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Oxytocin receptor (OXTR) is not associated with optimism in the Nurses' Health Study

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The oxytocin system is implicated in complex social behavior such as socioemotional functioning, social recognition and bonding, and in modulating biological responses to stress.[1,2] The oxytocin receptor (*OXTR*) gene encodes the OXTR; a G-protein-coupled receptor that mediates the effects of the neurohormone oxytocin. [3,4] Prior studies have reported associations between an intronic single-nucleotide polymorphism (rs53576) of *OXTR* and various stress-related and psychological traits.[4,5] Most recently, Saphire-Bernstein *et al*[6] reported that rs53576 A allele carriage conferred lower optimism relative to G homozygotes, among 344 men and women aged 18–36 years of various ethnicities. We sought to replicate the association between *OXTR* rs53576 and optimism in 1229 women from the Nurses' Health Study (NHS).

The NHS was established in 1976 when 121 700 women registered as nurses aged 30–55 years from 11 US states completed a mailed questionnaire on medical history and lifestyle characteristics.[7] Every 2 years, follow-up questionnaires are sent. The 2004 and 2008 questionnaires included information on antidepressant use and the revised life orientation test,[8] the same dispositional optimism measure used in the Saphire-Bernstein *et al*.[6] study. We generated five different optimism scores to provide a thorough investigation of the previously reported association. Year-specific optimism scores were derived by taking the mean of all non-missing items in 2004 (α =0.77) and also in 2008 (α =0.75). Individuals with >2 items missing were excluded (up to 8% of analytic sample). Using both assessments, an overall mean optimism score was also derived, as were two subscale scores reflecting an 'optimistic' or 'pessimistic' outlook.[8] Genotypes for the current analysis were available from two case-control nested genome-wide association studies, initially designed to assess kidney stone disease and glaucoma (total n= 1294).[9,10] Samples were genotyped for *OXTR* rs53576 at the Broad Center for Genotyping and Analysis using the Illumina

Conflict of interest

The authors declare no conflict of interest.

610Q or 660Q array (Illumina, San Diego, CA, USA). Genotyping success rate for rs53576 was > 98%.[9,10] Principal components analyses using genome-wide data were conducted to assess self-reported race. Genetically inferred non-Caucasian samples were too few (<3% of analytic sample) for meaningful analysis and therefore excluded.

The 2004 and 2008 optimism scores were moderately correlated ($r = 0.65$) in the 1229 women with complete genetic and phenotype data (2004 mean age = 71.3 years, s.d. = 6.7). Overall optimism scores ranged from 1.33 to 4.25 (overall mean = 4.13, s.d. = 0.68). Frequencies (%) of the GG, GA and AA genotypes were 491 (40%), 559 (45%) and 179 (15%), respectively, and did not depart from Hardy–Weinberg equilibrium ($P = 0.33$). The A allele frequency was 38% in NHS versus 28% among white participants ($n = 87$) in the Saphire-Bernstein *et al.*[6] study.

Table 1 indicates no significant differences in means across genotypes for any optimism scores (all $P_{ADD} > 0.35$). Optimism scores also did not differ between G homozygotes and A carriers (all $P_{DOM} > 0.17$). Linear regression models adjusting for age, genotype platform, and case-control status yielded no significant association between rs53576 and any optimism score, regardless of genetic model (all $P > 0.16$). The NHS sample had substantial power (> 99%) to detect the effect size reported previously: $\beta = -0.168$ under a dominant model.[6]

Unlike our sample, Saphire-Bernstein *et al.*'s[6] sample consisted of men and women recruited for a stress and coping study, was relatively young (mean age 21) and had mixed ethnic ancestry (for example, 36% Asian). However, although the frequency of the G allele and mean optimism scores differed somewhat across ethnic and gender groups in the Saphire-Bernstein *et al.*[6] study, the pattern of associations did not. Recognizing other differences between the two samples, we conducted several sensitivity analyses (Table 1), considering effects stratified by age or education, excluding women reporting antidepressant use, or with disease (that is, kidney stone or glaucoma). Associations between rs53576 and optimism were null in all analyses. We were limited in power to restrict analysis to even younger women. However, a formal test for *OXTR*–age interaction was marginally significant ($P = 0.10$), suggesting age may be an important modifier for future exploration.

In summary, we did not replicate the association between rs53576 and optimism in our sample of Caucasian women. Our findings do not exclude a possible role for *OXTR* in psychosocial resources. The link between rs53576 and optimism may be applicable to a population with characteristics similar to individuals in Saphire-Bernstein *et al.*'s[6] study. However, our findings suggest caution is warranted when considering the association between *OXTR* and optimism, and additional research is needed to determine the generalizability of the results reported by Saphire-Bernstein *et al.*[6]

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Table 1

Mean (s.d.) optimism scores by OXTR genotype

Scale	*n*	OXTR rs53576				P_{ADD}[b]	P_{DOM}[b]
		GG	GA	AA	GA/AA		
Optimism 2004	1200	4.14 (0.77)	4.19 (0.70)	4.22 (0.71)	4.20 (0.70)	0.35	0.17
Optimism 2008	1129	4.10 (0.73)	4.10 (0.73)	4.13 (0.75)	4.11 (0.74)	0.92	0.87
Overall optimism[a]	1229	4.10 (0.70)	4.15 (0.65)	4.16 (0.67)	4.15 (0.66)	0.49	0.24
Optimistic outlook	1228	4.05 (0.79)	4.10 (0.74)	4.08 (0.76)	4.09 (0.74)	0.54	0.29
Pessimistic outlook[c]	1228	4.17 (0.82)	4.21 (0.80)	4.23 (0.79)	4.22 (0.80)	0.54	0.29
Optimism[a]							
Age < 71 years	584	4.15 (0.74)	4.20 (0.65)	4.08 (0.71)	4.17 (0.67)	0.34	0.75
Age ≥71 years	645	4.07 (0.67)	4.10 (0.65)	4.24 (0.62)	4.13 (0.65)	0.11	0.21
< Bachelor degree	834	4.08 (0.72)	4.12 (0.66)	4.12 (0.66)	4.12 (0.66)	0.77	0.47
≥Bachelor degree	395	4.15 (0.67)	4.21 (0.63)	4.25 (0.69)	4.22 (0.64)	0.56	0.31
Number of antidepressants	1037	4.15 (0.70)	4.18 (0.65)	4.20 (0.63)	4.19 (0.64)	0.59	0.33
Number of disease	624	4.15 (0.68)	4.23 (0.61)	4.22 (0.62)	4.22 (0.61)	0.36	0.15

[a]Mean of 2004 and 2008 optimism scores.

[b]Results from analysis of variance assuming an additive (ADD) or dominant (DOM) genetic model.

[c]High scores suggest low pessimism.