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 genotype with the average level of a particular phenotype, ignoring more complicated genetic dynamics. Using National Longitudinal Study of Adolescent Health data, we investigate whether sibling genotype moderates individual genetic expression. We compare twin variation in health-related absences and self-rated health by genotype at three locations in the dopamine system – DRD2, DRD4, and DAT1 – to test sibship-level cross-person gene-gene interactions. Results suggest effects of allelic variation at these loci are moderated by the meta-genomic environment of the sibship unit. Evidence of frequency dependent selection suggests much genetic research may violate the stable unit treatment value assumption.

Keywords: genetics; twin studies; self-rated health; frequency dependent selection; SUTVA

INTRODUCTION

Research consistently suggests that siblings matter for individual outcomes (Powell and Steelman 1990; Conley 2000; Steelman et al. 2002; Hauser and Wong 1999). 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 (Steelman et al. 2002; Guo and VanWey 1999).

The potential importance of siblings for genetic expression 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 genotypes may only carry risk in certain contexts. The diathesis-stress model, for example, suggests that certain alleles increase the risk of negative outcomes, conditional on exposure to environmental stress (Caspi et al. 2002, 2003; Guo, Roettger, and Cai 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 characteristics, research has yet to investigate whether sibling genotype moderates individual genetic expression. 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, Coetzee et al. (2007) find that women with more

common alleles at the human leucocyte antigen (HLA) gene have fewer illnesses (including cold and flu episodes) and have higher self-rated health than women with rare HLA alleles. Thus, common HLA alleles appear to provide greater resistance to common or infectious pathogens and may therefore be subject to positive frequency dependent effects.[1]

At the same time, however, other research investigating this immunological genotype finds that genes involved in the major histocompatibility complex (HLA in humans) may be subject to *negative* frequency dependent selection (e.g., Borghans et al. 2004; Trachtenberg et al. 2003). Rare alleles provide better protection from viruses or pathogens through improved immune responses, which Borghans et al. (2004) suggest helps account for the high degree of polymorphism among genes that encode for molecules in the major histocompatibility complex. According to this evidence, HLA alleles appear to be subject to negative frequency dependent selection, because rare alleles provide an advantage.

Regardless of whether HLA is subject to positive or negative frequency dependent selection, the research outlined above suggests that the health implications of a genotype may be subject to the frequency of that genotype among those in the relevant environment, including among siblings in a given family. 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.

[1] Alternatively, the positive relationship between HLA allele frequency and health could be a sign that a particular allele has recently increased in frequency under selection for that particular allele. In that case, rather than positive frequency dependent selection, the advantage would come not from being common but from providing advantage at a moment in time.

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 phenotypes. Thus, results of this analysis have potentially wide-reaching methodological implications.

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 1999; Zajonc and Markus 1975). Beyond the number, order, density, or gender of siblings, however, sibling genotype may also be important for individual outcomes.

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 sensitive genotype.

The D4 dopamine receptor forms part of the neural signaling pathway for pleasure. At the D4 dopamine receptor gene locus (DRD4), the long allele (with 6 to 10 repeats as opposed to fewer) has been linked with risk-taking (Kuhnen and Chiao 2009; Dreber et al. 2009), novelty seeking (Benjamin et al 1996; Ebstein et al. 1996), and greater risk of attention deficit hyperactivity disorder (ADHD) in humans (Brookes et al. 2006; McCracken et al. 2000). Research also suggests the long DRD4 allele increases sensitivity to context (Bakermans-Kranenburg and van IJzendoorn 2006; Sheese et al. 2007; Bakermans-Kranenburg et al. 2008a, 2008b). Consistent with these studies, the long allele is considered the sensitive genotype here.

The dopamine active transporter 1 (DAT1) gene has a polymorphic 40-base pair repeat which generally repeats 9 or 10 times. The 10 repeat (10R) allele is the longer version of the

gene. Guo, Roettger, and Cai (2008) find an association between the longer 10R allele and delinquent behavior. The long DAT1 allele has also been associated with greater risk-taking (Mata et al. 2012), while the shorter DAT1 allele is associated with lower likelihood of smoking, particularly at early ages, and less novelty seeking (Lerman et al. 1999; Sabol et al. 1999). In addition, research suggests DAT1 genotype is associated with differential sensitivity to context (van den Hoofdakker et al. 2012; Sonuga-Barke et al. 2009; Belsky and Beaver 2011). We treat the long allele as the sensitive genotype.

The gene-related behaviors and characteristics discussed above are directly or indirectly related to health. Risk-taking and novelty seeking, for example, make smoking, alcohol and drug use, or even accidents more likely. Anxiety and depression are related to stress and health, and possibly self-perceived health in particular. DAT1, DRD2, and DRD4 genotype are therefore likely to be related to health.

Genes and Environment

Over the last decade, a growing body of research has suggested that certain human alleles can lead to deleterious behavioral phenotypes such as anti-social behavior, depression, smoking, obesity, risky behavior, and sensation seeking (Caspi et al. 2002, 2003; Erblich et al. 2005; Guo et al. 2007; Guo et al. 2010; Derringer et al. 2010). This research suggests certain alleles at these genetic loci are related to potentially harmful behaviors and, therefore, poor health.

Recently, however, research has found evidence of gene-environment interactions, with genetic effects conditional on environmental stressors, such as stressful life events (Caspi et al. 2002, 2003). More recently, the differential susceptibility model – also called the biological sensitivity to context hypothesis – suggests that certain genotypes are not necessarily negative, whether conditional on environment or not, but rather increase variation in outcomes depending

on environment (Belsky 2013, 2005; Belsky and Pluess 2009; Bakermans-Kranenburg et al. 2008a, 2008b; Boyce and Ellis 2005; Ellis and Boyce 2008; Obradovic et al. 2010). Thus, those with a particular genotype could experience more negative, but also more positive, outcomes than others given negative or positive environmental conditions.

We take a novel approach in an effort to better understand the relationship between genes and environment. Building on recent GxE research, we complicate the overly simplistic model of mean effects of genotype by asking whether these loci have effects on the average level of health that are contingent on the meta-genome—that is, on the distribution of genotypes around the individual. Since the family unit is the key institution in allocating attention and resources to children, we look for a sibship-level gene-gene interaction as indicative of such a dynamic. Namely, we ask if the phenotype of an individual child depends not just on her allele at the DRD2, DRD4, or DAT1 loci, but if such effects are conditional on the genotype of her siblings at that same locus.[2]

In evolutionary biology, frequency dependent selection involves variation in the selective value of a particular allele or genotype depending on its frequency in the population (Ayala and Campbell 1974). In some contexts and among some species, carriers of a rare genetic variant experience a selective advantage. In some flowering plant species, for example, carrying a genetic variant that produces a rare color can enhance reproductive fitness by attracting pollinators (Gigord et al. 2001). The benefit of the rare color genotype, however, hinges on its remaining rare among the population. Therefore, as its frequency increases, its benefits decrease, meaning in this case that the rare color genotype is subject to *negative* frequency dependent selection. In other contexts, rarity confers a disadvantage. Among a particular type of

[2] Cross-loci, cross-individual interactions could be at work, too, but to avoid ad hoc testing, we constrain the present analysis to cross-sibling interaction effects at the same locus.

snails, for example, in populations where the frequency of two shell coiling directions is approximately equal, the snails in each subgroup enjoy equal reproductive changes (Johnson 1982). In populations where one subgroup is rare, however, those with the rare phenotype face a reproductive disadvantage, indicating the underlying rare genotype is subject to *positive* frequency dependent selection.

As in the above examples, the consequences of carrying certain risky or sensitive alleles at the three dopaminergic genetic loci studied here could depend on their relative frequency in the family unit. For example, it could be adaptive to have the putatively more sensation-seeking and attention-demanding long DRD4 alleles when one is the only offspring with two copies of this allele, thereby garnering more parental attention. As with the classic prisoner's dilemma game, the long allele may be advantageous if you are the only carrier, but disadvantageous if you are not. In that case, the long DRD4 allele may be subject to negative frequency dependent selection. Alternatively, having the long allele could be advantageous when all offspring have it (positive frequency dependent selection), but deleterious when only one child carries it if that child is stigmatized, for example. Such an equilibrium might arise thanks to parent-offspring competition: When all offspring are emotionally demanding, it could pay off if parents are more likely to invest in existing children at the expense of future ones. However, when only one is demanding, that child could be stigmatized and disinvested vis-à-vis other siblings. Such a scenario would lead to an unstable equilibrium; because it is deleterious when rare but beneficial when common, the allele may be very slow to appear in a population but move to fixation quickly once it achieves a given threshold.

Alternatively, frequency dependent selection could involve the family unit as a whole. As summarized by Ellis et al. (2011), the evolutionary model underlying the differential susceptibility hypothesis suggests the presence of some sensitive alleles within the family

amounts to hedging the reproductive bets of the family. The future is unknown to both parents and children, but if the same childhood environment results in different outcomes depending on genotype, then having offspring with both sensitive and stable alleles at the DRD2, DRD4, and DAT1 loci could help increase the likelihood that at least some children will reproduce in the future. Because the same childhood environment would encourage different outcomes, some of the family's genes have a greater likelihood of being passed on regardless of what environment the future holds. In this scenario, the sensitive alleles could be subject to positive or negative frequency dependent selection within the population of families. On one hand, families carrying sensitive alleles could benefit when those alleles are rare among other families if their greater adaptability or flexibility allows a reproductive advantage in the context of environmental change. On the other hand, families carrying sensitive alleles could benefit when those alleles are more common if the variety of outcomes among children is more normative and the potentially drastic differences from one's siblings are perceived as less risky.

Regardless of the direction, the genetic loci studied here may be subject to frequency dependent selection, consistent with the evolutionary model underlying the differential susceptibility model. The specific neurotransmitter genes studied here are candidates for experiencing frequency dependent selection because they are associated with behaviors that have implications for reproductive chances, including 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). In a context where risky behavior is common, for example, an allele associated with risky behavior or sensation seeking could increase the likelihood of accidents or death while providing little benefit, thereby reducing reproductive fitness. In a context where risky behavior is rare, however, an allele associated with risky behavior could encourage innovation and provide reproductive benefits that outweigh the

risks. Either within or between families, the fitness of each of the alleles studied here could confer varying advantage or disadvantage depending on the genetic context.

Consistent with Freese's (2008) "phenotypic bottleneck" argument, the likely mechanism for an interaction between individual and sibling genotype is sibling phenotype. Having a very healthy sibling, for example, could enable an individual to be sickly or hypochondriacal (e.g., have frequent health-related absences from school). The particular sibling phenotype of importance, however, is unknown. That is, the mechanism through which sibling genotype moderates the individual genotype-health relationship could be sibling health, but could equally be sibling personality, thrill-seeking, academic achievement, or a complex combination of other phenotypes Furthermore, sibling phenotype partially depends on genotype, which (within families) is randomly assigned at conception. Therefore, genotype precedes phenotype and an interaction between individual and sibling genotype would illustrate a unique form of gene-environment correlation.

With this theoretical background in mind, we make the following hypothesis: The phenotypic effect of an individual's genotype is conditional on the genotype of her siblings at that same locus.

METHODS

The National Longitudinal Study of Adolescent Health (Harris 2009) provides sequenced genotype data for five genes, including three related to the dopamine system. We focus on the third wave of panel data for sibling pairs, which surveyed respondents in 2001-2 when they were ages 18-26.[3] Buccal swabs were collected in wave 3 from 2,612 of the 3,139 eligible siblings

[3] Siblings of individuals identified as twins in the stratified (nationally representative) sample were added, yielding 64% of sibling pairs from the probability sample and 36% from convenience sampling. In other words, to increase

from wave 1 (a compliance rate of 83 per cent) for DNA sequencing at the Institute for Behavioral Genetics (Harris et al. 2006).

The typical approach to testing gene-environment interaction effects has been to interact genotype by some measure of environment such as parenting style or socio-economic status (e.g., Guo et al. 2008; Shanahan et al. 2008). This approach is problematic because non-random distribution of alleles in the population (population stratification) could be associated with environmental differences, which are actually driving the variation in the outcomes rather than the genetic differences. In other words, the genetic effect could be spurious and a particular allele could be acting as proxy for ethnic background, region, religion or any number of other factors.

Sibling analyses represent a modest advance over typical studies of gene-environment interaction effects. Within full sibling pairs, each individual has an equal chance of inheriting one of two alleles from each parent. Thus, while typical environment measures such as family meals or parental social capital may be a reflection of rather than a moderator of genotype (Conley and Rauscher 2014), sibling genotype may be correlated with but cannot be caused by individual genotype.

While genotype within full sibling pairs is random, Add Health does not have information about parental genotype. We are therefore unable to account for parental genetic differences across sibling pairs and cannot adequately address population stratification. However, sibling analyses address population stratification concerns more than typical analyses in the general population. To further reduce concern, we limit our sample to white siblings. Finally, estimates of genotype effects among full siblings could be confounded with age or other

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the number of pairs, some siblings were added after the random sampling strategy. Sampling weights are therefore not available for sibling genetic data.

environmental differences. We therefore limit this analysis to fraternal twins because they have a great deal of environmental similarity but do not have identical genomes. Our sample includes 123 fraternal twin pairs, based on genetically confirmed zygosity.[4] Throughout the analyses, we exclude the set of fraternal triplets who appear in the data out of concern that relationships may differ. Although twin analyses increase internal validity, they reduce external validity because the sibling interactions among twins may differ from those of most children. To assess whether results among twins generalize to siblings in general, we conduct sensitivity analyses among all white full sibling pairs in Add Health.

We focus on variation at three genetic loci in the dopamine system: DRD2, DRD4, and DAT1. We specify these genotypes in multiple ways. The number of putatively "risky" or sensitive alleles per individual and twin pair is measured to identify whether twin variation in health measures is sensitive to each additional sensitive allele. We also test models in which twin pairs homozygous for (that is, with two copies of) the "risky" allele or homozygous for the "benign" allele are specified separately and compared to the other groups. We show results from two of these approaches below, but results are similar using other specifications. While some research (e.g., Dreber et al. 2009; Guo et al. 2007) specifies DRD4 alleles with 7 repeats, we include those with 6 to 10 repeats in the long allele category, leaving those with 2 through 5 repeats in the short, "non-risky" category. However, results are similar when specifying DRD4 7R alleles.

Most research focuses on the relationship between dopamine genes and specific behavioral or health outcomes, such as smoking, obesity, alcoholism, risky behavior, and sensation seeking (Erblich et al. 2005; Guo et al. 2007; Finckh et al. 1997; Guo et al. 2010;

[4] Monozygosity classification required complete matches on 11 "highly polymorphic, unlinked short tandem repeat (STR) markers: D1S1679, D2S1384, D3S1766, D4S1627, D6S1277, D7S1808, D8S1119, D9S301, D13S796, D15S652 and D20S481" and a sex chromosome identification marker (Harris et al. 2006:992).

Derringer et al. 2010). These outcomes are all related to general health (Cherpitel 1999; Manderbacka et al. 1999), but less research has addressed the relationship between the genes we study and overall health measures. Because our goal is to understand the relationship between these genotypes and overall health, we pass over the intermediary, specific health-related outcomes and examine effects on general health using two measures. First, health-related absences are measured using a frequency score of how often an individual reports missing school or work due to health problems in the last month. Answers range from zero (never) to four (every day), with a mean of about 0.2 (see Tables 1 and 2 for descriptive statistics). Second, we create an indicator of self-rated health: individuals who rate their general health very good or excellent (about 75%). Separate analyses using an indicator for those who report excellent health (about 34%) yield consistent results.

In equation 1 below, *i* indexes individual fraternal twins. Individual health is predicted by twin's health (sibling phenotype), individual genotype, sibling genotype, and the interaction between the two, controlling for sex. With a sample of 246 individual DZ (dizygotic or fraternal) twins, regressions are powered at 0.8 to detect an effect size of at least 0.03 at α=.05. We use Huber-White standard errors to adjust for family-level clustering.

$$\text{Health}_i = a + \beta_1 \text{SibHealth}_i + \beta_2 \text{Genotype}_i + \beta_3 \text{SibGenotype}_i + \beta_4 \text{Gen} * \text{SibGen}_i + \beta_5 \text{Sex}_i + \varepsilon_i \quad (1)$$

A concern is that these genetic markers may act as proxies for behavioral phenotypes which are difficult to measure. For example, the long DRD4 allele could cause addictive behavior in siblings, reducing sibling health. In that case, controlling for the allele in question and sibling health would result in multicollinearity and misestimate the model. This issue, however, is common to molecular genetic association studies.

Table 1 provides descriptive information for individual fraternal twins. Each individual in Table 1 would appear as both an individual and a sibling. Therefore, the individual and sibling means would be identical (at the group but not the individual level) and sibling means are therefore not shown.

RESULTS

Table 2 shows mean health outcomes by individual and sibling genotype among white fraternal twins. These descriptive statistics illustrate that – among individuals with the same genotype – phenotype varies by sibling genotype. For example, among fraternal twins with no DRD2 A1 alleles, health absences average only 0.19 if their twin also has no A1 alleles. However, if their twin has one A1 allele, health absences average 0.25 days and 0.4 days if their twin has two A1 alleles.

Although the mechanism of any interaction effect between individual and sibling genotype is likely phenotype (or some combination of phenotypes), an alternative possibility is that the effect actually reflects parental genotype. In that case, sibling genotype could act as a rough proxy for parental genotype and an apparent interaction between individual and sibling genotype could reflect an interaction with parental genotype (via parental phenotype). Unfortunately, we do not have information on parental genotype. However, such a scenario would still suggest that the effect of individual genotype depends on the genotype of those in the environment. Nevertheless, in an attempt to indirectly address this possibility, Table 3 shows the distribution of parental characteristics (education, unemployment status, self-rated very good health, frequency of alcohol use, and reported happiness) by combined sibling genotype (the sibling pair total number of sensitive alleles at each genetic locus). With only a few exceptions (for biological father's education and happiness in Panel B), there is not a linear relationship

between parental characteristics and the distribution of sibling pair genotype. In general, therefore, Table 3 suggests that parental characteristics are not linearly related to sibling pair genotype, which reduces the likelihood that sibling genotype is simply acting as a proxy for parental phenotype or genotype.

Table 4 presents results from regressions which check whether the differences in individual health by sibling genotype are statistically significant, controlling for sex and sibling phenotype. We find some evidence to support frequency dependent effects. Individual fraternal twins with two copies of the long DAT1 allele report significantly fewer health-related absences, but only if their twin does not also carry two copies of the long DAT1 allele ($p<.10$). As illustrated in Figure 1, the health implications of DAT1 genotype seem to depend on sibling DAT1 genotype. Similarly, fraternal twins report fewer health absences if they or their twin have two copies of the long DRD4 allele, but significantly more health absences if they both do. These findings suggest that, while the long DRD4 and DAT1 genotype may be associated with better health individually, when one's sibling shares the same genotype it can yield significantly poorer health.

When predicting very good health, individuals are more likely to report very good health if they have two copies of the long DRD4 allele or if their sibling has this genotype. If both the individual and the sibling share an alternative DRD4 genotype, however, individuals are less likely to report very good health. This relationship is shown in Figure 2. This finding suggests that the long DRD4 genotype may be associated with better health whether carried by the individual or the sibling.

When the number of long DRD4 alleles is specified continuously, we find that having additional long alleles at the DRD4 locus has no significant independent effect. When considered in context with sibling DRD4 genotype, however, long alleles are associated with a

greater likelihood of very good health as the number of long sibling alleles increases (Figure 3). Thus, if one's sibling has no long DRD4 alleles, additional long DRD4 alleles do not significantly change the likelihood of reporting very good health. If one's sibling has two long alleles, however, each additional long DRD4 allele increases the likelihood of reporting very good health. Specifying number of long DRD4 alleles continuously, therefore, suggests the long DRD4 genotype may be associated with better health, but only if one's sibling shares the same genotype.

Sibling phenotype could partially mediate the interaction effect between individual and sibling genotype. To assess the extent to which sibling self-rated health explains the pattern we find, we conduct a path analysis of Model 4B in Table 4. The resulting path diagram is presented in Figure S1 in the Appendix. The standardized path coefficients illustrate that sibling self-rated health does not mediate the interaction between individual and sibling DRD4 genotype. Nevertheless, a complex combination of other sibling phenotypes could still constitute the pathway through which sibling genotype moderates the effect of individual genotype. Given the potential complexity, identification of the mechanism is beyond the scope of this analysis.

Finally, consistent with the results for DRD4, an individual fraternal twin is slightly less likely to rate her health as very good if she or her sibling has two copies of the DRD2 A1 allele. However, if both twins have two A1 alleles, she is significantly more likely to report very good health. Thus, having two copies of the DRD2 A1 allele is associated with very good health, but only if one's sibling shares the same genotype.

To summarize results in Table 4, holding two copies of the long DAT1 or DRD4 allele is associated with fewer health-related absences, but only if one's twin does not carry the same genotype. When predicting very good health, however, long DRD4 alleles and DRD2 A1 alleles may be associated with better health, but only if one's sibling does carry the same genotype. In

both cases, there is evidence that the relationship between individual genotype and health varies by sibling genotype. In the case of DRD4, however, the implications of sibling genotype seem to differ by outcome.

The differences by outcome could reflect the specific measures used here: health absences and self-rated very good health. The putatively more sensation-seeking and attention-demanding long DRD4 alleles may garner enough parental resources to reduce health absences, but only when one's twin does not also have two copies of this allele. As with the classic prisoner's dilemma game, the long allele may be advantageous (reducing health absences) if you are the only carrier, but disadvantageous if you are not.

At the same time, however, carrying the long allele could be advantageous (for relatively more common outcomes such as self-rated very good health) when all offspring have it, but deleterious when only one child carries it. For less exceptional outcomes such as very good health, the long DRD4 allele may be subject to positive frequency dependent selection. While speculative at this point, such a scenario of positive frequency dependent selection for some outcomes and negative selection for others could help explain why these putatively disadvantageous alleles have reached equilibrium in the population.

Table 5 includes results from the same regressions as Table 4, but limited to same sex fraternal twins. With a few exceptions, results are similar when limited to same sex twins. The individual and sibling gene-gene interaction does not reach significance when specifying number of long DRD4 genotypes, predicting very good health with an indicator for two copies of the long DRD4 genotypes, or predicting health absences with an indicator for two copies of the long DRD4 allele. In general, however, the relationship between health and individual genotype varies by twin genotype regardless of the sex of one's fraternal twin.

To assess whether results generalize beyond twins to singleton siblings, we conduct sensitivity analyses among white full sibling pairs. Results presented in Table S1 of the Appendix provide some additional evidence that the effects of individual genotype are moderated by sibling genotype and generalize beyond twins to siblings.

DISCUSSION

Our results are consistent with the hypothesis that the effects of allelic variation at three genetic loci are moderated by the genetic environment of the sibship unit. We had predicted that, from a parental investment point of view, it might be advantageous to have the putatively more sensation-seeking and attention-demanding alleles when one is the only offspring to be homozygous for this allele, thereby garnering more parental attention. We found evidence of this dynamic for long DRD4 and DAT1 alleles, but only when predicting health-related absences. For the DRD2 A1 allele – and when specifying the number of long DRD4 alleles linearly – we found evidence of the opposite sort of interaction effect: When one has the "risky" alleles, it is more disadvantageous to be the only one in the brood with this genotype. In other words, the sole sensation-seeking offspring may be stigmatized and isolated, which in turn, could lead to poorer health. Such a scenario could reflect the different outcomes studied and suggests the possibility that it is not frequency dependent selection (i.e. fitness advantage) that is at work, but rather some cross-individual pleiotropic effect (on multiple phenotypes) that may be operant within the social network of the family household.

Regardless of the direction of effects or the underlying mechanism, however, if the behavioral phenotype of an individual is not just contingent on her own genotype but that of her siblings, then it suggests non-independence of the units of analysis (i.e. violation of the Stable Unit Treatment Value Assumption) in much genetic research of human behavior. The non-

independence of sibling genotypes has implications for models that include molecular markers as covariates (investigating allelic or gene-environment interaction effects) and for those that use variance decomposition methods to generate estimates, as in classic heritability analysis. In fact, this non-independence may help explain why classic additive heritability estimates cannot be replicated (or even approached) by GWAS studies that regress phenotypes against all known polymorphic loci. Namely, depending on how SUTVA is violated, it could result in attenuation bias in genome-wide marker regressions and/or overestimation of MZ-DZ differences in intra-class correlations for given phenotypes. Such biases could question the reliability of heritability estimates based on twins and introduce much unobserved heterogeneity to models predicting effects of a particular allele. These possibilities should be explored by future researchers with genome-wide data.

More broadly, our results suggest the importance of moving beyond average treatment effects to investigate a potentially more complex relationship between genes and health. The findings outlined above suggest that, not only are genetic effects dependent on context, they are dependent on genetic context – or the genes of our siblings. While the specific genes and outcomes investigated here may have limited potential to understand within-family dynamics, our results suggest that sibling gene-gene interactions could help explain the high degree of inequality among siblings within the same family (Conley 2004).

Finally, while research on sibling effects has focused largely on social characteristics, our findings suggest that sibling genotype can also carry important implications for individual outcomes and, in fact, moderates individual genetic expression. This paper thus expands the research on sibling effects to incorporate genetics. If future research supports our findings, it could expand social and medical focus from individual genotype to the genetic makeup of a larger social unit, such as the family.

These implications are highly speculative at this point, given the limitations of this particular analysis. Limitations include the lack of parental genotype data and relatively small number of sibling pairs. In addition, sibling genotype could act as a proxy for parental genotype. If parents are homozygous for the sensitive genotype, sibling genotype cannot differ. In that case, the apparent effect of sibling genotype could reflect a different within-family dynamic. Also, absent parental genotype controls, alleles could be non-randomly distributed across environments. That is, conditional on a given individual's genotype, the genotype of his/her sibling may be reflecting not just random assignment inherent to allele recombination and segregation but also population differences in frequencies. Future research should seek to replicate our findings using datasets that have measured parental genotype in addition to sibling genotype.

Despite these limitations, however, we believe the ideas and findings presented here should at least open this avenue of research to those interested in exploring how genetic variation affects health. It is possible, for example, that the non-independence of individual genotypes or the genetic effect on phenotypic variation is limited to the three genes in the dopamine system studied here. We do not have any reason to believe this is the case, because these genes are not extraordinary. However, future research should investigate potentially similar effects of other candidate genes that may have health implications. Similarly, while this study offers some evidence of effects for self-rated health and health absences, future research could investigate whether genetic effects and non-independence are relevant for other health and behavioral outcomes. Such research can take advantage of genome-wide data to address these questions – ideally incorporating parental genetic data as well. Additionally, in all of these potential studies, evidence found here suggests that we should address potential SUTVA violations when investigating genetic effects. All said, a much more complicated view of how genotypes interact

with the environment and with each other must suffuse empirical models if a complete understanding of genetics is to be fully realized.

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TABLES

Table 1: Descriptive Statistics – White Fraternal Twins with Complete Individual and Sibling Data

	Mean	Std. Dev.
Health Absences	0.20	0.41
Very Good Health	0.75	0.43
DRD2 A1/A1 *	0.05	0.21
DRD2 # A1 alleles *	0.42	0.58
DRD4 6-10R/6-10R	0.04	0.20
DRD4 # 6-10R alleles	0.36	0.56
DAT1 10R/10R	0.60	0.49
DAT1 # 10R alleles	1.53	0.62
Male	0.54	0.50
N	246	

* N = 244

Table 2: Mean Individual Phenotype by Sibling Genotype – White Fraternal Twins

	Health Absences	Very Good Health	N
DRD2 no A1 Alleles			
Sib 0 A1 alleles	0.19	0.78	149
Sib 1 A1	0.25	0.70	77
Sib 2 A1	0.40	0.60	5
DRD4 no 6-10R			
Sib 0 6-10R	0.20	0.76	167
Sib 1 6-10R	0.21	0.67	63
Sib 2 6-10R	0.00	1.00	4
DAT1 both 10R			
Sib 0 10R	0.00	1.00	2
Sib 1 10R	0.00	0.74	23
Sib 2 10R	0.21	0.72	122
DAT1 no 10R			
Sib 0 10R	0.21	0.93	14
Sib 1 10R	0.25	0.80	60
Sib 2 0R	0.24	0.68	25

Table 3: Parental Characteristics by Sibling Pair Genotype
Panel A: Biological Mother

	Education	Unemployed	Very Good Health	Alcohol Frequency	Happy	N
DRD2 A1 Alleles						
0	13.39	0.07	0.61	1.17	0.98	115
1	13.33	0.00	0.56	1.56	1.00	40
2	12.04	0.00	0.44	1.04	0.92	53
3+	13.33	0.00	0.75	1.42	1.00	12
DRD4 6-10R Alleles						
0	13.22	0.05	0.54	1.20	0.95	119
1	12.92	0.04	0.62	1.45	1.00	52
2	12.97	0.00	0.45	0.97	1.00	35
3+	12.29	0.00	0.86	1.14	1.00	14
DAT1 10R Alleles						
<2	11.90	0.00	0.30	1.30	1.00	20
2	13.15	0.05	0.67	1.81	1.00	46
3	13.10	0.05	0.71	1.12	1.00	41
4	13.19	0.04	0.52	1.00	0.94	113

Panel B: Biological Father

	Education	Unemployed	Very Good Health	Alcohol Frequency	Happy	N
DRD2 A1 Alleles						
0	13.67	0.00	0.73	1.66	0.99	110
1	13.55	0.00	0.78	2.15	0.96	31
2	12.93	0.00	0.25	2.19	0.86	44
3+	10.75	0.00	0.25	0.50	1.00	8
DRD4 6-10R Alleles						
0	13.38	0.00	0.62	2.01	0.94	102
1	13.10	0.00	0.53	1.55	0.97	50
2	14.03	0.00	0.78	1.56	1.00	29
3+	12.67	0.00	0.60	1.40	1.00	12
DAT1 10R Alleles						
<2	12.78	0.00	0.50	2.50	1.00	18
2	13.05	0.00	0.55	2.13	0.90	41
3	13.52	0.00	0.71	1.63	1.00	33
4	13.54	0.00	0.62	1.67	0.96	101

Includes white fraternal twins with complete individual, sibling, and parent data.

Table 4: Coefficients from Models Investigating Individual-Sibling Genotype Interaction among White Fraternal Twins

	Health-Related Absences A		Self-Rated Very Good Health B		Model
Sibling Phenotype	0.01		0.01		
DRD2 A1/A1	-0.23	*	-0.15		1
Sibling DRD2 A1/A1	0.15		-0.14		
A1/A1 * Sibling A1/A1	0.01		0.54	*	N = 244
Sibling Phenotype	0.00		0.02		
DRD2 #A1 alleles	-0.06		-0.01		2
Sibling DRD2 #A1 alleles	0.02		-0.07		
#A1 * Sibling #A1	0.05		0.03		N = 244
Sibling Phenotype	0.01		-0.01		
DRD4 6-10R/6-10R	-0.20	*	0.27	*	3
Sibling DRD4 6-10R/6-10R	-0.20	*	0.27	*	
6-10R/6-10R * Sibling 6-10R/6-10R	0.51	*	-0.26	*	N = 246
Sibling Phenotype	0.02		-0.01		
DRD4 #6-10R alleles	-0.11	+	-0.06		4
Sibling DRD4 #6-10R alleles	0.04		-0.16	+	
#6-10R * Sibling #6-10R	0.02		0.19	*	N = 246
Sibling Phenotype	0.00		0.01		
DAT1 10R/10R	-0.24	*	-0.06		5
Sibling DAT1 10R/10R	-0.01		-0.14		
10R/10R * Sibling 10R/10R	0.22	+	0.10		N = 246
Sibling Phenotype	0.01		0.01		
DAT1 #10R alleles	-0.23	*	0.00		6
Sibling DAT1 #10R alleles	-0.02		-0.11		
#10R * Sibling #10R	0.08		0.01		N = 246

* $p < 0.05$; + $p < 0.10$ All models control for sex (male) and standard errors are adjusted for family clustering.
Note: Sibling Phenotype indicates Health-Related Absences or Self-Rated Very Good Health according to the column. Individual phenotype depends on own genotype, twin phenotype, and twin genotype, providing tentative evidence for the possibility of frequency dependent selection.

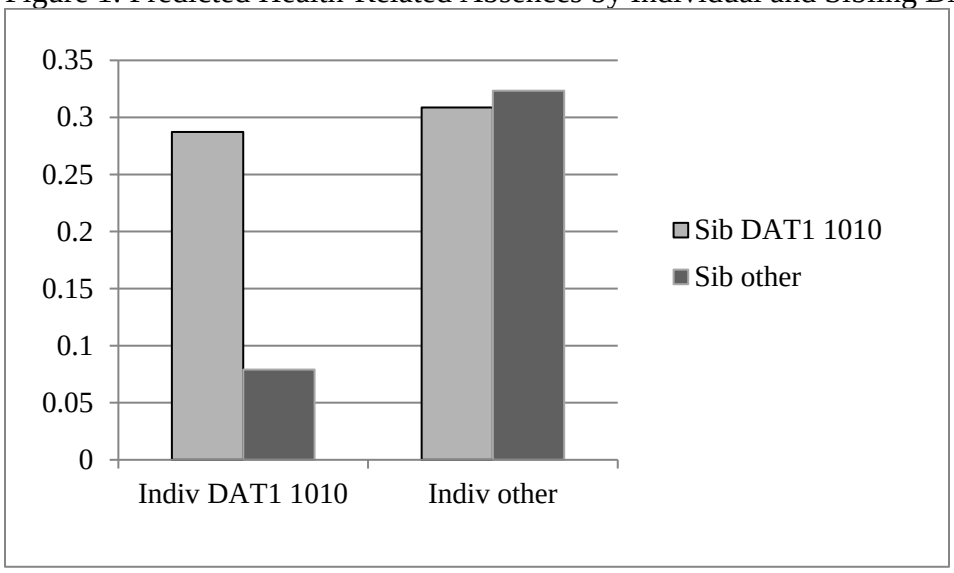
Table 5: Coefficients from Models Investigating Individual-Sibling Genotype Interaction among Same Sex White Fraternal Twins

	Health-Related Absences A		Self-Rated Very Good Health B		Model
Sibling Phenotype	-0.02		0.08		
DRD2 A1/A1	-0.23	*	-0.75	*	1
Sibling DRD2 A1/A1	0.26		0.33	*	
A1/A1 * Sibling A1/A1	-0.27		0.67	*	N = 140
Sibling Phenotype	-0.04		0.05		
DRD2 #A1 alleles	-0.12		-0.06		2
Sibling DRD2 #A1 alleles	-0.07		0.00		
#A1 * Sibling #A1	0.09		0.00		N = 140
Sibling Phenotype	-0.04		0.04		
DRD4 6-10R/6-10R	-0.18	*	0.22	*	3
Sibling DRD4 6-10R/6-10R	-0.18	*	0.22	*	
6-10R/6-10R * Sibling 6-10R/6-10R	0.65	*	-0.16		N = 142
Sibling Phenotype	-0.03		0.04		
DRD4 #6-10R alleles	-0.07		0.01		4
Sibling DRD4 #6-10R alleles	-0.01		-0.12		
#6-10R * Sibling #6-10R	0.02		0.14		N = 142
Sibling Phenotype	-0.02		0.05		
DAT1 10R/10R	-0.22	*	-0.02		5
Sibling DAT1 10R/10R	0.00		-0.10		
10R/10R * Sibling 10R/10R	0.15		0.13		N = 142
Sibling Phenotype	-0.02		0.05		
DAT1 #10R alleles	-0.21	*	-0.02		6
Sibling DAT1 #10R alleles	-0.04		-0.14		
#10R * Sibling #10R	0.08		0.06		N = 142

* p <0.05; + p<0.10 All models control for sex (male) and standard errors are adjusted for clustering.
Note: Sibling Phenotype indicates Health-Related Absences or Self-Rated Very Good Health according to the column. Individual phenotype depends on own genotype, twin phenotype, and twin genotype, providing tentative evidence for the possibility of frequency dependent selection.

FIGURES

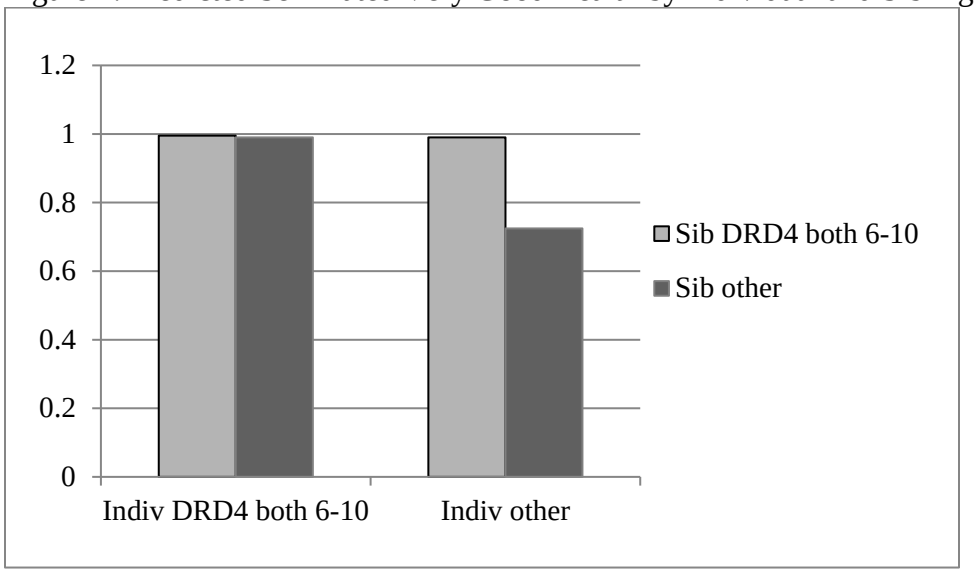
Figure 1: Predicted Health-Related Absences by Individual and Sibling DAT1 Genotype



p<0.1

Based on Model 5A in Table 4. Individual phenotype – in this case health-related absences – depends on individual and sibling DAT genotype.

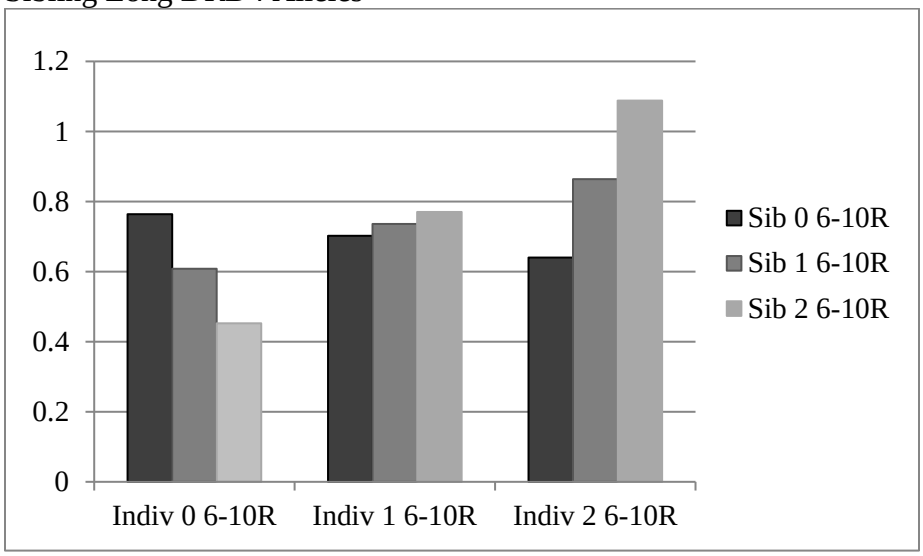
Figure 2: Predicted Self-Rated Very Good Health by Individual and Sibling DRD4 Genotype



p<.05

Based on Model 3B in Table 4. Individual phenotype – in this case the likelihood of an individual self-reporting very good health – depends on individual and sibling DRD4 genotype.

Figure 3: Predicted Likelihood of Self-Rated Very Good Health by Number of Individual and Sibling Long DRD4 Alleles



$p<.05$

Based on Model 4B in Table 4. Individual phenotype – in this case the likelihood of an individual self-reporting very good health – depends on individual and sibling DRD4 genotype.

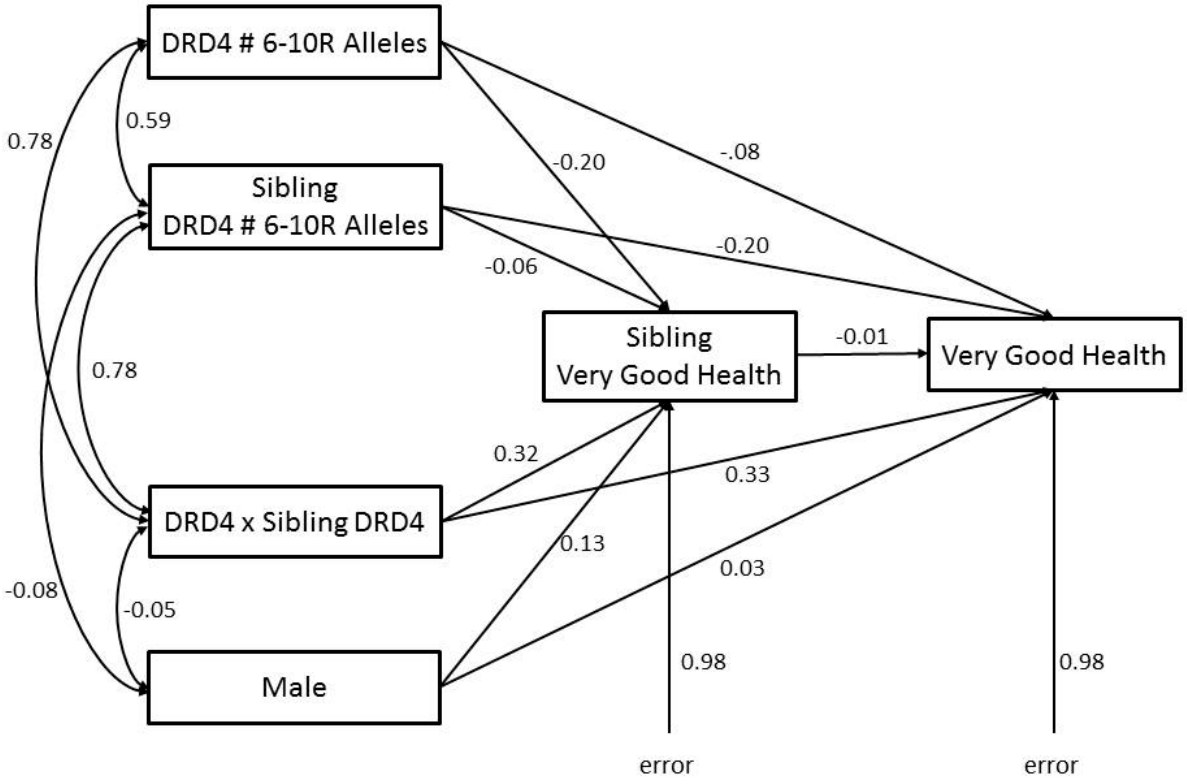
APPENDIX

Table S1: Coefficients from Models Investigating Individual-Sibling Genotype Interaction among White Full Siblings

	Health-Related Absences A		Self-Rated Very Good Health B		Model
Sibling Phenotype	0.12	*	0.10	*	
DRD2 A1/A1	-0.09	+	-0.09		1
Sibling DRD2 A1/A1	-0.09	+	0.15	*	
A1/A1 * Sibling A1/A1	0.22	*	0.01		N = 1396
Sibling Phenotype	0.12	*	0.10	*	
DRD2 #A1 alleles	-0.02		0.01		2
Sibling DRD2 #A1 alleles	-0.03		0.01		
#A1 * Sibling #A1	0.03		0.00		N = 1396
Sibling Phenotype	0.12	*	0.10	*	
DRD4 6-10R/6-10R	-0.03		-0.11		3
Sibling DRD4 6-10R/6-10R	0.00		0.03		
6-10R/6-10R * Sibling 6-10R/6-10R	-0.01		0.10		N = 1404
Sibling Phenotype	0.12	*	0.10	*	
DRD4 #6-10R alleles	0.04		0.02		4
Sibling DRD4 #6-10R alleles	-0.01		-0.03		
#6-10R * Sibling #6-10R	-0.02		0.01		N = 1404
Sibling Phenotype	0.12	*	0.09	*	
DAT1 10R/10R	-0.12	*	0.04		5
Sibling DAT1 10R/10R	-0.02		0.03		
10R/10R * Sibling 10R/10R	0.13	*	-0.05		N = 1406
Sibling Phenotype	0.12	*	0.09	*	
DAT1 #10R alleles	-0.13	*	0.03		6
Sibling DAT1 #10R alleles	-0.05		0.01		
#10R * Sibling #10R	0.07	*	-0.01		N = 1406

* $p < 0.05$; + $p < 0.10$ All models control for sex (male) and age; standard errors are adjusted for family clustering.
Note: Sibling Phenotype indicates Health-Related Absences or Self-Rated Very Good Health according to the column. Individual phenotype depends on own genotype, sibling phenotype, and sibling genotype, providing tentative evidence for the possibility of frequency dependent selection.

Figure S1: Path Diagram of Model Predicting Very Good Health



Path analysis of regression model 4B in Table 4. Straight lines represent standardized path coefficients. Curved lines represent correlations.