Development and Psychopathology **19** (2007), 1105–1116

Printed in the United States of America
DOI: 10.1017/S0954579407000569

Evidence for a gene–gene interaction in predicting children's behavior problems: Association of serotonin transporter short and dopamine receptor D4 long genotypes with internalizing and externalizing behaviors in typically developing 7-year-olds

LOUIS A. SCHMIDT,[a] NATHAN A. FOX,[b] AND DEAN H. HAMER[c]
[a]*McMaster University;* [b]*University of Maryland; and* [c]*National Institutes of Health*

Abstract

Recent work on the molecular genetics of complex traits in typical and atypical human development has focused primarilyon associations of single genes with behavior. Disparate literature suggests that the presence of one or two copies of the short allele of the serotonin transporter (*5-HTT*) gene and the long allele (7-repeat allele) version of the dopamine receptor D4 (*DRD4*) gene predicts internalizing- and externalizing-related behaviors, respectively. Apparently for the first time in the extant literature, we report a gene–gene statistical interaction on behavior problems in a group of typically developing children at age 7. DNA was extracted from buccal cells collected from 108 children and genotyped for short and long alleles of the *5-HTT* gene and the short (2–5 repeats) versus long (6–8 repeats) allele of the *DRD4* gene. Mothers completed the Child Behavior Checklist. As predicted, children with one or two copies of the short allele of the *5-HTT* gene *and* the long allele version of the *DRD4* gene exhibited significantly more internalizing and externalizing behaviors at age 7 than children with other combinations of the *5-HTT* and *DRD4* short and long genotypes. As well, children with the *5-HTT* long *and DRD4* long genotypes had the lowest reported scores on internalizing and externalizing behaviors at age 7, suggesting that the presence of the *5-HTT* long genotype may serve as a protective factor against these behaviors in children with the long *DRD4* genotype. Implications of these findings for understanding cumulative biological risk and protective factors in childhood behavior problems and psychopathology are discussed.

Although the origins of childhood behavior problems are undoubtedly multiply determined, a burgeoning interest over the last decade has been directed toward examining the molecular genetic basis of complex traits and psychopathology in humans (see Benjamin, Ebstein, & Belmaker, 2002; Cloninger, Adolfsson, & Svrakic, 1996; Hamer & Copeland, 1998; Rutter, Moffitt, & Caspi, 2006; Schmidt & Fox, 2002, for reviews). However, the majority of the studies in this area of inquiry have focused exclusively on examining single genes or only reporting associations of single genes with behavior despite the multiple determinants and complexities of human behavior. Recently, researchers have begun to embrace these

This research was supported by a grant from the National Institutes of Health (HD 17899) awarded to Nathan A. Fox. The authors thank the parents and children for their participation; Stacy Barton, Susan Calkins, Genevieve Erb, Lisa Perry-Moss, Ariana Shahinfar, and Cindy Smith for their help with behavioral data collection at Maryland; and Stella Hu for her help with genotyping at the National Institutes of Health.

Address correspondence and reprint requests to: Louis A. Schmidt, Department of Psychology, Neuroscience and Behaviour, 1280 Main Street West, McMaster University, Hamilton, Ontario L8S 4K1, Canada; E-mail: schmidtl@mcmaster.ca.

complexities by moving beyond single gene hypotheses and examining gene–environment interactions (G × E) and gene–gene interactions and, in some instances, gene–gene–environment interactions, which may confer risk for human psychopathology (see Caspi & Moffitt, 2006, for a review). Much of this work has been guided by existing G × E models that are known to underlie other types of human diseases (e.g., Hunter, 2005).

The recent work of Caspi and colleagues (2002, 2003) provides a cogent example of the G × E interplay in understanding human psychopathology. Caspi et al. (2002) noted that maltreated children with a genotype that conferred high levels of the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) were less likely to develop antisocial behavior, suggesting that some genotypes may moderate a child's sensitivity to some environmental insults. Caspi's group also noted in another study that individuals with one or two copies of the short allele of the serotonin transporter (*5-HTT*) gene exhibited more depressive symptoms, diagnosable depression, and suicidal ideation in relation to stressful life events compared with individuals homozygous for the long allele (Caspi et al., 2003). These basic findings have been independently replicated in studies of children (Kaufman et al., 2004), adolescents (Eley et al., 2004), and young adults (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005).

Other examples of G × E involved in children's internalizing and externalizing-related behaviors have been recently published as well. For example, Fox and colleagues (2005) found that preschoolers with one or two copies of the short allele of the *5-HTT* gene and who had mothers who perceived themselves low in social support were more likely to be shy and behaviorally inhibited at age 7 than children homozygous for the long allele of the *5-HTT* gene and/or whose mothers were high in perceived social support. Bakerman-Kranenburg and van IJzendoorn (2006) noted that children with the long dopamine receptor D4 (*DRD4*) genotype and who had mothers who provided insensitive care exhibited more externalizing behaviors than children with the short *DRD4* genotype and/or had mothers who were sensitive to their child's needs.

In addition to G × E, there are several reports of gene–gene interactions underlying complex traits in humans (see Lesch, Greenberg, Higley, Bennett, & Murphy, 2002). Gene–gene interactions have been traditionally examined in relation to a wide range of human diseases, including asthma (Howard et al., 2002), hypertension (Moore & Williams, 2002), risk of thrombosis (Van Boven, Vandenbroucke, Briet, & Rosendaal, 1999), Crohn disease (Negoro et al., 2003), etiology of neural tube deficits (Botto & Mastroiacovo, 1998), and renal impairment after unilateral nephrectomy (Shiozawa, Provoost, Van Dokkum, Majewski, & Jacob, 2000). Recently, researchers have examined gene–gene statistical interactions in relation to complex traits in human infants and adults.

In a series of studies, Ebstein and colleagues (1998) examined gene–gene interactions in relation to neonatal temperament, infant attention (Auerbach, Benjamin, Faroy, Geller, & Ebstein, 2001), and the adult personality trait of reward dependence (Ebstein, Segman, et al., 1997). Ebstein et al. (1998) investigated the interaction of *5-HTT* and *DRD4* genes in 81 healthy 2-week-old neonates in relation to temperament that was indexed by the Brazelton Neonatal Assessment Scale (NBAS). Neonates with the homozygous short *5-HTT* genotype (*s*/*s*), but lacking the longer allele form of the *DRD4* gene, scored lower on the NBAS orientation score compared with other neonates. In another study by Ebstein's group (Auerbach et al., 2001), these researchers noted a significant interaction between the *5-HTT* gene and the *DRD4* gene on a measure of sustained attention in a group of 61 healthy 1-year-old infants. Infants with the homozygous short allele of the *5-HTT* gene and the long allele of the DRD4 had the lowest scores of duration of looking while involved in an information processing task. Ebstein, Segman, and colleagues (1997) also examined the interaction of the serotonin 2C receptor gene (*5-HT2C*; Lappalainen et al., 1995) and *DRD4* gene in relation to adult personality. They found an association between a cysteine to serine coding sequence polymorphism in the *5-HT2C* gene and the personality trait of reward dependence, especially in individuals with the *DRD4* long genotype. This latter finding of a gene–gene interaction in relation

to the personality trait of reward dependence has been independently replicated (e.g., Kuhn et al., 1999).

Most recently, independent groups of investigators have examined Gene × Gene × Environment interactions. Kaufman and colleagues (2006) found a significant three-way interaction between the brain-derived neurotrophic factor (*BDNF*) gene, the 5-HTT linked promoter region (*5-HTTLPR*) gene, and maltreatment history in predicting depression. Children with the methionine (Met) allele of the *BDNF* gene and two short alleles of the *5-HTTLPR* gene had the highest depression scores; however, the vulnerability linked to these two genotypes was only evidenced in the maltreated group. In addition, they noted that a significant four-way interaction revealed that social supports moderated the risk for depression. Mandelli and colleagues (2007) examined the interactions among the *5-HTT*, *DRD4*, and catechol-*O*-methyltransferase (*COMT*) genes, and stressful life events in mood disorders. A significant interaction between the *5-HTT* and *COMT* genes was found such that individuals with the *5-HTT* short allele and *COMT* Met alleles showed the highest occurrences of stressors at the first lifetime mood-disorder episode. Taken together, the findings from the disparate studies reviewed above suggest that particular combinations of genotypes may confer risk for psychopathology. Overall, the presence of one or two copies of the short allele of the *5-HTT* gene and the presence of the long allele version of the *DRD4* gene may confer a risk for internalizing- and externalizing-related behaviors, respectively, but particular environments may moderate the outcome.

In a group of typically developing children, we examined whether the presence of the *5-HTT* short and *DRD4* long genotypes in the same individual would confer risk for more internalizing and externalizing behaviors than children with other combinations of the *5-HTT* and *DRD4* short and long genotypes. We collected buccal cells from 108 typically developing children who had been followed longitudinally since infancy (see Calkins, Fox, & Marshall, 1996; Fox, Calkins, & Bell, 1994; Fox et al., 1995, 2001, 2005; Fox, Schmidt, Calkins, Rubin, & Coplan, 1996), and their mothers completed the Child Behavior Checklist (CBCL) when the child turned 7 years old. The DNA was extracted from the buccal cells and genotyped for the presence of short (*s*/*s*, *s*/*l*) and long alleles (*l*/*l*) of the *5-HTT* gene and the short (2–5 repeats) versus long (6–8 repeats) alleles of the *DRD4* gene. We next stratified the *5-HTT* and *DRD4* genotypes. We created a 2 (*5-HTT*: short vs. long alleles) × 2 (*DRD4*: short vs. long alleles) design, resulting in four groups of children: *5-HTT* short/*DRD4* long, 5-*HTT* short/*DRD4* short, *5-HTT* long/*DRD4* short, and *5-HTT* long/*DRD4* long. We then examined whether the four groups were distinguishable on the maternal report of CBCL for internalizing and externalizing behavior at age 7. To our knowledge, there are no published studies examining gene–gene interactions in typically developing children's behavior problems.

We examined the serotonin transporter gene because of its well-documented role in anxiety-related problems in humans. Lesch et al. (1996) reported that adults carrying one or two copies of a short allele of the regulatory DNA sequence polymorphism in the *5-HTTLPR* gene self-reported higher levels of neuroticism, anxiety, and depression compared with individuals homozygous for the long allele of this polymorphism. In addition, euthymic adults with the short allele of the *5-HTT* gene are known to be low on novelty seeking (Serretti et al., 2006). In vitro and in vivo expression studies have shown that the short allele leads to less gene transcription and protein production than does the long allele (Greenberg et al., 1999; Heils et al., 1996; Lesch et al., 1996; Little et al., 1998). Serotonin has been also implicated as a major neurotransmitter of anxiety and withdrawal behaviors because of its effects on regulating mood and emotional states (see Westernberg, Murphy, & Den Boer, 1996, for a review). The association between the serotonin transporter gene and anxiety-related symptoms has been replicated in culturally diverse populations, including the United States, Europe, Israel, and Japan (e.g., see Greenberg et al., 1999, for a review), although it is important to point out that some studies have failed to find any association of the *5-HTT* gene with anxiety (Ball et al., 1997; Deary et al., 1999; Kumakiri et al., 1999; Schmidt, Fox, Rubin, Hu, & Hamer, 2002).

The second gene of interest to us was the *DRD4* gene. This gene contains a functional repeated sequence polymorphism within its coding sequences and was originally studied for its role in personality traits related to novelty seeking. The initial two studies (Benjamin et al., 1996; Ebstein et al., 1996) found that adults with longer versions (6–8 repeats) of the *DRD4* gene self-reported higher novelty seeking scores than adults with shorter versions (2–5 repeats) of the coding sequence polymorphism. Dopamine has been implicated as a major neuromodulator of novelty seeking because of its well-documented role in inducing euphoria in humans and approach behavior in animals (Cloninger, 1987). The shorter alleles code for a receptor that is apparently more efficient in binding dopamine compared with the larger alleles (see Plomin & Rutter, 1998, for a review). The association of the long allele of the *DRD4* gene with novelty seeking in young adults has been independently replicated in some populations (Ebstein, Nemanov, Klotz, Gritsenko, & Belmaker, 1997; Noble et al., 1998; Ono et al., 1997; Strobel, Wehr, Michel, & Brocke, 1999; Tomitaka et al., 1999). However, several studies have found either no association (Gelernter et al., 1997; Goldman et al., 1996; Jonsson et al., 1997; Pogue-Geile, Ferrell, Deka, Debski, & Manuck, 1998; Sander et al., 1997; Sullivan et al., 1998; Vandenbergh, Zonderman, Wang, Uhl, & Costa, 1997) or associations in the "opposite" direction relative to the initial reports (Malhotra, et al., 1996). The *DRD4* long genotype has also been linked to attention-related problems in human infants (Auerbach et al., 2001) and problems with attention (Schmidt, Fox, Perez-Edgar, Hu, & Hamer, 2001) and aggression (Schmidt et al., 2002) in children, and more recently, externalizing behaviors in children with low IQ (DeYoung et al., 2006) and low harm avoidance in euthymic adults (Serretti et al., 2006).

If the *5-HTT* short genotype is related to withdrawal behaviors, anxiety, and internalizing-related problems, and the *DRD4* long genotype is related to approach behaviors, novelty-seeking, and externalizing-related problems, then it is possible that individuals with the presence of this combination of genotypes would evidence more behavior problems because of the "double hit" than other individuals who possess different combinations of the *5-HTT* and *DRD4* genotypes. Accordingly, we predicted that children with one or two copies of the short allele of the *5-HTT and* the long allele of the *DRD4* gene would exhibit more internalizing and externalizing behaviors at age 7 than children with other combinations of the *5-HTT* and *DRD4* short and long allele genotypes.

Method

Participants

The participants in this study were 108 typically developing children who had complete gene and behavioral data. These children have been followed longitudinally since infancy as part of a larger study examining the psychology and psychophysiology of socioemotional development (see Calkins et al., 1996; Fox et al., 1994, 1995, 1996, 2001, 2005). The children were primarily Caucasian and of middle-class background. All of the parents had completed high school, and a majority of the mothers and fathers were college graduates. The children were mostly living with their families in or near College Park, Maryland. Original exclusion criteria were that the child had no peri- or postnatal complications and no known neurological problems.

Maternal report of childhood behavior problems

The parent (primarily mothers) completed the CBCL (Achenbach, 1991; Achenbach & Edelbrock, 1981) on the child at age 7. The CBCL is a widely used questionnaire completed by parents of children aged 4–18 years to assess child behavioral problems. The CBCL contains eight narrowband, less general syndromes: aggression, delinquency (externalizing), withdrawal, anxiety/depression and somatic complaints (internalizing), thought problems, task persistence, and social problems (neither clearly internalizing nor externalizing). Each item is scored on a 3-point scale, ranging from 0 = *not true* to 2 = *very true*. Two broadband clusters of internalizing and externalizing behaviors

are derived. Achenbach (1991) reported mean α coefficients of .89 and .93 for the internalizing and externalizing scales, respectively. Of particular interest to the present study were the internalizing and externalizing broadband factors.

DNA preparation and genotyping

Genomic DNA was prepared from buccal swabs (Epicentre Technologies, Madison, WI). Children were instructed by an investigator or parent to collect cheek cells by rolling a buccal brush firmly on the inside of the cheek, approximately 20 times on each side. The brushes were air dried for 10–20 min then sent to the laboratory at the National Institutes of Health for extraction within 3 days. DNA was prepared by absorption to a bead matrix and heat elution according to the manufacturer's instructions.

5-HTT. 5-HTTLPR was analyzed by polymerase chain reaction (PCR) amplification followed by agarose gel electrophoresis as described by Lesch et al. (1996). Allele frequencies were 59.0% for the *s* allele and 41.0% for the *l* allele; no extralong alleles were observed in this population. Based on previous results (Lesch et al., 1996), genotypes were dichotomized as short (*S*) for *s*/*s* and *s*/*l* and long (*L*) for *l*/*l*.

DRD4. The *DRD4* gene exon III polymorphism was assayed by PCR using the primers and reaction conditions described by Lichter et al. (1993) combined with a "hot start." The number of repeats was determined by electrophoresis through a 3.5% agarose gel and ethidium bromide staining. Allele frequencies were 6.2% for allele 2, 1.9% for allele 3, 68.3% for allele 4, 1.6% for allele 5, 0.3% for allele 6, 21.4% for allele 7, and 0.3% for allele 8. Based on previous results (Benjamin et al., 1996), genotypes were classified into two groups: *S* for *s*/*s* and *L* for *s*/*l* and *l*/*l*, where *S* indicates alleles with 2–5 repeats and *L* indicates alleles with 6–8 repeats. Indistinguishable results were obtained when genotypes were coded according to the presence or absence of the 7-repeat allele (Ebstein et al., 1996) or as the sum of allele lengths.

Results

Figure 1 presents the differences among the *5-HTT* (short, long) and *DRD4* (short, long) genotype groups on CBCL internalizing and externalizing behaviors at age 7.

CBCL internalizing behaviors

An analysis of variance (ANOVA) with *5-HTT* (short, long) and *DRD4* (short, long) as the between-subjects factor was performed on CBCL internalizing scores. The analysis revealed a significant *5-HTT* (short, long) × *DRD4* (short, long) interaction, $F\,(1, 104) = 6.10$, $p < .015$. As predicted, children in the *5-HTT* short/*DRD4* long ($n = 32$, $M = 8.48$, $SE = 1.18$) group exhibited significantly more internalizing behaviors at age 7 than children in the *5-HTT* short/*DRD4* short ($n = 55$, $M = 5.59$, $SE = 0.56$), $t\,(85) = 2.49$, $p = .015$, and in the *5-HTT* long/*DRD4* long ($n = 9$, $M = 3.67$, $SE = 1.42$), $t\,(39) = 2.04$, $p = .049$, groups, but not the *5-HTT* long/*DRD4* short ($n = 12$, $M = 7.08$, $SE = 1.55$), $t\,(42) < 1$, group. The *5-HTT* short/*DRD4* short and *5-HTT* long/*DRD4* short genotype groups were not statistically reliably different from one another on CBCL internalizing behaviors at age 7. The separate main effects for *5-HTT* and *DRD4* groups were also not significant.

CBCL externalizing behaviors

An ANOVA with the *5-HTT* (short, long) and *DRD4* (short, long) group as the between-subjects factor was performed on the CBCL externalizing scores. The analysis revealed a significant *5-HTT* (short, long) × *DRD4* (short, long) interaction, $F\,(1, 98) = 4.06$, $p < .047$. As predicted, children in the *5-HTT* short/*DRD4* long group ($n = 29$, $M = 10.30$, $SE = 1.18$) exhibited significantly more externalizing behaviors at age 7 compared with children in the *5-HTT* long/*DRD4* long ($n = 8$, $M = 4.88$, $SE = 1.41$), $t\,(35) = 2.29$, $p = .028$, group and tended to exhibit more externalizing behaviors than children in the *5-HTT* short/*DRD4* short ($n = 53$, $M = 7.84$, $SE = 0.90$) group. However, this difference was only a trend, $t\,(80) = 1.65$, $p = .10$, and did not differ from those in the

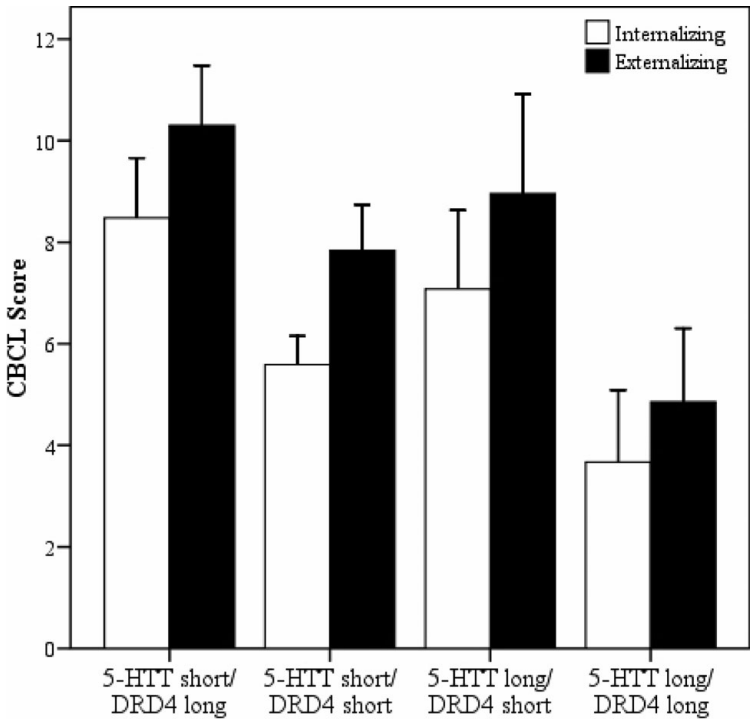

Figure 1. Mean (standard error bars) number of internalizing and externalizing behaviors, stratified for serotonin transporter (*5-HTT*) and dopamine receptor D4 (*DRD4*) genotypes in typically developing children at age 7. The *5-HTT* short/*DRD4* long genotype group is significantly different from the *5-HTT* long/*DRD4* long genotype group on internalizing and externalizing behaviors at age 7. The *5-HTT* short/*DRD4* short genotype group and *5-HTT* long/*DRD4* short genotype group were not statistically reliably different from one another on CBCL internalizing and externalizing behaviors at age 7.

5-HTT long/*DRD4* short ($n = 12$, $M = 8.96$, $SE = 1.96$), t (39) < 1, group. The *5-HTT* short/*DRD4* short and *5-HTT* long/*DRD4* short genotype groups were not statistically reliably different from one another on CBCL externalizing behaviors at age 7. The separate main effects for *5-HTT* and *DRD4* groups were also not significant.

Discussion

We found a significant interaction of the *5-HTT and DRD4* genes in relation to internalizing and externalizing behaviors in typically developing children at age 7. As predicted, children with one or two copies of the short allele of the *5-HTT* gene and the long allele of the *DRD4* gene exhibited significantly more internalizing behaviors at age 7 than children in the *5-HTT* short/*DRD4* short and in the *5-HTT* long/*DRD4* long groups and children in the *5-HTT* long/*DRD4* short group, although this difference was not statistically significant. We also found that, as predicted, children in the *5-HTT* short/*DRD4* long group exhibited significantly more externalizing behaviors at age 7 than children in the *5-HTT* long/*DRD4* long group, and they exhibited more externalizing behaviors than children in the *5-HTT* short/*DRD4* short and in the *5-HTT* long/*DRD4* short groups. However, these latter group differences were not statistically significant, although they were in the predicted direction. It is also important to point out that children with the *5-HTT* short/*DRD4* short and *5-HTT* long/*DRD4* short genotype groups were not statistically reliably different from one another on CBCL internalizing and externalizing behaviors (see Figure 1).

Disparate studies examining the *5-HTT* and *DRD4* genes have traditionally focused on associations of single genes with behavior. These studies have noted that individuals with one

or two copies of the short allele of the *5-HTT* versus those homozygous for the long allele are more likely to be depressed (Caspi et al., 2003), anxious (Lesch et al., 1996), or shy and behaviorally inhibited (Fox et al., 2005). As well, individuals with longer versus shorter allele repeats of the *DRD4* gene are more likely to be high in novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996; Noble et al., 1998; Ono et al., 1997; Strobel et al., 1999; Tomitaka et al., 1999), substance using behaviors (Gelernter et al., 1997) and aggression (Schmidt et al., 2002), and attention-related problems (Schmidt et al., 2001) and attention deficit and hyperactivity disorders (LaHoste et al., 1996; Swanson et al., 1998). Overall, the results of the present study are consistent with these earlier studies.

However, few studies have examined gene–gene interactions in relation to complex human traits in typical development, with the exception of the work by Ebstein and colleagues. Ebstein and his group have examined the interaction of *5-HTT* and *DRD4* genes in neonatal temperament (Ebstein et al., 1998) and infant attention (Auerbach et al., 2001). Neonates with the homozygous short *5-HTT* genotype (i.e., s/s), but lacking the longer allele form of the *DRD4* gene, scored lower on temperament measures of orientation compared with other neonates. Ebstein's group (Auerbach et al., 2001) also found that infants with the homozygous short allele of the *5-HTT* gene and the longer allelic repeats of the *DRD4* had the lowest scores of duration of looking during an information processing task. More recently, Kaufman et al. (2006) noted a significant gene–gene–environment interaction. Children with the Met allele of the *BDNF* and two copies of the short allele of the *5-HTT* gene exhibited more depression, but only if they had experienced child maltreatment. The results of the present study are based on sample sizes larger than those reported by Ebstein and colleagues, and are largely consistent with their findings and the findings by Kaufman's group. Although multiple genes may have been collected in these earlier studies, limited sample sizes often restrict the testing of gene-gene interactions (see Gauderman, 2002).

What role do the *5-HTT* and *DRD4* receptor genes play in children's behavioral problems? Serotonin is known to play a key role in avoidance-related behaviors. Serotonin has been implicated as a major neurotransmitter of anxiety and withdrawal because of its influences on mood and emotional states (see Westernberg et al., 1996, for a review). In vitro and in vivo expression studies have demonstrated that the *5-HTT* short genotype leads to less gene transcription and protein production than does the long allele (Greenberg et al., 1999; Heils et al., 1996; Lesch et al., 1996; Little et al., 1998). Children who are anxious, depressed, and shy withdraw from situations. It seems plausible then to argue that the short allele of the *5-HTT* may be a possible locus for internalizing-related behaviors in children.

In contrast, dopamine has been implicated as a major neurotransmitter involved in approach and reward-seeking behaviors (Cloninger, 1987). The shorter alleles code for a receptor that is apparently more efficient in binding dopamine compared with the larger alleles (see Plomin & Rutter, 1998, for a review). The *DRD4* gene appears to play some role in the cognitive and motivational aspects of behavioral regulation, as well as the inhibition of behavioral responses to stimulation. Children who are aggressive and engage in disruptive behaviors have problems with attending, staying on task, and actively seeking out stimulation. It is reasonable to argue then that the *DRD4* long genotype may be a possible locus for externalizing-related behaviors in children.

The present results have implications for understanding cumulative biological risk and protective factors in children's psychopathology. We found that children with one or two copies of the short allele of the *5-HTT* gene and the *DRD4* long genotype exhibited the highest amounts of internalizing and externalizing behaviors. These findings raise the possibility of a "double hit" model or cumulative biological risk hypothesis for some children with both of these genotypes. In addition, children who were homozygous for the long allele of the *5-HTT* gene and who had the *DRD4* long genotype exhibited the lowest amount of internalizing and externalizing behaviors. Given that the longer allele of the DRD4 by itself has been

linked to externalizing-related behaviors (LaHoste et al., 1996; Schmidt et al., 2001; Swanson et al., 1998), this finding raises the possibility that the presence of the long allele of the *5-HTT* gene may serve as a protective factor against behavior problems in some children with the *DRD4* long genotype.

The idea that genes and G × E serve as protective factors is not new (e.g., Cicchetti & Blender, 2004, 2006; Kaufman et al., 2006). Cicchetti and colleagues have suggested that, until recently, most studies examining the notion of resiliency have focused largely on psychosocial determinants of the phenomenon. They further argue the importance of considering genes and G × E for conferring resiliency and how the approaches that involve multiple levels of analysis (i.e., psychological, biological, and environment–contextual processes) are critical to fully understanding resiliency. This multilevel approach is evidenced in a recent study by Curtis and Cicchetti (2007), in which they found that a behavioral measure of both emotion regulation and left resting frontal EEG asymmetry contributed to the development of resiliency in maltreated children. In contrast, the only predictor of resilience in nonmaltreated children from similar social class backgrounds was the behavioral measure of emotion regulation.

The present findings have theoretical implications for understanding individual differences in temperament in normal development. The neurochemical substrates underlying approach–withdrawal motivational and behavioral responses are thought to be subserved by dopamine and serotonin, respectively (Gray, 1994). We have previously used an approach–withdrawal motivational heuristic to account for individual differences in temperament in children (Fox, 1991, 1994) and personality in adults (Schmidt, 1999; Schmidt & Fox, 1999). We have found that there are distinct behavioral and psychophysiological correlates associated with approach–withdrawal responses (see Fox, 1991, 1994; Schmidt, 1999; Schmidt & Fox, 1999, for reviews). Adults and children who are high on approach-related behaviors have been characterized as social and outgoing. These individuals exhibit greater relative left frontal EEG activity at rest. Adults and children who are high on withdrawal responses have been characterized as shy and anxious. These individuals display greater relative right frontal EEG activity at rest. Because approach–withdrawal motivational tendencies are conceptually and empirically orthogonal dimensions (Asendorpf & Meier, 1993; Cheek & Buss, 1981; Schmidt & Fox, 1999), each of which has distinct behavioral and psychophysiological correlates, it is possible to examine the interaction of the two dimensions in relation to individual differences in temperament. For example, we have termed individuals who are both high on social approach (i.e., social and outgoing) and high on social withdrawal (i.e., shy and anxious) tendencies as "socially conflicted." Socially conflicted individuals are known to exhibit a distinct pattern of greater relative right frontal EEG activity, high overall frontal EEG activity at rest (Schmidt, 1999), and more behavioral problems (e.g., substance use and abuse) in adolescence (Page, 1990) and as young adults (Santesso, Schmidt, & Fox, 2004) compared to individuals with other high and low combinations of social approach and social withdrawal.

We have argued that competing motivational tendencies in socially conflicted individuals, as evidenced in the endophenotypic (e.g., Segalowitz & Schmidt, in press) expression of distinct psychophysiological correlates and the phenotypic expression of behavioral responses, lead to behavioral problems (Santesso et al., 2004; Schmidt, 2003). Although the exact causal mechanism underlying and maintaining socially conflicted behavior and temperamental style remains unknown, the results of the present study suggest a combination of the *5-HTT* short and *DRD4* long genotypes as possible loci and one causal mechanism. Genes (e.g., the *5-HTT* short allele *and DRD4* long allele combination) may influence endophenotypes (e.g., resting right frontal brain activity asymmetry and high overall frontal activity), which in turn may influence behavior (e.g., social conflicted responses) (see Caspi & Moffitt, 2006, for a discussion of gene–endophenotype–behavior hypotheses).

The origins of children's behavioral problems are undoubtedly multiply determined. However, the last decade has witnessed a search

for the molecular genetics of complex traits in humans, including human psychopathology. Published work in this area has traditionally examined associations of single genes with behavior, often yielding mixed and inconsistent findings. More recently, researchers have begun to examine G × E to account for the complexities underlying human behavior. Such studies have been particularly important for informing theory and issues related to risk and protective factors. Here we extended this line of research by examining gene–gene interactions in relation to behavioral problems in typically developing children.

The present study appears to be the first documented evidence of a gene–gene interaction in relation to internalizing and externalizing behaviors in typically developing children. However, the results of the present study need to be interpreted with caution because they are based on a relatively small sample size and are in need of replication with a larger sample than reported herein. The typically developing children with the short *5-HTT* and long *DRD4* genotypes in the present study may be at risk for behavior problems, but it is important to note that their CBCL scores were not at clinical levels. It might be that particular environmental influences are needed for this vulnerability to manifest into clinical levels of behavioral problems. Given the multiple determinants of behavior problems in children, future studies should consider examining the interactions of multiple genetic and environmental influences (e.g., Kaufman et al., 2006; Mandelli et al., 2007) in typical and atypical human development.

References

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. Burlington, VT: University of Vermont, Department of Psychiatry.

Achenbach, T. M., & Edelbrock, C. S. (1981). Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. *Monographs of the Society for Research in Child Development*, *46*(1, Serial No. 188), 1–82.

Asendorpf, J. B., & Meier, G. H. (1993). Personality effects on children's speech in everyday life: Sociability-mediated exposure and shyness-mediated reactivity to social situations. *Journal of Personality and Social Psychology*, *64*, 1072–1083.

Auerbach, J. G., Benjamin, J., Faroy, M., Geller, V., & Ebstein, R. (2001). *DRD4* related to infant attention and information processing: A developmental link to ADHD? *Psychiatric Genetics*, *11*, 31–35.

Bakerman-Kranenburg, M. J., & van IJzendoorn, M. H. (2006). Gene–environment interaction of the dopamine D4 receptor (*DRD4*) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology*, *48*, 406–409.

Ball, D., Hill, L., Freeman, B., Eley, T. C., Strelau, J., Riemann, R., et al. (1997). The serotonin transporter gene and peer-related neuroticism. *NeuroReport*, *8*, 1301–1304.

Benjamin, J., Ebstein, R. P., & Belmaker, R. H. (Eds.). (2002). *Molecular genetics and the human personality*. Washington, DC: American Psychiatric Association Press.

Benjamin, J., Li, L., Patterson, C., Greenberg, B. D., Murphy, D. L., & Hamer, D. H. (1996). Population and familial association between D4 dopamine receptor gene and measures of novelty seeking. *Nature Genetics*, *12*, 81–84.

Botto, L. D., & Mastroiacovo, P. (1998). Exploring gene–gene interactions in the etiology of neural tube defects. *Clinical Genetics*, *53*, 456–459.

Calkins, S. D., Fox, N. A., & Marshall, T. R. (1996). Behavioral and physiological antecedents of inhibited and uninhibited behavior. *Child Development*, *67*, 523–540.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science*, *297*, 851–854.

Caspi, A., & Moffitt, T. E. (2006). Gene–environment interactions in psychiatry: Joining forces with neuroscience. *Nature Reviews Neuroscience*, *7*, 583–590.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the *5-HHT* gene. *Science*, *301*, 291–293.

Cheek, J. M., & Buss, A. H. (1981). Shyness and sociability. *Journal of Personality and Social Psychology*, *41*, 330–339.

Cicchetti, D., & Blender, J. A. (2004). A multiple-levels-analysis approach to the study of developmental processes in maltreated children. *Proceedings of the National Academy of Sciences of the USA*, *101*, 17325–17326.

Cicchetti, D., & Blender, J. A. (2006). A multiple-levels-analysis perspective on resilience: Implications for the developing brain, neural plasticity, and preventive interventions. *Annals of the New York Academy of Sciences*, *1094*, 248–258.

Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants. *Archives of General Psychiatry*, *44*, 573–588.

Cloninger, C. R., Adolfsson, R., & Svrakic, N. M. (1996). Mapping genes for human personality. *Nature Genetics*, *12*, 3–4.

Curtis, W. J., & Cicchetti, D. (2007). Emotion and resilience: A multilevel investigation of hemispheric electroencephalogram asymmetry and emotion regulation in maltreated and nonmaltreated children. *Development and Psychopathology*, *19*, 811–840.

Deary, I. J., Battersby, S., Whiteman, M. C., Connor, J. M., Fowkes, F. G., & Harmar, A. (1999). Neuroticism and polymorphisms in the serotonin transporter gene. *Psychological Medicine*, *29*, 735–739.

DeYoung, C. G., Peterson, J. B., Seguin, J. R., Mejia, J. M., Pihl, R. O., Beitchman, J. H., et al. (2006). The dopamine D4 receptor gene and moderation of the association between externalizing behavior and IQ. *Archives of General Psychiatry*, *63*, 1410–1416.

Ebstein, R. P., Levine, J., Geller, V., Auerbach, J., Gritsenko, I., & Belmaker, R. H. (1998). Dopamine D4 receptor and serotonin transporter promoter in the determination of neonatal temperament. *Molecular Psychiatry*, *3*, 238–246.

Ebstein, R. P., Nemanov, L., Klotz, I., Gritsenko, I., & Belmaker, R. H. (1997). Additional evidence for an association between the dopamine D4 receptor (D4DR) exon III repeat polymorphism and the human personality trait of novelty seeking. *Molecular Psychiatry*, *2*, 472–477.

Ebstein, R. P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., et al. (1996). Dopamine D4 receptor (*D4DR*) exon III polymorphism associated with the human personality trait of novelty seeking. *Nature Genetics*, *12*, 78–80.

Ebstein, R. P., Segman, R., Benjamin, J., Osher, Y., Nemanov, L., & Belmaker, R. H. (1997). *5-HT2C* (*HTR2C*) serotonin receptor gene polymorphism associated with the human personality trait of reward dependence: Interaction with dopamine D4 receptor (*D4DR*) and dopamine D3 receptor (*D3DR*) polymorphisms. *American Journal of Medical Genetics*, *74*, 65–72.

Eley, T. C., Sugden, K., Corsico, A., Gregory, A. M., Sham, P., McGuffin, P., et al. (2004). Gene–environment interaction analysis of serotonin system markers with adolescent depression. *Molecular Psychiatry*, *9*, 908–915.

Fox, N. A. (1991). If it's not left, it's right: Electroencephalogram asymmetry and the development of emotion. *American Psychologist*, *46*, 863–872.

Fox, N. A. (1994). Dynamic cerebral processes underlying emotion regulation. *Monographs of the Society for Research in Child Development*, *59*(2–3, Serial No. 240).

Fox, N. A., Calkins, S. D., & Bell, M. A. (1994). Neural plasticity and development in the first two years of life: Evidence from cognitive and socioemotional domains of research. *Development and Psychopathology*, *6*, 677–696.

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development*, *72*, 1–21.

Fox, N. A., Nichols, K. E., Henderson, H. A., Rubin, K. H., Schmidt, L. A., Hamer, D., et al. (2005). Evidence for a gene–environment interaction in predicting behavioral inhibition in middle childhood. *Psychological Science*, *16*, 921–926.

Fox, N. A., Rubin, K. H., Calkins, S. D., Marshall, T. R., Coplan, R. J., Porges, S. W., et al. (1995). Frontal activation asymmetry and social competence at four years of age. *Child Development*, *66*, 1770–1784.

Fox, N. A., Schmidt, L. A., Calkins, S. D., Rubin, K. H., & Coplan, R. J. (1996). The role of frontal activation in the regulation and dysregulation of social behavior during the preschool years. *Development and Psychopathology*, *8*, 89–102.

Gauderman, W. J. (2002). Sample size requirement for association studies of gene–gene interaction. *American Journal of Epidemiology*, *155*, 478–484.

Gelernter, J., Kranzler, H., Coccaro, E., Siever, L., New, A., & Mulgrew, C. L. (1997). D4 dopamine-receptor (*DRD4*) alleles and novelty seeking in substance-dependent, personality-disorder, and control subjects. *American Journal of Human Genetics*, *61*, 1144–1152.

Goldman, D., Malhotra, A., Urbanek, M., Guenther, D., Robin, R., Virkkunen, M., et al. (1996). The dopamine *DRD2* and *DRD4* receptors: Lack of association to alcoholism, substance abuse and novelty seeking in Finnish Caucasians and Southwestern American Indians. *Psychiatric Genetics Abstracts*, *6*, 162.

Gray, J. A. (1994). Three fundamental emotion systems. In P. Ekman & R. J. Davidson (Eds.), *The nature of emotion: Fundamental questions* (pp. 243–247). New York: Oxford University Press.

Greenberg, B. D., Tolliver, T. J., Huang, S. J., Li, Q., Bengel, D., & Murphy, D. L. (1999). Genetic variation in the serotonin transporter promoter region affects serotonin uptake in human blood platelets. *American Journal of Medical Genetics*, *88*, 83–87.

Hamer, D., & Copeland, P. (1998). *Living with our genes*. New York: Doubleday.

Heils, A., Teufel, A., Petri, S., Stöber, G., Riederer, P., Bengel, D., et al. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry*, *66*, 2621–2624.

Howard, T. D., Koppelman, G. H., Xu, J., Zheng, S. L., Postma, D. S., Meyers, D. A., et al. (2002). Gene–gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. *American Journal of Human Genetics*, *70*, 230–236.

Hunter, D. J. (2005). Gene–environment interactions in human diseases. *Nature Reviews Genetics*, *6*, 287–298.

Jonsson, E. G., Nothen, M. M., Gustavsson, J. P., Neidt, H., Brene, S., Tylec, A., et al. (1997). Lack of evidence for allelic association between personality traits and the dopamine D4 receptor gene polymorphisms. *American Journal of Psychiatry*, *154*, 697–699.

Kaufman, J., Yang, B. Z., Douglas-Palumberi, H., Grasso, D., Lipschitz, D., Houshyar, S., et al. (2006). Brain-derived neurotrophic factor–*5-HTTLPR* gene interactions and environmental modifiers of depression in children. *Biological Psychiatry*, *59*, 673–680.

Kaufman, J., Yang, B. Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J. H., et al. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences of the USA*, *1010*, 17316–17321.

Kendler, K. S., Kuhn, J. W., Vittum, J., Prescott, C. A., & Riley, B. (2005). The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: A replication. *Archives of General Psychiatry*, *62*, 529–535.

Kuhn, K. U., Meyer, K., Nothen, M. M., Gansicke, M., Papassotiropoulos, A., & Maier, W. (1999). Allelic variants of dopamine receptor D4 (*DRD4*) and serotonin receptor *5HT2C* (*HTR2C*) and temperament: Replication tests. *American Journal of Medical Genetics*, *88*, 168–172.

Kumakiri, C., Kodama, K., Shimizu, E., Yamanouchi, N., Okada, S., Noda, S., et al. (1999). Study of the association between the serotonin transporter gene regulatory region polymorphism and personality traits in a Japanese population. *Neuroscience Letter*, *263*, 205–207.

LaHoste, G. J., Swanson, J. M., Wigal, S. B., Glabe, C., Wigal, T., King, N., et al. (1996). Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. *Molecular Psychiatry*, *1*, 121–124.

Lappalainen, J., Zhang, L., Dean, M., Oz, M., Ozaki, N., Yu, D. H., et al. (1995). Identification, expression, and pharmacology of a cys(23)–ser(23) substitution in the human *5-HT2C* receptor gene (*HTR2C*). *Genomics*, *27*, 274–279.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, *274*, 1527–1531.

Lesch, K. P., Greenberg, B. D., Higley, J. D., Bennett, A., & Murphy, D. L. (2002). Serotonin transporter, personality, and behavior: Toward dissection of gene–gene and gene–environment interaction. In J. Benjamin, R. P. Ebstein, & R. H. Belmaker (Eds.), *Molecular genetics and the human personality* (pp. 109–135). Washington, DC: American Psychiatric Association Press.

Lichter, J. B., Barr, C. L., Kennedy, J. L., Van Tol, H. H., Kidd, K. K., & Livak, K. J. (1993). A hypervariable segment in the human dopamine receptor D4 (*DRD4*) gene. *Human Molecular Genetics*, *2*, 767–773.

Little, K. Y., McLaughlin, D. P., Zhang, L., Livermore, C. S., Dalack, G. W., McFinton, P. R., et al. (1998). Cocaine, ethanol, and genotype effects on human midbrain serotonin transporter binding sites and mRNA levels. *American Journal of Psychiatry*, *155*, 207–213.

Malhotra, A. K., Virkkunen, M., Rooney, W., Eggert, M., Linnoilia, M., & Goldman, D. (1996). The association between the dopamine D4 receptor (*D4DR*) 16 amino acid repeat polymorphism and novelty seeking. *Molecular Psychiatry*, *1*, 388–391.

Mandelli, L., Serretti, A., Marion, E., Pirovano, A., Calati, R., & Colombo, C. (2007). Interaction between serotonin transporter gene, catechol-*O*-methyltransferase gene and stressful life events in mood disorders. *International Journal of Neuropsychopharmacology*, *10*, 437–447.

Moore, J. H., & Williams, S. M. (2002). New strategies for identifying gene–gene interactions in hypertension. *Annals of Medicine*, *34*, 88–95.

Negoro, K., McGovern, D. P. B., Kinouchi, Y., Takahashi, S., Lench, N. J., Shimosegawa, T., et al. (2003). Analysis of the IBD5 locus and potential gene–gene interactions in Crohn's disease. *Gut*, *52*, 541–546.

Noble, E. P., Ozkaragoz, T. Z., Ritchie, T. L., Zhang, X., Belin, T. R., & Sparkes, R. S. (1998). D2 and D4 dopamine receptor polymorphisms and personality. *American Journal of Medical Genetics*, *81*, 257–267.

Ono, Y., Manki, H., Yoshimura, K., Muramatsu, T., Mizushima, H., Higuchi, S., et al. (1997). Association between dopamine D4 receptor (*D4DR*) exon III polymorphism and novelty seeking in Japanese subjects. *American Journal of Medical Genetics*, *74*, 501–503.

Page, R. M. (1990). Shyness and sociability: A dangerous combination for illicit substance abuse in adolescent males? *Adolescence*, *25*, 803–806.

Plomin, R., & Rutter, M. (1998). Child development, molecular genetics, and what to do with genes once they are found. *Child Development*, *69*, 1223–1242.

Pogue-Geile, M., Ferrell, R., Deka, R., Debski, T., & Manuck, S. (1998). Human novelty-seeking personality traits and dopamine D4 receptor polymorphisms: A twin and genetic association study. *American Journal of Medical Genetics*, *81*, 44–48.

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene–environment interplay and psychopathology: Multiple varieties but real effects. *Journal of Child Psychology and Psychiatry*, *47*, 226–261.

Sander, T., Harms, H., Dufeu, P., Kuhn, S., Rommelspacher, H., & Schmidt, L. G. (1997). Dopamine D4 receptor exon III alleles and variation of novelty seeking in alcoholics. *American Journal of Medical Genetics*, *74*, 483–487.

Santesso, D. L., Schmidt, L. A., & Fox, N. A. (2004). Are shyness *and* sociability still a dangerous combination for substance use? Evidence from a U.S. and Canadian sample. *Personality and Individual Differences*, *37*, 5–17.

Schmidt, L. A. (1999). Frontal brain electrical activity in shyness *and* sociability. *Psychological Science*, *10*, 316–320.

Schmidt, L. A. (2003). Shyness *and* sociability: A dangerous combination for preschoolers. *International Society for the Study of Behavioural Development Newsletter*, *27*, 6–8.

Schmidt, L. A., & Fox, N. A. (1999). Conceptual, biological, and behavioral distinctions among different categories of shy children. In L. A. Schmidt & J. Schulkin (Eds.), *Extreme fear, shyness, and social phobia: Origins, biological mechanisms, and clinical outcomes* (pp. 47–66). New York: Oxford University Press.

Schmidt, L. A., & Fox, N. A. (2002). Molecular genetics of temperamental differences in children. In J. Benjamin, R. P. Ebstein, & R. H. Belmaker (Eds.), *Molecular genetics and the human personality* (pp. 247–257). Washington, DC: American Psychiatric Association Press.

Schmidt, L. A., Fox, N. A., Perez-Edgar, K., Hu, S., & Hamer, D. H. (2001). Association of *DRD4* with attention problems in normal childhood development. *Psychiatric Genetics*, *11*, 25–29.

Schmidt, L. A., Fox, N. A., Rubin, K. H., Hu, S., & Hamer, D. H. (2002). Molecular genetics of shyness and aggression in preschoolers. *Personality and Individual Differences*, *33*, 227–238.

Segalowitz, S. J., & Schmidt, L. A. (in press). Capturing the dynamic endophenotype: A developmental psychophysiological manifesto. In L. A. Schmidt & S. J. Segalowitz (Eds.), *Developmental psychophysiology: Theory, systems, and methods*. Cambridge: Cambridge University Press.

Serretti, A., Mandelli, L., Lorenzi, C., Landoni, S., Calati, R., Insacco, C., et al. (2006). Temperament and character in mood disorders: Influence of DRD4, SERTPR, TPH and MAO-A polymorphisms. *Neuropsychobiology*, *53*, 9–16.

Shiozawa, M., Provoost, A. P., Van Dokkum, R. P. E., Majewski, R. R., & Jacob, H. J. (2000). Evidence of gene–gene interactions in the genetic susceptibility to renal impairment after unilateral nephrectomy. *American Society of Nephrology*, *11*, 2068–2078.

Strobel, A., Wehr, A., Michel, A., & Brocke, B. (1999). Association between the dopamine D4 receptor (*DRD4*) exon III polymorphism and measures of novelty seeking in a German population. *Molecular Psychiatry*, *4*, 378–384.

Sullivan, P. F., Fifield, W. J., Kennedy, M. A., Mulder, R. T. T., Sellman, J. D., & Joyce, P. R. (1998). No association between novelty seeking and the type 4 dopamine receptor gene (*DRD4*) in two New Zealand samples. *American Journal of Psychiatry*, *155*, 98–101.

Swanson, J. M., Sunohara, G. A., Kennedy, J. L., Regino, R., Fineberg, E., Wigal, T., et al. (1998). Association of the dopamine receptor D4 (*DRD4*) gene with a refined phenotype of attention deficit hyperactivity disorder (ADHD): A family-based approach. *Molecular Psychiatry*, *3*, 38–41.

Tomitaka, M., Tomitaka, S., Otuka, Y., Kim, K., Matuki, H., Sakamoto, K., et al. (1999). Association between novelty seeking and dopamine receptor D4 (*DRD4*) exon III polymorphism in Japanese subjects. *American Journal of Medical Genetics*, *88*, 469–471.

Van Boven, H. H., Vandenbroucke, J. P., Briet, E., & Rosendaal, F. R. (1999). Gene–gene and gene–environment interactions determine risk of thrombosis in families with inherited antithrombin deficiency. *Blood*, *94*, 2590–2594.

Vandenbergh, D. J., Zonderman, A. B., Wang, J., Uhl, G. R. & Costa, P. T., Jr. (1997). No association between novelty seeking and dopamine D4 receptor (D4DR) exon III seven repeat alleles in Baltimore Longitudinal Study of Aging participants. *Molecular Psychiatry*, *2*, 417–419.

Westernberg, H. G., Murphy, D. L., & Den Boer, J. A. (Eds.). (1996). *Advances in the neurobiology of anxiety disorders*. New York: Wiley.