EDITORIAL

The Differential Susceptibility Hypothesis
Sensitivity to the Environment for Better and for Worse

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It has long been appreciated by those studying diverse aspects of health and human development that some individuals may be more vulnerable to adversity than others. That is, because of some personal attribute(s) that could be genetic, physiologic, and/or behavioral in character, some children and adults are more likely than others to succumb to the negative effects of problematic environmental conditions (eg, poverty, malnutrition, or pathogen exposure). Research on obesity, the focus of the article by Silveira et al[1] in this issue of *JAMA Pediatrics*, certainly raises this issue given, on the one hand, genome-wide association study findings highlighting obesity genes[2] and, on the other hand, research calling attention to the obesogenic consequences of growing up in a community or society in which fat intake is especially high.[3] Collectively, such work raises the prospect that, in a gene-environment interaction, the adverse effect of exposure to such environmental conditions will be especially, if not exclusively, evident among those individuals carrying more rather than fewer obesity genes.

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This classic vulnerability framework, based as it is on dual-risk conditions, has been challenged by evolutionary-minded scholars who contend that the individuals most vulnerable to adversity are most likely to benefit from supportive or enriched—or even just benign—contextual conditions.[4,5] Indeed, the claim has been made by those embracing this differential susceptibility (to environmental influences) hypothesis that a medical or pathologic model, focused as it is on disease and dysfunction, is problematic because it risks misconstruing general plasticity or malleability in response to good and bad contextual conditions as vulnerability to adversity. This risk arises because so much health-related research has focused exclusively—even if for understandable, humanitarian reasons—on risk factors associated with disease and disorder phenotypes. Had this work also measured supportive environmental conditions and good health—not just the absence of adversity and disease—it would have discovered that the very same individual attributes, including genotype, that predispose one to develop or function poorly under adverse conditions also predispose one to develop or function especially well under positive circumstances. In other words, there are individual differences in plasticity or malleability that operate in a for-better-and-for-worse manner[6] depending on the circumstances in which a child grows up or an individual finds himself or herself. Thus, although some people are highly sensitive and responsive to their environment, good or bad, others are much less so.

There is increasing evidence, especially within the behavioral sciences, consistent with this claim.[7] Indeed, it was appreciation of this body of work chronicling differential susceptibility to environmental influence that informed the genotypic focus of the study by Silveira et al.[1] Even though *DRD4* has not been directly linked to obesity, it has been repeatedly found to operate as a plasticity factor, making individuals more or less responsive to positive and negative contextual conditions. In fact, not only did the long or 7-repeat allele emerge in the meta-analysis by van Ijzendoorn and Bakermans-Kranenburg[8] of research on dopaminergic gene-environment interactions in children as being associated with greater and lesser responsiveness to a variety of contextual conditions, but also data consistent with this observation have emerged in randomized clinical trials of gene-intervention interactions. Thus, for example, Beach et al[9] found that the Strong African American Families' intervention resulted in the prevention of adolescent substance use, principally among 7-repeat carriers.

What findings, such as those that informed the work by Silveira et al,[1] on fat intake indicate is that certain genes may make individuals more or less sensitive to diverse environmental conditions. In fact, it is for this reason that these investigators predicted—and found—that girls (but not boys) carrying the 7-repeat allele of *DRD4* derived the most calories from fat of all children if they lived in more economically disadvantaged families but the least calories if they grew up in more economically advantaged ones. Fat consumption proved to be unrelated to such family circumstances among children who did not carry the putative, 7-repeat plasticity allele. Thus, whereas some children proved highly susceptible to environmental conditions—for better and for worse—others appeared not to be affected at all.

In observational and intervention research, *DRD4* is not the only polymorphism found to operate as a plasticity gene.[6,10] In fact, in 1 study[11] of the efficacy of a lifestyle intervention for obese children, only those carrying the C allelic variant of the *DRD2* gene evinced noteworthy body mass index (calculated as weight in kilograms divided by height in meters squared) change (ie, not TT homozygotes). What data like these imply is that it would be a mistake to think exclusively in terms of one gene at a time and thus of individuals being malleable or not. Because many genes contribute to child and adult sensitivity and responsiveness to the environment, plasticity is better conceptualized as a gradient, with some individuals being more and some less responsive to environmental conditions, rather than categorically, with some being malleable and oth-

ers not at all.[12] Indeed, elsewhere I have speculated that there is probably a bell-shaped curve for the phenotype of environmental sensitivity and responsiveness.[6]

Findings, such as those of Silveira et al[1] that provide yet more support for the differential susceptibility hypothesis carry implications for research and, perhaps, treatment. With regard to the former, these new data underscore once again the need to move beyond a medical or disease model focused solely on disease (and its absence) and adversity (and its absence) to include measurements of good health and supportive contextual conditions. Only by doing so will it be possible to distinguish results that support a vulnerability model of person-environment interaction from those consistent with the differential susceptibility framework. That is, without determining whether the attributes that seem to predispose individuals to develop or function poorly under problematic environmental circumstances also predispose them to develop or function especially well under positive conditions, it will be impossible to know whether the attribute in question truly promotes vulnerability or, more generally, plasticity or malleability—for better and for worse.

Should more observational and experimental evidence emerge indicating that genetic or other personal attributes make some individuals more vs less susceptible to positive and negative contextual influences, this will have implications for health services, a point highlighted in the article by Silveira et al.[1] After all, if health care professionals prove able to identify with reasonable confidence those most and least likely to benefit from efforts to promote good health or remediate poor health, would it not make sense to serve the former individuals first, especially in a world of limited resources? After all, would not such individuals be most likely to be harmed by the absence of such services, as well as be most likely to benefit from their provision? Some who value equity (treating everyone the same) over efficacy could find such a personalized or targeted approach problematic, even unethical. But what is ethical about providing assistance to those least likely to be helped by it, especially if doing so denies assistance to those most likely to benefit?

ARTICLE INFORMATION

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Published Online: February 1, 2016. doi:10.1001/jamapediatrics.2015.4263.

Conflict of Interest Disclosures: None reported.

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