Using Genetically Informed, Randomized Prevention Trials to Test Etiological Hypotheses About Child and Adolescent Drug Use and Psychopathology

In this essay, we describe a new era of public health research in which prevention science principles are combined with genomic science to produce gene × intervention (G×I) research.

We note the roles of behavioral and molecular genetics in risk and protective mechanisms for drug use and psychopathology among children and adolescents, and the results of first-generation genetically informed prevention trials are reviewed. We also consider the need for second-generation research that focuses on G×I effects on mediators or intermediate processes.

This research can be used to further understanding of etiological processes, to identify individual differences in children's and adolescents' responses to risk, and to increase the precision of prevention programs. We note the caveats about using genetic data to select intervention participants. (*Am J Public Health.* 2013;103:S19–S24. doi:10.2105/AJPH.2012.301080)

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MORBIDITY AND MORTALITY

from noncommunicable diseases among children and adolescents have risen worldwide, whereas for infectious diseases they have declined.[1] Accordingly, the prevention of noncommunicable causes of childhood and adolescent mortality has risen in importance. Problem behaviors that increase the short- and long-term likelihood of morbidity and mortality are largely preventable. These behaviors include unsafe sex; the use of alcohol, tobacco, and other drugs; and depression and antisocial behavior.[2] Prevention science was established as a discipline more than 30 years ago to mitigate these public health problems. Guided by longitudinal, epidemiological studies that provided an understanding of risk and protective factors relevant to many of these problem behaviors, developmentally appropriate prevention programs were constructed that evince both short- and long-term reductions in behaviors that compromise adolescents' health. In this essay, we describe a new era of public health research in which the principles of prevention science are combined with genomic science to obtain new insights into the etiology and prevention of adolescent problem behaviors. In the sections that follow, we

1. provide an overview of the roles of behavioral and molecular genetics in the etiology of risk and protective mechanisms,
2. describe the ways in which randomized prevention trials can be used to test etiological hypotheses involving gene × environment interactions (G×E) and gene–environment correlations (rGE),
3. review existing and forthcoming gene × intervention interaction (G×I) research,
4. explain how G×I research can increase the precision of preventive interventions through fostering a greater understanding of nonspecific environmental effects, and
5. offer some caveats about the use of genetic data to select participants for preventive interventions.

We provide a glossary of terms that may be unfamiliar to some readers in the box on the following page.

GENOTYPIC INFORMATION AND PREVENTION SCIENCE

To date, etiological models of drug use disorders, psychopathology, and the studies they have sponsored have focused primarily on social (e.g., family, peer, and community-level processes) and psychological (e.g., temperament and self-regulation) determinants. Such models, however, are incomplete. Vulnerabilities to tobacco, alcohol, and marijuana dependence, emotional problems, and behavioral problems are likely to be influenced by a combination of environmental and genetic factors, mediated in part through psychological processes.[3,4] These contributions include genetic main effects, G×E, and rGE, which are collectively called gene–environment (G–E) interplay.[4] G×E can be seen either as the moderation of genetic effect by environmental influence or the moderation of environmental influence by genotype. For example, human children and primates whose genotypes predispose them to high impulsivity may develop poorly in adverse environments but develop normally in nurturing environments.[5,6]

Most existing findings on G–E interplay in humans as it relates to drug use and psychopathology have come from genetic epidemiology, a branch of science that seems ideal for demonstrating that G×E and rGE exist in nature and affect etiology. Prevention science has less often been considered as an important source of basic information about the impact of genetic variation on drug use and psychological adjustment outcomes. This oversight is unfortunate, because prevention science has considerable potential to refine G–E hypotheses and to investigate causal mechanisms that are difficult to explicate in traditional genetic epidemiological designs. We propose that, through manipulated environments in randomized

Glossary of Terms for Etiological Hypotheses about Child and Adolescent Drug Use and Psychopathology

Gene-environment correlations (rGE): rGE occur (1) when genetic factors contribute to individual differences in exposure to positive or negative life events (e.g., when genetically influenced characteristics such as sociability or irritability evoke positive or negative responses from others), or (2) when genetically influenced behavior (such as risk-taking propensities) affects the individual's choice of environmental experiences.

Gene × environment interactions (G×E)[a]: occur when genetic variation alters an individual's sensitivity to specific environmental effects or when environmental effects exert differential control by ameliorating or amplifying genetic effects.

Indicated interventions: Interventions that target individuals at high risk (such as those exposed to chronic adversities, including poverty and harsh parenting) who do not meet the criteria for a diagnosable disorder.

Prevention science: A public health approach to prevention that uses risk and protective mechanisms identified through epidemiological research with target populations as the basis for prevention program content.

Quantitative behavioral genetics: The use of naturally occurring variation in the genetic relatedness of family members to identify genetic and environmental contributions to behavior. The most common example is the twin design, in which similarities and differences in identical (monozygotic) and fraternal (dizygotic) twins are compared as a means of estimating genetic and environmental influences.

Selective interventions: Interventions that target individuals who have 1 or more risk factors (such as peer drug use or parental depression), but who are not symptomatic (do not themselves use drugs or experience depressive symptoms).

Universal interventions: Interventions designed to improve targeted outcomes for everyone in the population, regardless of risk status.

[a]Examples of G×E effects include specific genotypes' rendering individuals more susceptible to all experiences, good or bad, and high levels of parental involvement and monitoring decreasing the association of a risk genotype with youth conduct problems and drug use.

prevention trials, preventive interventions permit a more facile disentangling of environments from genetic influences and, therefore, greater flexibility in characterizing the nature of G–E interplay. Thus, the use of randomized intervention designs brings the power of experimental manipulation to the study of G–E interplay, advancing understanding of drug use, drug abuse, and psychopathology and, thereby, increasing the power of future prevention efforts.[7]

GENETICS IN RISK AND PROTECTIVE MECHANISMS

This article focuses particularly on G×E and rGE processes. Behavioral genetic approaches (including, for example, twin studies) have demonstrated the interplay of genetics and social determinants in drug use etiology. Through comparisons of monozygotic and dizygotic twins, significant heritability has been documented for drug use, drug abuse, and psychopathological propensities, providing much of the impetus for subsequent molecular studies.[8] The interaction of heritability estimates with sociodemographic factors such as poverty[9] and rural versus urban residence,[10] a G×E effect, has further illustrated the ways in which environments constrain the expression of genetic tendencies. Quantitative genetic studies have also been particularly instrumental in sensitizing researchers to rGE that occur when genetic variation influences exposure to life circumstances, such as harsh parenting[11] and stressful life events.[12] Because such rGE can masquerade as environmentally mediated events, for example, the effects of parents' own genes on the environments they create for the children who share those genes, scientists must be cautious about inferring direct environmental causation.

In addition, rGE findings may help with the identification of modifiable phenotypes and intervening processes that potentially mediate between genotypic variation and outcomes involving drug use, emotional problems, and behavior problems. For example, if genetic variation contributes to impulsivity or child conduct problems, and parental responses to these behaviors predict later adolescent substance use,[13] this mediated rGE may highlight an important intermediate phenotype (impulsivity or child conduct disorder) and a potential moderating environmental process (parent negativity) that form a pathway to adjustment and drug use problems.[14] In such cases, prevention trials could be used to test the practical significance of targeting such hypothesized mediators. If the E (parent negativity) identified in an rGE mediates the impact of G on substance use and can be modified, this makes the E an interesting potential target for a preventive intervention. If the environmental mediator can be changed through a preventive intervention (e.g., if parents can be taught not to respond with hostility to their children's coercive behavior), prevention trials can demonstrate the practical significance of rGEs for identifying points of intervention in prevention programs. Of course, in the process of demonstrating this practical significance, the prevention design will show that the environment can be made less responsive, turning the rGE into a G×E effect through successful intervention.

Molecular (i.e., measured gene) G×E studies in the etiology of drug use and psychopathology are relatively new. Many of these initial G×E studies examined the influence of variations in particular candidate genes (e.g., dopamine receptor and serotonin transporter). Recently, rather than focusing on the effect of variations in single candidate genes, researchers are increasing their emphasis on gene sets[15,16] and pathway-based approaches.[17,18] Evidence for G×E influences informed by molecular genetics is also available in animal models. For example, Suomi[19] demonstrated that monkeys at genetic risk that were raised in a supportive social environment did not consume alcohol excessively. This finding has parallels with substance use among human

adolescents. Parental monitoring of youths' whereabouts and activities substantially alters the impact of genetic contributions to smoking.[20] Other research demonstrated that the prospective association of racial discrimination with adolescent conduct problems emerged only for youths who carried a gene that increases sensitivity to threatening events and punishment cues.[21] These findings suggest considerable grounds for optimism about the application of molecular genetics in prevention program evaluations.

USE OF RANDOMIZED PREVENTION TRIALS TO TEST HYPOTHESES

The use of randomized prevention trials is an effective means of determining whether an environmental factor has attained causal status. Through the implementation of such trials, a causal relationship between an environmental manipulation and the alteration of a targeted outcome can be identified.[22] Randomized prevention trials rule out rGE as rival explanations. Experimental random assignment of participants to a prevention or control condition eliminates biases that reflect rGE. For example, youths with certain genotypes may select deviant peers (active rGE), or parents with specific genotypes that their children share produce particular kinds of family environments (passive rGE). Accordingly, random assignment has the advantage of ruling out these potential rGE confounders that, in epidemiological designs, may be mistaken for pure environmental effects. Finally, the testing of G×E hypotheses using randomized prevention trials may enhance statistical power as much as 5-fold over epidemiological genetic approaches[23]; consequently, fewer participants may be needed to detect G×E in a randomized trial. Most importantly, testing G×E hypotheses in the context of prevention trials broadens the conceptual models guiding such trials, contributing to progress within the Institute of Medicine[2] prevention development cycle.

FIRST-GENERATION GI RESEARCH AND DATA INTEGRATION

Existing prevention trials can serve as experimental contexts into which genetic assessments can be integrated. We term this first-generation G×I research. To date, approximately 10 such studies have been funded through the National Institutes of Health, as identified through searches of NIH RePORTER (http://projectreporter.nih.gov/reporter.cfm; March 7, 2012). Several first-generation studies have provided provocative initial evidence of the utility of randomized controlled trials in circumventing the issues inherent in epidemiological G×E studies. In a randomized trial of a family-centered intervention designed to delay initiation and escalation of risk behaviors during preadolescence among African American youths, Brody et al. found that the intervention protected children carrying 1 or 2 copies of the serotonin transporter short allele at the 5-HTTLPR.[24] Other preliminary evidence has shown intervention efficacy to be genetically moderated by the 7-repeat version of the dopamine receptor-4 gene (*DRD4*). Specifically, toddlers who carried this allele showed a greater reduction in disruptive behavior after parenting skill intervention than did children who did not carry this allele.[25] In another experiment, kindergarten students with this genotype were affected more positively than were those without it when randomly assigned to play computer games designed to enhance their phoneme awareness skills.[26] Beach demonstrated that preadolescents who carried the 7-repeat version of *DRD4* and were assigned to take part in an intervention program evinced considerably less drug use across 2 years than did youths with the same genotype who were assigned to the control group.[27] Finally, Brody et al. found that African American adolescents carrying the 7-repeat allele benefitted most from a family-centered prevention program designed to prevent the use of alcohol and other drugs.[28] Taken together, this literature suggests that those at highest genetic risk may be most likely to benefit from behavioral or environmental interventions.

Although these genetically moderated intervention effects are based on rather small samples (numbers ranged from 157–400), they provide experimental support for the importance of G×E while suggesting etiological hypotheses and powerful strategies for examination of candidate G×E effects. These studies also indicate that, for genetic reasons, individuals differ in the extent to which they are affected by exposure to environmental influences.[29,30] These first-generation G×I studies were designed to document that genetic variation interacts with the environments that existing interventions create, thereby forecasting phenotypic variations. Future first-generation research will examine G×I effects for networks of candidate genes, across different developmental stages, across gender, across cultural and community contexts, and for different outcomes (e.g., drug use, conduct problems, depression) to determine generalizability.

SECOND-GENERATION GI RESEARCH ON MECHANISMS

Prevention scientists only recently have begun to examine the processes that account for or mediate first-generation G×I findings. Research designed to lead to an understanding of the locus of G×I effects can be termed second-generation G×I research. For example, in the context of family-centered substance use prevention trials, Brody et al.[28] demonstrated that G×I effects on increases in protective parenting accounted for G×I effects on targeted prevention outcomes. Although randomized trials such as these provide a powerful context for examining mediators and intervening processes,[7] they are constrained by their considerable cost and logistical complexity. This is particularly true when hypothesized mediators are not yet well understood. In such cases, microtrials, a complementary experimental research design, may be used to provide more precise tests of mediational hypotheses. Microtrials are randomized experiments that test the effects of relatively brief and focused environmental manipulations that are designed to suppress specific risk mechanisms or enhance specific protective mechanisms, but not to bring about full prevention effects in distal outcomes.[31] Microtrials are designed to test the malleability of specific risk or protective mechanisms and to provide information indicating whether and how

specific prevention program components bring about meaningful change in those mechanisms. Microtrials can provide a translational bridge between basic laboratory or observational longitudinal field studies and full-scale prevention trials.

Genetic information can be incorporated into microtrials in 2 ways. First, existing research on rGE and putative risk or protective mechanisms can guide the development of carefully tailored brief preventive interventions that serve as environmental manipulations to change key mechanisms. For example, recent studies of variants of the serotonin transporter gene suggest that individuals with the less efficient allele may be more emotionally reactive to stressful life events[32] and more responsive to social validation and support.[24] To test the applicability of such findings to preventive interventions, a relatively inexpensive microtrial might be used to determine whether brief validation and support sessions reduce individuals' reactivity to socially stressful situations and do so to a greater degree for those with the less efficient allele of *5-HTT*. If so, this underscores the potential importance of this pathway in reaching some vulnerable individuals. Second, genetic information can be used directly to inform the microtrial design through use of a 2-stage sampling procedure in which DNA is collected and assignment to condition is stratified based on genotype. This design permits the creation of optimal genotype distributions, thus maximizing the statistical power of G×E tests.

Microtrials have important advantages as tests of both etiological theory and theories of change relevant to prevention science. Compared with observational field studies, they are likely to have much greater power to detect G×E using much smaller samples because of direct control of environmental factors, use of stratification to insure independence of genetic and environmental variables, and greater measurement precision.[23] Microtrials also are inexpensive compared with full-scale trials because they involve much smaller samples and more limited intervention and measurement. In addition, microtrial designs can be used in genetically informed studies to test the malleability of risk or protective mechanisms before the development or refinement of a larger prevention program that more extensively targets multiple factors.

GI RESEARCH AND PREVENTIVE INTERVENTIONS

Based on information gained from etiological G×E studies of drug use, drug abuse, and psychopathology, and from first- and second-generation G×I studies, research can be designed to increase the precision of preventive interventions by addressing questions concerning nonspecific environmental effects. Various environmental risk mechanisms have nonspecific effects on the use and abuse of alcohol and other drugs and on the intermediate phenotypes that forecast them. For example, exposure to family conflict and violence, harsh parenting, stressful life events involving loss or threat, and economic insecurity all forecast both internalizing and externalizing problem phenotypes as well as drug use and abuse.[33] A potential explanation for these nonspecific effects may be that particular adverse childhood events are connected to different intermediate phenotypes and different drug use and psychopathology outcomes through different G×E pathways. For example, it has been shown that early adversity forecasts depressive symptoms among carriers of the short allele at the 5-HTTLPR and antisocial behavior among carriers of high-activity alleles of *MAOA*. These findings show that exposure to early adversity in combination with different gene systems culminates in different adjustment phenotypes.[34,35]

Identifying protective mechanisms in individuals, families, schools, and communities; linking their beneficial effects to various intermediate phenotypes that forecast drug use initiation and escalation, emotional problems, and behavior problems; and insuring that they constrain the combined impact of genomic and environmental effects will provide important information for building a new generation of preventive interventions that target multiple positive outcomes. If genetically susceptible or vulnerable subgroups can be identified for analysis, modest associations may prove to be stronger and more specific than was previously believed. It will be important in building this next generation of preventive interventions to describe the extent to which developmental stage, gender, and significant contextual factors modify the impact of nonspecific protective factors.

USING GENETIC DATA TO SELECT PARTICIPANTS

The discussion thus far has focused on the ways in which the integration of genetic data into prevention trials can enhance understanding of etiology and the design of more effective interventions. It is natural, therefore, to ask whether such preventive interventions would also be more efficacious and cost-effective if only those individuals who responded most strongly were selected to receive them. That is, if genes moderate response to preventive interventions, should we identify and select individuals for preventive interventions based on genotypes? Targeting interventions by genotype is problematic for several reasons, 4 of which are reviewed briefly in the following sections.

Targeted Intervention and the Prevention Paradox

A major concern about targeting preventive interventions to individuals at high risk, whatever risk mechanisms are involved, is the so-called "prevention paradox." This phenomenon is a seemingly contradictory situation in which the majority of cases of a complex disorder come from a population at low or moderate risk for that disorder, with only a minority of cases coming from the high-risk population.[36] Aiming prevention only at those at high relative risk might reduce their individual risk, but it would do little to reduce the total prevalence of the disorder in the population. This concern is well worth considering before genotype is used as a selection criterion for preventive intervention, even in the case of selective prevention programs.

Potential for Discrimination or Stigmatization

Another major concern in identifying and selecting individuals for preventive interventions is the possibility of stigmatization

or discrimination arising from such selection.[37,38] Asymptomatic individuals or their family members may be treated differentially based on real or presumed genotype.[39] Conversely, and similarly to the prevention paradox, negative effects could also accrue to those not selected. Children or parents not selected for prevention programming might feel inappropriately invulnerable to the risk of drug-related, emotional, or conduct problems. These concerns are reasons to avoid the adoption of genetically targeted interventions.

Growing Impracticality of Genotypic Targeting

We anticipate that the number of genotypes found to confer susceptibility, vulnerability, or risk at various developmental stages and in different contexts will continue to increase, particularly as candidate gene approaches are replaced with gene-network approaches. As the list of relevant genes becomes longer, the direct use of genotypes in the selection of individuals for participation in prevention programs will become increasingly impractical for several reasons. First, given a sufficient number of relevant genes, the number of "risk-free" individuals will become negligible. Second, even if one assumes that multiple, independently distributed genes contribute by themselves to susceptibility, vulnerability, and risk, the distribution of risk genes is likely to take on the shape of a normal (Gaussian) distribution, confounding efforts to create clear "risk" and "nonrisk" groups. In such circumstances, creation of genetic risk groups will be arbitrary, with most of the general population having intermediate risk status. To the extent that selection for risk is desirable in the context of prevention trials, it is likely that high-risk status will be captured best by giving attention to the intermediate phenotypes and intervening processes that genes influence and moderate rather than to discrete genotypes.

Recommendations

We believe that broadly delivering both universal and selective preventive interventions without targeting individuals based on genetic vulnerability may reach a larger segment of the genetically vulnerable population[37] and, consequently, be more effective in affecting population-level prevalence of these common and costly public health problems. Nevertheless, we believe that incorporation of G–E interplay processes will benefit prevention programs by expanding understanding of the intermediate phenotypes and processes that account for preventive intervention program success, enabling program designers to incorporate new targets and enhancing overall impact in the general population.

SUMMARY

Children's and adolescents' drug use and abuse, emotional problems, and behavior problems have well-documented environmental causes. First- and second-generation G×I research will help expand scientific understanding of etiological mechanisms underlying these problems, and this progress will continue as more data become available over the next several years. As with all research, initial significant G×I findings must be replicated to determine their robustness and generalizability. These data will help to inform the development of a new generation of prevention programs that target multiple outcomes and impart to researchers greater precision regarding population-level impact. Genomics and prevention science research are joining forces to look for answers and, in so doing, increase the impact of preventive interventions. We look forward to seeing the results. ■

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