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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).

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2. Materials and methods

2.1. Study sample

The study includes participants from 7 genome-wide association (GWA) case-control studies nested within the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) cohorts. More description of the cohort has previously been published (Colditz and Hankinson, 2005) and specific details on how participants were selected into each of these GWA studies have also been published elsewhere (Cornelis et al., 2011).

Briefly, the NHS recruited 121,700 female US-registered nurses ages 30—55 years old residing in 11 large US states who completed and returned an initial self-administered questionnaire on their medical histories and baseline health-related exposures in 1976. Since then, biennial questionnaires with prospective collection of exposure information on risk factors and follow-up of health outcomes have been collected. The response completion rate is more than 90% in over 20 years of follow-up. The NHS participants included in the current study are from the blood subcohort that comprised 32,826 women in the NHS who gave blood specimens between 1989 and 1990.

The HPFS recruited 51,529 men from all 50 US states in health professions (dentists, pharmacists, optometrists, osteopath physicians, podiatrists, and veterinarians) aged 40—75, who at the start of the study answered a detailed questionnaire by mail. Similar to the NHS, health- and disease-related information was collected via biennial questionnaires in HPFS. The HPFS participants included in the current study are from the blood subcohort of 18,159 men who provided blood samples between 1993 and 1994.

The analytic sample for the analyses presented here was from a subsample (n = 6992) of the Nurses' Health Study and a subsample (n = 4177) of the Health Professional Follow-up Study with genome-wide single nucleotide polymorphism (SNP) information and at least one of the social integration phenotypes available.

2.2. Measure of social integration

Measures of social integration were developed using items from a commonly used simplified Berkman—Syme Social Network Index (BSSNI) (Berkman and Syme, 1979). The items were assessed at multiple time points in both NHS and HPFS, 5 times from 1992 to 2008 at intervals of 4 years in the NHS and in 1988, 1996, and 2008 in the HPFS, and included four types of social connections: (1) marital status (married/having a domestic partnership, separated/divorced, widowed, or single), (2) contact with close friends (none, 1—2, 3—5, 6—9, 10+ friends), (3) regular attendance at religious meetings or services (never or almost never attend, twice a month to once a year, once/week, >once/week), and (4) participation in any community or volunteer groups or other organizations (such as church-connected groups, self-help group, charity, and public service) (none, 1—2, 3—5, 6—10, 11—15, 16+ h/week). In the HPFS, the marital status was also assessed in additional questionnaire waves, i.e., examined every two years from 1986 to 2008.

In this study, the phenotype of social integration was measured in three ways: (1) being continuously married (yes/no), (2) being socially connected (dichotomized: yes/no), and (3) level of social connectedness (continuous). We used being continuously married to capture the ability to maintain a long-term stable intimate relationship. Being continuously married was derived from the marital status item of the BSSNI, and the dichotomized and continuous measures of social connectedness were derived from all four items of the BSSNI. For each item of the BSSNI, we carried forward the information reported in the prior questionnaire cycle if it was missing in the current cycle.

For the continuously married phenotype, an individual was scored as 1 if s/he was married or living with a partner at all waves up until they died and 0 otherwise. The total number of waves at which marital status was assessed were 5 for the NHS (marital status assessed every 4 years from 1992 to 2008) and 12 for the HPFS (marital status assessed every 2 years from 1986 to 2008). Participants were included in the analysis in they provided information on marital status in all waves during the follow-up period. To derive the dichotomized definition of social connectedness phenotype, at each time point each component was defined in Table 1.

At each wave, individuals had to have at least 2 non-missing values out of four components to be scored. To avoid unfairly penalizing individuals missing scores in one or another category, we took an average across four social integration components, ranging from 0 (socially isolated) to 1 (socially connected). The dichotomized definition of social connectedness (summarizing over all time points) was scored 0 if subjects had an average score below or equal to 0.25 in any given wave (ever socially isolated) and 1 if subjects had an average score above 0.25 at all waves (socially connected). Among the NHS participants who had genotype data, 2.4% had missing information on the "continuously married" variable and 0.9% had missing information on the "socially connected" variable. Among the HPFS participants with genotype data, 0.7% and 11.9% had missing information on "continuously married" and "socially connected" variable, respectively. A small proportion of NHS participants (0.58%) were excluded from the analytic sample because they did not have any information on the phenotypes; these individuals were on average older and had higher BMI than the participants with information on some or all phenotypes regarding social integration. All participants in the HPFS gave at least some information on social integration.

Table 1 Phenotype scoring criteria for binary social connectedness phenotype.

Item	Score of 1 if:	Score of 0 if:
Marital status	Married, living with a partner	Widowed, separated, divorced, single
Religious meeting or service attendance	Regularly with varying frequency	Never or almost never
Contact with close friends	At least one	None
Group participation	At least 1 h/week	No participation in any groups

Table 2 Phenotype scoring criteria for continuous social connectedness phenotype.

Item	Score of 3 if:	Score of 2 if:	Score of 1 if:	Score of 0 if:
Marital status	Married, living with a partner	N/A	N/A	Widowed, separated, divorced, single
Religious service attendance	>Once/week	Once/week	<Once/week	Never
Contact with close friends	10+	3–9	1–2	None
Group participation	11+ h/week	3–10 h/week	1–2 h/week	None

Social connectedness was also assessed via a continuous scale to maintain the original outcome variation. Instead of assigning a binary value to each social integration component following prior work with this measure (Eng et al., 2002), at each time point we categorized each component according to the component score, as shown in Table 2. For each wave, we averaged the category scores across the four components to create a continuous social connectedness score. The same carry-forward approach described above was applied for missingness. A final long-term cumulative social connectedness measure was derived by taking the average of the continuous social connectedness score across waves, ranging from 0 to 3.

Because a great deal of research has suggested that involvement in religious institutions provides people a sense of belongingness and general social identity, religious meeting or service attendance has frequently been included in social network measures in prior literature. However, people also attend religious meetings or services regularly for religious reasons. As a result a measure of religious service attendance may not accurately capture the aspects of social integration of interest in this study. To address this concern, we also conducted a secondary analysis excluding religious service attendance from the social integration phenotypes.

2.3. Selection and analysis of single nucleotide polymorphisms

Genotypes for the current analysis were derived from seven nested case-control genome-wide association substudies in the Nurses' Health Study and Health Professional Follow-Up Study, initially designed to assess female breast cancer (BrCa), and coronary heart disease (CHD), kidney stone (KS), and type 2 diabetes (T2D) in men and women. 10,905 individuals with genotype data and information on social integration phenotypes were included in the study. Population structure was investigated by principal component analysis using the genome-wide data. Due to very few people with genetically inferred non-Caucasian ancestry, these individuals were excluded from our analysis. Genotyping and quality control have been detailed elsewhere (Cornelis et al., 2011). SNP imputation was performed using MACH software (v1.0.16) with HapMap CEU phased II data (Release 22) as the reference panel. Imputation probabilities rounded to most likely genotypes were used or analysis.

For the current targeted analysis, based on prior theory and empirical findings we selected 98 SNPs located in the chromosomal regions containing *AVPR1A* (8 SNPs), *OXTR* (29 SNPs), and *CD38* (61 SNPs). 7 SNPs (1 in OXTR and 6 in CD38) with minor allele frequency (MAF) less than 1% and 3 additional SNPs (1 in OXTR and 2 in CD38) with imputation quality of less than 0.5 in one or more of seven NHS/HPFS GWA substudies were further removed, leaving a set of 88 SNPs to be included in the final analysis. A number of studies have identified *OXTR* rs53576 as being associated with loneliness, empathy, and trust behavior (Krueger et al., 2012; Lucht et al., 2009; Rodrigues et al., 2009). Unfortunately this was only available (also directly genotyped) in two of our 7 NHS/HPFS substudies. Because it has been one of the most extensively assessed SNPs in the literature, we additionally examined rs53576 in the two substudies (N = 1043; 553 men and 490 women) which included this SNP in relation to social integration.

2.4. Statistical analyses

Logistic regression models were used to estimate the effect magnitude [odds ratio (OR) and 95% confidence interval (95% CI)] of genetic markers on dichotomous outcomes (i.e., being socially connected, or being continuously married). Linear regression models were used to estimate the effect of each polymorphism on the continuous social connectedness score. Initially, analyses were conducted in each of the NHS and HPFS substudies separately using PLINK toolset, adjusted for the disease status of each initial GWA substudy and the top three or four eigenvectors. Fixed-effect meta-analyses of the overall SNP effects were then used to combine results across 7 NHS/HPFS substudies using the GWAMA program. Gender-specific effects were also examined in GWAMA to assess potential heterogeneous SNP effects by gender. Associations were examined under the additive mode of inheritance. In the analysis with rs53576 only, we further considered both the dominant and recessive models because both models have also been suggested in the literature.

To correct for multiple testing of single markers within each gene, the effective number of independent tests was determined using the method proposed by Nyholt (2004) and modified by Li and Ji (2005), as implemented in the SNP Spectral Decomposition (SNPSpD) (http://gump.qimr.edu.au/general/daleN/SNPSpD/). Following this procedure, the Bonferroni-adjusted p-value was computed, so the overall type I error was maintained at 0.05 for each gene. The adjusted p-value was set to 1 if the value exceeded 1. We did not further adjust for number of phenotypes examined because the three phenotypes are nested in/associated with each other.

In addition to SNP analyses, gene-based analyses were also performed on all SNP-level results from the meta-analysis of all three phenotypes using VEGAS (Liu et al., 2010). The software applies a test that incorporates information from a set of markers within a gene and accounts for LD between markers by using simulations from the multivariate normal distribution. A Bonferroni-corrected threshold of $p < 0.017$, which equaled to 0.05/3 (number of genes tested), was used to indicate a significant gene-based association.

Table 3 Characteristics of study participants.[a]

	NHS		HPFS	
	Mean/ frequency	%/standard deviation (range)	Mean/ frequency	%/standard deviation (range)
Age at first social integration measurement (years)	60.2	6.7	57.6	9.7
Continuously married	6313	91.9	3655	88.1
Dichotomized social connectedness	6200	88.9	3471	94.4
Continuous social connectedness score	1.9	0.5 (0.1—3)	1.8	0.5 (0—3)

[a] The number of individuals varies from 6869 for being continuously married as an indicator of the ability to maintain a stable relationship to 6973 for binary social connectedness in the NHS and varies from 3678 for binary social connectedness to 4147 for being continuously married in the HPFS.

3. Results

Table 3 describes the characteristics of the sample. Of 11,169 participants with information on social connectedness over time or having a stable relationship, 63% were female. The participants had an average age over 57 years old when the first social integration measurement was administered. The majority of the participants were continuously married over the follow-up period. Women reported almost twice the prevalence of social isolation as men in our study. The Pearson correlation coefficient of continuous social connectedness score between the first and last assessment across 16 years in the NHS was 0.62; the corresponding correlation across 20 years in the HPFS was 0.72, suggesting that social integration was relatively stable over time.

Table 4 presents the top 5 SNP-phenotype associations per gene associated with each phenotype. Overall we found little evidence of significant association of *AVPR1A*, *OXTR*, and *CD38* genetic polymorphisms with any of the social integration phenotypes measured in our study after accounting for multiple testing. The only exception was for rs12644506 in the intronic region of *CD38* in relation to binary social connectedness, in which the T allele was associated with 24% lower odds of being socially connected (adjusted $p = 0.02$). To address concerns for the presence of allelic heterogeneity that may have reduced our power to observe significant associations at an individual SNP-level (Slager et al., 2000), all SNP-level results from the meta-analysis of the three phenotypes were additionally subject to gene-based analyses using VEGAS (Liu et al., 2010), but still no significant gene associations were observed (all p-values > 0.10). After excluding religious service attendance from the phenotype measures, only two SNPs were nominally associated, including rs1803404 in *OXTR* with the dichotomized form of social connectedness (nominal $p = 0.02$) and rs237897 in *CD38* with continuous form of social connectedness (nominal $p = 0.02$). Neither of these SNPs remained statistically significant after correction for multiple testing (data not shown).

When considering a potential gender-specific effect, a missense mutation in the *OXTR*, rs4686302, showed a statistically significant heterogeneous effect by gender (adjusted gender-heterogeneity $p = 0.02$) (Table 5). The T allele was borderline statistically associated with dichotomized definition of more social connectedness in men after adjusting for multiple testing (OR = 1.72, 95% CI = 1.18—2.51, adjusted $p = 0.08$) but not in women. A gender-dependent association of rs4686302 with the other two phenotypes was not statistically significant, but the pattern was consistent with what emerged with the binary social connectedness phenotype (i.e., T allele being associated with higher social integration in men but not in women).

In the subset of 1043 participants with data available (553 men and 490 women), overall there were no statistically significant associations between *OXTR* rs53576 genotype and any of the three social integration measures. When considering a potential gender-dependent effect, the A allele was significantly associated with the binary social connectedness phenotype in women but not in men, assuming an additive mode of inheritance after correction of multiple testing (Table 6; adjusted $p = 0.02$ in women). The magnitude of the effect estimate was larger in models specified with a dominant mode of inheritance, in which AA carriers had 3.31-fold odds of reporting social connectedness compared with AG/GG carriers (adjusted $p = 0.003$), with the adjusted p-value of the gender heterogeneity effect of 0.11. When considering the continuous social connectedness phenotype, the significance was diminished but the patterns were consistent. We did not observe rs53576 to be associated with being continuously married in either women or men in the study.

4. Discussion

In this study we investigated the associations of genetic polymorphisms in *OXTR*, *CD38*, and *AVPR1A* genes with social integration using phenotypes characterized by the ability to maintain long-term stable relationships and being socially connected. From 88 SNPs tested, we observed only one significant association that met multiple-comparisons adjusted criteria for statistical significance between a *CD38* intronic SNP rs12644506 and dichotomized definition of social connectedness. This particular SNP has not yet been reported to be associated with any disease or trait examined thus far in the literature. Given rs12644506 is an intronic SNP, the functional importance of this SNP remains to be determined. In addition, we observed a significant gender-specific association in one *OXTR* SNP with respect to a dichotomized definition of social connectedness; specifically, rs4686302 T allele was nominally associated with social connectedness in men, whereas the association was non-significant but in the opposite direction in women (adjusted gender heterogeneity $p = 0.02$). Furthermore, rs53576 A allele was significantly associated with social connectedness only in women

Table 4 Meta-analyzed association results across 7 NHS/HPFS substudies of the top 5 SNPs per gene based on significance.[a]

SNPs	Phenotypes																	
	Being continuously married						Binary social connectedness						Continuous social connectedness score					
	SNP	Effect allele	MAF	OR	p^b	p^c	SNP	Effect allele	MAF	OR	p^b	p^c	SNP	Effect allele	MAF	beta	p^b	p^c
AVPR1A	rs11174810	T	0.02	0.82	0.29	0.87	rs1042615	A	0.42	1.04	0.44	1.00	rs11174811	A	0.16	0.014	0.10	0.30
	rs3741865	A	0.02	0.82	0.29	0.87	rs3021529	A	0.16	0.97	0.64	1.00	rs10877968	C	0.18	0.008	0.32	0.96
	rs3021528	C	0.02	0.82	0.29	0.87	rs10877968	C	0.18	0.98	0.72	1.00	rs3021529	A	0.16	0.008	0.38	1.00
	rs11174811	A	0.16	1.07	0.30	0.90	rs3803107	A	0.18	0.98	0.73	1.00	rs3803107	A	0.18	0.007	0.39	1.00
	rs3021529	A	0.16	1.07	0.31	0.93	rs11174811	A	0.16	0.99	0.90	1.00	rs1042615	A	0.42	0.004	0.53	1.00
CD38	rs2286553	T	0.04	0.80	0.05	0.51	rs12644506	T	0.06	0.76	0.002	**0.02**	rs6449195	C	0.10	-0.023	0.02	0.20
	rs1112243	T	0.04	0.80	0.06	0.61	rs6449195	C	0.10	0.81	0.005	0.05	rs12644506	T	0.06	-0.028	0.03	0.30
	rs10805347	A	0.31	1.10	0.06	0.61	rs6836946	G	0.28	0.88	0.01	0.10	rs6449197	T	0.11	-0.019	0.06	0.61
	rs1112244	C	0.04	0.81	0.07	0.71	rs6841880	A	0.28	0.88	0.01	0.10	rs3796863	T	0.30	-0.012	0.08	0.81
	rs1004124	G	0.04	0.81	0.07	0.71	rs3796867	A	0.07	0.81	0.02	0.20	rs6836946	G	0.28	-0.010	0.14	1.00
OXTR	rs2268490	T	0.13	1.16	0.04	0.60	rs237887	G	0.44	1.09	0.07	1.00	rs237897	A	0.38	-0.013	0.05	0.75
	rs2268491	T	0.12	1.16	0.05	0.75	rs2268490	T	0.13	1.14	0.08	1.00	rs237895	T	0.38	-0.010	0.12	1.00
	rs2254295	C	0.12	1.16	0.05	0.75	rs237885	T	0.48	1.09	0.09	1.00	rs4564970	C	0.08	0.015	0.19	1.00
	rs2254298	A	0.12	1.15	0.06	0.91	rs2268491	T	0.12	1.13	0.12	1.00	rs2301261	T	0.08	0.015	0.19	1.00
	rs4564970	C	0.08	1.16	0.10	1.00	rs2254295	C	0.12	1.12	0.14	1.00	rs2268496	A	0.22	0.009	0.24	1.00

[a] Significant Bonferroni-corrected p-value (adjusted p-value < 0.05) was bold.
[b] Unadjusted p-value.
[c] Bonferroni-corrected p-value.

Table 5 Gender-specific effect of OXTR rs4686302T-phenotype association (T allele frequency = 0.12).[a]

Phenotype	Gender heterogeneity p		Overall effect			Male-specific effect			Female-specific effect		
	p^b	p^c	OR/beta[d] (95% CI)	p^b	p^c	OR/beta[d] (95% CI)	p^b	p^c	OR/beta[d] (95% CI)	p^b	p^c
Being continuous married			*N* = 11,015			*N* = 4146			*N* = 6869		
	0.10	1.00	1.04 (0.90, 1.20)	0.60	1.00	1.19 (0.96, 1.49)	0.12	1.00	0.94 (0.78, 1.13)	0.51	1.00
Binary social connectedness			*N* = 10,650			*N* = 3677			*N* = 6973		
	0.001	**0.02**	0.96 (0.83, 1.11)	0.57	1.00	1.72 (1.18, 2.51)	0.005	0.08	0.87 (0.74, 1.01)	0.07	1.00
Continuous social connectedness score			*N* = 10,651			*N* = 3679			*N* = 6972		
	0.11	1.00	0.01 (−0.01, 0.03)	0.41	1.00	0.03 (−0.003, 0.06)	0.07	1.00	−0.003 (−0.03, 0.02)	0.80	1.00

[a] Significant Bonferroni-corrected *p*-value (adjusted *p*-value < 0.05) was bold.
[b] Unadjusted *p*-value.
[c] Bonferroni-corrected *p*-value.
[d] For binary outcome, we calculated odds ratio to present the effect magnitude; for continuous outcome, beta was calculated.

(adjusted $p = 0.02$), and the effect magnitude was stronger in a dominant genetic model (adjusted $p = 0.003$). *OXTR*, *CD38*, and *AVPR1A* were not associated with the phenotype of being continuously married in either main or gender-specific analyses. The gender difference was not evident in relation to the continuous scale of social connectedness, although the direction of gender-stratified associations was consistent to those in the dichotomized form. Because both dichotomized and continuous measures of social connectedness were expected to share some underlying genetics, the discrepant findings suggested that either the estimations were unstable or the associations were likely non-linear, so the power was decreased when modeling the association linearly.

Participating in community, voluntary, and religious organizations provides a sense of social connectedness, which has long been linked with health benefits (Kawachi and Berkman, 2001). Although attending religious meetings or services increases the likelihood of constructing and maintaining interactive ties in social networks, because people also attend religious services for religious rather than social reasons, including religious attendance into social integration measures may result in misclassifying non-believers and nontraditional worshippers into a less socially integrated category. However, the results similarly suggest that social integration is not correlated with common genetic variations in *OXTR*, *AVPR1A*, and *CD38* genes whether including or excluding religious attendance in the social integration phenotype measure.

Although this study is exploratory and false positives cannot be ruled out, the observed gender-dependent effect of *OXTR* merits further investigation. In fact, there has been evidence that oxytocin and vasopressin release and receptor bonding are expressed in a gender-dependent manner, in which the binding capacity was higher in women than in men (Elands et al., 1990). It has also been reported in previous studies that certain genetic polymorphisms in *OXTR* show a gender-specific effect on specific social behaviors. For example, Walum et al. found that rs7632287 G/G genotype was related to partner bonding and affection in women but not in men (Walum et al., 2012), and Wu et al. observed a significant rs4686302 genotype by gender interaction (Wu et al., 2012); however, it was not consistent in direction with our results, thus should not be considered as replication. Observed gender differences, if confirmed in future work, could be due partially to the fact that OXT synthesis and OXTR are exceptionally sensitive to gonadal steroids (Smeltzer et al., 2006). It remains to be elucidated in future studies how these *OXTR* genetic polymorphisms influence social connectedness via a gender-specific manner.

Oxytocin and arginine vasopressin have been shown to regulate a suite of behaviors which support the formation and maintenance of attachment bonds in animals (for review see Kim et al., 2010b). Prosocial effects of oxytocin in humans have also been reported (Heinrichs et al., 2009; Israel et al., 2009; Macdonald and Macdonald, 2010). However, genetic studies of a broad range of social behaviors with oxytocin pathway genes including *OXTR*, *CD38*, and *APVR1A* have had mixed results. Our study suggests that effects may be small and therefore difficult to detect. Here, we use the most studied SNP, rs53576, as an example for discussion. There has been intense research on this particular SNP in relation to various social and behavioral phenotypes in the past 3 years,

Table 6 OXTR rs53576A-phenotype associations (A allele frequency = 0.33).[a]

Phenotype/genetic model	Gender		heterogeneity *p*	Overall effect			Male-specific effect			Female-specific effect	
	p^b	p^c	OR/beta[d] (95% CI)	p^b	p^c	OR/beta[d] (95% CI)	p^b	p^c	OR/beta[d] (95% CI)	p^b	p^c
Being continuously married			*N* = 970			*N* = 480			*N* = 490		
Additive	0.88	1.00	1.16 (0.87, 1.55)	0.32	1.00	1.14 (0.78, 1.67)	0.51	1.00	1.19 (0.76, 1.87)	0.45	1.00
Dominant	0.99	1.00	1.22 (0.84, 1.76)	0.3	1.00	1.22 (0.74, 2.01)	0.43	1.00	1.21 (0.70, 2.11)	0.49	1.00
Recessive	0.76	1.00	1.15 (0.60, 2.21)	0.67	1.00	1.07 (0.47, 2.41)	0.88	1.00	1.32 (0.44, 3.96)	0.62	1.00
Binary social connectedness			*N* = 970			*N* = 480			*N* = 490		
Additive	0.01	0.15	1.55 (1.04, 2.31)	0.03	0.45	0.91 (0.51, 1.62)	0.74	1.00	2.51 (1.45, 4.37)	0.001	0.02
Dominant	0.007	0.11	1.93 (1.17, 3.16)	0.01	0.15	0.81 (0.36, 1.80)	0.61	1.00	3.31 (1.76, 6.22)	0.0002	0.003
Recessive	0.7	1.00	1.28 (0.53, 3.07)	0.59	1.00	1.07 (0.30, 3.76)	0.92	1.00	1.51 (0.44, 5.13)	0.51	1.00
Continuous social connectedness			*N* = 1035			*N* = 548			*N* = 487		
Additive	0.15	1.00	0.001 (−0.05, 0.05)	0.97	1.00	−0.03 (−0.10, 0.03)	0.33	1.00	0.04 (−0.03, 0.10)	0.29	1.00
Dominant	0.03	1.00	0.01 (−0.05, 0.07)	0.72	1.00	−0.06 (−0.15, 0.03)	0.19	1.00	0.08 (−0.01, 0.16)	0.08	1.00
Recessive	0.58	1.00	−0.03 (−0.13, 0.08)	0.61	1.00	−0.0003 (−0.14, 0.14)	1	1.00	−0.06 (−0.22, 0.10)	0.45	1.00

[a] Significant Bonferroni-corrected *p*-value (adjusted *p*-value < 0.05) was bold.
[b] Unadjusted *p*-value.
[c] Bonferroni-corrected *p*-value.
[d] For binary outcome, we calculated odds ratio to present the effect magnitude; for continuous outcome, beta was calculated.

although no prior study specifically examined social integration, the phenotype investigated in the present study. In reviewing the literature considering the association between rs53576 genotype and various phenotypes broadly used to characterize social integration, ranging from partner bonding to generosity (see supplement for summary of literature, Table S1), we observe that approximately half of the studies reported a positive association with rs53576A while the rest reported a null association. It is noteworthy that the two studies with the largest sample size failed to observe a significant association between rs53576A and prosocial behaviors, including pair bonding behaviors, trust, and generosity (Apicella et al., 2010; Walum et al., 2012). Several of the studies reporting a significant association between rs53576A and prosociality were conducted in small samples (for example, study (Kogan et al., 2011) had only 23 participants) or were investigated in a specific disease group (Park et al., 2010). Given the small sample or particular populations considered, positive findings could be due to chance, or may not be applicable to the general population. The phenotypes examined in these various studies and in our study are different but they do share some common features, leading to the hypothesis that the oxytocin might influence the indicators of social integrations we used here. Walum et al. examined the effect of rs53576 on romantic relationship quality/partner bonding (Walum et al., 2012), the phenotype that is closest to the phenotype characterized by ability to maintain a stable romantic relationship examined in this study, and both studies reported null associations.

True associations may not be reproducible across different studies for a number of additional reasons, including insufficient statistical power or effect modification. Our sample is substantially larger than previous studies. The study has over 80% power to detect a genetic risk variant with an odds ratio (OR) of 1.25 for $\alpha = 0.05$, if the risk allele frequency in the population is 0.1, assuming population risk of social isolation of 8%, the additive genetic model, and complete linkage disequilibrium between a genotyped and a causal genetic variant. However, although it is the largest study to date to examine the effects of genetic variation of *OXTR*, *CD38*, and *AVPR1A* genes and social integration, our study is likely underpowered to detect smaller effects. The potentially limited statistical power in prior work along with the fact that the first set of published studies often overestimate effect sizes due to the winner's curse (Zollner and Pritchard, 2007) could explain our failure to find an association observed in the present study. In addition, gene by environment interactions may have an important influence on social functioning (Bradley et al., 2011). Bradley et al. did not identify overall associations of rs53576 with adult emotional dysregulation or attachment style phenotypes, but there was a significant interaction of the SNP with childhood maltreatment to predict social traits in adulthood. The findings may suggest that rs53576 A allele carriers are resilient against the effects of severe childhood adversity and protected against adult emotional dysregulation and disorganized attachment that often occurs among people who experience childhood adversity. These are phenotypes associated with pair-bonding relationships and marital quality. In our study, assessments of chronic stress or childhood adverse experiences were not available. If a substantial number of participants experienced severe chronic stress earlier in life, it may have been more difficult to detect an effect of oxytocin-pathway genes on social integration. Future studies are warranted to investigate whether effects of genetic variations in *OXTR*, *CD38*, and *AVPR1A* influence social integration depend on childhood socioemotional experience.

Several potential limitations should be noted. First, participants in the NHS and HPFS cohorts are all health care workers. If such individuals are more socially oriented toward other people than those in the general public, this might result in more limited variation in the phenotype, which could reduce study power to detect significant associations if any. In addition, individuals who are less religious may in fact have strong social bonds that will not be captured by a measure of religious service attendance. For example, Saslow et al. have shown that individuals who are less religious may be as or more likely as those who are more religious to be bound to others by strong emotional connections (Saslow et al., 2013b), and spirituality (with or without religiosity) may give rise to prosociality because it is strongly associated with compassion and altruism (Saslow et al., 2013a). Furthermore, religious service attendance may vary depending on culture and age. Given these possible sources of variation, the observed associations may not be generalizable. To address this potential concern, we compared the level of social integration in NHS/HPFS participants with that among participants in the US National Health Interview Survey (NHIS), a nationally representative sample of adult households. Although NHS and HPFS participants were older and had attained higher levels of education, the degree of social integration was relatively similar to that reported in the NHIS (Barger, 2013). Similar to participants in the NHS and HPFS, participants in the NHIS generally reported having medium to high social integration levels.

Secondly, existing genotype arrays and HapMap data may not have captured the true causal SNPs (if they exist) in the genetic pathways of interest; a limitation applied more broadly in current genome era. In addition, because the study included a sample with a homogenous ethnicity background, it is not capable to assess gene-by-ethnicity or gene-by-culture interaction, especially in the *OXTR*, as suggested previously (Chen et al., 2011; Kim et al., 2010a). Thirdly, the study was conducted in an older population. Genetic effects may diminish while environmental effects increase as people age, especially for complex traits. For example, Cornelis et al. observed a marginally significant OXTR rs53576-age interaction for predicting optimism, where rs53576 had stronger effect in younger people than in older people (Cornelis et al., 2012).

Lastly, in this study, information on social relationships was updated every four years or longer in the NHS and HPFS (every two years on marital status in the HPFS); therefore, if participants changed their behaviors or even marital status, for example, due to unexpected life events, we were unable to capture such changes occurring between questionnaire cycles. This could lead to non-differential misclassification of the measured outcome. However, because the social behaviors are relatively stable across time and remarriage occurs primarily among younger to middle aged adults (Kreider, 2006), we expect this issue did not have substantial impact. Furthermore, we used marital status as a surrogate to indicate one's ability to maintain a stable romantic relationship and connect to others. Initial hypotheses regarding social

benefits of oxytocin revolved around its role in being able to develop social bonds and recognize social cues. While a role for oxytocin in developing high quality social relationships or greater intimacy within social relationships has also been posited, it has not been explored in detail empirically. Walum et al. (2012) recently reported that women carrying a particular SNP allele (rs7632287A) in *OXTR* have lower levels of partner bonding or affection toward their partners. Thus, it may be that marital quality, rather than marital status may more appropriately capture the fundamental pair bonding feature, and we might have seen stronger relationships with such a measure. However, we did not have a measure of marriage quality. Such misclassification is likely to be non-differential, potentially biasing our effects toward the null. However, this study also has a number of strengths, including phenotype assessments at multiple time points to ensure a more stable and accurate measurement, high-quality genetic data, and participants with a genetically inferred homogeneous ethnic background, which minimizes bias due to population stratification and admixture.

In summary, we investigated variation in 3 genes in the oxytocin pathway — *OXTR*, *CD38*, and *AVPR1A* — in relation to three measures of social integration in a large sample of men and women. We find little evidence of overall effects of any genes, with only 1 *CD38* SNP showing a statistically significant result with one dichotomized form of social integration measure with requires replication. However, there was evidence of a gender-specific association of *OXTR* with social integration. Our findings are based on a sample many times larger than any prior study and suggest that prior work may have over stated the associations, if any, between oxytocin pathway genes and prosocial behaviors. However, the measure of social integration in this study is somewhat limited. If there is a better measure, it is possible that we would have seen something different. Furthermore, as behaviors such as social integration, like all complex traits, are influenced by multiple genes each with a small effect, it may be that there are other genes, gene-by-gene or gene-by-environment interactions that are more strongly involved in social behavior. Our findings and other work hint that the effects may be partially modified by gender or by other social experiences like chronic stress or aspects of childhood upbringing. Further work considering these genetic pathways in relation to social integration may be more fruitful if these additional factors can be more comprehensively assessed and evaluated.

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The corresponding author should confirm that she has full access to all the data in the study and has final responsibility for the decision to submit for publication.

Conflicts of interest

The authors do not have conflicts of interest.

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