Published in final edited form as:

Prev Sci. 2018 January ; 19(1): 101–108. doi:10.1007/s11121-017-0828-7.

Commentary for Special Issue of Prevention Science “Using Genetics in Prevention: Science Fiction or Science Fact?”

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Abstract

A growing number of prevention studies have incorporated genetic information. In this commentary I discuss likely reasons for growing interest in this line of research, and reflect on the current state of the literature. I review challenges associated with the incorporation of genotypic information into prevention studies, as well as ethical considerations associated with this line of research. I discuss areas where developmental psychologists and prevention scientists can make substantive contributions to the study of genetic predispositions, as well as areas that could benefit from closer collaborations between prevention scientists and geneticists to advance this area of study. In short, this commentary tackles the complex questions associated with what we hope to achieve by adding genetic components to prevention research and where this research is likely to lead in the future.

Keywords

gene environment interaction; prevention; genetics; GxI; gene by intervention interaction

Introduction

The number of studies devoted to understanding how genetic and environmental influences operate together has increased drastically over the past decade plus. When I defended my graduate dissertation on gene-environment interaction sixteen years ago, my committee gave me some good-natured chiding about choosing a topic with so little research literature to review (and no, for the younger generation of students, they were not being facetious). With PubMed now returning >10,000 records for gene-environment interaction, there is no longer a paucity of research in this area! The study of genetic influences on human behavior has become mainstream, and the analysis of genetic information is now routinely included in many developmental studies, and, more recently, in prevention studies.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest: The author declares no conflicts of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by the author.

Informed Consent: Because this article is a commentary, informed consent is not applicable.

Overview of the Special Issue

This special issue contains a collection of papers that address different aspects of incorporating genetic information into prevention studies. Several are illustrative of the growing body of literature (Albert et al., 2015; Bakermans-Kranenburg, Van, Pijlman, Mesman, & Juffer, 2008; Brody, Beach, Philibert, Chen, & Murry, 2009; Brody et al., 2014) that demonstrates that part of what contributes to differential outcomes across children in prevention studies is differences in their genetic predispositions (Cleveland et al., 2017; Glenn et al., 2017; Russell et al., 2017; Zheng, Albert, McMahon, Dodge, & Dick, 2016). Prevention is not equally effective for everyone, and there is suggestion that genetic information could be one way to help determine which children will respond best to which intervention. It is the prevention extension of “personalized medicine” (Burke & Psaty, 2007; Guttmacher & Collins, 2003; Guttmacher, Porteous, & McInerney, 2007).

Other papers in this issue focus on the need to ensure that the incorporation of genetic information into prevention science represents the state of the science (Latendresse, Musci, & Maher, 2017) and/or novel study designs for understanding genetic and environmental influences on behavioral outcomes (Leve et al., 2017; Maher, Latendresse, & Vanyukov, 2016). Latendresse et al. (2017) provide an overview of the history and current methods used in large-scale genetic analyses, with guidelines for how to conduct genetically informative studies. Leve et al. (2017) discuss the use of different natural designs to disentangle genetic and environmental influences in order to identify “true” environmental effects, and Maher et al. (2016) discuss the novel strategy of focusing on finding genes involved in resistance, rather than risk, and how best to design studies to do this.

The importance of incorporating a developmental perspective into studies of gene by intervention interaction, in order to test whether gene by intervention effects vary across time, is highlighted by the work of Russell et al. (2017). The main effect of genes has been shown to vary across time; for example, genes involved in alcohol use outcomes appear to become more important in emerging adulthood when regulations surrounding access to alcohol are relaxed (Dick et al., 2006; Guo, Wilhelmsen, & Hamilton, 2007; Irons, Iacono, Oetting, & McGue, 2012). Further, the importance of gene-environment interaction effects has been shown to vary across time (Dick et al., 2007), with environments varying in importance at different developmental stages. Accordingly, it follows that gene-by-intervention effects may also be time-sensitive.

Finally, in this issue, Beach et al. (Beach, Lei, Brody, & Philibert, 2016) report an epigenetic study that begins to investigate how environmental interventions “get under the skin”. It asks, how do environmental manipulations change our biology to produce differential outcomes? The complexities inherent in analyzing epigenetic data are also discussed in Latendresse et al.’s methodological overview (Latendresse et al., 2017). Jointly, the papers in this special issue come together to produce a compelling overview of the state of the science with respect to the incorporation of genetic information into prevention studies, and illustrate the diversity of questions that can be addressed with the addition of genetically informative data into prevention science.

Overview of this Commentary

Accordingly, with growing attention focused on the incorporation of genetic information into prevention science, it is worth pausing to think critically about why we are investing considerable time and effort into genetically informative prevention studies, and where this line of research is likely to lead. What are the opportunities and challenges associated with this line of research? In what areas of genetically-informed prevention science are we doing well, and in what areas do we fall short? And, importantly, what implications do these studies have for the practice of prevention/intervention in the future? In this commentary, I address these questions. I certainly do not pretend to have all the answers; rather, I hope that this commentary will stimulate conversation about the future role of genetic information in prevention science.

Why the growing interest in incorporating genetics into prevention studies?

There are probably numerous reasons for the growing number of psychological studies incorporating genetic information, including falling genotyping costs, the relative ease of obtaining DNA via noninvasive methods such as saliva sampling, and increased interest from funding agencies in studies that involve genetic components [as further delineated in 2011 review “Incorporating Genetics into Your Studies: A Guide for Social Scientists” (Dick, Riley, & Latendresse, 2011)]. Human behavior clearly involves complex interactions between the individual’s genome and a myriad of environmental influences across multiple levels of analysis (Bronfenbrenner, 1994). The idea that genetics can lead to “precision medicine” – tailoring health care and treatment to an individual’s personalized risk profile – has gained widespread attention and investment (Collins & Varmus, 2015). It is widely recognized that not all children respond equally well to prevention programs; accordingly, it logically follows that some of that individual variation in response may be due to differences in genetic predispositions. This hypothesis has been born out in a growing number of studies that repeatedly find evidence for differential intervention response based on genotypes as measured across a variety of neurotransmitter systems. (Cleveland et al., 2017; Glenn et al., 2017; Russell et al., 2017; Zheng et al., 2016)

Opportunities and Challenges

The papers in this special issue provide illustrations of places where developmental psychologists and prevention scientists can make substantive contributions to the study of genetic predispositions, as well as areas that could benefit from closer collaborations between prevention scientists and geneticists. In general, psychologists tend to do an excellent job of grounding their studies in theory, and prevention science is no exception. As genetic information has been incorporated into prevention science, this method of grounding the research in theory has transferred to the selection of particular genes, which are generally included for study based on an underlying biological rationale. For example, several papers in this issue focus on the oxytocin receptor gene (Glenn et al., 2017); (Cleveland et al., 2017); (Beach et al., 2016), based on previous studies suggesting a role in bonding and

social behavior, which may support the hypothesis that this gene could be involved in differential response to prevention, which often involves various interpersonal components.

However, the selection of genetic information for incorporation into a prevention study is not straightforward. Some studies focus on specific variants within a candidate gene with demonstrated or purported functional relevance.(Caspi et al., 2002; Caspi et al., 2003) Other studies systematically genotype genetic variation across a gene of interest, with the rationale that there could be multiple locations in the gene that alter function, and accordingly, risk¹ (Carlson et al., 2004; Dick et al., 2008). In other words, there could be a compelling rationale to study a particular gene, but what variants in that gene are likely to be relevant remain unknown(Zheng et al., 2016). The biological rationale for focusing on any one gene can be problematic at best, as delineated in Cleveland et al (2017), in this issue, as can identifying a particular allele as a “risk” allele. In truth, we are only studying genetic variation, not genetic “risk”, and though an allele may be associated with a deleterious outcome, for example substance use, it may be conferring risk via a mechanism such as sensation-seeking, which is in itself not problematic *per se*. Most prevention scientists have extensive training in psychology and development; accordingly, theories about behavior change stem from this deep scholarship. However, most prevention scientists do not have nearly the depth of training in molecular biology, which makes theory-driven selection of candidate genes for study more challenging and potentially problematic.

The fact that the incorporation of single variants from theoretically-based biological candidate genes remains the most widely used strategy in prevention research is in stark contrast to the current state of psychiatric and behavioral genetics, where large-scale gene identification efforts systematically scan variation across the genome in an intentionally *atheoretical* manner. This strategy evolved after candidate gene studies yielded inconsistent effects, and subsequent systematic scans of the genome indicated that many of the “classic candidates” that had been the product of extensive study based on hypothesized biological rationale, yielded no evidence of association with expected outcomes in larger, more powerful studies (Farrell et al., 2015). Accordingly, there is concern that the candidate gene studies that are commonplace in prevention studies will be viewed as naïve, with respect to the current state of the science in genetics. Genes are necessarily involved in complex biological systems, and the effect associated with any one genetic variant on a complex behavioral outcome is likely to be extremely small (O’Donovan, 2015).

Some prevention studies are now incorporating polygenic risk scores (PRS)(Musci et al., 2016), in which a weighted score is created based on a linear combination of risk variants identified in another, larger gene identification study (Li et al., 2017; Musci et al., 2016; Salvatore et al., 2015). These scores are also referred to as genome-wide polygenic scores (GPS)(Webb et al., 2017), to eliminate reference to “risk”, for the reasons delineated above. For a handful of psychiatric and behavioral traits for which extremely large gene identification consortia have already amassed hundreds of thousands of individuals, these polygenic scores are beginning to account for non-trivial portions of the variance. For example, for schizophrenia, 108 significant loci were found when a pooled sample of 37,000

¹This technique is called LD-tagging

cases and 113,000 controls was analyzed, with polygenic risk scores accounting for 7% of the variance in disorder liability (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). A similar story has been found for other complex, highly heritable traits such as height, where no significant variant associations were detected with 5,000 genomes, but an analysis of 250,000 individuals was able to identify over 400 significant loci and account for up to 29% of the trait variance (Wood et al., 2014). Parallel analyses for multiple disorders indicate there is a “breakthrough point” of sample size after which discovery rates increase exponentially, although this threshold differs across phenotypes (O’Donovan, 2015). The incorporation of these genome-wide polygenic scores based on findings from large-scale genetics consortia represents a more direct bridge from prevention science to cutting-edge genetics. And as the predictive ability of these scores improves, so too will their utility for inclusion in prevention studies.

However, there are several challenges that the strategy of including GPSs in prevention studies will entail. Firstly, it necessitates genome-wide data on the sample. Although this is commonplace in larger genetic studies, some prevention studies included DNA collection via older buccal swab methodologies and, accordingly, a more limited quantity of DNA is available, since the samples were intended only for small-scale genotyping of a handful of candidate genes initially. A second challenge is that prevention scientists will be limited in what GPSs are available for study based on the state of gene finding for the particular behavior/outcome of interest to that group. Disorders that have had the most success in gene identification are the most highly heritable conditions like schizophrenia (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). For many of the behavioral outcomes of interest to prevention scientists, such as aggression, conduct problems, depressive affect, or anxiety, there has been far less progress in gene identification, and GPSs that account for significant portions of the variance are not yet available (Dick et al., 2004; Hettema, Neale, & Kendler, 2001; Pappa et al., 2016; Ripke et al., 2013). These disorders are less heritable, and accordingly, larger numbers of individuals must be amassed for gene identification in order to create GPSs that account for nontrivial amounts of variance. However, analyses by the Social Science Genetics Association Consortium (SSGAC) demonstrate that these obstacles can be overcome with sufficiently large samples. For example, the most recent analyses of educational attainment, a phenotype with a heritability of only ~20%, consisted of 293,723 individuals and identified 74 genome-wide significant loci, that replicated in an independent sample and showed enrichment for biologically relevant variants (Okbay et al., 2016). Further, new methods are also advancing gene identification efforts by facilitating the ease of combining information from multiple studies, with related, but distinct, phenotypes (Turley et al., 2017). Accordingly, it is only a matter of time before the complex behavioral outcomes of interest to prevention scientists are likely to advance further in terms of gene identification, and GPSs with more robust predictive value will be available for study.

A third major challenge with the inclusion of GPS in prevention studies is that many of these large-scale genetics consortia focus on samples of European descent (Salvatore et al., 2014), as gene identification is more straightforward and powerful in more homogeneous populations. Many prevention samples have far more racial/ethnic diversity (Brody, Chen, Beach, Philibert, & Kogan, 2009; Dishion et al., 2014). This complicates the creation of

GPSs, since allele frequencies differ in individuals of varying ancestral background (Hendrickson et al., 2009; Schlaepfer et al., 2008). Additionally, the creation of GPSs involves a number of technical decisions regarding issues such as genetic reference panel and minor allele frequency cut-offs (McCarthy et al., 2016); accordingly, collaborations between prevention scientists and statistical geneticists will be critical.

Finally, it is possible that some genetically influenced outcomes of interest to prevention scientists are not currently the focus of extant gene identification efforts. For example, prevention scientists might be interested in including an index of genetic risk for self-regulation or emotion-regulation. However, most large-scale gene identification efforts focus on diagnosable psychiatric outcomes (hence the Psychiatric Genomics Consortium). Accordingly, GPS for outcomes such as depression will have to serve as proxies for genetic predispositions to actual constructs of interest, such as emotion regulation (with the assumption that part of the genetic predisposition to depression likely involves mechanisms related to emotion regulation). Maher et al. (2016) in this issue make a compelling case for the importance of pursuing genes involved in resistance as a complement to the identification of risk genes. Psychiatric genetics has focused nearly exclusively on finding genes involved in why people develop disorders; studying why some people are particularly likely to remain unaffected would likely be extremely beneficial in helping us understand health-related outcomes as well.

A construct of deep interest to prevention science – the idea that there may be a predisposition to environmental sensitivity (Belsky, 1997; Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Belsky et al., 2009), which, if correct, would be important to include in prevention studies, is not the subject of current gene identification efforts. Genes that influence *intervention response* will not necessarily overlap with genes involved in disorder. If large numbers of prevention scientists came together to share their data on prevention outcomes, it could be possible to identify genes involved in prevention response. Assuming that genes involved in sensitivity to the environment would follow a similar pattern to genetic influence on other complex behavioral outcomes (e.g., a complex genetic architecture with many genes of small effect), finding these genes would necessitate extremely large sample sizes, unattainable by any single group, and the coming together of different prevention studies to form consortia, share data, and navigate authorship issues, in the way that geneticists have had to over the past decade. However, there is great potential for prevention scientists to make a significant contribution to understanding genetic influences on environmental response by pursuing a collaborative venture such as this.

Practical and Ethical Implications Associated with Genotyping in Prevention Science

The rationale often provided for including genetic information in prevention science is that it could allow interventions to be individualized based on child characteristics. But as a field it is worth taking a collective step back to ask if that possibility is something we realistically envision. Do we really envision a future where we will be genotyping individuals to determine access to or placement into prevention intervention programs? That possibility

seems highly unlikely in a school or community setting. And genotyping children to make decisions about prevention placement also carries a host of ethical questions. Genotyping is expensive, and genomes carry a wealth of health information, much of which will be unrelated to the original outcome of interest. There is currently an active discussion in the field of genetics about the return of incidental findings (Christenhusz, Devriendt, & Dierickx, 2013; Green et al., 2013; Wolf et al., 2008). That is to say, when we conduct a genome-wide screen (for example), to try to find genes involved in alcohol dependence, or, in the future, hypothetically, to create a score to assess likely prevention response, then we will necessarily have information about that person's risk for a host of medical outcomes, ranging from cancers, to cardiovascular outcomes, to drug response. Do we have a responsibility to return this information to individuals? This has been something that genetics researchers have felt uncomfortable taking on; would prevention scientists feel any better equipped to enter this arena? I would imagine that genotyping information will have to result in large gains in the ability to predict prevention effectiveness to make it worth taking on the ethical and medical implications that generating that information would entail.

Further, in a hypothetical world where genotypic information is used to make decisions about prevention intervention, what do we do about the kids that are deemed "less likely to respond"? Fortunately, many studies thus far suggest that those who are most at risk are actually most likely to respond to intervention (Albert et al., 2015; Bakermans-Kranenburg & van Ijzendoorn, 2011; Brody et al., 2013). If personalized prediction is used to make choices between different programs, the issue of how to handle "likely unresponsive" children becomes less problematic. But we need to be careful about the possibility of classifying kids in ways that could result in labeling and/or potential for discrimination or self-fulfilling prophecies. If a group of kids are identified for whom prevention is less effective, it will be an important area of study to determine how better to support these children.

Possible Other Uses of Genetic Information in Prevention Science

As we have robust genome-wide polygenic scores and identified genes from large-scale gene identification consortia, developmental scientists can play an active role in mapping the behavioral phenotypes that represent earlier manifestations of genetic predispositions and how these outcomes are moderated by the environment (Dick, 2017). Characterizing these pathways will inform our understanding of how genetic risk unfolds across time, and the nature of malleability of associated outcomes as a function of intervention. The intermediary behavioral phenotypes mapped to genetic risk may very well be more useful in making decisions about which children are likely to be responsive to which interventions than the genetic risk scores themselves. Identifying child characteristics that modify intervention effectiveness is not a new area for prevention scientists (Bates, Pettit, Dodge, & Ridge, 1998), but genetic information may help inform our understanding of the complex web of etiological pathways, which can be used to inform prevention science. It is possible that a combination of behavioral and genetic information may be most effective in providing information to make decisions about health interventions. Machine learning methods hold promise in identifying combinations of factors that yield the best prediction (Walsh, Ribeiro, & Franklin, 2017).

Another possible way that genetic information may prove useful is in helping differentiate the root cause of an individual's symptoms. Many behavioral challenges cluster (Dick, Viken, Kaprio, Pulkkinen, & Rose, 2005; Kessler et al., 1997), so it can be challenging clinically to know the root cause of the underlying problems for which intervention is desired. For example, it may be unclear whether it is underlying anxiety or issues with self-control that are leading to a child's disruptive behavior. In another example, it may be unclear whether underlying depression led to alcohol misuse, or whether an individual's alcohol misuse led to depression. It is possible that genetic information will be able to assist with differential diagnosis, which may help guide decisions about intervention.

Conclusions

Human variability is an inevitability – and that is a good thing, as variation is the basis for evolution and the survival of a species. Why some kids are more likely to respond to prevention than others is an inherently interesting question; the idea that the answer lies in their genes is appealing. But surely there is no gene for prevention response, just as there is no gene for alcohol dependence. Genes are simply strings of nucleotides that code for amino acids; that create proteins; that affect the structure, function, and regulation of the body's tissues and organs; that affect behavioral characteristics, response patterns, and temperaments; that can ultimately influence prevention response. It is a long, winding pathway from genotype to behavior! And it may end up being far easier and cheaper to assess the intermediary behaviors that reflect genetic risk and/or behavioral response than it will be to genotype individuals. Understanding the pathways of genetic risk will likely advance our understanding of mechanism and intermediary risk factors, which can be another piece of information to inform prevention and intervention.

The field of prevention science has been in the phase of demonstrating that gene by intervention (GxI) effect exist. This finding is inherently interesting, but prevention scientists will ultimately have to face the same questions that geneticists have faced: what are we going to do with this information? Just as psychiatric genetics has had to move beyond creating laundry lists of associated genes, prevention science will need to move beyond cataloging GxI effects. One could even argue that genetics is now passé, replaced by genomics (Feero & Guttmacher, 2014), epigenomics (Friedman & Rando, 2015), proteomics (Humphrey-Smith, 2015), metabolomics (Bujak, Struck-Lewicka, Markuszewski, & Kaliszan, 2015), and the study of the microbiome (McDonald, Birmingham, & Knight, 2015). We now know that people respond differently to prevention intervention and that differential response is in part correlated with their genetic predispositions. What do we do with this information? Why is it important and how will it be used? It is not enough to say that genetic information may be used to help us understand what child will respond best to what intervention. Prevention scientists need to think carefully about the logistics of how that might actually play out. Because of the rapidly evolving landscape in genomics, it will also be critical for prevention scientists to collaborate closely with statistical geneticists, to ensure that genetically-informative prevention studies represent the state of the science in genetics.

Acknowledgments

Funding: Dr. Danielle M. Dick is supported by grants R01 AA015416; K02 AA018755; P50 AA0022537; R37 AA011408; and U10 AA008401 from the National Institutes of Health(NIH)/National Institute on Alcohol Abuse and Alcoholism (NIAAA), as well as the BTtoP Category II Research Grant from the Bringing Theory to Practice (BTtoP) Project.

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