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Sibling genes as environment: Sibling dopamine genotypes and adolescent health support frequency dependent selection

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ABSTRACT

While research consistently suggests siblings matter for individual outcomes, it remains unclear why. At the same time, studies of genetic effects on health typically correlate variants of a gene with the average level of behavioral or health measures, ignoring more complicated genetic dynamics. Using National Longitudinal Study of Adolescent Health data, we investigate whether sibling genes moderate individual genetic expression. We compare twin variation in health-related absences and self-rated health by genetic differences at three locations related to dopamine regulation and transport to test sibship-level cross-person gene–gene interactions. Results suggest effects of variation at these genetic locations are moderated by sibling genes. Although the mechanism remains unclear, this evidence is consistent with frequency dependent selection and suggests much genetic research may violate the stable unit treatment value assumption.

1. Introduction

Research consistently suggests that siblings matter for individual outcomes (Powell and Steelman, 1990; Conley, 2000; Steelman et al., 2002; Hauser and Wong, 1989). There is less consensus, however, about why siblings matter. Disagreement focuses, for example, on whether the number, order, density, or gender of siblings is important, or if apparent effects are spurious reflections of unmeasured differences between families (Steelman et al., 2002; Guo and VanWey, 1999).

The potential importance of siblings for the realization of genetic effects on behavior has received little attention. Recent developments in behavioral genetics suggest, however, that sibling characteristics could have important moderating effects on individual genetic expression. Specifically, evidence of gene–environment interaction (Caspi et al., 2002, 2003) suggests that particular variants of a gene (or genotypes) may only carry risk in certain contexts. The diathesis–stress model, for example, suggests that certain alleles (forms of a gene at a particular location) increase the risk of negative outcomes, conditional on exposure to environmental stress (Caspi et al., 2002, 2003; Guo et al., 2008; Shanahan et al., 2008; Pescosolido et al., 2008). In contrast, the biological sensitivity to context hypothesis – also called the differential susceptibility model – suggests that rather than necessarily harming individual chances, these alleles make an individual more sensitive to context (Belsky, 2013, 2005; Belsky and Pluess, 2009; Boyce and Ellis, 2005; Ellis and Boyce, 2008; Obradovic et al., 2010).

According to both models, sibling characteristics may moderate effects of individual genotype. To date, however, research on sibling effects has focused largely on social characteristics such as sibship size, order, or density. Beyond sibling social

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characteristics, research has yet to investigate whether sibling genotype moderates an individual's genotype–phenotype relationship – that is, the relationship between the genetic variants they carry and their health or behavioral characteristics. Biological theory suggests this type of gene–gene interaction is possible – or even likely. Specifically, frequency dependent selection occurs when the frequency of a genotype in a population influences its fitness. For example, research suggests that the health implications of certain genotypes may be subject to the frequency of those genotypes among those in the relevant environment (Coetzee et al., 2007; et al., 2004; Trachtenberg et al., 2003), including among siblings in a given family. Of course, in the present paper, we are not testing reproductive fitness per se nor searching for signals of selection. Rather, we are merely suggesting that historically, this may be a mechanism that would explain the persistence of genetic variation and could also produce the kind of sibling-level interaction effects we seek to test here. Ultimately, however, the core of our argument is not about selection but about cross-person genetic interaction effects. In this way, frequency dependent selection is more of a metaphor and a possible mechanism than a direct hypothesis we seek to test.

The idea of the genotype–phenotype relationship for an individual being dependent on the genotype of his/her sibling can be illustrated through the adage that "the squeaky wheel gets the grease." A characteristic that generates a disadvantage when everyone has it could provide an advantage if very few have it. Within families, for example, a sibling with more problems (health or otherwise) may get more attention from parents and achieve better outcomes, but only if she is the only one with these problems. If another sibling shares these problems, however, they may present more of a burden than an advantage as parents treat children more equally.

The sibling with more environmentally sensitive alleles could be thought of as the squeaky wheel. Though the individual effects of these alleles could be relatively weak within siblings, their effects could depend strongly on sibling's genotype. If one's sibling carries no risky or sensitive alleles, then the individual with more risky alleles may be squeakier and receive special treatment. In contrast, if both children carry a high number of risky alleles, then they may be equally squeaky and receive more equal treatment. In this example, the relative differences are important. Although both children may have more risky alleles than the general population, their differences relative to each other are important within the family. Consistent with the idea of frequency dependent selection, these relative differences could be equally important in other social contexts such as classrooms.

Combining research on sibling effects and genetic sensitivity to context, this study asks whether gene–gene interaction effects on health exist within sibling pairs. In other words, while we know that health outcomes are related to genotype (e.g., Erblich et al., 2005; Lerman et al., 1999), does the genotype–health relationship depend on sibling genotype? This novel question expands our understanding of both sibling effects and the relationship between genes and environment.

If gene–gene interactions exist within sibling sets, they could help explain the high degree of sibling inequality (Conley, 2004) as well as further question simplistic and deterministic claims about genetic effects (c.f., Herrnstein and Murray, 1994). Furthermore, gene–gene interactions within sibling sets would suggest non-independence of the units of analysis (i.e. violation of the Stable Unit Treatment Value Assumption or SUTVA) in much genetic research, with methodological implications for regression estimates of allelic effects as well as for variance decomposition methods used in classic heritability analysis. Depending on how SUTVA is violated, it could result in attenuation bias in genome-wide risk score (or candidate gene) regressions and/or overestimation of heritability estimates for various health or behavioral outcomes or phenotypes. Thus, results of this analysis have potentially wide-reaching methodological implications.

2. Theoretical and empirical background

Whether through intellectual climate (confluence theory), parental resources (resource dilution theory), or some other mechanism, there is consistent evidence that siblings matter for individual outcomes (Powell and Steelman, 1990; Conley, 2000; Steelman et al., 2002; Hauser and Wong, 1989; Zajonc and Markus, 1975). Beyond the number, order, density, or gender of siblings, however, sibling genotype may also be important for individual outcomes.

2.1. Candidate genes

The present study explores the possibility that the genes of those around us affect the expression of our own genotype through a candidate gene study on three well-known polymorphisms (genetic variants) at the DRD2, DRD4, and DAT1 genes. All three of these polymorphisms are in the dopamine system, which plays an important role in a variety of behaviors related to general and self-perceived health. For example, variation at DRD2, DRD4, and DAT1 has been associated with smoking (Erblich et al., 2005), obesity (Guo et al., 2007), alcoholism withdrawal and relapse (Finckh et al., 1997), risky behavior (Guo et al., 2010) and sensation seeking (Derringer et al., 2010). More details about each gene are provided below.

At the D2 dopamine receptor gene locus (DRD2), a genetic variant known as the Taq1A polymorphism, also called the DRD2 A1 allele, is related to fewer dopamine receptor binding sites in the brain (Pohjalainen et al., 1998). Compared to the A2 allele, possessing the A1 allele has been associated with anxiety, depression, novelty seeking, impulsiveness, lack of inhibition, and substance use (Lawford et al., 2006; Noble et al., 1998; Wiers et al., 1994; Blum et al., 1991; Bowirrat and Oscar-Berman, 2005; Connor et al., 2007). Furthermore, research finds that the consequences of carrying the A1 allele depend on context (DeLisi et al., 2009) and growing evidence suggests the A1 allele increases sensitivity to context (Mills-Koonce et al., 2007; Propper et al., 2008; Keltikangas-Jarvinen et al., 2007; see Belsky and Pluess, 2009 for a comprehensive review). Consistent with previous research, we treat the A1 allele as the risky or sensitive genotype.