite the exponential growth of the gaming industry during the past 30 years, the prevalence rate of pathological gambling has held steady. Approximately 1 percent of the population suffers from pathological gambling, and an additional 2 percent have problems gambling” (Fahrenkopf, 2010). If the availability of gambling created problem gamblers,
Fahrenkopf implies, the prevalence rate of pathological gambling should be increasing along with the growth of the gaming industry.

These quite plausible-sounding arguments regarding the prevalence rates suggested by Fahrenkopf and others, combined with idea that there is something about the individuals that makes those people become problem gamblers, are what allows people like Governor Rendell to claim that creating new opportunities to gamble does not create new problem gamblers, but rather simply results in problem gamblers gambling in one location (or on one kind of game) rather than another. It suggests that any attempt to address problem gambling must address those particular problem gamblers (or people at a high risk of becoming problem gamblers), because, given the impossibility of completely eliminating gambling opportunities, no other approach could reasonably be expected to reduce the prevalence of problem gambling. Of course, it also permits cities and states to support gambling as a revenue source without having to acknowledge that their actions might create problem gamblers where none were before.

This reasoning fails to take into account several lines of evidence. The prevalence of problem gambling does seem to depend critically on the availability of (particular) kinds of gambling opportunities. Perhaps the most famous example comes from the 14-week period in 1994 when video lotteries, which had been widespread, were unavailable in South Dakota (the South Dakota courts having declared them illegal), before a voter referendum reinstated them (see Carr et al., 1996). During that time, other forms of gambling remained available (“regular” lotteries, “scratch ticket” lotteries, and Native American casinos all remained legally available). However, South Dakota agencies treating problematic gambling reported a sharp drop in both inquiries and the number of gamblers actually treated during that period, with a return to higher numbers after the video lottery games were reinstated (Carr et al., 1996: 31). There is also considerable evidence that proximity to particular kinds of gambling opportunities does influence the chances that a person will engage in problematic gambling behavior and/or become a pathological gambler. The National Gambling Impact Study found that pathological gambling risk roughly doubles within 50 miles of gambling facilities, and that “some of the greatest increases in the number of problem and pathological gamblers shown in these repeated surveys came over periods of expanded gambling opportunities in the states studied” (NGIS, 1999; see also Reith and The Scottish Centre for Social Research, 2006 for similar results in the context of Scotland; on more multidimensional approaches to opportunity, see for example Thomas et al., 2011). How the results of these studies jibe, or fail to jibe, with the data on the relative stability of problem gambling rates in the United States as a whole is an interesting problem; the suggestion that the relative stability of problem gambling rates in US surveys is an artifact of the survey methodology and the ways in which the gaming industry has so far grown should not be dismissed.

It is not obvious what policy implications, if any, should be drawn from these more social (or “ecological,” see, e.g., Welte et al., 2006) accounts of gambling addiction, including the substantial evidence that gambling availability influences the rate of problem gambling. However, it is obvious that these more multidimensional accounts point toward more options for policymakers than do strictly individual accounts. If problem gambling is seen to be the result only of features internal to the problem gambler, rules limiting the kinds of gambling available and/or the locations of availability will simply not be considered; if problem gambling is considered a multidimensional problem in which particular kinds of games and availability will come together with individuals to produce particular kinds and numbers of problem gamblers, such changes will at least be seen as possible responses. Whether
modifying the availability of (kinds of) gambling opportunities would have benefits that outweigh the costs is of course debatable and, indeed, should be a matter for policymakers and public debate; however, a view of gambling addiction as caused by something *internal to the addict* cuts off that debate before it can start.

A similar scenario may be playing out now with respect to nicotine addiction. The tobacco industry, having been forced to admit to the serious health impacts of tobacco use, would seem to be poised to argue that nicotine is not addictive *per se*, but rather is only addictive for those people who are genetically predisposed to be nicotine addicts. For most people, smoking would be a "choice," but for those genetically predisposed to addiction, it would be the result of a genetic disease; in neither case would tobacco companies be to blame (or liable) for people’s smoking habits. Gundle et al. (2010) argue that as early as the mid-1970s tobacco industry public relations and legal teams had considered actively pursuing the idea that nicotine might be addictive for *some* people genetically predisposed to nicotine addiction, but nonaddictive for everyone else; Gundle et al. argue that the primary reason the tobacco industry did not actively pursue that argument was that the industry was still officially denying that nicotine was addictive *at all* and did not want to be seen to be supporting research that might undermine that official position (Gundle et al., 2010: 976–978). However, given that the addictive nature of nicotine is now well established, Gundel et al. argue that research pointing toward nicotine addiction as a feature of particular individuals with particular genetic traits, rather than a feature of the nicotine itself, could be useful to the tobacco industry for both legal defenses and, perhaps more importantly, for advertising to future smokers (Gundle et al., 2010: 979). "The tobacco industry can argue that the genetic revolution, including genetic research not funded by the industry, is confirming what they have long known: that a crucial component of nicotine addiction is genetic and that there is a small number of people who should not smoke, but for the vast majority of people cigarettes are a product that can be used in a responsible and voluntary way" (Gundle et al., 2010: 979). Genetic tests could be marketed, and the idea is that those people who are less susceptible to nicotine addiction could "safely" choose to smoke, as they would be able to control the quantity and style of their smoking, and that they would be able to quit any time they chose.

This is not a message that most researchers interested in improving public health could possibly approve of; increased rates of tobacco use would be problematic from a public health standpoint, even if those people *most* susceptible to nicotine addiction were somehow alerted to their special risk and were able to avoid smoking. Indeed, Gundle et al. argue that the "tobacco industry's agenda in promoting the notion of 'addiction-free' smokers is at odds with goals of genetic researchers who hope to understand more clearly the biology of addiction or provide new and better targeted therapies for tobacco dependence," and that research focused on finding genetic variation between individuals in how susceptible they are to nicotine addiction is in danger of being "co-opted" by the tobacco industry (Gundle et al., 2010: 979). But research that is focused on each potential smoker's individual risk, and on developing new treatments for individual smokers, is easy to co-opt. The idea behind such research, after all, is that individuals who are particularly susceptible to nicotine addiction can be targeted for particular interventions, including being warned of their particular susceptibility; those who are already addicted can be targeted with specific pharmacological treatments aimed at the particular pathways that make them addicts. In principle, this would address the goal of ameliorating the harms of smoking, a goal shared by many researchers. And of course, this position aligns nicely with a position that makes smoking – or at least
nicotine addiction – out to be a matter of factors that are internal to the addict, a view that the tobacco industry might very well find useful.

Although it might be possible to target high-risk individuals for intervention, the goal of using these screening techniques and associated interventions to actually improve population health (that is, to have a meaningful impact on the costs and harms associated with tobacco use) will remain unrealized in the vast majority of those cases in which smoking remains a major health concern. One problem is that the very people who suffer most from tobacco-related illnesses and other attendant costs are the least likely to benefit from individualized high-technological approaches; these include particular subpopulations within societies (usually the poor, but also the disenfranchised more generally) as well as, for example, developing nations. Again, one of the lessons of a public health approach to improving population health is that individual interventions aimed at “high-risk” individuals rarely have a measurable impact on population health (Rose, 1985; see Frohlich and Potvin, 2008 and citations therein for a more contemporary review). In this case, given that the people currently most at risk (Cokkinides, 2009) from smoking-related illnesses are those who are least likely to have access to personalized medicine (such as personal genetic-pharmacological and genome-based medicines, etc.), the ability of these approaches based on individual risk to make a substantial difference should seem even more dubious (for further discussion of these related difficulties, see e.g., Hall et al., 2008; for skepticism regarding the clinical utility of genetic testing for addiction more generally, see Munafó, 2009a). On the other hand, reducing the harms of nicotine addiction and smoking via policy shifts is likely to be efficacious and requires no new technologies or discoveries, and it can be implemented at a variety of different levels of social organization (see e.g., Levy et al., 2007; Cokkinides et al., 2009; Levy et al., 2010; but see Holder, 2009 for a more cautious appraisal of the success of current public programs).

**Conclusions: Thinking about risk**

Human behavioral genetics can highlight the roles that people’s different genetic endowments play in behaviors that vary within particular social environments. Research on the genetics of addiction/addictive behaviors has tended to follow this path, focusing on the genetics of the different levels of risk for addiction or addictive behaviors associated with different individuals. Although the hype surrounding the possibility of using genetic discoveries to develop new treatments has so far outpaced the reality, there can be little doubt that most researchers in this area are driven by a sincere desire to understand addiction and work toward ameliorating the harms associated with addiction and addictive behaviors (see, e.g., Smith et al., 2005; O’Brien, 2007).

However, in thinking through the results of contemporary genetics research into addiction, we should remain mindful of the lessons of public-health approaches to improving the health of populations. Even if we find genes that “predispose” particular people to addiction (either to particular addictions or to addictions in general) within a particular social environment, those genes may or may not be associated with an increased risk of addiction in a different social environment, and even if they are so associated, the risk of addiction in different social environments may be very different indeed. It may turn out that if we want to reduce the harms associated with addiction and addictive behavior, looking to the reasons that rates of addictive behaviors vary between populations will reveal more effective possible interventions than will attention to individual variation. Indeed, even where rates of
addiction may be similar in different social environments, the harms associated with those addictions may be very different in those different social environments, and attention to those kinds of differences may point toward effective interventions that can lessen the harms associated with the addictions (see, e.g., Stegmayr et al., 2005 on “snus” use and nicotine addiction in Sweden).

Human behavioral genetics is fraught with difficulties, but the potential for it to generate real insights should not be dismissed. But these insights, focused as they so often are on explaining individual variation within societies, are not guaranteed to be useful – indeed, they may not even be likely to be useful – for making major improvements in population health, or for significantly reducing the costs and harms associated with addiction. And the excitement surrounding the insights of human behavioral genetics on addiction must not be permitted to distract us from aggressively pursuing research into the public-health aspects of addiction and addictive behaviors. Although it is often unclear that there is the political will to pursue the kinds of population-based strategies for harm reduction that public health approaches give us good reason to believe would be effective, such research at least invites consideration of those sorts of policies.

References


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