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Interactions Between Serotonin Transporter Gene Haplotypes and Quality of Mothers' Parenting Predict the Development of Children's Noncompliance

Michael J. Sulik,

Department of Psychology, Arizona State University

Nancy Eisenberg,

Department of Psychology, Arizona State University

Kathryn Lemery-Chalfant,

Department of Psychology, Arizona State University

Tracy L. Spinrad,

School of Social and Family Dynamics, Arizona State University

Kassondra M. Silva,

School of Social and Family Dynamics, Arizona State University

Natalie D. Eggum,

Department of Psychology, Arizona State University

Jennifer A. Betkowski,

Department of Psychology, Arizona State University

Anne Kupfer,

Department of Psychology, Arizona State University

Cynthia L. Smith,

Department of Psychology, Arizona State University

Bridget Gaertner,

School of Social and Family Dynamics, Arizona State University

Daryn A. Stover, and

Center for Evolutionary Medicine and Informatics & School of Life Sciences, Arizona State University

Brian C. Verrelli

Center for Evolutionary Medicine and Informatics & School of Life Sciences, Arizona State University

Abstract

The LPR and STin2 polymorphisms of the serotonin transporter gene (SLC6A4) were combined into haplotypes that, together with quality of maternal parenting, were used to predict initial levels and linear change in children's ($N = 138$) noncompliance and aggression from age 18–54 months.

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Correspondence concerning this article should be addressed to Nancy Eisenberg, Department of Psychology, Arizona State University, Tempe, AZ 85287-1104. Nancy.Eisenberg@asu.edu.

Natalie D. Eggum is now at the School of Social and Family Dynamics, Arizona State University. Cynthia L. Smith is now at the Department of Human Development, Virginia Polytechnic Institute and State University.

Quality of mothers' parenting behavior was observed when children were 18 months old, and nonparental caregivers' reports of noncompliance and aggression were collected annually from 18 to 54 months of age. Quality of early parenting was negatively related to the slope of noncompliance only for children with the LPR-S/STin2-10 haplotype and to 18-month noncompliance only for children with haplotypes that did not include LPR-S. The findings support the notion that SLC6A4 haplotypes index differential susceptibility to variability in parenting quality, with certain haplotypes showing greater reactivity to both supportive and unsupportive environments. These different genetic backgrounds likely reflect an evolutionary response to variation in the parenting environment.

Keywords

differential susceptibility; serotonin transporter gene; aggression; noncompliance; SLC6A4 (5-HTT)

The importance of examining interactions between dispositional characteristics (including heredity) and environmental parameters when predicting children's adjustment has been recognized for decades and currently is a prominent focus in developmental psychology. From an evolutionary perspective, genetic variation associated with plasticity may be adaptive if this variation enables the individual to respond to the environment in a manner that optimizes survival to reproduction (e.g., Chisholm, 1988; Draper & Harpending, 1982; Hamilton, 1964; Wilson, 1975). Thus, the developing child can be viewed as exhibiting *conditional adaptation*, or as having "evolved mechanisms that detect and respond to specific features of childhood environments, features that have proven reliable over evolutionary time in predicting the nature of the social and physical world into which children will mature" (Boyce & Ellis, 2005, p. 290). From this perspective, it has been suggested that children have been shaped by natural selection to detect and encode information about levels of stress and support in the rearing environment and to adjust phenotypic behavior to match the environment.

Belsky, Steinberg, and Draper (1991) described an evolutionary model in which the social context is associated with certain types of parenting that lead to differences in children's social perceptions and social behaviors, which in turn affect the emergence of puberty and reproductive strategies. They argued that an adverse family ecology tends to result in parenting that is harsh, rejecting, insensitive, and inconsistent, whereas an advantageous family environment tends to result in parenting that is supportive, responsive, and affectionate. In turn, children who are recipients of harsh parenting tend to perceive others as untrustworthy and relationships as opportunistic and self-serving, whereas sensitive, supportive parenting leads to the opposite perceptions. These beliefs affect the degree to which children have opportunist or trusting relationships and exhibit problem behaviors (including noncompliance, especially for boys) or cooperative, considerate, and caring relationships and behavior.

Parental warmth and support have been viewed as aspects of the environment that condition children's development. Hinde (1991) suggested that children have evolved to use variation in parental style as a cue to the context within which they will mature. Similarly, MacDonald (1992) argued that the human affectional behavior has evolved to be rewarding to children and is programmed to match the child's environmental affectional stimulation. Specifically, children who receive high levels of rewarding parental warmth and positive emotion during development become more sensitive to its reward value, whereas those who receive lower levels become less responsive. Variations in sensitivity might therefore be

expected to affect children's compliance with, and internalization of, parental demands and values.

Recent theoretical perspectives suggest that the assumption that children's behavior has adaptively evolved in response to specific social environments should be qualified by attention to individual differences in such adaptability. According to the differential susceptibility hypothesis (Belsky & Pluess, 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011), individual differences in developmental plasticity and, more specifically, susceptibility to environmental influences, result in some individuals being more reactive than others to variation in environmental context. Moreover, Ellis et al. (2011) argued that individuals who are more susceptible to context are more likely to experience sustained developmental changes in reaction to contextual factors (for a similar view, see Boyce and Ellis's 2005 biological sensitivity-to-context hypothesis). Differences in neurobiological susceptibility are viewed as evolutionarily adaptive because they are believed to have been conserved by selective pressures that generated different fitness payoffs (i.e., had different costs and benefits) across diverse social, physical, and historical contexts (Ellis et al., 2011; Wolf, van Doorn, & Weissing, 2008). For example, behaviors exhibited by reactive or plastic individuals in negative contexts, although they may seem to be maladaptive (e.g., vigilant or aggressive behavior), might be adaptive in an evolutionary sense if they enhance self-protection or secure resources (Boyce & Ellis, 2005). In contrast, in supportive, low-stress environments, reactive children are expected to exhibit high levels of socially desirable behavior, resulting in the best individual outcomes. For example, in supportive contexts, reactive children should be especially compliant because such behavior is effective for garnering support and resources from supportive parents.

Interactions between genes and the environment can take numerous forms (see Luthar, Cicchetti, & Becker, 2000), including those different than predicted by differential susceptibility theory. The most commonly examined alternative type of interaction is tested in diathesis-stress models (e.g., Monroe & Simons, 1991) that view reactive individuals as having a vulnerability in their temperament, endophenotype (e.g., high physiological reactivity), or genotype such that they are disproportionately or even exclusively likely to be affected adversely by most environmental stressors. In the absence of environmental adversity, the biological vulnerability is not realized, and these individuals are similar to those without the vulnerability. This approach has been used in work on anxiety, depression, and externalizing problems wherein the focus has been primarily on the detrimental effects of a dispositional or biological vulnerability in an adverse environment. An implicit assumption of this approach is that people are acted upon, often victims of the environment, and their role in adapting to the social context is minimized.

The growing body of research on Gene $\times$ Environment ($G \times E$) interactions is highly relevant to the testing of hypotheses stemming from the differential susceptibility perspective. Functional variation at a given gene may serve as support for evolutionary adaptation in specific ecological niches (e.g., Hamilton, 1964; Williams, 1996; Wilson, 1975). In this study, we considered the interaction of genetic polymorphisms of the commonly studied serotonin transporter (solute carrier family 6, member 4, or SLC6A4; formerly called "5-HTT") gene with early parenting when predicting initial levels of noncompliance and aggression at 18 months, as well as changes across early childhood.

Reduced central nervous system serotonin has been associated with aggression in animals, adults, and children (Flory, Newcorn, Miller, Harty, & Halperin, 2007; Swann, 2003; Zaboli et al., 2008). Carver, Johnson, and Joormann (2008) argued that experimentally increasing serotonergic function reduces responsiveness to negative emotional stimuli and decreases aggression and increases cooperation. They also reviewed research suggesting that

serotonergic function plays a major role in the interplay of more reflective cortical systems and more emotionally based reactive systems driven in part by amygdalae activity, with low serotonin function resulting in less constraint of amygdalae activity. Further, serotonin regulates morphogenetic activities during early brain development, influencing neurogenesis, neuronal apoptosis, cell migration, cell differentiation, and synaptic plasticity (Azmitia & Whitaker-Azmitia, 1997; Gould, 1999; Lauder, 1993; Sodhi & Sanders-Bush, 2004), resulting in alterations in brain function and behavior (Whitaker-Azmitia, 2001). Serotonin impacts centrally controlled functions such as circadian rhythms, sensorimotor activity, sexual behavior, mood, cognition, and aggression (Zaboli et al., 2008). Thus, genes affecting the serotonin system are candidates for predicting change in externalizing and noncompliant behavior across childhood.

Consequently, we examined the SLC6A4 gene, which encodes the serotonin transporter protein that is the major regulator of serotonin concentration in the brain (Risch & Nemeroff, 1992). Magnitude and duration of serotonin neurotransmission are determined by synaptic action of SLC6A4, which is necessary for reuptake of serotonin from the synaptic cleft. SLC6A4 is well studied as it is the target for the most commonly used serotonin-selective reuptake inhibitors or 'SSRIs' (Murphy et al., 2008), and two polymorphisms have been predominantly examined with respect to their relation with behavioral variation.

The first polymorphism is located in the SLC6A4 promoter that regulates general transcriptional expression and has been named the *linked polymorphic region* (LPR; formerly HTTLPR). The LPR consists of a variable number of tandem repeats (VNTR) of a specific 20–23 base pair sequence (Heils et al., 1996; Lesch et al., 1996). There are two common repeat alleles: short (S; 14 repeat) or long (L; 16 repeat), both of whose functional associations have been well-studied. The S and L alleles differentially modulate the transcription of SLC6A4, with the S allele predicted to have less transcriptional efficiency. Because the S allele is believed to be functionally “dominant,” SS and SL genotypes are often grouped together and compared with the LL genotype in analyses. For example, lymphoblastoid cell lines with the LL genotype produced higher concentrations of SLC6A4 than cells containing either the SS or SL genotype. In analyses of in vivo single-photon emission computed tomography (SPECT) imaging of SLC6A4 in the human brain, SLC6A4 concentrations in the raphe complex of human postmortem brain and platelet serotonin uptake and content confirm the relation between the dominant S allele and lower SLC6A4 expression and function (Greenberg et al., 1999; Hanna et al., 1998; Heinz et al., 2000).

The association between LPR variants and aggression has been inconsistent. On the one hand, the LPR-S allele sometimes has been associated with children's or youths' higher conduct problems or aggression (e.g., Haberstick, Smolen, & Hewitt, 2006; contrast with Davidge et al., 2004), as well as with impulsivity and low agreeableness (Lesch et al., 1996; Sadeh et al., 2010; Walderhaug, Herman, Magnusson, Morgan, & Landrø, 2010). In addition, the quality of early rearing environments predicts aggression in monkeys who carry the LPR-S variant (Barr et al., 2004). Similar relations between adverse environments (including emotional family climate, dysfunction parenting) and violent conduct have been found in human populations for LPR-S carriers (Li & Lee, 2010; Reif et al., 2007). LPR-S also predicts adolescents' agreeable autonomy in the context of a secure attachment but more hostile autonomy in the context of an insecure attachment (Zimmermann, Mohr, & Spangler, 2009). LPR-S combined with an insecure attachment was also associated with poor self-regulation, whereas it was associated with regulatory capacities similar to those of LPR-LL children when in the context of a secure attachment (Kochanska, Philibert, & Barry, 2009). Kochanska, Kim, Barry, and Philibert (2011) found that LPR-S carriers (relative to LPR-LL homozygotes) were, at 67 months, more competent with peers and higher on prosocial cognitions, moral self, and academic skills and engagement if their

mothers had shown more responsive parenting when the children were between 15 and 52 months old. Other researchers have found that LPR-S boys with attention deficit/hyperactivity disorder (ADHD) had fewer conduct problems when their mothers showed high warmth and low criticism; LPR-LL boys did not vary as a function of environment (Sonuga-Barke et al., 2009). Thus, LPR-S may confer an advantage in supportive contexts (also see Belsky & Beaver, 2011).

On the other hand, the LPR-LL genotype can lead to reduced central serotonergic activity (because it is efficient in synaptic reuptake of 5-HT), which is implicated in poor impulse regulation and ADHD (Kent et al., 2002; Li et al., 2007; Retz et al., 2008). The LPR-LL genotype was found to interact with socioeconomic status (SES) to predict relatively high levels of externalizing problems in low-SES preadolescents (Nobile et al., 2007). Moreover, callous-unemotional and narcissistic traits were negatively associated with SES only among LPR-LL youths (Sadeh et al., 2010). Thus, LPR-LL individuals may provide plasticity in certain contexts or for certain behaviors.

Findings from neuroscience help elucidate these seemingly contradictory associations. LPR-S carriers, compared with LPR-LL homozygotes, direct processing resources toward danger-relevant stimuli (Thomason et al., 2010; see also Munafò, Brown, & Hariri, 2008) such as subliminally presented fearful and angry faces, suggesting greater amygdalae reactivity to emotional faces (see Carver et al., 2008, for a review). This hypervigilance may be protective in supportive contexts but may also create a susceptibility to mood and behavioral disorders in stressful contexts (see Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). The association of the LPR-S allele with stress reactivity also may be due to its link to amygdalae reactivity (Hariri & Holmes, 2006; Kalin et al., 2008; see Caspi et al., 2010, for a review). Moreover, if the LPR-S allele is associated with less constraint on the amygdalae, it might be associated with impulsive, emotionally driven externalizing problems.

Most of the investigators who have studied $G \times E$ interactions have not explicitly tested the predictions of the differential susceptibility hypothesis. Belsky and Pluess (2009) reviewed evidence for the better-or-worse pattern for LPR-S carriers. Most of the studies examined relations to depression or anxiety, not aggression or related behaviors in contexts varying in risk or supportiveness. Many of the existing studies (Belsky and Pluess cited 10) supported differential susceptibility hypothesis; however, it was not clear if the cross-over effects (i.e., positive effects in supportive contexts and negative effects in nonsupportive contexts) in most of the studies were significant. Nonetheless, in one study (Retz et al., 2008), ADHD increased substantially with an adverse childhood sociodemographic environment for LPR-S carriers, but not for LPR-LL young adult male delinquents; the two groups appeared to differ most, however, in low- rather than high-risk contexts (because LPR-S was associated with low ADHD under low risk). Moreover, Kochanska and colleagues (2011) found that for academic and social competence, the Parenting $\times$ LPR interaction supported the diathesis-stress but not differential-susceptibility model. In contrast, findings for moral internalization provided more support: LPR-S carriers with unresponsive mothers had particularly unfavorable outcomes, whereas those with responsive mothers had better outcomes than LPR-LL children.

We also examined the functionally relevant serotonin transporter intron 2 (STin2) polymorphism (Ogilvie et al., 1996), which consists of a 17-base pair VNTR in the second intron. Specifically, common repeats of STin2 are the 10 and 12 alleles, the latter of which is related to increased transcriptional effects both in human differentiating embryonic stem cells (Fiskerstrand, Lovejoy, & Quinn, 1999) and in mouse embryos (MacKenzie & Quinn, 1999).

Unlike LPR, STin2 variants have few associations with externalizing behaviors. Lopez de Lara et al. (2006) found no relation between variation in STin2 genotype and adults' impulsive-aggressive or cooperative behavior. However, Davidge et al. (2004) found that the STin2 10 variant was more common in highly aggressive children, and Saiz et al. (2010) found that STin2 interacted with sex to predict cooperation in adult Spaniards; cooperation behavior was high in women only if they carried the 10 variant.

Although many researchers have examined LPR polymorphisms in relation to aggression, it may be important to consider LPR and STin2 in combination as haplotypes, which are groups of alleles on a single chromosome that are usually inherited together. For example, Ali et al. (2010) showed that the haplotype of the LPR-S and STin2-12 alleles (S12 combination) possessed the highest SLC6A4 transcriptional expression compared with the lowest expression for the LPR-L and STin2-10 alleles (L10 combination). Garcia, Aluja, Fibla, Cuevas, and Garcia (2010) reported that male inmates carrying the S12 haplotype were more likely to be classified as having antisocial personality disorder than those with other haplotypes. Although few studies have examined LPR/STin2 haplotypes, these results suggest that the two polymorphisms interact and that it is necessary to know the allelic combinations when making inferences about functional and phenotypic associations; these interactions may account for some of the contradictory results.

In summary, the literature on LPR polymorphisms is somewhat inconsistent in regard to their relations with behaviors such as aggression and noncompliance. In general, however, more research suggests that LPR-S confers risk or plasticity, depending on one's perspective. The evidence on interactions of the LPR polymorphism with environmental variables also provides some tentative support for the view that children with the S allele are more reactive to their environments. Data on relations between the STin2 polymorphism and noncompliance or externalizing problems are rare. The inconsistent patterns related to positive and negative behavioral outcomes in studies with the SLC6A4 may be explained by differences in measures, samples, or the use of single polymorphisms (vs. haplotypes). Because several of these polymorphisms are quite common in the general population (e.g., 20%–50%), their combinations may provide an adaptive response in certain circumstances, as previously discussed. Evidence on LPR/STin2 haplotypes is too sparse to make firm predictions, although we expected better prediction from the haplotypes than from either LPR or STin2 alone.

In the present study, we examined LPR and STin2 variants (alone and in combination as haplotypes) in interaction with quality of maternal parenting as predictors of children's caregiver or teacher-rated noncompliance or aggression. Children's noncompliance and aggression were assessed multiple times between that ages of 18 and 54 months and maternal parenting behavior was observed when children were 18 months of age. Our outcome measures were the 18-month intercept of noncompliance and aggression and the linear slopes from 18 to 54 months. Thus, we could assess whether the interaction between genetic polymorphisms and parenting quality predicted noncompliance and aggression at the initial time point or the pattern of change over time. We tested predictions from diathesis-stress and differential susceptibility models.

Method

Participants

Participants were a subsample from a longitudinal study of toddlers' emotions, regulation, and social functioning that was approved by our institution's ethics review board. Mothers and their infants were recruited very shortly after the infants' birth at three hospitals in a large metropolitan area in the southwestern United States. All infants were healthy, full-term

children of adult, English-speaking parents. In the full study, 352 families provided consent for researchers to contact them later, and 276 (78%) were successfully contacted later and agreed to participate when the infants were 6 months old. Observational data were collected in laboratory visits when children were approximately 18, 30, 42, and 54 months old. Mothers and toddlers from 247 families came to the lab at the first (18-month) assessment; 216, 192, and 168 dyads, respectively, attended subsequent assessments. Nonparental caregivers provided questionnaire data at 18, 30, 42, and 54 months. Caregivers were nonrelatives providing care in the home, another household, or day care facility, or nonparental relatives (e.g., grandmother) if children had no external caregiver (see Gaertner, Spinrad, & Eisenberg, 2008; Spinrad et al., 2007).

When the children were approximately 72 months old, cell samples for genetic analyses were collected for all participants for whom parental consent was obtained (few parents refused consent). Children were included in the present study if they had genetic data, observed parenting at 18 months, and at least one caregiver report for noncompliance and aggression. Thus, 138 children were included for analyses. For the subsample of 138 families with caregivers' reports and genetic and parenting data, children ranged in age from 17.03 to 19.95 ($M = 17.73$, $SD = 0.51$) months at the first laboratory visit. Fifty-two percent were boys. The median annual family income ranged from \$45,000 to \$60,000; 7% of the parents reported receiving welfare. Racial composition was approximately 86% White, 6% Native American, 5% African American, 2% Asian, 1% mixed between two minorities, and 1% other; 20% reported Hispanic/Latino ethnicity. Five percent of mothers did not complete high school, 9% graduated from high school, 40% attended some college, 33% graduated college, and 13% had a graduate or professional degree. Most (80%) mothers were married (M years = 6.75 years). Others were single (4%), living with a partner (7%), divorced (2%), separated (2%), or did not report marital status (4%).

We examined mean differences on study variables between children included in our analyses and children who were not included due to missing parenting data, caregiver report data, or genetic data. Children in the analytic sample came from families with a higher SES (calculated as an average of standardized family annual income, mothers' highest level of education, and fathers' highest level of education; $M = 0.12$) compared with those without genetic, parenting, or caregiver report data ($M = -0.13$), $t(239) = 2.24$, $p < .05$. There were no differences for parenting, aggression, or noncompliance at any time point.

In addition, we examined mean differences on 18-month aggression, noncompliance, and parenting for children who did not have caregiver data provided at 54 months versus those who had caregiver data at both 18 and 54 months. The sample with care-giver data at both 18 and 54 months did not differ from the sample without data at both times on caregivers' reports of noncompliance or aggression at any assessment. Moreover, age of the child at assessments, sex, and SES did not differ as a function of caregivers' attrition. Caregiver attrition was unrelated to the LPR polymorphism and the STin2 polymorphism.

Procedures

At each lab visit, mothers were asked to give permission for questionnaires to be sent to the child's nonparental caregiver or teacher. Quality of parenting was observed in the laboratory when the toddler was 18 months old. Cell tissue samples for genetic analyses were collected in the home when the children were 72 months old. Mothers were paid \$20 for the 18-month lab visit (and up to \$50 at 72 months). Caregivers were paid \$20 (18 – 42 months) or \$25 (54 months) for filling out questionnaires.

Measures

Child noncompliance and aggression—Because it is beneficial to test differential susceptibility hypotheses with outcomes that range considerably from negative to positive, we included both socially desirable and undesirable behavior in the outcome measure (Ellis et al., 2011). At each time point, caregivers completed parts of the Infant–Toddler Social and Emotional Assessment (ITSEA; Briggs-Gowan & Carter, 1998). Adults rated each item (range: from 0, *not true*, to 2, *very true*) on the eight-item Compliance subscale (e.g., “Follows rules,” “Tries to do as you ask”) and four 3-item subscales pertaining to aggression and defiance: Aggression/Defiance (e.g., “Has temper tantrums”), Dispositional Aggression (e.g., “Acts aggressive when frustrated”), Relational Defiance (e.g., “Misbehaves to get attention from adults”), and Oppositional Defiance (e.g., “Purposely tried to hurt you [or other parent]”). We averaged the four aggression and defiance subscales to obtain a measure of aggression, and reversed the Compliance subscale to obtain a measure of noncompliance. Alpha reliability across the four assessments ranged from .77 to .85 for aggression and from .75 to .79 for noncompliance.

Parenting quality—Toddlers and mothers came to the laboratory on campus to participate in a session lasting from 1.5 to 2.0 hr. As part of a series of tasks, mothers were videotaped interacting with their toddler during free play, a challenging teaching task, and a clean-up task.

Maternal sensitivity and intrusiveness were assessed during a free-play interaction and teaching task. In the former, mothers were given a basket of toys and instructed to play with their child as they would at home for 3 min. In the teaching task, mothers and children were given a challenging puzzle, and mothers were asked to teach their child to complete the puzzle. Mothers and children were given 3 min to complete the puzzle. Sensitivity and intrusiveness were rated every 15 s during the free-play interaction and every 30 s during the puzzle task (Fish, Stifter, & Belsky, 1991). Mothers’ behaviors that provided evidence of attentiveness to the child, as well as responsiveness to the child’s affect, interests, and abilities, were rated to assess sensitivity: ratings ranged from 1 = *no evidence of sensitivity* to 4 = *mother was very aware of the toddler, contingently responsive to his or her interests and affect, and had an appropriate level of response/stimulation* (interrater reliabilities [ICCs] = .81 and .82, for free play and puzzle, respectively). Mothers’ overcontrolling, intrusive behaviors included overstimulating the child with toys, employing intrusive physical interactions, or intervening to help the child when not required (1 = *no overcontrolling behavior observed*; 4 = *extreme intrusive or overcontrolling behaviors*; ICCs = .82 and .81 for free play and puzzle task, respectively).

Maternal warmth was also coded every 30 s during the puzzle task. Mothers’ friendliness, displays of closeness, physical affection, encouragement, and positive affect with the child, as well as the quality of their tone and conversation, were used to assess warmth (1 = *no evidence of warmth*; 5 = *very engaged with the child, positive affect was predominant, and the mother was physically affectionate*; ICC = .83).

Maternal verbal control was assessed during a 3-min clean-up task. Mothers were instructed to have their child pick up toys and put them in a basket. Control was based on verbal directives that were given by mothers in a nonforceful, yet assertive matter (e.g., “We have to clean up NOW”). Maternal control was rated every 15 s as either present or absent (1 = *yes*; 0 = *no*). The reliability for observed control was $\kappa = .70$.

All parenting measures were correlated in expected directions. Absolute values of the r s ranged from .19 to .85, all p s < .05. We created a composite of parenting quality by reverse scoring maternal control and intrusiveness, standardizing scores, and computing the average.

Genotyping—Buccal oral cheek samples were collected from children, and DNA extractions were performed on samples using a standard isolation protocol (Sambrook & Russell, 2001). PCR (polymerase chain reaction) primers were designed to span and amplify markers genotyped at SLC6A4. Primers designed for the LPR polymorphism were GGC GTT GCC GCT CTG AAT GC (forward) and GAG GGA CTG AGC TGG ACA ACC AC (reverse), which amplify fragments of 484-base pairs (S allele) to 528-base pairs (L allele). Primers designed for the STin2 polymorphism were TGG ATT TCC TTC TCT CAG TGA TTG G (forward) and TCA TGT TCC TAG TCT TAC GCC AGT G (reverse), which amplify fragments of typically 338-base pairs (9 allele) to 389-base pairs (12 allele). These PCR fragments were subsequently screened via direct gel electrophoresis visualization of 2% agarose gels in 1X sodium borate buffer with ethidium bromide staining. A set of homozygotes for each of the two polymorphisms (i.e., LPR-LL and SS; STin2 10-10 and 12-12) was confirmed via direct DNA sequencing of these PCR fragments (following protocol of Claw, Tito, Stone, & Verrelli, 2010). Our chi-square tests of independence confirmed that genotype frequencies for both markers were in Hardy–Weinberg equilibrium (LPR: $\chi^2 = 0.55$, $p = .46$; STin2: $\chi^2 = 3.20$, $p = .09$), which is necessary for all of our statistical analyses (e.g., Hedrick, 2010).

Forming haplotypes—We used the PHASE v. 2.1.1 program (Stephens, Smith, & Donnelly, 2001) to statistically estimate how the genotypes at the two variants LPR and STin2 within individuals form a haplotype yielding frequencies of L10 = 32%, L12 = 26%, S10 = 6%, and S12 = 36%, replicating frequencies in global sampled populations (Claw et al., 2010).

Population admixture—We genotyped 10 unlinked VNTRs distributed across the genome to identify and control for any population stratification in our sample. The VNTRs were D1S1612, D2S1356, D4S1280, D5S1471, D6S1006, D7S2847, D17S1308, D18S535, D19S714, and D20S604 (described previously in Egan et al., 2001; Straub et al., 1993). Using the STRUCTURE program (Pritchard, Stephens, & Donnelly, 2000), we found no statistical evidence to reject a single population sample (i.e., all individuals could be genetically assigned to one group); thus, no correction for population stratification was needed in subsequent analyses of the full sample.

Results

Analysis Plan

First, we present descriptive data and correlations among key variables. Then we present the primary analyses, in which multilevel modeling (i.e., mixed or hierarchical linear modeling) is used to predict initial levels and change in caregivers' reports of children's noncompliance or aggression from 18 to 54 months of age. We first present the best fitting random effects models without substantive predictors. These models are the basis of subsequent analyses and describe the average trajectory of noncompliance or aggression in our sample. Then we present results for the substantive models in which LPR and STin2 polymorphisms and parenting are used as predictors.

Descriptive Analyses

Means and standard deviations for all study variables are presented in Table 1. No variables needed to be transformed due to excessive skew or kurtosis.

There were no sex differences in reports of parenting, noncompliance, or aggression at any time point. Chi-square tests examining the sex distribution across the SLC6A4 genotypes (LPR-SS/SL vs. LL; STin2-10-10 vs. 10-12 vs. 12-12) were not significant. Children's age

at assessments did not vary greatly, but relations with caregivers' reports of noncompliance and aggression were examined. None of these correlations was significant. SES was positively correlated with parenting quality, $r(135) = .51, p < .001$, and was negatively correlated with aggression at 18, 30, and 42 months, $r(102-108) = -.36$ to $-.20, ps < .05$, and noncompliance at 42 and 54 months, $r(105) = -.22$ and $r(107) = -.20, ps < .05$.

Aggression was related across time, $r(80-86) = .27$ to $.59, ps < .02$, as was noncompliance, $r(79-86) = .28$ to $.56, ps < .02$, with the exception of the correlation between noncompliance at 30 and 54 months, $r(85) = .12, ns$. Within time, noncompliance was positively correlated with aggression at all ages, $r(102-107)$ ranged from $.38$ to $.64, ps < .001$. Time 1 parenting quality was negatively related to noncompliance and aggression at all ages, $r(102-108) = -.24$ to $-.35, ps < .02$.

Consistent with Belsky, Bakermans-Kranenburg, and IJzendoorn's (2007) procedures for testing differential susceptibility, we first verified that our plasticity factors (LPR and STin2) were mostly unrelated to the other predictor (parenting) and the dependent variables (noncompliance and aggression). Children with the STin2 10-10 variant were higher in noncompliance relative to children with the 10-12 and 12-12 variants at 30 months, $t(101) = 2.27$ and $2.01, ps < .05$. No other associations were significant (analogous findings for haplotypes discussed later).

Random Effects Model

Adopting Singer and Willett's (2003) recommendation, we used a model-building approach. We began with a random intercept model with time centered at 18 months and added fixed and random effects for time and quadratic time until model fit could no longer be improved; likelihood ratio tests were used to compare the fit of nested models.

For noncompliance and aggression, the best fitting random effects models included fixed and random effects for the intercept, linear slope, and quadratic slope. Covariances among these effects were freely estimated. The random effects model explained 5.0% of the variance in noncompliance and 3.2% of the variance in aggression.

Fixed effects—The intercept was $.35$ for aggression and $.70$ for noncompliance. There were significant linear effects for aggression and noncompliance, $bs = 0.18$ and $-0.14, ts = 4.17$ and $-2.85, ps < .001$ and $< .01$. There was a significant quadratic slope for aggression, $b = -.05, t = -3.50, p < .001$; although the fixed effect for the quadratic slope was not significant for non-compliance, $b = 0.02, t = 1.49, ns$, this term was retained in subsequent models because adding a random quadratic slope coefficient improved model fit.

Random effects—The residual (within-person) variance was $.051$ for aggression and $.045$ for noncompliance. All three random effect variances made up a smaller proportion of the total variability in the aggression model relative to the noncompliance model, indicating that there is less between-person variability in initial levels and change over time in aggression than there was for noncompliance. For aggression and noncompliance, respectively, the variances of the random effects were $.030$ and $.096$ for the intercept, $.062$ and $.151$ for the linear slope, and $.007$ and $.015$ for the quadratic slope; covariances between the intercept and linear slope were $.004$ and $-.066$, covariances between the intercept and quadratic slope were $-.002$ and $.016$, and covariances between the linear and quadratic slope were $-.020$ and $-.046$.

The trajectories for aggression and noncompliance were quite different. Aggression was best characterized by a quadratic trajectory that peaked around 42 months, whereas the

noncompliance trajectory showed linear declines. Although the quadratic fixed effect was included in the noncompliance model, this term was not significant (see Figure 1).

Substantive Models

We added predictors to the models in two steps, using a procedure conceptually similar to hierarchical linear regression. In the first step, we examined the main effects of the genetic predictor(s) and parenting. In the second step, we added the $G \times E$ interaction(s). For both of these models, we tested whether each set of predictors provided additional predictive power over the more parsimonious model. In addition, for each model, we calculated a pseudo r^2 value by computing the squared correlation between the model-predicted scores and the observed scores; we examined the increase in this statistic corresponding to the addition of each set of predictors. We performed these analyses separately for noncompliance and aggression for each of three genetic predictors: LPR, STin2, and haplotypes that combine information from these two polymorphisms. This resulted in six sets of models. Marginal or significant interactions were examined only if their inclusion significantly improved a model fit relative to the main effects model. For interactions that did so, we probed the effects by computing simple slopes (Aiken & West, 1991). Because we modeled the average quadratic slope, which causes the average linear slope to vary across time, all simple effects for the slope represent a deviation from the average slope. As such, they indicate an increase or decline relative to the sample average, rather than a slope that is positive or negative in absolute terms. We also probed the interactions by determining the *regions of significance* (Johnson & Fay, 1950; Johnson & Neyman, 1936), which are important when testing differential susceptibility (Kochanska et al., 2011). This technique was used to determine whether genetic groups differed in noncompliance at low and high values of parenting quality and to determine how extreme parenting would have to be in order to observe a significant genetic difference.¹

LPR—Because the LPR-S allele is functionally dominant (Heils et al., 1996; Lesch et al., 1996), SS and SL genotypes were grouped together in analyses and compared with LL. In the main effects model, parenting was a predictor of the intercept for aggression and noncompliance, $b_s = -0.11$ and -0.15 , $t_s = -3.26$ and -3.45 , $p_s < .01$ and $< .001$. There were no significant genetic main effects. The main effects model accounted for 11.0% of the variance in aggression and 13.3% of the variance in noncompliance. Both of these models fit the data significantly better than the random effects model, $\chi^2(4) = 19.5$ and 24.8 , $p_s < .001$. The model with $G \times E$ interactions was an improvement over the main effects model for noncompliance, $\chi^2(2) = 9.4$, $p < .01$, and explained 16.2% of the variance, an increase of 2.9%. The interaction between LPR and parenting was a significant predictor of the intercept², $b = -0.26$, $t = -3.02$, $p < .01$, but not the slope (see Figure 2a). For aggression, the interaction model did not fit better than the main effects model, $\chi^2(2) = 3.1$, $p = .21$, despite a marginal interaction of LPR with parenting, $b = -0.122$, $t = -1.72$, $p < .10$.

We examined simple slopes for the interaction in the noncompliance model to determine whether parenting was related to noncompliance for each of the genetic polymorphisms. Parenting was unrelated to the intercept for the LPR-SS/SL genotype, $b = -0.04$, $t = -0.78$, $p = .43$, but was negatively related to the intercept for the LPR-LL genotype, $b = -0.31$, $t =$

¹Unlike for linear regression, in which the values of the simple slopes increase or decrease monotonically as values on the moderator increase or decrease, multilevel modeling does not generalize the simple slopes beyond the range of the data. Instead, simple slopes rapidly converge to their maximum value at the edge of the observed data. This constrains our ability to extrapolate beyond the range of parenting that was actually observed in this sample.

²In supplemental analyses, we examined the interaction between genetic variants (LPR and haplotype groups) and parenting as a predictor of 18-month caregiver-reported noncompliance and found substantively identical results; thus, these interactions are not primarily a result of the longitudinal nature of the data.

−4.60, $p < .001$ (see Figure 2b). We tested the region of significance for the genetic simple slopes, finding that the two genetic groups differed on the intercept of noncompliance at values of parenting 0.45 (+0.63 *SD*) above the mean and −0.82 (−1.16 *SD*) below the mean. The pattern for aggression was similar, but it is not examined further because adding the interaction term did not improve model fit.

STin2—We compared children with the STin2 10-10, 10-12, and 12-12 genotypes. The main effects models for STin2 fit significantly better than the random effects models for aggression and noncompliance, $\chi^2(6) = 25.0$ and 33.9, $ps < .001$. In these models, parenting predicted the intercept of aggression and non-compliance, $bs = -0.11$ and -0.15 , $ts = -3.26$ and -3.58 , $ps < .01$ and $< .001$. In addition, there was a genetic main effect of STin2 on the intercept of noncompliance and the slopes of aggression and noncompliance. Children with the 10-12 genotype were lower in noncompliance at 18 months relative to the children with the 10-10 and 12-12 genotypes, $bs = -0.22$ and -0.14 , $ts = -2.26$ and -2.10 , $ps < .05$, but the slope for noncompliance was more positive for 10-12 than 12-12, $b = 0.05$, $t = 1.70$, $p < .10$, suggesting the 10-12 heterozygotes were becoming more like other children in their noncompliance over time. Children with the 10-10 genotype had a more positive slope of aggression compared with those with the 10-12 and 12-12 genotypes, $bs = -0.09$ and -0.08 , $ts = -2.22$ and -1.93 , and $ps < .05$ and $< .10$. The main effects model explained 12.8% of the variance in aggression and 15.7% of the variance in noncompliance. The models with STin2 $\times$ Parenting interactions did not fit better than the main effects models for aggression and noncompliance, $\chi^2(4) = 4.1$ and 1.2, $ps = .39$ and $.88$, and there were no significant interactions predicting the intercepts or linear slopes.³

SLC6A4 haplotype groups—We created three genetic groups based on combinations of the LPR-S and L alleles and the STin2-10 and 12 alleles. As previously reviewed, the LPR-S and STin2-10 alleles have each been related to reduced serotonin function, whereas some have shown that the S12 haplotype may actually be associated with increased serotonin function (Ali et al., 2010). Thus, we may expect that individuals with either the S10 and S12 haplotypes to be different from those with other haplotypes including LPR-LL individuals. Besides this hypothesis based on functional observations, we also have additional evidence to suggest that individuals with LPR-LL should be further differentiated. Specifically, because we found a $G \times E$ interaction for LPR-LL individuals, it made sense to separate haplotypes that included LPR-LL homozygotes (i.e., L10-L10, L10-L12, L12-L12) from haplotypes that included LPR-SS and SL genotypes. With these considerations in mind, we divided the children into three groups based on their haplotypes. Group 1 (henceforth called *S10 group*) consisted of the following combinations: S10-S12, S10-L10, and S10-L12; these individuals had the critical S10 haplotype (no children had S10-S10). Group 2 (called *S12 group*) included S12-S12 and S12-L10 haplotypes (we had no S12-L12). Group 3 (called *L10-L12 group*) included haplotypes including the LPR-LL genotype (e.g., L10-L10, L10-L12, and L12-L12). Sample sizes for the groups are in Table 1; results are in Table 2. As done for LPR and STin2, we examined relations between the haplotype groups and 18-month parenting, and aggression and noncompliance at each time point. The only significant difference for these variables was found for noncompliance at 30 months; the S10 group was higher relative to the S12 group, $t(101) = 2.72$, $p < .01$.

In the model with the main effects of the haplotype and parenting, parenting was a significant predictor of the intercept of aggression and noncompliance, $bs = -0.11$ and -0.15 , $ts = -3.26$ and -3.42 , $ps < .01$ and $.001$, but not the linear slope. There were no

³In supplemental analyses, we controlled for mothers' income and education in the first step of the models. This did not substantively affect any of the results, and in no case did a significant effect (at $p < .05$) become nonsignificant due to the inclusion of these covariates.

haplotype main effects for aggression, but the S10 group was marginally higher in noncompliance relative to the S12 and L10-L12 groups, $bs = 0.18$ and 0.16 , $ts = 1.92$ and 1.69 , $ps < .10$. These models explained 12.2% and 14.5% of the variance in aggression and noncompliance, respectively. Both of these models fit the data better than the random effects models, $\chi^2(6) = 22.4$ and 28.6 , $ps < .01$ and $< .001$. For aggression, none of the Haplotype $\times$ Parenting interactions predicted the intercept or slope, and the model containing the interaction terms fit no better than the main effects model, $\chi^2(4) = 6.1$, $p = .19$. For noncompliance, however, the relation between parenting and the intercept differed between the L10-L12 group and the S10 and S12 groups, $bs = 0.38$ and 0.22 , $ts = 3.19$ and 2.38 , $ps < .01$ and $.05$. There was also a significant $G \times E$ interaction predicting the slope of noncompliance. The relation between parenting and the slope for the S10 group differed from those of the S12 and L10-L12 groups, $bs = 0.11$ and 0.14 , $ts = 1.90$ and 2.53 , $ps < .10$ and $.05$. The model with $G \times E$ interactions fit better than the main effects model, $\chi^2(4) = 13.6$, $p < .01$, and explained 18.1% of the variance, an increase of 3.6% over the main effects model (see Figure 3).

We probed each interaction by examining the simple slope of parenting on the outcome of interest for the relevant haplotype groups (Aiken & West, 1991). Quality of parenting was negatively related to the intercept of noncompliance for the L10-L12 group, $b = -0.31$, $t = -4.72$, $p < .001$, but was unrelated to the intercept for the S10 and S12 groups, $bs = 0.08$ and -0.09 , $ts = 0.75$ and -1.37 , $ps = .45$ and $.17$. Parenting was negatively related to the slope of noncompliance for the S10 group, $b = -0.10$, $t = -2.21$, $p < .05$, but was unrelated for the S12 group or the L10-L12 group, $bs = 0.00$ and 0.04 , $ts = 0.12$ and 1.24 , and $ps = .90$ and $.22$.

In tests of the regions of significance for noncompliance, for the 18-intercept, there were significant differences between the S12 and L10-L12 groups for values of parenting 1.10 points (1.55 *SD*) above the mean and -0.99 points (1.40 *SD*) below the mean. In addition, the S10 and L10-L12 groups differed on the intercept for values of parenting 0.03 points (0.04 *SD*) above the mean and -1.50 points (2.12 *SD*) below the mean (see Figure 4). For the linear slope, there were significant differences between S10 and L10-L12 groups at 0.54 points (0.76 *SD*) above the parenting mean, and -1.68 points (2.37 *SD*) below the parenting mean, and differences between the S10 group and the S12 group at > 0.69 points (0.98 *SD*) above the mean, but the two groups never differed at the low end of parenting.⁴

Discussion

As predicted based on functional studies, the LPR and STin2 haplotypes appeared to better represent the relevant genetic variance when predicting noncompliance. Thus, it appears that LPR effects on SLC6A4 gene expression can be more precisely specified by also including the STin2 polymorphism; genetic variation is not always “additive”; and interactions among polymorphisms, even within single genes, contribute to many complex traits (Belsky & Beaver, 2011; Claw et al., 2010).

Of most interest are the significant interactions between parenting quality and the SLC6A4 haplotype predicting growth in children’s noncompliance. Splitting the LPR-S carriers into

⁴In addition to testing predictors of the linear slope, we also tested predictors of the quadratic slope for caregivers’ reports of aggression. There was a significant Parenting $\times$ STin2 interaction predicting the quadratic slope, such that the quadratic slope differed as a function of parenting for the 12-12 genotype relative to 10-10 and 10-12 genotypes, $bs = -0.11$ and -0.13 , $ts = -2.12$ and -1.69 , $ps < .05$ and $< .10$. An examination of the simple slopes revealed that parenting was significantly related to the quadratic slope for the 12-12 group, $b = 0.11$, $t = 2.19$, $p < .05$, but was unrelated to the quadratic slope for the 10-10 and 10-12 groups, $bs = -0.02$ and -0.00 , $ts = -0.34$ and -0.13 , $ps = .73$ and $.89$. For all other models, adding predictors of the quadratic slope did not significantly improve model fit.

the S10 and S12 haplotypes provided a more differentiated pattern of results relative to using LPR alone. Specifically, as parenting quality increased, children with an S10 haplotype were more likely to exhibit declines (compared with the average slope) in noncompliance across time. Although parenting was not initially related to noncompliant behavior for children with the S10 haplotype, the prediction by parenting on their behavior grew over time. Moreover, there was evidence of a slope difference between the S10 group and the L10-L12 group at both high and low levels of parenting quality: relative to children with the L10-L12 haplotype, those with an S10 haplotype showed more growth in noncompliance in the context of poor-quality parenting and less growth in noncompliance in the context of high-quality parenting. This difference was especially evident at high levels of supportive parenting. In addition, the difference in slope between the S10 and S12 groups, although only marginally significant, was also most evident for positive parenting (and in the same direction). Parenting quality was negatively related to the slope of noncompliance only for the S10 group, indicating that this was the only genetic group for which the relation between parenting and noncompliance changed over time.

The findings for the intercept were also of interest. Parenting was differentially related to initial levels of noncompliance for the L10-L12 haplotype relative to both S10 and S12 haplotypes. Specifically, parenting quality was negatively related to initial levels of noncompliance only for children with L10-L12 haplotype; unlike the results for the slope, this pattern of results was similar to the results for LPR, although differences from the L10-L12 group for the intercept were more evident for children in the S10 group than for the S12 group. The differences in initial levels of noncompliance between the L10-L12 and S10 groups were most evident at high (rather than low) levels of parenting quality.

To summarize the pattern of results for the haplotypes, the L10-L12 group was more susceptible to parenting than the S10 or S12 groups when the children were young. In contrast, parenting did not have much of an effect for the S10 group early on, but these children had development that was contingent on parenting. Because parenting tends to be stable over time, this finding may indicate that the L10-L12 group was most sensitive to variation in parenting because these children were able to calibrate their behavior as a function of parenting early in life. In contrast, the S10 group was unaffected by parenting early on, but appeared to be increasingly affected by parenting over time. Finally, the S12 group was relatively insensitive to parenting across the entire study. Thus, there was evidence for differential susceptibility for the S10 and L10-L12 groups, albeit following a different time course.

These findings provide support for the prediction that reactive children are especially likely to comply with adults if reared in an environment that is rewarding and in which compliance is likely to elicit benefits. Furthermore, we also find evidence that this $G \times E$ interaction is conditional within a time context. Such findings support evolutionary perspectives that view parenting as an important environmental cue used by even young children to calibrate their behavior in ways that enhance their ability to survive and eventually reproduce later in life (MacDonald, 1992).

Noncompliant behavior at 18 months is likely to reflect high levels of defiant behavior, and such behavior often leads to a coercive pattern of interactions between mother and child (Patterson, Reid, & Dishion, 1992). Children's externalizing behavior at age 2, including noncompliance, has been found to relate to low levels of maternal warmth or sensitivity; moreover, coercive patterns of mother-child interaction often are evident when the child is 2 years old and predict later aggression (Shaw, Bell, & Gilliom, 2000). Children in the L10-L12 group (or just two LLs on LPR) who are exposed to nonsupportive parenting (likely in part because they elicit it) appear to have already developed a relatively high level of

noncompliance by age 18 months (see Figure 3). Moreover, this pattern appeared to be stable across the next few years in this sample, perhaps because a coercive cycle had been established early and was stable.

There were also some findings for LPR or STin2 in isolation. For LPR, children with the LL genotype appeared more susceptible to parenting at 18-months relative to children with the SS or SL genotype. Supportive parenting was negatively related to noncompliance at 18 months for the LL group but not for the S carriers, and the pattern of results was similar (although only marginal) for aggression. LPR-LL genotypes differed in noncompliance from LPR-S carriers at both low and high quality of parenting. This interaction replicates some other studies showing greater aggression in adverse settings for LPR-LL individuals (Nobile et al., 2007; Sadeh et al., 2010), although there is little research with children on LPR and noncompliance or on LPR and change in noncompliance. Interestingly, this interaction was only important at a young age; as children aged, the main effect of parenting became a more important predictor of noncompliance, to the detriment of the $G \times E$ interaction (see Fig. 2a). Thus, although it appears that there is evidence for early differential susceptibility indexed by the LPR polymorphism, this effect may diminish over time.

For STin2 by itself, there were no significant interactions, but there were genetic main effects on the initial level of noncompliance and the slope of aggression. Children with the 10-10 genotype had a less negative slope for aggression than children with the 10-12 and 12-12 genotypes (although the latter comparison was marginally significant). Thus, 10-12 individuals appeared to be relatively compliant initially but were decreasing in that characteristic over time, whereas 10-10 individuals were becoming more aggressive relative to other genotypes.

Unexpectedly, early aggression was predicted primarily by quality of parenting and the main effect of STin2, with 10-10 homozygotes being especially prone to an increase in aggression. We are unclear why noncompliance was more likely to be predicted by the haplotypes; perhaps aggression—because it is more extreme than most instances of mere noncompliance at the ages observed in this study—differs in its development. It is quite possible with age that the quality of parenting and STin2 interact in predicting aggression, but that possibility remains to be tested. It should be noted that the measure of noncompliance varied somewhat more than that for aggression across children, which likely increased power in terms of its prediction from statistical interactions.

On average, aggression increased and then declined somewhat with age, similar to findings reported in some other research (see Dodge, Cole, & Lynam, 2006). In contrast, noncompliance declined with age. The decline in noncompliance over time is likely at least partly due to the increase in language ability, which allows children to negotiate their needs (Kopp, 1992).

Degree of positive parenting was negatively related to both aggression/defiance and noncompliance at 18 months. Moreover, in zero-order correlations, parenting at 18 months was negatively related to caregiver-reported aggression/defiance and noncompliance at all ages. Thus, as would be expected from prior literature on aggression (Dodge et al., 2006; Shaw et al., 2000) and compliance (Kochanska, Forman, Aksan, & Dunbar, 2005), parenting had a predictable and ongoing relation with noncompliance. However, there were not main effects of parenting on the slope of the toddlers' behavior. Parenting did predict the trajectory of noncompliance, but this effect varied with children's serotonin-related haplotype.

Strengths of the current study include not only the focus on haplotypes rather than single genetic polymorphisms, but also the longitudinal design, use of observed parenting, and

involvement of a reporter of the children's behavior other than the mother (given that parenting was assessed). Specifically, certain outcomes are revealed only with certain allelic combinations as haplotypes and only at certain time intervals of age. Limitations of the study include the moderate sample size and our inability to examine some genotypes by themselves (e.g., the S10-S10). However, it should be noted that this genotype (individuals with two S10 haplotypes) is quite rare (<3% worldwide; Claw et al., 2010); thus, even very large samples are unlikely to include significant representation of this group. In addition, our findings may not generalize to other groups such as children in different cultural and ethnic groups. For example, the $G \times E$ interactions identified here are conditional upon genetic background as found within a certain ethnicity; thus, varying ethnic background with our $G \times E$ model would be an obvious future consideration when attempting to generalize the findings across human populations. Despite the weaknesses and the need for replication, the study findings support the importance of examining haplotypes, Gene $\times$ Environment interactions, and change in outcome variables over time when assessing how children respond to their environments. The results also support the conclusion that children—some more than others—may be predisposed to adapt their social behavior depending on their social environment. In future studies, it would be useful to examine $G \times E$ interactions at multiple ages and to examine different aspects of parenting and discipline.

Although we found two polymorphisms in the commonly studied SLC6A4 gene to be important, this gene is clearly only one of many that influence endophenotypes such as serotonin in the brain and phenotypes such as externalizing problems in children. In fact, large-scaled genomic and population analyses implicate many serotonin- and dopamine-related genes and pathways in common behavioral variation (e.g., Malhotra, Lencz, Correll, & Kane, 2007). In this respect, not only is it going to be necessary to identify combinations of functional polymorphisms within genes as haplotypes as we have done, but also across multiple pathways in detecting interactions that explain significant variation at the genomic level. As high-throughput data collection and statistical analyses continue to evolve from genome-wide association analyses, these approaches will be realized. Additionally, as gene-environment interplay is clearly key to identifying the role played by genetics, integrating the study of gene-environment correlations and epigenetics with gene-environment interaction will be necessary to elucidate mechanisms of development (Lemery-Chalfant, 2010). Parenting may be passively correlated with children's genotypes because parents' heritable personality influences their parenting (i.e., passive gene-environment correlation), and children's heritable traits such as externalizing problems may also elicit different parenting behaviors (i.e., evocative gene-environment correlation; see Bakermans-Kranenburg & van IJzendoorn, 2006, for an example of using an experimental intervention to test causal relations for a Gene $\times$ Environment interaction). At a different level of analysis, environmental exposure can alter gene expression, and these epigenetic changes are sometimes stable and can influence behavior. It is important to note that the presence of epigenetics does not negate findings from candidate gene studies; both genetic polymorphisms that are stable across individual lifespans and epigenetic tags can contribute to trait variation.

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Figure 1.
Unconditional growth models for caregivers' reports of aggression and noncompliance.

Figure 2.

a. Predicted trajectories of caregivers' reports of noncompliance for LPR Variants. These trajectories represent the model-predicted noncompliance scores based on specific parenting and genetic values. b. Simple slopes of parenting on caregivers' reports of noncompliance for LPR variants. Two common repeat alleles: short (S) or long (L). *** $p < .001$.

Figure 3. Predicted trajectories of caregivers' reports of noncompliance for haplotypes. These trajectories represent the model-predicted noncompliance scores based on specific parenting and genetic values.

Figure 4.

Simple slopes of parenting on caregivers' reports of noncompliance for the SLC6A4 haplotype variants: 18-month intercept and deviations from the average slope. * $p < .05$. ** $p < .01$. *** $p < .001$.

Table 1
Means and Standard Deviations of Parenting and Caregiver-Reported Aggression and Noncompliance

Variable	Parenting		Trait	18 months		30 months		42 months		54 months	
	N	M (SD)		N	M (SD)	N	M (SD)	N	M (SD)	N	M (SD)
Total	138	0.01 (0.71)	Aggression/defiance	107	0.34 (0.28)	104	0.50 (0.35)	106	0.49 (0.35)	110	0.46 (0.36)
			Noncompliance	106	0.70 (0.38)	104	0.58 (0.33)	107	0.52 (0.36)	109	0.48 (0.35)
SLC6A4: S/L											
LL	48	-0.14 (0.81)	Aggression/defiance	36	0.36 (0.27)	35	0.53 (0.34)	33	0.53 (0.32)	41	0.44 (0.35)
			Noncompliance	36	0.65 (0.41)	35	0.61 (0.36)	34	0.57 (0.38)	40	0.45 (0.34)
SS/SL	90	0.09 (0.63)	Aggression/defiance	71	0.33 (0.29)	69	0.48 (0.35)	73	0.48 (0.36)	69	0.47 (0.36)
			Noncompliance	70	0.72 (0.37)	69	0.56 (0.31)	73	0.49 (0.35)	69	0.50 (0.36)
SLC6A4: 10/12											
10-10	13	-0.08 (0.67)	Aggression/defiance	11	0.32 (0.31)	12	0.60 (0.31)	12	0.76 (0.33)	13	0.62 (0.40)
			Noncompliance	11	0.84 (0.40)	12	0.78 (0.36)	12	0.65 (0.31)	13	0.62 (0.44)
10-12	76	-0.03 (0.79)	Aggression/defiance	61	0.36 (0.29)	57	0.49 (0.37)	60	0.49 (0.34)	61	0.44 (0.35)
			Noncompliance	60	0.63 (0.34)	57	0.55 (0.34)	61	0.52 (0.37)	61	0.47 (0.35)
12-12	49	0.09 (0.57)	Aggression/defiance	35	0.31 (0.27)	35	0.49 (0.32)	34	0.40 (0.34)	36	0.43 (0.35)
			Noncompliance	35	0.77 (0.43)	35	0.56 (0.29)	34	0.47 (0.36)	35	0.45 (0.32)
SLC6A4 haplotype											
S10	15	0.02 (0.81)	Aggression/defiance	15	0.39 (0.26)	12	0.63 (0.49)	13	0.59 (0.38)	13	0.58 (0.37)
			Noncompliance	15	0.80 (0.33)	12	0.79 (0.35)	13	0.59 (0.36)	13	0.52 (0.39)
S12	75	0.11 (0.60)	Aggression/defiance	56	0.32 (0.30)	57	0.45 (0.31)	60	0.45 (0.36)	56	0.45 (0.36)
			Noncompliance	55	0.70 (0.38)	57	0.52 (0.28)	60	0.47 (0.35)	56	0.50 (0.36)
L10/12	48	-0.14 (0.81)	Aggression/defiance	36	0.36 (0.27)	35	0.53 (0.34)	33	0.53 (0.32)	41	0.44 (0.35)
			Noncompliance	36	0.65 (0.41)	35	0.61 (0.36)	34	0.57 (0.38)	40	0.45 (0.34)

Table 2
Parenting and SLC6A4 Haplotypes as Predictors of Caregivers' Reports of Aggression and Noncompliance

Fixed effects	Aggression						Noncompliance					
	Main effects			Interactions			Main effects			Interactions		
	b	t	p	b	t	p	b	t	p	b	t	p
Intercept ^a (18 months)	0.409			0.408			0.848			0.843		
S10 vs. S12	-0.083	-1.11		-0.082	-1.12		-0.176	-1.92	[†]	-0.175	-1.99	*
S10 vs. L10-L12	-0.041	-0.51		-0.045	-0.58		-0.164	-1.69	[†]	-0.173	-1.86	[†]
L10-L12 vs. S12	-0.042	-0.79		-0.037	-0.70		-0.012	-0.18		-0.002	-0.04	
Parenting	-0.114	-3.26	**	-0.025	-0.30		-0.149	-3.42	***	0.075	0.75	
Parenting × S10 vs. S12				-0.056	-0.57					-0.164	-1.37	
Parenting × S10 vs. L10-L12				-0.164	-1.63					-0.382	-3.19	**
Parenting × L10-L12 vs. S12				0.107	1.42					0.218	2.38	*
Linear slope ^b	0.206	3.95	***	0.207	4.00	***	-0.166	-2.76	**	-0.163	-2.78	**
S10 vs. S12	-0.018	-0.48		-0.023	-0.64		0.043	0.98		0.036	0.87	
S10 vs. L10-L12	-0.041	-1.01		-0.041	-1.06		0.031	0.69		0.031	0.71	
L10-L12 vs. S12	0.022	0.81		0.017	0.67		0.011	0.37		0.005	0.18	
Parenting	-0.010	-0.55		-0.071	-1.74	[†]	-0.004	-0.20		-0.102	-2.21	*
Parenting × S10 vs. S12				0.079	1.62					0.106	1.90	[†]
Parenting × S10 vs. L10-L12				0.076	1.57					0.138	2.53	*
Parenting × L10-L12 vs. S12				0.003	0.08					-0.032	-0.76	
Quadratic slope	-0.049	-3.62	***	-0.049	-3.56	***	0.021	1.36		0.021	1.39	
Pseudo r^2 (%)	12.2			13.7			14.5			18.1		
-2LL (deviance)	176.6			170.5			232.6			219.0		

Note. Group 1 = S10-S12, S10-L10, and S10-L12; Group 2 = S12-S12, S12-L10, and S12-L12; Group 3 = L10-L12, L10-L10, and L12-L12.

^aThis coefficient refers to the intercept for the S10 group at the mean level of parenting. The difference between the intercept for the S10 group and the other genetic groups at the mean level of parenting is represented by the genetic main effects.

^bDue to the presence inclusion of a fixed effect for quadratic time, this coefficient varies as a function of how time is centered. In these analyses, this coefficient refers to the linear effect with time centered at 18 months. The genetic main effects on the slope represent the difference between this coefficient for the S10 group and the other genetic groups.

[†] $p < .10$.

* $p < .05$.
** $p < .01$.
*** $p < .001$.