Review

Biological Psychiatry

Oxytocin Pathway Genes: Evolutionary Ancient System Impacting on Human Affiliation, Sociality, and Psychopathology

Ruth Feldman, Mikhail Monakhov, Maayan Pratt, and Richard P. Ebstein

ABSTRACT

Oxytocin (OT), a nonapeptide signaling molecule originating from an ancestral peptide, appears in different variants across all vertebrate and several invertebrate species. Throughout animal evolution, neuropeptidergic signaling has been adapted by organisms for regulating response to rapidly changing environments. The family of OT-like molecules affects both peripheral tissues implicated in reproduction, homeostasis, and energy balance, as well as neuromodulation of social behavior, stress regulation, and associative learning in species ranging from nematodes to humans. After describing the OT-signaling pathway, we review research on the three genes most extensively studied in humans: the OT receptor (*OXTR*), the structural gene for OT (*OXT*/neurophysin-I), and *CD38*. Consistent with the notion that sociality should be studied from the perspective of social life at the species level, we address human social functions in relation to OT-pathway genes, including parenting, empathy, and using social relationships to manage stress. We then describe associations between OT-pathway genes with psychopathologies involving social dysfunctions such as autism, depression, or schizophrenia. Human research particularly underscored the involvement of two *OXTR* single nucleotide polymorphisms (rs53576, rs2254298) with fewer studies focusing on other *OXTR* (rs7632287, rs1042778, rs2268494, rs2268490), *OXT* (rs2740210, rs4813627, rs4813625), and *CD38* (rs3796863, rs6449197) single nucleotide polymorphisms. Overall, studies provide evidence for the involvement of OT-pathway genes in human social functions but also suggest that factors such as gender, culture, and early environment often confound attempts to replicate first findings. We conclude by discussing epigenetics, conceptual implications within an evolutionary perspective, and future directions, especially the need to refine phenotypes, carefully characterize early environments, and integrate observations of social behavior across ecological contexts.

Keywords: CD38, Epigenetics, Genetics, OXT, OXTR, Oxytocin

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EVOLUTIONARY ASPECTS OF THE OXYTOCIN SIGNAL PATHWAY

Vasopressin (AVP) and oxytocin (OT)—two closely related nonapeptides—are ancient and conserved peptides dating back more than 600 million years (1). The AVP/OT family originates from an ancestral peptide anteceding protostomian and deuterostomian animals that appears in different variants in all vertebrates, including mammals (oxytocin/arginine-vasopressin), bony fish (isotocin/vasotocin), and other nonmammalian vertebrates (mesotocin/vasotocin), and several invertebrates, including echinoderms (echinotocin), mollusks (cephalotocin/lys-conopressin), annelids (annetocin/lys-conopressin), arthropods (inotocin/crustacean-VP), and nematodes (nematocin) (2,3). The AVP/OT family presumably evolved via gene duplication from the ancestral vasotocin peptide of jawed vertebrates (4); gene duplication is a common evolutionary pathway toward the adaptation of genes to new functions (5). Within the mammalian lineage, peptides vary by a single amino acid and their genes are found near each other on the same chromosome (6), and variants in this receptor are thought to account for species-selective recognition, ligand binding profiles, and activation of receptors (7).

Throughout animal evolutionary history, neuropeptidergic signaling has been adapted by organisms for regulating physiological and behavioral response to rapidly changing environments, and the OT molecule is critically involved in multiple life-sustaining social and nonsocial functions in species ranging from nematodes to humans (Figure 1). In invertebrates, OT is implicated in associative learning and sensory processing in nematodes and egg-laying behaviors in annelids. In nonmammalian vertebrates, OT analogues have been shown to modulate male courting behavior in lizards, long-term memory formation and vocal circuitry in fish, flocking behavior in birds, and reproduction-related behavior in toads. Finally, in mammalian vertebrates, the AVP/OT family affects both peripheral tissues implicated in reproduction, homeostasis, osmotic regulation, gustatory functions, and energy balance, as well as central neuromodulation of social behavior, stress regulation, and associative learning (8–10). Such wide-ranging roles for the OT

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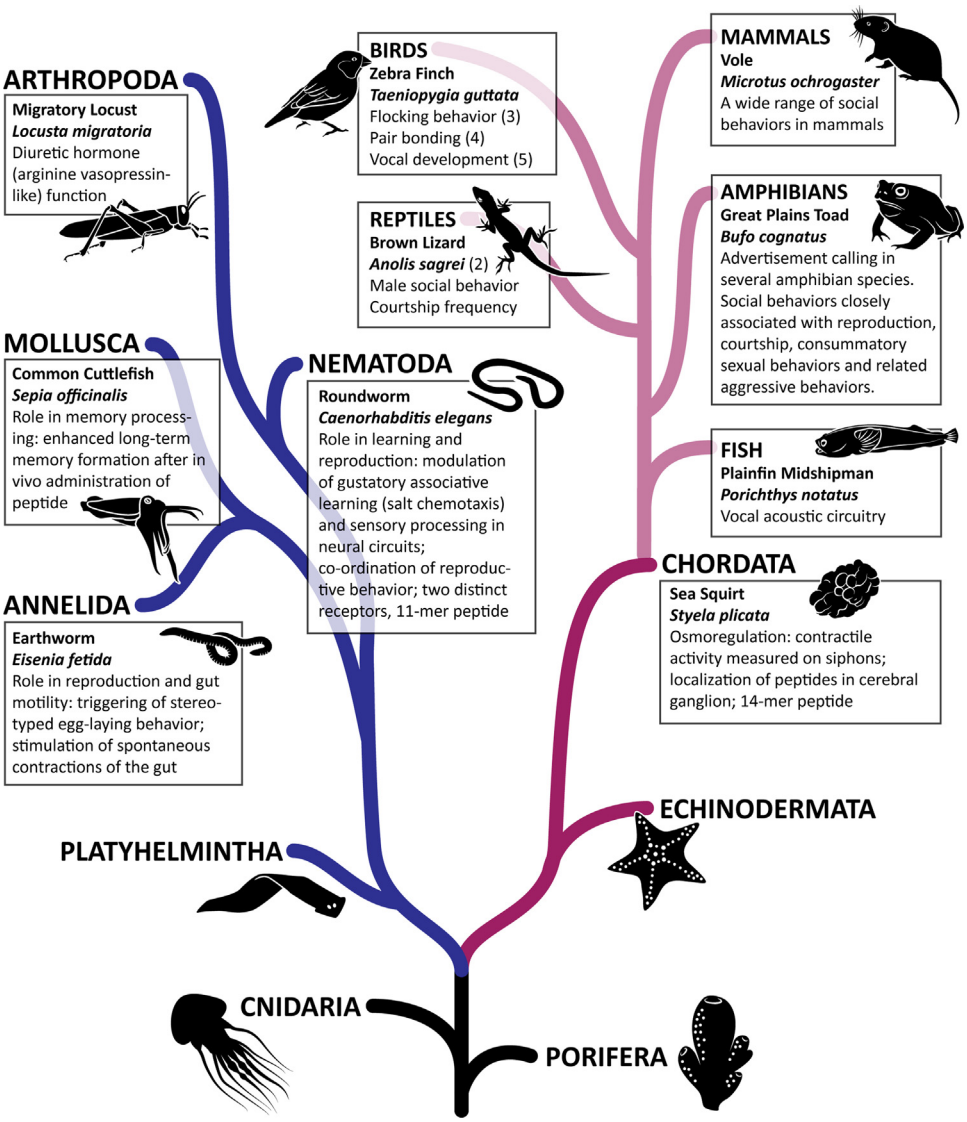

Figure 1. The role of oxytocin across animal evolution. The scheme illustrates the widespread distribution of oxytocin–vasopressin-like signaling system with roots deep in evolutionary time, attesting to the unique properties of such short peptides as information molecules both peripherally and in central nervous systems.

molecule across evolution demonstrates its critical importance for a variety of basic life functions. Moreover, these functions have been repurposed in diverse ways at the level of the species to underpin social life in ways that support the social organization of that species. Overall, the multipurpose species-specific OT system lends support to evolutionary perspectives theorizing that complex abilities co-opt basic ones and social functions are superimposed upon fundamental regulatory pathways (11).

Understanding how OT played a role in fine-tuning neuronal circuits for social behavior across evolution leading to the complexity of human social functions is a central challenge in the construction of a comprehensive theory for social neuroscience (12,13). Detecting commonalities in pleiotropic effects that describe the influence of a single gene on apparently nonrelated phenotypes may help define the underlying neurochemical pathways that buttress human-specific social traits (14). For instance, myoactivity—the stimulation of tissue contraction—is among the most conserved functions of OT (15). Myoactive effects of the OT family peptide on rhythmic-patterned behavior are observed in egg laying in invertebrates (16–19), stereotypical twisting in leeches (20), coordinated male mating behavior in nematodes (21), coupling of peptide secretion with light cycles in fish (22), and resonating with the repetitive-rhythmic synchronous exchange during human parent-infant interactions that introduce 3-month-olds into the social world and foreshadow human social competencies (23,24). The sequencing of such patterned motifs is coordinated by OT-like signaling between sets of cells in the simplest organisms, like *C. elegans,* that involve sexually dimorphic and nondimorphic neurons comprising both central and peripheral effects (3). Cells producing OT-related peptides are found in similar neurosecretory brain centers across species and taxa and are characterized by a typical molecular fingerprint (7,25). Gene regulatory features of the OT-type neuronal cell point to dual sensory-neurosecretory properties, suggesting that the ancient OT signaling system functioned to convert sensory inputs into online behavioral response supported by peptidergic secretion (3).

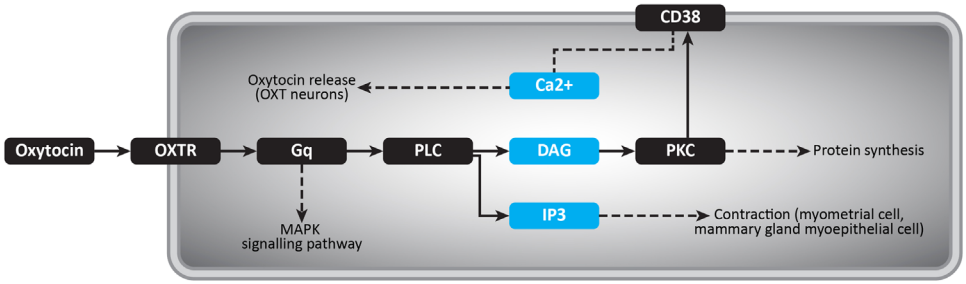

Figure 2. Schematic presentation of the oxytocin signaling pathway. Gq is a heterotrimeric G protein subunit that activates phospholipase C (PLC); PLC is important in signal transduction pathways (second messenger generation); diacylglycerol (DAG) functions as a second messenger signaling lipid; PKC is protein kinase C, a class of enzymes that cleave phospholipids and is important in signal transduction pathways. MAPK, mitogen-activated protein kinase; OXT, oxytocin; OXTR, oxytocin receptor.

Despite the rich evolutionary history of the OT signaling pathway, this review focuses on OT-pathway genes and social functions in humans. Yet, our review adapts an evolutionary perspective and follows three principles advocated by comparative OT research: 1) deconstructing sociality (26); 2) repurposing of nonsocial to social brain functions as mediated by OT (25); and 3) utilizing a behavior-based approach to understanding OT's role in mammals (27).

Deconstructing sociality is a term coined by Goodson (26) to argue that OT effects on social functions, as well as organization of OT neurocircuitry and receptor localization, did not evolve in a uniform fashion. Rather, OT effects on sociality were assembled from loosely tied species-specific modules—components that define social life in that species, such as parenting, mating, group living, or social hierarchies that also include behaviors such as cooperation (trust), territoriality (outgroup derogation), gregariousness (loneliness), or the sensory and cognitive processes required for navigating the social ecology (social cognition/empathy). Thus, OT effects on sociality must be studied in relation to the relevant modules that define what it means to be social in that species. Repurposing of nonsocial to social functions is among the most conspicuous threads in the evolutionary history of OT. A central motivating force behind such repurposing is the use of social functions to manage stress, particularly regulating the stress involved in adaptation to harsh ecologies and managing life within large social groups (9,26). Finally, a behavior-based approach utilizes specific processes that define mammals as windows to study OT's role in humans, particularly parent-infant and pair bonding (27). For instance, OT's role in human social behaviors was initially informed by research in voles, which showed that differences in OT receptor distribution in monogamous and polygamous vole species that display marked differences in bonding-related behavior often depend on a few polymorphic genes (28).

GENETICS OF THE OXYTOCIN SIGNAL PATHWAY

Figure 2 illustrates the architecture of the OT-signaling pathway. From this complex pathway, the literature suggests that only three genes have been investigated in relation to human social behavior: the OT receptor (*OXTR*) (29), the structural gene for OT (*OXT*)/neurophysin-I (30), and *CD38* (31), with human studies mainly focused on *OXTR* (32) and *CD38* (23).

OXTR is a 389 amino acid polypeptide with 7 transmembrane domains and belongs to class I G protein-coupled receptors that are located at 3p25–3p26.2 (8). The length of the gene region is 17 kilobase and it consists of three introns and four exons. Tagging single nucleotide polymorphisms (SNPs) examined in association with social behavior are shown in Figure 3.

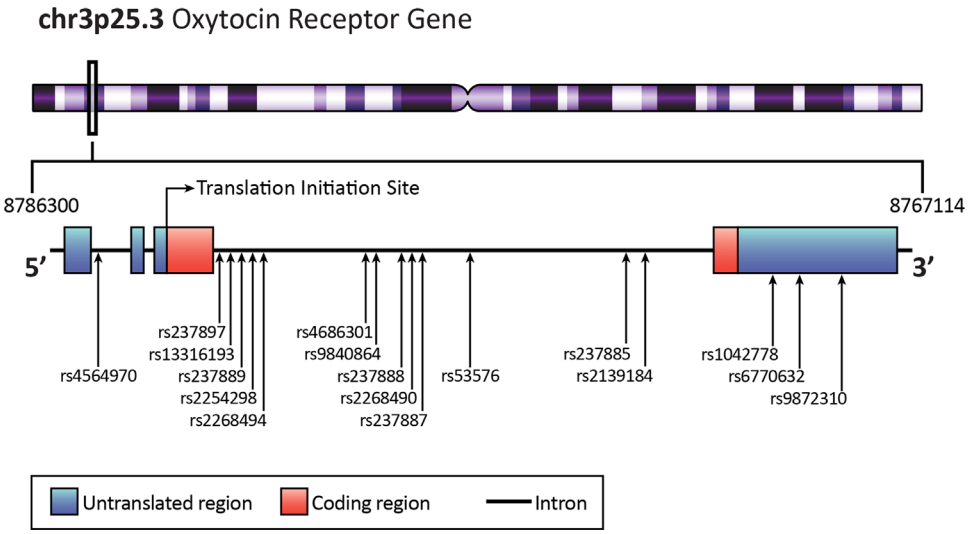

Figure 3. The oxytocin receptor gene. The oxytocin receptor is a representative member of the rhodopsin-type (class I) G-protein coupled receptor family. The 5′ upstream region is characterized by a number of transcription factor binding sites that are important in regulation of receptor transcription.

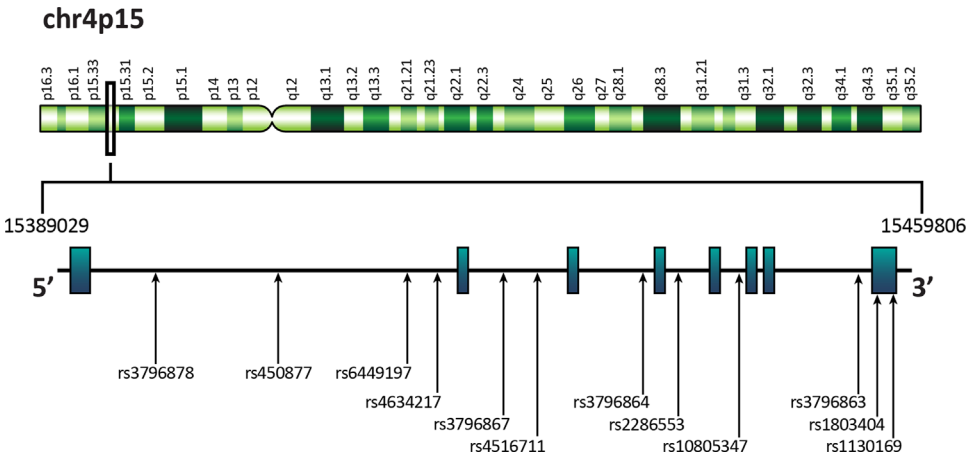

Figure 4. The *CD38* gene. We also note a rare polymorphism that caused tryptophan to replace arginine at amino acid residue 140 (R140W; [rs1800561, 4693C > T]) was found in .6% to 4.6% of the Japanese population, but not in Korean or Caucasian population, and was associated with autism spectrum disorder in a small case-control study. This rare single nucleotide polymorphism is not shown in the diagram but is located in exon III.

CD38 is a nicotinamide adenine dinucleotide ectoenzyme, generating cyclic adenosine diphosphate-ribose and adenosine diphosphate-ribose, in addition to nicotinic acid adenine dinucleotide phosphate (33). CD38/adenosine diphosphate-ribosyl cyclase plays a role in hormone secretion and cell proliferation, differentiation, and migration. It is a transmembrane receptor with adenosine diphosphate-ribosyl cyclase activity that mobilizes downstream intracellular calcium signaling pathways (34). Interestingly, CD38 expression is high in the brain, plays an obligatory role in central OT release (31), and modulates social memory in rodents (35). The structure of the CD38 gene and tagging SNPs is shown in Figure 4.

Neurophysin I and neurophysin II, which code, respectively, for OT and AVP, are located on 20p13 in humans (8). Across species, OT and AVP genes are on the same chromosomal region but are oppositely transcribed, suggesting that the origin of these two nonapeptides is the result of an ancestral gene duplication. Neurophysin I has three exons: the first exon encodes a translocator signal, the nonapeptide hormone, the tripeptide processing signal (glycine-lysine-arginine), and the first nine residues of neurophysin; the second exon encodes the central part of neurophysin; and the third exon encodes the carboxyl-terminus-terminal region of neurophysin.

A central question underpinning genetic research on OT-pathway genes involves the mechanisms by which allelic variability impacts human social functions. One possibility is that so-called efficient gene variants, encoding a more efficient receptor and hence more robust OT signaling, may open individuals to the beneficial effects of a social/affiliative process, for instance, using social support during stress (36). It is also possible that for individuals with more efficient variants, social stimuli are more salient, enhancing social information processing (37). Finally, the close links between the oxytocin and dopamine systems (38,39) give rise to the hypothesis that individuals with more efficient alleles draw more reward from social contact, leading to approach orientation and reducing susceptibility to psychopathologies of social isolation (40).

OT PATHWAY GENES AND HUMAN SOCIAL FUNCTIONS

Consistent with our view that this ancient peptide system played a key role in evolutionary processes that supported survival-related social functions and increased fitness by enhancing affiliative behavior (10,41) and augmenting salience of crucial social phenomena (42,43), human research has demonstrated associations between OT-pathway genes with social functions essential for the individual's integration into various social milieus. In the following, we detail association studies between OT-pathway genes and human social functions and psychopathology. Findings on *OXTR* are summarized in Table S1 in Supplement 1.

Affiliation

Parental Attachment. There is evidence linking more efficient variants of OT-pathway genes with more optimal parental behavior. Mothers carrying the *OXTR* rs53576GG genotype engaged in more sensitive interactions with their infants (44). Two neurophysin-I (OXT) SNPs, rs2740210 and rs4813627, were associated with motherese vocalizations during mother-infant interactions (45) and genotype by early caregiving effect emerged for maternal instrumental care. A study of 323 mothers, fathers, and nonparents showed that risk alleles on *OXTR* (rs2254298, rs1042778) and *CD38* (rs3796863) genes were associated with less parental touch and the interaction of high plasma OT and low-risk *CD38* alleles predicted longer durations of parent-infant gaze synchrony. Parents who reported more optimal caregiving in childhood had greater plasma OT, low-risk *CD38* alleles, and more touch toward their infants (23). Following parents and their firstborn infants from birth to 3 years, parents' behavioral synchrony at 1 and 6 months and mothers' *CD38* allele predicted children's social reciprocity during interactions with their best friend at 3 years, indicating that the transfer from parent-infant attachment to attachment with close friends is supported by OT-pathway genes mediated by parenting behavior (46). Continuity in attachment security from 12 months to 26 years was moderated by *OXTR* rs53576; only among GG homozygous subjects was attachment security in infancy predictive of attachment to romantic partner in adulthood (47).

OXTR has been studied in relation to parents' brain patterns. Two *OXTR* SNPs (rs1042778, rs53576) were associated with brain responses to child stimuli in the orbitofrontal cortex, anterior cingulate cortex, and hippocampus; the

rs53576A allele correlated with positive parenting and with activations in these areas (48). Similarly, only *OXTR* rs53576GG homozygotes preferred infant faces after OT administration (49) and displayed greater reactivity to cry sounds, except among those reporting high depressive symptoms (50). Finally, assessing mothers' and nonmothers' event-related potential response to infant and adult faces of strong and mild intensity, mothers with *OXTR* rs53576GG genotype showed early-latency differential frontal response to intense facial expression, particularly infants' faces, suggesting that differential brain responses to infants' and adults' emotional cues are mediated by *OXTR* (51).

In a family-based study, *OXTR* rs53576AA homozygous mothers were less warm toward their children (52). African-American adults with the *OXTR* rs53576G genotype coupled with more constructive childhood memories reported greater positive affect and resilient coping (53). *OXTR* rs2254298 A allele was associated with infant attachment security but only in non-Caucasian infants (54). Maltreated *OXTR* rs53576GG homozygous adolescents reported more internalizing symptoms, with no allelic effect on nonmaltreated children (55), suggesting that *OXTR* rs53576GG homozygotes may be more attuned to negative rearing experiences. These findings indicate that *OXTR* effects are partly mediated by early environment and the more efficient genotype may open children to greater susceptibility to contextual influences.

Romantic/Couple Relationship. Among Swedish twins, *OXTR* rs7632287A-carrying women reported more marital crisis and less pair-bonding behavior (56). *OXTR* polymorphisms buffered spillover between marital and parenting quality; association between marital conflict and maternal sensitivity was found only for rs53576GG carriers but not for AA/AG (57). Among new lovers, five *OXTR* SNPs, rs1042778 (exon 4), rs13316193, rs2254298, rs2268494, and rs2268490 (intron 3), were combined into a cumulative genetic risk index and higher cumulative risk predicted lower observed empathy during support-giving interactions between new lovers (58). Combined with findings that plasma OT levels increase during human pair-bond formation, results implicate OT in the capacity to form partner relationship, possibly by supporting social behaviors that promote pair bonding (25). Further support for this notion comes from neural imaging studies (59), suggesting that both maternal attachment and romantic love activated overlapping regions in the brain's reward system that are rich in OT receptors.

Friendship. Although no study examined *OXTR* in relation to observed behavior between friends, A SNP on the *CD38* gene, rs12644506, was associated with social integration and social connectedness (60), and *OXTR* rs4686302 (exon 3) correlated with social connectedness in men. Women, but not men, with the *OXTR* rs53576A allele reported more social connectedness than GG homozygous subjects. Conversely, OXTR rs53576A-carrying girls reported higher loneliness (61). Finally, *OXTR* rs53576GG homozygotes were rated by independent judges as more prosocial than A carriers and expressed more affiliative cues (62). Overall, these findings highlight the involvement of OT-pathway genes in bond formation and reciprocal behavior within social relationships.

Human Social Competencies

Whereas bonding describes a mammalian general process, OT-pathway genes have also been implicated in higher order human social functions that rely on cortical structures and associative processes, including empathy, generosity, social information processing, social networks, or creativity in studies utilizing self-reports, brain imaging, and economic games. Here, we detail studies on empathy/theory of mind and research addressing other social functions appears in Supplement 1.

Empathy, Theory of Mind. Empathy, "the capacity to share, understand, and respond with care to the affective states of others" (63), is considered a hallmark of human sociocognitive function, develops on the basis of synchronous parenting (64), and requires regulatory skills and mentalizing abilities (65). Although most studies examined *OXTR* and empathy in adults, a family-based study of 350 toddlers showed that a haplotype located in the third intron (comprising markers from rs11131149 to rs2254298) correlated with higher social cognition, including joint attention, empathy, and self-recognition (66). Among 4.5-year-olds, more copies of the major allele on OXTR rs11131149 interacted with maternal sensitivity to predict children's theory-of-mind (ToM) skills, the ability to infer others' mental states from behavior (67).

In adults, *OXTR* rs53576GG homozygous subjects displayed greater sympathetic arousal and self-reported empathic concern to pictures of others' pain (68). *OXTR* rs2268498CC carriers and *OXTR* rs53576AA carriers displayed higher empathic accuracy, and among *OXTR* rs2268498CC homozygous subjects, empathic accuracy correlated with stronger superior temporal sulcus response to others' pain (69). Two studies demonstrated that *OXTR* rs53576A carriers showed reduced empathy in the Reading the Mind in the Eyes Test (70,71), a ToM test requiring inference of mental state from pictures of eyes. Only among rs53576GG and rs2254298A-carrying mothers was association found between maternal empathy and tendency to stop smoking during pregnancy (72). Differences in hypothalamic gray matter and structural coupling of hypothalamus and anterior cingulate cortex were observed among *OXTR* rs53576A carriers, and AA homozygous subjects scored lower on empathy (73). Finally, variations in *OXTR* rs53576 interacted with fetal testosterone (ratio of the length of the second and fourth digits [2D:4D] as proxy) to predict men's, but not women's, ToM performance on Reading the Mind in the Eyes Test (74), and *OXTR* rs53576G carriers showed enhanced empathy in research using both genetic association and imaging genomic strategies (75).

Utilizing Social Relationships to Manage Stress

Polymorphic variability on OT-pathway genes has been implicated in the propensity to use social relationships to manage stress; however, culture and gender often moderate these effects. Distressed American *OXTR* rs53576G carriers tended to seek emotional support, while AA homozygous subjects did not, and no differences were found among Koreans (76). Notably, differences were also found in the stress response; male *OXTR* rs53576A carriers showed higher sympathetic cardiac control in response to stress, whereas GG

homozygous subjects showed lower cortisol awakening response (77). Using functional imaging, *OXTR* rs53576AA-carrying female subjects showed increased harm avoidance scores relative to G carriers, in addition to smaller amygdala volumes and reduced resting-state functional coupling between prefrontal cortex and amygdala, indicating greater stress susceptibility (78). Greater perceived threat interacted with *OXTR* rs53576 in predicting engagement in volunteer work (79), and higher perceived threat correlated with less charitable/volunteer activity among *OXTR* rs53576AA/AG carriers but not among GG (79). In a study of altruistic attributes, charitable behavior buffered the association of life stress on new physical ailments among *OXTR* rs53576A carriers but not among GG (80).

To assess the links between *OXTR*, stress, and social relationships in an experimental paradigm, adult male subjects were randomly assigned to prepare for the Trier Social Stress Test alone or with support from a female partner or close friend. *OXTR* rs53576G carriers showed lower cortisol stress response after social support compared with no support, whereas no effect was observed in AA homozygous subjects, suggesting that the protective effects of support may depend on *OXTR* (81) and is consistent with research showing that *OXTR* rs53576G carriers have lower cortisol response to the Trier Social Stress Test (36). Love *et al.* (82) used positron emission tomography scans with the dopamine ligand raclopride to understand how *OXT* (neurophysin-I) is linked to dopaminergic function in humans. Only female rs4813625C-allele carriers showed increased stress-induced dopamine release; more stress-induced dopamine release was linked with lower emotional well-being only in female rs4813625C-allele carriers. Overall, these studies lend support to the notion that OT functions as an antistress hormone, possibly by enhancing social behaviors and the ability to draw comfort from social contacts.

OT-PATHWAY GENES AND PSYCHOPATHOLOGY

The involvement of OT-pathway genes in multiple psychiatric conditions highlights the social components of these disorders and their underlying neurobiology as core features of most psychiatric illnesses. Both family-based and population-based studies linked allelic distributions on several *OXTR* SNPs with pathologies involving social dysfunction. Studies related to autism spectrum disorder (ASD), depression, and schizophrenia are reported here, whereas studies associated with post-traumatic stress disorder, borderline personality disorder, and psychopathy appear in Supplement 1.

Autism Spectrum Disorder

ASD has been the focus of much research on OT-pathway genetics reflecting the hypothesis that OT synaptic transmission may play a role in the disorder (83). Several studies showed association between ASD and *OXTR* (84–91) and *AVPR1a* (92–96) polymorphisms. Associations between the *OXT* (neurophysin-I) rs2770378 and autism-like traits were observed for language impairment and restricted behaviors among 1774 Swedish twin female, but not male, subjects (97). Whereas associations between *OXTR* rs2770378 and ASD were found in one study (98), they were not replicated (99). Skuse *et al.* (100) examined 198 probands with ASD, 153 unaffected siblings, and 311 parents and found that *OXTR* rs237887A homozygous subjects showed better face recognition memory. A recent meta-analysis (101) found associations between ASD and the *OXTR* SNPs rs7632287, rs237887, rs2268491, and rs2254298, and *OXTR* was also associated with ASD in a gene-based test. This meta-analysis is the most complete examination of the association of *OXTR* with ASD to date.

Several studies examined *CD38* in autism (97,102–105). In the first study (103), 10 SNPs and mutations of *CD38* were examined and the *CD38* SNPs rs6449197 and rs3796863 were linked with high-functioning ASD in US participants but not Japanese participants and findings were partially replicated among Israeli subjects (105). Ebstein *et al.* (106) genotyped 170 subjects with ASD, testing both individual SNPs and haplotypes in *OXT* (neurophysin-I). Nominal association was observed between ASD and *OXT* rs6133010, as well as two-locus, three-locus, and four-locus haplotypes; however, this association was not replicated (97).

Depression

Of particular importance in the context of depression is *OXTR* rs2254298. Brune (107) suggests that the A allele on the *OXTR* rs2254298 is a more evolutionarily recent allele that confers resilience under harsh rearing conditions, which often play a role in susceptibility for depression.

Having a mother with recurrent major depressive disorder (MDD) interacted with *OXTR* rs2254298 to predict daughters' depression and social anxiety (108), but these findings did not replicate (109). *OXTR* rs53576A-carrying adolescents whose mothers were depressed showed the highest depression scores (110), and among adolescent girls, maternal MDD combined with *OXTR* rs2254298 predicted daughters' depression with the heterozygous genotype AG constituting the greatest risk (108). Interaction between *OXTR* rs139832701 and early stress predicted depressive symptoms and increased anxiety; however, there was no effect of this SNP on brain expression using in silico analysis (111). In a community cohort (112), maternal MDD was measured repeatedly from birth to 6 years. The *OXTR* rs2254298GG genotype was overrepresented in depressed mothers, their husbands, and their children, and all family members showed lower salivary OT. Children of depressed mothers had a fourfold increase in the propensity to develop a psychiatric disorder by age 6. However, presence of the *OXTR* rs2254298A allele in the depressed mothers markedly decreased the risk of child psychopathology. Finally, only among children of depressed mothers who were *OXTR* rs53576GG homozygotes was there an increased sensitivity to detect sad faces and reduced sensitivity to detect happy faces, which was not found among A carriers (113).

Two recent reviews discuss the role of OT in mood disorders and depression (114,115). *OXTR* rs53576G carriers were characterized by greater depressive symptoms than AA homozygous subjects but only among individuals reporting early maltreatment (116), possibly suggesting that the positive effects of the G allele may be dependent on rearing conditions. Among individuals with unipolar and bipolar depression (117), *OXTR* rs53576GG carriers with unipolar depression reported higher separation anxiety.

Schizophrenia

Several studies examined the association between *OXTR* and schizophrenia (118,119). Among schizophrenia patients, *OXTR* rs53576A carriers had more empathic concern than GG homozygous subjects (120). Comparing 406 schizophrenia patients with 406 control subjects, associations were found between *OXTR* rs53576A carriers and rs237885T carriers and diagnosis of schizophrenia (119). Among patients, the *OXTR* rs2268493 T allele was related to poorer social-cognitive index but not with clinical symptoms (121). Variants in the *OXTR* were nominally associated with severity of symptoms (rs237885, rs237887) and improvement in positive symptoms following clozapine treatment (rs11706648, rs4686301, rs237899) (122).

Overall, the associations found between OT-pathway genes and psychiatric disorders lend support to the aforementioned evolutionary perspectives and suggest that for a species as hypersocial (eusocial) as humans, social abilities are most relevant for the individual's adaptation, whereas psychiatric disorders reflect primary disruptions in social functions as mediated by its biological underpinning.

EPIGENETICS, CONCEPTUAL IMPLICATIONS, AND FUTURE DIRECTIONS

Epigenetics

Methylation modulation of the *OXTR* gene at the level of DNA is a topic of increasing interest (123,124). Methylation is a chemical modification of DNA that plays an important role in gene activity by regulating transcription and ultimately the amount of protein produced. High levels of methylation on cytosine-phosphate-guanine (CpG) sites typically lead to decreases in gene expression. Studies of DNA methylation, as well as other modifications of DNA and structural proteins of chromosomes, comprise the so-called epigenetic approach, and recent methylation studies attempt to provide deeper understanding on how early environments influence adult behavior (123). In the human *OXTR* gene, there is a CpG island from 140 base pair upstream to 2338 base pair downstream of the transcription start site and the methylation status of this region affects transcription (125). Methylation of the *OXTR* CpG island promoter inhibits its transcription, as shown in the liver (125), and is likely to regulate tissue-specific gene expression across various organs. There is a growing consensus that early environments can modulate methylation of genes crucial for neurodevelopment (126–128) including OXTR methylation. Studies on methylation of *OXTR* in relation to psychopathology and stress response are described in Supplement 1.

Importantly, failure to examine epigenetic modulations of OT-pathway genes may be one reason for the lack of conclusive findings in a recent meta-analysis on *OXTR* rs53576 and rs2254298 (129). In addition to the combination of multiple behaviors under global categories, which may be poor phenotypes for genetic association studies, expression of *OXTR* may be impacted by epigenetic signatures (126). Animal studies suggest that epigenetic markers, including methylation and histone acetylation of *OXTR*, are important in regulating *OXTR* and *AVPR1a* receptor genes (130,131). New strategies such as gene-set analysis of OT-signaling pathways in social behavior have yet to be implemented and may help overcome issues of small effect sizes and multiple testing, especially when larger data sets become available.

Conceptual Implications and Future Directions

Research on OT-pathway genes and human social functions lends support to the three evolutionary-based principles outlined above. Consistent with deconstructing sociality, findings demonstrate the involvement of OT in the special abilities that define social life in our species and show that polymorphic variations are sensitive to cultural contexts and rearing conditions. The repurposing hypothesis is seen most robustly in studies demonstrating OT's role in the use of social relationships to accomplish basic life functions, for instance, parenting behavior and stress management or its lack thereof in cases of psychopathology. Finally, consistent with our behavior-based biobehavioral synchrony model (27,132), which describes the coordination of behavior and biology during social contact, findings indicate that OT binds members into social units via neurocircuitry that integrates online signals from organism and environment and between members of a social group. Much further conceptual work is required to build models that detail the involvement of OT in various social processes as they are embedded in specific cultural ecologies in health and pathology at the level of genetic variability and epigenetic methylation and in relation to a range of peripheral processes.

Finally, a critical next step requires better characterization of the early environment. Most genetic effects are expressed as gene by environment interactions rather than main effects (133). Yet, most human research has utilized adults' retrospective accounts of early caregiving, accounts often colored by current state (134). Much human research is needed to characterize early environments in greater detail, include careful observations of parenting behavior, and employ prospective longitudinal designs. Integrating information from imaging, genetic, and neuroendocrine biomarkers, combined with careful assessments of social behaviors and major efforts in longitudinal follow-ups, are required to understand the involvement of OT-pathway genes in underpinning the important modules of social life in our species—the social functions that make us human.

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ARTICLE INFORMATION

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