

Research Article

Open Access

Association with Autism of Two Polymorphisms in Gene Encoding Oxytocin Receptors in Slovakia

Silvia Lakatosova*, Lenka Dudova, Anna Pivovarciova, Veronika Husarova, Katarina Babinska, Aneta Kubranska and Daniela Ostatnikova

Institute of Physiology, Faculty of Medicine, Comenius University in Bratislava, Slovakia, Europe

Abstract

Study background: Autism is a complex neurodevelopmental disorder involving genetic components in its etiology. Oxytocin is a neuropeptide affecting social behavior acting in the CNS via binding its only type of receptor (OXTR). A number of studies have shown an association of polymorphisms in the OXTR gene and the diagnosis of autism in different ethnic populations. The aim of this study is to find an association of polymorphisms in the OXTR gene and the diagnosis of autism in Slovakia.

Methods: After acquiring informed consent, 108 autism patients were recruited into the study (83 males, 25 females), in addition to 131 healthy children as a control group (106 males, 25 females). DNA was extracted from whole blood and four single nucleotide polymorphisms (rs223785, rs2270465, rs2268498, rs53576) were assessed using the PCR-RFLP method.

Results: We found two positive associations of polymorphisms in OXTR with autism in boys, namely markers rs2270465 and rs237851 ($p < 0.0001$ and $p = 0.0016$). Both markers survived multiple comparison testing ($p < 0.0005$, $p < 0.001$, respectively). There were no significant differences in the genotype and allelic distribution among groups in girls.

Conclusion: Polymorphisms in oxytocin receptor are associated with autism. The addition of psychological profiling may reveal possible correlations of genotypes/alleles within OXTR with symptom severities.

Keywords: Autism; Oxytocin receptor; Single nucleotide polymorphism

Introduction

Autism is a neurodevelopmental disorder characterized by social deficits, impaired language, communication and repetitive behaviors. It has a wide clinical heterogeneity, therefore, the term autism spectrum disorders (ASD) is used. Deficits in social interaction represent a core symptom of ASD. The etiology of ASD is not clear. It is a complex disease, involving both genetic and environmental factors. High heritability suggests that genes play a major role in autism etiology [1]. A number of candidate genes have been identified by whole genome scans using both population and family-based approaches [2]. Candidate genes involve genes encoding neurotransmitters and neuromodulators in the central nervous system. Of particular importance is a gene encoding oxytocin (OT) and oxytocin receptor (OXTR). The oxytocin system seems to play a specific role in autism pathogenesis, since deficits in oxytocin plasma levels have been identified in autism patients [3-6]. Oxytocin is a prosocial hormone acting as a facilitator of social interactions, both in rodents, as well as in humans. Animal studies show that oxytocin plays a role in social interactions, attachment, pair bonding, sexual behavior and social memory [7]. Moreover, oxytocin increases trust among humans, improves eye contact and empathy and other aspects of human social behavior [8-10].

The involvement of oxytocin in autism etiology is strengthened by the still growing evidence that intranasal administration of the hormone is capable of restoring some aspects of social deficits in children with ASD [6,11-13].

Several genetic studies focused their attention on searching for the connections between gene variants of OXTR and ASD diagnosis. The OXTR gene is located on chromosome 3p25.3 and has 17kb. The gene contains 3 introns and 4 exons. The OXTR protein (389 amino acids) belongs to class 1 G protein coupled receptor proteins including 7 transmembrane domains [14]. After ligand binding, it triggers

intracellular cell signaling leading to increased intracellular calcium. In neuronal cells, this process leads to increased neuronal excitability and neurotransmitter release [15].

Approximately, 30 single nucleotide polymorphisms (SNPs) in OXTR have been identified and connections of some of them to ASD diagnosis was confirmed by family or population based association studies. Wu et al. [16] analyzed 4 SNPs in 195 Chinese Han trios and found a positive association of rs2254298 and rs53576 with autism. Jacob et al. [17] examined 2 SNPs in 57 Caucasian autism trios and found a positive association for rs2255298. Another study on 177 Caucasian autism patients revealed an association of rs2268493 and rs2740204 and autism [18]. Lerer et al. [19] examined 18 SNPs in 152 autism patients and found an association of a haplotype containing 5 SNPs and a diagnosis of autism. Japanese autism populations also showed a positive association between 4 SNPs in OXTR gene and autism [20]. Wermter et al. [21] examined 22 SNPs in 100 families with high functioning autism patients and found an association of one SNP (rs2270465) and one haplotype (combination of alleles of more than two SNPs that are inherited together) with the condition.

Although one would predict that these SNPs may have functional

***Corresponding author:** Silvia Lakatosova, Institute of Physiology, Faculty of Medicine, Comenius University in Bratislava, Sasinkova 2, 81372 Bratislava, Slovakia, Europe, Tel: 00421-2-59357520; Fax: 00421-2-59357515; E-mail: silvia.lakatosova@gmail.com

Received November 03, 2013; **Accepted** November 26, 2013; **Published** December 02, 2013

Citation: Lakatosova S, Dudova L, Pivovarciova A, Husarova V, Babinska K, et al. (2013) Association with Autism of Two Polymorphisms in Gene Encoding Oxytocin Receptors in Slovakia. Autism 3: 121. doi:10.4172/2165-7890.1000121

Copyright: © 2013 Lakatosova S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

roles influencing OXTR expression or binding patterns, leading to alterations in oxytocin signaling in the brain, the function of a majority of the SNPs remains unknown. Some of the SNPs have been linked to a certain domains of ADI-R, ADOS or CARS autism diagnostic tools. For instance, Wermter et al. [21] found an association of a haplotype rs237851, rs6791619, rs53576, rs237884 and four domains in social interactions and communication measured by ADI-R questionnaire. Aforementioned study by Yrigollen et al. [18] revealed positive connection among rs2268493 and rs2740204 and communication skills and repetitive behaviors. Egawa et al. [22] found an association of rs237887 and imitation score measured by CARS. Campbell et al. [23] found an association of rs2268493, rs1042778 and rs7632287 with social domain dysfunction measured by ADI-R and ADOS.

In non-clinical populations, several SNPs in OXTR have been shown to be associated with different aspects of social cognition and empathy. For instance, rs53576 has been associated with empathy, stress reactivity and parental sensitivity [24,25]. In a different study, rs53576 was associated with socio-emotional sensitivity [26]. Rs53576 is a SNP with possible functional relevance, since it has been shown to influence transcriptional repression of OXTR [27]. Other polymorphisms in OXTR have been identified to influence attachment-related behavior and social cognition [28,29]. However, precise mechanisms of these actions remain to be clarified.

We have previously investigated rs2228485 lying in OXTR gene in Slovak autism population, however, we have not found positive association with the diagnosis [30].

Since there is growing evidence that OXTR may modulate genetic vulnerability to autism, we aimed to reveal possible associations among other four polymorphisms in OXTR gene and autism diagnosis in Slovakia. Importance of studying gene variants in OXTR in different populations is given by the fact that genetic differences in OXTR between populations have been found [16,17]. These authors investigated two SNPs in Chinese and Caucasian populations and they found opposite alleles of rs2254298 to be associated with autism. In addition, Liu et al. [20] found the same association in Japanese autism population as Wu found in Chinese population [16].

Selection of SNPs for our study was based on previous studies by Wermter et al. [21] and Jacob et al. [17], who found a positive association of these SNPs (rs2270465 and rs237851) in Caucasian populations of ASD patients, and/or functional connections among these SNPs and different aspects of social behavior. Other two selected SNPs seem to be functional polymorphisms, since rs2268498 is located in the promoter region of OXTR gene and rs53576 lies in the third intron of OXTR gene, a region found to be responsible for transcriptional suppression of OXTR [27,31].

Materials and Methods

The study was approved by the Ethical Committee at the Faculty of Medicine, Comenius University in Bratislava.

After acquiring informed consent, 108 autism patients were recruited into the study (83 males, 25 females). Boys were between 2 years to 22 years of age (mean age 7 ± 5 years) and girls ranged from 2 to 22 years of age (mean age 7 ± 6 years). Recruited as control groups were 131 healthy children (106 males, 25 females). Control boys were in the age range of 2 to 20 years (mean age 11 ± 6 years) and control girls were in the age range of 2-25 years (mean age 10 ± 8 years).

Children with autism were recruited from the local Autism Centers for children in Bratislava, Trnava and Presov, Slovakia. All autistic boys

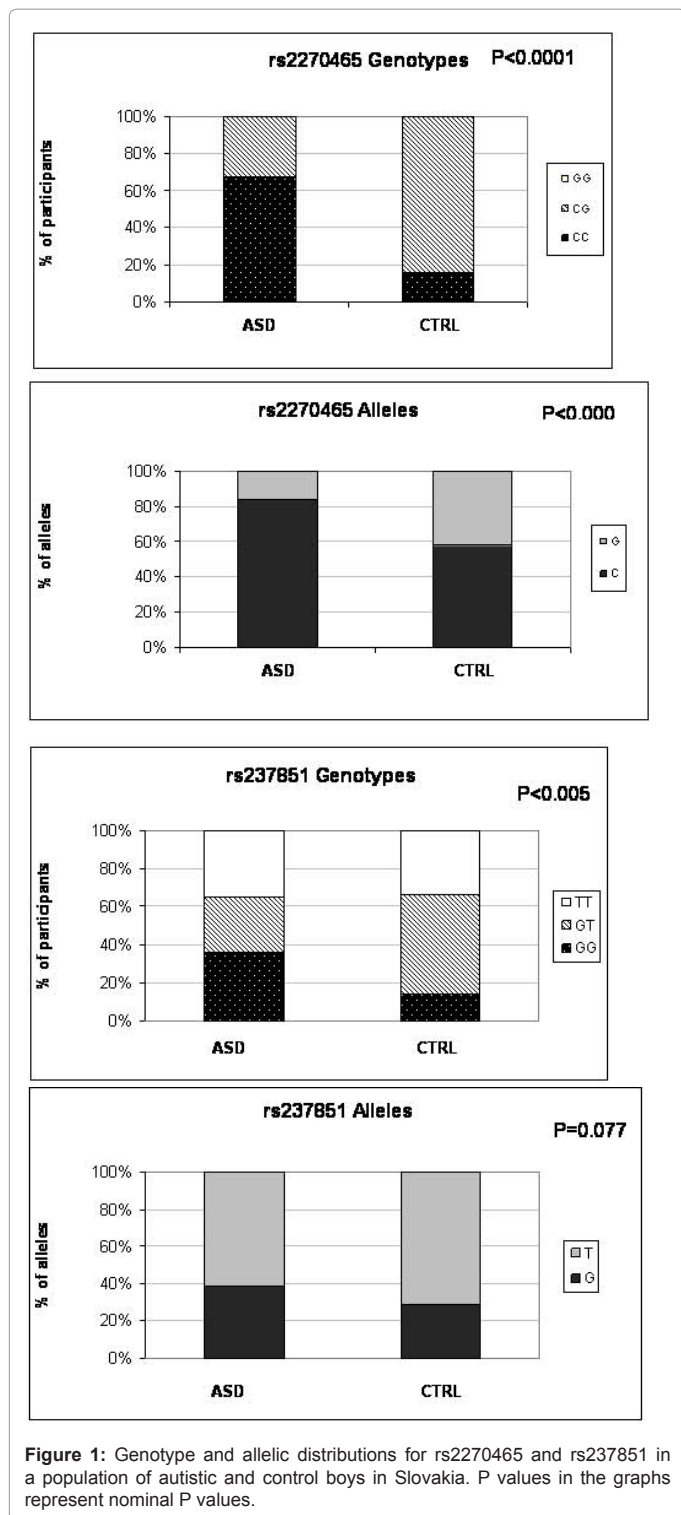
were diagnosed as meeting criteria for ICD-10 childhood autism by a clinical child psychologist in the cooperation of a child psychiatrist, who confirmed all diagnoses. All subjects were medication-free. Control subjects were recruited through local pediatrician clinic after regular pediatric examination or mild physical condition due to which they attended pediatrician. All subjects were at the time of blood sample intake healthy and without any known physical condition that was confirmed by pediatrician. All control subjects were without any psychiatric condition confirmed by child psychiatrist, according to their examinations and parent interview. All subjects were of Caucasian race and Slovak ethnicity.

Venous blood samples were obtained from all children and DNA was extracted from whole blood using standard protocols (QIAamp DNA Blood Mini kit, Qiagen, Hilden, Germany). Four polymorphisms in OXTR gene (rs237851, rs2270465, rs2268498, rs53576) were assessed using standard PCR, followed by the RFLP (restriction fragment length polymorphism) method. Primer sequences for rs237851 were Fw. CACGGTGATTTCAGAGTCCA, Rev. GCCATCACTGTTGGAAGGAT. Length of PCR product was 451 bp, after digestion by BpiI restriction enzyme (ThermoFisher Scientific), RFLP profiles were recognized by 2% agarose gel electrophoresis (TT 451 bp, GG 314 bp and 137 bp, GT 451 bp, 314 bp, 137 bp). Primer sequences for rs2270465 were Fw. ACACGGAGAATGCAATGGTT and Rev. TACCTTTCAGGGAGGCCTTT. Length of PCR product was 499 bp, after digestion by HinfI restriction enzyme (ThermoFisher Scientific), RFLP profiles were recognized by 2% agarose gel electrophoresis (CC 265 bp, 225 bp, 9 bp, GG 265 bp, 204 bp, 21 bp, 9 bp, CG 265 bp, 225 bp, 204 bp, 21 bp, 9 bp). Primer sequences for rs2268498 were Fw. TAGGCTGTCTCACGGGCTAC and Rev. TCGGCCTCGAAAATTACAGA. Length of PCR product was 448 bp, after digestion by BsiI restriction enzyme (ThermoFisher Scientific), RFLP profiles were recognized by 2% agarose gel electrophoresis (AA 262 bp, 131 bp, 54 bp, 1 bp, GG 226 bp, 131 bp, 54 bp, 36 bp, 1 bp, AG 262 bp, 226 bp, 131 bp, 54 bp, 36 bp, 1 bp). Primer sequences for rs53576 were GCTGGACTCAGGAGGAATAGGGAC and Rev. GCCCACCATGCTCTCCACATC. Length of PCR product was 340 bp, after digestion by Sau96I restriction enzyme (ThermoFisher Scientific), RFLP profiles were recognized by 2% agarose gel electrophoresis (TT 277 bp, 57 bp, 6 bp, CC 216 bp, 61 bp, 57 bp, 6 bp, CT 277 bp, 216 bp, 61 bp, 57 bp, 6 bp).

Differences in genotype distribution and allelic distributions were determined using χ^2 test and Fisher's exact test. Bonferroni correction method was used to counteract the problem of multiple comparisons.

Results

We found two positive associations of polymorphisms in OXTR and autism in boys, namely markers rs2270465 and rs237851 ($p < 0.0001$ and $p = 0.0016$) (Figure 1). Both markers survived multiple comparison testing ($p < 0.0005$, $p < 0.001$, respectively). However, allelic frequencies differed significantly between the groups only in the case of rs2270465 (Figure 1). The C allele of this polymorphism was significantly more prevalent in the autism sample ($p < 0.0001$), supposedly due to a higher prevalence of CC homozygotes in autistic boys (67.9%), in comparison to controls (16.1%). In the control group, there was a higher prevalence of CG heterozygotes. No GG homozygotes were found in either of the examined groups. In the case of rs237851, the distributions of genotypes differed significantly among groups, showing lower prevalence of GT heterozygotes and higher prevalence of GG homozygotes in the autism group. However, allelic frequencies were not significantly different among groups.



Genotype and allelic distributions for all four examined polymorphisms are displayed in Table 1A. No significant differences in genotype/allelic distributions were observed in girls (Table 1B).

Discussion

In the present study, we examined four single nucleotide polymorphisms in the OXTR gene in patients with autism in Slovakia

in comparison to healthy controls.

Marker rs2270465 in the OXTR gene showed significantly different distributions of genotypes, as well as allelic frequencies among boys with autism and healthy controls. C allele was more frequent in boys with autism (84%), which is in contrast to Wermter et al. [21], who found minor G allele more frequently transmitted by parents to the affected children on a high functioning level in the German population. This finding, however, did not correlate with correction for multiple testing. These different findings may have arisen due to differences in Slovak and German populations, as well as due to the different parts of the autism spectrum involved in the two studies. Marker rs2270465 was not investigated in any other population, neither was the function of this polymorphic site determined. Studies investigating correlation of the genotypes in this polymorphism with different aspects of human

A

rs237581	Genotype	$\chi^2=12.88$	P=0.0016	Allele	P=0.077
	GG	GT	TT	G	T
ASD	29 (35.8%)	24 (29.6%)	28 (34.6%)	82 (50.6%)	80 (49.4%)
CTRL	12 (14.3%)	44 (52.4%)	28 (33.3%)	68 (40.5%)	100 (59.5%)

rs2270465	Genotype			P<0.0001	Allele	P<0.0001
	CC	CG	GG	C	G	
ASD	53 (67.9%)	25 (32.1%)	0 (0%)	131 (84%)	25 (16%)	
CTRL	14 (16.1%)	73 (83.9%)	0 (0%)	101 (58%)	73 (42%)	

rs2268498	Genotype	$\chi^2=0.34$	P=0.819	Allele	P=0.819
	TT	CT	CC	A	G
ASD	23 (28.4%)	41 (50.6%)	17 (21%)	75 (47.5%)	87 (53.7%)
CTRL	34 (32.1%)	49 (46.2%)	23 (21.7%)	85 (44.8%)	117 (55.2%)

rs53576	Genotype	$\chi^2=0.908$	P=0.635	Allele	P=1
	AA	AG	GG	A	G
ASD	7 (8.9%)	61 (77.2%)	11 (13.9%)	75 (47.5%)	83 (52.5%)
CTRL	12 (12%)	71 (71%)	17 (17%)	95 (47.5%)	105 (52.5%)

B

rs237851	Genotype	$\chi^2=0.6920$	P=0.7075	Allele	P=0.6595
	GG	GT	TT	G	T
ASD	4 (21.1%)	8 (42.1%)	7 (36.8%)	16 (42.1%)	22 (57.9%)
CTRL	5 (21.8%)	7 (30.4%)	11 (47.8%)	17 (37%)	29 (63%)

rs2270465	Genotype			P=0.0716	Allele	P=0.1752
	CC	CG	GG	C	G	
ASD	13 (52%)	12 (48%)	0 (0%)	38 (76%)	12 (24%)	
CTRL	5 (23.8%)	16 (76.2%)	0 (0%)	26 (61.9%)	16 (38.1%)	

rs2268498	Genotype	$\chi^2=1.556$	P=0.4594	Allele	P=0.5406
	TT	CT	CC	C	T
ASD	7 (28%)	14 (56%)	4 (16%)	22 (44%)	28 (56%)
CTRL	11 (44%)	10 (40%)	4 (16%)	18 (36%)	32 (64%)

rs53576	Genotype	$\chi^2=0.2984$	P=0.8614	Allele	P=0.8395
	AA	AG	GG	A	G
ASD	3 (13%)	14 (60.9%)	6 (26.1%)	20 (43.5%)	26 (56.5%)
CTRL	3 (12%)	17 (68%)	5 (20%)	23 (46%)	27 (54%)

Table 1: Genotype and allelic distributions for rs237851, rs2270465, rs2268498, rs53576 in Slovak autistic and control populations; A: boys; B: girls. The number of participants and their percentages are displayed for each genotype. The number of alleles and percentages are displayed for each allele. P values are nominal values prior to multiple comparison testing.

behavior are also lacking. However, marker rs2270465 lies 5.7kb upstream of the transcription start site of OXTR gene in the flanking region may affect binding of transcription factors, and thus, alter OXTR gene expression in patients with autism [21].

Marker rs237851 showed different distributions among the two populations, however, allelic distributions did not reach a statistically significant level. Significant difference in genotype distribution was due to excess of GT heterozygotes in the control group. Since allelic frequencies did not differ significantly among groups, we cannot clearly conclude positive association with autism diagnosis in Slovak population. This marker was shown in a study by Wermter et al. [21], to be associated with an ASD diagnosis as a part of 4 marker haplotype. Moreover, this haplotype was associated with four subdomains of ADI-R involving socio-emotional aspects of interpersonal relationships [21].

Markers rs2268498 and rs53576 have not shown significant differences in genotype or allelic distributions among autistic and control groups in Slovakia. Marker rs2268498 is a functional polymorphism lying in the promoter region of the OXTR gene, previously shown to affect moral judgments [31], and was associated with negative emotionality [32]. Marker rs53576 lies in the third intron of OXTR gene, a region found to be responsible for transcriptional suppression of OXTR [27]. It was broadly studied in clinical and non-clinical populations. Wu et al. [16] found an association of this marker with autism in Chinese populations. However, we have not confirmed this finding in autistic children in Slovakia. In addition, this marker was found to be associated with a number of socio-emotional aspects of human behavior, such as empathy, negative affects and social and emotional loneliness, coping with psychological distress and stress-protective effects of social support [24,26,33-35].

In girls with autism, we did not find any significant results probably due to low sample size. The addition of psychological profiling may reveal possible correlations of genetic variants in the OXTR gene, with manifestation of symptoms and symptom severities in children with autism in Slovakia.

Since ASD displays a broad genetic heterogeneity, more homogenous samples are needed to find the connections of gene variants and the diagnosis, as well as traits or symptoms. Homogeneity of the samples must be kept in mind from an ethnicity point of view, since the same markers show different patterns in different ethnic groups of autism populations [16,17]. The main limitation of the present study is the absence of behavioral parameters in the sample of patients that could be found in association with the genetic markers examined in this study of Slovak autism patients. Addition of these data would bring more clinical relevance to the study.

Autism is a complex disease, possibly including both genetic and environmental factors in its etiology. Several studies suggest that behavior expression of certain genotypes in OXTR may be sensitive to input from social environments [26]. For instance, environmental adversity may trigger the development of the disease (or trait) in individuals carrying responsible risk alleles. This phenomenon makes the study of autism etiology even more challenging.

Acknowledgement

Authors thank all participants for their cooperation. Authors thank to Dr. Adela Corejova and Dr. Anna Gvozdzakova for their help with organization of sample collections.

This project was supported by grants: APVV-0253-10, VEGA 1/0066/12, APVV-0254-11.

References

1. Trikalinos TA, Karvouni A, Zintzaras E, Ylisaukko-oja T, Peltonen L, et al. (2006) A heterogeneity-based genome search meta-analysis for autism-spectrum disorders. *Mol Psychiatry* 11: 29-36.
2. Li X, Zou H, Brown WT (2012) Genes associated with autism spectrum disorder. *Brain Res Bull* 88: 543-552.
3. Modahl C, Green L, Fein D, Morris M, Waterhouse L, et al. (1998) Plasma oxytocin levels in autistic children. *Biol Psychiatry* 43: 270-277.
4. Green L, Fein D, Modahl C, Feinstein C, Waterhouse L, et al. (2001) Oxytocin and autistic disorder: Alterations in peptide forms. *Biol Psychiatry* 50: 609-613.
5. Al-Ayadhi LY (2005) Altered oxytocin and vasopressin levels in autistic children in Central Saudi Arabia. *Neurosciences (Riyadh)* 10: 47-50.
6. Andari E, Duhamel JR, Zalla T, Herbrecht E, Leboyer M, et al. (2010) Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proc Natl Acad Sci U S A* 107: 4389-4394.
7. Insel TR, O'Brien DJ, Leckman JF (1999) Oxytocin, vasopressin, and autism: Is there a connection? *Biol Psychiatry* 45: 145-157.
8. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E (2005) Oxytocin increases trust in humans. *Nature* 435: 673-676.
9. Guastella AJ, Mitchell PB, Dadds MR (2008) Oxytocin increases gaze to the eye region of human faces. *Biol Psychiatry* 63: 3-5.
10. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC (2007) Oxytocin improves "mind-reading" in humans. *Biol Psychiatry* 61: 731-733.
11. Hollander E, Bartz J, Chaplin W, Phillips A, Sumner J, et al. (2007) Oxytocin increases retention of social cognition in autism. *Biol Psychiatry* 61: 498-503.
12. Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, et al. (2010) Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry* 67: 692-694.
13. Anagnostou E, Soorya L, Chaplin W, Bartz J, Halpern D, et al. (2012) Intranasal oxytocin versus placebo in the treatment of adults with autism spectrum disorders: A randomized controlled trial. *Mol Autism* 3: 16.
14. Inoue T, Kimura T, Azuma C, Inazawa J, Takemura M, et al. (1994) Structural organization of the human oxytocin receptor gene. *J Biol Chem* 269: 32451-32456.
15. Yamasue H (2013) Function and structure in social brain regions can link oxytocin-receptor genes with autistic social behavior. *Brain Dev* 35: 111-118.
16. Wu S, Jia M, Ruan Y, Liu J, Guo Y, et al. (2005) Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. *Biol Psychiatry* 58: 74-77.
17. Jacob S, Brune CW, Carter CS, Leventhal BL, Lord C, et al. (2007) Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. *Neurosci Lett* 417: 6-9.
18. Yrigollen CM, Han SS, Kochetkova A, Babitz T, Chang JT, et al. (2008) Genes controlling affiliative behavior as candidate genes for autism. *Biol Psychiatry* 63: 911-916.
19. Lerer E, Levi S, Salomon S, Darvasi A, Yirmiya N, et al. (2008) Association between the oxytocin receptor (OXTR) gene and autism: Relationship to Vineland Adaptive Behavior Scales and cognition. *Mol Psychiatry* 13: 980-988.
20. Liu X, Kawamura Y, Shimada T, Otowa T, Koishi S, et al. (2010) Association of the oxytocin receptor (OXTR) gene polymorphisms with autism spectrum disorder (ASD) in the Japanese population. *J Hum Genet* 55: 137-141.
21. Wermter AK, Kamp-Becker I, Hesse P, Schulte-Körne G, Strauch K, et al. (2010) Evidence for the involvement of genetic variation in the oxytocin receptor gene (OXTR) in the etiology of autistic disorders on high-functioning level. *Am J Med Genet B Neuropsychiatr Genet* 153B: 629-639.
22. Egawa J, Watanabe Y, Endo T, Tamura R, Masuzawa N, et al. (2012) Association between OXTR and clinical phenotypes of autism spectrum disorders. *Psychiatry Res* 6.
23. Campbell DB, Datta D, Jones ST, Batey Lee E, Sutcliffe JS, et al. (2011) Association of oxytocin receptor (OXTR) gene variants with multiple phenotype domains of autism spectrum disorder. *J Neurodev Disord* 3: 101-112.
24. Rodrigues, SM, Saslow LR, Garcia N, John OP, Keltner D (2009) Oxytocin

- receptor genetic variation relates to empathy and stress reactivity in humans. *Proc Natl Acad Sci U S A* 106: 21437-21441.
25. Bakermans-Kranenburg MJ, van Ijzendoorn MH (2008) Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Soc Cogn Affect Neurosci* 3: 128-134.
26. Kim HS, Sherman DK, Sasaki JY, Xu J, Chu TQ, et al. (2010) Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking. *Proc Natl Acad Sci U S A* 107: 15717-15721.
27. Mizumoto Y, Kimura T, Iwll R (1997) A genomic element within the third intron of the human oxytocin receptor gene may be involved in transcriptional suppression. *Mol Cell Endocrinol* 135: 129-138.
28. Ebstein RP, Israel S, Chew SH, Zhong S, Knafo A (2010) Genetics of human social behavior. *Neuron* 65: 831-844.
29. Gillath O, Shaver PR, Baek JM, Chun DS (2008) Genetic correlates of adult attachment style. *Pers Soc Psychol Bull* 34: 1396-1405.
30. Kelemenova S, Schmidtova E, Ficek A, Celec P, Kubranska A, et al. (2010) Polymorphisms of candidate genes in Slovak autistic patients. *Psychiatr Genet* 20: 137-139.
31. Walter NT, Montag C, Markett S, Felten A, Voigt G, et al. (2012) Ignorance is no excuse: Moral judgments are influenced by a genetic variation on the oxytocin receptor gene. *Brain Cogn* 78: 268-273.
32. Montag C, Fiebach CJ, Kirsch P, Reuter M (2011) Interaction of 5-HTTLPR and a variation on the oxytocin receptor gene influences negative emotionality. *Biol Psychiatry* 69: 601-603.
33. Lucht MJ, Barnow S, Sonnenfeld C, Ulrich I, Grabe HJ, et al. (2013) Associations between the oxytocin receptor gene (OXTR) and "mind-reading" in humans--an exploratory study. *Nord J Psychiatry* 67: 15-21.
34. Lucht MJ, Barnow S, Sonnenfeld C, Rosenberger A, Grabe HJ, et al. (2009) Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 33: 860-866.
35. Chen FS, Kumsta R, von Dawans B, Monakhov M, Ebstein RP, et al. (2011) Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans. *Proc Natl Acad Sci U S A* 108: 19937-19942.