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COMMENTARY

The Implications of Genetics for Prevention and Intervention Programming

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With recent advances in high-throughput technology, genetic and other biological data have been increasingly incorporated in social science research, including prevention/intervention studies. Understanding the role genetics play in complex behaviors commonly evaluated in prevention/intervention research may have important implications for designing prevention programing, determining who receives certain prevention programs, and understanding individual differences in programming effectiveness (see Jaffee and Price 2007; Moffitt et al. 2006). This special issue, *Incorporating Genetics in Prevention Science: Considering Methodology and Implications*, seeks to advance work in this area by presenting empirical research and methodological reviews that examine the role genetics has in behavioral research. This special issue highlights the strengths, challenges, and methodological approaches that can be used to incorporate genetic and other biological data (e.g., epigenetic markers) into prevention science. The papers in this special issue cover several overarching themes that have emerged as critical for adequately incorporating genetics into prevention and other behavioral research, including gene-by-intervention (GxI) studies. The collection of papers reflect examples, suggestions, opportunities, and pitfalls (and how to avoid them) when incorporating genetics or other biological data into prevention research. Below, we highlight some of the themes and strengths of GxI research as reflected in the set of studies included in this special issue.

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Polygenic Approaches

Early molecular genetic research was focused on single-gene-phenotype associations under the one-gene one-disease model. This approach was successful at identifying genetic liability for single-gene disorders governed by Mendelian inheritance. However, most human characteristics are more complex and underlain by multiple genes. While single-gene—candidate—approaches can be useful for identifying probable mechanisms, prevention researchers also must consider the various benefits of polygenic approaches. One commonly used polygenic approach involves leverage existing, large-scale genome-wide association studies (GWAS) to create a score where the number of risk alleles in a target dataset associated with a particular phenotype are summed across independent loci and weighted according to effect size. This method is often used when no single gene or loci has shown genome-wide significance. In some cases a polygenic approach can significantly increase the power of a given analysis. For example, Musci et al. (2017) utilize this methodology in their paper "Polygenic score x intervention moderation: An application of discrete-time survival analysis to model the timing of first marijuana use among urban youth." In this study, timing of first marijuana use was examined using discreet-time survival analysis. Data were initially collected on children when they were in first grade, then again during sixth grade and then annually through 12 grade. The authors examined the effect a classroom-based (the Good Behavior Game) and a family-based (family-school partnership) intervention in conjunction with a polygenic risk score (PRS) derived from GWAS findings (Musci et al. 2017). In prior research, the PRS—consisting of

over 12,000 single-nucleotide polymorphisms (SNPs)—was linked to variation in successful tobacco cessation and shown to interact with environmental risk and protective factors that predict tobacco and marijuana use (Musci et al. 2015). Results from the survival models showed no main effects of either intervention on first marijuana use and no main effect of the PRS. A statistically significant interaction between the classroom-based intervention and the PRS was found whereby those in the intervention who were also high on the PRS score were lowest on risk for marijuana use from 6 to 18 years of age. The authors suggest the PRS, given its links with multiple substances, may reflect a more general genetic liability for substance use.

Population Stratification

A unique issue in genetic research is population stratification, which refers to naturally occurring allele frequency differences among populations with different genomic ancestries. When both a phenotype and genotype are correlated with genetic ancestry, population stratification can lead to spurious results (see Cardon and Palmer 2003). A classic example comes from a study of diabetes in Pima Indians that showed a link between a specific haplotype (a cluster of interrelated SNPs) and diabetes risk. However, both the haplotype and diabetes risk were more common among those with greater Native American ancestry. When controls for genetic ancestry (i.e., admixture) were included in the analysis, the association disappeared (Knowler et al. 1988). Because the haplotype was not associated with diabetes risk across ancestral groups, this research demonstrated that the association between the haplotype and diabetes risk could be explained by genetic ancestry rather than the haplotype itself leading to diabetes risk.

Given the risk for false positives exemplified in the Pima Indians study, accounting for population stratification in GxI research is key. Fortunately, controlling for population stratification is straightforward and can be implemented in relatively small samples characteristic of intervention research. Using high density genetic data, Musci et al. (2017) randomly selected one million SNPs from across the genome to identify clusters of individuals based on common genetic ancestry. Each individual in the study was assigned a score on each cluster that quantifies membership in a given cluster.

In the absence of high density genetic data, ancestry informative markers (AIMs) can be used measure genetic ancestry. Cleveland et al. (2017) analyzed a set of 34 AIMs (SNPs) using principal coordinates analysis to create a continuous measure of European/Non-European genetic ancestry (PC1). A European ancestry cutoff score derived from PC1 closely approximated self-report ethnicity within the sample (Cleveland et al. 2017). Like Musci et al., Cleveland et al. used their genetic ancestry measure as a co-variate in correlation-based analyses to adjust associations for potential population stratification confounds. Failure to appropriately control for population stratification increases the likelihood of spurious results. It would benefit prevention science researchers to keep apprised of ongoing research related to population stratification as statistical geneticists develop novel techniques to handle this complex issue.

Quantitative Traits

Historically, gene association studies have used binary dependent variables that distinguish between case/control (disease/no disease) phenotypes. This approach stems from clinical studies that aim to identify genes associated with a particular disease. This approach is still in use and has utility; however, a binary diagnosis vs. no diagnosis phenotype can be a psychometrically poor measure. The DSM-V (APA 2013) lists 11 characteristics that can contribute to alcohol use disorder (AUD) and only 2 need to be present in the prior year for an AUD diagnosis. As a result, any given AUD diagnosis reflects 1 of over 2000 possible symptom combinations (MacKillop and Munafò 2013). To maximize the opportunity to statistically detect gene-phenotype associations and GxI, prevention researchers should focus on quantitative traits that vary in terms of degree and where possible use prospective measures of a specific phenotype.

Prevention/intervention research is well suited for taking advantage of prospective measurement given the basic pretest post-test design of many intervention studies. All empirical studies in this special used either continuously measured outcomes and/or prospective measurement. For example, Russell and colleagues used a repeated alcohol misuse measure to model change in adolescent alcohol use (Russell et al. 2017). Glenn et al. used the well-validated Behavior Assessment System for Children (BASC) to measure internalizing and externalizing behavior problems (Glenn et al. 2017). Well-measured phenotypes such as these can help increase power to detect genetic associations by minimizing error and increasing measurement precision.

Genetics and Prevention Science Methodology

Further, prevention science may benefit from the exploration of resistance factors, their genetic predictors, as well as the prevention and intervention programs which may influence those factors. Maher et al. (2017) discuss the benefits of incorporating resistance genetics into prevention and intervention trials. Their results suggest that a modified high-risk design may yield the greatest statistical power for detecting significant genetic and environmental effects (Maher et al 2017).

Additional methodologies for the inclusion of genetic data in prevention work can be found in Latendresse et al. (2017). The

authors present a useful set of "how to" guidelines for working with genomic data, including quality control, population structure/stratification, genotype imputation, and statistical approaches designed to maximize power. In doing so, the authors provide a bit of history regarding research with candidate genes and GWAS, including successes and failures of both and possible solutions (Latendresse et al. 2017). In addition, the authors include sections on methylation, gene-environment interplay, and genetics in randomized controlled trials that describe exciting opportunities for prevention researchers.

Another avenue for the inclusion of genetics in prevention work may lie in the natural experimental designs available within the human population (Leve et al. 2017). Leve et al. (2017) explore these possibilities, with special focus on three design types: children adopted at birth to unrelated parents, sibling designs where one sibling is genetically related to the parents and one is not, and finally in vitro fertilization designs. Leve et al. (2017) present example findings from each of these unique designs and how they may be relevant to prevention science.

The Future: Genetically Informed Interventions?

While the studies included in this special issue are focused primarily on understanding potential moderation effects that genetics may have in existing prevention programs, the future of prevention science may lie in genetically informed prevention/interventions. With the increasing emphasis on personalized or precision medicine, the studies presented in this special issue contribute to our understanding of the mechanisms behind individual differences in prevention program effectiveness. Knowledge of these mechanisms will lead to enhanced efforts to create biologically informed, evidenced-based prevention programs targeted towards those who would benefit most. In evaluations of universal preventive interventions, variation in intervention response is often the rule rather than the exception. Consistent with the elaboration of the prevention research cycle in the Institute of Medicine's 2009 (O'Connell et al. 2009) report on prevention, understanding the source of such variation is critical to improving upon extant preventive interventions and informing the next generation of intervention.

Several of the studies that make up this special issue address variation in intervention effectiveness and provide insight into mechanisms that account for these individual differences. Russell et al. examined the relation between *GABRA2* genotype (rs279845) and substance use prevention/interventions on developmental change in adolescent alcohol misuse. *GABRA2* has been linked to alcohol use problems in adolescents and adults as well as more general conduct problems during adolescence. A unique aspect of this work is the use of time-varying effect modeling (TVEM), which is a novel analytic technique for evaluating how associations change over time. Russell et al. modeled the interaction between intervention exposure and *GABRA2* and found the intervention most strongly mitigated *GABRA2* alcohol use during middle adolescence (13 to 16). In another study on adolescent alcohol use, Zheng et al. (2017) explored whether intervention effects on developmental trajectories of alcohol use were moderated by variation in the glucocorticoid receptor (*NR3C1*) gene. Results suggested that a single SNP in the *NR3C1* gene moderated the impact of the intervention in question, highlighting the importance of understanding subgroups of individuals who may benefit most from intervention and prevention programming targeted towards reducing adolescent alcohol use (Zheng et al. 2017).

Based on evidence for the role of oxytocin in affiliative behaviors, combined with adolescents' heightened sensitivity to peer influence, Cleveland et al., hypothesized, and found, that *OXTR* variation was related to higher affiliation with substance using peers, and that this association was moderated by a substance use prevention/ intervention. In addition, intervention moderation of the association between substance using peer affiliations and adolescent alcohol use was conditioned by *OXTR*. The authors discuss the possibility that the intervention may facilitate selection of low substance using peers at low *OXTR* risk, which may, in turn, be driven by lower affiliative need among these lower *OXTR* risk adolescents (Cleveland et al. 2017).

Beach et al. examined the combined effects of the Strong African American Families (SAAF) intervention, early substance use, and variation in *5-HTTLPR* on differential methylation of *OXTR*. Based on their prior work that showed *5-HTTLPR* moderates the effect of SAAF on risk behaviors (Brody et al. 2009), they hypothesized that the effect of SAAF on *OXTR* methylation would be mediated by early substance use and that this mediational model would be moderated by *5-HTTLPR*. Results showed early substance use was related to higher *OXTR* methylation among *5-HTTLPR* short (*s* or *sl*) allele carriers compared to long homozygotes (*ll*) and the indirect effect of SAAF on *OXTR* methylation via early substance use was present for only for s-carriers. These results suggest that SAAF may prevent *OXTR* methylation, and thus downregulate or completely silence of the gene, by delaying early substance use. Because *OXTR* is believed to be a key regulator of the oxytocin system, downregulating this gene may be linked to lower attachment and higher anxiety given existing research on oxytocin's role in affiliative behaviors.

Along with genetics moderating the prevention program effects, researchers are also exploring how genetics may moderate the effects of a prevention program in regards to delivery format. Glenn et al. (2017) explored how variants in the oxytocin receptor gene moderated the impact of Coping Power with regards to the delivery format of the intervention. Results suggested that the gene variant moderated the effectiveness of the intervention based on group coping power versus individual coping power (Glenn et al. 2017). Future work may explore

the mechanisms through which delivery format of prevention programs is important for the effectiveness of the program.

Conclusions and Implications

With increasing technology and improvements in our understanding of biological mechanisms for behavior and psychological constructs, researchers are just beginning to incorporate genetic and genomic data into their prevention and intervention studies. As prevention scientists move forward with the exploration of genetics in their intervention/ prevention trials, they can utilize the comprehensive set of studies included in this special issue as a guide and starting point for future research. Examining conditional effects of interventions using candidate genes, polygenic risk scores, and/or epigenetic makers are the cutting edge of this science. Likewise, understanding how and why interventions can mitigate genetic risks holds promise for calibrating and improving interventions (Dick 2017).

This special issue has brought together key scholars in the field at the intersection between genetics and prevention science. Greater direction in prevention science is needed as researchers more commonly incorporate genetic or other biological markers in prevention efficacy studies. The field will benefit from a base of research to turn to for methodology, theory, and examples for including genetic data into prevention program analytic models. We highlight methodologically sound gene-by-intervention moderation studies, which may help to inform future prevention programming. In addition, included are studies that utilize different methodologies and theoretical bases useful for integrating genetics in prevention science. With a combination of substantive, theoretical, and how-to pieces, this special issue will serve as a guide for those interested in integrating genetics into their studies or those who want to gain a better understanding of the biological mechanisms behind individual differences in prevention program effectiveness.

Last, it is important to note that although each of the empirical studies included in this special issue found significant gene-by-intervention interactions, thereby suggesting prevention effect heterogeneity as a result of genetics, we are likely far from utilizing genetic data to select individuals for targeted prevention programs. This is particularly evident given the polygenic nature of most behavioral or mental health targets for prevention programs. Previous molecular genetic work in psychology and other behavioral sciences suggest that extensive replication needs to occur before implementing such novel selection processes (Brody et al. 2013). Intervention studies have a special role to play not only due to the potential for applications, but also in terms of the strength of the research design. The articles that make up this special issue reflect many characteristics that genetic research should optimize. New findings with strong methodological and conceptual grounding, and replications of these findings, will be necessary before moving the field closer to personalized interventions that utilize genetic information.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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