Altered DNA Methylation of the Oxytocin Receptor Gene is Associated with Susceptibility to Psychosis and Anhedonia-asociality in Females: Epigenetic Evidence in Recent-onset Schizophrenia and Ultra-high risk for Psychosis

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BACKGROUND

Oxytocin is one of the key hormones involved in human social and emotional processing. In this regard, abnormal functioning of the oxytocin system has been suggested to influence on the clinical manifestation of schizophrenia, especially negative symptoms. The aim of the present study was to investigate epigenetic modification of the oxytocin receptor gene (OXTR) and its association with negative symptoms in individuals with recent-onset schizophrenia (ROS) and at ultra-high risk (UHR) for psychosis.

METHOD

Sixty-four ROS patients (< 5 years of duration of illness; 25 men, 39 women), 46 UHR individuals (27 men, 19 women), and 98 healthy controls (HCs; 46 men, 52 women) participated in the present study. DNA methylation was quantified from peripheral blood using pyrosequencing at CpG sites in OXTR intron 1 (hg19, chr3: 8,810,729–8,810,845) and exon 3 (hg19, chr3: 8,809,281–8,809,534; Figure 1). The severity of negative symptoms in clinical groups was measured using the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS). All statistical procedures were conducted separately for males and females.

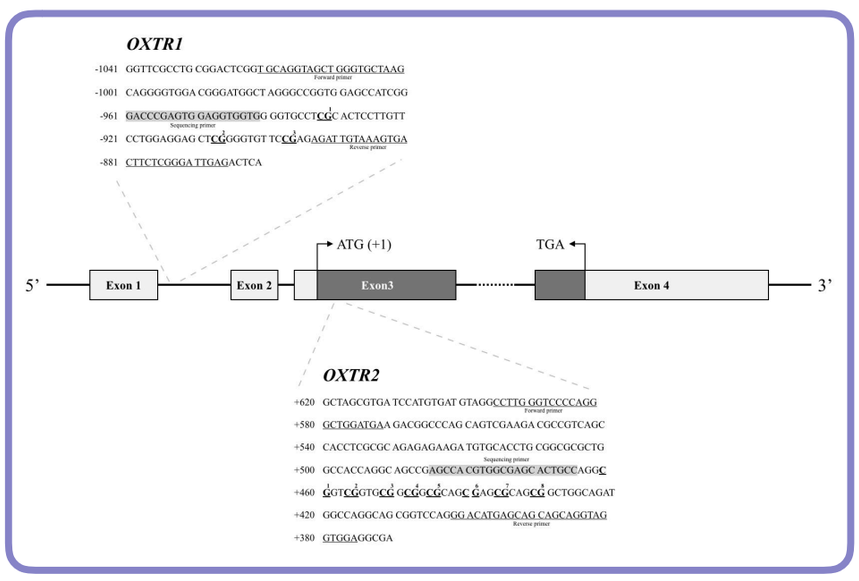

Figure 1.
Target sequences of OXTR methylation analysis using pyrosequencing

RESULTS

ROS and UHR participants showed significantly decreased percentages of methylation at 3 CpGs of OXTR1 in male and female particiapants, with large effect sizes at CpG1 and CpG2 (Table 1). No significant difference was found in the average percentage of methylation at CpGs of OXTR2. Therefore, the relationship with negative symptoms in ROS and UHR participants were examined for the methylation level of OXTR1. In the combined group of ROS and UHR participants, who showed the similar severity of negative symptoms (Figure 2) and OXTR methylation status, only females were found to have a significant negative association between the methylation level at CpG1 and the anhedonia-asociality scores, independent of age and diagnosis ($F(3, 54) = 4.46$, $p = 0.007$; $B = -2.05$, $p < 0.001$). The other two CpGs demonstrated no significant association with negative symptoms, including anhedonia-asociality.

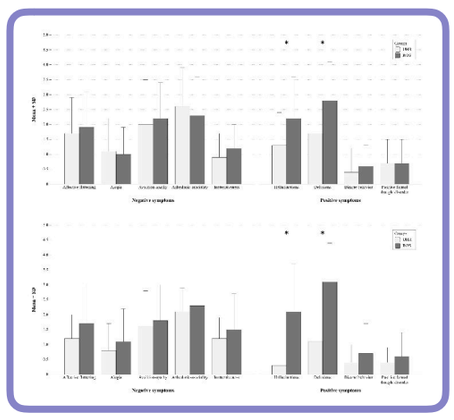

Figure 2.
The severity of positive and negative symptoms in ROS and UHR participants (up: males, down: females)

CONCLUSION

The present study demonstrated decreased OXTR methylation in both UHR and ROS individuals compared to HCs. Furthermore, the severity of anhedonia-asociality was significantly associated with the degree of OXTR methylation in female UHR and ROS individuals. These findings suggest that epigenetic aberration of OXTR may confer susceptibility to schizophrenia spectrum psychosis and influence the early pathogenesis of schizophrenia prior to the onset of overt psychosis, particularly in females.

CpG sites		HCs Males (*n* = 46)	HCs Females (*n* = 52)	UHR Males (*n* = 27)	UHR Females (*n* = 19)	ROS Males (*n* = 25)	ROS Females (*n* = 39)	Statistics[a, b] Males	Statistics[a, b] Females	Post-hoc comparisons[a] Males	Post-hoc comparisons[a] Females
OXTR1	CpG1	46.9 (4.2)	47.7 (3.9)	37.6 (4.0)	40.5 (5.3)	38.7 (4.6)	41.1 (5.6)	$F(2, 106) = 50.72$; $P < 0.001$; ES = 0.42	$F(2, 106) = 26.78$; $P < 0.001$; ES = 0.34	HCs > UHR ($P < 0.001$) HCs > SCZ ($P < 0.001$) UHR = SCZ ($P > 0.999$)	HCs > UHR ($P < 0.001$) HCs > SCZ ($P < 0.001$) UHR = SCZ ($P > 0.999$)
	CpG2	51.2 (4.3)	52.5 (3.1)	46.0 (4.4)	46.2 (5.7)	45.5 (5.0)	47.7 (6.3)	$F(2, 106) = 17.58$; $P < 0.001$; ES = 0.25	$F(2, 106) = 16.88$; $P < 0.001$; ES = 0.24	HCs > UHR ($P < 0.001$) HCs > SCZ ($P < 0.001$) UHR = SCZ ($P > 0.999$)	HCs > UHR ($P < 0.001$) HCs > SCZ ($P < 0.001$) UHR = SCZ ($P > 0.999$)
	CpG3	59.8 (3.9)	60.7 (3.7)	57.1 (3.7)	57.6 (5.2)	55.9 (6.5)	58.5 (5.2)	$F(2, 106) = 6.65$; $P = 0.008$; ES = 0.09	$F(2, 106) = 4.64$; $P = 0.047$; ES = 0.08	HCs = UHR ($P = 0.067$) HCs > SCZ ($P = 0.003$) UHR = SCZ ($P > 0.999$)	HCs > UHR ($P = 0.039$) HCs = SCZ ($P = 0.052$) UHR = SCZ ($P > 0.999$)
OXTR2	CpG1-8	13.2 (5.9)	14.1 (4.6)	13.2 (6.3)	15.1 (6.9)	13.5 (7.0)	14.2 (5.8)	$F(2, 106) = 0.03$; $P > 0.999$; ES = 0.0004	$F(2, 106) = 0.29$; $P > 0.999$; ES = 0.006		

Abbreviations: OXTR, oxytocin receptor; HCs, healthy controls; UHR, ultra-high risk for psychosis; ROS, recent-onset schizophrenia; ES, effect size.
[a] All *P*-values were Bonferroni-corrected.
[b] Effect sizes were calculated using partial eta squared.

Table 1.
Methylation status (%) at OXTR CpG sites of the participants

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