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RESEARCH ARTICLE

Genetic differential susceptibility to the parent–child relationship quality and the life span development of compassion

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Abstract

The development of compassion for others might be influenced by the social experiences made during childhood and has a genetic component. No research has yet investigated whether the parent–child relationship quality interacts with genetic variation in the oxytocin and dopamine systems in predicting compassion over the life span. In the prospective Young Finns Study ($N = 2099$, 43.9% men), we examined the interaction between mother-reported emotional warmth and intolerance toward their child assessed in 1980 (age of participants, 3–18 years) and two established genetic risk scores for oxytocin levels and dopamine signaling activity. Dispositional compassion for others was measured with the Temperament and Character Inventory 1997, 2001, and 2012 (age of participants, 20–50 years). We found a gene–environment interaction ($p = .031$) that remained marginally significant after adjustment for multiple testing. In line with the differential susceptibility hypothesis, only participants who carry alleles associated with low dopamine signaling activity had higher levels of compassion when growing up with emotionally warm parents, whereas they had lower levels of compassion when their parents were emotionally cold. Children's genetic

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variability in the dopamine system might result in plasticity to early environmental influences that have a long-lasting effect on the development of compassion. However, our findings need replication.

KEYWORDS
compassion, dopamine and oxytocin signaling pathways, gene–environment interaction, parenting, personality development

1 | INTRODUCTION

Compassion can be defined as a disposition that is characterized by a feeling evoked by witnessing the unjust suffering of another person and the authentic desire to help (Goetz et al., 2010; Lazarus, 1991). Individuals characterized as high in compassion further recognize that all people experience hardship, are caring and concerned for others' pain, and tolerate the sometimes uncomfortable emotions arousing in response to the suffering person (Pommier et al., 2019; Strauss et al., 2016). Trait-like compassion for others transcends situations (unlike more variable compassionate states and emotions) and plays an important role in fostering interpersonal trust and cooperation (Allred et al., 1997; Liu & Wang, 2010) and directing prosocial behavior (Goetz et al., 2010). Being compassionate also contributes to building harmonic relationships and managing interpersonal conflicts, as it is related to better emotion regulation skills (Eisenberg, 2000; Lebowitz & Dovidio, 2015). Compassion may help to respond to stressful social situations (Abelson et al., 2014; Pace et al., 2009; Perrone-Mcgovern et al., 2014) and anger (Kahle et al., 2016), and more compassionate individuals display less distributive or aggressive behavior when dealing with conflict (Zhang et al., 2014).

Compassion is a topic of timely relevancy (Galea, 2020). Compassion-related phenotypes have declined from one birth cohort to the next in the United States and across wide parts of Europe (Dobewall et al., 2017; Zarins & Korath, 2017). This is alarming because compassion facilitates cooperation beyond the family and addresses a society's need to protect the weak (Goetz et al., 2010).

It has been suggested that parents have a substantial influence on their children's development, yet parental influences are differentiated and complex rather than direct and unambiguous (Collins et al., 2000; Eisenberg, Spinrad, et al., 2015). Also, compassion for others has been found to be influenced by environmental factors, one has experienced during childhood, such as different aspects of parenting (Eisenberg, VanSchyndel, et al., 2015; Hintsanen et al., 2019) and forms of early child care arrangements (Gluschkoff et al., 2018). It has further been shown that compassion and compassion-related phenotypes have a significant genetic component (Ando et al., 2004; Dobewall et al., 2021; Gillespie et al., 2003; Pełka-Wysiecka et al., 2012). Twin studies have shown that it is difficult to distinguish shared genetics from environmental effects (Avinun & Knafo-Noam, 2015; Eisenberg, Spinrad, et al., 2015; Knafo-Noam et al., 2020) suggesting that parental influences are often explained by the genotype, not environmental effects. Kandler et al. (2016), for instance, did not find evidence for parental influences beyond genetic influences when investigating intrafamilial similarity. Moreover, parenting is known to be in part evoked by genetically influenced characteristics of the child (Avinun & Knafo, 2014; Dobewall et al., 2019). Most importantly, a lack of environmental or parenting effects observed in twin studies could also indicate the presence of gene–environment interactions (Belsky & Pluess, 2009; Ellis et al., 2011; Zuckerman, 1999). Effects of parenting are indeed often moderated by characteristics of the child that are partly heritable (Belsky & van IJzendoorn, 2017; Pluess & Belsky, 2010); however, no research today has investigated the role of the gene–environment interactions in the development of compassion over the life span.

1.1 | The genetic component of compassion

Compassion has been found in a large twin study to be 34% heritable (Ando et al., 2004). Research has subsequently tried to identify specific genes that account for this variance based on the putatively underlying biological processes (Dobewall et al., 2021; Keum & Shin, 2019; Knafo-Noam et al., 2018; Knafo & Israel, 2010; Pełka-Wysiecka et al., 2012). A review by Knafo-Noam et al. (2018) found that the oxytocinergic and vasopressinergic systems (involved in social bonding and affiliative behaviors) and dopaminergic system (executive function, learning, and reward) are regularly implicated in compassion-related phenotypes, although some researchers have tested broader sets of neurochemicals (Assary et al., 2018; Jern et al., 2017; Pearce et al., 2017). Further, compassion is evolutionarily linked to caring motivation (Gilbert, 2015), which has been suggested to be neurologically related to oxytocin and dopamine signaling (Carter et al., 2017; Ebert et al., 2018; Klimecki et al., 2013). Single-nucleotide polymorphisms (SNPs) in the dopamine and oxytocin signaling pathway have indeed found to be related to empathy (Gong et al., 2017; Pearce et al., 2017), prosocial behavior and temperament (Poulin & Holman, 2013; Reuter et al., 2011; Tost et al., 2010), and sensitive parenting (Feldman et al., 2012; Peltola et al., 2014; Skuse et al., 2014; Van IJzendoorn et al., 2008).

1.2 | The important role of early-environmental factors

As important as the selection of genetic variants is the selection of the environmental factor under study (Dick et al., 2015). The parenting one has experienced during childhood and the overall emotional

atmosphere between parent and child are important and modifiable early-environmental factors (Armstrong et al., 2018; Collins et al., 2000; Thomas & Zimmer-Gembeck, 2007). Conceptually several mechanisms have been proposed to operate during childhood that might account for individual differences in compassion development. For instance, children might learn how to be compassionate as later adults to some degree already by observing the positive parenting of their parents (Bandura, 1978). Caring parenting further creates a sense of safety—a source of soothing and comfort—and provides a secure base—a source of protection, validation, and guidance (Ebert et al., 2018; Gilbert, 2020). An emotionally warm parent–child relationship quality has also been found to be associated with secure attachment (Güngör & Bornstein, 2010), which in turn has been found to stimulate compassion and prosocial behavior (Mikulincer et al., 2005). (Eisenberg et al., 2015) reported a positive association of maternal warmth and support during childhood and adolescence with adulthood sympathy and concern, whereas maternal negative affect was negatively related. Another recent study has found that the parent–child relationship quality has a long-lasting effect on the life span development of dispositional compassion for others (Hintsanen et al., 2019). More precisely, higher emotional warmth but not lower intolerance is a robust predictor of adulthood compassion. The presence of gene–environment interactions might explain the fact that this earlier study has found an effect for emotional warmth, but not for intolerance.

1.3 | Genetic differential susceptibility and the life span development of compassion

Available genome-wide association studies (GWAS) in similar socioemotional phenotypes found only a relatively small proportion of the total variance to be explained per SNP or by the most significant SNPs taken together (Warrier, Grasby, et al., 2018; Warrier, Toro, et al., 2018). One potential explanation for this finding is the presence of gene–environment interactions (Arnau-Soler et al., 2019; Assary et al., 2018), which suggests that genes in the dopamine and oxytocin signaling pathway might have a conditional rather than a direct influence on the development of compassion. Oxytocin plasma levels, for instance, were found to be related to both the recall of parental warmth during childhood and being compassionate to oneself and others (Ebert et al., 2018). Evidence is accumulating that it is the major role of early-environmental influences to interact with genetic predispositions in the activation of social learning processes during personality development (Zwir et al., 2019). Neurochemical systems involving dopamine and oxytocin signaling can thus be tuned by early-life experience (Carter et al., 2017). Some individuals might be more vulnerable to negative early-environmental factors than others as proposed by the diathesis–stress model (Zuckerman, 1999). Further, individuals might differ in their susceptibility with some being more affected than others by both positive as well as negative developmental experiences as postulated by differential susceptibility theory (Belsky & Pluess, 2009; Ellis et al., 2011). Much of the research on gene–environment interactions has looked at the genetic differential susceptibility to variation in parenting (Jokela et al., 2007; Pluess & Belsky, 2010), and the empirical evidence suggests that the strength of gene–environment interactions is the greater the more plasticity alleles an individual carries (Belsky & van IJzendoorn, 2017). Because the influence of genes tends to increase as children grow older and enter larger and more complex social environments (Knafo & Plomin, 2006), gene–environment interactions may also play an important role in the development of dispositional compassion over the life span.

Previous gene–environment interaction studies have demonstrated that the effect of childhood experiences on later socioemotional development is indeed conditional to allelic variation in dopaminergic and oxytocinergic genes. For instance, polymorphisms in dopamine receptors interact with the family environment during childhood in predicting behavior problems and creativity consistent with the diathesis–stress model (Belsky & Pluess, 2013; Si et al., 2018), whereas results for social skills are more in line with the differential susceptibility hypothesis (Belsky & Pluess, 2013). Differential susceptibility to parental influence has also been observed for prosocial behavior by variation in the dopamine receptor D4 (DRD4) gene (Knafo et al., 2011). A recent study on parenting style counting the minor alleles in multiple loci of the dopamine receptor D2 (DRD2) and COMT genes again has favored the differential susceptibility rationale (Si et al., 2020). Although one study identified carrying the DRD2 Del (rs1799732) allele and other studies carrying the DRD4 7-repeat allele (Belsky & Pluess, 2013; Knafo et al., 2011) as indicators of plasticity, the latter was attributed to a putatively low capacity to respond to dopamine (Asghari et al., 1995; Tovo-Rodrigues et al., 2012).

Furthermore, studies on the development of perceived social support (Dobewall, Hakulinen, Keltikangas-Järvinen, et al., 2018), emotion-related personality traits, and social cognition (Schneider-Hassloff et al., 2016) have reported that some individuals are more susceptible to the quality of the relationship between parent and child and childhood attachment security due to carrying certain plasticity alleles in the oxytocin receptor gene (OXTR). Concerning the self-regulatory responses of toddlers, it has been found that some individuals are more vulnerable to a lack of early maternal sensitivity than others conditional to allelic variation in oxytocin but not dopamine receptors (Augustine et al., 2018). Generally, OXTR genotypes that have been associated with higher oxytocin levels are hypothesized to predict susceptibility to early-environmental influences (Augustine et al., 2018; Feldman et al., 2012) but the reviewed empirical evidence is inconclusive. There are also other gene–environment interaction studies that have been unable to find robust associations (Belsky et al., 2015; Border et al., 2019; Dobewall, Hakulinen, Pulkki-Råback, et al., 2018) or have not related their findings to either one of the two theoretical perspectives (Blair et al., 2015). To our best knowledge, no previous research on the associations between normal variation in parenting variables and phenotypes closely related to compassion has explored variation by dopaminergic and oxytocinergic genes. The current literature does not allow us to speculate whether stronger conditional effects will emerge for dopamine signaling compared to oxytocin levels, or vice versa.

1.4 | The current study

The current study investigated in a large, population-based sample of Finns the effects of genetic differential susceptibility to the parent–child relationship quality on the life span development of dispositional compassion. We assessed compassion over a 15-year prospective follow-up with a reliable and well-known personality inventory. The childhood family environment was assessed by parents three decades before the last assessment of adult compassion. Most of the reviewed studies have investigated gene–environment interactions in socioemotional phenotypes with single candidate genes, whereas the current study relies on two established genetic risk scores in the oxytocin and dopamine signaling pathways that combine the effects of the number of the plasticity alleles an individual carries. Finally, we informed our study design by recent theoretical advances on individuals' differential susceptibility to both negative as well as positive environmental influences, going beyond a narrow understanding of genetic vulnerability.

2 | METHODS

2.1 | Procedure and participants

The prospective cohort Young Finns Study (YFS; Akerblom et al., 1991; Raitakari et al., 2008) has followed its participants since 1980. At baseline, the parents of six population-based birth cohorts (aged 3, 6, 9, 12, 15, and 18 years) were surveyed. In 1983, the parent survey was repeated (both waves were combined to T0). In the current study, we further used participants' self-reports from the 1997, 2001, and 2012 waves in which compassion was included (T1–T3, respectively). The participants were 20–50 years old when dispositional compassion for others was assessed.

The original sample consisted of 3596 individuals. We included participants who completed the dependent variable at least once, underwent genotyping, and had information on the parent–child relationship quality during childhood. The resulting analytical sample consisted of 2099 participants (58.4% of the original sample, 44.0% male).

The YFS was approved by all participating universities' ethics committees at the beginning of the study in 1980, and the follow-ups were approved by the ethics committee of the University of Turku (vernacular institution name: Varsinais-Suomen sairaanhoitopiirin kuntayhtymä, Eettinen toimikunta, Meeting Number 9/2010; study name, "Lasten sepelvaltimotaudin riskitekijät projekti (Laseri) 30-vuotis seurantatutkimus, 25.8.2010"). The study was conducted in accordance with the Helsinki declaration. Written informed consent was obtained from the participants or their guardians.

2.2 | Measures

2.2.1 | Compassion

We used the dispositional compassion scales of the Cooperativeness character trait (C4) of Cloninger's Temperament and Character Inventory (TCI) (Cloninger et al., 1993). The compassion (vs. revengefulness) scale includes 10 items (e.g., "I like to imagine my enemies suffering" [reverse scored]; It gives me pleasure to help others, even if they have treated me badly" [positively scored]; "It gives me pleasure to see my enemies suffer" [reverse scored]; and "I hate to see anyone suffer" [positively scored]), which were answered on a 5-point Likert scale. Reverse-scored items were rescored before calculating the means for T1–T3, respectively. Criterion validity of the TCI compassion scale has been demonstrated by positive correlations with social warmth, sociability, and positive emotions (García et al., 2012), and well-being (Saarinen et al., 2019) and negative correlations with anger, hostility, and verbal and physical aggression (García et al., 2012), narcissistic personality (De Fruyt et al., 2006), depressive symptoms (Saarinen et al., 2019), and unhealthy behaviors (Gluschkoff et al., 2019). In this YFS subsample, the dispositional compassion had high reliability (Cronbach's $\alpha_{T1-T3} \geq 0.86$) and rank-order stability over time ($r_{T1\rightarrow T2} = .69$; $p < .001$ / $r_{T1\rightarrow T3} = .60$; $p < .001$). Confirmatory factor analyses confirm a very good fit for a one-factor model that accounts for the common variance between the reversed scored items (Dobewall et al., 2021; Saarinen et al., 2019).

2.2.2 | Parent–child relationship quality

The relationship quality between participants and their parents during childhood in terms of emotional warmth and intolerance was assessed in 1980 (if missing, then we used the 1983 assessment). The scale was derived from the Operation Family Study (Makkonen et al., 1981) consisting of four items to capture emotional warmth ("My child is emotionally important to me"; "I enjoy spending time with my child"; "I am emotionally important to my child"; and "My child enables me to self-actualize myself") and three items to capture intolerance (e.g., "In difficult situations, my child is a burden"; "I often become irritated with my child"; and "My child takes too much of my time"). Rather than parenting, these items measure child-rearing attitudes that capture the overall atmosphere within a parent–child dyad (Katainen et al., 1999). These two subscales can be assigned in the broader literature to parental positivity and parental negativity (Avinun & Knafo, 2014; Knafo & Plomin, 2006) and are related to the dimension of love versus hostility in the Circumplex Model for Maternal Behavior (Schaefer, Earl, 1959). Emotional warmth measures parents' unconditional positivity toward the child and his/her (sometimes difficult) behaviors, whereas intolerance captures a lack of acceptance and responsiveness as well as in part negative parenting experiences (Knafo & Plomin, 2006). Participants' parents (97% were mothers) answered the items on a 5-point Likert scale (Räikkönen & Keltikangas-Järvinen, 1992; Savelieva et al., 2017). Emotional warmth and intolerance were kept separate because they quantify different aspects of parenting (Savelieva et al., 2017), form discrete factors (Hintsanen et al., 2019; Räikkönen & Keltikangas-Järvinen, 1992), and have distinct associations with other constructs (Gluschkoff et al., 2017; Hintsanen et al., 2019). Although the face validity of the scale may not be very high, it has shown criterion validity by predicting personality development, including compassion for others several decades later (Hintsanen et al., 2019; Josefsson et al., 2013), and various adulthood measures from the

mental health domain, such as depression and work stress (Gluschkoff et al., 2017; Hintsanen et al., 2010). Emotional warmth and intolerance are independent of parental role satisfaction and well-being (Katainen et al., 1999). In this YFS subsample, the two subscales of the parent–child relationship quality had acceptable reliability (Cronbach's α_{T0} = 0.68 for intolerance / 0.78 for emotional warmth). Following previous research, emotional warmth and intolerance were standardized within the six birth cohorts to account for age-dependent developmental differences and then cubic transformed to better follow a normal distribution (Hintsanen et al., 2019).

2.2.3 | Genotyping

In 2009, the GWAS was performed on those 2443 participants who consented to be genotyped (Smith et al., 2010) using an Illumina 670k genotyping array. Imputation was performed using the IMPUTE2 software (Howie et al., 2009) and the 1000 Genomes Project March 2012 haplotypes as a reference (Imputation quality info ~ 0.99). Because complex traits such as compassion are polygenic and affected by many genes of small effect (Manolio et al., 2009; Warrier, Grasby, et al., 2018; Warrier, Toro, et al., 2018), we use genetic risk scores that are an additive summary of risk (or plasticity) information from several genetic variants earlier identified in the literature (Assary et al., 2018; Belsky & Israel, 2014).

2.2.4 | Genetic risk scores for dopamine activity and oxytocin levels

We build on previous research when creating a dopaminergic risk score of multiple loci (Nikolova et al., 2011; Stice et al., 2012). The polymorphisms were selected in the original study based on functional changes associated with variation in dopamine signaling activity (Nikolova et al., 2011), such as reduced gene expression (Arinami et al., 1997) and ventral striatum reactivity modulation (Forbes et al., 2009) (rs1799732), reduced receptor-binding density and availability (Pohjalainen et al., 1998) (rs1800497), and lower enzymatic activity (Stein et al., 2006) (rs4680). Polymorphism is defined as functional if it alters the function of a gene or set of genes (Albert, 2011). We coded genotypes related to low dopamine activity as 1, intermediate heterozygotes were coded with 0.5, and genotypes expected to associate with high dopamine activity were coded with 0. Specifically, TaqIA A1/A1 (rs1800497), DRD2-141C Ins/Ins carriers (rs1799732), and COMT Met/Met (rs4680) genotypes were assigned a score of 1 ("low"); TaqIA A2/A2, DRD2-141C Ins/Del and Del/Del carriers, and COMT Val/Val genotypes were assigned a score of 0 ("high"); and TaqIA A1/A2 and COMT Met/Val genotypes received a score of 0.5 (Stice et al., 2012). Two copy number variants included in the original dopaminergic risk score—DRD4-L and DAT1 10R/10R—were not available for this study. We substituted them with the functional C-1021T SNP (rs1611115) located in the direct neighborhood of the DBH gene. TT homozygotes (received a score of 1) have very low DBH enzyme activity compared to C-allele heterozygotes (score of 0.5) and homozygotes (score of 0) (Zabetian et al., 2001), and this forth SNP was previously found to be weakly associated with the development of dispositional compassion (Dobewall et al., 2021). For all SNPs included in the final risk score for dopamine signaling activity, the functions are known in humans.

Feldman et al. (2012) developed a cumulative oxytocinergic score to capture the combined effects of the risk alleles in OXTR and CD38 genes. The included risk alleles were each associated with lower plasma oxytocin levels (Feldman et al., 2012) as well as were related to activation and volume of the amygdala and structural alterations of the oxytocinergic brain regions when processing social cues (Inoue et al., 2010; Tost et al., 2010) (rs2254298, rs53576), empathic responses linked to altruistic behaviors (Liu et al., 2017) (rs3796863), and modulating effect of family environment on the perception of social support (Dobewall, Hakulinen, Keltikangas-Järvinen, et al., 2018) (rs1042778). This risk score has been updated in a later publication to include more OXTR SNPs and variation in the vasopressin receptor gene (Feldman et al., 2014). Genotypes putatively associated with higher plasma oxytocin levels were coded as 1 ("high"), and those expected to relate to lower oxytocin levels were coded as 0 ("low"). Specifically, OXTR rs1042778 A-allele, rs2254298 TT, rs53576 GG genotype, and CD38 rs3796863 A-allele carriers received a score of 0; OXTR rs1042778 TT genotype rs2254298 GG genotype, rs53576 A-allele carriers, and CD38 rs3796863 CC genotypes received a score of 1. A copy number variant—AVPR1a RS3—originally included in the oxytocinergic risk score of Feldman et al. (2014) was not available for this study.

Nine more SNPs of OXTR (rs2268498), CD38 (rs6449182, rs12644506), ANKK1/DRD2 (rs1801028, rs468317), COMT (rs4633, rs4818), and DBH (rs2519152, rs6271) genes were available in the dataset but not tested in the current study. The eight SNPs used to produce the two genetic risk scores followed the Hardy–Weinberg equilibrium after taking into account the number of conducted tests ($p > .029$).

2.2.5 | Covariates

We controlled for participants' age at first assessment of compassion (years of birth 1962, 1965, 1968, 1971, 1974, and 1977) and gender (male = 0, female = 1).

Socioeconomic status was assessed twice, first during childhood (SESC) in 1980 when participants were between 3 and 18 years old and later during adulthood (SESA) in 2001 when they aged 24–39 years (we used a second measurement in 2012 to replace missing values). SESC was measured with two indicators: the average of parents' education (in years) and the annual household income. SESA was measured with participants' self-reported education and income. In both generations, high SES corresponds to having a high educational level (tertiary education) and a high income (highest 25%). Low SES indicates secondary education or lower and belonging to the 75% lowest income category. Average SES means a high educational level but low income, or vice versa.

Descriptives of the main study variables are listed in Table 1. The top 10 principal components, obtained in GWAS (Smith et al., 2010), were controlled to rule out that population stratification drives the obtained results (Border et al., 2019; Price et al., 2006).

TABLE 1 Descriptives of main study variables

Variable	*N*	Mean	*SD*	Min	Max
Compassion in 1997	1600	3.60	0.68	1	5
Compassion in 2001	1728	3.68	0.65	1	5
Compassion in 2012	1447	3.75	0.60	1.5	5
Gender (ref. female)					
% male	2099	0.44	0.50	0	1
Age in 1997	2099	27.48	5.02	20	35
Nikolova risk score (low dopamine activity)	2099	1.79	0.65	0	3.5
Feldman risk score (high oxytocin levels)	2099	2.06	0.83	0	4
Socioeconomic status in 1997 (ref. low SES)	2017				
Average SES		0.21	0.41	0	1
High SES		0.14	0.34	0	1
Socioeconomic status in 2012 (ref. low SES)	1851				
Average SES		0.62	0.49	0	1
High SES		0.19	0.39	0	1
Intolerance in 1980 (cubic transformed)	2096	0.04	0.89	−1.91	1.77
Emotional warmth in 1980 (cubic transformed)	2097	0.14	0.86	−1.98	1.95

2.3 | Analyses

We compared excluded with included participants on the main study variables to estimate the degree to which selective attrition might have influenced the results.

Next, we ran multilevel models for repeated measures to separate the between- and within-person variance components in the development of dispositional compassion for others (Hox, 2010). Estimating the models with maximum likelihood allows us to include cases with missing values in the dependent variable (Von Hippel, 2007) (imputed $n = 2099$). Missing values in the predictor variables, which can be assumed to be missing at random (see Zwir et al., 2019), were imputed using multivariate imputation with chained equations (Royston & White, 2011) (for the number of missing values in each variable, see Table 1). We report the unstandardized beta coefficient (*b*) with 95% confidence intervals. Statistically significant effects ($p < .050$) were interpreted considering the number of conducted tests by accounting for the false discovery rate (FDR) (Anderson, 2008; Benjamini et al., 2006). Thus, we reported, in addition to *p*-values, sharpened *q*-values that indicate the expected proportion of Type I errors across analyses.

We fitted our baseline model with a random intercept and a random slope for age controlling for age at the first assessment of compassion, gender, SES in childhood and adulthood, and the top 10 genetic principal components. For the interpretability of the estimates, age was centered at 20 years. A quadratic effect for age was added to take previous findings into account that have shown that change in compassion over time is following a curvilinear trajectory (Hintsanen et al., 2019).

In the next step, we added the two aspects of the parent–child relationship quality into two separate analyses.

This was followed by assessing the direct effects of the genetic risk scores for dopamine activity, and oxytocin levels were again added into two separate models while simultaneously accounting for emotional warmth and intolerance.

Lastly, we ran a series of multilevel models one for each of the four possible gene–environment interactions.

To assess the robustness of our findings, we examined the degree to which imputation might have influenced our results and tested for gender effects in the gene–environment interaction by analyzing male and female participants separately (a three-way interaction was conducted to justify this step, $p = .050$). To test if the influence of genes increases with age, we compared a group consisting of the three youngest age groups, that is, children up to age 9 when parenting was assessed, with another group consisting of the three oldest age groups, adolescents from 12 to 18 years old at baseline. It was also tested if children's allelic variation in the dopamine and oxytocin pathway might have evoked the parenting they have received to rule out the presence of gene–environment correlations (Avinun & Knafo, 2014; Dobewall et al., 2019).

Data preparation, attrition analyses, and standard genetic tests were done in R relying on the "psych" and "genetics" packages. Main analyses were performed with Stata version 15.1.

3 | RESULTS

As indicated by chi-squared independence tests and independent samples *t*-tests, excluded participants were more often male (43.9% vs. 58.9%; $p < .001$), carrier of the rs4680 AA genotype (29.4% vs. 37.8%; $p < .001$), raised in families with lower SES (64.8% vs. 69.0%; $p = .040$) and a more intolerant parent–child relationship (mean 3.9 vs. 4.0; $p < .001$), and had more often lower SES themselves (19.7% vs. 30.4%; $p < .001$) compared to included participants. Selective attrition did not influence any of the other study variables.

Results of our baseline multilevel model for repeated measures ($n = 2099$) suggest that compassion increased with age (age $b = .017$ [012, .023]; $p < .001$ / $q = .001$) in slightly curvilinear fashion (age squared $b = -.001$ [−.000, −.001]; $p = .006$ / $q = .021$). Other significant predictors of compassion trajectories included gender (male $b = -.194$ [−.245, −.143]; $p < .001$ / $q = .001$) and adulthood socioeconomic status (reference = low SES, average $b = .139$ [.072, .205], high $b = .185$ [.100, .269]; both $p < .001$ / $q = .001$).

Of the two parent–child relationship quality scales, emotional warmth ($b = .029$ [.001, .057]; $p = .043$ / $q = .063$) was associated with the development of compassion like we have previously reported in YFS data (Hintsanen et al., 2019).

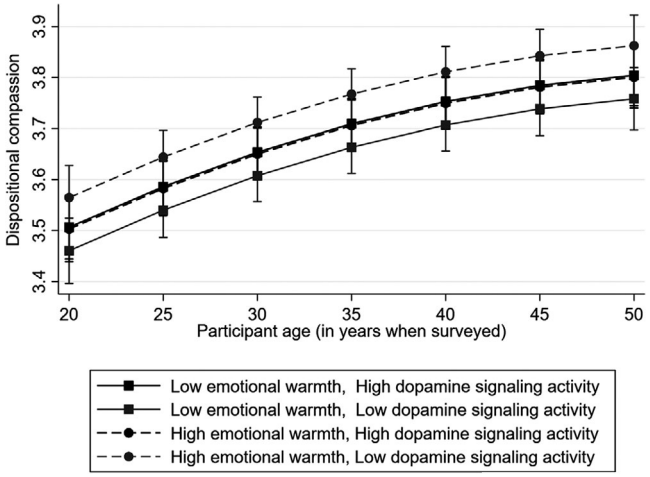

FIGURE 1 Predictive margins with 95% confidence intervals (Cis) of dispositional compassion from age 20 to 50 ($n = 2099$). For the two groups with low dopamine signaling activity levels, CIs were overlapping at the ages of 20, 25, and 50 years. For the two groups with high dopamine signaling activity levels, CIs were overlapping at all ages

Neither the genetic risk score for low dopamine activity nor for lower oxytocin levels was directly associated with the compassion trajectories.

We, however, found a significant gene–environment interaction between emotional warmth and the genetic risk score for dopamine activity ($b = .048$ [.005, .092]; $p = .031$). The effect for the gene–environment interaction should be interpreted as marginally significant after accounting for multiple testing ($q = .049$). The compassion trajectories at high and low levels (± 1 *SD*) of the early-environmental and genetic predictors are illustrated in Figure 1. In line with the differential susceptibility hypothesis, participants with low dopamine signaling activity had higher levels of compassion when growing up with emotionally warm parents, whereas they had lower levels of compassion when their parents were emotionally cold. Compassion development of those participants with high dopamine signaling did not vary with this early-environmental factor. That most of the 95% confidence intervals for the low signaling group include the mean of the high signaling group at the same age, in Figure 1, can be interpreted as evidence against differential susceptibility hypothesis.

The identified gene–environment interaction was also confirmed in complete case analysis ($n = 1771$; $b = .063$ [.018, .109]; $p = .007$), clearly surviving correction for multiple testing ($q = .021$). R-squared change, calculated with the Snijders & Bosker (1994) approach, from a model without the interaction between emotional warmth and dopamine signaling (level 1 = 5.32% / level 2 = 5.63%) to the model including the conditional effect was below 0.5% (increase at level 1 = 0.30% / level 2 = 0.36%, respectively). The effects size of the found gene–environment interaction therefore suggests that the actual difference in adulthood compassion between the low signaling group and the high signaling group due to differences in the parent–child relationship quality experienced during childhood is overall weak. The conditional effect turned out to be stronger in males ($n = 923$; $b = .067$ [.001, .134]; $p = .049$ / $q = .066$) than in females. We found in the three older cohorts (observed age range 29–50 years) a significant gene–environment interaction between emotional warmth and dopamine signaling activity ($n = 1052$; $b = .074$ [.0164, .131]; $p = .012$ / $q = .026$) but not in the three younger cohorts (observed age range 20–41 years).

When excluding the substituted SNP (rs1611115) from the genetic risk score for low dopamine activity to account for potential overfitting, the significance level dropped to $p = .071$ in imputed data but remained at $p = .013$ in full case analysis ($b = .065$ [.014, .116]; $q = .026$).

The two gene–environment interactions for oxytocin levels were not significant nor were the interactions between dopamine signaling activity and intolerance.

Finally, neither of the two genetic risk scores was associated with emotional warmth or intolerance. Thus, we did not find any indication that gene–environment correlations could have been held accountable for our findings.

4 | DISCUSSION

We found a gene–environment interaction in the life span development of compassion indicating that only participants who carry alleles associated with low dopamine signaling activity (previously linked to higher plasticity) were affected by normal variation in parental emotional warmth during childhood. For participants without these alleles, the parent–child relationship quality did not contribute to compassion development over time. This finding remained marginally significant when accounting for the proportion of expected Type 1 errors across analyses. It was further rather robust as the association was even stronger in full case analyses and was also found in the smaller subsamples of male participants. The found gene–environment interaction was also supported by prior theory. Because these participants were affected for better or worse by this important early-environmental factor, the finding suggests that the SNPs used to produce the cumulative genetic "risk" scores indicate plasticity rather than vulnerability. The observed pattern thus corresponds to our understanding of the differential susceptibility hypothesis (Belsky et al., 2013; Belsky & Pluess, 2009; Keers & Pluess, 2017). The variance in the outcome explained by this conditional effect was small (corresponding to Cohen's $d \sim 0.120$), however, limiting the practical significance of the findings. However, no single study can be conclusive and our promising findings need replication in independent samples (Duncan & Keller, 2011; Hewitt, 2012).

The gene–environment interaction was in line with prior empirical evidence as previous research has found genetic differential susceptibility due to carrying certain plasticity alleles in the dopamine pathway (Belsky & Pluess, 2013; Knafo et al., 2011; Si et al., 2020). At the same time, we did not find gene–environment interaction for oxytocinergic genes. Therefore, we cannot confirm the results of previous OXTR gene–environment interaction studies (Augustine et al., 2018; Dobewall, Hakulinen, Keltikangas-Järvinen, et al., 2018; Schneider-Hassloff et al., 2016). Our study contributes to the literature on personality development that suggests that genetic predispositions and

early-environmental influences interact in the activation of social learning processes (Zwir et al., 2019). Emotionally warm parenting experiences might have tuned the dopamine system in such a way that some more susceptible individuals became more compassionate over time (Carter et al., 2017). The finding that children differ in the degree they are affected by early environmental factors may also explain why shared environment commonly accounts for relatively little variance in twin models (Pluess & Belsky, 2010). Ando and colleagues (2004), for instance, reported that a model including only additive genetic and nonshared environmental influences fits best the data for compassion. Differential susceptibility could also be one of the reasons why many attempts to identify and replicate associations between single candidate genes and compassion-related traits and states have failed. That the gene–environment interaction was more robust in participants who were in adolescence when the parent–child relationship was measured is in line with findings showing that the influence of genes increases with age and in larger and more complex social environments (Knafo & Plomin, 2006).

The number of plasticity alleles in the dopaminergic and oxytocinergic signaling pathways was not directly related to dispositional compassion for others. This is in some conflict with previous studies that reported associations with related phenotypes such as empathy (Gong et al., 2017; Pearce et al., 2017), prosociality (Poulin & Holman, 2013; Reuter et al., 2011; Tost et al., 2010), and sensitive parenting (Feldman et al., 2012; Peltola et al., 2014; Skuse et al., 2014; Van IJzendoorn et al., 2008). One possible explanation could be that these socioemotional phenotypes may differ from compassion in their genetic underpinnings (Dobewall et al., 2021). Feldman and colleagues (2012) reported an association between plasma oxytocin levels and each of the polymorphisms included in the risk score used in the current study. Other studies, however, could not confirm this association (e.g., Parker et al., 2014). The limited knowledge about the exact function of variation in OXTR genes is thus another potential explanation for the lack of association with compassion development. Moreover, these mixed findings might be explained by the presence of gene–environment interaction, as suggested by the current study.

Although the development of compassion is recognized to be influenced by childhood social experiences and has a significant genetic component, these are the first gene–environment interaction results that support the importance of the quality of the relationship between parent and child in the development of compassion. In line with our earlier study (Hintsanen et al., 2019), only emotional warmth in a parent–child dyad was associated with the development of compassion over time. Also in this smaller YFS sample, variation in parental intolerance was not related to compassion. As we found a gene–environment interaction for emotional warmth but not for intolerance, this further supports that these two aspects of parenting should be studied separately. At the same time, twin studies, as well as molecular genetic evidence, suggest that also children have a substantial influence on their environments, partially evoking the parenting they experience during childhood (Avinun & Knafo, 2014; Dobewall et al., 2019). The parent–child relationship quality is a modifiable early life experience that may be improved with targeted interventions (see Armstrong et al., 2018; Collins et al., 2000; Thomas & Zimmer-Gembeck, 2007). However, the current study has shown that some individuals might be more strongly affected by this environmental factor than others for a genetic reason. Our results suggest that more susceptible individuals profit not only from interventions designed to prevent negative early-life experiences but also from provided support for positive parenting.

4.1 | Strengths and limitations

The current study has several noteworthy strengths. We began with specific hypotheses (i.e., genetic differential susceptibility to the parent–child relationship quality predicts the life span development of compassion) that correspond well to the observed findings (see Figure 1). The strengths further include an exceptionally long follow-up period over three decades and with the TCI (Cloninger et al., 1993), a well-established instrument to measure dispositional compassion repeatedly throughout adulthood. Another strength is the prospective study design, which made preregistration of the study less feasible. Study variables, on the other hand, were only handed out to the researchers after submitting a binding study plan to the YFS group.

We followed the recommendations of Dick and colleagues (2015) to increase confidence in positive findings after proper correction for multiple testing. We accurately report how many SNPs were available to us in total and how many of these were excluded in the current study. Furthermore, the genetic plasticity to early-environmental influences was measured with earlier established risk scores (Nikolova et al., 2011; Schneiderman et al., 2014). This reduces the number of tests being conducted, whereas in single-SNP analyses the resulting more stringent *p*-value adjustment would reduce the power of any given test (Anderson, 2008; Assary et al., 2018; Belsky & Israel, 2014). We justified why we selected our environmental factors over others, how they were operationalized, and which data transformations were performed based on previous research (Dick et al., 2015; Hintsanen et al., 2019). Parent–child relationship quality was reported by the parents of the participants ruling out the possibility that common method variance has driven the associations with self-reported compassion (Podsakoff et al., 2003). Finally, to guard against inflation of Type 1 errors we accounted for the FDR when interpreting our findings (Anderson, 2008; Benjamini et al., 2006). Bonferroni correction, as outlined above, would have been too conservative in our setting. We make clear that the found gene–environment interaction became marginally significant after considering multiple testing. We also performed several robustness checks and ruled out that the presence of gene–environment correlations has produced the observed findings (Avinun & Knafo, 2014; Dobewall et al., 2019).

The current study has also limitations. Selective attrition might have influenced the current results. Specifically, that excluded participants had parents who reported a more intolerant relationship with their child than the included participants might explain why we did not find an association between this early-environmental factor and the development of compassion. And, our parent–child relationship quality measure was not validated against other measures. The copy number

variants included in the original risk scores of Nikolova and colleagues (2011) and Schneiderman and colleagues (2014) were not available for this study, and we can only gauge if the associations would hold or might have even been stronger when including them. We were not able to rule out the possibility that their substitution might have resulted in overfitting our data because the substituted SNP (rs1611115) has been used in a previous publication (Dobewall et al., 2021). Unfortunately, the parents of the YFS participants have not been genotyped yet and it was thus not possible to control for genetic overlap within a parent–child dyad to rule out that observed parental influences are primarily due to their shared genotype (Avinun & Knafo-Noam, 2015; Kandler et al., 2016; Knafo-Noam et al., 2020).

Even though the YFS sample is representative of the Finnish population (Akerblom et al., 1991; Raitakari et al., 2008) and larger than the vast majority of previous gene–environment interaction studies (Dick et al., 2015; Duncan & Keller, 2011), it is relatively small for genetically informed analyses and the identified gene–environment interaction must be interpreted with caution unless replicated. Although the interaction between emotional warmth and dopamine activity was only approaching significance, it was supported by prior theory and empirical evidence, and we hope that the current study encourages and merits further investigation to see if it is replicable in other independent samples.

4.2 | Conclusions

We found a gene–environment interaction corresponding to the recently formulated differential susceptibility hypothesis. Compassion development over the life span was affected by variation in parental emotional warmth—for better or worse—only for those individuals who carry alleles associated with low dopamine signaling activity. For individuals without these plasticity alleles, the parent–child relationship quality did not contribute to the development of compassion. Our findings suggest that children's genotype in the dopamine signaling pathway might result in plasticity to early environmental influences that have a long-lasting effect on dispositional compassion for others. When accounting for the number of conducted tests, the association remained marginally significant, yet, unless replicated, the findings must be interpreted with caution.

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DATA AVAILABILITY STATEMENT

The dataset supporting the conclusions of this article was obtained from the Cardiovascular Risk in Young Finns Study (YFS), which comprises health-related participant data. The use of data is restricted under the regulations on professional secrecy (Act on the Openness of Government Activities, 612/1999) and on sensitive personal data (Personal Data Act, 523/1999, implementing the EU data protection directive 95/46/EC). Due to these restrictions, the data cannot be stored in public repositories or otherwise made publicly available. Data access may be permitted on a case-by-case basis upon request only. Data sharing outside the group is done in collaboration with the YFS group and requires a data-sharing agreement. Investigators can submit an expression of interest to the chairman of the publication committee (Prof. Mika Kähönen, Tampere University, Finland).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

L.K.-J., O.R., T.L., and M.H. contributed to data collection. H.D. conducted the statistical analyses and drafted the manuscript. L.-P.L. and I.Z. assisted with the statistical analyses. H.D., L.K.-J., A.S., L.-P.L., I.Z., C.R.C, O.R., T.L., and M.H. contributed to the interpretation of the results and contributed to the writing and revising of the manuscript.

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