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Are genetic variations in *OXTR*, *AVPR1A*, and *CD38* genes important to social integration? Results from two large U.S. cohorts

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Summary Some evidence suggests that genetic polymorphisms in oxytocin pathway genes influence various social behaviors, but findings thus far have been mixed. Many studies have been based in small samples and there is possibility of publication bias. Using data from 2 large U.S. prospective cohorts with over 11,000 individuals, we investigated 88 SNPs in *OXTR*, *AVPR1A*, and *CD38*, in relation to social integration (measured as social connectedness in both binary and continuous forms and being continuously married). After correction for multiple testing only one SNP in *CD38* (rs12644506) was significantly associated with social integration and that SNP predicted when using a dichotomized indicator of social connectedness (adjusted $p = 0.02$), but not a continuous measure of social connectedness or the continuously married outcome. A significant gender-heterogeneous effect was identified in one *OXTR* SNP on dichotomized social connectedness; specifically, rs4686302 T allele was nominally associated with social connectedness in men, whereas the association direction was opposite in women (adjusted gender heterogeneity $p = 0.02$). Furthermore, the rs53576 A allele was significantly associated with social connectedness only in women, and the effect magnitude was stronger in a dominant genetic model (adjusted $p = 0.003$). In summary, our findings suggested that common genetic variants of

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OXTR, *CD38*, and *AVPR1A* are not associated with social integration as measured in this study using the simplified Berkman–Syme Social Network Index, but these findings and other work hint that effects may be modified by gender or other social experiences. Further work considering genetic pathways in relation to social integration may be more fruitful if these additional factors can be more comprehensively evaluated.

1. Background

The importance of social relationships in human health has long been recognized. For example, social integration, defined as the presence of close personal and social relationships, has been shown to be associated with multiple physical and psychological health outcomes such as depression, cardiovascular disease, and mortality (Kawachi and Berkman, 2001; Kawachi et al., 1996). However, the biological mechanisms underlying behaviors related to being socially connected are not well understood. The neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) are two of the most-studied brain signaling molecules encoding proteins relevant to social behavior. This OXT–AVP neural pathway has received the most attention to date in research considering the underlying biology of social behavior in humans given prior work on the function and plausible effects of these neuropeptides (Insel, 2010; Lee et al., 2009a; Meyer-Lindenberg et al., 2011). OXT and AVP have been implicated in shaping social behaviors in mammals ranging from rodents to humans (Heinrichs et al., 2009), including attachment (Insel and Young, 2001), parent–infant bonding (Gordon et al., 2010), social recognition (Winslow and Insel, 2002, 2004), and aggression (Bosch et al., 2005; Lee et al., 2009b). This neuropeptide system also plays a role in pathological human behaviors that involve social deficits, such as autism (Hammock and Young, 2006).

Studies of intranasally administered OXT and AVP [summarized in Meyer-Lindenberg et al. (2011)] as well as correlation studies between peripheral levels of OXT and AVP and behaviors such as trust, physical contact with a partner, stressor response, and social memory (Grewen et al., 2005; Rimmele et al., 2009; Taylor et al., 2006; Zak et al., 2005) provide accumulating evidence that these neuropeptide molecules are involved in modulating a spectrum of social behaviors. Both OXT and AVP are sexually dimorphic and mediate action of sex hormones in the regulation of social cognition (Gabor et al., 2012). Because of the high degree of preservation of neuropeptide system across mammals and the heritability of social behaviors in humans (Maher et al., 2011; Scourfield et al., 1999), greater understanding of variation in genes that encode neuropeptides may shed light on the nature of social relationships individuals form. Research investigating the effect of genetic variation in the genes encoding OXT and AVP on social behaviors has not provided conclusive evidence, but additional evidence now implicates the genes that encode their receptors (Meyer-Lindenberg et al., 2011). The oxytocin receptor (*OXTR*) gene encodes a protein that belongs to the class I G protein-coupled receptor family. The neuroimaging study supported the implication of *OXTR* in hypothalamic–limbic circuits for emotional regulation and sociality (Tost et al., 2010). The AVP receptor 1A (*AVPR1A*) gene encodes the AVP receptor in the human brain that differs in structure with OXT by just two amino acids.

Recently, the transmembrane protein CD38 has also received attention as it is involved in oxytocinergic neural transmission (Jin et al., 2007). CD38−/− knockout mice had both decreased plasma OXT level and significant social impairments, including poorer maternal nurturing and less effective social behaviors (Jin et al., 2007). Research investigating association between *CD38* genetic polymorphisms or expression levels in relation to autism also suggests a role for *CD38* in regulating OXT release and contributing to disorders characterized by social deficits (Ebstein et al., 2011; Lerer et al., 2010; Munesue et al., 2010; Riebold et al., 2011).

Studies have provided some evidence for an association of genetic polymorphisms in *OXTR* (3p25), *AVPR1A* (12q14-q15), or *CD38* (4p15) genes with behaviors related to forming social relationships, including social recognition and empathy in humans. However, most of the studies conducted to date used small samples, sometimes with fewer than 100 individuals. Studies have shown that behavioral traits are complex, and multiple genetic loci are involved in their variation, each with a small to moderate effect (McGuffin et al., 2001). Given that social integration is a complex trait, a study trying to assess its genetic contributions with small sample size is likely to be underpowered for detection of a true association. Furthermore, to our knowledge there is no study that has examined the effects of these genes specifically on social integration. However, using the most intensively studied SNP in the *OXTR* gene, rs53576 as an example, even when we reviewed the literature that examines the effects of this particular SNP on phenotypes broadly related to social integration, we identified relatively inconsistent findings (Table S1). To try to resolve some of the inconsistencies in prior work, and to consider effects more directly in relation to social integration, in the present study, we examined the associations between genetic polymorphisms in *OXTR*, *AVPR1A*, and *CD38* genes, in relation to social integration measured across multiple time points in two large prospective cohorts of men and women. Given the important role of these genes in various social behaviors, we hypothesized that genetic polymorphisms in each of these genes would be associated with social integration. Because behaviors are relatively stable across time (Huesmann et al., 1984; Weisbuch et al., 2010), we used an average social integration score across repeated measures over time to reduce extraneous (i.e., non-genetic) variability in the phenotype and increase power to detect genetic determinants. In addition, we explore whether there is a sex-dependent mechanism impacting the association in the present study given the evidence of sex-dependent action of OXT and AVP (Carter, 1998; Gabor et al., 2012; Wu et al., 2012).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2013.09.024.