DRD4 and DRD2 genes, parenting, and adolescent delinquency: Longitudinal evidence for a gene by environment interaction

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DRD4 and *DRD2* Genes, Parenting, and Adolescent Delinquency: Longitudinal Evidence for a Gene by Environment Interaction

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Gene by environment (G × E) research has been increasingly appreciated as it relates to the development of psychopathology. In particular, interactions between dopaminergic genotypes and maladaptive parenting have been prominently in the spotlight. In this study, we investigated whether high parental psychological control and low support would be differentially related to the development of delinquency in adolescents based on their genetic background (i.e., *DRD4* and *DRD2* genotypes). Data were derived from a 5-wave longitudinal survey among adolescents ($N = 308$; $M_{age} = 13.4$ at Time 1). After accounting for possible passive genetic effects (i.e., parents' genotype, Parents' Genotype × Adolescents' Genotype, and Parents' Genotype × Parenting, cf. Keller, 2014), latent growth modeling revealed a significant interaction of *DRD2* × Parental Support, indicating that adolescents with the *DRD2* A2A2 genotype were more vulnerable for low parental support, developing more delinquent behavior as a consequence. No significant interactions emerged for *DRD4* with parental support and psychological control, nor for *DRD2* with parental psychological control. The observed effect size of the identified *DRD2* × parental support interaction was modest, emphasizing that replication is essential to confirm the present evidence.

General Scientific Summary
A negative parenting environment is a key factor predicting adolescent delinquent behavior. This study supports the notion that the association between a negative parenting environment and delinquent behavior is stronger for adolescents that carry a specific risk variant of the *DRD2* gene.

Keywords: gene by environment interactions, delinquency, *DRD4*, *DRD2*, parenting

Juvenile delinquency has high economic and social costs and impacts directly on social welfare, criminal justice, and health care systems (Scott, Knapp, Henderson, & Maughan, 2001). In addition, delinquency in adolescence is a known precursor of the development of serious violent crime and antisocial behavior in adulthood. Given these adverse consequences, it is pivotal to identify risk mechanisms underlying the development of delin-

quency in early adolescence. One of the strongest predictors of delinquency is harmful parenting behavior, such as high psychological control (Bean, Barber, & Crane, 2006) and low support (Barnes, Farrell, & Cairns, 1986). At the same time, specific genetic polymorphisms—located downstream of the *DRD2* gene and in the *DRD4* gene—have been associated with the development of aggression, conduct disorder, and other externalizing

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problem behaviors (Marino et al., 2004). However, we know relatively little about specific interactions between these biological and environmental risks. Also, we know relatively little about possible effects of parents' genotypes that might provide an alternative account of observed gene by environment interactions (G × E); that is genetic relatedness between parent and their offspring (i.e., heritability of "risky genes") may account for observed interactions between maladaptive parenting and adolescents' genotype. In a 5-wave longitudinal study we (1) investigated G × E interactions involving variations of the *DRD4* and *DRD2* dopamine receptor genes with parental psychological control and support in the development of delinquency and (2) accounted for possible "passive genetic effects" (i.e., parents' genotype, Parents' Genotype × Adolescents' Genotype, and Parents' Genotype × Parenting), conform recent specifications by Keller (2014), that might influence the interactions.

Several behavioral genetic studies have demonstrated that monozygotic twins have a significantly higher concordance rate for delinquent behavior than dizygotic twins (e.g., Joseph, 2001), indicating that heritability plays a role in the development of delinquent behavior—but see Burt and Simons (2014) for a critique of methods and conclusions. In the search for genes that may be associated with the development of delinquency, previous studies have identified several dopamine related candidate genes, among which the *DRD4* and *DRD2* dopamine receptor genes have received most attention (Elliot, 2000). Dopamine is an excitatory neurotransmitter related to motivation for obtaining rewards (Kelley, 2004), but also to the regulation of the anticipation of rewards (Blum et al., 1996). Studies suggest that delinquent behavior may be influenced by dopaminergic pathways in the brain (e.g., the ventral tegmental area, nucleus accumbens, and prefrontal cortex; Blum et al., 1996). Activation of these dopaminergic pathways may result in an intense feeling of pleasure or well-being and increased physiological arousal (Schultz, 2002). However, altered dopaminergic functioning in these pathways can affect motivation, reward processing, and consequently, the decision-making process may be aimed at increasing feelings of pleasure and physiological arousal (Matthys, Vanderschuren, & Schutter, 2013). Specifically, sensation seeking has been related to an altered functioning in dopaminergic pathways in the brain (Derringer et al., 2010; Harden, Quinn, & Tucker-Drob, 2012). Adolescents with a genetically induced disposition to seek exciting experiences, due to a blunted dopamine response to reward, may be at increased risk to develop delinquent behavior. The *DRD4* and the *DRD2* genes are known to be involved in the regulation of these dopaminergic pathways and have been putative targets of studies on the etiology of externalizing problem behaviors, but how they are involved exactly is largely unknown (e.g., Elliot, 2000; Munafò, Yalcin, Willis-Owen, & Flint, 2008).

The *DRD4* gene encodes the D4 subtype of the dopamine receptor. Main attention has been given to the 48-base-pair variable number of tandem repeats (VNTR) polymorphism in exon 3 of this gene, consisting of 2 to 11 repeats. Specifically, the 7-repeat allele is of interest, not only because of its association with dopaminergic functioning, but also because of its association with alcoholism (Laucht, Becker, Blomeyer, & Schmidt, 2007), attention-deficit/hyperactivity disorder (Li, Sham, Owen, & He, 2006), behavioral disinhibition (Congdon, Lesch, & Canli, 2008), novelty

seeking (Ebstein et al., 1996), and impulsivity (Eisenberg et al., 2007).

The *DRD2* gene encodes the D2 subtype of the dopamine receptor which has a different function and structure than the *DRD4* gene (e.g., receptor coding region contains six vs. three introns). But the specific structure-activity requirements necessary to be selectively active at each receptor subtype are still unknown and need more investigation (see Missale, Nash, Robinson, Jaber, & Caron, 1998). Main attention has been given to a single-nucleotide polymorphism (SNP) with two variants at the TaqIA locus. This TaqIA locus is located 10 kb downstream from the *DRD2* gene (Dubertret et al., 2004) and has been thought to be part of an adjacent protein kinase gene (i.e., ankyrin repeat and kinase domain containing 1; *ANKK*; Neville, Johnstone, & Walton, 2004). Specifically, the TaqI A1 allele is of interest, not only because of its association with dopaminergic functioning (e.g., Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991; Pohjalainen et al., 1998), fewer D2 dopamine receptors (Berman & Noble, 1995), and decreased D2 binding (Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997), but also because of its association with sensation seeking (Ratsma, Van der Stelt, Schoffelmeer, Westerveld, & Gunning, 2001), impulsive behavior (Eisenberg et al., 2007), and externalizing problem behaviors (Beaver et al., 2007). However, some other studies identified the TaqI A2 allele as marker for aggression (Vasilyev, 2011), and inattentive and impulsive behavior (Rowe et al., 1999; Waldman, 2007). Also, a study based on the Add Health data found that *DRD2* heterozygotes were most at risk for serious delinquent behavior in comparison with peers who carried either the A2/A2 or the A1/A1 genotype, respectively (Guo, Roettger, & Shih, 2007). These discrepant results are not uncommon in molecular genetic studies (see Lin, Vance, Pericak-Vance, & Martin, 2007; Marsman, Oldehinkel, Ormel, & Buitelaar, 2013; Waldman, 2007), and demonstrate that further research is needed to better understand the relation between the *DRD2* TaqI variant and delinquency. This is especially needed given the fact that the *ANKK1* and *DRD2* genes are thought to be coactors in a complex system of functionally related genes affecting the functioning of dopaminergic neurotransmitter pathways (Ponce et al., 2009).

Genetic vulnerabilities may be expressed particularly when adolescents are exposed to maladaptive environmental factors, such as high parental psychological control and low support (Rutter, 2012). Decades of research informed by the diathesis-stress model of person-environment interactions showed that some individuals are more vulnerable to aversive effects than others because of individual characteristics such as temperamental, physiological, or genetic factors (Zuckerman, 1999). Notably, Caspi and colleagues (2002) found that maltreated children with the low-activity allele of the MAOA, more often developed conduct disorders than children with the high-activity allele of this gene. Ever since then, the notion that individuals may have an innate risk characteristic or diathesis that is expressed under aversive condition has burgeoned new evidence of G × E (e.g., Martel et al., 2011; Sheese, Voelker, Rothbart, & Posner, 2007). More recently, scholars have acknowledged that "vulnerable" individuals might even do better than those without such a vulnerability under supportive conditions (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Belsky & Pluess, 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011).

Indeed, an extant body of research demonstrated interactions of the *DRD4* gene and *DRD2* TaqI variant with maladaptive parenting in the development of antisocial behavior (e.g., Beaver, Gibson, DeLisi, Vaughn, & Wright, 2012; Dmitrieva, Chen, Greenberger, Ogunseitan, & Ding, 2011; Martel et al., 2011; Sheese, Voelker, Rothbart, & Posner, 2007; Waldman, 2007; Zohsel et al., 2014). To illustrate, Bakermans-Kranenburg and Van IJzendoorn (2006) found that exposure to low maternal sensitivity exacerbated child externalizing behavior but only in carriers of the *DRD4* 7-repeat allele. Relatedly, they also found that exposure to high maternal sensitivity decreased externalizing behavior but again only in children carrying the 7-repeat allele. Focusing on children's dysfunction, Sheese and colleagues (2007) demonstrated that lower quality parenting was related to higher levels of sensation seeking, but only for children with the *DRD4* 7-repeat allele. Also, the work of DeLisi, Beaver, Vaughn, and Wright (2009) revealed that having a criminal parent—placing children in a maladaptive parenting environment conducive to offending—was related to higher levels of serious and violent delinquency in African American children, but only for those carrying the A1 allele.

Studies also found that high psychological control (i.e., parents' manipulative strategies in order to control adolescents' behavior) and low support (i.e., lack of encouragement in the face of failures) are aversive conditions consistently related to the development of adolescent delinquent behavior (e.g., Hoeve et al., 2009; Steinberg, Lamborn, Darling, Mounts, & Dornbusch, 1994); and that specifically adolescents carrying a specific *DRD4* or *DRD2* TaqI variant—linked to blunted dopaminergic functioning, suboptimal physiological arousal, and less intense feelings of pleasure—may experience such maladaptive parenting as highly discomforting (Schultz, 2002). From a diathesis-stress perspective it might be that specifically these adolescents are more vulnerable to adverse effects of maladaptive parenting experiences than others due to their "risky genes" and altered dopamine availability in the brain (Belsky & Pluess, 2013). As a consequence, these adolescents might be at increased risk of getting stuck in coercive cycles with their parents, which are strongly predictive of deviant peer associations that, in turn, may lead to a higher likelihood that adolescents will develop delinquent behavior (Patterson & Yoerger, 2002).

Although many G × E findings have been reported over the last decade, there are concerns about whether these findings really constitute evidence for G × E. Specifically, in longitudinal designs alternative explanations for G × E findings cannot completely be accounted for. It may very well be that parents with a specific genetic variant of the *DRD4* or *DRD2* TaqI have an increased probability to use maladaptive parenting strategies because they have a genetic disposition toward anger or impulsivity, and in such a way transmit a genetic risk for externalizing behavior on to their children (i.e., passive *r*GE). Thus, parents' genotype might affect the relation between parenting and adolescents' behavior and these effects might genetically mediate the G × E between risk exposure (i.e., maladaptive parenting) and problem behavior (i.e., adolescents' delinquency). To our knowledge, the existing (longitudinal) research has not accounted for such possible effects of parents' genotypes. We made a first attempt to do so by adopting the Keller (2014) approach. Keller argued that to properly control for effects that might cause spurious observed interactions, one should not only test the main effects of such a covariate but also include interactions of Covariate × Gene and Covariate × Environmental Effects. We used this approach as a way of expanding the search for passive *r*GE effects in observed G × E by accounting for possible passive genetic effects. More specifically, we accounted for main effects of parents' genotype and for what we call *passive G × E*: Parents' Genotype × Parenting and Parents' Genotype × Adolescents' Genotype. What makes this approach distinct relative to the traditional approach is that here we test whether perceived maladaptive parenting could be part of a different, more pathogenic, constellation of parenting behaviors related to parents' genotype. This relation could give rise to passive G × E effects in which parents' genotype is a stronger moderator of parenting effects than is adolescents' genotype (i.e., Passive Parents' Genotype × Environment) or in which parents' genotype might moderate the effect adolescents' genotype may have on delinquent behavior (i.e., Passive Parents' Genotype × Adolescents' Genotype).

The aim of the current study was to examine G × E interactions of the *DRD4* and *DRD2* TaqI variants with two maladaptive parenting styles (high psychological control and low support) in predicting the development of adolescent delinquency. We expected that for *DRD4* 7-repeat carriers high perceived psychological control and low support would be more strongly related to the presence and development of delinquent behavior, than for those without such an allele. Because of inconsistent effects in the *DRD2* literature we explored whether either the *DRD2* TaqI A1 or A2 variant was associated with higher risk for the presence and development of delinquent behavior in the light of high perceived psychological control and low support. In addition, we examined G × E more thoroughly by accounting for possible passive genetic effects (i.e., parents' genotype, Parents' Genotype × Adolescents' Genotype, and Parents' Genotype × Parenting) that might provide an alternative account of observed moderating effects of adolescents' genotype.

Method

Participants and Procedure

Data for the present study were derived from the 5-wave longitudinal Dutch survey study Family and Health, which investigates family processes in relation to various health behaviors in adolescence (e.g., Harakeh, Scholte, De Vries, & Engels, 2005). Addresses of families with at least two adolescents, aged 13 to 16 years, were derived from registers of 22 municipalities. A letter was sent to all these families inviting them to participate in the longitudinal study: 885 families responded that they were willing to participate and gave their informed consent. These families were telephoned to make sure they fulfilled the entry criteria: parents were married or living together, all family members were biologically related to each other, and participating siblings were neither twins nor mentally or physically disabled. Of the 765 families that fulfilled these criteria, 428 families were selected to ensure an equal distribution of adolescent educational level and an equal number of all the possible sibling dyads (i.e., boy–boy, girl–boy, boy–girl, girl–girl). Chi-square statistics showed no significant difference between included (*N* = 428) and excluded (*N* = 337)

families with regard to educational level for either father or mother ($p > .05$).

The present study used data of the youngest adolescent in each family because patterns of delinquency underlie an age-crime curve, which tends to peak between early to mid-adolescence. Of the 428 included families, 311 families agreed to be genotyped; three adolescents could not be genotyped. The final sample consisted of 308 families who provided us with full information across all five waves. Attrition analyses were performed to investigate whether families who gave their consent for genotyping and took part at all waves (participants: $N = 308$) differed from those who did not (dropouts: $N = 120$). T tests showed that participants and dropouts did not significantly differ in terms of delinquent behavior, psychological control, support, and age ($p > .05$). Also, chi-square statistics showed no significant difference with regard to educational level and sex.

Data collection of Wave 1 took place in the winter of 2002 to 2003, with Waves 2 through 5 taking place after 1, 2, 3, and 4 years, respectively. A trained interviewer visited participating families at their homes. In the presence of the interviewer, all family members individually completed extensive questionnaires, which took approximately two hours. Family members were not allowed to discuss questions with each other. When all family members had completed the questionnaires, the family received €30 ($33.00) at each wave. At the Wave 4, DNA samples were collected by means of saliva.

At Time 1 (T_1) the mean age of mothers and fathers was 43.9 ($SD = 3.59$) and 46.2 ($SD = 3.97$), respectively. Parents were relatively highly educated. Of the mothers, 38.9% followed higher education (i.e., university of applied science—also known as higher vocational education—and university of science), 24.4% intermediated education (i.e., intermediate vocational education within vocational schools that prepares people to a specific trade), and 36.7% lower education (i.e., elementary school 2.6%; high school 34.1%); of the fathers, 51.3%, 22.8%, and 25.9% (i.e., elementary school 1.7%; high school 24.2%), respectively. The mean age (T_1) of participating adolescents was 13.4 ($SD = .51$) of whom 47% were boys. The range of age for the younger siblings at the successive waves was 12 to 14 years (T_1), 13 to 15 years (T_2), 14 to 16 years (T_3), 15 to 17 years (T_4), and 16 to 18 years (T_5). A small group of adolescents was not born in The Netherlands (<4%). Roughly one third (33.3%) attended lower education (i.e., vocational or technical secondary education), one third (36.5%) attended intermediate general education, and one third (30.2%) attended the highest education level in secondary school (i.e., pre-university education). There were no drop outs from high school. Explicit approval for the data collection was obtained from Central Committee on Research involving Human Subjects in The Netherlands.

Measures

Delinquent behavior. Delinquency was measured with a Dutch questionnaire that specifies frequencies of participation in criminal acts by adolescents (Houtzager & Baerveldt, 1999). This measurement was chosen because it is widely used in The Netherlands and because it includes most frequent delinquent behaviors within this age group (Nijhof, Scholte, Overbeek, & Engels, 2010). Specifically, adolescents were asked whether they engaged in 13

rule-breaking activities in the past 12 months (e.g., "Have you ever set fire to a building?", "Have you ever participated in a serious physical fight?", "Have you ever stolen a moped or a scooter?", "Have you ever seriously beaten someone with an object or injured someone?") at each wave. These 13 items were scored on a four-point Likert scale (l = *never*, 2 = *once*, 3 = *two or three times*, and 4 = *four or more times*). The distribution of delinquency was relatively low in absolute terms and highly skewed. Therefore, in line with prior research (e.g., Caspi & Moffitt, 1991; Overbeek, Vollebergh, Meeus, Engels, & Luijpers, 2001; Piatigorsky & Hinshaw, 2004), each item was dichotomously coded as 0 (*never happened*) and 1 (*happened at least once*). The dichotomized items were then summed to create a scale describing the number of delinquent acts perpetrated at each time point. Cronbach's alphas were 65, .83, .88, .85, and .74, respectively.

Parenting. Parenting was rated by adolescents for parents separately at T_1. The support scale of parenting was assessed with a subscale of the Relational Support Inventory (Scholte, Van Lieshout, & Van Aken, 2001). The 12-item questionnaire (e.g., "My mother shows me that she loves me" and "My mother supports me in the things I do") was rated on a response scale, ranging from 1 (*very untrue*) to 5 (*very true*). A Dutch translation (Beyers & Goossens, 1999) of the Steinberg Parenting Instrument (Steinberg et al., 1994) was used to assess psychological control. Psychological control was measured with an eight-item questionnaire (e.g., "My mother makes me feel guilty when I fail at school, "My mother behaves in a cold and unfriendly manner if I do not do what she wants") and rated on a response scale ranging from 1 (*completely untrue*) to 5 (*completely true*). Research on psychometric properties provide evidence for external validity, internal consistency, and test–retest reliability (e.g., Glasgow, Dornbusch, Troyer, Steinberg, & Ritter, 1997; Gray & Steinberg, 1999; Lamborn, Mounts, Steinberg, & Dornbusch, 1991). The Cronbach's alpha in the present study was satisfactory for both parenting scales: .81 for support and .87 for psychological control.

***DRD4* genotyping.** The 48-base-pair direct repeat polymorphism (VNTR) in *DRD4* was genotyped by amplifying 10 ng of genomic DNA in a 10-μl volume with the following components: 0.05 μmol/L of fluorescently labeled forward primer VIC-5′-GCGACTACGTGGT CTACTCG-3′ (Applied Biosystems, Nieuwerkerk aan de IJssel, The Netherlands), reverse primer 5′-AGGACCCTCATGGCCTTG-3′, 0.4 mM of deoxynucleoside triphosphates (dNTPs), and 0.5 U of La Taq (Takara, Lonza Verviers S.p.r.l., Verviers, Belgium). These were in a GC I buffer (Takara, Lonza Verviers S.p.r.l.) with 1 M betaine. The cycling conditions for amplification involved 1 min at 94°C, 35 cycles of 30 s at 94°C, 30 s at 58°C, and 1 min at 72°C, with an additional 5 min at 72°C. The length of the alleles was determined by direct analysis on an automated capillary sequencer (ABI3730, Applied Biosystems, Nieuwerkerk aan de IJssel, The Netherlands). Hardy-Weinberg equilibrium (HWE) proportions were estimated, and no deviations from these proportions were found in adolescents, fathers, or mothers ($p = .12–.90$). The *DRD4* genotype was dummy-coded into 0 (i.e., no 7-repeat allele) and 1 (i.e., at least one 7-allele). We followed the same procedure to genotype the *DRD4* gene of both mothers and fathers.

***DRD2* genotyping.** The TaqI A C>T allele (rs1800497) was genotyped using Taqman analysis (assay ID: Taqman assay: C_7486676_10; reporter 1: VIC-A-allele, reverse assay; Applied Biosystems, Nieuwerkerk aan de IJssel, The Netherlands). Geno-

typing was carried out in a volume of 10 ll containing 10 ng of genomic DNA, 5 ll of Taqman Mastermix (2; Applied Biosytems),0.125 ll of the Taqman assay, and 3.875 ll of H2O. Genotyping was performed on a 7500 Fast Real-Time PCR System and genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems). To investigate the random genotyping error rate, the lab included five duplicate DNA samples per 96-well plate, which were 100% consistent. In addition, four blanks were included in each plate, which were required to be negative. By running PEDCHECK (O'Connell & Weeks, 1998) for single-point Mendelian inconsistencies on the markers, we identified one family with potential pedigree errors. This family was removed from the analysis. HWE proportions were estimated from parental genotype information using the Markov chain Monte Carlo approximation of the exact test implemented in the GENEPOP package V3.3 (Raymond & Rousset, 1995). No deviations from HWE were detected for either adolescents, fathers, and mother ($p = .41–.90$). The *DRD2* genotype was dummy-coded into 0 (i.e., A2A2) and 1 (i.e., A1A2 and A1A1). We followed the same procedure to genotype the *DRD2* gene of both mothers and fathers.

Analytic Strategy

Latent growth curve modeling (LGCM) was used in Mplus (Muthén & Muthén, 1998). As individual growth is estimated for each adolescent separately, LGCM is an excellent way to take individual variation in the development of delinquent behavior into account and to investigate whether certain predictors are related with differential developmental patterns. As delinquency was not normally distributed, the parameters in the models were estimated by applying the maximum likelihood estimator with robust standard errors that corrects for a non-normal distribution of the dependent variable.

First, we specified a basic developmental model estimating an intercept (i.e., initial level), linear slope (i.e., mean change across one year time intervals), and quadratic slope (i.e., mean change of the slope parameter across time intervals) of delinquent behavior. Building on this basic developmental model, we entered variables that permitted a deeper understanding of the change processes of the G × E of interest. In total, we tested the following four LGCM models: (a) *DRD4* × Psychological Control, (b) *DRD4* × Support, (c) *DRD2* × Psychological Control, and (d) *DRD2* × Support. In the simple models, we included adolescents' genes, parenting, and the interaction between adolescent' genes and parenting in the analyses. In the advanced models, we additionally included single effects of parents' genes and the passive G × E between parents' genes and parenting and between parents' genes and adolescents' genes as variables in the analyses. These passive genetic effects were entered in either the *DRD4* interaction or *DRD2* interaction model (see Table 2 and 3). To avoid multicollinearity, variables were centered before computing the interaction terms. Model fit is considered adequate if the root mean square error of approximation (RMSEA) is < .05 and comparative fit index (CFI) and Tucker-Lewis index (TLI) values are >.95 (Hu & Bentler, 1999). If $\chi^2 < df$, the CFI and RMSEA are set to 1.00 and <.001, respectively, constituting a normed fit index. In that case, it is sufficient to check the p value of the chi-square test of model fit.

A good fit is present when the p value is not significant (Van de Schoot, Lugtig, & Hox, 2012).

Effect sizes (i.e., R^2 were derived by comparing the residual error variances across models plus the deviance (Hox, 2010). The basic developmental model of delinquent behavior was used as a baseline model to examine effect sizes of the main effects. This is because the basic developmental model did not introduce any explanatory variables (except intercept, linear slope, and quadratic slope) and decomposes the total variance of delinquent behavior over time. Because there are no explanatory predictors in the model, the total variance of delinquent behavior is equivalent to the total error variance. To examine effect sizes of G × E, the residual error variance of the main effect model was used as a baseline model to which the residual variance of the G × E was compared with.

Results

Descriptive Statistics

Of the 308 adolescents studied, 108 (35.1%) carried at least one *DRD4* 7-repeat allele. For the *DRD2* gene, a total of 205 adolescents (66.3%) were A2 homozygous, thus with 104 (33.7%) being heterozygous or A1 homozygous. Of the mothers and fathers studied, 36.3% and 36.0% carried a *DRD4* 7-repeat allele and 34.3% and 29.8% were A2 homozygous, respectively. Means of psychological control and support were 2.20 (0.50) and 4.01 (0.93), respectively. Percentage of engaging in one or more rule-breaking activities—among all participants (i.e., basic developmental model) – ranged from 29.9% to 44.8%. The distribution of delinquent behavior was comparable with other studies on nonclinical samples (e.g., Harden et al., 2012).

Correlations among model variables are illustrated in Table 1. The *DRD4* and *DRD2* genes of both adolescents and parents were not correlated significantly with delinquent behavior. Perceived psychological control at T_1 was significantly correlated with higher delinquent behavior at most waves, whereas perceived support at T_1 was significantly correlated with lower delinquent behavior at most waves. Also, the point biserial correlation between *DRD4* gene and adolescents' self-reports of psychological control and support was significant, showing that adolescents with the *DRD4* 7-repeat allele reported more psychological control and less parental support than adolescents without the *DRD4* 7-repeat allele. Parents' *DRD4* or *DRD2* genes were not correlated with parenting or adolescent delinquency.

LGCM Results

Development of delinquent behavior. Results showed that a linear model did not fit the data well, $\chi^2(N = 308, df = 10) = 48.28, p < .001$ (CFI = .71, and RMSEA = .11). To improve fit, we specified a model including a quadratic growth parameter. This model fit the data well, $\chi^2(N = 308, df = 6) = 5.26, p = .51$ (CFI = 1.00, and RMSEA < .001). The estimates for all parameters were significant, meaning that delinquency rates differed significantly from zero. The intercept estimate demonstrated the mean of delinquency at baseline ($i = 0.99, p < .001$). The linear slope estimate ($s = 0.25, p = .014$) demonstrated that delinquency increased over time. The quadratic slope estimate ($q = -0.08, p <$

Table 1

Correlations Between DRD4/DRD2 *Genes, Perceived Parental Psychological Control and Support, and Delinquent Behavior at Waves 1–5*

Variable	1[a]	2[a]	3[a]	4[a]	5[a]	6[a]	7	8	9	10	11	12	13
1. *DRD4* adolescent													
2. *DRD4* mother													
3. *DRD4* father													
4. *DRD2* adolescent													
5. *DRD2* mother													
6. *DRD2* father													
7. Psychological control	.11*	−.01	−.09	−.03	.10	−.01	—						
8. Parental support	−.16**	−.05	.10	−.02	−.04	.00	−.06**	—					
9. Delinquency (Time 1)	.00	.03	.05	−.08	−.10	−.05	.20*	−.20**	—				
10. Delinquency (Time 2)	.01	−.09	.01	−.03	.09	−.00	.19*	−.14*	.50**	—			
11. Delinquency (Time 3)	.04	.10	.01	−.04	−.01	−.03	.16*	−.14*	.40**	.50**	—		
12. Delinquency (Time 4)	−.02	.05	−.07	−.05	.03	−.01	.12*	−.05	.30**	.38**	.66**	—	
13. Delinquency (Time 5)	.00	−.07	−.07	.02	.02	.03	.04	−.04	.42**	.34**	.48**	.56**	—

Note. DRD4 = dopamine D4 receptor gene, 0 = both alleles shorter than 7-repeat allele, 1 = at least one 7-repeat allele; DRD2 = dopamine D2 receptor gene, 0 = A2A2, 1 = A1A1 and A1/A2.
[a] Point biserial correlations.
* $p < .05$. ** $p < .01$.

.001) demonstrated that delinquency increased across early and mid-adolescence but then decreased across late adolescence (see Tables 2 and 3).

DRD4 × Parental Psychological Control. In a simple model, we found that the *DRD4* was not related to the intercept (β = .00, $p = .940$, $R^2 = .00$) or slopes (β = .05, $p = .461$, $R^2 = .00$; β = −.05, $p = .461$, $R^2 = .00$) of adolescents' delinquency. Psychological control was not significantly related to the intercept (β = .12, $p = .070$, $R^2 = .03$) and linear slope (β = .14, $p = .057$, $R^2 = .03$) but was significantly negatively related to the quadratic slope (β = −.17, $p = .015$, $R^2 = .04$), indicating that adolescents perceiving higher levels of psychological control did not show higher levels of delinquent behavior at intercept or a steeper

increase of delinquent behavior across early and mid-adolescence, but did show the highest decrease across late adolescence.

Also, we found a significant interaction between *DRD4* gene and psychological control at intercept (β = .18, $p = .041$, $R^2 = .06$); there was no relation between psychological control and delinquent behavior for those carrying two short alleles of the *DRD4* gene ($R^2 = .00$), but higher psychological control was significantly related to higher levels of delinquent behavior for those carrying at least one *DRD4* 7-repeat allele ($R^2 = .08$). However, in an advanced model—after *DRD4* mother, *DRD4* father, *DRD4* Mother × Psychological Control, *DRD4* Father × Psychological Control, *DRD4* Mother × *DRD4* Gene Adolescent, and *DRD4* Gene Father × *DRD4* Adolescent were entered in the

Table 2

Outcomes of Latent Growth Curve Modeling Regarding Gene by Environment Interactions in Delinquent Behavior Involving DRD4 *Gene and Perceived Parental Psychological Control*

Variable/passive genetic effects	Intercept β (SD)	Linear slope β (SD)	Quadratic slope β (SD)	χ^2 (df)	CFI	RMSEA	p value
Initial developmental model	0.99 (0.09)***	0.25 (0.10)**	−0.08 (0.02)***	5.27 (6)	1.00	<.001	.51
Simple model							
DRD4 adolescent	0.00 (0.06)	0.05 (0.07)	−0.05 (0.07)	8.55 (10)	1.00	<.001	.93
Psychological control	0.12 (0.07)	0.14 (0.07)	−0.17 (0.07)*				
DRD4 Adolescent × Psychological Control	0.18 (0.09)*	−0.05 (0.11)	−0.10 (0.10)	14.43 (12)	0.99	0.03	
Advanced model							
DRD4 mother	−0.02 (0.07)	−0.23 (0.12)	−0.28 (0.12)*	32.80 (26)	0.96	0.03	
DRD4 father	0.08 (0.10)	−0.01 (0.10)	−0.06 (0.10)				
DRD4 Mother × Psychological Control	−0.04 (0.08)	−0.11 (0.15)	−0.10 (0.15)				
DRD4 Father × Psychological Control	0.03 (0.09)	−0.06 (0.12)	0.08 (0.12)				
DRD4 Mother × *DRD4* Adolescent	0.18 (0.12)	−0.20 (0.18)	0.19 (0.19)				
DRD4 Father × *DRD4* Adolescent	0.08 (0.15)	−0.12 (0.18)	0.13 (0.18)				
DRD4 adolescent	−0.18 (0.16)	−0.23 (0.20)	−0.19 (0.21)				
Psychological control	0.03 (0.07)	0.12 (0.09)	−0.17 (0.10)*				
DRD4 Adolescent × Psychological Control	0.17 (0.09)	0.03 (0.14)	−0.08 (0.14)				

Note. Means of the initial developmental model are presented. df = degree of freedom; DRD4 = dopamine D4 receptor gene; 0 = both alleles shorter than 7-repeat allele, 1 = at least one 7-repeat allele; CFI = comparative fit index; RMSEA = root mean square error of approximation. As $\chi^2 < df$, the CFI is set to 1.0 and RSMEA to <.001, which makes it sufficient to read off whether the p value is not significant.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3

Outcomes of Latent Growth Curve Modeling Regarding Gene by Environment Interactions in Delinquent Behavior Involving DRD2 *Gene and Perceived Parental Support*

Variable/passive genetic effects	Intercept β (SD)	Linear slope β (SD)	Quadratic slope β (SD)	χ^2 (df)	CFI	RMSEA	p value
Initial developmental model	0.99 (0.09)***	0.25 (0.10)**	−0.08(0.02)***	5.26 (6)	1.00	<.001	.51
Simple model							
DRD2 adolescent	0.08 (0.06)	−0.13 (0.05)*	0.12 (0.05)*	7.53 (10)	1.00	<.001	.94
Support	−0.20 (0.06)**	0.00 (0.07)	0.04 (0.07)				
DRD2 Adolescent × Parental Support	−0.02 (0.06)	0.17 (0.08)*	−0.17 (0.08)*	10.38 (12)	1.00	<.001	.94
Advanced model							
DRD2 mother	−0.01 (0.07)	−0.03 (0.09)	0.02 (0.09)	21.63 (24)	1.00	<.001	.98
DRD2 father	0.12 (0.09)	−0.03 (0.09)	−0.01 (0.10)				
DRD2 Mother × Parental Support	−0.01 (0.06)	−0.01 (0.07)	−0.01 (0.07)				
DRD2 Father × Parental Support	0.03 (0.09)	−0.09 (0.10)	0.10 (0.10)				
DRD2 Mother × DRD2 Adolescent	0.18 (0.11)	0.02 (0.13)	−0.03 (0.12)				
DRD2 Father × DRD2 Adolescent	−0.09 (0.14)	0.03 (0.13)	0.01 (0.13)				
DRD2 adolescent	−0.04 (0.16)	−0.13 (0.14)	0.12 (0.14)				
Parental support	−0.19 (0.09)*	−0.05 (0.12)	0.09 (0.12)				
DRD2 Adolescent × Parental Support	0.04 (0.09)	0.21 (0.09)*	−0.21 (0.08)*				

Note. Means of the initial developmental model are presented. *DRD2* = dopamine D2 receptor gene; 0 = A2A2, 1 = A1A1 and A1/A2; CFI = comparative fit index; RMSEA = root mean square error of approximation. As $\chi^2 < df$, the CFI is set to 1.0 and RSMEA to <.001, which makes it sufficient to read off whether the *p* value is not significant.
* $p < .05$. ** $p < .01$. *** $p < .001$.

analysis—no significant interaction emerged between *DRD4* gene and psychological control at intercept, $\chi^2(26) = 32.80$, β = .17, $p = .060$, $R^2 = .02$ (see Table 2). Thus, the interaction did not survive when passive genetic effects were trimmed from the model. The effect size between psychological control and delinquent behavior was only .02 for those carrying the *DRD4* 7-repeat allele.

DRD2 × Parental Support. In a simple model, we found that the *DRD2* gene was not related to the intercept (β = .08, $p = .163$, $R^2 = .00$). The *DRD2* gene was, however, negatively related to the linear slope (β = −.13, $p = .011$, $R^2 = .01$) and positively related to the quadratic slope (β = .12, $p = .017$, $R^2 = .01$), indicating that adolescents with the A2A2 genotype showed a steeper increase of delinquent behavior in early and mid-adolescence, but the highest decrease across late adolescence. Parental support was negatively related to the intercept (β = −.20, $p = .001$, $R^2 = .05$) but not to the linear and quadratic slopes (β = .00, $p = .958$, $R^2 = .01$; β = .04, $p = .588$, $R^2 = .01$), indicating that adolescents reported higher levels of delinquent behavior when perceiving lower levels of parental support at baseline.

Also, we found a significant interaction between *DRD2* gene and parental support. The interaction was positively related to the linear slope (β = .17, $p = .034$, $R^2 = .02$) and negatively related to the quadratic slope (β = −.17, $p = .029$, $R^2 = .02$); there was no relation between low and high support and delinquent behavior for those carrying at least one A1 allele (linear slope: $R^2 = .01$; quadratic slope: $R^2 = .00$). However, those with the A2A2 genotype reported a significant steeper increase in delinquent behavior across early and mid-adolescence when perceiving low parental support (linear slope: $R^2 = .04$), but also showed a significantly stronger decrease in levels of delinquent behavior across late adolescence when perceiving low support (quadratic slope: $R^2 = .05$).

In an advanced model, we found that the *DRD2* main effects disappeared after entering *DRD2* mother, *DRD2* father, *DRD2*

Mother × Psychological Control, *DRD2* Father × Psychological Control, *DRD2* Mother × *DRD2* Adolescent, and *DRD2* Father × *DRD2* Adolescent in the regression model, $\chi^2(24) = 21.63$ (linear slope: β = −.13, $p = .375$, $R^2 = .00$; quadratic slope: β = .12, $p = .372$, $R^2 = .00$; see Table 3). However, the interaction effects remained significant for both slopes (linear slope: β = .21, $p = .013$, $R^2 = .02$; quadratic slope: β = −.21, $p = .014$, $R^2 = .02$) with interpretations of results being the same (see Figure 1). This indicates that no passive G × E effects emerged and thus the observed interaction of *DRD2* × Parental Support survived as significant. Notably, the effect sizes between support and delinquent behavior were also maintained for those carrying the *DRD2* A2A2 genotype (linear slope: $R^2 = .04$; quadratic slope: $R^2 = .05$). The interactions between *DRD4* gene and support and *DRD2* gene
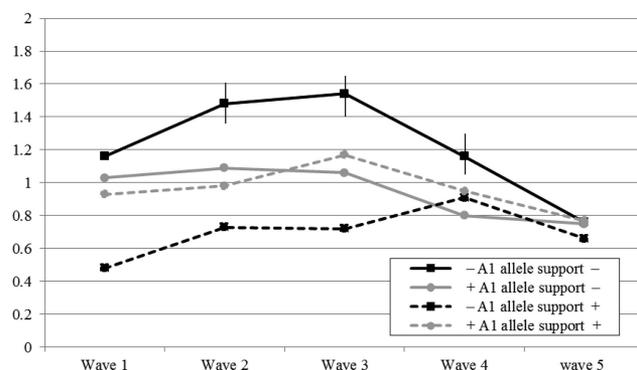

Figure 1. Development of delinquent behavior (as indicated by mean scores) across five yearly waves with low (–) or high (+) perceived parental support for adolescents with (+A1) or without (–A1) the dopamine D2 receptor (*DRD2*) A1 allele, after accounting for passive genetic effects in the advanced model. With significant differences at Wave 2, Wave 3, and Wave 4.

and psychological control were not significant, neither in a simple nor advanced model.

Discussion

This study tested whether the *DRD4* and *DRD2* genes interacted with adolescent-reported psychological control and parental support in predicting development of delinquent behavior in a general population sample of early adolescents. After accounting for passive genetic effects (i.e., parents' genotype, Parents' Genotype × Adolescents' Genotype, and Parents' Genotype × Parenting), results from LGCM indicated that the *DRD4* 7-repeat allele and *DRD2* A2A2 genotype were not related to adolescents' delinquent behavior. As parents are likely to transmit genes that might promote oppositional and rule-breaking behavior onto their children, it is plausible that parents' genes explain a part of the associations between adolescents' genes and their delinquent behavior. However, results did reveal a significant interaction between *DRD2* and parental support, indicating that adolescents with the *DRD2* A2A2 genotype were more vulnerable for maladaptive parenting, developing more delinquent behavior as a consequence. No significant interactions emerged for *DRD4* with parental support and psychological control, nor for *DRD2* with parental psychological control.

It is interesting to note that the point biserial correlation between *DRD4* and adolescents' self-reports of their parents' psychological control and support was significant, showing that adolescents with the *DRD4* 7-repeat allele reported more psychological control and less parental support than adolescents without the *DRD4* 7-repeat allele. This could be an indication of perceptual *r*GE, in that adolescents with such an allele were inclined to experience less support and more psychological control than those without such an allele. Results further showed that, again after accounting for passive genetic effects, *DRD4* 7-repeat and *DRD2* A2A2 carriers were not at higher risk for the presence and development of delinquency in adolescence. This is not surprising, as it is well-known that direct associations between genes and complex phenotypes such as delinquency are unlikely (Rutter et al., 1997) and we accounted for heritability of "risky genes."

Interaction Effect of *DRD2* × Parental Support

We found a G × E interaction between *DRD2* gene and support in the development of delinquent behavior, implying that especially adolescents with the A2A2 genotype who experienced low levels of support showed a stronger increase in delinquent behavior across early and mid-adolescence but a steeper decrease across late adolescence, compared with the other three groups. After accounting for passive genetic effects, the *DRD4* × Psychological Control interaction was no longer significant. Although we found no credible evidence that *DRD4* 7-repeat carriers were more vulnerable for high psychological control, none of the passive genetic effects itself significantly predicted adolescents' delinquent behavior (except for one association with the quadratic component of the model; Table 2). Thus, the changes in observed G × E estimates were probably not explained by passive G × E. Needless to say, replication is important to confirm the present evidence.

With regard to the maintained *DRD2* × Parenting interaction (see Figure 1), we see a clear age-crime curve. Delinquent behavior increases with age until adolescents reach mid-adolescence and then decreases with age (Farrington, 1986). However, this developmental trend was only observed among A2A2 carriers that perceived low parental support. Specifically, those adolescents reporting lower levels of parental support did not show higher levels of delinquency at early and late adolescence (i.e., Wave 1 and Wave 5), but did show a steeper increase in delinquency during the transition from early to mid-adolescence (i.e., Waves 2 through 4). However, this age-crime curve does not explain why specifically this subgroup of adolescents was more vulnerable for low perceived support during this period.

There have been mixed results regarding the functional significance of the A1 and A2 allele. Although most studies specifically related the Taq A1 allele to decreased receptor density in the brain (e.g., Pohjalainen et al., 1998), others did not (Laruelle, Gelernter, & Innis, 1998). Therefore, it may be that an altered dopaminergic function linked to a specific allele is not the straightforward reason why adolescents carrying a certain *DRD2* genotype would be more likely to be vulnerable for low support. Specially, the TaqI A1 allele in the *DRD2* gene is functionally related to another gene nearby the *DRD2* gene (i.e., *ANKK1* gene). The *ANKK1* and *DRD2* genes may be co-actors in a genetic haplotype (i.e., a complex of functionally related genes) that affects the functioning of dopaminergic neurotransmitter pathways (Ponce et al., 2009). We recommend that future research should not focus only on the interpretability of G × E results in the light of passive genetic effects, but also in the light of more complex indices of genetic functioning such as haplotypes (see Dick, Latendresse, & Riley, 2011).

Effect Sizes of Gene by Environment Interactions

The effect sizes in the present study (i.e., R^2) are clearly very modest. Before passive genetic effect were trimmed from the models, the effect sizes for main effects of genes were not detectable (i.e., *DRD4*) or accounted at most for only 1% in the development of delinquent behavior over time (i.e., *DRD2*). The observed effect sizes for the interaction effects between genes and maladaptive parenting were also small. When examining effect size differences for parenting on the development of delinquency across genotypes, effect sizes increased among those most genetically vulnerable for maladaptive parenting. Psychological control accounted for 8% in delinquency among those most vulnerable for high psychological control (i.e., *DRD4* 7-repeat: intercept) and parental support for 4% and 5% among those most vulnerable for low parental support (i.e., *DRD2* A2A2: linear and quadratic slope, respectively). After passive genetic effects were trimmed from the models, no effect sizes for main effects were detected. The effect sizes for the interaction effects were respectively .02 and .04 and .05 among those most genetically vulnerable for maladaptive parenting.

It is well-known that the explained variance of genetic main effects in the development of psychopathology is very low or even absent (Manolio et al., 2009; Risch & Merikangas, 1996). This is not surprising because genes might not be directly related to psychopathology but may lead to increased risk in interaction with specific environmental factors (Rutter, 2012). Effect sizes of G × E are, however, often not much larger (Mechanic & Hutter, 2015; Rutter, Moffitt, & Caspi, 2006), as was also evident from our present analyses. Testing G × E involves measuring how much behavioral variation is attributed to the interaction and will there-

fore be subject to a lot of noise. However, some noise might have a plausible reason to account for additional behavioral variance. In the present study, we specifically accounted for passive G × E. This resulted in more accurate effect sizes of observed G × E but also in evidence that passive genetic effects might additionally account for variance in outcomes. It is important that further research takes into account this possibility. Issues surrounding the correlation between genetic and environmental variables, restriction of range, and an overall limited variance in measurement of environmental factors have been identified as main causes of the difficulty to detect and replicate G × E (e.g., Dick et al., 2011; Duncan & Keller, 2011). All these issues should be considered carefully in interpreting G × E evidence. What is needed in future replication efforts for the present findings, therefore, are large sample sizes, experimental designs, and well operationalized constructs. This will minimize the risk of coming up with Type I errors (i.e., false positives).

The evidence for G × E underscores the diathesis-stress model (Zuckerman, 1999). This is consistent with numerous previous studies that found G × E related to child's dysfunction (e.g., Caspi, Hariri, Holmes, Uher, & Moffitt, 2011; Caspi et al., 2002; Sheese et al., 2007). Although there is evidence that children with "risky genes" will also benefit most from environmental enrichment, here we found that adolescents with a specific genetic disposition are more likely to do worse under adversity. However, in future studies, a stringent test of the differential-susceptibility hypothesis (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Belsky & Pluess, 2009, 2013; Boyce & Ellis, 2005) could be made by measuring adolescents' functioning along a continuum from dysfunction to competence rather than from dysfunction to its absence (Belsky & Pluess, 2009) or by using experimental designs to test variation in response to exclusively positive experiences (Bakermans-Kranenburg & Van IJzendoorn, 2015; Pluess & Belsky, 2013).

An important observation is the fact that the hypothesized G × E interactions were not systematically found across the models tested. Perhaps, this has to do with statistical power that may remain a problem in longitudinal G × E studies. More stringent replications in large-scale prospective or experimental studies are therefore recommended. This is especially relevant in light of the fact that almost all originally published candidate based G × E results in the field of psychiatry are significant (45/47; 96%), less than one third of the replication attempts is (10 out of 37; 27%; Duncan & Keller, 2011). This may represent a publication bias toward significant, perhaps less stringently controlled, results. In light of this possible publication bias, reporting both models with and without additional "control" variables is crucial, to make transparent the extent to which a result is accounted by (or robust against) such a control effect (Simmons, Nelson, & Simonsohn, 2011). An important related point here is that we conducted four separate tests of G × E (i.e., psychological control × *DRD4*, Psychological Control × *DRD2*, Parental Support × *DRD2*, Parental Support × *DRD2*), with two opportunities (i.e., simple model, advanced model) for significant effects in each case. Accordingly, a traditional Bonferroni correction for multiple testing would have resulted in nonsignificant effects for all G × E findings, stipulating the need for replication of the patterns here.

Limitations and Strengths

Some limitations have to be mentioned. First, most adolescents were from an indigenous Dutch background and lived with both parents. Therefore, our results may not be general to populations that are more heterogeneous. Then again, with regard to genetic stratification it is better to have a homogeneous ethnic group as was the case in our sample. Second, both parenting as well as delinquent behavior were assessed by adolescent-reports. It might be that perceived parenting is not a measure of an environmental factor, but may in part also measure a child characteristic. However, the data showed significant correlations between parents' reports and adolescents' self-reports on parenting, indicating that adolescents' self-reports of parenting converged with those of parents themselves. In the present analyses, we examined the way adolescents perceive parenting, as this has been argued to be pivotal; adolescents' perceptions of parent behaviors will determine their impact (Steinberg et al., 1994). In addition, it is well-known that parents' reports on parenting practices are vulnerable to social desirability response bias and therefore are more likely to outline the positive characteristics of families (Steinberg, 2001). As values of the parenting styles were relatively stable over time we did not investigate whether the impact of parenting changed as a function of developmental stage. However, it could be interesting for future research to also investigate such changes in parenting over time. Also, further research could benefit from including earlier assessments of parenting to explain the development of delinquency observed at baseline.

Furthermore, we must acknowledge that complex phenotypes such as delinquent behavior may have multifactorial polygenic etiologies (i.e., polygenic or multigenic effects). Although we followed strategic steps (e.g., providing a biological rationale, and working with a prospective design and established environmental risk measurement) to organize a high quality single candidate study (Moffitt, Caspi, & Rutter, 2005), this approach carries limited information about the overall variation within and between coacting genes. Therefore, future research should also focus on more complex indices of genetic functioning (Dick et al., 2011) because currently high-throughput genotyping technologies are available to test such complex multifactorial polygenic etiologies.

Chief among the strengths of the present study are the genetically informed longitudinal design with its adequate sample size and the sophisticated analytic strategy. We longitudinally investigated G × E interactions of the *DRD4* and *DRD2* variants with psychological control and support in the development of delinquent behavior and accounted for passive genetic effects by adopting a new approach using the Keller (2014) proposal. We demonstrated that passive G × E were negligible but that the observed G × E only survived in case of the *DRD2* × Support interaction. Also, we demonstrated that passive genetic effects accounted for additional variance in delinquent behavior.

Conclusion

The present study demonstrates that adolescents with the *DRD2* A2A2 genotype were more vulnerable for lower parental support, developing more delinquent behavior as a consequence. What makes this study especially distinct relative to other longitudinal G × E studies is that rather than focusing only on G × E, we adopted a new approach of accounting for parents' genotypes and

passive G × E. Although the *DRD2* × Support interaction survived as significant, its observed effect size was relatively modest. Replication studies are thus needed to confirm the present evidence that maladaptive parenting is more strongly related to delinquency in adolescents carrying the *DRD2* A2A2 genotype.

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