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A Missense Mutation in *CD38* Associated with Autism Spectrum Disorder in Three Pedigrees

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1. Introduction

Autism spectrum disorder (ASD) or pervasive developmental disorder (PDD) is a neurodevelopmental disease, beginning in childhood but extending through to adulthood. ASD is characterised by impairments in reciprocal social interaction and communication, and by restricted or stereotyped patterns of interests and activities. This disorder has received much scientific and social attention[1,2]. ASD is more common than previously supposed with a frequency of 0.6-3 out of 100 births[2-6] and occurs either sporadically or in a familial pattern, and far more commonly in males[7-9]. The etiology remains largely unknown[10]. Previously we demonstrated that CD38 acts as a 'niceness' protein for mouse social behavior, by regulating release of oxytocin (OT)[11], which seems to be essential for mutual recognition and trust[12,13]. Therefore, here, we describe our results on single nucleotide polymorphisms (SNPs) of CD38 in ASD patients and control subjects[14]. In addition, we report our experience of treatment of one ASD patient with a CD38 SNP by nasal OT administration.

2. Results

Figures 1 and 2 show human CD38 expression in the frontal cortex, cerebellum, hypothalamus and amygdala, by RT-PCR with human brain RNA samples which were used for synthesizing cDNAs. CD38 mRNA was highly expressed in the hypothalamus in the human brain, suggesting that CD38 has an important role on human social behavior, as in the mouse[11].

Armed with this new information about CD38 in the human brain, we set out to examine the human *CD38* gene. The mRNA for CD38 is transcribed from human chromosome 4p15[15,16]. The *CD38* gene consists of 8 exons, spanning a genomic stretch of 70.51 kb (mRNA: 1227 bases) (http://www.broad.mit.edu/mpg/haploview; Figure 3a). SNP screening in 8 exons and their flanking introns was performed by direct sequencing in 29 unrelated

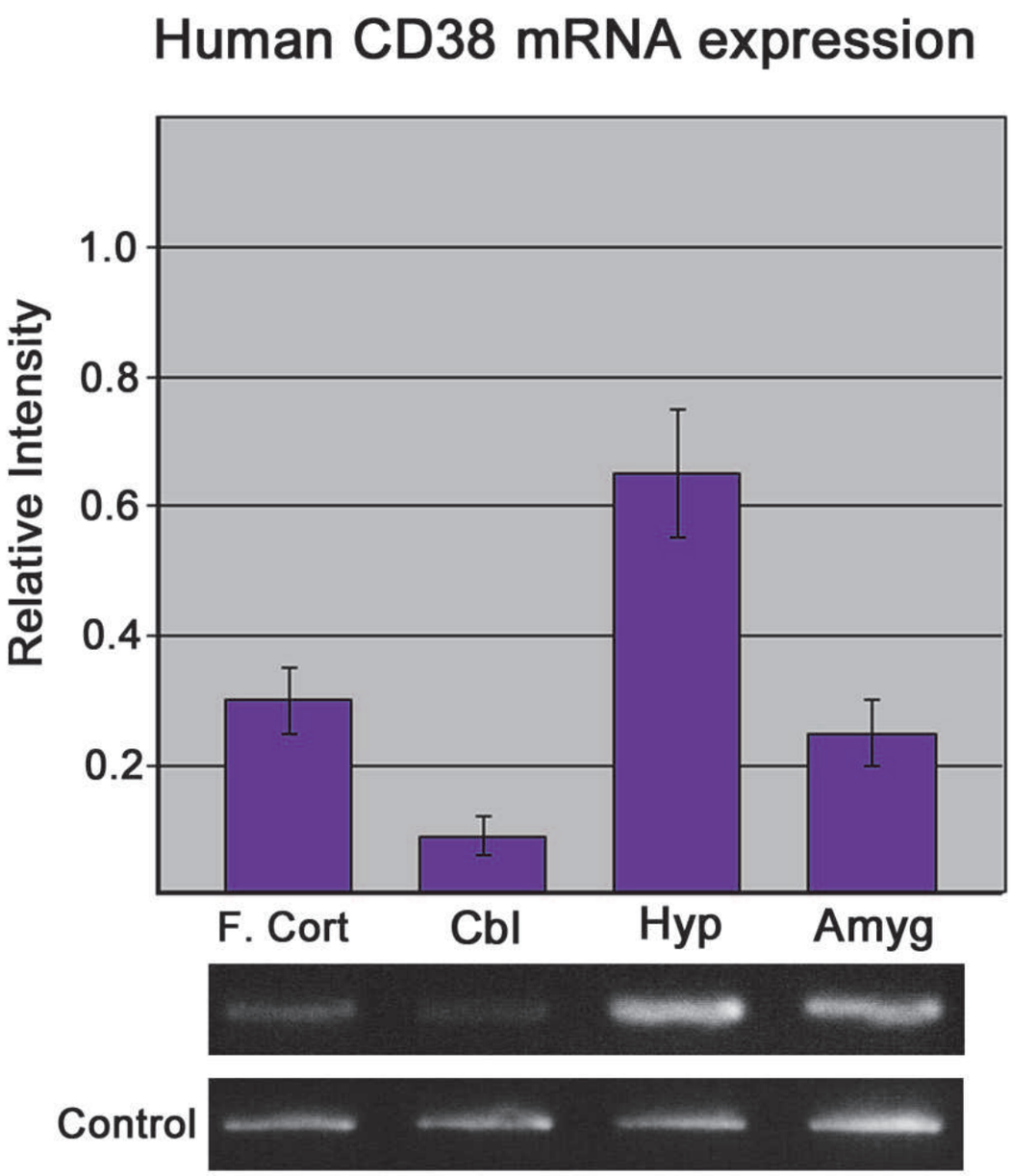

Fig. 1. **Semi-quantitative RT-PCR confesses human CD38 expression in the frontal cortex (F. Cort), the cerebellum (Cbl), the hypothalamus (Hyp) and the amygdala (Amyg).** Human brain RNA samples provided commercially (Ambion) were used for synthesizing cDNAs. Relative intensity was calculated by comparing with β-actin expression as a control.

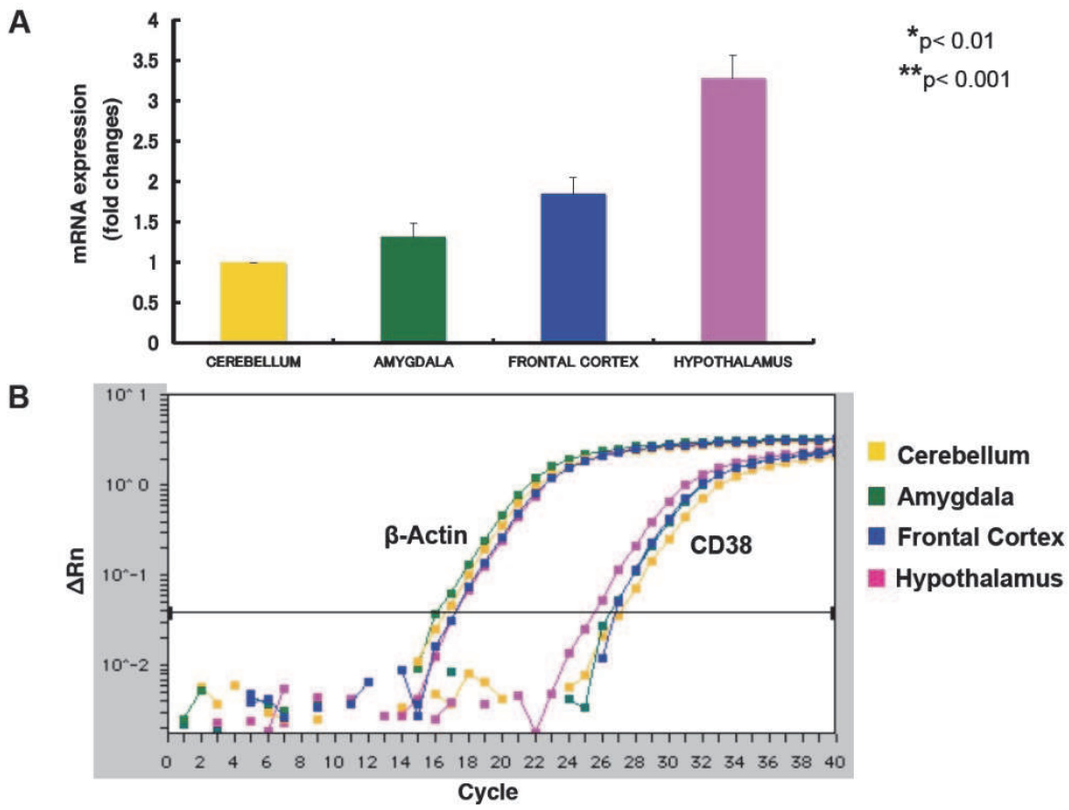

Fig. 2. **mRNA expression levels of CD38 gene in various human brain tssues.** (a) The relatve expression level of human CD38 gene was determined in RNA samples from frontal cortex, cerebellum, hypothalamus and amygdala using real-tme quantitatve PCR. Housekeeping normalized units (threshold cycle) for each gene obtained in the PCR analysis were used to determine the fold-change among samples. Bars represent fold-changes of the mRNA level of CD38 when comparing cerebellum with other tssues. Data are expressed as the mean ± S.D., performed in duplicate and repeated 3 times. *p<0.01, **p<0.01, Significantly increased from cerebellum value (P<0.01 and P<0.001). (b) Each plot represents the baseline-subtracted fluorescence intensity (ΔRn) that reflects mRNA levels of CD38 or β-actin genes. Horizontal lines indicate threshold lines set in the exponentially increasing area calculated by using SDS software.

subjects (the sample set A in Table 1) fulfilling *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV, American Psychiatric Association, 1994), criteria for ASD, and in 201 non-clinical control subjects (sample set E), in the Kanazawa area in Japan. We detected 12 SNPs that had already been reported, plus 3 novel mutations (Figure 3a). Allelic and genotypic frequencies in these samples are summarized in Tables 2 and 3. Among them, as shown in Figure 3b, we detected the C4693T mutation in exon 3 (SNP13; rs1800561) that leads to an arginine (R)-to-tryptophan (W) substitution at amino acid 140, R140W.

In the following experiments, we focused mainly on this mutation, because of functional abnormality in R140W-substituted-CD38: (1) The R140 is relatively well conserved among multiple species except for the rodent (Figure 3c). R140 is located in the flexible loop (137-141) at the midpoint of the N- and C-ternimus domains between two helical domains (αa4

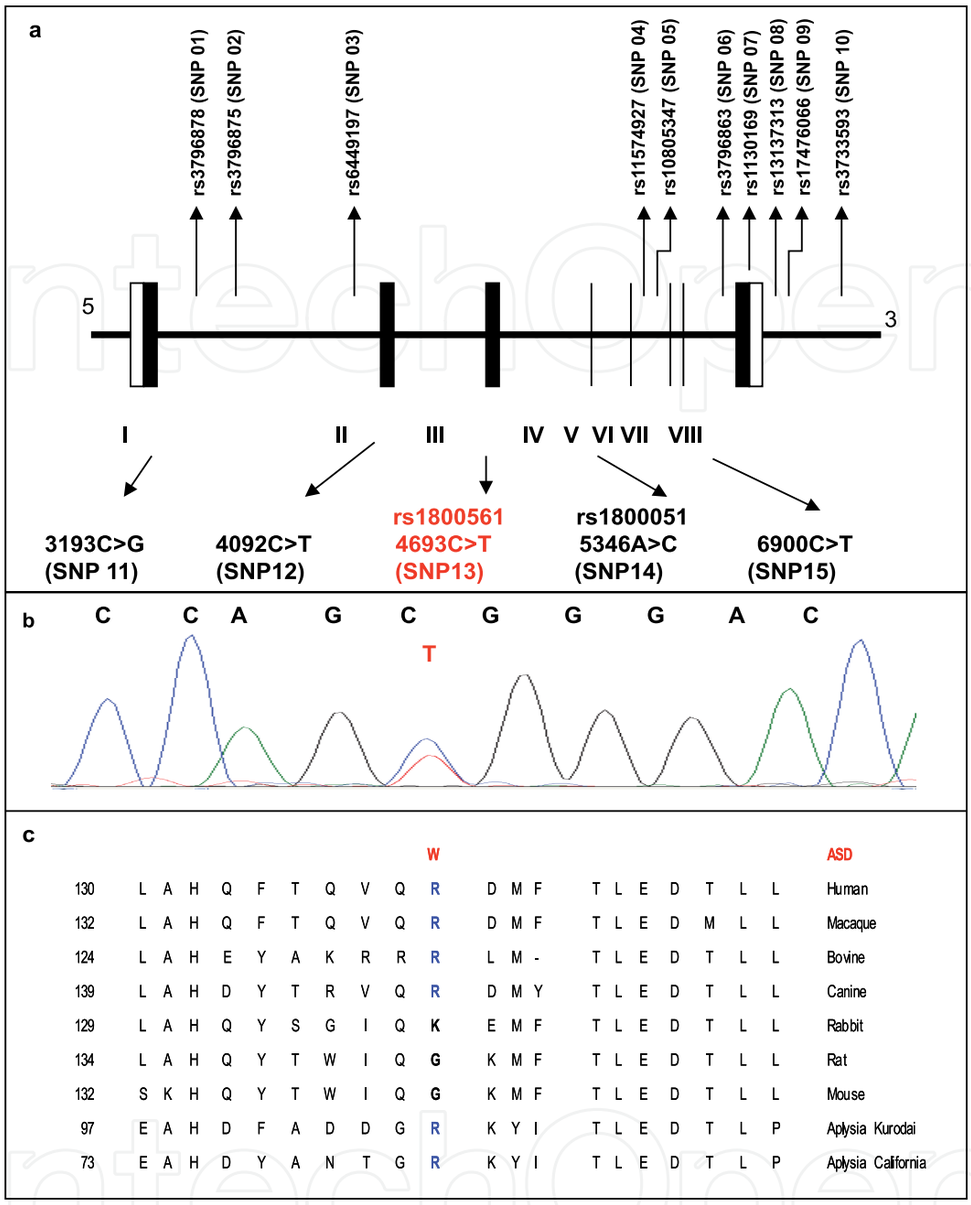

Fig. 3. **Genome and molecular structures and mutations of CD38.**
(**a**) Genomic structure of *CD38* and locations of SNPs in introns (upper) and in exons (lower). Exons are indicated by boxes, with translated regions in closed boxes, and untranslated regions in open boxes. Mutations at amino acids at positions of 47, 116, 140, 168 and 264 of CD38 are indicated. Numbering of the nucleotides starts at the A of ATG encoding the initial methionine and refers to Genbank accession number D84284.
(**b**) Sequence trace was derived from a blood DNA sample of 4693C/T heterozygote.
(**c**) Conservation of R at the 140th amino acid among different species, except for the rodent. Sequences were obtained through the accession numbers of NM001775, AY555148, NM175798, AF117714, AF272974, NM013127, NM007646, D30048, and M85206/M37644 for the indicated species, respectively. It is noted that mutant structure has more open-form conformation than wild-type and its variation is slightly larger.

and αa5) and is the pivot of the hinge region connecting two regions of L-shaped molecule[17]. Therefore, the mutation (W140) causes severe perturbations of the predicted protein structure, if compared with the human (R140), rabbit (K140) or mouse (G140) CD38 (see Figure 7 in ref.14). (2) Indeed, the mutant W140-CD38 showed one third of ADP-ribosyl cyclase activity of wild-type CD38 expressed in the CHO cells[15]. (3) Social amnesia was not rescued by local expression of W140-CD38 in the hypothalamus in *Cd38* knockout mice[11].

Sample set	Subject number	Male/Female	Age range	Age average	Description	Country	W140 allele frequency	Reference
A	29	(23/6)	12 to 44	22.8+/-7.6	Unrelated ASD	Japan*	0.052	
B	3	(3/0)	21 to 44	30.0+/- 7.1	3 probands in A	Japan*	1	
C	25	(15/10)	21 to 84	53.0+/-4.6	3 families in B	Japan*	0.32	
D	252	(252/0)			ASD	USA**	0	20, 21
E	201	(106/95)	22 to 64	32.5+/-0.9	Unscreened control	Japan*	0.007	

*In the Kanazawa area **AGRE samples

Table 1. **Sample sets in this experiment**

	SNP*		Control			ASD		
			N	Allele counts	Frquency	N	Allele counts	Frequency
SNP01	rs3796878	G>A	400	4	0.01	58	0	0
SNP02	rs3796875	A>G	398	100	0.25	56	18	0.321
SNP03	rs6449197	C>T	392	81	0.207	58	16	0.275
SNP04	rs11574927	A>G	402	78	0.195	58	6	0.103
SNP05	rs10805347	A>G	400	180	0.452	58	22	0.379
SNP06	rs3796863	C>A	398	148	0.371	58	20	0.345
SNP07	rs1130169	C>T	398	36	0.341	56	15	0.268
SNP08	rs13137313	A>G	398	176	0.442	58	28	0.483
SNP09	rs17476066	T>C	392	46	0.117	58	6	0.103
SNP10	rs3733593	C>T	398	128	0.32	56	17	0.305
SNP11		C>G	402	1	0.002	58	0	0
SNP12		C>T	402	0	0	58	1	0.017
SNP13	rs1800561	C>T	402	3	0.008	58	3	0.052
SNP14	rs1800051	A>C	402	59	0.146	58	13	0.22
SNP15		C>T	402	6	0.015	58	0	0

*SNPs are denoted as major allele>minor allele

Table 2. **Alleleic frequency of SNPs in control and ASD subjects**

The 140R/W (C4693T) heterozygotes were found in 3 male subjects (sample set B; two autistic and one Asperger) out of 29 ASD patients examined (23 males and 6 females with the mean age = 22.8 ± 7.6; prevalence of 10.3% of ASD samples). We examined whether or not the W140 allele seems to be co-segregated with ASD and ASD-related traits in 3 probands' families. Twenty five members of the 3 kindred families (sample set C) were available for detailed clinical and genetic analyses (Figure 4). The 4693C-to-T change was found in all probands' fathers in the 3 families and brothers in the 2 families (Family #1 and #3). The mutation is present in the grandmother of the father's side in the Family #1 (1-I-4) and is also predicted to be transmitted from the late grandmother of the father's side in the

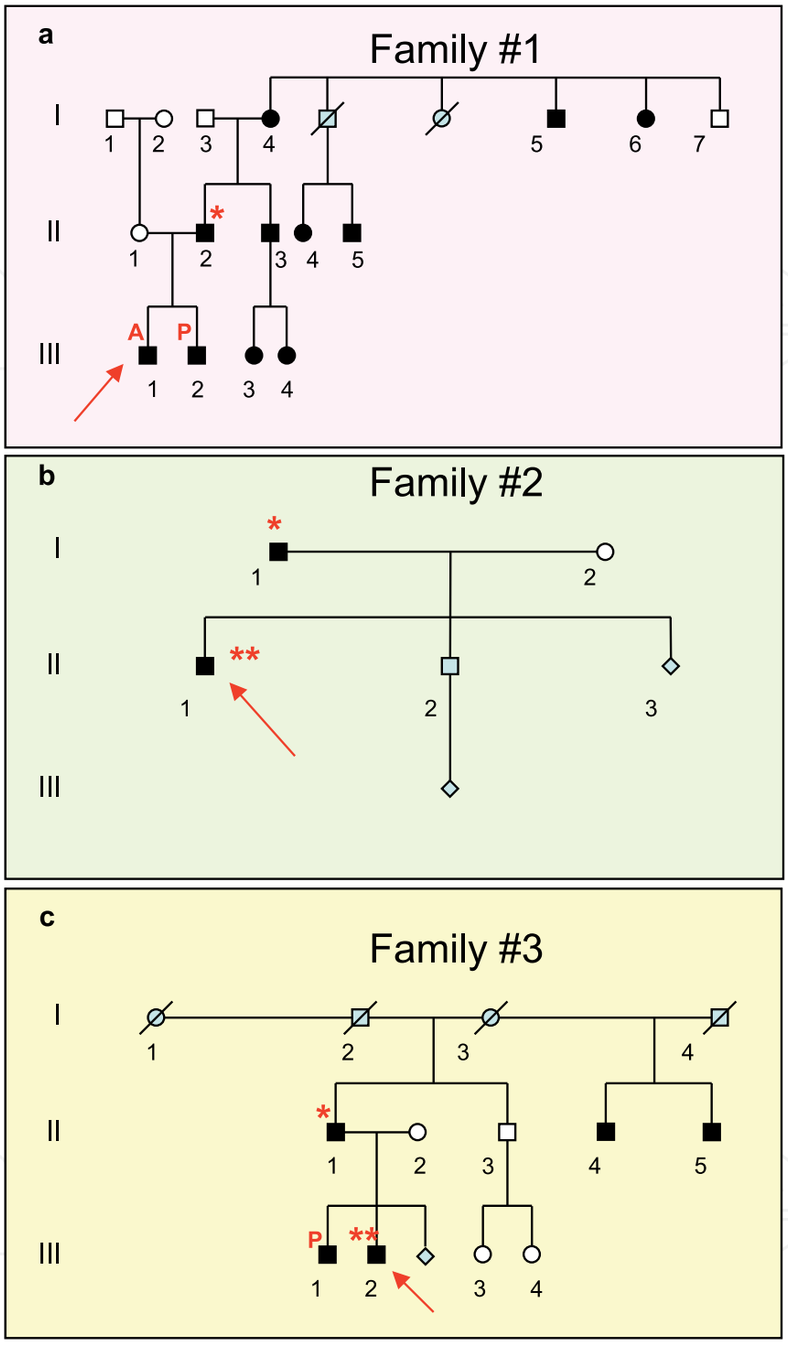

Fig. 4. **Pedigrees for three families of ASD probands carrying the W140.** Affected males (probands) are indicated with red arrows. Affected or carrier males or females are indicated by filled squares or circles, respectively. Empty symbols denote individuals with no mutation. Gray symbols indicate undetermined with no DNA available for analysis. Sexes are hidden by diamond symbols upon request. The subjects are indicated by progressive Arabic numbers according to the three generations. The current study was approved by the ethical committee of Kanazawa University Graduate School of Medicine. Subjects marked with symbols are: **, denotes ASD; *, ASD traits; P, PDD-NOS; A, Asperger disorder.

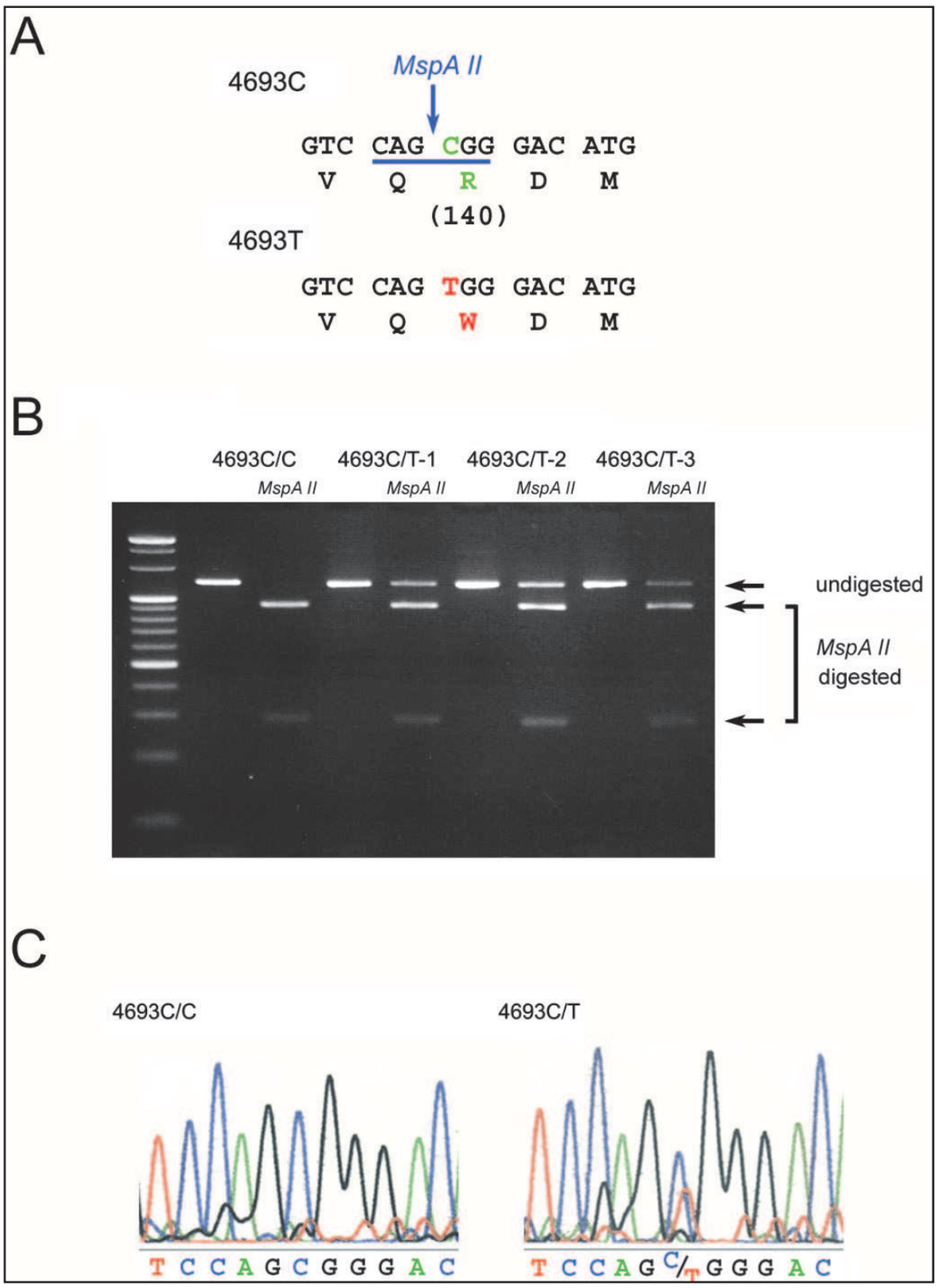

Fig. 5. **Expression of the minor allele of rs1800561**
(A) cDNA with 4693C has *Msp*AII site. (B) RT-PCR products from blood RNA samples were digested by *Msp*AII. An RT-PCT product from a homozygous 4693C/C subject gives two bands, while a heterozygous 4693C/T subject giving three bands. (C) Sequencing of RT-PCR products confirms the SNP.

Family #3 (3-I-3), in an apparently autosomal dominant fashion. We found a total of 18 carriers in 28 family members cooperative (prevalence=64%). In all cases the mutation was heterozygous (allelic frequency=0.32). The mutant allele was indeed transcribed in the subjects tested (Figure 5).

The kindred were clinically evaluated by interviewing. The probands' young (1-III-2 in the Family #1) and old (3-III-1 in the family #3) brothers showed clinical features conforming to PDD-NOS (PDD not otherwise specified) or Asperger. Two fathers (1-II-2 and 3-II-1) in their 50s and another father (2-I-1) in his 70s were all diagnosed as having with ASD traits. Most other adults over 50 years old in these pedigrees had not been clinically diagnosed with ASD or other psychiatric diseases, though some showed personal traits such as eccentricity, resulting in 8 ASD subjects out of 13 male carriers (62%). Interestingly, four young female cousins with (1-III-3 and 1-III-4 in the family #1) and without (3-III-3 and 3-III-4 in the family #3) the mutation, had no clinical ASD phenotype.

We also evaluated them from the score of the Autism-Spectrum Quotient (AQ)[18,19], in which older subjects esteemed themselve by recalling behaviours at their life period of 20s. AQ scores in two young male carriers in the family #1 (1-III-1 and -2) fulfilled the criteria (cut-off point of 28) of ASD, though this score was not obtained from two other ASD probands (in the families #2 and #3), because of low intelligence (Figure 6). Some carriers' scores were above the standard deviation of average values in noncarrier family members who showed normal control scores, indicating that such carriers may be considered to manifest ASD traits, even though not affected at the clinical level (Figure 6a). Statistically there is no difference between three different age groups (young, middle and old generations), but the males' score was significantly higher than that of females ($p<0.05$; Figure 6b). These clinical and self-describing evaluations suggest that this gene polymorphism is important to determine the ASD or ASD trait phenotype.

Given these results, we obtained serum samples from the kindreds to further study the connection between the human *CD38* mutation and plasma OT or arginine vasopressin (AVP) levels, since we previously showed that a null mutation of *Cd38* resulted in the selective decrease of plasma OT levels in mice[11], and low levels of OT have been reported in autistic children[20]. The plasma OT levels in the carriers (161.3 ± 26.5 pg/ml, n=12) were lower than those of kindred non-carriers (345.8 ± 61.3 pg/ml, n=10; $p<0.01$), as shown in Figure 7. The differences seem to be found in the younger generation but not so in older subjects (Figure 7c). The OT levels of three probands and two young carriers were compared with ASD patients without the W140 mutation (in the sample set A): the levels of five W140 carriers (79.2 ± 16.6 pg/ml; n=5) were lower than those without the mutation (147.7 ± 15.0 pg/ml; $p<0.01$, n=26). Furthermore, the OT level of the carrier ASD probands was significantly lower when compared with that in 101 adult control (198.2 ± 24.7 pg/ml; $p<0.01$). As expected, there is no difference in AVP levels between *CD38*-mutation-carriers and –noncarriers in the pedigrees (Figure 7b and d). Low plasma hormone levels were frequently observed in subjects with high AQ scores in carriers in the pedigrees (Figure 7e and f).

We also analysed the R140W mutation in 252 ASD subjects (excluding Hispanic and Asian peoples) recruited to the Autism Genetic Resource Exchange (AGRE; http://www.agre.org)[21] in USA (sample set D[22]). No mutation was found, suggesting ethnicity-dependent frequency differences. Finally, from 201 healthy unscreened control subjects (sample set E), 2 females and 1 male were positive for the mutation, representing allelic frequency of 0.007 (Tables 2 and 3). This frequency is 7.4-fold lower than those (0.052) in ASD patient group in the same residential area ($p<0.028$; Table 3).

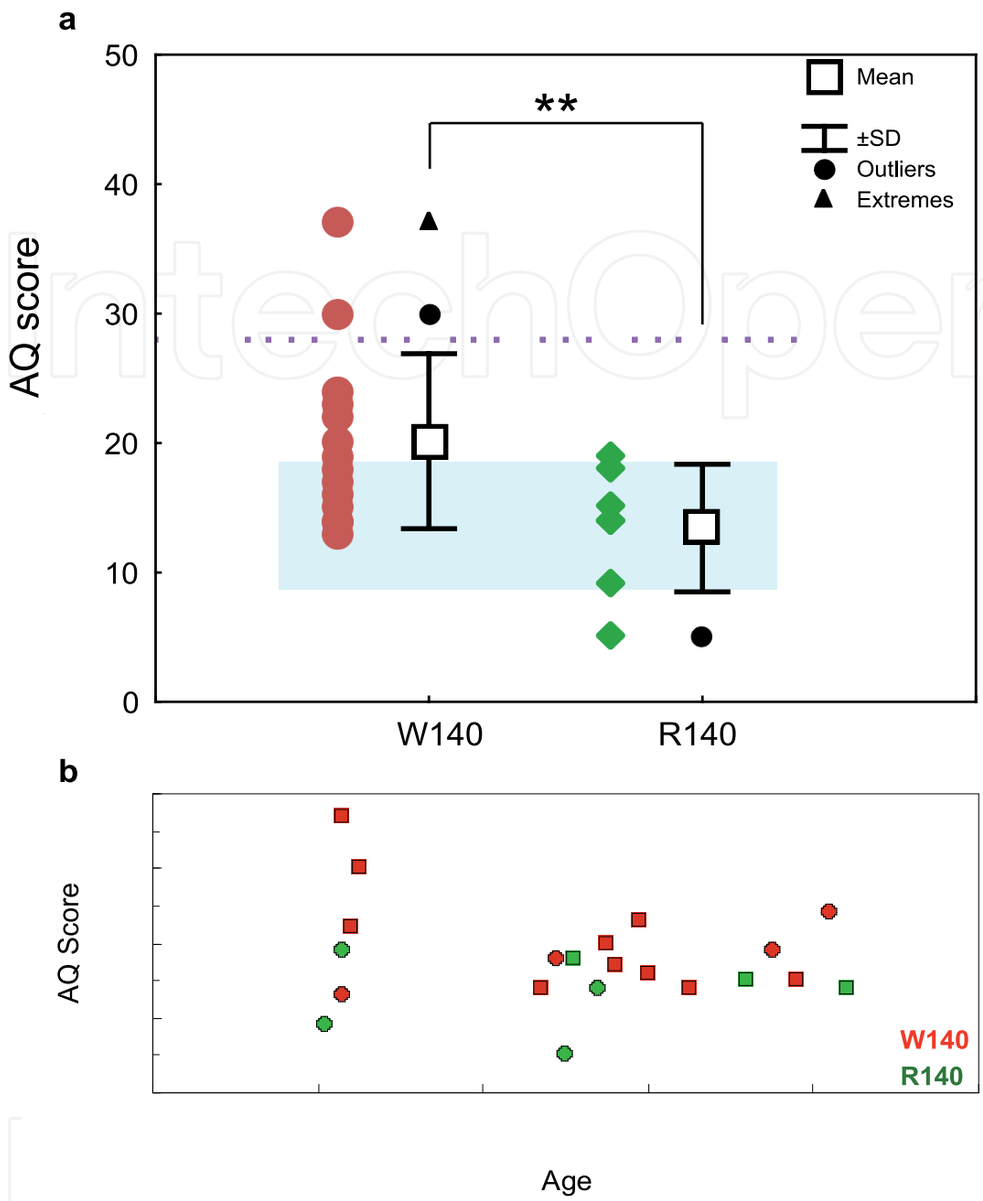

Fig. 6. **AQ score in family members in the three pedigrees.** (**a**) Assessment groups were: W140: n=14 family members with the monoallelic R140W mutation; R140: n=7 persons without the mutation in the families. Horizontal dashed bar indicates the critical score of 28 obtained from clinical ASD group in a separate experiment[18]. The mean and standard deviation range of AQ scores were illustrated. Note that 5 individuals show the intermediate score above the control range but below the ASD score. The score with R140W is higher than that without (one-way ANOVA, $p<0.05$). (**b**) A plot of AQ scores of each individual of family members with or without the R140W mutation according to age. No significance was found between three generations (20<age<40, 40<age<60 and 60<age) by two-way ANOVA. The scores of males are significantly higher than those of females ($p<0.05$). Circles indicate female, and squares, male.

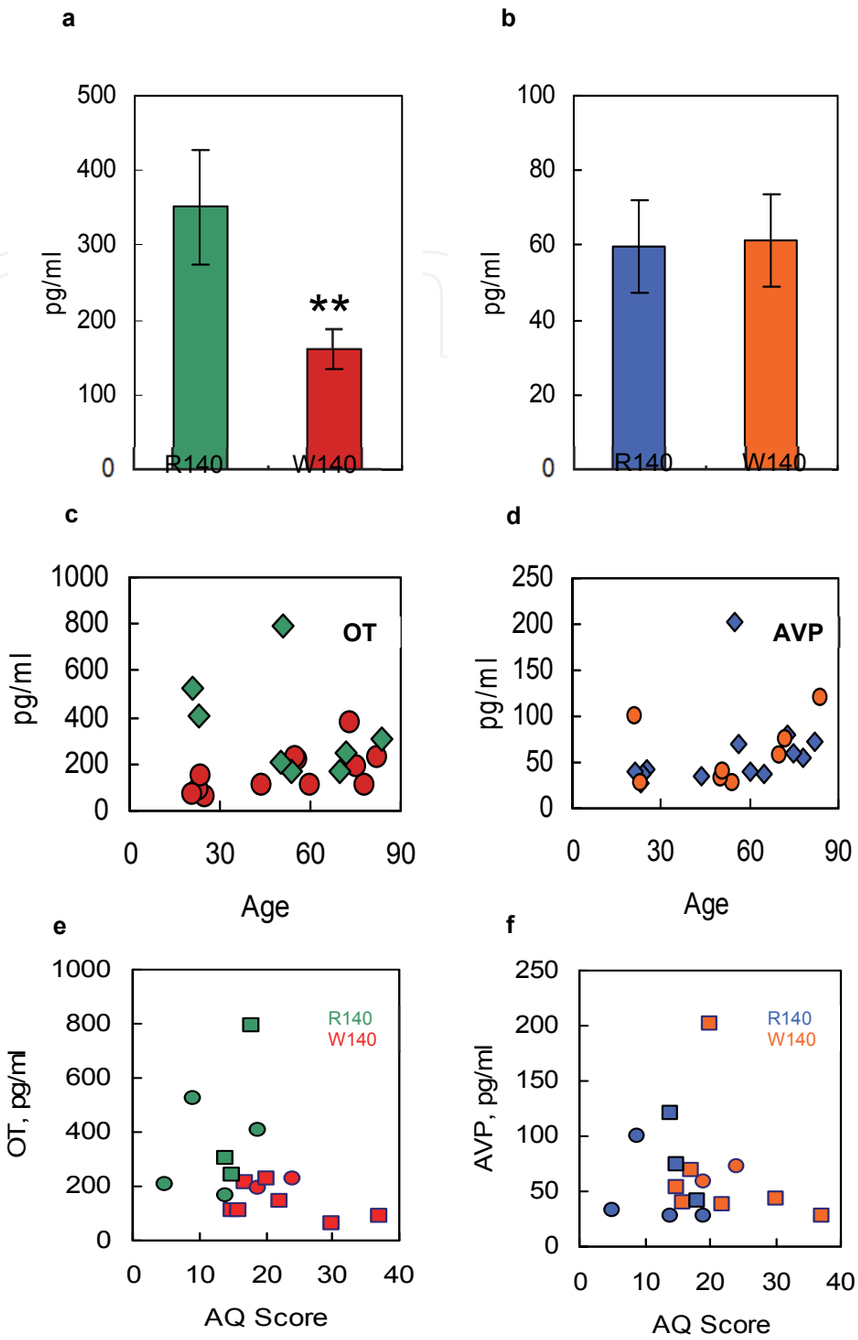

Fig. 7. **Plasma oxytocin and vasopressin levels in family members.** Plasma concentrations of OT (**a**) and AVP (**b**) levels in family members with (W140; n=12, red or orange bar) or without (R140; n=10, green or blue bar) heterozygous R140W allele. Mean ± s.e.m. **, $p<0.01$ (one-way ANOVA). OT (**c**) or AVP (**d**) levels in the three kindred according to age. OT (**e**) or AVP (**f**) levels as a function of AQ scores. Red and orange symbols or green and blue symbols indicate levels from persons with or without the R140W mutation, respectively. Circles denote female and diamonds or squares, male.

SNP	Sample	HWE	Genotype (No. & Frequency)						*p-value	Allele (No. & Frequency)				*p-value
SNP01			A/A		A/G		G/G			A		G		
	Control	0.89	0	0.00	4	0.02	196	0.98	1	4	0.01	396	0.99	1
	ASD	-	0	0.00	0	0.00	29	1.00		0	0.00	58	1.00	
SNP02			A/A		A/G		G/G			A		G		
	Control	0.83	111	0.56	76	0.38	12	0.06	0.602	298	0.75	100	0.25	0.416
	ASD	0.6	13	0.46	13	0.46	2	0.07		39	0.70	17	0.30	
SNP03			T/T		T/C		C/C			T		C		
	Control	0.55	7	0.04	67	0.34	122	0.62	0.236	81	0.21	311	0.79	0.234
	ASD	0.26	1	0.03	14	0.48	14	0.48		16	0.28	42	0.72	
SNP04			A/A		A/G		G/G			A		G		
	Control	0.78	129	0.65	64	0.32	7	0.04	0.089	322	0.81	78	0.20	0.104
	ASD	0.17	24	0.83	4	0.14	1	0.03		52	0.90	6	0.10	
SNP05			A/A		A/G		G/G			A		G		
	Control	0.12	55	0.28	110	0.55	35	0.18	0.363	220	0.55	180	0.45	0.672
	ASD	0.43	11	0.38	12	0.41	6	0.21		34	0.59	24	0.41	
SNP06			A/A		A/C		C/C			A		C		
	Control	0.17	23	0.12	102	0.51	74	0.37	0.959	148	0.37	250	0.63	0.771
	ASD	0.71	3	0.10	14	0.48	12	0.41		20	0.34	38	0.66	
SNP07			T/T		T/C		C/C			T		C		
	Control	0.18	19	0.10	98	0.49	82	0.41	0.226	136	0.34	262	0.66	0.293
	ASD	0.34	3	0.11	9	0.32	16	0.57		15	0.27	41	0.73	
SNP08			A/A		A/G		G/G			A		G		
	Control	0.75	63	0.32	96	0.48	40	0.20	0.594	222	0.56	176	0.44	0.574
	ASD	0.36	9	0.31	12	0.41	8	0.28		30	0.52	28	0.48	
SNP09			T/T		T/C		C/C			T		C		
	Control	0.83	153	0.78	40	0.20	3	0.02	0.261	346	0.88	46	0.12	0.657
	ASD	0.06	25	0.86	3	0.10	1	0.03		53	0.91	5	0.09	
SNP10			T/T		T/C		C/C			T		C		
	Control	0.85	20	0.10	88	0.44	91	0.46	0.373	128	0.32	270	0.68	1
	ASD	0.1	1	0.04	16	0.57	11	0.39		18	0.32	38	0.68	
SNP12			T/T		T/C		C/C			T		C		
	Control	-	0	0.00	0	0.00	201	1.00	0.126	0	0.00	402	1.00	0.126
	ASD	0.92	0	0.00	1	0.03	28	0.97		1	0.02	57	0.98	
SNP13			T/T		T/C		C/C			T		C		
	Control	0.91	0	0.00	3	0.01	198	0.99	**0.028**	3	0.01	399	0.99	**0.029**
	ASD	0.77	0	0.00	3	0.10	26	0.90		3	0.05	55	0.95	

P-value from Fisher's exact test. SNPs11, 14 and 15 were not analysed.

Table 3. **Statistical analysis of SNPs in 29 ASD and 201 control subjects in the Kanazawa area**

One proband receiving intranasal OT for 6 months showed improvements in the area of social approach, eye-contact and communication behavior without serious adverse effects. These results suggest that the *CD38* W140 allele could be a possible risk factor for one form of ASD by abrogating OT function and the carriers become candidates for the OT treatment[14].

3. Discussion

ASD is heterogeneous and forms a continuum, and thus is likely to involve many genes[7-10,23-26]. *De novo* mutations related to ASD are rarely inherited[7], but some ASD also can be inherited from pre-existing genetic variants in parents, for both of which a unified mechanism was proposed[9]. Our results shed light on genetic mutations of *CD38* in relatively mature ASD patients and the inheritable ASD subgroups of three independent families in which the CD38-R140W mutation showed relative co-segregation with diverse phenotypes of ASD. In such multiplex families, the risk of autism or ASD traits in young male offsprings is nearly ~100%, representing dominant transmission of a mutation with high penetrance. However, we cannot completely exclude as yet unidentified contributing factors.

The heterozygous 4693C/T carriers were identified in Japanese and Italian general populations[16,27]. The presence of this mutation in Japanese has already been reported in the HapMap site (http://www.hapmap.org/) and by Yagui *et al.* in 1998[15]. Surprisingly, the carriers were also identified in females. Therefore, it is highly possible that even clinically-unaffected female carriers with this mutant allele could in turn transmit the mutation to their offspring with high penetrance in males. Currently, we are intensively collecting blood samples for mutation analysis from many ASD and control subjects in different cities and countries to support our finding, which so far has been carried out in a relatively small group in a restricted area.

A noteworthy role for OT in social recognition has been shown in rodent and human studies[12,13]. Recently, a 1.1-Mb deletion of 20p13 including the OT gene (copy number decrease) has been detected in a child with Asperger disorder[8]. An association of one or two intronic SNPs in the OT receptor gene with autism has also been reported[25,28,29], suggesting that defects in OT signaling confer genetic vulnerability to ASD. Though the R140W mutation was not found in 252 American AGRE samples, the association study with tagSNPs showed one SNP (SNP06; rs3796863) that is positively related (p<0.004) with American high functioning autism[14].

In conclusion, *CD38* mutations provide one genetic basis for those instances of ASD that arises from disruption of the OT signaling. Thus, our finding provides the first theoretical background for the evidence-based treatment by OT infusion for a subgroup of ASD patients with the lower plasma OT level[14], which has already been tried for non-selected ASD subjects[30,31].

4. Methods summary

Clinical and genetic studies were carried out according to institutional guidelines after ethical approval of participating institutions and informed consent was obtained from all participating patients. A total of 29 unrelated affected individuals out of 96 in the Kanazawa area in Japan (Sample set A) were admitted the Kanazawa University Hospital diagnosed with DSM-IV in accordance with clinical criteria. Blood and platelet biochemical analyses were performed in 29 ASD probands and their parents and family members who agreed to supply. Genotyping for the association study and mutation screening were performed by direct sequencing or TaqMan technology. PCR products were sequenced with the BigDye Terminator Cycle Sequencing Kit (V3.1, Applied Biosystems, Foster City, CA, USA). Samples were then subjected to electrophoresis, using an ABI PRISM genetic analyzer (Applied Biosystems). Absence of genotyping errors was controlled by sequencing the PCR product with the opposite primer in a subset of patients.

Statistics: Data are expressed as mean ± s.d. or s.e.m. Statistical analysis was performed using one-way or two-way ANOVA. The criterion for significance in all cases was p<0.05.

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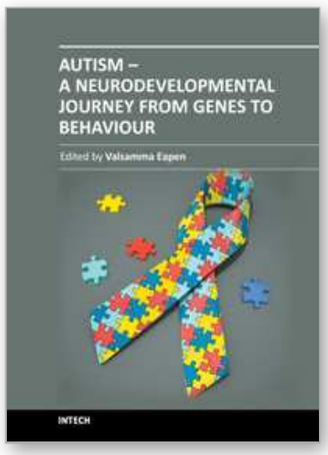

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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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