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Genetic mechanisms of parenting

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ABSTRACT

This article is part of a Special Issue "Parental Care".

The complexities of parenting behavior in humans have been studied for decades. Only recently did we begin to probe the genetic and epigenetic mechanisms underlying these complexities. Much of the research in this field continues to be informed by animal studies, where genetic manipulations and invasive tools allow to peek into and directly observe the brain during the expression of maternal behavior. In humans, studies of adult twins who are parents can suggest dimensions of parenting that might be more amenable to a genetic influence. Candidate gene studies can test specific genes in association with parental behavior based on prior knowledge of those genes' function. Gene-by-environment interactions of a specific kind indicating differential susceptibility to the environment might explain why some parents are more resilient and others are more vulnerable to stressful life events. Epigenetic studies can provide the bridge often necessary to explain why some individuals behave differently from others despite common genetic influences. There is a much-needed expansion in parenting research to include not only mothers as the focus—as has been the case almost exclusively to date—but also fathers, grandparents, and other caregivers.

Introduction: Mammalian mothering and its multiple influences

Colloquial references to a 'maternal instinct' or a 'maternal drive' are common and reveal a general presupposition about mothers: that there are innate rules shaped by the long course of evolutionary history and hardwired into the DNA, which drive all mothers to respond to, nurture, and protect their offspring (Rosenblatt, 1967). The focus of this review is to explore the current evidence of such a genetic component to mothering.

The evidence for intergenerational transmission of parental behavior is clear: mothering begets mothering (Fleming et al., 2002). Both positive and negative aspects of early experience being parented tend to be repeated by the next generation, in humans and animals alike (Belsky et al., 1989, 2005; Capaldi et al., 2003; Chen and Kaplan, 2001; Chen et al., 2008; Gonzalez et al., 2001; Kovan et al., 2009; Maestripieri, 2005; Maestripieri et al., 2007; Newcomb and Locke, 2001; Suomi, 1999; van IJzendoorn, 1992). Just how these behaviors are transmitted across generations is as yet unclear. Does the transmission stem from underlying similarities in genetic code, or are behaviors repeated because environments are similar? The short answer based on the evidence to date is: neither, and both.

Complex biological organisms function at the interface between their genetic programming and the environment in which they dwell. Myriad contextual or 'external' influences shape mothering, and much work has been done in this area. A smaller but growing number of studies have examined the heritable components of mothering and peered deeper at the molecular level of genetic variation to ask how DNA might shape parenting. Finally, we are beginning to understand the bridge between environmental and genetic influences: epigenetic changes. Epigenetic changes are more or less stable modifications of gene regulatory machinery occurring *outside* the level of DNA sequences. They might be the bridge or "physical point of connection" (Boyce and Kobor, 2015) between genes and environment that can account for some portion of the behavioral plasticity we see across an individual's development. For instance, early neglect and abuse tends to be repeated in the new generation, but not for everyone. Only about 30–40% of mothers who were abused as children go on to abuse their own children (Kaufman and Zigler, 1987; Sroufe et al., 2005), and the complex associations between early life abuse and later abuse toward one's own children might be in part owing to differential epigenetic changes. The epigenome represents a way to introduce plasticity in behavior, via plasticity in the expression of genetic products, despite the underlying stability of structural DNA.

The mammalian order presents species with vast differences in the types and quantities of parental care, from the simple licking and grooming behavior of the mother rat to the highly complex parenting behavior of humans. This review is aimed at the genetic underpinnings

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of *human* mothering, but we will provide multiple examples from other mammalian species used in parenting research (e.g., rats, sheep, voles, monkeys). Even though there are basic features in human parenting—including the provision of caretaking, ambulation, and feeding—we see much fine-tuning or variation according to cultural or environmental pressures (Bornstein, 1989; Bornstein et al., 1992, 2007; Harwood et al., 1999; Keller, 2004; Quinlan, 2007; Trehub et al., 1993). For instance, mothers around the globe engage in face-to-face communication, infant body contact/stimulation, and primary care (e.g. nursing) (Mesman et al., 2012; Mileva-Seitz and Fleming, 2011). Yet mothers can differ in their perception and processing of infant cues, and in their motivation to attend to them (Barrett and Fleming, 2011; Leavitt, 1998, 1999; Mileva-Seitz and Fleming, 2011; Mileva-Seitz et al., 2012a). When looking for genetic underpinnings of parental behavior it might be helpful to start at the systems that regulate these perceptual and motivational processes in the brain. In the present review, we will consider studies of three broad dimensions of 'parenting': (1) macro-analytic parental behaviors, such as the more global scales of *quality* of parental interactions (e.g., sensitivity and warmth); (2) micro-analytic parental behaviors, such as the *quantity* (duration, frequencies) of discrete parental behaviors (e.g. frequency of touch, orienting away from the infant); and (3) prenatal parenting effects, such as the nutritional and hormonal prenatal environment a fetus is exposed to. Before turning to specific genes of interest in parenting, we review the evidence for a heritable component of parenting.

The early evidence for heritability in parenting: Behavioral genetics

The original way to explore genetic effects on human behavior was through the use of 'behavioral genetics' studies, which employ multiple types of families including twins and adoptive vs. biological siblings. In twin studies, genetic contributions to behavior are inferred from quantification of behavioral differences between monozygotic (MZ) and dizygotic (DZ) twins. MZ and DZ twins differ in their genetic similarity. The environment is shared when it makes them more similar to one another, and unique or non-shared when it makes them more different. Behavioral genetics makes it possible to differentiate between the contribution of these three components—genetics, shared, and non-shared environment—to a behavior or trait. Examining the heritability of parenting, researchers have made use of twin studies that allow for comparison of parenting behavior between adult parent twin-pairs (parent-based in contrast to child-based designs, see Bakermans-Kranenburg and Van IJzendoorn, *in press*). Six parent-based behavioral genetic studies that addressed the heritability of different dimensions of parenting were meta-analyzed (Klahr and Burt, 2014). Non-shared influences (experiences that are unique for each sibling) including measurement error accounted for 63–90% of the variance in parenting. For parental control the combined genetic estimate was zero, whereas the combined genetic estimates for warmth and negativity were around 30% (Klahr and Burt, 2014). Twin studies however do not reveal the genetic mechanisms underlying variation in phenotypes. A second approach—the exploration of genetic variance at the molecular level of the DNA—is therefore a useful and timely complement to behavioral genetics efforts to gain a fuller understanding of genetic mechanisms in parenting.

Molecular genetics, candidate genes

Molecular genetic studies in humans examine particular DNA sequences that might be associated with traits of interest. Human maternal responsiveness might be influenced by large networks of interacting genes, in addition to the plethora of environmental influences. Given such complexity and the sheer volume of potential candidates for gene analysis, prior knowledge about function—of the genes, proteins, and associated biochemical networks resulting from the genes of interest—helps to narrow down the candidate genes. This is the 'hypothesis driven' or 'mechanistic' approach (Dalziel et al., 2009; Tabor et al., 2002). In accordance with this, genetic factors that regulate key brain systems related to perceptual and motivational processes are likely to also influence maternal behavior. The search for candidate genes associated with human parenting has centered on three key neurotransmitter systems (Bakermans-Kranenburg and van IJzendoorn, *in press*) to which we turn next: dopamine, oxytocin, and serotonin.

Dopamine

Dopamine has a crucial role in regulating maternal care in rats. This role can be better understood by considering the neural circuitry of the maternal rat. This circuit consists of several major regions: the medial preoptic area (MPOA), the ventral bed nucleus of the stria terminalis (vBST), the nucleus accumbens (NA) and the medial and cortical amygdala (MCA) (Numan, 2015). These regions either directly receive dopaminergic innervation, or interact with other regions of the brain that are under dopaminergic control. For instance, the MPOA stimulates dopaminergic neurons via the ventral tegmental area to the NA, which increases maternal responsiveness to pup stimuli (Numan, 2006). In virgin rats, electrical or hormonal stimulation of the MPOA/vBST induces maternal behavior (Numan et al., 2006), as does the application of dopamine receptor agonists into the NA (Numan et al., 2005). Conversely, lesions or the administration of dopamine receptor antagonists either systemically or in the MPOA, VTA, and NA *reduce* the naturally rewarding properties of pups in maternal rats (Lee et al., 2000), disrupt normal maternal behaviors (e.g. pup approach and pup retrieval) (Byrnes et al., 2002; Hansen et al., 1991; Keer and Stern, 1999; Li and Fleming, 2003a,b; Li et al., 2004, 2005; Numan et al., 2005; Parada et al., 2008), and block the consolidation of postpartum maternal experiences (Li and Fleming, 2003a,b).

There are also natural differences between rat dams in the levels of dopamine release into the NA: Those who are considered high-lickers and groomers have a greater dopamine release than those who have low levels of pup licking and grooming (Champagne et al., 2004). Postpartum females have naturally suppressed dopamine baseline levels, but these levels increase significantly when they are exposed to pups (Afonso et al., 2009), or following reunion with pups after a separation (Hansen et al., 1993). Pups are so rewarding that new rat mothers prefer pups to cocaine until about day 8 postpartum (Mattson et al., 2001). Even cycling (non-postpartum) females, for whom avoidance is the typical response to pups, show a dopamine increase when exposed to pups that is proportional to their prior pup exposure (Afonso et al., 2008). At the genetic level, early evidence suggests that expression of dopamine receptor genes D1 (DRD1) and D2 (DRD2) is upregulated during pregnancy in the rat (Mann, 2014). Furthermore, there is upregulated expression of dopamine receptor D4 (DRD4) and dopamine transporter DAT1 mRNA in the MPOA following pup exposure, regardless of maternal parity (Akbari et al., 2013). Taken together, this evidence suggests a strong role of dopamine in rat maternal regulation. As Rosenblatt (1967) already shown, pups may be partially responsible for the onset and ongoing maintenance of maternal behavior, and the mechanism might be the stimulation of gene expression in the mother. Natural bursts of dopamine firing neurons in the mammalian striatum are said to be crucial for the pup-regulated aspects of maternal care (i.e. maternal care in response to pup-cues) (Robinson et al., 2011). However, individual differences in dopamine gene function unrelated to pup cues (e.g., from early rearing effects or underlying genetic variation) might predict individual differences in maternal behavior. Other rodent models have provided evidence for the dopamine-mothering link. For instance, an interesting study of hypodopaminergic mice (mice genetically engineered to express less dopamine) indicated that striatal dopamine is crucial for 'active' maternal behaviors such as pup-retrieval and liking/grooming of pups, and not for 'passive' behaviors such as nursing (Henschen et al., 2013). In voles, the effects of a dopamine antagonist (haloperidol) had similar effects on parenting behavior as are found in rats, generally reducing 'active' components of maternal

behavior (e.g. duration of licking), although species-specific differences in the effects can be seen (Lonstein, 2002).

Dopamine and human mothering

Given dopamine's key role in mothering in rodents, it seems only logical to explore genetic variants (polymorphisms) underlying dopamine transmission (e.g. D'Souza and Craig, 2006) for their potential influences on human maternal behavior. In humans, the non-genetic evidence for dopamine's role in parental care is indirect. It comes chiefly from a series of functional magnetic resonance imaging (fMRI) studies in which mothers were exposed to infant vocalizations (Lorberbaum et al., 2002; Sander et al., 2007; Seifritz et al., 2003), pictures (Barrett et al., 2011; Bartels and Zeki, 2004; Leibenluft et al., 2004; Nitschke et al., 2004; Strathearn et al., 2008), or video fragments (Noriuchi et al., 2008; Ranote et al., 2004). These studies report activity in brain regions occupied by the vBST and VTA, striatum, amygdala, cingulate cortex, thalamus, medial prefrontal cortex, and right orbitofrontal cortex. Most of these are either dopaminergic regions, or directly interact with dopaminergic regions (Georges and Aston-Jones, 2002).

Only a handful of candidate gene studies have explored dopamine gene polymorphisms in relation with individual differences in human parenting (Table 1). For instance, polymorphisms of DRD4 and COMT (coding for catechol-O-methyltransferase, a dopamine deactivating enzyme) genes interact with maternal daily hassles to predict differences in maternal sensitive responding to toddlers (van IJzendoorn et al., 2008). Polymorphic variation on DAT1 is associated with more negative maternal behaviors and commands to their 5-year-old children (Lee et al., 2008). Furthermore, polymorphisms on both DRD1 and DRD2—key receptors in rat maternal regulation—are also associated with differences in observed maternal care in humans: DRD1 polymorphisms associate with how often mothers turn away from their 6-month old infants during a 20-min free-play episode; and DRD2 polymorphisms associate with how long mothers vocalize (talk and sing) to these infants (Mileva-Seitz et al., 2012b). Not all studies find significant associations, however. Mills-Koonce et al. (2007) failed to find an association between maternal genotype at another dopamine-related polymorphism (on the gene ANKK1, close to DRD2) and observed maternal sensitivity. Among the notable strengths of these studies is that they used observed measures of parenting. Nonetheless, in the absence of knowledge about the specific function of these genetic polymorphisms, further replication is necessary before their role in the regulation of maternal sensitivity and maternal behavior is clear.

Oxytocin/vasopressin

Another neurotransmitter important to mothering is the nine-amino acid peptide oxytocin (or alpha-hypophamine). Oxytocin is synthesized mostly in the hypothalamus (Lee et al., 2009) and oxytocin neurons in rats project to brain regions important for social and maternal behavior regulation, including the MPOA and NA (Carter, 2014; Francis et al., 2000; Numan, 2015). In addition to its crucial peripheral (hormonal) role during labor and delivery and lactation, in many non-primate mammalian species oxytocin is also key to regulating (the onset of) maternal behavior (Fahrbach et al., 1985; Kendrick, 2000; Numan, 2015; Pedersen et al., 1994). Oxytocin receptor binding is higher in rat dams who are naturally high-lickers and groomers (Francis et al., 2000). Accordingly, oxytocin receptor antagonist infusions into the VTA and MPOA immediately postpartum inhibit maternal behavior onset (Pedersen et al., 1994), whereas antagonist infusion into the cerebral ventricles inhibits the expression of maternal behavior in rats (van Leengoed et al., 1987). Individual differences in centrally inducible oxytocin receptors predict natural differences in rat maternal behavior (Champagne et al., 2001). Oxytocin may also mediate maternal behavior in rat dams *indirectly*, by altering the dam's anxiety levels, which themselves relate to maternal behavior (Bosch, 2010). Other species also provide evidence of the importance of oxytocin in mothering: in sheep, oxytocin administration results in maternal behavior toward foreign lambs (Keverne and Kendrick, 1992) and decreases the aggression and aversion to newborn lambs (Insel and Young, 2001). In mutant mice lacking the oxytocin receptor gene, maternal behavior is impaired (Takayanagi et al., 2005).

In primates, oxytocin is not *essential* for the establishment of maternal care, but it is important in post-parturition bonding and maternal behavior (Broad et al., 2006; Saltzman and Maestripieri, 2010). Pregnancy hormones prime the mesolimbic dopamine projections to the NA and up-regulate oxytocin receptors in the brain. These modulations of the reward system facilitate mother–infant bonds at birth (Broad et al., 2006). Additionally, peripheral administration of an oxytocin receptor blocker in rhesus macaques reduces interest in the infant (e.g. lip-smacking, approaching, touching) (Boccia et al., 2007). Furthermore, whereas cerebrospinal levels of oxytocin in multiparous rhesus macaque females do not correlate with mother-infant interaction (Cooke et al., 1997), *plasma* levels of oxytocin are highly correlated with 'maternal warmth' (Maestripieri et al., 2009). The behavioral and physiological evidence from both rodents and primates gives reason to examine genetic variation in the oxytocin system in human parenting.

Oxytocin and human mothering

In humans, an increase in plasma oxytocin level from early to mid-late pregnancy correlates with higher scores on ratings of attachment to the fetus (Levine et al., 2007). Thus oxytocin might be important for bonding even before the infant has been born. In the postpartum period, maternal and infant salivary oxytocin levels are correlated with each other and with mother-infant affect synchrony (Feldman et al., 2010b); and high levels of plasma oxytocin predict high levels of affectionate touch toward infants (Feldman et al., 2010a). Increased oxytocin levels are found in mothers who recently touched or interacted with their infants (Light et al., 2000). Thus, oxytocin is important for human parenting (Galbally et al., 2011), and this is not limited to parturition and breastfeeding but rather extends to the expression of behavioral responses toward infants. Among the limitations of this research is that oxytocin levels are difficult to quantify. This is for several reasons: oxytocin has a multiple-site release, many functions, and a diurnal rhythm in the cerebrospinal fluid but not peripherally (Amico et al., 1983). Moreover, because oxytocin does not cross the blood–brain barrier in adult animals (Saltzman and Maestripieri, 2010), plasma and cerebrospinal fluid levels may not be identical. However, plasma and cerebrospinal fluid oxytocin levels have been found strongly correlated (Carson et al., 2014).

A next step has been to determine whether genetic variation in the human oxytocin genes is associated with differences in maternal behavior or related functions. The first study of this kind showed a significant association between the rs53576 polymorphism on the oxytocin receptor gene (OXTR) and parental sensitive responsiveness in a sample of mothers with toddlers (Bakermans-Kranenburg and van IJzendoorn, 2008). A later study in 500 families with twins indicated that maternal genotype at this site is also associated with maternal warmth (Klahr et al., 2014). This same polymorphism has since been associated with differences in positive parenting and with differences in neural activation of brain regions previously associated with positive parenting in a longitudinal study spanning 15 years (Michalska et al., 2014). The OXTR rs53576 SNP also appears to be associated with cardiac reactivity to infant cries: Non-mothers with the GG genotype had greater heart rate responses to infant cries, but only when they had low depression scores (Riem et al., 2011). This genetic polymorphism is likely one of many other variants involved in cardiac reactivity to infant distress. In fact, a twin study indicates that nearly half of variance in adults' cardiac reactivity to infant cry stimuli is explained by genetic factors (Out et al., 2010). However, as with dopamine polymorphisms, one of the difficulties with the use of polymorphisms in association studies is the lack of clear evidence of a functional impact. Although the OXTR rs53576 SNP has been suggested to influence oxytocin function (Meyer-Lindenberg

Table 1
Candidate gene studies in parenting.

Neurobiological system	Gene	Parental polymorphism[a]	Moderator[b]	Outcome[c]	Sample size	Child age	Reference
Dopamine	Dopamine Receptor D1 (DRD1)	**rs265981** rs5326 rs4532 **rs686** rs265976	–	Sensitivity (M) Vocalization duration (M) **Orienting away from infants frequency (M)**	187 Caucasian	6 mo (healthy)	Mileva-Seitz et al., 2012a
	Dopamine receptor D2 (DRD2)	rs1799978 **rs1799732** **rs6277**	–	Sensitivity (M) **Vocalization duration (M)** Orienting away from infants frequency (M)	187 Caucasian	6 mo (healthy)	Mileva-Seitz et al., 2012a
	Dopamine receptor D4 (DRD4)	Exon III 7-repeat	Daily hassles COMT genotype **Daily hassles × COMT genotype**	Sensitivity (M)	176 Caucasian	23 mo (at risk)	Van IJzendoorn et al., 2008
	Dopamine transporter (DAT1)	10-repeat	Disruptive child behavior	Positive parenting (M) **Negative parenting (M)** **Number of commands (M)**	259 Mixed ethnicity	3.8–7.0 years (ADHD cases & controls)	Lee et al., 2008
	Ankyrin repeat and kinase domain containing 1 (ANKK1)	Taq1A	Child genotype	Sensitivity (M)	172 Mixed ethnicity	6–12 mo (healthy)	Mills-Koonce et al., 2007
	Catechol-O-methyltransferase (COMT)	Val158met	Daily hassles DRD4 genotype **Daily hassles × DRD4 genotype**	Sensitivity (M)	176 Caucasian	23 mo (at risk)	Van IJzendoorn et al., 2008
Oxytocin	Oxytocin receptor (OXTR)	**rs53576**	5HTT genotype	**Sensitivity (M)**	159 Caucasian	2 years (at risk)	Bakermans-Kranenburg and van IJzendoorn, 2008
	Oxytocin receptor (OXRT)	**rs53576**	–	**Warmth** (**M**, F) Control (M, F) Negativitiy (M, F)	500 Mixed ethnicity	6–10 years (healthy)	Klahr et al., 2014
	Oxytocin receptor (OXTR)	**rs53576** **rs1042778**	–	**Positive parenting (M)** Negative parenting (M) **Hemodynamic responses to child stimuli in orbitofrontal cortex, anterior cingulate cortex, and hippocampus**	34 Mixed ethnicity	4–6 years (at risk)	Michalska et al., 2014

	Oxytocin receptor (OXTR)	rs53576	**Depression**	Cardiac reactivity to infant cries (N)	40 Caucasian	–	Riem et al., 2011
	Oxytocin receptor (OXTR)	**rs2254298 rs1042778**	Plasma oxytocin	Parental Gaze (B) Parent–infant gaze synchrony (B) **Parental Touch (B)**	272 Caucasian	4–6 mo (healthy)	Feldman et al., 2012
	Oxytocin receptor (OXTR)	rs237885	Early life adversity	Breastfeeding duration	201 Mixed ethnicity + 151 Mixed ethnicity (replication sample)	0–12 mo (healthy)	Jonas et al., 2013
	Oxytocin receptor (OXTR)	rs237885	Early care quality	Sensitivity (M) Orienting away from infant frequency (M) Infant-directed vocalizing duration (M) Instrumental care (M)	187 Caucasian	6 mo (healthy)	Mileva-Seitz et al., 2013
	Oxytocin (OXT)	**rs2740210 rs4813627**	**Early care quality**	Sensitivity (M) Orienting away from infant frequency (M) **Infant-directed vocalizing duration (M)** **Instrumental care (M)**	187 Caucasian	6 mo (healthy)	Mileva-Seitz et al., 2013
	Oxytocin (OXT) rs4813627	**rs2740210**	**Early life adversity**	Breastfeeding duration	201 Mixed ethnicity + 151 Mixed ethnicity (replication sample)	0–12 mo (healthy)	Jonas et al., 2013
	Cluster of differentiation 38 (CD38)	**rs3796863**	**Plasma oxytocin**	Parental Gaze (B) **Parent-infant gaze synchrony (B)** **Parental Touch (B)**	272 Caucasian	4–6 mo (healthy)	Feldman et al., 2012
Vasopressin	Arginine Vasopressin Receptor 1A (AVPR1A)	**RS3 microsatellite** rs1042615 rs7298346	**Early life adversity**	Sensitivity (M)	151 Caucasian	18 mo (healthy)	Bisceglia et al., 2012
	Arginine Vasopressin Receptor 1A (AVPR1A)	RS3 microsatellite	-	Positive parenting (M) Controlling behavior (M) **Focused support (M)**	135 Caucasian	3.5 years (healthy)	Avinun et al., 2012
Serotonin	Serotonin transporter (5HTT)	5HTTLPR	OXTR genotype	Sensitivity (M)	159 Caucasian	2 years (at risk)	Bakermans-Kranenburg and van IJzendoorn, 2008
	Serotonin transporter (5HTT)	**5HTTLPR + rs25531**	**Early care quality**	**Sensitivity (M)** **Orienting away from infant frequency (M)** **Perceived attachment to infant (M)**	166 Caucasian	6 mo (healthy)	Mileva-Seitz et al., 2011
	Serotonin transporter (5HTT)	**5HTTLPR**	Observed fearfulness	Sensitivity (M)	767 Caucasian	14 mo, 36 mo, 48 mo (repeated measures) (healthy)	Cents et al., 2014
	Serotonin transporter (5HTT)	5HTTLPR	**Child sex**	Positive parenting (M)	228 Caucasian	3.5 years (healthy)	Pener-Tessler et al., 2013

[a] Bolded values indicate a main effect of genotype and/or interaction effect (genotype × moderator) on the outcome.
[b] Bolded values indicate a significant interactive effect between the moderator and the genotype.
[c] M indicates this variable was measured for mothers; F indicates fathers; B indicates a mixed report of fathers and mothers; and N indicates a non-parent sample; bolded values indicate a significant effect on the outcome.

et al., 2011), a meta-analysis of 48 studies (combined N = 17,559) using this polymorphism found no significant combined effect sizes for five domains of outcomes (biology, personality, social behavior, psychopathology, and autism) (Bakermans-Kranenburg and van IJzendoorn, 2014).

Other SNPs in OXTR-related genes have also been explored in relation to differences in human parenting. For instance, an Israeli study examined three SNPs (OXTRrs2254298 and rs1042778, and CD38 rs3796863) in association with parent-infant gaze synchrony and parental touch (Feldman et al., 2012). Parents with the CD38 CC genotype and the OXTR rs1042778 TT genotype touched their infants less frequently than parents with other genotypes, whereas no genetic associations were found for gaze synchrony (Feldman et al., 2012). This is an interesting finding as CD38 regulates oxytocin release and has been found related to autism spectrum disorders (Munesue et al., 2010). Mice-knockouts for the CD38 gene exhibit reduced oxytocin levels and deficits in social and maternal behavior (Jin et al., 2007).

Finally, two recent studies indicate that polymorphic variation in the vasopressin receptor 1A gene associates with differences in maternal sensitivity (Bisceglia et al., 2012) and structuring and support (Avinun et al., 2012) toward their children. Vasopressin has structural similarity to oxytocin and there is mounting evidence for its implication, too, in the regulation of social behavior (Ebstein et al., 2012; Heinrichs and Domes, 2008; Meyer-Lindenberg et al., 2011). More work is needed to establish a potential role for vasopressin in human mothering.

In prairie voles, oxytocin and vasopressin dynamics during pregnancy are primarily regulated not by the *receptors* for these peptides (which remain fairly stable in the brain throughout pregnancy), but instead by the synthesis and release of the peptides themselves (Ophir et al., 2013). Thus polymorphisms on the peptide-coding genes, rather than on the receptor-coding genes, might prove useful to study, also in human parenting. In this vein, a longitudinal study on Maternal Adversity, Vulnerability, and Neurodevelopment (MAVAN) examined two SNPs in the oxytocin peptide gene (OXT rs2740210 and OXT rs4813627) and one polymorphism in the oxytocin receptor gene (OXTR rs237885) in association with several dimensions of observed maternal behavior (Mileva-Seitz et al., 2013). The two OXT SNPs were significantly associated with differences in maternal vocalizing to the infant, but not maternal 'sensitivity' (a more global measure of parental quality; Ainsworth et al., 1978). That SNPs associate with some but not other maternal behavior outcomes could indicate that the multiple dimensions of parental behavior have differential genetic regulation. A subsequent study in the same sample revealed that the OXT rs2740210 genotype was also related to breastfeeding duration, with replication in an independent sample (Jonas et al., 2013). The OXTRrs237885 genotype was not related to either vocalizing or maternal sensitivity or breastfeeding. Oxytocin has an undisputed role in parenting, and yet the evidence for a significant association between genetic variants in oxytocin genes and human parental behavior is not conclusive. OXTR genotypes have been suggested as an important direction in parenting research (Taylor, 2008), but the results from human studies are less consistent than might be expected on the basis of animal research. The lack of functional knowledge about many of these SNPs limits the conclusions that can be drawn. Once more, replications and functional studies of the oxytocin and vasopressin genes are necessary.

Serotonin

Serotonin (5-hydroxytryptophan; 5-HT) is another monoamine with major function in the brain. It is involved in regulating mood, emotion, cognition, and vital functions like sleep, appetite, and sexuality. Animal studies provide evidence that 5-HT plays at least an indirect role in parental behavior. For instance, juvenile rats have higher levels of 5-HT in the MPOA and lower levels of dopamine in the NA than adults, correlating with a shorter time to spontaneous maternal behavior (1–3 days) than in adult rats (5–7 days) (Olazábal et al., 2004). The underlying differences in dopamine and 5-HT levels between juvenile and adult brains may explain differences in neophobia towards pups (Olazábal et al., 2004). Early work inducing lesions in the rat median raphe, a region responsible for the primary serotonin production, showed resulting deficits in pup retrieval and increased pup cannibalism (Barofsky et al., 1983). Serotonin reuptake inhibition with fluoxetine increases the appetitive aspects of rat maternal behavior (Johns et al., 2005). Finally administration of clozapine results in impairments in rat maternal behavior and due to the pharmacology of the drug, specifically implicates the 5-HT_2 serotonin receptor in this process and in interaction with the dopamine system (Zhao and Li, 2009). In primates, 5-HT is implicated in anxiety arousal of mothers (Maestripieri, 2010). Infants of abusive or restrictive mothers have lower levels of 5-HT metabolites (5-HIAA)(Maestripieri et al., 2006). Conversely, monkeys with lower CSF 5-HIAA levels are more restrictive and rejecting (Maestripieri et al., 2007). Together this evidence suggests the serotonin system is an important modulator of parental behavior, either directly or when acting in concert with the dopamine and oxytocin systems. Moreover, the serotonin system might indirectly impact parenting through its regulation of related processes like mood and emotion, both of which are important to parenting.

Serotonin and human mothering

In humans, dysregulations in brain 5-HT levels are associated with increased aggressive behaviors, and with the development of psychopathologies, particularly in the affective spectrum (Lucki, 1998). A single study assessing the effects of SSRI use on maternal behavior in women with postpartum depression found an increase in maternal reported appreciation of motherhood, but no accompanying differences in mother–infant interactions at 8 weeks postpartum (Logsdon et al., 2009). A handful of candidate gene studies have explored genetic variants on serotonin genes in association with differences in parenting behavior. For instance, a first study reported that the short allele on the serotonin transporter gene 5HTT was related to lower maternal sensitive responsiveness (Bakermans-Kranenburg and van IJzendoorn, 2008). A subsequent study showed the opposite: mothers with the short allele were *more* sensitive during interactions with their 6-month old infants, and less often oriented away from their infants (Mileva-Seitz et al., 2011). Mileva-Seitz et al. speculated that the discrepant findings in those first two studies of the short 5HTT allele were owing to methodological differences: if it can be assumed that carriers of the short allele are more responsive to environments, both good and bad, then a less stressful experimental protocol (as in the Mileva-Seitz et al. study involving home visits) might be associated with greater parental sensitivity than a more stressful experimental protocol (as in the Bakermans-Kranenburg and Van IJzendoorn study involving structured laboratory tasks and children with high levels of externalizing behavior). The findings initially reported by Mileva-Seitz et al. (2011) were later replicated in a large cohort using repeated measures of observed maternal sensitivity (Cents et al., 2014). A twin study revealed a gender effect in the association between the short allele and parenting: for mothers of boys, positive parenting decreased with the number of maternal short alleles, whereas for mothers of girls positive parenting was not associated with the number of short alleles (Pener-Tessler et al., 2013). These findings emphasize the importance of study design and covariates in the search for replication.

Other genetic pathways

There is considerable overlap in both region of expression and functional significance of the three neurotransmitter systems described above—oxytocin, dopamine, and serotonin—and interactions between these systems could influence social behavior (Baskerville and Douglas, 2010; Emiliano et al., 2007; Skuse and Gallagher, 2011). In rats, an interaction between oxytocin and dopamine helps regulate maternal behavior (Shahrokh et al., 2010). However, almost nothing else is known about the potential overlap between these three systems in the expression of maternal care. Additional closely related systems might

also be involved. For instance, variation in the mu opioid receptor gene, OPRM1, is associated with maternal attachment to infants in free-ranging rhesus macaques (Higham et al., 2011). Mu opioid receptor genes are good candidate genes for study in human parenting for several reasons: they are implicated in social reward processing in the NA of the rat (Trezza et al., 2011) and are regulated by both the dopamine and oxytocin systems in the brain (Gigliucci et al., 2014). Finally, the SNP on the OPRM1 gene in rhesus macaques has a functionally similar ortholog in humans (Bond et al., 1998; Miller et al., 2004).

Another useful strategy for identifying genes and pathways involved in parenting has been to identify sexually dimorphic genes: that is, genes that are expressed at different levels in females and males. Subsequently their expression can be experimentally disrupted to detect resulting changes in parental behavior. This approach has led to the successful identification of several other genes without which normal maternal behaviors (e.g. retrieval of pups to the nest and aggression toward intruders) are disturbed (Xu et al., 2012). An early study in mice indicated that the deletion of the paternally imprinted Peg3 gene leads to impairments of maternal behavior so severe they often led to the death of the offspring (Li et al., 1999). Maternal memory and learning in the mouse appears to be partially dependent on the estrogen receptor-β (Esr2) and oxytocin, and appears to require stable changes in gene expression to maintain heightened maternal responsiveness for long durations (Stolzenberg et al., 2014). Subsequent studies have shown that compared with virgin mice, postpartum mice exhibit enrichment in the expression of *hundreds* of genes involved in reward and addiction (Zhao et al., 2014). This suggests that the shift to parenting is intricately tied to changes in the reward-processing mechanisms in the brain. Studies comparing wide-scale gene expression in postpartum and virgin rats, specifically in brain regions thought to be involved in parenting (e.g. MPOA, medial prefrontal cortex), support the notion that subsets of genes regulating maternal behavior and maternal memory are also implicated in psychopathologies like social disorders, depression, psychosis, and bipolar disorder (Driessen et al., 2014; Eisinger et al., 2014; Zhao et al., 2014). Thus the neural plasticity required during the normal shift to parenting also puts mothers at risk for mental health disorders often associated with the postpartum period.

Limitations of the candidate gene approach

Though candidate gene studies have reported thousands of genetic variants associated with a range of complex phenotypes, such studies suffer from a general lack of replication among a suite of other limitations (e.g., neglecting the importance of the environment; Rutter, 2005). On the one hand, such studies often use invalid measure for complex traits (Ebstein, 2006) and small sample sizes with insufficient power to detect true effects (false negatives). On the other hand, an inconsistent use of correction for multiple testing often results in spurious effects (false positives). Moreover, even when effects can be replicated, meta-analyses often reveal non-significant combined effects after taking into account multiple studies conducted in a variety of environments and populations, reporting findings in the opposite directions. Finally, the functional significance of most of these variants—even some of the most widely studied (e.g. DRD4 Exon III 7-repeat)—is still unclear (Pappa et al., in preparation).

The role of genes as moderators of environmental influences on parenting (G × E)

Main effects of genetic variants on parenting might represent only a small part of the genetic influences on parental behavior. In fact the most important genetic effects in shaping parenting may reside in the interaction of genes with the environment. In the words of Urie Bronfenbrenner (1979): main effects are to be found in interactions. Gene-by-environment interactions may explain why some parents are more and others less impacted by disadvantageous childhoods or concurrent daily stresses in parenting their offspring. For example, in the MAVAN study mentioned before, OXTR rs2740210 moderated the effect of early life experiences on depressive feelings, which in turn affected breastfeeding. In mothers with the CC genotype childhood abuse experiences were related to lower maternal mood at 6 months postpartum, which was associated with reduced breastfeeding duration across the first year (Jonas et al., 2013).

Parents may be differentially susceptible to environmental influences *for better and for worse*. In a study with Israeli mothers of twins, mothers with the DRD4 7-repeat allele who experienced more stress around child birth (e.g., low gestational age, low birth weight, and prolonged stay at the neonatal intensive care unit) were less sensitive in the interaction with their children at age 3.5 than other mothers, whereas mothers with the DRD4 7-repeat allele whose children had few complications around birth showed the highest levels of parental sensitivity (Fortuna et al., 2011). Mothers without the 7-repeat allele seemed less affected by the perinatal strains and stresses in their parenting interactions with the toddlers. In another G × E study on parenting not only DRD4, but also the COMT gene polymorphisms were included. Mothers and toddlers were observed in a series of problem-solving tasks, and parents reported on their daily hassles (van IJzendoorn et al., 2008). The two dopamine-related genes moderated the negative influence of daily hassles on sensitive parenting behavior to their offspring. In parents with the combination of genes leading to the least efficient dopaminergic system functioning (COMT*val* allele, DRD4 7-repeat allele), more daily hassles were associated with less sensitive parenting, but in this group lower levels of daily hassles were associated with more sensitive parenting. The other combinations of COMT and DRD4 polymorphisms did not show significant associations between daily hassles and maternal sensitivity.

In a large cohort (the Fragile Families and Child Wellbeing Study) of American children born between 1998 and 2000, and going through the Great Recession of 2007 to 2009, Lee et al. (2013) examined the effects of economic hardships on harsh parenting, and explored whether this association was moderated by dopamine-related genes. Harsh parenting was assessed at three time-points throughout the first 10 years after birth using a selection of items from the Conflict Tactics Scales (Straus et al., 1998). More than 2600 mothers were genotyped, and the researchers focused on Taq1A rs1800497 of the DRD2-related gene ANKK1, because in previous work it had been related to the number of D2 dopamine receptors in the brain and seemed associated with being more or less susceptible to aggression. The authors found support for the differential susceptibility theory. For mothers with a T allele, harsh parenting increased as macroeconomic conditions worsened but decreased as conditions improved. By contrast, for mothers with the CC genotype, harsh parenting did not change in response to changes in macroeconomic conditions. Thus, parenting of the T allele carriers was more susceptible than those with the CC genotype to environmental changes, for better and for worse.

In these G × E studies for carriers of dopamine-related genes similar patterns of results emerge: Parents with the DRD4 7-repeat allele, Taq1A T-allele, or a COMT *val* allele were more affected by socio-emotional stressors than parents without these susceptible genotypes. Under conditions of stress, they are among the least sensitive parents, but lower levels of stress are accompanied by an increase in caregiving sensitivity, much stronger so than for parents without this genotype. The role of DRD4 and other dopamine genes as susceptibility markers may thus not be limited to children, where these markers were discovered first (Bakermans-kranenburg and van IJzendoorn, 2006), but rather might extend to parents (Bakermans-Kranenburg and van IJzendoorn, 2015). Differential susceptibility theory suggests that the same genotype that make individuals vulnerable to adversity may also make them disproportionately likely to benefit from contextual support (Belsky et al., 2007). The differential susceptibility hypothesis proposes that in positive environments 'vulnerable' individuals, the so-called 'orchids', may flourish even more than their peers who are less

susceptible, the so-called 'dandelions' (Bakermans-Kranenburg and van IJzendoorn, 2007; Belsky et al., 2007; Ellis et al., 2011). The model's evolutionary foundation implies that certain genotypes must be called *susceptibility* alleles instead of *risk* alleles as was common in the traditional diathesis-stress or cumulative risk models of the past three decades (Bakermans-Kranenburg and van IJzendoorn, 2015).

The mechanism of environmental mediation: Epigenetics

In the past behavioral and molecular genetics assumed that the genetic make-up of every individual was invariable, originating from conception to remain basically the same across the whole life-span, except in rare cases of mutations through radiation or other toxic influences. This assumption is valid as far as it pertains to the fixed sequence of the DNA base-pairs. But the expression of genes is (partly) regulated by epigenetic influences, and epigenetic changes through methylation, acetylation or other pathways affect the functional significance of structurally identical genotypes (Brookes and Shi, 2014; Kundakovic and Champagne, 2014; Meaney, 2010). The most widely studied epigenetic mechanisms is methylation, which is simply put the blocking of gene expression through the linking of a methyl (CH3) molecule to one of the bases, cytosine, at a CpG site located in a gene-promoter region. Methylation might be loosely compared to a cork on a bottle of champagne, down-regulating the escape of bubbles (messenger RNA) and thus modulating the level of protein and enzyme production encoded for by the specific gene (van IJzendoorn et al., 2011).

Ironically, dandelions are a prime example of the power of epigenetics because they show flexible adaptation despite asexual reproduction (apomicts). The plants that grow from the mother plant's seeds are structurally genetic clones, identical to the mother plant, but they nevertheless adapt to a large variety of conditions. Their epigenetic patterns might be responsible for this adaptation as these patterns vary strongly in response to environmental conditions, and, moreover, epigenetic features seem to be transmitted across generations and thus become determinants of 'parenting' (Verhoeven et al., 2010). In an experiment with various nutrient conditions (sufficient food versus shortage of food) Verhoeven et al. (2010) demonstrated that compared to control plants growing in a high-nutrient environment, dandelions exposed to food shortage produced much less offspring shoot—which is an indicator of fitness. Moreover the offspring of the deprived dandelions adapted well to deprived circumstances, because they seemed to be preprogrammed for hardship, whereas the offspring of controls fared poorly in nutrient shortage. This difference in adaptation persisted into the third generation and was associated with differences in epigenetic characteristics in DNA methylation-sensitive regions of the dandelion genome.

Epigenetic studies of rodents (e.g., Meaney, 2010; Szyf et al., 2005) have made clear that the caregiving environment – for example the amount of licking and grooming and arch-back nursing that parents provide—may radically alter epigenetic patterns and consequently gene expression in the pups, and not only in the pups exposed to sensitive parenting themselves (or deprived thereof) but even in these pups' offspring. They carry on to be sensitive or insensitive parents themselves depending on the epigenetic changes they 'inherited' from their parents (Meaney, 2010). In particular altered methylation of the glucocorticoid receptor gene seems to induce long-term changes in response to stress, affecting the next generation (Weaver et al., 2004; Zhang and Meaney, 2010; Zhang et al., 2013). One of the first epigenetic studies on human behavioral development was also conducted by Meaney's team (McGowan et al., 2009). They examined the brains of deceased young males stored in the Quebec Suicide Brain Bank, matching suicide victims with and without a history of abuse, and comparing these two groups with age- and gender-matched victims of fatal accidents. They found that through methylation, glucocorticoid receptor (GR) gene expression in the hippocampus of the suicide victims was decreased but only when they had experienced child abuse. Hippocampal glucocorticoid receptors play a crucial role in down-regulating the HPA-axis that is responsible for the level of the stress hormone cortisol. In other studies similar epigenetic alterations have been found as a result of child maltreatment (Perroud et al., 2014) or structural neglect in orphanages (Naumova et al., 2012).

Even monozygotic twins with identical DNA structures may grow apart in gene expression. They may develop radically different parenting patterns because of changes in the epigenome that influences and regulates the expression of genes. Fraga et al. (2005) found for example that a 3-year-old monozygotic twin pair had about 1000 genes with differential gene expression, whereas a 50-year-old monozygotic twin pair showed more than 5000 differently expressed genes. Differences in the epigenome increase with age and with non-shared environmental influences, implying that they are larger when twins have spent more time in separate environments. In a sample of monozygotic twin pairs aged 18 to 89 years Talens et al. (2012) confirmed that with increasing age significantly more epigenetic changes of the differentially methylated region (DMR, representing an entire stretch of DNA rich in methylation sites and which exhibits a different methylation pattern among different samples) of the insulin-like growth factor 2 (IGF2) within these twin pairs could be observed.

Prenatal parenting

Parenting starts before birth, for example when pregnant mothers decide to continue or quit smoking or the use of SSRIs, or when they observe the moving fetus in the womb through ultrasound recordings and respond to these movements by gentle touch or vocalizations. Severe prenatal parental stress may also exert substantial influence on the fetus, continuing after birth, and methylation may be one of the mechanisms through which prenatal parenting is transmitted to the fetus. For instance, in pregnant rats, multiple genes are up- or down-regulated in the hypothalamus, including genes encoding for dopamine receptors, prolactin, and a number of cholinergic receptors (Mann, 2014). In humans, differential methylation may play a crucial role in intergenerational transmission of the Dutch Hunger Winter effects on birth weight and somatic issues (obesity, cardiovascular risks), and maybe also on patterns of parental behavior. In the harsh winter of 1944–1945 the Western and Northern part of the Netherlands were still occupied by the German forces who rationed food supply for the civilian population to a bare minimum of about 600 calories per day. Offspring conceived at the height of this Hunger Winter were born with a normal weight but they had elevated risk for obesity in adulthood, and their offspring (grandchildren of the pregnant women in the Hunger Winter) were born with higher weight. In contrast, offspring conceived a few months prior to the famine were born with lower weight but they did not develop obesity and their offspring (third generation) had normal birth weight (Roseboom et al., 2006). The first trimester in utero seemed to be critical. Heijmans et al. (2008) showed that IGF2 methylation might be the epigenetic mediating mechanism. Offspring exposed to the famine just after conception had about 5% lower methylation in the IGF2 region compared to their siblings conceived earlier or later, even 60 years after the Hunger Winter. In a recent study of the same sample, Heijmans and colleagues (Tobi et al., 2014) showed that methylation differences were not restricted to IGF2. They found six prenatal malnutrition related differentially methylated regions (p-DMRs), one of which was significantly associated with cholesterol levels in adulthood.

In the Generation R study, a large cohort study of about 10,000 children and their families in the Netherlands (Jaddoe et al., 2012) the question was addressed why smoking during pregnancy would lead to lower birth weight. Smoking was assessed at three time-points during the three trimesters of pregnancy and methylation of IGF2 DMR was analyzed in cord blood. A quarter of the pregnant mothers continued smoking, and smoking was indeed related to lower birth weight. Most importantly, smoking was associated with lower IGF2DMR methylation levels in a dose–response manner, also after controlling for potential

confounders such as socioeconomic status. IGF2 methylation mediated the effects of smoking on birth weight (Bouwland-Both et al., in preparation). Moreover, prenatal adversities impacting on the mothers were examined, including negative life-events, symptoms of depression and anxiety, conflicts between the partners, and social issues such as financial problems. The global risk factor was associated with level of problem behaviors of the children at 6 years of age. An Epigenome Wide Association Study (EWAS) showed several suggestive hits and one significant DMR on chromosome 20, covering 3 CpGs for which the functional meaning still has to be explored (Rijlaarsdam, in preparation). Although the sample (more than 900 newborns) was much larger than the average sample used in behavioral epigenetics, these preliminary findings have to be replicated before drawing firm conclusions.

A moderated mediation model of the (epi)genetics of parenting

There is a dearth of studies on the (epi)genetics of parenting, in particular on human parenting, in contrast to epigenetic studies on human diseases like cancer (Brookes and Shi, 2014). This is surprising because parenting is an all-pervasive phenomenon with high impact on everyone's life. But it is also a complex phenotype without consensus about how to measure parenting in the most reliable and valid way. Therefore, cooperation of large cohort studies needed to unravel the (epi)genetics of parenting on the molecular level has proven to be complicated, and most of the current findings are in need of replication. Nevertheless we brought together several strands of genetically informed research on parenting, with results from behavioral genetics, candidate-gene studies, G × E research, and epigenetics. We speculate that the various strands might be combined in a model in which there is room for main effects of genes, interactions between genes and environment, environmental main effects, and mediating effects of epigenetics in shaping parenting (see Fig. 1). The transmission of epigenetic marks to the next generation of parents may be just one of the many ways of non-genetic intergenerational transmission. Parenting-relevant information can be carried across generations by hormones, cytokines, and even microorganisms, without the involvement of the gametes (Toth, 2015). In fact, it is still unclear whether and how epigenetic signatures are transmitted across generations in humans.

In the model we have outlined, the parental epigenome mediates the influence of grandparenting on parental behavior. Abusive grandparental behavior may change methylation patterns of the OXTR, 5HTTLPR or GR genotypes in the offspring, and may thus change set-points for the oxytocin, serotonin, or cortisol levels which in turn might lead to insensitive or abusive parenting in adulthood. Parental susceptibility genes such as DRD4 and DRD2 may moderate this mediation as well as the influence of the parental environment on parental behavior. For example, stressful life-events and adverse conditions might have more impact on parents with susceptible genetic variants, and these parents might also have been more open to epigenetic changes in childhood. Parents inherit their susceptibility genes from the grandparents, which is of course a genetic main effect. Lastly, genes might be associated with the parental environment through passive or active gene–environment correlations as documented by twin studies. Parents with less efficient oxytocin genes might be less inclined to seek the stimulating and rewarding affective interactions and touch with their offspring, which might result in a downward spiral of ever more insensitive and disharmonious parent–child interactions.

The future of genetic parenting research

Despite the neural and behavioral differences between rodents and humans, animal models will continue to inform the field of human parenting at all levels, from the genetic, through the environmental, to the epigenetic. Mammals share an ancient evolutionary drive for parental responsiveness and appear to exhibit a general overlap in the neural regions dedicated to parental and other motivated behaviors, with some species-specific differences and exceptions. Human parenting seems more complex than rodent parenting, and yet what we have learned about the regulation of rodent maternal behavior has driven much of the work on the genetic influences in human parents (e.g. Mileva-Seitz et al., 2012b).

Far less explored in this field are the genetic mechanisms underlying caregivers other than the mother, including fathers. This is remarkable considering the fact that almost half a century ago Rosenblatt (1967) already had shown that 'there is a basic maternal responsiveness in rats which is not dependent upon hormones or sex for its arousal' and can be triggered solely by the exposure to pups, in female as well as male rats. Because across animal species and even across human

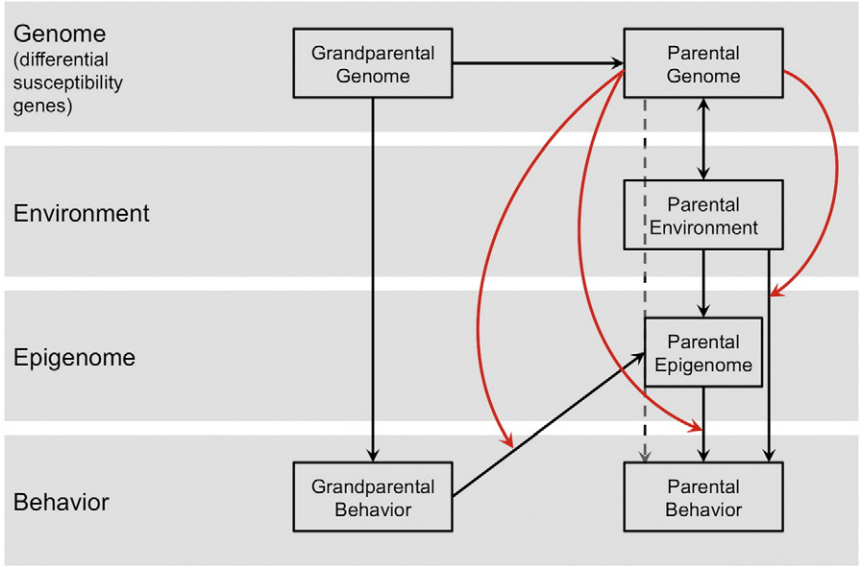

Fig. 1. The genetics of parenting: a mediated moderation model. Note: The parental epigenome mediates the influence of grandparenting on parental behavior but parental susceptibility genes may moderate this mediation as well as the influence of the parental environment (e.g. stress) on parental behavior.

cultures fathers often play differing roles in the raising of their offspring, fatherhood and its biological underpinnings have been put on the backburner and sometimes even ignored. A meta-analysis on twin studies of parenting indicated that heritability estimates are in fact similar for both fathers and mothers (Klahr and Burt, 2014). This suggests that the study of genetic mechanisms underlying fathers might be just as fruitful as the study of mothering. The 'father of mothering' (Fleming et al., 2009) would have applauded such an approach.

Finally, if we are to acknowledge that human parenting is infinitely more complex than rodent parenting, we must address the likelihood that diverse mechanisms regulate what parents think and do. We might begin to 'think smaller' when hypothesizing biological underpinnings to behavior, by examining sub-phenotypes of discrete, quantifiable behaviors. Behavioral microanalysis can untangle phenotypic complexities: the frequencies, durations, and contingencies with which parents perform behaviors X, Y, and Z, likely represent intricate layers of the overarching '*parental quality*' phenotype obtained from macroanalysis. A neural mechanism and its biological regulators (genetic or epigenetic marker) might more readily associate with a discrete micro-phenotype than with an overarching macro-phenotype. Or perhaps not, if the dyadic organization of discrete interactive behaviors is the hallmark of parenting (Sroufe and Waters, 1977; Feldman, 2007). This is a question that remains to be addressed.

Conflict of interest

None.

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