Effects of Dopamine System Genes and Maternal Parenting Behavior on Adolescent Depression: A Polygenic Study

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Full Text

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Abstract

In recent years, accompanied by the recognition of limitations in single-gene research and exploration of the "missing heritability,"an increasing number of studies have emphasized the importance of examining the polygenic mechanisms of depression. This study conducted a one-year follow-up of 1052 Han Chinese adolescents (12.31 ± 0.37 years, 50.2% girls), using a multilocus genetic profile score paradigm to investigate the longitudinal effects of dopaminergic system genes and maternal parenting on adolescent depression and their interaction patterns. Results showed: (1) Multilocus genetic profile scores and maternal negative parenting positively predicted adolescent depression risk; (2) After controlling for early depression, multilocus genetic profile scores interacted with both maternal positive and negative parenting to influence adolescent depression. In low positive/high negative parenting environments, adolescents with higher multilocus genetic profile scores exhibited higher depression levels compared to those with lower scores; however, in high positive/low negative parenting environments, no significant differences in depression levels were found among adolescents with different multilocus genetic profile scores. This interaction pattern is consistent with the "diathesis-stress" model. The findings provide evidence for the polygenic basis of depression.

Keywords: adolescent depression; maternal parenting behavior; dopamine; multilocus genetic profile score; gene × environment interaction

1.1 Dopaminergic System Genes and Depression: From Single-Gene to Polygenic Research

The factors influencing adolescent depressive disorders and their underlying mechanisms represent a critical research topic in developmental psychopathology. With the rise of molecular genetics, numerous studies over the past decade have examined the impact of genetic factors on adolescent depression from the perspective of single gene × environment interactions (G × E) (e.g., Xia & Yao, 2015), as well as the interactive effects of genes and environmental factors on adolescent depression (e.g., Cao et al., 2018; Zhang et al., 2015; Cao, Wang, Cao, Ji, & Zhang, 2017). Although single-gene studies have provided important insights into the mechanisms and individual differences in depression, the effect size of single genes on adolescent depression is typically less than 2%, and the replicability of findings is low (e.g., Dick et al., 2015).

In recent years, accumulating evidence has demonstrated that depression has a complex polygenic architecture. For instance, quantitative genetic studies based on polygenic and additive assumptions estimate that genetic factors can explain 30%–70% of the variance in depression (e.g., Nivard et al., 2015). Accompanied by the recognition of limitations in single-gene research and discussion of the "missing heritability," researchers in molecular genetics have begun employing multilocus genetic profile scores and gene × gene interactions to explore the complex polygenic mechanisms and processes of depression (e.g., Cao, Lin, Chen,

Ji, & Zhang, 2018; Stocker et al., 2017). The present study adopts a polygenic perspective to examine the effects of dopamine (DA) system multilocus genetic profile scores and maternal parenting on adolescent depression, and to test which theoretical hypothesis the polygenic × environment interaction pattern aligns with (the "diathesis-stress" model versus the "differential susceptibility" model), with the aim of enriching research on the polygenic mechanisms of depression.

According to the monoamine deficiency hypothesis, dopaminergic system dysfunction constitutes an important cause of depression (Belmaker & Agam, 2008). Dopaminergic system function is jointly influenced by multiple aspects of dopamine metabolism, transport, and transmission (Opmeer, Kortekaas, & Aleman, 2010). Furthermore, an increasing number of studies have shown that functional deficits in the mesolimbic and mesocortical dopamine pathways are closely associated with depression (Dunlop & Nemeroff, 2007). Based on this, among the many dopaminergic system genes, loci that both participate in regulating dopamine metabolism, transport, and transmission and are expressed in the mesolimbic and mesocortical dopamine pathways have received extensive research attention, such as the catechol-O-methyltransferase gene (COMT), dopamine transporter gene (DAT1), and dopamine receptor D2 gene (DRD2) (Cao et al., 2018; Lin et al., 2017; Pinsonneault et al., 2011).

The COMT enzyme encoded by the COMT gene degrades neurotransmitters including norepinephrine, epinephrine, and dopamine, reducing dopamine concentration in the synaptic cleft and thereby leading to depression. Among the many COMT gene polymorphisms, most researchers have focused on the association between the rs4680 (Val158Met) polymorphism and depression and other psychopathological problems; however, studies have shown that in Asian samples, the rs6267 polymorphism shows a stronger association with COMT enzyme activity than rs4680 (Lee et al., 2005). Therefore, the present study focuses on the rs6267 polymorphism located in the q11.2 region of chromosome 22. In this polymorphism, compared to the T allele, the G allele is associated with higher COMT enzyme activity (Lee et al., 2005), meaning the G allele has higher dopamine metabolism rates leading to lower dopamine concentrations. Lin et al. (2017) demonstrated that the rs6267 polymorphism is significantly associated with depressive symptoms in Parkinson' s patients.

The dopamine transporter encoded by the DAT1 gene transports dopamine from the synaptic cleft back into the presynaptic membrane, regulating dopamine content in the brain and thereby influencing depression. Existing research has primarily examined the DAT1 VNTR polymorphism, though there remains disagreement regarding which allele (9R or 10R) is associated with higher DAT expression activity (e.g., Costa, Riedel, Müller, Möller, & Ettinger, 2011; Heinz et al., 2000). In contrast, the rs27072 polymorphism located in the p15.33 region of chromosome 5 shows more stable expression activity, with in vivo and in vitro experiments consistently finding that the T allele has higher expression levels than the CC genotype (Pinsonneault et al., 2011). Research on bipolar disorder has shown that across multiple replication samples, the rs27072 polymorphism

demonstrates a stable association with bipolar disorder compared to other loci (Pinsonneault et al., 2011).

The D2 dopamine receptor encoded by the DRD2 gene influences depression risk by affecting dopaminergic activity in the mesolimbic system. The rs1799978 polymorphism, located in the q2.2-2.3 region of chromosome 11, is a functional polymorphism in the promoter region of the DRD2 gene, where adenine (A) replaces guanine (G) at the -241 position to form two alleles (Doehring, Kirchhof, & Lötsch, 2009), influencing D2 receptor expression (Zhang & Malhotra, 2011). Although direct evidence regarding the function of rs1799978 alleles is lacking, related research suggests that the A allele may be associated with lower dopamine receptor activity (Doehring et al., 2009) and higher depression risk (Cao et al., 2018). Specifically, pharmacological studies on risperidone (which produces antagonistic effects by binding to D2 receptors to reduce depression and schizophrenia symptoms) have shown that compared to the G allele, carriers of the A allele or AA genotype exhibit better treatment efficacy (Doehring et al., 2009). This suggests that the A allele may be associated with lower D2 receptor quantity, allowing higher binding rates with risperidone and thus better therapeutic effects. Furthermore, related studies have shown that in Asian samples, compared to other DRD2 polymorphisms, rs1799978 is associated with better risperidone efficacy (Xing et al., 2007) and stronger associations with depression (Cao et al., 2018).

Although single-gene studies have provided important insights into the mechanisms and individual differences in depression, the explanatory power of single-gene research is often extremely low. One reason for this weak genetic explanatory power may be that research has neglected the polygenic architecture of depression (Belsky & Pluess, 2009). In particular, studies have shown that COMT, DAT1, and DRD2 genes may not independently affect depression but rather exhibit joint effects. For example, early animal studies found that in DAT1 knockout mice, COMT enzyme content was 400% higher than in non-knockout mice, while D2 receptor expression levels decreased (Giros, Jaber, Jones, Wightman, & Caron, 1996). This indicates that COMT, DAT1, and DRD2 genes may have joint effects that collectively regulate dopaminergic system function.

Recently, researchers have measured polygenic joint effects by summing the number of susceptibility alleles carried by an individual, known as the multilocus genetic profile score (MGPS). The MGPS approach provides a new framework for studying the genetic mechanisms of depression, and studies to date have shown that polygenic effects are stronger than the effects of any single locus (Pearson-Fuhrhop et al., 2014; Vrshek-Schallhorn et al., 2015). For example, Pearson-Fuhrhop et al. (2014) examined the association between MGPS for five DA genes affecting dopamine metabolism, transport, and transmission (COMT, DAT1, DRD1, DRD2, and DRD3) and depression. Results showed that in both depressed patient and healthy control groups, the more risk alleles (low-activity dopamine alleles) an individual carried, the higher their depression level, and the MGPS explained more variance than any single gene locus. This suggests

that the MGPS approach can provide richer genetic information and increase genetic explanatory power. Additionally, in statistical analysis, MGPS can be used as a continuous variable, offering statistical advantages when testing gene × environment interactions (Dunn et al., 2011).

1.2 Multilocus Genetic Profile Score and Environmental Factors Interaction

Theoretical and empirical research shows that dopaminergic polygenic variants not only jointly influence individual depression risk but may also moderate environmental sensitivity. For instance, the biosocial developmental model (BDM) proposes that decreased dopamine levels trigger deficits in the behavioral approach system during adolescence, increasing sensitivity to adverse environments and raising risk for internalizing and externalizing problems (Beauchaine, Gatzke-Kopp & Mead, 2007). The prefrontal late-maturation theory suggests that limbic-prefrontal connectivity influences environmental sensitivity and is closely related to depressive mood (Andersen & Teicher, 2008). The primary expression brain regions of COMT, DAT1, and DRD2 genes are concentrated in the prefrontal cortex (Matsumoto et al., 2003), mesostriatal and limbic system regions (Lewis, Melchitzky, Sesack, Whitehead, & Sampson, 2001; Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997), respectively. Therefore, these three genes acting on the limbic-prefrontal pathway may jointly regulate environmental sensitivity and influence depression development. Empirical studies have also provided preliminary evidence for dopaminergic MGPS × environment interactions. For example, Davies, Cicchetti, and Hentges (2015) found that adolescents with higher MGPS exhibited more problem behaviors when experiencing maternal negative parenting. Research on ventral striatum activation showed that when facing reward feedback, individuals carrying more low-activity dopamine system alleles (DRD4, DAT1, DRD2, and COMT) displayed lower striatal reactivity (Nikolova, Ferrell, Manuck, & Hariri, 2011).

However, the few existing dopaminergic MGPS × environment studies have primarily focused on adverse family environmental factors, such as negative parenting (Davies et al., 2015), prenatal adversity (Bischoff et al., 2017), and early maltreatment (Coley, Sims, & Carrano, 2017), with no research examining the role of positive environments. Among various family environmental factors, maternal positive and negative parenting behaviors are important predictors of adolescent depression. Studies show that maternal positive parenting behaviors, such as warmth and supportive parenting, promote positive self-perception and better socioemotional functioning in adolescents, thereby reducing depression risk (Olino et al., 2016; Wang et al., 2016). Conversely, negative parenting behaviors, such as rejection and harshness, lead to poorer self-concept and self-esteem, resulting in higher depression risk (Wang et al., 2016). Therefore, one purpose of this study is to comprehensively utilize positive and negative parenting indicators to examine the potential interaction between MGPS for COMT, DAT1, and DRD2 genes and the environment.

1.3 The Diathesis-Stress Model and the Differential Susceptibility Model

The interaction pattern between MGPS and environment may be explained by two competing hypotheses: the diathesis-stress model and the differential susceptibility model. The former assumes that psychological disorders or behavioral problems result from the combination of risk genes and adverse environments (Monroe & Simons, 1991), while the latter posits that so-called risk genes are actually genetic plasticity, with more plastic individuals being more sensitive to both negative and positive environments (Belsky & Pluess, 2009). Based on these competing models, researchers debate whether MGPS essentially represents a "cumulative risk score" or a "cumulative plasticity score."

However, the problem is that current dopaminergic MGPS research has primarily measured environmental indicators limited to negative environments. Especially when the range of environmental values is limited, traditional regression methods may not reflect the full picture of interactions, and the validated "diathesis-stress" model may only represent part of the "differential susceptibility" model (Roisman et al., 2012). To address this, researchers have proposed a more accurate and novel statistical testing method—the re-parameterized regression model—which can test the form of gene × environment interactions from theoretical hypotheses (Widaman et al., 2012). Therefore, the second purpose of this study is to use this novel re-parameterized regression model to test the two competing hypotheses.

In summary, this study adopts a polygenic perspective to examine the effects of dopaminergic gene profile scores (COMT, DAT1, and DRD2) and maternal parenting on adolescent depression, focusing on two main questions: (1) the interaction between MGPS and maternal parenting on adolescent depression, and (2) testing the form of this interaction (diathesis-stress model vs. differential susceptibility model).

2.2.1 Maternal Parenting Behavior

Maternal parenting behavior was measured using the Chinese version of the Child-Rearing Practices Report (Chen, Bian, Xin, Wang, & Silbereisen, 2010), completed by mothers. Two dimensions—warmth (4 items, e.g., "I speak to my child in a gentle, affectionate manner") and guidance (4 items, e.g., "When my child encounters problems, I encourage him/her to talk about them")—were used as indicators of positive parenting behavior, while rejection (4 items, e.g., "If my child doesn' t bother me, I ignore him/her") served as an indicator of negative parenting behavior. The questionnaire used a 5-point scale (0 = not at all true, 4 = completely true), with higher average scores indicating more of that parenting behavior. In this study, Cronbach' s coefficients were 0.83 for positive parenting and 0.54 for negative parenting. Confirmatory factor analysis showed good fit for the two-factor model (2 = 223.58, df = 53, RMSEA = 0.06, CFI = 0.92, TLI = 0.90).

2.2.2 Adolescent Depression

Adolescent depressive symptoms were measured using the Children's Depression Inventory (CDI; Kovacs, 1992). The scale contains 27 items requiring adolescents to report depressive symptoms over the past two weeks, scored 0, 1, or 2, with mean scores calculated—higher scores indicating more depressive symptoms. This scale is widely used in normal adolescent populations (Zhang et al., 2015) and demonstrates good psychometric properties. In this study, Cronbach's coefficients for adolescent depression at both time points were 0.88. Confirmatory factor analysis showed good fit for the single-factor model at T1 (2 = 699.34, df = 324, RMSEA = 0.03, CFI = 0.95, TLI = 0.95) and T2 (2 = 736.72, df = 324, RMSEA = 0.04, CFI = 0.96, TLI = 0.96).

2.3 Research Procedure

The study was approved by the institutional ethics committee. First, the research team informed the participating schools, parents, and adolescents about the questionnaire assessment, saliva sample collection, DNA extraction and genotyping procedures, and obtained informed consent from all three parties before data collection. Second, all assessment procedures were completed by rigorously trained graduate student examiners.

2.3.1 Questionnaire Administration Procedure

First, adolescent depressive symptoms were assessed on-site in classrooms, with two rigorously trained and experienced graduate students serving as examiners for each class. Questionnaires were collected immediately after completion. Second, following the on-site assessment, adolescents took home envelopes containing the maternal parenting questionnaire for their mothers to complete, returning them to their homeroom teachers the next day for collection.

2.3.2 Saliva Sample Collection, DNA Extraction, and Genotyping Procedure

First, saliva samples were collected from adolescents in classrooms, ensuring at least 2ml per person. Following collection, DNA extraction and genotyping of the rs6267, rs27072, and rs1799978 polymorphisms were performed using the Sequenom (San Diego, CA, USA) chip-based matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry platform. PCR primers were: COMT gene: forward 5' -ACGTTGGATGTAGGTGTCAATGGCCTCCAG-3' , reverse 5' -ACGTTGGATGTCATGGGTGACACCAAGGAG-3' ; DAT1 gene: forward 5' -AGAACACAGTGCCCCTGGG-3', reverse 5'-AAAAACGTCTAACTTCATGCTGTCTG-3' ; DRD2 gene: forward 5' -AGGAGCTGGAGATGGAGATGCT-3' , reverse 5' -ATGCCCATTCTTCTCTGGTTTGGC-3' . PCR conditions: 94°C for 15 min; 45 cycles of 94°C for 20 s, 56°C for 30 s, 72°C for 1 min; final extension at 72°C for 3 min. Following single-base extension reactions, genotyping was analyzed

using the MassARRAY Typer 3.4 software system. The detection platform and technology used in this study demonstrate high reliability (genotyping success rate $> 97\%$).

2.4 Data Processing and Analysis

First, Hardy-Weinberg equilibrium tests were conducted for the three genetic polymorphisms and associations between different genes were examined. Second, linear gene effects[1] and equal gene effects[2] were tested to determine whether linear genetic coding was appropriate and whether any single gene had a dominant effect (Stocker et al., 2017). This statistical analysis tested three regression models: the disaggregated model included six gene main effects (dominant and recessive coding for three genes), six gene × environment interaction effects (interactions between dominant and recessive coding of three genes and parenting), and main effects of parenting and control variables (gender and early depression), totaling 15 parameter estimates; the linear gene effect model tested whether linear genetic coding was appropriate by constraining regression weights for dominant and recessive coding of the same gene to be equal (six constraints, including gene main effects and gene × environment interaction effects, allowing effects to differ across genes); the equal gene effect model constrained the effects of the three genes to be equal (four constraints, including gene main effects and gene × environment interaction effects). The advantage of linear gene effect and equal gene effect models is that they provide estimates of model constraints: if the linear gene effect model shows a significant change in explanatory power compared to the disaggregated model, it indicates that at least one gene has a non-linear effect and is not suitable for 0, 1, 2 linear coding, requiring adjustment of the coding scheme; if the equal gene effect model shows a significant change in explanatory power compared to the linear gene effect model, it indicates that the predictive strength of the three genes differs significantly, with at least one gene having different predictive strength or direction, possibly indicating a single gene' s dominant effect or cancellation of effects between genes, making it unsuitable for multilocus genetic profile research. Third, correlation analysis was used to examine relationships among main study variables. Fourth, hierarchical linear regression was employed to investigate the effects of MGPS and maternal parenting on adolescent depression. To avoid multicollinearity, both MGPS and maternal parenting behaviors were standardized. If gene × environment interactions were significant, simple slope tests were conducted. Gender and early depressive symptoms were included as control variables; controlling for T1 depression essentially examined the influence of genes and parenting on changes in depression from T1 to T2. Fifth, re-parameterized regression (Widaman et al., 2012) was used to test which theoretical model the interaction fit ("diathesis-stress" versus "differential susceptibility"). Finally, sensitivity analyses were conducted to verify result reliability. Sensitivity analyses were performed in five aspects: (1) testing each gene' s interaction with maternal parenting on depression and comparing significance differences between single-gene and multilocus results; (2) dividing MGPS into low, medium, and high groups for group re-

gression analysis to verify MGPS × environment interaction results; (3) testing gene × gene interaction effects to exclude interference from gene-gene interactions on multilocus additive effects; (4) following previous research (Cao et al., 2018), reverse-scoring all negative parenting items, then standardizing positive and negative parenting (after reverse-scoring) items and calculating the mean as maternal parenting sensitivity score, and repeating the above analysis steps to verify result reliability; (5) given that controlling for early depression may underestimate gene and parenting effects on depression, this study additionally examined the effects of MGPS and parenting on T1 depression and T2 depression (without controlling for T1 depression). To control Type I error, the B-H method based on false discovery rate (FDR) criteria was used for statistical correction (Benjamini & Hochberg, 1995). Data processing and statistical analysis were conducted using SPSS 23.0 and R 3.3.2.

3.1 Genotype Distribution of the Three Genetic Markers

The genotype distributions of COMT, DAT1, and DRD2 examined in this study are shown in Table 1 . Genotype distributions at all three loci were in Hardy-Weinberg equilibrium (2s $<$ 1.74, df = 1, ps $>$ 0.05). The minor allele frequencies (MAF) for all three polymorphisms were greater than 5%. Additionally, no significant associations existed among the three genes (2s $<$ 2.84, df = 4, ps $>$ 0.58).

3.2 Testing Different Effects of Genetic Markers

Before calculating MGPS, it is necessary to determine whether linear coding is appropriate for each gene, whether any single gene effect dominates the multilocus additive effect, and whether effects of multiple genes might cancel each other out due to coding schemes. Based on dopamine activity, we conducted dominant and recessive coding, coding low-activity dopamine alleles as risk/susceptibility alleles. Following previous research (Stocker et al., 2017), we tested linear gene and equal gene effect models. Results are shown in Table 2. The disaggregated model had the highest explanatory power, but changes in R^2 between different models were not significant. The three candidate genes in this study did not significantly deviate from linear and equal gene effect assumptions. Therefore, in subsequent analyses, we used linear coding (0, 1, 2) based on the number of low-activity dopamine alleles carried by individuals and calculated MGPS (MGPS distribution: 1 = 7 individuals, 2 = 43, 3 = 259, 4 = 487, 5 = 217, 6 = 39).

3.3 Correlation Analysis Results

Means, standard deviations, and correlations among main study variables are shown in Table 3 . MGPS was not significantly correlated with positive or negative parenting behavior, ruling out gene-environment correlation. Higher MGPS (i.e., lower dopamine activity) was associated with greater depression

risk. Maternal positive parenting significantly negatively predicted adolescent depression, while maternal negative parenting significantly positively predicted adolescent depression. Positive and negative parenting behaviors were significantly negatively correlated. Depressive symptoms across the one-year interval showed moderate positive correlation, indicating stability in adolescent depression. Paired samples t-test showed T2 depression was significantly higher than T1 depression ($t(1033) = -5.29$, $p < 0.001$). Additionally, consistent with related findings, independent samples t-tests indicated no significant gender differences in maternal positive parenting or depression (positive parenting: $t(1038) = 1.46$, $p = 0.14$; T1 depression: $t(1038) = -1.86$, $p = 0.06$; T2 depression: $t(1043) = -1.13$, $p = 0.26$), but mothers exhibited significantly more negative parenting toward boys than girls ($t(1040) = -2.54$, $p = 0.01$).

3.4 Interaction Effects of Multilocus Genetic Profile Score and Maternal Parenting on Adolescent Depression

Using T2 depression as the dependent variable, controlling for T1 depression and gender, hierarchical regression analysis was conducted with MGPS, maternal parenting behaviors, and gene × environment interaction terms as predictors. As shown in Table 4 , MGPS and maternal negative parenting significantly positively predicted adolescent depression, while maternal positive parenting did not significantly predict depression. After controlling for T1 depression and gender, MGPS interacted with both maternal positive and negative parenting to predict adolescent depression, and results remained significant after B-H statistical correction.

Further simple slope tests showed that, after controlling for T1 depression and gender, when maternal positive parenting was low, adolescents with higher MGPS exhibited higher depression levels than those with lower MGPS ($b = 0.03$, $t = 2.89$, $p = 0.004$); when maternal positive parenting was high, no significant differences in depression levels were found among adolescents with different MGPS ($b = -0.002$, $t = -0.21$, $p = 0.84$). Similarly, when maternal negative parenting was high, adolescents with higher MGPS showed higher depression levels than those with lower MGPS ($b = 0.03$, $t = 3.18$, $p = 0.002$); when maternal negative parenting was low, no significant differences in depression levels were found among adolescents with different MGPS ($b = -0.003$, $t = -0.42$, $p = 0.68$) (see Figure 1 [Figure 1: see original paper]).

As shown in Table 5 , this study used re-parameterized regression to test whether the above interactions fit the diathesis-stress model or the differential susceptibility model for both positive and negative parenting models. Results showed that for both positive and negative parenting models, the MGPS × parenting interaction fit the diathesis-stress model. Detailed statistical indicator analysis is as follows: (1) The diathesis-stress model itself showed good fit ($R^2 = 0.37$, $p < 0.001$); (2) In the differential susceptibility model, the point estimate of the crossover point C and its 95% confidence interval exceeded the range of parenting behavior values (positive parenting: -4.22 to 1.52; negative parenting:

-1.31 to 3.76; parenting sensitivity: -4.16 to 1.60), indicating that the gene × environment interaction pattern did not conform to the differential susceptibility hypothesis; (3) F-tests showed that although the differential susceptibility model added one parameter (C) compared to the diathesis-stress model, its explanatory power was not significantly higher (ΔR^2s = 0.00, ps > 0.05); (4) The diathesis-stress model had smaller AIC and BIC values than the differential susceptibility model. In summary, all parameters indicated that the diathesis-stress model fit the data better than the differential susceptibility model, suggesting that the interaction between dopaminergic MGPS and maternal parenting on adolescent depression is more consistent with the diathesis-stress model.

3.5 Sensitivity Analysis

To verify the reliability of the above findings, this study conducted sensitivity analyses. First, regression analysis was performed on the interaction between each single gene and maternal positive and negative parenting on depression. After B-H correction, except for the significant interaction between DAT1 gene and positive parenting (b = -0.05, t = -2.78, p = 0.006), all other single gene × parenting interactions were non-significant (|b|s < 0.04, |t|s = -2.27, ps > 0.05). This also demonstrates that multilocus genetic profile research has advantages over single-gene research in improving genetic explanatory power and significance.

Second, previous analyses treated MGPS as a continuous variable. Since few individuals carried 1, 2, or 6 low dopamine activity alleles, this might affect the reliability of interaction results. To further verify these results, this study recoded MGPS for group regression testing. Adolescents with MGPS of 1, 2, or 3 were coded as the low group, those with MGPS of 4 as the medium group, and those with MGPS of 5 or 6 as the high group. Group regression results were consistent with previous findings: compared to low and medium groups, high MGPS adolescents were more sensitive to maternal positive parenting (b = -0.04, t = -2.33, p = 0.02) and negative parenting (b = 0.04, t = 2.65, p = 0.01) (see Figure 2 [Figure 2: see original paper]).

Third, to exclude the influence of gene × gene interaction effects, this study analyzed G × G × G × E effects. It should be noted that using linear genetic coding (0, 1, 2) resulted in insufficient cell sizes for statistical analysis. This study alternatively used dichotomous coding (COMT: 0 = GG, 1 = T; DAT1: 0 = T, 1 = CC; DRD2: 0 = AA, 1 = G) for analysis. Results showed that all G × G, G × G × G, G × G × E, and G × G × G × E interaction effects were non-significant (|b|s 0.22, |t|s 0.90, p 0.37), largely ruling out potential gene × gene interaction interference.

Fourth, following previous research (Cao et al., 2018), negative and positive parenting items were combined into a total maternal parenting sensitivity score after reverse-scoring negative parenting items and standardizing all items. Repeating the above statistical analyses yielded patterns consistent with those for

positive and negative parenting analyzed separately, though interaction terms showed greater significance and effect sizes (see supplementary analysis sections in Tables 2, 4, and 5).

Fifth, supplementary analyses examined concurrent effects of MGPS and parenting on T1 depression and longitudinal effects on T2 depression (without controlling for T1 depression). Results showed increased main effects and significance for genes and parenting. However, except for the significant interaction between genes and negative parenting on T2 depression, all other gene × environment interactions were non-significant (see Tables 6 and 7).

This study used a multilocus genetic profile score paradigm with three dopaminergic system genes (COMT, DAT1, and DRD2) as genetic indicators to examine the effects of maternal parenting and MGPS on adolescent depression. Results showed that after controlling for early depression, MGPS significantly positively predicted adolescent depression. Dopaminergic MGPS interacted with both maternal positive and negative parenting to predict adolescent depression, with interaction patterns fitting the diathesis-stress model. Specifically, in low positive or high negative parenting environments, adolescents with higher MGPS exhibited higher depression levels than those with lower MGPS, while in high positive or low negative parenting environments, no significant differences in depression levels were found among adolescents with different MGPS.

Consistent with previous research (e.g., Wang et al., 2016), this study found that maternal negative parenting is a risk factor for adolescent depression. However, the effect of maternal positive parenting on adolescent depression did not reach significance. This may reflect differences in how positive and negative parenting affect adolescent depression. On one hand, positive and negative parenting may differ in their strength of prediction, as Dallaire et al. (2006) found that negative parenting more strongly predicted child and adolescent depression. On the other hand, Smokowski, Bacallao, Cotter, and Evans (2015) further revealed that different types of parenting behaviors show domain specificity in predicting adolescent adjustment outcomes, with positive parenting more closely associated with positive psychological characteristics and having smaller effects on negative adjustment outcomes, while negative parenting is a key risk factor for negative outcomes such as anxiety and depression. More importantly, the pathways through which positive and negative parenting affect adolescent depression may differ; for example, Luebbe and Bell (2014) found that negative family climate (including negative parenting) and positive family climate (including positive parenting) indirectly affected adolescent depression through negative and positive emotionality, respectively. Thus, future research should include positive adjustment outcomes to examine domain specificity between parenting and adjustment outcomes.

This study found that individuals carrying higher MGPS (i.e., lower dopaminergic system function) had higher depression levels, consistent with the monoamine deficiency hypothesis that dopaminergic system dysfunction increases depression risk. More importantly, this study supports the poly-

genic architecture of depression. However, the explanatory power of the polygenic joint effect in this study remained around 1%, suggesting that depression has complex etiological and developmental mechanisms and that the dopaminergic MGPS selected in this study only reflects the tip of the iceberg regarding pathogenic factors. Researchers should view these results with caution. Additionally, researchers should explore the mechanisms through which polygenic variants affect depression, such as multilocus genetic profile score × environment research.

Regarding interaction effects, after controlling for early depression, maternal parenting behavior interacted with dopaminergic MGPS to predict subsequent adolescent depression. Further analysis revealed that only in negative environments (including low positive parenting and high negative parenting) did adolescents with higher MGPS show higher depression risk than those with lower scores. Re-parameterized regression analysis further demonstrated that this interaction pattern better fit the diathesis-stress model. Consistent with these results, the aforementioned research on ventral striatum activity showed that individuals carrying more low-activity dopamine alleles exhibited lower striatal reactivity when facing external stimuli (Nikolova et al., 2011). Studies on reward and punishment sensitivity found that sensitivity to reward stimuli positively correlates with striatal activation, while sensitivity to punishment negatively correlates with striatal activation (Kim, Yoon, Kim, & Hamann, 2015). These findings suggest that individuals with more low-activity dopamine alleles have lower striatal activation levels, lower sensitivity to social reward stimuli (such as positive parenting environments) and thus cannot benefit from positive environments, but show higher sensitivity to negative environmental stimuli, thereby increasing depression risk. It should be noted that this interaction pattern may only depict gene × environment interactions during early adolescence; current researchers increasingly adopt a dynamic perspective on diathesis-stress and differential susceptibility models (Wang, 2015). For example, research found that the interaction pattern between MGPS (BDNF and 5-HTTLPR genes) and family environment quality on depression fit the differential susceptibility hypothesis in early adolescence (before age 15) but fit the diathesis-stress model in middle-to-late adolescence (Dalton, Hammen, Najman, & Brennan, 2014). Thus, future research should include participants from other age groups or use longitudinal designs to explore whether gene × environment interaction patterns show developmental dynamics.

Although the explanatory power of MGPS and its interaction with environment remained low (1%) in this study, sensitivity analyses showed that compared to single genes, MGPS still has advantages in improving genetic explanatory power and significance. Notably, this does not mean researchers can arbitrarily increase the number of gene loci to calculate MGPS to expand genetic effects. In fact, even when accumulating numerous SNP loci, the full genetic mechanisms of depression cannot be explained, and improvements in heritability are minimal. For example, Peyrot et al. (2014) used genome-wide association study (GWAS) methods to include 150–32,870 SNP loci in MGPS calculation, with

MGPS and its interaction with childhood maltreatment explaining only 0.09%–0.90% of variance. However, small genetic explanatory power does not mean it is negligible (Evans, 1985). Therefore, researchers should not blindly pursue increased explanatory power by misusing genetic indicators. How to select appropriate multilocus genetic indicators has become a focus of attention, especially with the discovery of increasing numbers of new functional genetic markers. Vrshek-Schallhorn et al. (2015) noted that to avoid data-driven and misuse risks, multilocus genetic studies should preferably select genes from the same neurotransmitter system rather than cross-system genes, as this facilitates exploration of associations between polygenic variants and endophenotypes, thereby identifying internal mechanisms of depression development.

Additionally, the limited explanatory power of MGPS has generated great interest in exploring "missing heritability." Manolio et al. (2009) suggested that reasons for missing heritability may include: First, numerous genetic variants with extremely small effects remain undiscovered. Therefore, using GWAS and GWEIS (genome-wide by environment interaction studies) methods to explore potential functional genes and gene × environment interactions remains a future research priority. Second, researchers should move beyond the "common disease, common variant" assumption to explore rare genetic variants with larger effects (variants with population frequencies below 5%). Third, existing research rarely measures DNA expression mechanisms, limiting genetic explanatory power for phenotypes. Epigenetic mechanisms such as methylation and histone modification can affect gene-phenotype associations without altering DNA structure. Therefore, examining changes in MGPS and gene expression levels can help identify missing genetic explanatory power and further dissect potential biological mechanisms of genetic factors. Fourth, MGPS fails to detect gene × gene interactions. In this study, due to cell size limitations, we used dichotomous coding to test gene × gene interaction effects and largely confirmed the reliability of multilocus genetic accumulation. However, future multilocus genetic studies should remain cautious about potential interactions between different genes. As Plomin, DeFries, McClearn, and McGuffin (2001) noted, polygenic genetic models need to consider not only additive effects of different alleles but also possible interactions between effects at different loci.

This study used a longitudinal design controlling for early depression to examine the effects of MGPS and maternal parenting on adolescent depression. The primary reason for this design is that adolescent depression and maternal parenting typically have bidirectional relationships (Hamza & Willoughby, 2011), where maternal parenting not only influences adolescent depression but is also affected by adolescent depressive symptoms. Therefore, without controlling for early adolescent depression, the effect of parenting on subsequent depression might be confounded with the effect of early depression on later depression. Controlling for early depression thus helps reduce the possibility that maternal parenting is a consequence rather than a cause of depressive symptoms (Chen, Li, & McGue, 2013). Although controlling for early depression offers advantages, it may also reduce effect sizes and significance of genetic and en-

vironmental effects. Considering results both with and without controlling for early depression, it is important to note that the interaction between MGPS and maternal parenting does not predict absolute levels of depressive symptoms at T1 and T2 but essentially predicts changes in depression from T1 to T2. Similar patterns were found in Petersen et al. (2012), where G × E did not predict baseline anxiety/depression symptoms but significantly predicted developmental changes in anxiety/depression, particularly explaining age-related trends in depression. Thus, even when genetic and environmental interaction effects on depression levels are not significant, this does not mean G × E is unrelated to depression development. Future research should more deeply examine the effects of genetics and environment on depression and its developmental changes to further elucidate this issue.

Several limitations of this study should be noted. First, this study lacks a replication sample. In recent years, with increasing controversy over gene × environment interaction research, more researchers have questioned the replicability of genetic studies and emphasized the need for external validation samples (Christ, Schwartz, Stoltenberg, Brauer, & Savolainen, 2018; Dick et al., 2015). However, this study does not have an external validation sample with identical measures and similar participant characteristics, and the replicability of its results awaits future verification. Second, the dopaminergic system contains many genes, and this study only examined three genetic polymorphisms; future research needs to examine other candidate polymorphisms to enrich this field. Third, the reliability index for negative parenting in this study was relatively low, possibly due to the small number of negative parenting items (4 items). Although confirmatory factor analysis in this study ensured its structural validity, results should be interpreted cautiously. Additionally, this study only measured maternal positive and negative parenting behaviors and did not assess paternal parenting. For a long time, researchers in molecular genetics have often overlooked differences and mutual influences between paternal and maternal parenting behaviors. To our knowledge, only one study has compared differences in interactions between MGPS and paternal versus maternal parenting without finding significant differences (Stocker et al., 2017). However, other research has shown that paternal and maternal parenting behaviors interactively affect adolescent depression (Quach, Epstein, Riley, Falconier, & Fang, 2015). Therefore, future research should examine differences in interactions between paternal and maternal parenting and genetic factors and consider mutual influences between paternal and maternal parenting. Finally, participants in this study were urban, typically developing adolescents; whether these findings apply to clinical samples, major depression, or adolescents from lower socioeconomic backgrounds requires future verification.

References

Aliev, F., Latendresse, S. J., Bacanu, S. A., Neale, M. C., & Dick, D. M. (2014). Testing for measured gene-environment interaction: Problems with the use of

cross-product terms and a regression model reparameterization solution. *Behavior Genetics, 44*, 165–181.

Andersen, S. L., & Teicher, M. H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neurosciences, 31*, 183–191.

Beauchaine, T. P., Gatzke-Kopp, L., & Mead, H. K. (2007). Polyvagal theory and developmental psychopathology: Emotion dysregulation and conduct problems from preschool to adolescence. *Biological Psychology, 74*, 174–184.

Belmaker, R. H., & Agam, G. (2008). Major depressive disorder. *New England Journal of Medicine, 358*, 55–68.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin, 135*, 885–908.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B (Methodological), 57*, 289–300.

Bischoff, A. R., Pokhvisneva, I., Léger, É., Gaudreau, H., Steiner, M., Kennedy, J. L., ···MAVAN research team. (2017). Dynamic interaction between fetal adversity and a genetic score reflecting dopamine function on developmental outcomes at 36 months. *PloS One, 12*, e0177344.

Cao, C., Rijlaarsdam, J., van der Voort, A., Ji, L., Zhang, W., & Bakermans-Kranenburg, M. J. (2018). Associations between dopamine D2 receptor (DRD2) gene, maternal positive parenting and trajectories of depressive symptoms from early to mid-adolescence. *Journal of Abnormal Child Psychology, 46*, 365–379.

Cao, Y., Lin, X., Chen, L., Ji, L., & Zhang, W. (2018). The catechol-O-methyltransferase and dopamine transporter genes moderated the impact of peer relationships on adolescent depressive symptoms: A gene–gene–environment study. *Journal of Youth and Adolescence, 47*, 2468–2480.

Chen, X., Bian, Y., Xin, T., Wang, L., & Silbereisen, R. K. (2010). Perceived social change and childrearing attitudes in China. *European Psychologist, 15*, 260–270.

Chen, J., Li, X., & McGue, M. (2013). The interacting effect of the BDNF Val66Met polymorphism and stressful life events on adolescent depression is not an artifact of gene-environment correlation: Evidence from a longitudinal twin study. *Journal of Child Psychology and Psychiatry, 54*, 1066–1073.

Christ, C. C., Schwartz, J. A., Stoltenberg, S. F., Brauer, J. R., & Savolainen, J. (2018). The effect of MAOA and stress sensitivity on crime and delinquency: A replication study. *Journal of Contemporary Criminal Justice, 34*, 336–353.

Cole, D. A., Tram, J. M., Martin, J. M., Hoffman, K. B., Ruiz, M. D., Jacquez, F. M., & Maschman, T. L. (2002). Individual differences in the emergence of

depressive symptoms in children and adolescents: A longitudinal investigation of parent and child reports. *Journal of Abnormal Psychology, 111*, 156–165.

Coley, R. L., Sims, J., & Carrano, J. (2017). Environmental risks outweigh dopaminergic genetic risks for alcohol use and abuse from adolescence through early adulthood. *Drug and Alcohol Dependence, 175*, 106–118.

Costa, A., Riedel, M., Müller, U., Möller, H. J., & Ettinger, U. (2011). Relationship between SLC6A3 genotype and striatal dopamine transporter availability: A meta-analysis of human single photon emission computed tomography studies. *Synapse, 65*, 998–1005.

Dallaire, D. H., Pineda, A. Q., Cole, D. A., Ciesla, J. A., Jacquez, F., LaGrange, B., & Bruce, A. E. (2006). Relation of positive and negative parenting to children' s depressive symptoms. *Journal of Clinical Child & Adolescent Psychology, 35*, 313–322.

Dalton, E. D., Hammen, C. L., Najman, J. M., & Brennan, P. A. (2014). Genetic susceptibility to family environment: BDNF Val66met and 5-HTTLPR influence depressive symptoms. *Journal of Family Psychology, 28*, 947–956.

Davies, P., Cicchetti, D., & Hentges, R. F. (2015). Maternal unresponsiveness and child disruptive problems: The interplay of uninhibited temperament and dopamine transporter genes. *Child Development, 86*, 63–79.

Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., ···Sher, K. J. (2015). Candidate gene-environment interaction research: Reflections and recommendations. *Perspectives on Psychological Science, 10*, 37–59.

Doehring, A., Kirchhof, A., & Lötsch, J. (2009). Genetic diagnostics of functional variants of the human dopamine D2 receptor gene. *Psychiatric Genetics, 19*, 259–268.

Duncan, L. E., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry, 168*, 1041–1049.

Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry, 64*, 327–337.

Dunn, E. C., Uddin, M., Subramanian, S. V., Smoller, J. W., Galea, S., & Koenen, K. C. (2011). Research review: Gene-environment interaction research in youth depression –a systematic review with recommendations for future research. *Journal of Child Psychology and Psychiatry, 52*, 1223–1238.

Evans, M. G. (1985). A Monte Carlo study of the effects of correlated method variance in moderated multiple regression analysis. *Organizational Behavior and Human Decision Processes, 36*, 305–323.

Ferro, M. A., Gorter, J. W., & Boyle, M. H. (2015). Trajectories of depressive symptoms during the transition to young adulthood: The role of chronic illness.

Journal of Affective Disorders, 174, 594–601.

Giros, B., Jaber, M., Jones, S. R., Wightman, R. M., & Caron, M. G. (1996). Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature, 379*, 606–612.

Hamza, C. A., & Willoughby, T. (2011). Perceived parental monitoring, adolescent disclosure, and adolescent depressive symptoms: A longitudinal examination. *Journal of Youth and Adolescence, 40*, 902–915.

Heinz, A., Goldman, D., Jones, D. W., Palmour, R., Hommer, D., Gorey, J. G., ···Weinberger, D. R. (2000). Genotype influences in vivo dopamine transporter availability in human striatum. *Neuropsychopharmacology, 22*, 133–139.

Kim, S. H., Yoon, H., Kim, H., & Hamann, S. (2015). Individual differences in sensitivity to reward and punishment and neural activity during reward and avoidance learning. *Social Cognitive and Affective Neuroscience, 10*, 1219–1227.

Kovacs, M. (1992). *Children' s depression inventory (CDI) manual*. Toronto, Canada: Multi-Health Systems Inc.

Lee, S. G., Joo, Y., Kim, B., Chung, S., Kim, H. L., Lee, I., ···Song, K. (2005). Association of Ala72Ser polymorphism with COMT enzyme activity and the risk of schizophrenia in Koreans. *Human Genetics, 116*, 319–328.

Lewis, D. A., Melchitzky, D. S., Sesack, S. R., Whitehead, R. E., & Sampson, A. (2001). Dopamine transporter immunoreactivity in monkey cerebral cortex: Regional, laminar, and ultrastructural localization. *Journal of Comparative Neurology, 432*, 119–136.

Lin, C. H., Chaudhuri, K. R., Fan, J. Y., Ko, C. I., Rizos, A., Chang, C. W., ···Wu, Y. R. (2017). Depression and catechol-O-methyltransferase (COMT) genetic variants are associated with pain in Parkinson' s disease. *Scientific Reports, 7*, 6306.

Luebbe, A. M., & Bell, D. J. (2014). Positive and negative family emotional climate differentially predict youth anxiety and depression via distinct affective pathways. *Journal of Abnormal Child Psychology, 42*, 897–911.

Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., ···Cho, J. H. (2009). Finding the missing heritability of complex diseases. *Nature, 461*, 747–753.

Matsumoto, M., Weickert, C. S., Beltaifa, S., Kolachana, B., Chen, J., Hyde, T. M., ···Kleinman, J. E. (2003). Catechol O-methyltransferase (COMT) mRNA expression in the dorsolateral prefrontal cortex of patients with schizophrenia. *Neuropsychopharmacology, 28*, 1521–1527.

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin, 110*, 406–425.

Natsuaki, M. N., Biehl, M. C., & Ge, X. (2009). Trajectories of depressed mood from early adolescence to young adulthood: The effects of pubertal timing and adolescent dating. *Journal of Research on Adolescence, 19*, 47–74.

Nikolova, Y. S., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2011). Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. *Neuropsychopharmacology, 36*, 1940–1947.

Nivard, M. G., Dolan, C. V., Kendler, K. S., Kan, K. J., Willemsen, G., Van Beijsterveldt, C. E. M., ···Middeldorp, C. M. (2015). Stability in symptoms of anxiety and depression as a function of genotype and environment: A longitudinal twin study from ages 3 to 63 years. *Psychological Medicine, 45*, 1039–1049.

Noble, E. P., Gottschalk, L. A., Fallon, J. H., Ritchie, T. L., & Wu, J. C. (1997). D2 dopamine receptor polymorphism and brain regional glucose metabolism. *American Journal of Medical Genetics, 74*, 162–166.

Olino, T. M., McMakin, D. L., Nicely, T. A., Forbes, E. E., Dahl, R. E., & Silk, J. S. (2016). Maternal depression, parenting, and youth depressive symptoms: Mediation and moderation in a short-term longitudinal study. *Journal of Clinical Child & Adolescent Psychology, 45*, 279–290.

Opmeer, E. M., Kortekaas, R., & Aleman, A. (2010). Depression and the role of genes involved in dopamine metabolism and signalling. *Progress in Neurobiology, 92*, 112–133.

Pearson-Fuhrhop, K. M., Dunn, E. C., Mortero, S., Devan, W. J., Falcone, G. J., Lee, P., ···Rosand, J. (2014). Dopamine genetic risk score predicts depressive symptoms in healthy adults and adults with depression. *PLoS One, 9*, e93772.

Petersen, I. T., Bates, J. E., Goodnight, J. A., Dodge, K. A., Lansford, J. E., Pettit, G. S., ···Dick, D. M. (2012). Interaction between serotonin transporter polymorphism (5-HTTLPR) and stressful life events in adolescents' trajectories of anxious/depressed symptoms. *Developmental Psychology, 48*, 1463–1475.

Peyrot, W. J., Milaneschi, Y., Abdellaoui, A., Sullivan, P. F., Hottenga, J. J., Boomsma, D. I., & Penninx, B. W. (2014). Effect of polygenic risk scores on depression in childhood trauma. *The British Journal of Psychiatry, 205*, 113–119.

Pinsonneault, J. K., Han, D. D., Burdick, K. E., Kataki, M., Bertolino, A., Malhotra, A. K., ···Sadee, W. (2011). Dopamine transporter gene variant affecting expression in human brain is associated with bipolar disorder. *Neuropsychopharmacology, 36*, 1644–1655.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2001). *Behavior Genetics*. New York: W. H. Freeman.

Quach, A. S., Epstein, N. B., Riley, P. J., Falconier, M. K., & Fang, X. (2015). Effects of parental warmth and academic pressure on anxiety and depression

symptoms in Chinese adolescents. *Journal of Child and Family Studies, 24*, 106–116.

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis-stress: Recommendations for evaluating interaction effects. *Development and Psychopathology, 24*, 389–409.

Smokowski, P. R., Bacallao, M. L., Cotter, K. L., & Evans, C. B. (2015). The effects of positive and negative parenting practices on adolescent mental health outcomes in a multicultural sample of rural youth. *Child Psychiatry & Human Development, 46*, 333–345.

Stocker, C. M., Masarik, A. S., Widaman, K. F., Reeb, B. T., Boardman, J. D., Smolen, A., ···Conger, K. J. (2017). Parenting and adolescents' psychological adjustment: Longitudinal moderation by adolescents' genetic sensitivity. *Development and Psychopathology, 29*, 1289–1303.

Vrshek-Schallhorn, S., Stroud, C. B., Mineka, S., Zinbarg, R. E., Adam, E. K., Redei, E. E., ···Craske, M. G. (2015). Additive genetic risk from five serotonin system polymorphisms interacts with interpersonal stress to predict depression. *Journal of Abnormal Psychology, 124*, 776–790.

Wang, C., Xia, Y., Li, W., Wilson, S. M., Bush, K., & Peterson, G. (2016). Parenting behaviors, adolescent depressive symptoms, and problem behavior: The role of self-esteem and school adjustment difficulties among Chinese adolescents. *Journal of Family Issues, 37*, 520–542.

Widaman, K. F., Helm, J. L., Castro-Schilo, L., Pluess, M., Stallings, M. C., & Belsky, J. (2012). Distinguishing ordinal and disordinal interactions. *Psychological Methods, 17*, 615–622.

Xia, L., & Yao, S. (2015). The involvement of genes in adolescent depression: A systematic review. *Frontiers in Behavioral Neuroscience, 9*, 329.

Xing, Q., Qian, X., Li, H., Wong, S., Wu, S., Feng, G., ···Gao, J. (2007). The relationship between the therapeutic response to risperidone and the dopamine D2 receptor polymorphism in Chinese schizophrenia patients. *International Journal of Neuropsychopharmacology, 10*, 631–637.

Zhang, J. P., & Malhotra, A. K. (2011). Pharmacogenetics and antipsychotics: Therapeutic efficacy and side effects prediction. *Expert Opinion on Drug Metabolism & Toxicology, 7*, 9-37.

Zhang, W., Cao, Y., Wang, M., Ji, L., Chen, L., & Deater-Deckard, K. (2015). The dopamine D2 receptor Polymorphism (DRD2 TaqIA) interacts with maternal parenting in predicting early adolescent depressive symptoms: Evidence of differential susceptibility and age differences. *Journal of Youth and Adolescence, 44*, 1428–1440.

Cao, Y., Wang, M., Cao, C., Ji, L., & Zhang, W. (2017). The interaction between dopamine D2 receptor gene TaqIA polymorphism and peer victimization on early adolescent depression. *Acta Psychologica Sinica, 49*, 28–39.

Wang, M. P. (2015). Theory models on gene-environment interaction. *Advances in Psychological Science, 23*, 1852–1858.

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[1] **Linear gene effect:** Genetic coding schemes affect genetic research results (Aliev, Latendresse, Bacanu, Neale, & Dick, 2014). To date, genetic studies may use dominant coding (0 = no risk alleles; 1 = carries 1 or 2 risk alleles), recessive coding (0 = carries 0 or 1 risk alleles; 1 = carries 2 risk alleles), or linear coding (0 = no risk alleles; 1 = carries 1 risk allele; 2 = carries 2 risk alleles). Multilocus genetic risk research typically uses linear coding while ignoring whether genetic function follows linear patterns, making it necessary to test linear effects of different genotypes.

[2] **Equal gene effect:** Multilocus genetic risk research typically sums effects of multiple genes but cannot exclude situations where a single gene with extremely large effects dominates the polygenic effect. Additionally, ignoring different gene functions may result in similar genes being coded in opposite directions, causing cancellation of polygenic effects. Therefore, it is necessary to test the equivalence of effect sizes and directions for multilocus genetic coding.

Note: Figure translations are in progress. See original paper for figures.