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Antagonistic Pleiotropy at the Human *IL6* Promoter Confers Genetic Resilience to the Pro-Inflammatory Effects of Adverse Social Conditions in Adolescence

Steven W. Cole, **Jesusa M. G. Arevalo**, **Kavya Manu**, **Eva H. Telzer**, **Lisa Kiang**, **Julienne E. Bower**, **Michael R. Irwin**, and **Andrew J. Fuligni**
Steven W. Cole, Department of Medicine, Norman Cousins Center, Jonsson Comprehensive Cancer Center, Molecular Biology Institute, and Department of Psychiatry & Biobehavioral Science, University of California, Los Angeles; Jesusa M. G. Arevalo and Kavya Manu, Department of Medicine, University of California, Los Angeles; Eva H. Telzer, Department of Psychology, University of California, Los Angeles; Lisa Kiang, Department of Psychology, Wake Forest University; Julienne E. Bower, Department of Medicine, Norman Cousins Center, Department of Psychiatry & Biobehavioral Science, and Department of Psychology, University of California, Los Angeles; Michael R. Irwin, Norman Cousins Center, Jonsson Comprehensive Cancer Center, and Department of Psychiatry & Biobehavioral Science, University of California, Los Angeles; Andrew J. Fuligni, Norman Cousins Center and Department of Psychiatry & Biobehavioral Science, University of California, Los Angeles.

Abstract

The authors tested the evolutionary genetic hypothesis that the functional form of an asymmetrically risky Gene × Environment interaction will differ as a function of age-related antagonistic pleiotropy (i.e., show opposite effects in young vs. old individuals). Previous studies have identified a polymorphism in the human *IL6* promoter (rs1800795; *IL6* –174 G/C) that interacts with adverse socioenvironmental conditions to promote chronic inflammation in older adults (elevated C-reactive protein). This study identifies a protective effect of the same polymorphism in 17- to 19-year-old adolescents confronting socioeconomic adversity. Over 60% of the environmental risk contribution to the *IL6* × Socioeconomic Status interaction could be accounted for by interpersonal stress and adult role burden. Thus, the *IL6* –174G allele does not represent an undifferentiated risk factor but instead sensitizes inflammatory biology to socioenvironmental conditions, conferring either genetic vulnerability or resilience depending on the developmental "somatic environment" that interacts with social conditions to influence gene expression.

Keywords

gene–environment interaction; SES; stress; adolescence; inflammation

Social conditions interact with genes to influence human health and longevity (Finch, 2007; Hernandez & Blazer, 2006; Robinson, 2004). For example, twin studies have shown that even the most robust socioenvironmental health risk factor—low socioeconomic status (SES)—impacts health outcomes differently depending upon an individual's total genetic endowment (Johnson & Krueger, 2005; Krieger, Chen, Coull, & Selby, 2005; Lichtenstein,

Correspondence concerning this article should be addressed to Steven W. Cole, 11-394 Factor Building, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1678. coles@ucla.edu.

Harris, Pedersen, & McClearn, 1993; Osler, McGue, & Christensen, 2007). Analyses of Gene × Social Environment (G × SE) interactions in health now seek to determine which specific molecular pathways mediate the biological impact of adverse social conditions (Caspi & Moffitt, 2006; Cole, 2009; G. Miller, Chen, & Cole, 2009; G. E. Miller, Chen, Fok, et al., 2009) and which specific genetic polymorphisms moderate those effects to render some people resilient as others remain vulnerable (Cole et al., 2010; Johnson & Krueger, 2005; Kim-Cohen, Moffitt, Caspi, & Taylor, 2004; Moffitt, Caspi, & Rutter, 2005).

Efforts to identify specific G × SE interactions have been complicated by frequent failures to replicate initial findings. Inconsistent results in subsequent studies have often been interpreted as indicating the absence of any true effect (Risch et al., 2009). However, the evolutionary genetic theory of antagonistic pleiotropy (Williams, 1957) suggests an alternative explanation: Differences in the magnitude of a true G × SE interaction are to be expected if the studied samples differ along some additional environmental dimension that affects the phenotypic expression of that interaction. One moderating dimension may be the changing "somatic environment" of the developing body (Williams, 1957). The evolutionary genetic theory of antagonistic pleiotropy was originally developed to explain the evolutionary maintenance of genetic features that are maladaptive late in life based on the assumption that they must be selectively advantageous earlier in life or else they would have been eradicated from the gene pool by adverse selection (Williams, 1957). In particular, genes that help individuals survive through the period of reproductive maturity (i.e., young adulthood) should be positively selected for, even if they also confer substantial fitness penalties later in life (i.e., older adulthood; Williams, 1957). Although theoretically logical, few instances of age-dependent antagonistic pleiotropy have actually been documented, particularly in the context of G × SE interactions.

In the present study, we tested the hypothesis that a genetic polymorphism in the human *IL6* promoter that was recently found to interact with adverse socioenvironmental conditions to increase chronic inflammation and mortality in older adults (Cole et al., 2010) would show the opposite effect in adolescents (i.e., would be associated with reduced inflammation during peak reproductive maturity). *IL6* is a logical candidate gene for examining antagonistic pleiotropy because the pro-inflammatory cytokine that it encodes (Interleukin-6 [IL-6]) plays a major role in defending the body against acute infection (a dominant factor in survival through reproductive maturity; Finch, 2010) but also fuels chronic inflammatory processes that contribute to the metabolic, cardiovascular, neurodegenerative, and neoplastic diseases that dominate late-life mortality (Finch, 2007). IL-6 levels show a general age-dependent increase over the lifespan (Ershler & Keller, 2000; Kiecolt-Glaser et al., 2003) and up-regulate in response to adverse socioenviron-mental conditions (Cole et al., 2010; Kiecolt-Glaser et al., 2011; Kiecolt-Glaser et al., 2003; Powell et al., 2009; Stark, Avitsur, Hunzeker, Padgett, & Sheridan, 2002).

A molecular basis for adversity-related increases in *IL6* expression has been identified in the sympathetic nervous system's (SNS) activation of the GATA1 transcription factor (Cole et al., 2010). In addition, a polymorphism in the promoter sequence of the *IL6* gene (rs1800795; *IL6* –174G/C) has been found to modulate individual sensitivity to the effects of threatening or adverse environments in activating *IL6* transcription (Cole et al., 2010). In people bearing the ancestral G allele of the polymorphism, adversity-induced activation of the GATA1 transcription factor leads to increased *IL6* gene transcription, and those individuals show increased risk of inflammation-related disease and mortality when confronted by extended periods of significant life adversity (Cole et al., 2010). In contrast, individuals bearing the C allele of the polymorphism are protected from such effects, because the GATA1 transcription factor cannot efficiently bind to the *IL6* –174 locus after SNS-induced activation (Cole et al., 2010). The *IL6* –174G/C polymorphism thus provides

one defined genetic element that influences individual sensitivity to the health effects of an adverse social environment (i.e., a specific G × SE interaction). Several additional studies have linked the same *IL6* promoter polymorphism to the risk of a variety of somatic illnesses (DeMichele et al., 2009; DeMichele et al., 2003; Finch, 2007; Fishman et al., 1998; comprehensively reviewed at OMIM, 2010; SNPedia, 2010) as well as brain-mediated affective and motivational processes (Bull et al., 2009; Collado-Hidalgo, Bower, Ganz, Irwin, & Cole, 2008).

Most of these studies have been conducted in older adults, and it is unclear whether similar *IL6* G × SE interactions would occur in younger individuals, or whether the functional form of such interactions might be reversed, as predicted by antagonistic pleiotropy. We focused on adolescence because it is a period when children face increased personal exposure to and involvement in the environmental stressors that are believed to interact with the *IL6* gene to influence inflammation (Larson & Amussen, 1991; Steinberg, 1990). In addition, IL-6 protein levels show an age-related increase (Kiecolt-Glaser et al., 2003), so adolescents would likely show more variance in inflammatory biology than would younger children. At the same time, the period of adolescence closely follows puberty, and the theory of age-related antagonistic pleiotropy implies that the differential effects of genes at younger ages would be most evident either before or soon after the attainment of reproductive maturity (Williams, 1957). Inflammation-related G × SE interaction in adolescence could have considerable significance for later health outcomes, because individual differences in chronic inflammation emerge early in life (Juonala et al., 2006), and socioenvironmental conditions appear to affect those dynamics both concurrently (Chen et al., 2006; Chen et al., 2009; Fuligni, Telzer, Bower, Cole, et al., 2009; Fuligni, Telzer, Bower, Irwin, et al., 2009; Howe et al., 2010; Kivimaki et al., 2005) and decades later in adulthood (Danese et al., 2008; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; G. E. Miller, Chen, Fok, et al., 2009; Taylor, Lehman, Kiefe, & Seeman, 2006). In addition to driving the development of chronic diseases in adulthood (Finch, 2007), inflammation may also influence affective and social processes in young adults (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Eisenberger, Berkman, et al., 2010; Eisenberger, Inagaki, Mashal, & Irwin, 2010; Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009). As such, inflammation-related G × SE dynamics may functionally parallel a growing body of literature documenting developmental evolution of G × SE interactions in the context of neurobiology and behavior (Casey et al., 2009).

Method

Sample and Design

The sample of 64 adolescents in the current study is a subsample of a group of 383 adolescents from three high schools in the Los Angeles, California area who took part in a larger study of the daily experience of adolescents when they were in the 12th grade (M_{age} = 17.79 years in the 12th grade). The current sample consisted of 39 participants from Latin American backgrounds, most of whom (95%) reported Mexican as their ethnic background, and 25 participants from a mix of European backgrounds (e.g., Irish, Jewish, German). All adolescents spoke and read English fluently, although this was not a requirement for participation in the study. The sample was 56.2% female.

During the spring of the 12th grade, participants filled out questionnaires during school hours and then completed a daily diary checklist each night before going to bed for 14 consecutive days. The diary checklists were only three pages long and took about 5–10 min to complete. To monitor completion of the diary checklists, participants were also provided with 14 manila envelopes and an electronic time stamper (Dymo Corporation, Stamford, CT). The time stamper is a small, hand-held device that imprints the current date and time

and is programmed with a security code so that the correct date and time cannot be altered. Participants were instructed to place their completed diary checklist into a sealed envelope each night and to stamp the seal of the envelope with the time stamper. At the end of the 2-week period, the adolescents returned the completed materials to the school and received $30 for participating in the study. In addition, the adolescents were told that they would receive two movie passes if inspection of the data indicated that they had completed the diaries correctly and on time. The time stamper method of monitoring the completion of the diaries and the cash and movie pass incentives resulted in a high rate of compliance, with 98.9% of the diaries being completed.

In the fall and winter after the 12th grade, the participants were re-contacted and recruited to participate in an additional round of data collection. Participants came to a lab at the University of California, Los Angeles (UCLA), where they completed questionnaires, had height and weight measurements taken using a stadiometer, and provided blood samples for the evaluation of C-reactive protein (CRP). Appointments took place an average of 7.79 months (range = 3.93 months to 12.24 months) after the participants completed their questionnaires and diary checklists during the 12th grade. Blood samples were drawn at a variety of times during the day, with the majority (84.7%) being obtained between the hours of 12:00 pm and 4:45 pm. The modal time was 1:30 pm. All procedures were approved by the UCLA Institutional Review Board, and all participants were over 18 years of age at the time of data collection.

Socioeconomic Status, Adult Domestic Role Burden, and Stress

A composite measure of adolescents' SES was created by standardizing and averaging adolescents' reports of their mothers' and fathers' education (1 = *did not complete high school*, 7 = *graduate or professional school*) and occupations (coded as 1 = *laborer*, 5 = *professional*).

Adult domestic role burden during the 12th grade was measured by a set of questions on the daily checklist that asked participants to indicate whether they did any of the following things to help their family each day: helped clean the apartment or house, took care of siblings, ran an errand for the family, helped siblings with their schoolwork, helped parents with official business (e.g., translating letters, completing government forms), helped to cook a meal for the family, helped parents at their work, and other. Participants then estimated the total amount of time they had spent in all of the activities that day. The list of activities was derived from focus group studies of adolescents and has been used successfully in previous studies with these populations (Hardway & Fuligni, 2006).

Stress was measured by adolescents' reports of whether any of 10 events occurred to them each day (yes/no): punished or disciplined by parents, something bad happened to someone in the family, parents had an argument, argued with mother, argued with father, argued with other family member, argued with a friend, argued with or punished by teacher, harassed or picked on by a student at school, and harassed or picked on by other person out of school. The events were selected because they are known to be psychological stressors for adolescents across the primary domains of family, peers, and school (Nishina & Juvonen, 2005; Steinberg, 1990). Although two of the items (something bad happened to someone in the family, parents had an argument) do not directly involve the adolescent, they are family stressors known to impact psychological well-being (Davies & Windle, 2001; Larson & Amussen, 1991). A summary variable was created that indicated the percentage of days on which any one of these 10 events occurred to the adolescent.

Inflammatory Phenotyping

Levels of chronic inflammation were assessed by blood plasma concentrations of the IL-6 biomarker, CRP (Gabay & Kushner, 1999; Pepys & Hirschfield, 2003). CRP is a more reliable measure of chronic IL-6 exposure than is a one-time determination of circulating IL-6 protein level because of the high volatility of circulating cytokine levels, the comparative stability of CRP, and CRP's slow, temporally integrated production by the liver as an acute phase protein predominately in response to IL-6 (Gabay & Kushner, 1999; Pepys & Hirschfield, 2003). Plasma was obtained from resting venous blood samples as previously detailed (Fuligni, Telzer, Bower, Cole, et al., 2009; Fuligni, Telzer, Bower, Irwin, et al., 2009), diluted 1:20 with N Diluent, and assayed for CRP concentrations by nephelometry using the Dade-Behring High-Sensitivity CRP assay on a BN II hematology analyzer (Siemens Medical, Malvern, PA) in the UCLA Norman Cousins Center Inflammatory Biology Core Laboratory, following the manufacturer's specified protocol. This assay has a lower limit of detection of 0.175 mg/L and intra- and interassay coefficients of variation of < 4%. All samples had detectable levels of CRP.

Genotyping

Individual status on the *IL6* –174 G/C polymorphism (rs1800795) was assayed by a commercial TaqMan Genotyping Assay (Applied Biosystems, Foster City, CA) performed on a iCycler real-time PCR instrument (BioRad, Hercules, CA) following the manufacturer's specified protocol, as previously described (Cole et al., 2010). All samples were assayed in duplicate, and discordant results (< 5%; i.e., > 95% test–retest reliability) were resolved by a third PCR reaction followed by restriction fragment length polymorphism analysis using the *Nla*III enzyme as previously described (DeMichele et al., 2003), yielding a total geno-typing error rate < 1% (i.e., reliability > 99%). Valid genotyping was confirmed by parallel assay of cloned plasmids containing a functional human *IL6* promoter bearing either the ancestral –174G allele, the variant –174C allele, or a 1:1 mixture of the two plasmids (modeling GC heterozygosity), as previously described (Cole et al., 2010). Validation analyses showed 100% accurate genotype classification.

Statistical Analysis

Consistency of the observed *IL6* –174 genotype distribution with Hardy-Weinberg equilibrium was tested by the standard chi-square test (Siegmund & Yakir, 2007). The functional form of the *IL6* –174 G × SE interaction was analyzed in a general linear model of plasma CRP levels varying as a function of a main effect of *IL6* genotype (GG/GC/CC), a main effect of social characteristic (SES, stress, or adult role burden, each represented as a continuous variable), and a Genotype × Social Characteristic interaction term. Initial analyses treated *IL6* genotype as a 1 degree-of-freedom allele frequency variable for an analysis of linear trend in CRP/social characteristic slope as a function of 0/1/2 C alleles (Siegmund & Yakir, 2007). However, the primary reported results come from more complex parameterizations treating *IL6* genotype as a three-level classification variable (GG, GC, CC) to capture any potential nonlinear effects (e.g., allelic dominance; Siegmund & Yakir, 2007). To ensure that observed genetic relationships did not stem from ethnicity-related population stratification (Siegmund & Yakir, 2007), additional analyses controlled for ethnicity (as a 1/0 indicator of Latino vs. European ancestry). All ancillary analyses also controlled for the known effects of gender and adiposity on inflammation by including body mass index (BMI; continuous) and gender (categorical 1/0) as covariates. Given the present sample size, power to detect a between-genotype difference of 2 mg CRP/L plasma per *SD* social condition was 85%. All analyses were conducted using SAS v9.1.3 PROC GLM (SAS Institute, Cary, NC). Levene's test (R. G. Miller, 1986) identified no significant difference in the variance of CRP, SES, adult role burden, or daily stress across genotype groups (all *p*s > .10). Household SES data were unavailable for six participants, so analyses

of SES and related mediational dynamics (Baron & Kenny, 1986) are based on 58 individuals.

Results

The IL6 –174 Gene × Social Environment Interaction in Adolescents

To assess the biological form of the *IL6* –174 G × SE interaction during early reproductive maturity, we quantified chronic inflammation by plasma levels of the stable IL-6 biomarker, CRP, in 64 17- to 19-year-old adolescents who were also genotyped for the rs1800795 (*IL6* –174 G/C) polymorphism and assessed for adverse socioenvironmental conditions by measures of household SES. Descriptive characteristics of this sample are presented in Table 1. Preliminary genetic analyses found the distribution of *IL6* genotypes to match that observed in other population genetic studies (dbSNP, 2009) and fall at Hardy-Weinberg equilibrium, test of departure from equilibrium, $\chi^2(1, N = 116) = 0.01$, $p = .924$. Genotype distributions did differ significantly as a function of participant ethnicity, and subsequent analyses thus controlled for ethnicity to avoid population-stratification confounding.

Consistent with previous research (Chen et al., 2006; Chen et al., 2009; Howe et al., 2010; Kivimaki et al., 2005), the present sample showed a trend toward higher plasma CRP levels with declining household SES, main effect = –0.03 mg/L CRP per *SD* SES; $F(1, 52) = 3.58$, $p = .0641$. However, the magnitude of that trend varied significantly as a function of *IL6* –174 genotype, Genotype × SES interaction, $F(2, 52) = 3.61$, $p = .0342$ (see Table 2). C allele homozygotes showed the expected elevation in plasma CRP levels under increasing socioenvironmental adversity. However, G allele homozygotes and GC heterozygotes showed no significant increase in CRP with increasing adversity (see Table 2). Similar results emerged when analyses adjusted for potential confounding by sex, ethnicity, and BMI (see Table 2). Average CRP levels did not differ significantly as a function of genotype (see Table 1), confirming that polymorphism-related differences in chronic inflammation emerged only in the presence of adverse socioenvironmental conditions and were not a basal physiologic consequence of the *IL6* –174 promoter polymorphism. *IL6* genotype was not associated with SES (see Table 1).

Stress Mediation of IL6 Gene × Social Environment Interaction

Previous laboratory studies suggest that adverse socioenvironmental conditions up-regulate *IL6* transcription via stress-induced SNS activation (Cole et al., 2010; Powell et al., 2009; Stark et al., 2002). Consistent with the hypothesis that individual-level stress responses might mediate the *IL6* × SES interaction, measures of individual daily social stress were also associated with elevated CRP levels, $F(1, 50) = 12.52$, $p = .0009$, and increasing prevalence of the *IL6* –174G allele was associated with significant diminution in the strength of that relationship, Genotype × Stress interaction, $F(2, 50) = 3.85$, $p = .0279$ (see Table 3). Multivariate mediation analyses indicated that variations in individual level stress could potentially account for up to 74% of the total *IL6* × SES interaction variance (residual unexplained Genotype × SES variance, $p = .2822$). *IL6* genotype was not directly associated with individual daily stress level (see Table 1).

To determine whether adversity-related alterations in individual level social dynamics might contribute to the stress component of the *IL6* × SES interaction, we gauged the total level of adult domestic role burden borne by adolescents (e.g., caring for siblings, shopping, cooking, cleaning, translating and completing official forms). As previously observed (Fuligni, Telzer, Bower, Irwin, et al., 2009), increasing burden of adult domestic roles was associated with elevated CRP levels, $F(1, 46) = 23.85$, $p < .0001$. However, the magnitude of that relationship was significantly diminished among individuals homozygous for the *IL6*

–174G allele, Genotype × Role Burden interaction, $F(2, 46) = 6.70$, $p = .0028$ (see Table 4). Multivariate mediation analyses indicated that variations in individual adult role burden could potentially account for up to 57% of the total *IL6* × SES interaction variance (residual unexplained Genotype × SES variance, $p = .1828$). *IL6* genotype was not significantly associated with adult role burden (see Table 1).

Discussion

These data show that a genetic polymorphism which interacts with adverse socioenvironmental conditions to increase health risk late in life may also provide biological resilience against adversity earlier in life. Previous analyses in older adults indicate that the *IL6* –174G allele sensitizes individual physiology to the pro-inflammatory influences of adverse socioenvironmental conditions as mediated by SNS activation (Cole et al., 2010). The present data show that the same allele can have the opposite effect during adolescence, acting to desensitize individual physiology to the pro-inflammatory effects of adverse socioenvironmental conditions and related individual stress and social role burdens. This developmental dependence of G × SE interaction is predicted by the evolutionary genetics of age-dependent antagonistic pleiotropy (Williams, 1957) and provides a plausible explanation for why the *IL6* –174G allele continues to persist in the human gene pool despite the fact that it confers a substantial risk of inflammation-related disease and mortality in old age. To the extent that the same allele also confers a benefit in protecting younger bodies from the physiologic impact of adversity through peak reproductive maturity, its selective advantage in promoting inclusive fitness may offset the later survival disadvantages associated with increased inflammation in old age (Williams, 1957). The *IL6* –174 promoter polymorphism is therefore best construed not as a uniform genetic risk factor but, rather, as a genetic sensitivity factor that alters inflammatory regulation by external environmental conditions depending on individual developmental status.

The present analyses indicate that individual-level social and psychological factors may play a key role in mediating the impact of adverse social environments on inflammatory biology. The contribution of low-SES environment to the *IL6* G × SE interaction was strongly associated with the degree to which adolescents assumed adult domestic roles (e.g., household work, caregiving, parental assistance) and experienced high levels of daily interpersonal stress (e.g., social conflict, punishment, harassment). These dynamics are anticipated by previous data suggesting that adverse socioenvironmental conditions may influence immune system gene expression via changes in individual-level social behavior and psychological conditions (Chen et al., 2009) and by data documenting age-dependent increases in the association between adverse life circumstances and circulating IL-6 levels (Kiecolt-Glaser et al., 2003). The present results are also consistent with previous laboratory studies indicating that adversity-related activation of the stress-responsive SNS activates *IL6* transcription via catecholamine stimulation of the GATA1 transcription factor (Cole et al., 2010). Thus, the present results not only identify the functional form of *IL6* G × SE antagonistic pleiotropy but they do so in a biological context in which the molecular mechanisms of those dynamics can potentially be mapped in future studies.

The consistent functional form of statistically significant *IL6* G × SE interactions across three conceptually distinct measures of socioenvironmental adversity (SES, individual stress, adult role burden) suggests the presence of a reliable biological mechanism and is unlikely to recur so consistently by chance alone. However, one unanticipated difference in the detailed pattern of results involves an apparently protective effect of *IL6* GC heterozygosity in mitigating the elevated inflammation associated with low SES and social stress (see Tables 2 and 3), but not that associated with adult role burden (see Table 4). The basis for this difference is not clear and could be a statistical consequence of limited

statistical power to precisely quantify an intermediate-magnitude correlation between adversity and inflammation in the GC heterozygote group (i.e., resulting in failure of an intermediate magnitude GC relationship to reach conventional statistical significance in analyses of SES or social stress but stochastic success in the case of adult role burden). Alternatively, the assumption of adult roles in adolescence may engage some additional biological processes that interact with the *IL6* promoter polymorphism in ways that are not fully shared by low SES or social stress (e.g., effects of domestic work or employment on tissue wear and tear or sleep patterns, both of which might influence inflammatory biology). The mediational analyses reported here suggest a substantial degree of shared variance among low SES, social stress, and adult role burden in their relationships to inflammatory biology, but those associations do not rule out the possibility that each factor might also entail some distinctive psychological and biological influences that impinge differently on the *IL6* promoter.

Several limitations need to be considered in interpreting the present findings. These data come from a cross-sectional observational study involving a relatively small cohort of adolescents from the Los Angeles metropolitan area and thus require replication in larger and more diverse samples. Future research should seek to map development-dependent changes in the nature of G × SE interactions within a single study framework that includes both young and older adults, or longitudinally in the context of lifespan development studies tracking individual biology from youth through old age. Additional studies will also be required to clarify the biological mechanism of the *IL6* promoter polymorphism's opposite effects on inflammation in adolescent versus older adults, as well as the health implications of the present G × SE interaction. One plausible molecular mechanism for the observed age-dependent reversal of G × SE functional form would involve the developmentally linked expression in young people of either a dominant negative transcription factor that competes with GATA1 for binding to *IL6* –174G but does not induce *IL6* transcription (Smale, 2001) or another transcription factor besides GATA1 that preferentially binds to the *IL6* –174C allele following activation by stress biology (e.g., as does the GATA1 factor in older adults). In addition to further studies clarifying the molecular basis for age-dependent antagonistic pleiotropy at the *IL6* –174 locus, additional studies will also be required to determine whether that polymorphism interacts in an age-dependent manner with other types of socioenvironmental adversity previously linked to chronic inflammation (e.g., interpersonal trauma, social threat, or social isolation; Cole et al., 2007; Danese et al., 2008; Danese et al., 2007; Miller et al., 2008).

Strengths of the present study include the focused testing of an a priori hypothesis derived from a well-established evolutionary genetic theory and clear separation of the observed G × SE interaction from a gene–environment correlation (i.e., no evidence of a direct causal effect of *IL6* polymorphism on putatively environmental risk factors such as SES, stress, or economic/domestic burden). Biological data collection during adolescence reduces the likelihood that the observed differences in chronic inflammation represent consequences of chronic disease, as opposed to effects of G × SE interaction. Another advantage involves the strong representation of Latino and low-SES adolescents in the present sample, which should enhance the generalizability of the present findings. Statistical control for ethnicity in all reported findings ensures that the genetic effects observed here cannot be attributed to population ethnic stratification (Siegmund & Yakir, 2007), and parallel control for BMI and sex ensures that observed G × SE relationships are independent of those variables' known relationship to inflammation. As noted previously, the parallel form of G × SE interaction across multiple measures of socioenvironmental adversity (contextual SES, subjective individual stress, and a comparatively objective measure of adult role burden) lends confidence that the observed relationships between adversity and *IL6* do not represent an isolated spurious finding.

The overarching implication of this study is that G × SE influences on health are likely to vary in form as a function individual developmental stage, much as do G × SE influences on neurobiology and behavior (Casey et al., 2009). Antagonistic pleiotropy should be routinely anticipated in contemporary genetic research, because natural selection will have eradicated most asymmetrically risky alleles while driving asymmetrically beneficial alleles to fixation (Levins, 1968; Williams, 1957). What genetic variation does remain in the human population likely reflects evolution's hedged bets based on the optimal biological responses to the range of environmental conditions that have proven relatively prevalent or recurrent over our history as a species. Analytic approaches that assume the continued prevalence of generally advantageous or deleterious polymorphisms would seem to be searching through the few remaining genetic crumbs not already consumed by natural selection. More success can be anticipated for discovery strategies that embrace the consequences of natural selection and presume that remaining genetic polymorphisms generally interact with prevalent dimensions of environmental variation to shape phenotypic responses. The results of this study suggest that the somatic environment of the developing body and the social environment in which it resides constitute some of the key environmental determinants that shape the impact of genetic variation on human physiology and health.

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Table 1

Sample Characteristics and IL6 – 174 Genotype

Characteristic	Total sample	GG (*n* = 35)	GC (*n* = 24)	CC (*n* = 5)	Significance[a]
Age (years)[b]	18.4 ± 0.3				
Sex[b]		18.5 ± 0.4	18.4 ± 0.3	18.3 ± 0.3	.395
Female	35 (55%)	15	16	5	.097
Male	29 (45%)	20	8	1	
Ethnicity					
European	26 (41%)	7	16	3	.001
Latino	38 (59%)	28	8	2	
BMI (kg/m^3)[b]	24.8 ± 7.1	26.5 ± 8.3	22.6 ± 5.6	24.6 ± 3.3	.147
SES (composite *Z*)[b]	0.02 ± 0.81	–0.11 ± 0.92	0.20 ± 0.69	0.08 ± 0.45	.374
Social stress (events/day)[b]	0.31 ± 0.26	0.32 ± 0.24	0.32 ± 0.29	0.16 ± 0.23	.526
Adult role burden (hr/day)[b]	0.71 ± 0.77	0.69 ± 0.77	0.57 ± 0.49	1.55 ± 1.63	.073
CRP (mg/L)[b]	1.54 ± 1.53	0.89 ± 0.94	1.35 ± 1.92	2.10 ± 2.67	.255

Note. BMI = body mass index; SES = socioeconomic status; CRP = C-reactive protein.

[a] *p* = two-tailed significance for one-way analysis of variance (continuous variables) or chi-squared (categorical).

[b] *M* ± *SD*.

Table 2

Relationship Between Family SES and Plasma CRP, by IL6 –174 Genotype

Model	*IL6* –174 genotype	Plasma CRP mg/L per SES *SD* (±*SE*)	Significance[a]
Simple[b]	GG	–0.29 ± 0.29	.3285
	GC	0.61 ± 0.45	.1840
	CC	–4.06 ± 1.90	.0374
Adjusted[c]	GG	–0.16 ± 0.30	.6016
	GC	0.88 ± 0.49	.0801
	CC	–4.32 ± 1.87	.0250

Note. SES = socioeconomic status; CRP = C-reactive protein.

[a] *p* = two-tailed significance level.

[b] Simple (unadjusted) association between CRP concentration and SES.

[c] Multivariate analysis controlling for sex, body mass index, and ethnicity.

Table 3

Relationship Between Individual Stress and Plasma CRP, by IL6 –174 Genotype

Model	*IL6* –174 genotype	Plasma CRP mg/L per daily stressor (±*SE*)	Significance[a]
Simple[b]	GG	1.07 ± 1.13	.3473
	GC	1.38 ± 1.05	.1955
	CC	11.52 ± 3.63	.0026
Adjusted[c]	GG	0.42 ± 1.13	.7154
	GC	2.15 ± 1.14	.0659
	CC	13.08 ± 3.61	.0007

Note. CRP = C-reactive protein.

[a] p = two-tailed significance level.

[b] Simple (unadjusted) association between CRP and average daily stressor frequency.

[c] Multivariate analysis controlling for sex, body mass index, and ethnicity.

Table 4

Relationship Between Adult Role Burden and Plasma CRP, by IL6 –174 Genotype

Model	*IL6* –174 genotype	Plasma CRP mg/L per adult role event (±*SE*)	Significance[a]
Simple[b]	GG	0.15 ± 0.33	.6615
	GC	2.50 ± 0.61	.0002
	CC	1.46 ± 0.47	.0030
Adjusted[c]	GG	–0.08 ± 0.34	.8202
	GC	2.30 ± 0.62	.0006
	CC	1.63 ± 0.49	.0018

Note. CRP = C-reactive protein.

[a] p = two-tailed significance level.

[b] Simple (unadjusted) association between CRP and daily adult role event frequency.

[c] Multivariate analysis controlling for sex, body mass index, and ethnicity.