Association of Oxytocin Receptor Gene (OXTR) rs53576 Polymorphism with Sociality: A Meta-Analysis

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Abstract

A common variant in the oxytocin receptor gene (OXTR), rs53576, has been broadly linked to socially related personality traits and behaviors. However, the pattern of published results is inconsistent. Here, we performed a meta-analysis to comprehensively evaluate the association. The literature was searched for relevant studies and effect sizes between individuals homozygous for the G allele (GG) and individuals with A allele carriers (AA/AG). Specifically, two indices of sociality were evaluated independently: i) general sociality (24 samples, n = 4955), i.e., how an individual responds to other people in general; and ii) close relationships (15 samples, n = 5262), i.e., how an individual responds to individuals with closed connections (parent-child or romantic relationship). We found positive association between the rs53576 polymorphism and general sociality (Cohen’s $d = 0.11$, $p = .02$); G allele homozygotes had higher general sociality than the A allele carriers. However, the meta-analyses did not detect significant genetic association between rs53576 and close relationships (Cohen’s $d = 0.01$, $p = .64$). In conclusion, genetic variation in the rs53576 influences general sociality, which further implies that it is worthy to systematically examine whether the rs53576 is a valid genetic marker for socially related psychiatric disorders.

Introduction

Social interaction is important to almost every aspect of human life. However, people differ in their degree of sociality. Whereas some people enjoy an active social life and easily interacting with others, some people avoid social interactions and have difficulty in dealing with people. Extreme examples of the latter condition include several socially related psychiatric disorders, including autism and social anxiety disorder. Understanding the molecular genetic basis of individual differences in sociality has received significant research interest of late [1,2].
Previous studies have implied that the oxytocin system plays an important role in human
socially related personality traits and behaviors [3,4], hereafter referred to as “sociality.” For
example, high levels of plasma oxytocin (OXT) have been associated with behaviors indicative
of enhanced sociality, such as increased physical contact with a partner [5] and trustworthiness [6]. Moreover, intranasal administration of OXT can specifically enhance sociality as well, by
increasing memory for social information [7], trust [6] and altruistic behaviors [8].

Due to the preservation of the oxytocin neuropeptide across mammalian species and the
heritability of sociality in humans [9], variations in genes encoding oxytocin may account for
individual differences in sociality [4]. The oxytocin receptor gene (OXTR), located on chromo-
some 3p25, is one such candidate. Indeed, several studies have examined the link between the
OXTR polymorphism and sociality. Compared with other single nucleotide polymorphisms
(SNPs) in OXTR, one SNP in the third intron of OXTR, rs53576 (G/A), has received the most
attention. Compared with A allele carriers (AA/AG), recent studies have found that the G allele
homozygotes (GG) were associated with high sociality, such as self-reported empathy [10],
dependence on social reward [11], social auditory ability [12], and general sociality as rated by
peers [13]. However, like many reported genetic associations, not all of these findings have
been successfully replicated [14,15].

Using a meta-analysis approach, a recent study conducted by Bakermans-Kranenburg and
van IJzendoorn attempted to evaluate the association between the rs53576 polymorphism and
sociality and did not establish a statistically significant genetic association [16]. However, we
argue that the results of that meta-analysis might be inconclusive in that the researchers might
have inadvertently conflated general sociality with a particular subtype of sociality— that is, soci-
ality in the context of close relationships [17]. Here, we define close relationships in the context
of the most important evolutionary purpose—reproduction. Thus, close relationships in our
study specifically correspond to three examples, i.e., relationships with a caregiver (i.e., father
or mother), one’s own child, or a romantic partner. However, other measures of sociality (e.g.,
extraversion, empathy, and trust) often involve how an individual responds to other people in
general, which involves not only caregivers, children, and partners, but also friends, teachers,
colleagues, and even strangers. According to evolutionary theory, our mind has evolved specific
mechanisms in service of social situations relevant to reproduction [18]. Therefore, given the
unique adaptive problems each type of response is intended to solve, individuals’ responses to
close individuals may differ considerably relative to their responses to others. This contention
has been supported by abundant psychological literature [17, 19]. For example, infants’
responses to their mothers differ considerably relative to those to strangers [20]. We suggest
that the genetic underpinning between these two psychological measures might be distinct. In
such a case, a comprehensive and appropriate evaluation of the association between rs53576
polymorphisms and sociality would require separate meta-analyses for, at the very least, gen-
eral sociality and sociality in the context of close relationships.

In this study, we reexamined the association between rs53576 polymorphisms and sociality
in humans with a meta-analytic approach. Compared with the previously mentioned meta-
analysis [16], our study differed in three aspects. First, and most critically, we performed sepa-
rated analysis on general sociality and close relationship. Second, withdrawal from social situa-
tions and activities is often associated with depression [21], and a study has reported genetic
associations between rs53576 polymorphism and depression [22] (see also [23] for a narrative
review on this issue). We assessed the possibility that genetic associations between rs53576 poly-
orphism and sociality might be mediated by depression. Specifically, we will first examine
whether rs53576 polymorphism is related to individual differences in depression; if positive
association was detected, we will then examine the possible mediation relationship [24]. Third,
compared to Bakermans-Kranenburg and van IJzendoorn’s meta-analysis, we drew from an
updated database of relevant genetic association studies such that 7 additional empirical studies consistent of 12 independent samples were assessed [12,25–30].

**Materials and Methods**

**Literature search**

To identify eligible studies for this meta-analysis, we searched the PubMed and ISI Web of Knowledge for all publications available up to May 1st, 2014 that examined the association between the OXTR rs53576 polymorphism and psychological traits. The following terms were included in the search: oxytocin receptor (or OXTR) and gene. In addition, we identified additional relevant studies from the references of initially identified studies and recent literature reviews.

**Selection of phenotype and data extraction**

We first identified all candidate measures from studies that examined the rs53576 polymorphism and psychological traits. Then, among all the psychological measures, phenotypes relating: 1) general sociality (e.g., extraversion, empathy, and social loneliness); 2) close relationship (including maternal sensitivity, child/adult attachment, and marital quality); and 3) depression were selected and classified into three independent categories respectively.

Data were extracted by the first and last author of the current manuscript independently and then cross-checked. In addition, when a sample consisted of more than one eligible phenotype, the phenotype that appeared most frequently in the literature was selected. If the relevant data were not reported in the article, the authors were contacted and requested for data releasing. 22 out of 27 authors released their data in an appropriate format. One data point (i.e., effect size) was extracted from one sample.

For each sample, the following information was extracted: first author, year of publication, country and ethnicity of the participants, proportion of females, diagnostic status (i.e., healthy individuals or patients), and age. Reverse scoring was used as necessary to maintain consistent measurement scaling across studies.

**Data analysis**

Following the convention in most published studies, OXTR rs53576 genotypes were grouped according to the presence and absence of the A allele (GG vs. GA+AA) [10,11,13,31]. We performed the analysis using the Metafor package in R [32]. Cohen’s *d* was used as the effect size measure, representing the standardized mean difference. Because the heterogeneous nature of included studies (e.g., differences in tasks to measure sociality), the weighted effect size and 95% confidence interval (95% CI) were generated via a random-effects analysis model by DerSimonian-Laird estimators [33]. In addition, the Q-profile method was used to confirm the heterogeneity of the included studies [34]. In the random-effects analysis model, between-study heterogeneity is proposed to result from both random variation and effects from individual studies. Random-effects models are generally more conservative (i.e., narrower CI) than fixed-effect models. Finally, *Z* scores were used to assess the statistical significance of the weighted effect size.

Publication bias was assessed by the Begg’s Test and the Funnel plot in order to assess the tendency to publish positive results rather than negative results. A sensitivity analysis was applied to examine whether the inclusion of a particular study had a significant effect on the overall weighted effect size. That is, studies were removed one at a time to examine whether the pooled effect size remained statistically significant or non-significant. Finally, to examine the...
potential influence of any moderator variables, we performed meta-regression analyses with the average age of the sample, proportion of female participants, and proportion of Caucasian participants in the sample as predictors. Because not all studies reported demographic information, not all samples were included in the moderation analyses.

Results

Our meta-analysis was performed according to two guidelines: the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement (S1 Table) [35] and the “Meta-analysis on Genetic Association Studies” statement (S2 Table) [36]. Fig 1 shows the flow chart of the literature search process. The excluded articles and reasons for exclusion were lists in the Supporting Information (S1 File). After the literature search was completed, we
conducted separated meta-analyses on the associations between the rs53576 polymorphism and three phenotype categories (i.e., general sociality, close relationship, and depression).

General sociality and close relationship

Eighteen studies [10–15,25,27,30–31,37–44] comprising twenty-four independent samples (Table 1) contributed to the meta-analysis of general sociality (total number of participants = 4955). As expected, there was evidence of between-study heterogeneity ($Q = 40.08$, $p = .02$). Critically, the random effects analysis indicated an association (Cohen’s $d = 0.11$, 95% CI = [0.02, 0.21], $Z = 2.28$, $p = .02$) such that G allele homozygotes had higher general sociality than A allele carriers (Fig 2A). The Begg’s test indicated no evidence of publication bias (Kendall’s tau = 0.09, $p = .54$) (Fig 2B). Because the sensitivity analysis indicated that pattern of results was similar after removal of any individual sample from the meta-analysis (i.e., all Cohen’s $ds > = 0.09$, $ps < .05$), the association observed in the meta-analysis was considered unlikely to be accounted for by any single outlying sample. Finally, meta-regression analyses suggested that the association was not significantly affected by sex ($k = 24$, $p = .20$), age ($k = 21$, $p = .31$), or ethnicity ($k = 24$, $p = .48$).

Next, we tested whether the rs53576 polymorphism influenced the quality of close relationship, a specific kind of sociality measurement. Ten studies [10,28,37,38,41,45–49] comprising 15 independent samples (Table 2) contributed to the meta-analysis (total n = 5262). Although there was no evidence of between-study heterogeneity ($Q = 10.86$, $p = .70$), we used a random-effects model in the following meta-analysis because the tasks measuring close relationships were subjectively disparate (c.f., Table 2, the last column). In contrast to the observed positive genetic association on general sociality, meta-analysis (GG vs. GA+AA) indicated no evidence of association for close relationship ($d = 0.01$, 95% CI = [-0.04, 0.07], $Z = 0.47$, $p = .64$) (Fig 3A). The Begg’s test (Kendall’s tau = -0.14, $p = .50$) indicated no evidence of publication bias (Fig 3B), and the sensitivity analysis indicated that the lack of association was not due to any particular data point in the overall sample (all Cohen’s $ds < = 0.02$, $ps > .42$). Finally, meta-regression analyses indicated that sex ($k = 15$, $p = .41$), age ($k = 13$, $p = .42$), and ethnicity ($k = 15$, $p = .90$) did not significantly influence the association.

In short, the aforementioned analyses revealed that rs53576 polymorphism explains the variances in general sociality, but not the variances in close relationship. This finding appears to be different from the findings of another meta-analytical study by Bakermans-Kranenburg and van IJzendoorn, who reported that no genetic association between rs53576 and sociality [16]. To explore possible reasons for this inconsistency, we compared the methodologies between two studies and performed additional analyses. The current meta-analysis differs from theirs in two major ways. First, we performed separate analyses on general sociality and close relationship, whereas Bakermans-Kranenburg and van IJzendoorn [16] did not distinguish these phenotypes. Second, the included empirical studies in the two meta-analyses were not identical. Because we perceived the theoretical significance of these contrasts between meta-analysis designs to differ (i.e., the separate analysis for distinct sociality phenotypes being more compelling than slight changes in the studies included), we repeated the previous analyses using only the studies that had also been used by Bakermans-Kranenburg and van IJzendoorn to try to rule-out the possibility that the inclusion of the additional studies were not responsible for the genetic association identified.

First, when general sociality and close relationships were categorized as a single phenotype, the random effects model indicated no evidence of genetic association between all sociality measures ($ps > .10$). Note that several studies simultaneously included measures of general sociality and intimate relationship [10,37,38,41]. Therefore, to ensure that each study
| Authors (Year)       | Country                | Ethnicity                  | % of Female | Diagnosis | Age (Mean/SD) | Phenotypes               | Measurement tools                                      |
|---------------------|------------------------|----------------------------|-------------|-----------|---------------|--------------------------|-------------------------------------------------------|
| Gillath et al., 2008 [38] | U.S.A.                 | 31% Caucasian & 44% Asian | 73%         | Healthy   | Range: 18–29  | Extraversion             | Big Five Personality Inventory                         |
| Lucht et al., 2009, adult [14] | Germany               | N.A.                       | 65%         | Healthy   | 41.7 (7.2)    | Social loneliness        | UCLA Loneliness Scale                                  |
| Lucht et al., 2009, adolescent [14] | Germany              | N.A.                       | 50%         | Healthy   | 15.1 (2.1)    | Social loneliness        | UCLA Loneliness Scale                                  |
| Rodrigues et al., 2009 [10] | U.S.A.                 | 35% Caucasian & 41% Asian | 59%         | Healthy   | 20.2 (N. A.)  | Empathy                  | Interpersonal Reactivity Index                         |
| Kim et al., 2010, High stress [25] | U.S.A.              | 77% Caucasian & 23% Asian | 56%         | Healthy   | 24.5 (N. A.)  | Emotional support seeking | The COPE Inventory: Emotion Coping Subscale           |
| Kim et al., 2010, High stress [25] | Korean                | 100% Asian                | 47%         | Healthy   | 25.1 (N. A.)  | Emotional support seeking | The COPE Inventory: Emotion Coping Subscale           |
| Kim et al., 2010, Low stress [25] | U.S.A.               | 77% Caucasian & 23% Asian | 56%         | Healthy   | 24.5 (N. A.)  | Emotional support seeking | The COPE Inventory: Emotion Coping Subscale           |
| Kim et al., 2010, Low stress [25] | Korean                | 100% Asian                | 47%         | Healthy   | 25.1 (N. A.)  | Emotional support seeking | The COPE Inventory: Emotion Coping Subscale           |
| Park et al., 2010 [43] | UK & Ireland          | 100% Caucasian             | 10%         | ADHD      | Range: 4–16   | Autistic traits          | Social and Communication Disorder Checklist           |
| Tost et al., 2010 [11] | U.S.A.                 | 100% Caucasian             | 53%         | Healthy   | 30.8 (9.2)    | Reward dependence       | Tridimensional Personality Questionnaire              |
| Chen et al., 2011 [31] | Germany               | 89% Caucasian              | 0%          | Healthy   | 23.2 (2.9)    | Empathy                  | Interpersonal Reactivity Index                        |
| Kawamura et al., 2011 [40] | Japan                 | 100% Asian                | 38%         | Healthy   | 40.9 (9.7)    | Social skill             | Autism Spectrum Quotient: Social Skill Subscale       |
| Kogan et al., 2011 [13] | U.S.A.                 | 100% Caucasian             | 48%         | Healthy   | 23.8 (3.5)    | Nonverbal cues of sociality | Laboratory Observation                                 |
| Tops et al., 2011 [12] | Netherlands            | 94% Caucasian              | 100%        | Healthy   | 29 (7.4)      | Social auditory ability | Self-Reported Social Auditory Ability                |
| Chen et al., 2012 [37] | U.S.A.                 | 42% Caucasian & 28% Asian  | 61%         | Healthy   | N.A.          | Social skill             | Autism Spectrum Quotient: Social Skill Subscale       |
| Krueger et al., 2012 [41] | U.S.A.                | 100% Caucasian             | 0%          | Healthy   | 20.2 (2.2)    | Empathy                  | Interpersonal Reactivity Index                        |
| Wu et al., 2012 [15] | China                  | 100% Asian                | 54%         | Healthy   | 22.5 (2.3)    | Empathy                  | Interpersonal Reactivity Index                        |
| Poulin et al., 2012 [44] | U.S.A.                 | 100% Caucasian             | 51%         | Healthy   | N.A.          | Civic duty               | Social And Political Survey                          |
| Johansson et al., 2012 [39] | Finland               | 100% Caucasian             | 58%         | Healthy   | 26.4 (4.8)    | Aggressive behavior     | Buss and Perry Aggression Questionnaire               |
| Malik et al., 2012 [42] | Canada                 | 82% Caucasian             | 31%         | Antisocial | 11. 5 (3.0)   | Aggressive traits       | Achenbach Child Behaviour Checklist                   |
| Wu et al., 2013, 3-years old [30] | China               | 100% Asian                | 49%         | Healthy   | 3             | Prosocial behavior      | Total scores of helping behavior, comforting behavior; sharing behavior |
| Wu et al., 2013, 4-years old [30] | China              | 100% Asian                | 49%         | Healthy   | 4             | Prosocial behavior      | Total scores of helping behavior, comforting behavior; sharing behavior |
| Wu et al., 2013, 5-years old [30] | China              | 100% Asian                | 49%         | Healthy   | 5             | Prosocial behavior      | Total scores of helping behavior, comforting behavior; sharing behavior |
| McQuaid et al., 2013 [27] | Canada                 | 58% Caucasian             | 74%         | Healthy   | 20.0(3.2)     | Distrust and Cynicism   | Distrust and Cynicism Scale                          |

doi:10.1371/journal.pone.0131820.t001
Fig 2. The association between rs53576 polymorphism and general sociality. A) Magnitudes of effect size for the association between rs53576 polymorphism and general sociality are illustrated by the forest plot (AA + GA vs. GG). Boxes represent the effect size (Cohen’s d) for each sample in the analysis; the size of the boxes represents the weighting for each study; lines represent the .95 confidence interval for each effect size;
and the diamond represents the overall effect of the meta-analysis, which was obtained by a random effects model. B) Publication bias is illustrated by the funnel plot. The horizontal axis represents the effect size of each study. The vertical axis represents the size of each study (indexed by the standard error of the effect size within each study). In consequence, large studies appear towards the top of the graph and small studies appear towards the bottom of the graph. A vertical line indicates the estimated overall effect size. A confidence interval region is drawn around this value with bounds equal to ± 1.96 standard error. In the absence of publication bias, the studies will be distributed symmetrically around the vertical line. Otherwise, the studies will be distributed asymmetrically.

doi:10.1371/journal.pone.0131820.g002

Table 2. Characteristics of studies on the association between rs53576 polymorphism and close relationship.

| Authors (Year)                  | Country | Ethnicity       | % of Female | Diagnosis            | Age (Mean/SD) | Phenotypes          | Measurement tools                                      |
|--------------------------------|---------|-----------------|-------------|----------------------|---------------|---------------------|-------------------------------------------------------|
| Bakermans-Krakenburg et al., 2008 [45] | Netherlands | 95% Caucasian | 100%        | Healthy              | 33 (4.1)      | Marital discord    | Dutch Family Problems Questionnaire (subscale)         |
| Gillath et al., 2008 [38]       | U.S.A.  | 31% Caucasian & 44% Asian | 73%        | Healthy              | Range: 18–29 | Attachment anxiety | Experiences in Close Relationships Inventory          |
| Costa et al., 2009 [48]        | Italy   | 100% Caucasian  | 73%        | Bipolar disorder     | 40.9 (11.7)   | Separation anxiety | Adult Separation Anxiety Checklist                     |
| Costa et al., 2009 [48]        | Italy   | 100% Caucasian  | 68%        | Unipolar depression  | 44.4 (12.5)   | Separation anxiety | Adult Separation Anxiety Checklist                     |
| Costa et al., 2009 [48]        | Italy   | 100% Caucasian  | 69%        | Healthy              | 42.2 (11.0)   | Separation anxiety | Adult Separation Anxiety Checklist                     |
| Rodrigues et al., 2009 [10]    | U.S.A.  | 35% Caucasian, 41% Asian | 59%        | Healthy              | 20.2 (2.8)   | Attachment anxiety | Experiences in Close Relationships Inventory          |
| Chen et al., 2012 [37]         | U.S.A.  | 42% Causion, 28% Asian | 61%        | Healthy              | N.A.          | Attachment anxiety | Experiences in Close Relationships Scale              |
| Krueger et al., 2012 [41]      | U.S.A.  | 100% Caucasian  | 0%         | Healthy              | 20.2 (2.2)   | Attachment (secure) | Relationship Scale Questionnaire                      |
| Luijk et al., 2011 [46]        | Netherlands | 100% Caucasian | 48%        | Healthy              | 1.3           | Attachment security | Strange Situation Procedure; Attachment Security Scale |
| Luijk et al., 2011 [46]        | N.A.    | 100% Caucasian  | 52%        | Healthy              | 1.3           | Attachment security | Strange Situation Procedure; Attachment Security Scale |
| Sturge-Appel et al., 2012 [47] | U.S.A.  | 100% Caucasian  | 100%       | Healthy              | 28.5 (6.0)   | Interpartner Conflict | Conflict Tactics Scale 2; Conflict and Problem-Solving Scale |
| Sturge-Appel et al., 2012 [47] | U.S.A.  | 100% non-Caucasian | 100%      | Healthy              | 25. 5 (5.8)  | Interpartner Conflict | Conflict Tactics Scale 2; Conflict and Problem-Solving Scale |
| Walum et al., 2012 (TOSS) [49] | Sweden  | 100% Caucasian  | 63%        | Healthy              | Range:32–74  | Pair-bonding       | Pair-bonding Scale                                    |
| Walum et al., 2012 (TCHAD) [49]| Sweden  | 100% Caucasian  | 57%        | Healthy              | Range:19–20  | Pair-bonding       | Relationship Quality Survey (affect scale)            |
| Raby et al., 2013 [28]         | U.S.A.  | 66% Caucasian  | 50%        | Healthy              | 26           | romantic relationship security | Current Relationship Interview                        |

doi:10.1371/journal.pone.0131820.t002
Fig 3. The association between rs53576 polymorphism and close relationship. A) Magnitudes of effect size for the association between rs53576 polymorphism and individual differences in close relationship are illustrated by the forest plot (AA + GA vs. GG). Boxes represent the effect size (Cohen’s d) for each sample in the analysis; the size of the boxes represents the weighting for each study; lines represent the .95 confidence interval for each effect size; and the diamond represents the overall effect of the meta-analysis, which was obtained by a random effects model. B) Publication bias is illustrated by the funnel plot. The horizontal axis...
95% CI = [-0.002, 0.17], Z = 1.91, p = 0.06). Third, when data on close relationships were included, there was no evidence of genetic association (k = 14, Cohen’s d = 0.01, 95% CI = [-0.04, 0.07], Z = 0.41, p = 0.69).

Taken together, our meta-analysis included more empirical studies, which increased the statistical power of the meta-analysis and facilitated detection of the genetic association; however, the phenomenon of increased effect size when the data were separated according to general sociality and close relationships was maintained even when only literature included in the previous meta-analysis was evaluated.

**Depression**

As we noted previously, depression and lack of sociality are often related [21]. Therefore, the association between rs53576 polymorphism and general sociality might be mediated by depression. To examine this possibility, we also examined the association between the rs53576 polymorphism and depression using meta-analysis. For depression, nine studies [22,26,27,29,45,47,48,50,51], comprising 12 independent samples (Table 3), contributed to the meta-analysis (total \( n = 2177 \)). As expected, there was evidence of between-study heterogeneity (\( Q = 59.43, p < .0001 \)). The random effects analysis (GG vs. GA+AA) indicated no evidence of association (Cohen’s \( d = 0.12, 95\% \) CI = [-0.12, 0.36], Z = 0.99, \( p = .32 \)) (Fig 4A). Begg’s test (Kendall’s tau = 0.09, \( p = 0.74 \)) indicated no evidence of publication bias (Fig 4B), and meta-regression analyses indicated that sex (\( k = 12, p = .70 \)), age (\( k = 11, p = .85 \)), and ethnicity (\( k = 12, p = .86 \)) did not significantly influence the association. In summary, there was no evidence of an association between the polymorphism and depression. Therefore, the genetic association with general sociality was unlikely to be mediated by depression.

**Discussion**

In this study, we examined the relationship between the polymorphism of a widely-investigated common variant (rs53576) in OXTR and sociality. The meta-analysis on the overall samples revealed that G allele homozygotes were generally more sociable than A allele carriers (Cohen’s \( d = 0.11 \)). In addition, we did not find an association between rs53576 polymorphism and depression, suggesting that its genetic association with general sociality was unlikely to be influenced by depression. On the other hand, somewhat surprisingly, we did not find significant difference in measures of close relationship between G allele homozygotes and A allele carriers. In summary, our study suggested that the rs53576 polymorphism in the OXTR predicts how an individual generally responds to other people, but the polymorphism might be unrelated to individual differences in close relationships (i.e., parent-child or romantic/marital).

Because general sociality behaviors and behaviors in close relationship are functionally distinct constructs, it is necessary to perform separate meta-analyses on these two constructs. Indeed, when these constructs were combined into a single construct, the genetic association between rs53576 polymorphism and this monolith construct was not detected. This result was consistent with that of Bakermans-Kranenburg and van IJzendoorn [16], who performed a similar meta-analysis on the relationship between rs53576 polymorphism and socially related personality traits and behaviors, but did not distinguish general sociality from sociality in the context of close relationships in their analysis.
At first glance, the lack of association between the rs53576 polymorphism and sociality in close relationships appears inconsistent with the popular notion that oxytocin is critical to love [52]. For instance, the mortality rate of offspring increased in oxytocin receptor knockout female mice [53]. Similarly, intranasal oxytocin facilitates recognition of positive sex and relationship words [54]. One possibility is that some OXTR SNP other than rs53576 modulates individual differences in close relationship sociality. For instance, a study has found that individual differences in attachment are associated with the rs2254298 genetic polymorphism, another SNP in OXTR [37].

Our finding of the association between rs53576 polymorphism and general sociality converges with other lines of evidence from the oxytocin literature [3,4,55]. For instance, OXTR knockout mice display deficits in social memory [56] and exhibit autistic-like symptoms [57]. G allele homozygotes (rs53576) have shown greater amygdala activation than A allele carriers when processing socially relevant information [11]. Based on the current literature, future animal and human neuroimaging studies are needed to further explore the exact biological mechanisms that may account for this relationship.

Our study raises a broad question that whether general sociality and close relationships are interrelated. One possibility is that general sociality serves as a basis for other types of sociality, such as close relationships. Another possibility is that these two constructs are completely independent. To solve this question, one might rigorously evaluate the correlations of individual differences in these constructs. The results may be broadly relevant to the search for genetic associations of sociality phenotypes. For example, if there are shared variances between these constructs, it will be more efficient to measure them together when searching for genetic

| Authors (Year)        | Country       | Ethnicity | % of Female | Diagnosis          | Age (Mean/SD) | Phenotypes | Measurement tools                                      |
|-----------------------|---------------|-----------|-------------|--------------------|---------------|------------|-------------------------------------------------------|
| Bakermans-Kranenburg et al., 2008 [49] | Netherlands   | 95% Caucasian | 100%         | Healthy           | 33 (4.1)      | Depression | Short Form of Young Adult Self-Report                 |
| Costa et al., 2009 [48] | Italy         | 100% Caucasian | 73%          | Bipolar disorder  | 40.9 (11.7)   | Depression | Hamilton Depression Rating Scale                      |
| Costa et al., 2009 [48] | Italy         | 100% Caucasian | 68%          | Unipolar depression | 44.4 (12.5)   | Depression | Hamilton Depression Rating Scale                      |
| Kawamura et al., 2010 [50] | Japan         | 100% Asian   | 38%          | Healthy           | 40.9 (9.7)    | Depressive | Temperament Evaluation of Memphis, Pisa, Paris and San Diego |
| Riem et al., 2011 (sample1) [51] | Netherlands   | 87.5% Caucasian | 100%         | Healthy           | 27.5 (7.6)    | Depression | Center for Epidemiological Studies Depression Scale |
| Riem et al., 2011 (sample2) [51] | Netherlands   | 87.5% Caucasian | 100%         | Healthy           | 27.5 (7.6)    | Depression | Center for Epidemiological Studies Depression Scale |
| Saphire-Bernstein et al., 2011 [22] | U.S.A.        | 27% Caucasian | 61%          | Healthy           | 21.3 (Range:18–36) | Depression | Beck Depression Inventory                            |
| Sturge-Appel et al., 2012 [47] | U.S.A.        | 100% Caucasian | 100%         | Healthy           | 28.5 (6.0)    | Depression | Computerized Diagnostic Interview Schedule IV         |
| Sturge-Appel et al., 2012 [47] | U.S.A.        | 100% non-Caucasian | 100%       | Healthy           | 25.5 (5.8)    | Depression | Computerized Diagnostic Interview Schedule IV         |
| McQuaid et al., 2013 [27] | Canada        | 58% Caucasian | 74%          | Healthy           | 20.0 (3.2)    | Depression | Beck Depression Inventory                            |
| Wang et al., 2014 [29] | China         | 100% Asian   | 53%          | Healthy           | 23.7 (2.5)    | Depression | Beck Depression Inventory-II                         |
| Bryant et al., 2013 [26] | Australia     | 100% Caucasian | N.A.         | Healthy           | N.A.          | Depression | Beck Depression Inventory                            |

doi:10.1371/journal.pone.0131820.t003
Fig 4. The association between rs53576 polymorphism and depression. A) Magnitudes of effect size for the association between rs53576 polymorphism and depression are illustrated by the forest plot (AA + GA vs. GG). Boxes represent the effect size (Cohen’s d) for each sample in the analysis; the size of the boxes represents the weighting for each study; lines represent the .95 confidence interval for each effect size; and the diamond represents the overall effect of the meta-analysis, which was obtained by a random effects model. B) Publication bias is illustrated by the funnel plot. The horizontal axis represents the standardized mean difference; the vertical axis represents the standard error.
associations. Otherwise, conducting separate genetic association studies on each of them would be sufficient.

Furthermore, several studies have examined the genetic association between the rs53576 polymorphism and depression, and both positive [22] and null results [26, 27, 29, 45, 48, 51] have been reported. By synthesizing these results, the current meta-analysis revealed a lack of association. As we noted previously, depression is often associated with withdrawal from social activities [21]. However, depression also is a state of low mood. Consequently, individual differences in sociality and depression may only share a small portion of variance, and such overlapping may not be affected by the rs53576 polymorphism. Therefore, it is not surprising that the rs53576 polymorphism is only selectively associated with general sociality but not depression.

In addition, several other limitations of the current study deserve consideration. First, the current study is based mainly on results from published studies. Future analyses may include data from more unpublished datasets, such as large-sample databases from genome-wide association studies (GWAS) [58]. Second, compared with many large-sample genetic association studies, the sample size of included studies in our meta-analysis is relatively small which may limit the statistical power of our meta-analysis. Third, interactions between the rs53576 polymorphism and culture (e.g., American vs. East Asian culture) have been suggested to impact sociality [25]. However, we were unable to evaluate this potential interaction in the present study due to the small number of available samples. Fourth, because of a lack of sufficient studies for any single measure of sociality, various measures of general sociality (e.g., extraversion, empathy, and social support seeking) were categorized into a single phenotype. Therefore, we were unable to evaluate possible genetic associations for a specific measure (e.g., empathy). Future studies are needed to test such possible associations in details.

In conclusion, our study provides clear evidence of a relationship between the rs53576 polymorphism and general sociality. In the recent decade, genetic investigation of endophenotypes offers great opportunity as an alternative to investigations of categorical disease phenotypes [59]. It is possible that the general sociality serve as an endophenotype of socially related psychiatric disorders, such as autism and social anxiety disorder. For instance, a recent meta-analysis have revealed that several OXTR SNPs are associated with autism spectrum disorder (ASD) [60], although such an association was not found on rs53576. Potential reasons for the lack of association between rs53576 polymorphism and ASD in that meta-analysis are manifold and include i) a legitimate lack of genetic association, and ii) lack of statistical power (N = 2800, 5 independent samples). Additional studies with adequate methodology are needed to explore the relation between OXTR polymorphism and these socially related psychiatric disorders.

Supporting Information

S1 File. List of excluded articles.
(DOCX)

S1 Table. PRISMA 2009 Checklist.
(DOC)

S2 Table. Meta-analysis on Genetic Association Studies Checklist.
(DOCX)
Acknowledgments
We are grateful to the researchers who provided their data for these analyses.

Author Contributions
Conceived and designed the experiments: JL SY. Performed the experiments: JL SY YZ CZ.
Analyzed the data: JL SY RL LSB. Contributed reagents/materials/analysis tools: JL SY YZ CZ.
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