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Gene x responsive parenting interactions in social development: Characterizing heterogeneity in autism spectrum disorder

Barbara Caplan[1] | Jan Blacher[2] | Abbey Eisenhower[3] | Bruce L. Baker[1] | Steve S. Lee[1]

[1]Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA

[2]Department of Education, University of California, Riverside, Riverside, CA, USA

[3]Department of Psychology, University of Massachusetts, Boston, Boston, MA, USA

Correspondence
Barbara Caplan, Department of Psychiatry, UC San Diego, San Diego, CA, USA.
Email: bcaplan@ucsd.edu

Present address
Barbara Caplan, Department of Psychiatry, UC San Diego, San Diego, CA, USA

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Abstract

Emerging research suggests that caregiving environments and genetic variants independently contribute to social functioning in children with typical development or autism spectrum disorder (ASD). However, biologically plausible interactive models and complimentary assessment of mechanisms are needed to: (a) explain considerable social heterogeneity, (b) resolve inconsistencies in the literature, and (c) develop and select optimal treatments based on individual differences. This study examined the role of child genotypes and responsive parenting in the social development of 104 children with ASD (ages 4–7 years). We utilized a longitudinal, multi-informant design and structural equation models to evaluate: (a) the additive and interactive effects of biologically plausible candidate genes (5-HTTLPR, OXTR, DRD4) and responsive parenting in predicting prospective social development in ASD across three time points spanning 1.5 years, and (b) whether child emotion regulation mediated observed gene x environment interactions (GxEs). Responsive parenting positively predicted prospective change in child social skills; these associations were moderated by 5-HTTLPR and DRD4 in teacher-report models, and DRD4 in parent-report models. No GxE effects were found for OXTR. Emotion regulation did not significantly mediate the GxEs involving 5-HTTLPR and DRD4. Acknowledging the complexities of GxE research, implications for future research, and targeted intervention efforts are discussed.

KEYWORDS
autism spectrum disorder, gene–environment interaction, parenting, social development

1 | INTRODUCTION

Social skills are tools to build, maintain, and improve the quality of interpersonal relationships, and are essential for successful academic, vocational, and emotional development (Denham, 2006). Social skills develop substantially during the early school years, as more sophisticated cognitive, perspective taking, and regulation skills emerge (Racz et al., 2017). However, there are vast individual differences in trajectories of social skills development, with those with poorer trajectories experiencing risk for poor outcomes in adolescence and adulthood (e.g., Bornstein et al., 2010). This is particularly true for children with autism spectrum disorder (ASD) who exhibit core deficits in social communication skills including eye contact and reciprocity (Lord & Bishop, 2015), yet the degree of early social impairments is predictive of downstream functioning in relational, occupational, and social–emotional domains (e.g., Caplan et al., 2016; White & Roberson-Nay, 2009). Furthermore, ASD is characterized by considerable heterogeneity in social functioning and long-term outcomes (Masi et al., 2017), making this an ideal population in which to identify complex processes contributing to individual differences in early social development. The present study takes

a biopsychosocial approach to assess determinants of heterogeneous social skills development in ASD.

1.1 | Genetic and environmental influences on social development in ASD

Both genetic and environmental factors play a role in the social development of children with and without ASD. Heritability rates for ASD vary according to study methodology but tend to be moderate to high (Hallmayer et al., 2011; Sandin et al., 2017; Taylor et al., 2020), with a substantial minority of variance attributable to shared and nonshared environmental factors including social environments (Sandin et al., 2017). Genetic influences on ASD are likely diverse, spanning common disease/common variant modes as well as rare variants (Jeste & Geschwind, 2014). Extant genetics studies, though promising, are limited by reliance on dichotomous phenotyping of continuous traits and the lack of consideration of relevant environmental influences and gene–environment interactions (GxEs), which serve to systematically reduce power and obstruct the ability to assess contributors to continuous and developmental phenotypes in complex conditions such as ASD. The present study builds on previous genetics and behavioral approaches to understanding heterogeneous social development in ASD by assessing the role of biologically plausible interactions between socially relevant parenting behavior and individual child genetics.

1.1.1 | Responsive parenting and social development

While parenting has long been refuted as a *cause* of ASD (see Fombonne, 2003), individual differences in parenting behavior nonetheless inform the social development of children with ASD. Responsive parenting is an ideal social context in which to explore the proposed GxEs, given its emphasized role in attachment and developmental theories in relation to social development (Cassidy & Shaver, 2016), as well as predictive relationships with social and developmental outcomes in children with or without developmental risk (Mahoney & Nam, 2011). The key feature of responsive parenting is that the parent's behaviors follow the child's current focus of attention, with the parent responding in a manner consistent with ongoing child activity (Mahoney & Nam, 2011). For children with typical development, responsive parenting is consistently linked to positive outcomes across social, language, and cognitive domains (e.g., Landry et al., 2006). Responsive parenting may be of even greater importance for children with ASD, who provide fewer communicative leads for their caregivers to follow (Warren & Brady, 2007). In line with the transactional model of development (Sameroff, 2009), children with or at-risk for ASD whom demonstrate relatively limited social orienting and engagement skills may be at-risk for eliciting fewer responsive behaviors from their parents (e.g., Schwichtenberg et al., 2019). Over time, this may result in maladaptive transactions between parenting behavior and child social communication skills (Rice & Warren, 2004). Yet within ASD, more responsive parenting has been linked to positive trajectories in terms of communication and social skills (Siller & Sigman, 2008), including in the current sample of children (Caplan, Blacher & Eisenhower, 2019). Further inquiry is needed to understand why individual children with ASD vary in their response to responsive parenting interventions (e.g., see Carter et al., 2011), including biologically driven sensitivities to social environments.

1.1.2 | Gene–environment interactions in social development

Developmental theories increasingly recognize that development arises from the complex interplay of internal and external processes (Calkins et al., 2013). Indeed, across human and non-human animal models, parenting behavior biologically interacts with specific genes to produce social phenotypes (Meaney, 2010). Assessment of GxEs has enhanced our understanding of the behavioral development of children across a spectrum of disruptive behavior (e.g., Tung & Lee, 2017) to prosocial behavior (e.g., Caplan, Morgan, et al., 2019). Nearly unexplored in ASD, examination of GxEs may resolve inconsistencies across genetics and behavioral research and characterize sources of heterogeneity for this population. However, the first few decades of GxE research has also received scrutiny for issues of false positives and publication bias (Duncan & Keller, 2011), which call to question the reproducibility of many GxE findings. Thus, it is important moving forward as a science that we acknowledge the limitations of this line of research and interpret GxE findings with caution until supported with replication in independent samples.

Developmental theorists posit two primary models for understanding the nature of GxE. The longstanding diathesis-stress (aka dual risk) model posits that certain biological-driven characteristics (e.g., genotype, temperament) predispose individuals to be more vulnerable in the context of negative or harsh environments (Monroe & Simons, 1991). However, many studies assuming a diathesis-stress process fail to consider the role of positive as well as negative environments in GxE. Taking an evolutionary perspective, the differential susceptibility hypothesis theorizes that the same biological markers may actually confer environmental susceptibility "for better and for worse," rather than vulnerability to risk alone (Pluess & Belsky, 2010). The present study tests these two competing models of GxE for three biologically plausible candidate genes: the serotonin transporter (5-HTTLPR), oxytocin receptor gene (OXTR), and dopamine receptor (DRD4).

5-HTTLPR, OXTR, and DRD4

Functional polymorphism from candidate genes of 5-HTTLPR (functional polymorphisms rs4795541 and rs2553), OXTR [single nucleotide polymorphisms (SNPs) rs535676a, rs2254298,

rs237887, rs7632287], and DRD4 (48 base pair variable tandem repeated located on 11p15.5 on exon 3) were selected for examination of GxE given their: (a) role in neural networks related to the salience of social environments (i.e., "social salience"), (b) relationship to social and ASD-related phenotypes, and (c) preliminary evidence for GxE of relevant social phenotypes. In terms of neural mechanisms, 5-HTTLPR has been linked to corticolimbic system functioning. 5-HTTLPR is comprised of short (S) and long (L) alleles, with the SS genotype linked to differential activity in neural systems relevant for social cognition and emotional salience as compared to the SL/LL genotypes (e.g., Drabant et al., 2012). In turn, the SS genotype has been linked to behavioral phenotypes relevant for social learning and adaptive social functioning (e.g., Gyurak et al., 2013). Low-expressing variants of OXTR SNPs are likewise associated with social phenotypes and overly transmitted in autism (Meyer-Lindenberg & Tost, 2012). These social phenotypes are mediated through neural endophenotypes including limbic circuitry involving the amygdala, cingulate gyrus, and hypothalamus (Meyer-Lindenberg & Tost, 2012). In contrast, DRD4 contains 2–11 repeats, with the 7-repeat allele (7+) associated with less efficient dopamine binding and functioning of neural circuits implicated in social reward salience (Camara et al., 2010).

Together, these polymorphisms show preliminary evidence of GxE on social and behavioral phenotypes. 5-HTTLPR has been found to moderate the influence of caregiving quality on relevant social phenotypes (e.g., Caplan, Morgan, et al., 2019; Tung & Lee, 2017). OXTR has been proposed as a marker of social salience to positive and negative environmental stimuli (Tabak, 2013). Preliminary evidence of GxE suggests that OXTR influences important social–emotional outcomes via interactions with early social environments, including maternal cognitive stimulation (Wade et al., 2015) and child maltreatment (McQuaid et al., 2013). DRD4 has been well studied as a marker of GxE in non-ASD populations, with the 7+ allele suggested as a marker of susceptibility to caregiving through both observational and experimental designs (e.g., van Ijzendoorn & Bakermans-Kranenburg, 2015). Thus, as suggested by previous research, the present study seeks to test whether the above polymorphisms serve as markers of differential susceptibility (as opposed to diathesis stress) to parenting behavior as it informs social development in ASD, as well as identify mechanisms of these GxEs.

1.2 | Emotion regulation as a mechanism for GxE in ASD

Examination of mechanisms of differential predictions of child outcomes from measured genotypes and the environment (i.e., GxE) allows for greater scientific precision and opportunities for clinical translation. Emotion regulation is a suitable candidate for mediation of proposed GxEs, as it is fundamental to positive social functioning (Gross, 2014) and is associated with core features and behavioral phenotypes in ASD (Samson et al., 2014). Definitions of emotion regulation often emphasize the dynamic interplay of internal and external processes involved in initiating and modulating the occurrence, intensity, and expression of emotions (Morris et al., 2017) Thus, while caregiving is central to regulatory development (Morris et al., 2017), it may interface with child biology to inform regulatory development. Specifically, 5-HTTLPR and OXTR are implicated in neurobiological functioning essential for emotion regulation (Meyer-Lindenberg & Tost, 2012) and show preliminary evidence for GxE in regulatory development (e.g., Noroña et al., 2017). In the present study, we will examine whether the associations between GxEs and child social development in ASD are mediated by child emotion regulation.

1.3 | The present study

The present study sought to characterize novel sources of heterogeneous social development in ASD. We tested competing models of GxE with biologically plausible candidate genes for environmental sensitivity and social functioning. We aimed to evaluate: (a) the additive or interactive effects of observed responsive parenting and child genotype (5-HTTLPR, DRD4, OXTR) in predicting trajectories of social skills for young children with ASD, and (b) child emotion regulation as a mediator of GxEs in predicting trajectories of social skills over time (i.e., mediated moderation). Building on previous GxE designs, the present study utilized multi-informant assessment including both parents and teachers, as is recommended to sensitively capture differences in social skills as they present across settings (home, school; Luiselli et al., 2005). Furthermore, the rigorous assessment of both parenting behavior (observational measurement) and child phenotype (repeated measures, multi-rater assessment) served to reduce measurement error and enhance predictive power of GxE relatively to traditional GxE study designs. We hypothesized that the genetic variants (5-HTTLPR, OXTR, DRD4) would interact with observed parenting in a differential susceptibility manner, such that children with the low-expressing variants will be more strongly influenced by both low and high levels' responsive parenting. We anticipated that child emotion regulation would mediate GxEs on social development for 5-HTTLPR and OXTR only.

2 | METHODS

2.1 | Participants

Participants were sampled from the pool of families who originally participated in the Smooth Sailing Study, a longitudinal study of children with ASD and their families (see Llanes et al., 2018). Families of children aged 4–7 years were recruited through in-print and online recruitment flyers that were distributed to local service agencies for individuals with developmental disabilities and local preschools. Families were recruited from the Greater Boston area of Massachusetts (n = 57) as well as Southern California (n = 105).

Following completion of informed consent procedures, parent–child dyads participated in four visits for the initial project: an eligibility visit (EV), a Time 1 visit (in the fall of the school year), a Time 2 visit (in the spring), and a Time 3 visit (in the following winter; approximately 15–18 months following Time 1). Eligible children were enrolled in school, had a documented ASD diagnosis which was confirmed via the autism diagnostic observation schedule (ADOS), and an IQ of 50 or higher. At the Time 1 visit, parents and children participated in a 10-min free-play interaction. Parents and teachers provided ratings of child social skills at Times 1, 2, and 3.

For the current study, families who participated in the original study including the observed parent–child interactions at Time 1 and provided written consent to be contacted in the future (N = 176) were invited to participate in a follow-up DNA collection procedure 3–5 years after their original participation, when children were 7–12 years old. Families were asked to provide saliva samples for the participating child and parent using Oragene DNA Collection Kits (OGR-500). Families were given the option to participate via mail or in person, with the majority participating via mail. Research staff obtained verbal consent over the phone and families were mailed consent forms to provide written consent. Research staff also provided verbal and written instructions for collection procedures. Families were provided with DNA collection kits and (when applicable) prepaid envelopes to mail their samples back to the research center. When children had difficulty using the traditional collection kit (OG-500), they were provided with a swab collection method (OG-575; ORAcollect for Pediatrics; n = 6). All procedures were reviewed and approved by the Institutional Review Board (IRB) of the sponsor institution. Families were provided an honorarium ($30 gift card) for participation in the DNA procedures.

Families who provided samples for both the child and biological parent (N = 104) were included in the study. Of the original 176 families, 28 were not able to be reached, 19 declined to participate, and 18 agreed to participate via mail but failed to return the kits to the laboratory. Another three families withdrew following difficulty using the traditional collection kit (OG-500) and opted not to pursue the swab collection alternative method offered; seven additional families provided child samples but were excluded from the study due to the participation of a non-biological caregiver. Compared to those who participated at Time 1 but did not complete the DNA follow-up study (n = 72), children who participated in the DNA follow-up were more likely to have higher IQs (mean IQ: 90.5 versus 84.1; t = −2.39, p < 0.05), and a greater proportion were female (25.0% versus 10.0%; χ^2 (1) = 6.60, p < 0.05). No significant differences between the two groups were found by child age, race, family income, and parent education. Table 1 reports demographic information for the present sample by 5-HTTLPR, OXTR, and DRD4 genotypes. No significant differences in child IQ or the demographic variables above were found by child genotype, with the exception of more OXTR minor ("A") alleles being associated greater ADOS autism severity. Participating caregivers were biological mothers (88.5%) or fathers (10.6%), with one biological grandmother (0.9%).

2.2 | Measures

2.2.1 | Autism diagnostic observation schedule

The ADOS is a clinician administered assessment of autism symptomology and is considered the gold standard diagnostic instrument for autism spectrum disorders. The ADOS demonstrates strong specificity and sensitivity and incorporates age- and language-specific modules (Lord et al., 2000). Ratings were determined using the revised ADOS algorithms (Gotham et al., 2008) that generate scores for Social Affect and Restrictive/Repetitive Behavior, consistent with the later released DSM 5 criteria for ASD and ADOS-2.

2.2.2 | Wechsler preschool and primary scale of intelligence-third edition

The Wechsler preschool and primary scale of intelligence-third edition (WPPSI-III) is a widely used assessment instrument of cognitive abilities in children aged 2 years 6 months to 7 years 3 months. The instrument yields IQ scores with a normative mean of 100 and a standard deviation of 15. The WPPSI-III demonstrates strong psychometric properties, including excellent internal consistency (0.86–0.97) and test–retest reliability (0.84–0.92; Wechsler, 2002). Three subtests were administered (Vocabulary, Matrix Reasoning, Picture Completion) from which a full-scale IQ score was estimated using Sattler's conversion tables (Sattler, 2008). The composite score from these subtests correlates strongly (r = 0.90) with the full-scale IQ in the normative sample (Sattler, 2008).

2.2.3 | Parent directiveness and interference-revised

Parent–child interactions were videotaped during the Time 1 laboratory-based assessment. Parents and children were provided with a standardized set of toys and asked to play together as they normally would at home for 10 min. Interactions were later coded for aspects of responsive parenting using the parent directiveness and interference-revised (PDI-R) coding system (Caplan, Morgan, et al., 2019). The PDI-R distinguishes between parent direction that is responsive to a child's needs or focus of attention (Supportive Directiveness) and that which redirects the child's ongoing behavior or focus of attention (Interference). Supportive Directiveness includes verbal (e.g., comments, questions) and nonverbal (e.g., demonstrations of play, giving of objects) parenting behavior that is used to supportively direct, shape, or guide child behavior in a manner consistent with ongoing child activity or interests. The PDI-R also rates non-directive aspects of responsive parenting (Supportive Engagement), including contingent responses to the child's ongoing activity (e.g., narrating the child's play, repeating child statements) and behaviors to support social engagement within ongoing child

TABLE 1 Demographics for overall sample and by child genotype (N = 104)

	Overall sample	5-HTTLPR			DRD4			OXTR A alleles[a]
	Mean (SD) or %	SS (n = 34)	SL/LL (n = 69)	t-test or χ^2	7+ (n = 34)	7- (n = 70)	t-test or χ^2	r or F
Child age	5.64 (1.0)	5.57 (0.9)	5.65 (1.1)	t = 0.37	5.90 (0.9)	5.51 (1.1)	t = −1.80†	r = 0.03
Child IQ	90.3 (17.4)	91.9 (17.3)	89.6 (17.3)	t = −0.64	90.0 (17.2)	90.5 (17.6)	t = 0.13	r = −0.12
ADOS-2 Severity Score	7.4 (1.7)	7.0 (1.5)	7.6 (1.5)	t = 1.84†	7.4 (1.7)	7.4 (1.7)	t = −0.06	r = 0.23*
Child sex (% male)	75.7%	76.5%	75.4%	χ^2 = 0.02	70.6%	78.6%	χ^2 = 0.80	t = −0.62
Chile race	–	–	–	χ^2 = 6.39	–	–	χ^2 = 5.15	F = 1.22
White (%)	52.9%	38.2%	59.4%	–	44.1%	57.1%	–	–
Latinx (%)	11.5%	11.8%	11.6%	–	14.7%	10.0%	–	–
Black/African American (%)	5.8%	5.9%	5.8%	–	11.8%	2.9%	–	–
Asian (%)	5.8%	11.8%	2.9%	–	2.9%	7.1%	–	–
Bi-/multi-racial (%)	24.0%	32.4%	20.3%	–	26.8%	22.9%	–	–
Family household income (% > $65,000)	57.3%	55.9%	58.0%	χ^2 = 0.04	58.6%	55.9%	χ^2 = 0.07	t = −1.14
Parent education[b] (% BA or above)	59.6%	64.7%	56.5%	χ^2 = 0.63	55.9%	61.4%	χ^2 = 0.29	t = 0.03
Parent genotype[c] (% with low-expressing genotype)	–	50.0%	14.5%	χ^2 = 14.85***	79.4%	17.1%	χ^2 = 38.86***	r = 0.39***
School setting (% public school)	84.5%	88.5%	82.8%	χ^2 = 0.45	96.3%	79.3%	χ^2 = 4.10*	t = −1.09
Classroom setting (% special education[d])	41.0%	50.0%	36.8%	χ^2 = 1.28	48.1%	36.8%	χ^2 = 0.97	t = −0.73

S, short allele; L, long allele; 7+, Presence of one or more 7 repeat alleles; 7-, no presence of 7 repeat allele.

[a]A alleles represent the additive number of A alleles observed across OXTR SNPs rs53576, rs2254298, rs237887, rs7632287 (mean = 2.51, standard deviation = 1.06).

[b]Parent education: Assessed as percentage of parents with a bachelor's degree or more education.

[c]Parent genotype: Assessed within each genotype as: 5-HTTLPR (% SS), DRD4 (% with one or more 7 repeats), OXTR (number of a alleles across four SNPs reported above).

[d]Special education: child reported to be in special education setting >50% of time.

*p < 0.05,

**p > 0.01,

***p < 0.001,

$^{\dagger}p$ < 0.10.

interests (e.g., facial expressions or interjections in response to the child's play). Supportive Directiveness, Interference, and Supportive Engagement were rated on a 1 (minimal) to 5 (high) Likert scale. These global ratings take into account the frequency and quality of parenting behavior (e.g., appropriateness of the pacing and complexity of parent statements relative to the child's developmental level). See Caplan, Morgan, et al. (2019) for further description of the coding system. Pairs of coders met weekly with the first author to train to initial benchmarks of reliability (70% exact, 95% within one code), and then participated in reliability checks for 20% of ongoing videos. Raters demonstrated adequate to good levels of interrater reliability, with the following intraclass correlations (ICCs) observed: Supportive Directiveness (0.73), Interference (0.82), Supportive Engagement (0.63).

2.2.4 | Social skills improvement system

The social skills improvement system (SSiS) is a standardized, norm-referenced assessment of social skills for children aged 3–18 years

(Gresham & Elliott, 2008). The SSiS utilizes parent (SSiS-P) and teacher (SSiS-T) ratings of the frequency of a variety of child social behaviors on a 3-point scale from 0 (never) to 2 (very often). Both versions of the SSiS yield a Social Skills Total standard score with a mean of 100 and a standard deviation of 15. The SSiS Total scores demonstrate high internal consistency (α = 0.96–0.97), test–retest reliability (r = 0.82–0.84), and convergent validity with the Vineland Adaptive Behavior Scale, 2nd edition and the Behavioral Assessment System, 2nd edition (see Gresham & Elliott, 2008). The SSiS has been widely used to assess social skills in children with ASD (e.g., Kasari et al., 2016) and in the current sample, demonstrates adequate convergent validity with the Social Responsiveness Scale (Constantino et al., 2003; r = −0.58). The SSiS-P and SSiS-T were collected at Times 1, 2, and 3.

2.2.5 | Emotion regulation checklist

The emotion regulation checklist (ERC) is a parent report measure of a child's methods for managing emotional reactions (Shields & Cicchetti, 1997). The 24 items of the ERC yield scores for two subscales. The Negativity/Lability scale assesses a child's lack of flexibility, rapid mood changes, and dysregulation of affect. The Emotion Regulation scale measures a child's overall mood and ability to label and express appropriate levels of positive and negative emotion in social contexts. The ERC has been successfully used with children with ASD, demonstrating high reliability (α = 0.84) and predictive validity (Berkovits et al., 2017). For the current study, the Emotion Regulation and Negatively/Lability scales of the ERC at Times 2 and 3 were assessed as indicators of one latent "emotion regulation" variable.

2.3 | Genotyping

DNA saliva samples were extracted using Oragene DNA collection kits or ORAcollect for Pediatric kits (Ottawa, ON, Canada). All SNP genotyping (OXTR) and repeat length sequencing (DRD4, 5-HTTLPR) were performed by Laragen, Inc. (Culver City, CA). See Appendix 1 for detailed description of genotyping procedures and observed allele frequencies. 5-HTTLPR S and L alleles were determined using standard primers (Hu et al., 2006), including rs25531. In concordance with previous studies (Cervilla et al., 2007; Noroña et al., 2017), we compared individuals with two-low expressing alleles (i.e., SS, SL_G, L_GL_G; annotated as "SS"; n = 34) with others (SL/LL; n = 69). OXTR SNPs (rs53576A, rs2254298, rs237887, rs7632287) were selected due to their established relationships with social phenotypes and implicated neurobiology (Kumsta & Heinrichs, 2013) and implication in GxE (Brüne, 2012; Flasbeck et al., 2018). An additive model for OXTR was assessed, as additive allele risk for OXTR demonstrates predictive relationships to key neural networks of reward processing in youth with or without ASD (Hernandez et al., 2017). For DRD4 analyses, individuals with one or more 7-repeat sequences (7+; n = 34) were compared to those without a 7-repeat sequence (7-; n = 70).

All genotypes were in Hardy–Weinberg equilibrium (p = 0.08–0.77). Child race and genotype were unrelated in the sample (see Table 1), minimizing concern for population stratification effects (Hutchison et al., 2004). Nevertheless, race was conservatively controlled in all analyses. Child genotypes for 5-HTTLPR, DRD4, and OXTR were unrelated to one another (p = 0.29–0.81).

2.4 | Data analytic plan

Structural equation models (SEM) were implemented in MPlus Version 8 (Muthén & Muthén, 2017) to examine the contributions of responsive parenting, genotype, and their interaction on child social skills. In all models, responsive parenting was assessed as a latent variable, with Supportive Directiveness and Supportive Engagement positively, and Interference negatively, loading onto the factor. Models were run separately by gene (5-HTTLPR, OXTR, DRD4), and by parent and teacher report of social skills, given the modest correlations between raters (r = 0.26–0.35). GxEs were modeled using a latent variable interaction approach; as latent variable interactions in MPlus do not yield traditional fit indicators, guidelines for testing progressive fit indices as recommended by Muthén and Asparouhov (2019) were followed. All SEMs yielded adequate model fit (see Table A1). Full information maximum likelihood (FIML) was used to estimate missing data.

Parent-report models utilized latent growth curve models (LGCMs) to assess the relationship of responsive parenting, genotype, or the latent GxE interaction with linear growth in social skills across three time points. As teachers changed between Time 2 and Time 3, an autoregressive model was utilized in lieu of an LGCM for the teacher-report models, assessing prediction to Time 2 and Time 3 social skills (controlling for ratings from the previous time point). Covariates were selected to control for theoretical or observed confounding relationships for responsive parenting (child sex, parent education; see Caplan, Morgan, et al., 2019) and child genetics (child race/ethnicity, parent genotype). Importantly, controlling for parent genotype allows for the inference of GxE relationships over and above the potential influence of gene–environment correlation (Knafo & Jaffee, 2013). Significant GxEs were probed using region of significance procedures (Preacher et al., 2006); simple slopes were also calculated using tools developed by Jeremy Dawson (Dawson, 2014).

To test our second hypothesis, mediated moderation was examined by assessing bootstrap confidence intervals of the indirect effect of parenting–gene interactions on social skills through emotion regulation utilizing Mplus code from Stride and colleagues (Stride et al., 2015). Such methods are considered superior to and more powerful than causal steps approaches (Hayes, 2009), and sufficiently test whether mediated moderation effects and direct effects significantly differ from 0. The data that support the findings of this study are available on request from the corresponding

author. The data are not publicly available due to privacy or ethical restrictions.

3 | RESULTS

3.1 | Preliminary analyses

Table 2 reports the descriptive statistics and correlations for key study variables. Parent Supportive Directiveness was positively associated with teacher-reported social skills at Time 2 and Time 3, as well as parent-reported social skills at Time 3 at a trend level. Supportive Engagement was positively associated with teacher-reported social skills at Time 2 at a trend level, while Interference was negatively associated with teacher-reported social skills at Time 1 and, at a trend level, Time 3. Supportive Engagement and Interference were not significantly associated with parent-reported social skills for the overall sample.

Differences in key study variables (responsive parenting indices, teacher- and parent-reported social skills) were also assessed by child genotype. No differences in responsive parenting indices were found by 5-HTTLPR genotype (SS versus SL/LL; t = −1.21 to 0.85, p = 0.23–0.98) or DRD4 genotype (7 + versus 7-; t = 0.53–1.59, p = 0.13–0.60). Moreover, the additive OXTR genotype (i.e., number of A alleles across SNPs) was not associated with responsive parenting (r = 0.04–0.07, p = 0.42–0.71), limiting our concern regarding passive gene–environment correlation. No differences in teacher- nor parent-reported social skills were found for 5-HTTLPR (t = −0.85 to 1.49, p = 0.13–0.93) or DRD4 (t = −0.13 to 1.32, p = 0.19–0.91). The number of A alleles (OXTR) was negatively associated with teacher-reported social skills at Time 1 only (r = −0.23, p = 0.03).

3.2 | Gene–environment interactions

3.2.1 | Teacher-reported social skills

The first model examined GxE with 5-HTTLPR (see Table 3). Results yielded a significant GxE effect for predicting change to Time 3 child social skills, such that children with the 5-HTTLPR SS genotype demonstrated a positive predictive association between responsive parenting and Time 3 social skills (controlling for prior social skills; β = 0.43, p < 0.01), while those with the SL/LL genotypes did not (β = 0.02, p = 0.90; see Figure 1). Tests of regions of significance revealed a disordinal interaction, such that slopes between the SS and SL/LL groups significantly differed both at lower levels of responsive parenting (2.83 *SD* below the mean and below) and higher levels of responsive parenting (0.11 *SD* above the mean and above). Although the GxE term did not reach significance in predicting Time 2 social skills, examination of simple effects revealed that, similar to the Time 3 findings, responsive parenting positively predicted changes in social skills from Time 1 to Time 2 for children with the SS genotype (β = 0.24, p = 0.04), but not those with the SL/LL genotypes (β = 0.12, p = 0.16).

Models of GxE were also assessed for OXTR (see Table 3). OXTR x parenting interactions did not significantly predict changes in teacher-reported social skills to Time 2 nor Time 3. Significant main effects were found for responsive parenting, with higher responsive parenting predicting positive growth in social skills to Time 2 but not Time 3. Significant main effects were also found for parent genotype, with a greater number of parent A alleles associated with negative growth in child social skills to Time 2 but not Time 3.

Models assessing the role of DRD4 and DRD4 x responsive parenting interactions in predicting teacher-reported social skills are shown in Table 3. Models revealed a significant GxE predicting change

TABLE 2 Descriptive statistics and correlations for key study variables

Variable	Mean (SD)	1	2	3	4	5	6	7	8	9
1. Supp. Dir.	3.6 (0.9)	1								
2. Supp. Eng.	2.9 (0.9)	0.58***	1							
3. Interference	2.0 (0.9)	−0.54***	−0.28**	1						
4. SSiS-T (Time 1)	83.5 (16.6)	0.19†	0.17	−0.24*	1					
5. SSiS-T (Time 2)	86.1 (16.4)	0.26*	0.20†	−0.14	0.76***	1				
6. SSiS-T (Time 3)	87.5 (14.3)	0.27*	0.19	−0.21†	0.33*	0.39**	1			
7. SSiS-P (Time 1)	76.3 (15.3)	0.04	−0.02	−0.02	0.26*	0.31**	0.28*	1		
8. SSiS-P (Time 2)	74.9 (16.5)	0.17	0.01	−0.09	0.34**	0.35**	0.38**	0.80***	1	
9. SSiS-P (Time 3)	77.5 (16.9)	0.20†	0.16	−0.11	0.19†	0.42***	0.26*	0.67***	0.63***	1

Supp. Dir.: Supportive Direction. Supp. Eng. Supportive Engagement. Responsive parenting domains are reported on a 1–5 (high) Likert scale. SSiS-P: Social Skills Improvement System, Social Skills Total Standard Score, Parent report. SSiS-T: Social Skills Improvement System, Social Skills Total Standard Score, Teacher report.

*p < 0.05,

**p > 01,

***p < 0.001,

†p < 0.10.

TABLE 3 Structural equation model predicting changes in teacher-reported social skills to time 2 and time 3 (N= 101)

	5-HTTLPR[a]				OXTR				DRD4			
	B	*SE* (*B*)	Beta	*p*-value	*B*	*SE* (*B*)	Beta	*p*-value	*B*	*SE* (*B*)	Beta	*p*-value
(a) SSiS-T – Time 2												
SSiS-T – Time 1	**0.78*****	**0.08**	**0.76**	**<0.001**	**0.80*****	**0.08**	**0.77**	**<0.001**	**0.75*****	**0.09**	**0.74**	**<0.001**
Race 1[b]	0.00	9.07	0.00	1.00	3.64	6.16	0.05	0.55	2.11	7.33	0.03	0.77
Race 2[b]	−0.88	4.16	−0.01	0.83	1.02	4.95	0.01	0.84	7.03	4.79	0.08	0.14
Race 3[b]	0.94	4.14	0.02	0.82	2.60	3.65	0.05	0.48	2.16	3.72	0.04	0.56
Race 4[b]	4.93	3.10	0.13	0.11	**5.64***	**2.62**	**0.15**	**0.03**	**5.31***	**2.48**	**0.14**	**0.03**
Parent Education[c]	−0.82	3.69	−0.02	0.82	0.43	4.28	0.01	0.92	0.61	3.48	0.01	0.86
Sex: Female	3.63	2.99	0.09	0.23	2.54	2.57	0.07	0.32	4.39	2.88	0.11	0.13
Parent Genotype	−2.72	2.61	−0.07	0.30	**−2.70***	**1.22**	**−0.16**	**0.03**	2.68	2.77	0.01	0.33
Res. Parenting	2.10	1.55	0.12	0.16	**2.85***	**1.28**	**0.16**	**0.03**	1.66	1.45	0.09	0.25
Child Genotype	4.37	2.79	0.13	0.30	1.30	1.12	0.08	0.25	−3.97	3.12	−0.12	0.20
GxE	2.28	2.48	0.06	0.36	*−1.11*	*1.40*	*−0.07*	*0.43*	**5.51***	**2.68**	**0.15**	**0.03**
(b) SSiS-T – Time 3												
SSiS-T – Time 2	**0.26**	**0.11**	**0.29**	**0.02**	**0.32****	**0.10**	**0.36**	**0.002**	**0.33****	**0.11**	**0.37**	**0.004**
Race 1[a]	2.73	9.70	0.04	0.78	3.43	7.06	0.05	0.63	0.01	7.15	0.00	0.99
Race 2[a]	−5.64	5.76	−0.09	0.33	−10.09	8.70	−0.15	0.35	**−14.09**†	**8.09**	**−0.19**	**0.08**
Race 3[a]	1.75	3.64	0.04	0.63	1.95	5.92	0.04	0.74	2.31	3.77	0.05	0.54
Race 4	−6.94	5.12	−0.21	0.18	**−8.60***	**4.30**	**0.25**	**0.04**	−6.73	5.30	−0.20	0.20
Parent Education[c]	1.20	4.17	0.03	0.77	0.26	5.24	0.01	0.96	0.13	4.00	0.00	0.97
Sex: Female	−3.45	3.51	−0.10	0.33	−4.06	3.69	−0.12	0.27	−5.22	3.82	−0.15	0.17
Parent Genotype	1.69	3.22	0.10	0.60	2.32	1.96	0.16	0.24	−3.67	3.48	−0.12	0.29
Res. Parenting	0.25	2.10	0.02	0.90	1.21	2.08	0.08	0.56	**4.05***	**1.86**	**0.26**	**0.03**
Child Genotype	3.44	3.01	0.10	0.25	0.49	1.53	0.04	0.75	5.23	4.59	0.17	0.26
GxE	**6.60**	**2.32**	**0.20**	**0.004**	*−0.22*	*1.15*	*−0.02*	*0.85*	−6.22	4.57	0.13	0.17

Statistically significant results are bolded for emphasis. Italics reflect nonsignificant GxE terms ($p < 0.10$) that were dropped to examine main effects. Main effect coefficients represent the final model with GxE terms removed.

B, unstandardized coefficient; *SE*(*B*), standard error of unstandardized coefficient; β, standardized coefficient; GxE, Gene–environment interaction..

[a]$n = 100$.

[b]Race is effect coded.

[c]Mother education is assessed as the highest grade completed per mother report.

*$p < 0.05$,

**$p < 0.01$,

***$p < 0.001$,

†$p < 0.10$.

in child social skill to Time 2 (but not Time 3), such that children with the 7+ allele demonstrated a positive association between responsive parenting and change in child social skills ($\beta = 0.40$, $p < 0.01$), while those without the allele (7-) did not ($\beta = 0.09$, $p = 0.25$). Tests of regions of significance revealed an ordinal interaction, such that slopes between the two groups (7+ and 7-) significantly differed at low levels (0.49 *SD* below the mean and below) of responsive parenting only (see Figure 2). In predicting Time 3 social skills, only a main effect of responsive parenting was found, such that higher levels of responsive parenting were associated with positive change in social skills over time.

3.2.2 | Parent-reported social skills

Child genotype x responsive parenting interactions were also assessed via LGCM models of parent-reported social skills across Times 1, 2, and 3 (see Table 4). No significant 5-HTTLPR x responsive parenting interactions were found in predicting the intercept or slope of child social skills; these GxE terms were dropped from the model and main effects were assessed. Results indicated a nominal positive association of responsive parenting such that higher levels of responsive parenting were associated with marginally more positive growth in social skills. In addition, a trend-level association was

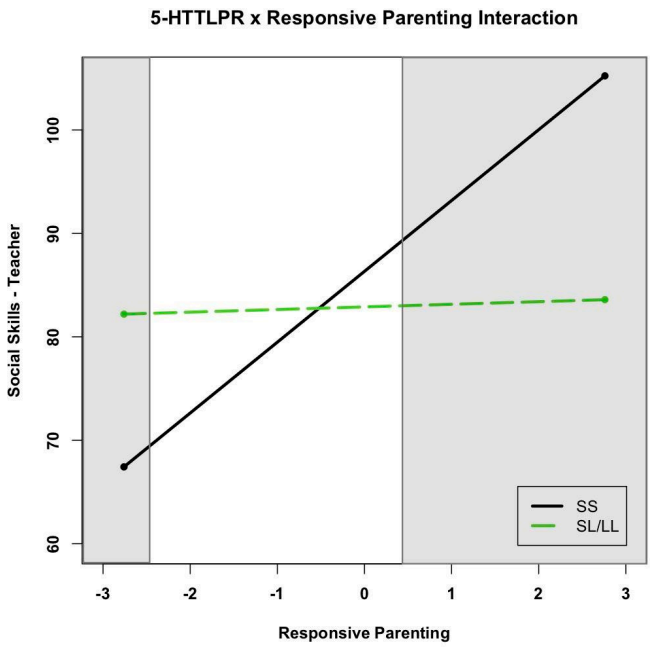

FIGURE 1 5-HTTLPR x responsive parenting interaction predicting teacher-rated social skills. Note: Depicted is the significant child 5-HTTLPR genotype x responsive parenting interaction in predicting teacher-reported social skills at Time 3, controlling for Time 2 social skills. Responsive parenting displayed in latent variable units (mean = 0, standard deviation = 0.917). Shaded areas depict regions in which slopes are significantly different by child genotype. Social skills – Teacher: Time 3 Social Skills Improvement System, Total Social Skills standard score, teacher-report

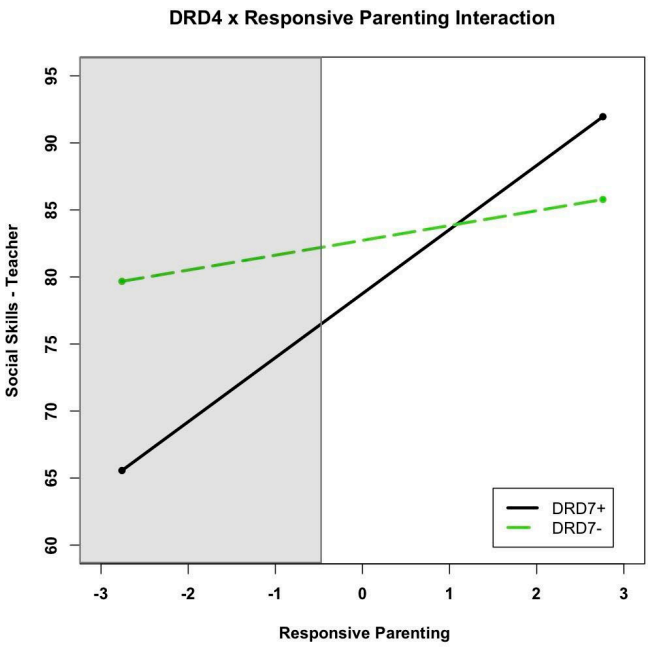

FIGURE 2 DRD4 x responsive parenting interaction predicting teacher-rated social skills. Note: Figure 2 displays the significant child DRD4 genotype x responsive parenting interaction in predicting teacher-reported social skills at Time 2, controlling for Time 1 social skills. Responsive parenting displayed in latent variable units (mean = 0, standard deviation = 0.917). Shaded area depicts region in which slopes are significantly different by child genotype. Social skills – Teacher: Time 2 Social Skills Improvement System, Total Social Skills standard score, teacher-report. DRD4 7+: Children with one or more 7 repeat alleles. DRD4 7-: Children with no 7 repeat alleles

found for child genotype, with the SS genotype associated with relatively poorer growth in social skills over time.

No significant OXTR x responsive parenting interactions were found in predicting the intercept or slope of parent-reported social skills (see Table 4). Child sex significantly predicted of initial social skills (boys > girls). Only responsive parenting significantly predicted growth in child social skills, controlling for child and parent OXTR genotype and other covariates.

DRD4 x responsive parenting interactions significantly predicted linear slope in social skills (see Table 4). The results revealed an unexpected direction of effect, such that responsive parenting positively predicted growth in parent-reported social skills for children with the 7- allele (β = 0.74, p < 0.01), but not the 7+ allele (β = −0.11, p = 0.62; see Figure 3). Slope tests yielded significant differences in slopes by genotype and high levels of responsive parenting (2 *SD* above the mean; t = −2.69, p < 0.01) and low levels of responsive parenting (2 *SD* below the mean; t = −2.68, p < 0.01), suggesting a disordinal interaction.

In summary, responsive parenting interacted with 5-HTTLPR and DRD4, but not OXTR, in predicting changes in teacher-reported social skills. In the 5-HTTLPR and DRD4 models, the low-expressing variants (SS of 5-HTTLPR and 7+ of DRD4) demonstrated stronger relationships with teacher-reported social skills growth, consistent with study hypotheses. However, in the models of parent-reported social skills, only DRD4 significantly interacted with responsive parenting to predict social skills growth. Here, the alternative variant than what was hypothesized (7-) demonstrated relationships between responsive parenting and social skills.

3.3 | Mediation by emotion regulation

Mediated moderation models were assessed for the significant GxEs found (i.e., those involving 5-HTTLPR and DRD4) to assess whether these interactions were mediated by emotion regulation. First, we assessed emotion regulation as a mediator of 5-HTTLPR x responsive parenting interactions. Results indicated no significant mediated moderation effect of emotion regulation (B = −1.02, p = 0.34; 95% CI: −3.14 to 1.09); the indirect effect of responsive parenting on social skills via emotion regulation was not significant for the SS group (B = −0.63, p = 0.42), nor the SL/LL group (B = 0.38, p = 0.49). Thus, contrary to hypotheses, emotion regulation did not surface as a significant mediator of the association between 5-HTTLPR x responsive parenting interaction and social skills growth. Results also indicated no significant mediated moderation effect of emotion

TABLE 4 Latent growth curve models (LCGMs) predicting parent-reported social skills from time 1 to time 3 (N = 104)

	5-HTTLPR[a]				OXTR				DRD4			
	B	*SE* (*B*)	Beta	*p*-value	*B*	*SE* (*B*)	Beta	*p*-value	*B*	*SE* (*B*)	Beta	*p*-value
(a) Intercept												
Race 1[a]	−8.75	6.30	−0.14	0.17	−8.87	6.28	−0.14	0.16	−9.36	6.82	−0.16	0.17
Race 2[a]	−5.80	6.49	−0.09	0.37	−8.14	6.73	−0.13	0.23	**−8.59**†	**4.81**	**−0.11**	**0.08**
Race 3[a]	−7.45	4.64	−0.16	0.11	**−8.59**†	**4.76**	**−0.18**	**0.07**	**−8.59***	**4.00**	**−0.18**	**0.03**
Race 4[a]	−3.75	3.54	−0.11	0.29	−4.51	3.51	−0.13	0.20	−5.43	3.30	−0.16	0.10
Parent Education[b]	−0.08	4.84	0.00	0.99	1.38	4.82	0.03	0.78	3.00	4.35	0.06	0.49
Sex: Female	**−13.04*****	**3.54**	**−0.38**	**<0.001**	**−13.50*****	**3.56**	**−0.38**	**<0.001**	**−12.86*****	**3.35**	**−0.37**	**<0.001**
Parent Genotype	0.24	3.55	0.01	0.95	−0.36	1.56	0.02	0.82	2.65	3.04	0.09	0.38
Res. Parenting	2.08	1.73	0.13	0.23	0.90	1.71	0.06	0.60	0.12	2.59	0.01	0.97
Child Genotype	2.71	3.26	0.09	0.41	1.43	1.51	0.10	0.34	−0.40	3.46	−0.01	0.91
GxE	1.99	3.05	0.06	0.51	−1.70	1.59	−0.11	0.29	1.66	4.02	0.05	0.68
(b) Linear Slope												
Race 1[a]	−0.58	3.02	−0.03	0.85	−1.32	3.00	−0.08	0.66	−3.54	2.42	−0.21	0.14
Race 2[a]	4.14	3.30	0.23	0.21	3.18	3.38	0.18	0.35	**7.56**	**1.43**	**0.35**	**<0.001**
Race 3[a]	0.31	2.14	0.02	0.89	−0.57	2.18	−0.04	0.79	0.62	2.75	0.05	0.82
Race 4[a]	0.44	1.68	0.04	0.80	−0.03	1.67	−0.00	0.98	1.07	1.51	0.11	0.43
Parent Education[b]	0.95	2.27	0.07	0.48	−0.42	2.24	−0.03	0.85	−0.65	2.33	−0.05	0.32
Sex: Female	1.19	1.69	0.12	0.68	1.19	1.68	0.12	0.48	1.31	1.65	0.14	0.78
Parent Genotype	0.45	1.66	0.05	0.79	0.58	0.73	0.14	0.43	−0.91	1.38	−0.11	0.51
Res. Parenting	**1.41**†	**0.79**	**0.32**	**0.07**	**1.63***	**0.78**	**0.37**	**0.04**	**3.32****	**1.10**	**0.74**	**0.003**
Child Genotype	**−2.98**†	**1.54**	**−0.33**	**0.05**	0.82	0.71	0.21	0.24	−1.79	1.47	0.21	0.22
GxE	*−0.93*	*1.52*	*−0.10*	*0.54*	*−0.31*	*0.97*	*−0.07*	*0.75*	**−3.71****	**1.28**	**−0.39**	**0.004**

Statistically significant results are bolded for emphasis. Italics reflect nonsignificant GxE terms (p < 0.10) that were dropped to examine main effects. Main effect coefficients represent the final model with GxEs removed.

GxE, Gene–environment interaction; *B*, unstandardized coefficient; *SE*(*B*), standard error of unstandardized coefficient; β, standardized coefficient.

[a]n = 103.

[b]Race is effect coded.

[c]Mother education is assessed as the highest grade completed per mother report.

$^{*}p$ < 0.05,

$^{**}p$ < 0.01,

$^{***}p$ < 0.001,

$^{\dagger}p$ < 0.10.

regulation for the teacher-report (B = −1.02, p = 0.34; 95% CI: −1.92 to 2.59), nor the parent-report (B = −0.07, p = 0.88; 95% CI: −1.02 to 0.88) models in involving DRD4. Thus, as hypothesized, emotion regulation was not observed to be a significant mediator of DRD4 x parenting interactions.

4 | DISCUSSION

This study is one of the first to assess the independent and interactive associations of several functional polymorphisms and observed parenting behavior with respect to individual differences in social functioning in ASD. Improving upon prior methodologies, the present study utilized multi-rater assessment of the social phenotype, which was critical in revealing differing trends in GxEs across reporters. Furthermore, the study leveraged a longitudinal design to elucidate the link between GxEs and developmental changes in social skills over time during an crucial developmental period for social development.

Consistent with study hypotheses, developmentally sensitive GxEs were observed for 5-HTTLPR and DRD4 genotypes, but not OXTR. Findings suggest that the 5-HTTLPR and DRD4 genes may play a role in environmental sensitivity in childhood in ASD, as has been found for other child populations (e.g., Tung & Lee, 2017; see Tielbeek et al., 2016 for a meta-analysis). Thus, while diverse genetic pathways including complex constellations of rare and/or common variants contribute to the presence of ASD (Jeste & Geschwind, 2014), the present findings suggest that specific common variants (5-HTTLPR, DRD4) may further regulate how the ASD phenotype manifests over time and in response to the social

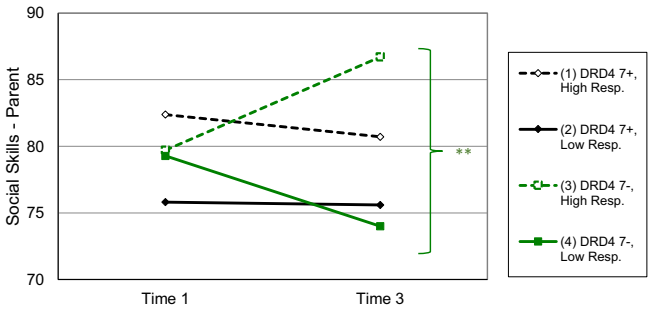

FIGURE 3 DRD4 x responsive parenting interaction predicting parent-rated social skills. Note: Figure 3 depicts the significant child DRD4 genotype x responsive parenting interaction in predicting linear growth in parent-reported child social skills from Time 1 to Time 3. High Resp.: 1 *SD* above the mean on the latent variable of responsive parenting. Low Resp.: 1 *SD* below the mean on the latent variable of responsive parenting. Social skills – Parent: Social Skills Improvement System, Total Social Skills standard score, parent report. DRD4 7+: Children with one or more 7 repeat alleles. DRD4 7-: Children with no 7 repeat alleles. **Significant slope difference at $p < 0.01$

environment. However, these results should be viewed as preliminary and interpreted with due caution until supported through replication and further research in this population.

While few studies have directly assessed GxE in ASD, neurogenetic research supports the role of 5-HTTLPR and DRD4 in relevant behavioral phenotypes and in environmental susceptibility within ASD. For example, DRD4 has been linked to ASD pathology and neurodevelopment (Nguyen et al., 2014). In terms of 5-HTTLPR, Wiggins et al. (2014) found that individuals with ASD demonstrated differential amygdala responses to social stimuli (emotional faces) as a product of 5-HTTLPR genotype, with greater activation and less habituation for those with the SS genotype. These behavioral and neural endophenotypes may explain the link between the observed GxEs and heterogeneous social development in ASD, as differential brain development and response by 5-HTTLPR and DRD4 genotypes may cue individuals with certain genotypes to "tune in" to the social environments, thus explaining individual differences in response to these environments. This has important implications for developmental research in ASD, as it has been proposed that there is a *biological constraint effect* in ASD, such that children with ASD are less susceptible to the influences of social environments such as parenting due to their "inborn limited social information processing" (Van IJzendoorn et al., 2007, p. 604). Importantly, the present findings provide evidence against a biological constraint effect for all children with ASD, and alternatively suggest that the *biological variability within ASD* may be an important indicator of susceptibility to social environmental influences.

We further predicted that emotion regulation would mediate the observed interaction between responsive parenting and 5-HTTLPR (but not DRD4) due to implicated neurobiology; however, no mediated moderation effects were found. This nonsignificant finding is important to furthering research in this area, as it suggests that more robust mechanisms may be at play in these GxEs in ASD and should be addressed in future research. Neural endophenotypes, also known as "intermediate phenotypes," are heritable neurological markers of complex disorders or phenotypes such as ASD, and are proposed to have simpler and more readily detectible genetic underpinnings (Caspi & Moffitt, 2006). Future studies may enrich our understanding of GxE by assessing neural systems involved in emotion and reward processing as potential mechanisms of GxE, rather than more distal measures such as parent-reported emotion regulation. For example, translational research with 5-HTTLPR suggests that the SS genotype is associated with neural networks involved in social cognition and emotion regulation and emotional salience (Drabant et al., 2012; Hariri & Holmes, 2006), and that these same neural networks are sensitive to epigenetic modification of 5-HTTLPR (Nikolova et al., 2014). It may be that these neural markers of emotion regulation are more salient than broad assessments of emotion regulation. Furthermore, in line with our finding that emotion regulation did not mediate GxEs involving DRD4, it is likely that different neural and behavioral mediators may be at play for DRD4, as DRD4 is often associated reward circuitry and reward sensitivity (Camara et al., 2010). Thus, further investigation into the different neural mechanisms that may explain environmental sensitivity by 5-HTTLPR and DRD4 in ASD is warranted.

Beyond identifying putative GxE as explanatory factors in social heterogeneity, a primary goal of the study was to characterize the nature of GxEs as a means of informing developmental perspectives and clinical translational efforts in ASD. The present study thus assessed both positive (responsive direction and engagement) and negative (interfering behaviors) indicators of responsive parenting and utilized statistical methods necessary to distinguish differing models of GxE (Pluess & Belsky, 2010). Consistent with study hypotheses, 5-HTTLPR surfaced as a marker of differential susceptibility to the responsive parenting environment, for better and for worse (Pluess & Belsky, 2010) in predicting teacher-reported social skills. This finding has potential implications for characterizing developmental psychopathology, as children with low-expressing SS genotype share adjunct risk for poor social development in the context of minimally responsive parenting. However, these same children may be most responsive to high levels of responsive parenting. However, as noted above, results should be interpreted with caution until supported with future research given concern for false positives and lack of replication in GxE (Duncan & Keller, 2011). However, should the present findings replicate as well as extend to other parenting behaviors and parent-mediated interventions, GxEs such as those involving 5-HTTLPR may be key in understanding which children are most likely to benefit from parent-focused interventions, and thus inform targeted treatment efforts in ASD.

Contrary to study hypothesis, DRD4 demonstrated differential effects across raters, with a diathesis-stress model (Monroe & Simons, 1991; with 7+ as the marker) supported for the teacher-report model, and a differential susceptibility model (with 7- as the marker) supported for the parent-report model. Although the

reasons for differential GxE findings across raters are not entirely clear, research supports that parents and teachers differ in their ratings of social behavior in ASD, such that parents tend to endorse social initiation behaviors while teachers endorse social response/maintenance behaviors for children with ASD (Murray et al., 2009). Thus, subtypes of social behaviors, which are not effectively parsed in a global measure of social skills, may be differentially sensitive to DRD4 x responsive parenting interactions in ASD. Another possibility is that parents may be more likely to endorse social skills that are linked to behavior problems (Winsler & Wallace, 2002), which would be supported by findings that DRD4 7- (but not 7+) is linked to a negative association between warm-responsive caregiving and externalizing problems for young children (Propper et al., 2007). Future research assessing the nature of DRD4 x parenting interactions in ASD would benefit from greater specificity in the measurement of social phenotypes (e.g., item or subscale analysis), as well as measurement of related behavioral phenotypes (i.e., behavior problems), to refine developmental models and enhance the clinical applications of this work.

Current findings do not support the role of OXTR in GxE for ASD, though the detection of very small effects may be precluded by a relatively small sample. Assessments of GxE by OXTR are in their relative infancy, and further research will be necessary to determine if and when OXTR plays a role in GxE in ASD. Although several studies have emerged implicating OXTR in GxE, these studies often find different SNPs playing a role in environmental susceptibility (e.g., rs11131149: Wade et al., 2015, rs2254298: Brüne, 2012). One possibility is that OXTR SNPs may play different roles in GxE depending on the environmental agent and the social phenotype assessed. While certain SNPs have been implicated in GxE of social cognitive phenotypes (e.g., theory of mind; Wade et al., 2015), others have been connected to social ability and risk for ASD (Brüne, 2012). Future studies may choose to compare GxEs across OXTR SNPs and various social outcomes to elucidate the specificity of OXTR x parenting interactions in ASD. For example, McDonald and colleagues (McDonald et al., 2016) found that the OXTR rs53576, but not rs2254298, moderated the association between one aspect of positive parenting (affective mutuality) and empathy in toddlers at high or low biological risk for developing ASD.

4.1 | Limitations and strengths

The present findings should be interpreted in the context of study limitations. While the study exhibited strength in sampling from a large, community-based sample, the significant demographic differences that arose between participants and non-participants in the DNA collection (e.g., higher mean IQs, greater proportion of females for participants) raise questions regarding generalizability. The issue of overrepresentation of high-functioning individuals is pervasive in biological and behavioral research in ASD (Russell et al., 2019); future studies should strive to over-select for individuals with low IQs and include procedures that are tolerable and valid for this population (e.g., DNA swab collection). The present study should also be considered within the context of criticisms common to the field of candidate GxE research (Duncan & Keller, 2011), including the potential for type I error and replication failure. The present sample size was quite modest for candidate gene research, and findings should be interpreted as exploratory in nature until replicated in larger samples. Other areas of ASD genetics research, including heritability and gene association studies, have benefitted from data sharing and consortium models that allow for the assessment of the very large samples needed to perform such research. While the rigorous assessment of the environment and phenotype represented in the current study may be difficult to replicate in large data repositories, further collaborative efforts are needed to assess such GxEs across very large samples of children with ASD. The science of GxE in ASD will advance with a balance of large-scale designs with more modestly sized, yet rigorously assessed samples. Furthermore, while the present findings suggest similar GxE effects as have been found for children with typical development, future research assessing children with ASD or typical development within the same study may more sensitively assess differences in GxEs that may be present across the diagnostic groups. Finally, the present findings should be interpreted within the context of the developmental period assessed and study design. It is widely accepted that behavior patterns between parents and their children are transactional in nature (Sameroff, 2009), and thus, levels of responsive parenting may differ earlier in a child's development. While studies of responsive parenting suggest similarly positive effects in ASD earlier in development (e.g., Harker et al., 2016), it would be important for future research to characterize potential developmental changes in responsive parenting and transactions between parent and child behaviors over time as they impact child social development and parenting x child genotype interactions.

The present study exhibited several methodological strengths rarely utilized in GxE research, including prospective longitudinal design, observational measurement of parenting, and use of advanced structural equation modeling, all of which serve to increase power by reducing measurement error. The current study enhanced our understanding of the specificity of GxE effects by employing multi-rater assessment of child social functioning. Results suggest that the impact of responsive parenting and GxEs on social development may differ across reporters. Finally, the present study assessed and controlled for parent genotype in analyses of GxE, which improves internal validity by controlling for the potential confounding effects of passive gene–environment correlation (see Knafo & Jaffee, 2013).

5 | CONCLUSIONS

Taken together, the present findings hold important implications for the scientific understanding of child social development and ASD heterogeneity, as well as efforts for tailored treatment in ASD. In

terms of ASD etiology, refining genetic etiologies through behavioral phenotypic subgroups has proven difficult, likely due to issues of equifinality and multifinality informed by GxEs among other processes. Genetics studies in ASD may thus be enhanced through joint consideration of important environmental agents such as those assessed in the current study. Findings also hold implications for tailoring ASD interventions based on individual differences. While mounting evidence supports the efficacy of combined responsivity and behaviorally based interventions on social and developmental outcomes in ASD (see Schreibman et al., 2015), substantial heterogeneity remains in regard to response to intervention. GxEs such as those found in this study may help to explain differential findings across intervention trials as well as discrepant responses across individuals within trials (e.g., Carter et al., 2011). Thus, evidence of GxEs in ASD such as those found in the present study may improve the efficacy of developmental and behavioral interventions and inform novel treatment approaches based on child biology.

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ORCID

Barbara Caplan https://orcid.org/0000-0003-0563-5411

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APPENDIX 1.

Genotyping Procedures and Allele Frequencies

5-HTTLPR short and long alleles (43-base pair deletion/insertion) were determined by the ABI 3,730 Sequencer with Genemapper Mode using standard primers (Hu et al., 2006; 5′-GGCGTTGCCGCTCTGAATGC-3′ forward, and 5′-GAGGGACTGAGCTGGACAACCAC-3′ reverse), including the downstream SNP rs25531 that influences 5-HTTLPR functionality, such that the G allele, when paired with the L allele, results in a low-expressing variant (L_G). One sample could not be successfully genotyped for 5-HTTLPR and was removed from 5-HTTLPR analyses only. OXTR SNPs were genotyped using predesigned assays from Applied Biosystems (*Assay-on-Demand by Applied Biosystems®*; Foster City, CA, USA) following manufacturer protocols. These markers were genotyped with the ABI 7900-HT Sequence Detection System® using the TaqMan 5′ nuclease assay for allelic discrimination. The *DRD4* exon 3 VNTR was amplified with primer sets (5′-FAM-CGC GACTACGTGGTCTACTCG-3′ and 5′-AGGACCCTCATGGCCTTG-3′). Polymerase chain reactions (PCRs) were conducted in 20 μl volumes using Thermo Start PCR master mix. The size of PCR products was then determined with ABI 3,730 Sequencer with GeneMapper mode.

We observed the following allele frequencies: 5-HTTLPR (S: 0.56, L: 0.44), OXTR rs53576 (A: 0.34, G: 0.66), OXTR rs2254298 (A: 0.19, G: 0.81), OXTR rs237887 (A: 0.52, G: 0.48), OXTR rs7632287 (A: 0.21, G: 0.79). Child DRD4 genotypes were as follows: 2/2 (*n* = 2), 2/3 (*n* = 3), 2/4 (*n* = 16), 2/7 (*n* = 1), 3/4 (*n* = 5), 3/5 (*n* = 2), 3/10 (*n* = 1), 4/4 (*n* = 47), 4/7 (*n* = 25), 4/8 (*n* = 1), 4/9 (*n* = 1), 6/7 (*n* = 1), 7/7 (*n* = 7).

APPENDIX 2

TABLE A1 Indicators of model fit for structural equation models

	Main effects model					Latent interaction (Gxe) model	
	χ^2 (39, 41)	*p*-value	RMSEA	AIC	BIC	AIC	BIC
Social skills—teacher							
5-HTTLPR	51.37	0.088	0.056	2,571	2,665	2,571	2,670
OXTR	51.53	0.105	0.053	2,588	2,679	2,593	2,692
DRD4	53.25	0.064	0.060	2,598	2,693	2,598	2,697
Social skills—parent							
5-HTTLPR	54.43	0.078	0.056	3,043	3,133	3,048	3,146
OXTR	53.85	0.086	0.055	3,073	3,163	3,078	3,175
DRD4	59.85	0.068	0.057	3,073	3,168	3,074	3,176

Indicators of model fit for the six models predicting growth in child social skills by rater and by child genotype. Main effect models include responsive parenting and child genotype as predictors in addition to identified covariates. Latent interaction models include the child genotype x responsive parenting latent interaction as an additional predictor. Chi-square and RMSEA are not available for latent interaction models. Social Skills—Teacher: Social Skills Improvement System, Total Score, Teacher Report. Social Skills—Parent: Social Skills Improvement System, Total Score, Parent Report. RMSEA: Root Mean Square Error of Approximation.