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The CD38 genotype (rs1800561 (4693C>T): R140W) is associated with an increased risk of admission to the neonatal intensive care unit

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ABSTRACT

Backgrounds: Preterm birth (PTB)/admission to the neonatal intensive care unit (NICU) is a complex disorder associated with significant neonatal mortality and morbidity and long-term adverse health consequences. Multiple lines of evidence suggest that genetic factors play an important role in its etiology.
Aim: Given the role of CD38 in term delivery through oxytocin (OXT) release, we hypothesized that OXT signaling may play a role in the etiology of PTB/admission to the NICU. This study was designed to identify genetic variation in the CD38-oxytocin pathway associated with PTB/admission to the NICU.
Methods: To identify common genetic variants predisposing individuals to PTB/admission to the NICU, we genotyped two single nucleotide polymorphisms (SNPs) in the CD38-oxytocin pathway in 63 case mothers, 55 control mothers, and 188 female volunteers in Nara Medical University Hospital, Japan.
Results: Maternal genetic effect analysis of the SNP genotype data revealed a significant association between an SNP in *CD38* (rs1800561 (4693C>T): R140W), which was reported to be correlated with diabetes and autism, and the risk of NICU admission. On the other hand, an SNP in the oxytocin receptor (*OXTR*) (rs2254298) showed no correlation with the risk of NICU admission.
Conclusion: Our study points to an association between maternal common polymorphisms in the *CD38* (rs1800561) gene in Japanese women and susceptibility to PTB/admission to the NICU. Future studies with larger sample sizes are needed to confirm the findings of this study.

1. Introduction

Preterm birth (PTB) is a major public health problem that accounts for approximately 10% of all births worldwide [1]. In 2013, PTBs, occurring before 37 completed weeks of gestation, comprised 11.39% of live births in the U.S. [2]. Prematurity is a leading cause of perinatal mortality and a significant contributor to short- and long-term morbidity in survivors [3]. The etiology of PTB is not completely understood, but multiple lines of evidence suggest that genetic factors play an important role, with PTB showing a high rate of recurrence in individuals with a history of previous preterm delivery, a tendency to occur within families, and racial disparity [1,3].

Single nucleotide polymorphisms (SNPs) are DNA sequence variations involving a single nucleotide present in at least 1% of the population. If an SNP is present in the protein coding sequences of a gene, it can change the amino acid sequence of the product. Clinically, these differences may lead to significant phenotypic variation, different responses to drugs, and different responses to exposure to adverse environmental conditions. An increasing body of research has identified specific SNPs believed to be associated with varying levels/kinds of health problems.

The oxytocin (OXT)-oxytocin receptor (OXTR) system provides promising candidate genes for studies of genetic contributions to PTB. Although components of the system influence a wide range of physiological, behavioral, and emotional processes in humans, most studies have focused only on its role in reproduction, particularly labor and parturition [4]. OXT acts as an inducer of uterine contraction, and the myometrium becomes increasingly sensitive to the action of OXT towards term [4]. This increase in uterine sensitivity to OXT occurs concomitantly with an up-regulation of *OXTR* mRNA and a dramatic increase in the myometrial OXTR number, which peaks during early labor [4]. The OXTR is a G protein-coupled receptor, which, upon stimulation, activates various intracellular signaling pathways, such as the phosphoinositide cascade, eventually leading to uterine contraction [4,5]. The efficacy of Atosiban, an OXT antagonist, in stopping premature

Abbreviations: cADPR, cyclic adenosine diphosphate ribose; IL, interleukin; NICU, neonatal intensive care unit; OXT, oxytocin; OXTR, oxytocin receptor; PTB, preterm birth; SNP(s), single nucleotide polymorphism(s).

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uterine contractions and delaying PTB [6], provides further support for the importance of this hormonal system in PTB. Therefore, the *OXTR* gene polymorphism has been considered a possible candidate for PTB/admission to the neonatal intensive care unit (NICU) [7]. Recently, impaired Oxt secretion from the pituitary gland was observed in *Cd38* knockout mice, and local re-expression of human CD38 (wild-type) reversed the impaired Oxt secretion, whereas Trp^{140} (TGG)-CD38 did not [8].

Cyclic adenosine diphosphate ribose (cADPR), which was discovered more than two decades ago, together with inositol 1,4,5-trisphosphate and nicotinic acid adenine dinucleotide phosphate, cADPR has been recognized as a principal second messenger involved in intracellular Ca^{2+} mobilization [9,10]. Extracellular stimuli can induce the production of cADPR, which leads to Ca^{2+} mobilization from intracellular stores, as well as Ca^{2+} entry from the extracellular compartment and the initiation of diverse cellular responses [11,12]. cADPR is synthesized by ADP-ribosyl cyclases (CD38 and CD157/BST-1), and the major ADP-ribosyl cyclase in mammals is CD38. CD38 was originally recognized as a leukocyte antigen and shown to have enzymic activities of cADPR synthesis and hydrolysis (ADP-ribosyl cyclase and cADPR hydrolase activities) [12]. Human *CD38* is located on chromosome 4p15 [10,13] and is composed of eight exons and seven introns, which encompass more than 77 kb of genomic DNA [10,14]. The rs1800561 SNP, which resulted in an amino acid substitution of Arg^{140} (CGG) to Trp (TGG), is located in exon 3 of the human *CD38* gene and resulted in an increased risk of type 2 diabetes in Japanese via decreased ADP-ribosyl cyclase activity of CD38 [10,15].

In the present study, we explored whether the *CD38* rs1800561 SNP (4693C>T) genotype, which results in an amino acid substitution of Arg^{140} (CGG) to Trp (TGG), is associated with an increased likelihood of PTB and/or admission to the NICU.

2. Patients and methods

2.1. Subjects

Subjects were recruited at Nara Medical University Hospital in Kashihara, Japan. All eligible mothers were enrolled in a research protocol, which requested permission to collect genomic DNA from the mother for research purposes. The exclusion criteria included: (1) serious medical illness (renal insufficiency, congestive heart disease, etc.); (2) refusal to provide written informed consent, and (3) a clinical emergency, such as fetal distress or maternal hemorrhage, that prevented counseling of the patient about participating in the study. A buccal swab sample for isolation of genomic DNA was obtained from the mother at the time of enrollment in the protocol. For control samples, female volunteers (medical students) in Nara Medical University were also enrolled. The collection of the samples and their utilization for research purposes were approved by the Human Genome Research Committee of Nara Medical University.

2.2. Genotyping

DNA was extracted from the buccal swabs using a QIAamp® DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions as described [15]. The DNA samples were stored at 4 °C until testing. An allele-specific PCR method was developed to detect SNPs of *OXTR* (rs2254298) and *CD38* (rs1800561) in human samples. Allele-specific primers were designed by using appropriate software to permit the PCR amplification only if the nucleotide at the 3′-end of the primer complemented the base at the wild-type or variant-type DNA sample. The uniqueness of the primers was then confirmed. The *OXTR* rs2254298 SNP was detected using sequence-specific PCR. A common forward primer, 5′-TGCCAACTCTCTTCACTTGG-3′, and two sequence-specific reverse primers, 5′-GGAAACCATCCCTGTTTTCC-3′ for a major allele and 5′-GGAAACCATCCCTGTTTTCT-3′ for a minor allele, were used. The *CD38* rs1800561 SNP was also detected using sequence-specific PCR. A common reverse primer, 5′-GGCAATCCCACA GGGCCCAG-3′ and two sequence-specific forward primers, 5′-TCAGTT CACACAGGTCCAGC-3′ for a major allele and 5′-TCAGTTCACACAGGTC CAGT-3′ for a minor allele, were used. All the PCR primers were synthesized by Nihon Gene Research Laboratories, Inc. (Sendai, Japan). To perform the PCR, reaction tubes preloaded with 5 U of TaKaRa Ex Taq HS® DNA polymerase (Takara Bio Inc., Otsu, Japan), 200 μM of deoxyribonucleotide triphosphates, 25 mM of *N*-Tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid (pH 9.3), 50 mM KCl, 2 mM $MgCl_2$, and 0.1 mM dithiothreitol were used. The total reaction volume was 20 μL, and this contained 1 μL of template DNA, 1 μL of each primer (10 pmol/μL), and 17 μL of H_2O. PCR was performed using a PCR Thermal Cycler Dice® (Takara Bio Inc.) using the following cycling conditions: 94 °C for 5 min; 35 cycles at 94 °C for 30 s; 60 °C for 20 s, and 72 °C for 30 s, with a final extension step of 72 °C for 3 min. After the PCR, the samples were electrophoresed onto 2.5% agarose gel. The amplified DNA was visualized by staining with 0.5 μg/mL of ethidium bromide. Amplification products of 150 bp for *OXTR* rs2254298 and 129 bp for *CD38* rs1800561 were detected and recorded.

2.3. Statistical analysis

The data were first tabulated in Microsoft® Excel® for Mac 2011 (Redmond, WA) and transferred into Prism (version 5, GraphPad Software, La Jolla, CA). Statistical differences between the genotype and allele frequencies were compared using a Chi-square test (χ^2-test). A Chi-square test was performed to determine whether the association between the genotype and allele frequencies of the patients and control subjects was statistically significant.

3. Results

3.1. Demographics of the sample population

The demographics of the sample population are shown in Table 1. During the 6 months from June 2011 to October 2011, 895 births were recorded at Nara Medical University Hospital, Kashihara, Japan. We recruited a convenience sample of 116 mothers of newborns for the present study. Of this sample group, the babies of 63 mothers were cared for in the NICU because of a low body weight at birth (<2500 g), and the babies of 53 mothers were not. Although the maternal BMIs of the two groups differed (22.99 ± 0.4773 in mothers whose babies were admitted to the NICU vs. 25.12 ± 0.5496 in mothers whose babies were not admitted to the NICU), no other differences regarding maternal age, gravidity, and parity were observed. Apgar scores at 1 and 5 min and maternal diabetes were also recorded (Table 1).

3.2. Genotype and likelihood of admission to the NICU

3.2.1. CD38 (rs1800561)

he genotype and the likelihood of admission to the NICU are shown in Fig. 1 and Table 2. The majority (94.8%) of the study population had a

Table 1
Basic sample characteristics by admission to NICU.

	Admission to NICU		
	Yes	No	*P*
Gestational age (weeks)	33.21 ± 0.5972	38.57 ± 0.1887	<0.0001
Infant BW (grams)	1861 ± 92.25	2991 ± 52.16	<0.0001
Infant gender (male/female)	36/29	25/23	0.5819
Apgar score (1 min)	6.831 ± 0.3018	8.741 ± 0.09228	<0.0001
Apgar score (5 min)	8.540 ± 0.2019	9.833 ± 0.05119	<0.0001
Maternal age at delivery (years)	31.87 ± 0.7021	31.9 ± 4.84	0.401
Maternal BMI	22.99 ± 0.4773	25.12 ± 0.5496	0.0039
Maternal Diabetes (%)	0	1.82	0.470

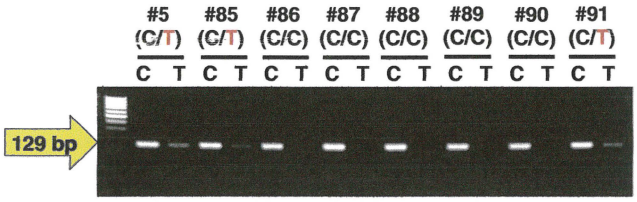

Fig. 1. Representative genotyping pattern of *CD38* polymorphism (rs1800561: 4693C/T: R140W) by allele-specific PCR. For each sample, two PCR reactions were performed and run side by side on agarose gel. A 129-bp band indicated the presence of the allele; amplification failure indicated the absence of the allele. In the gel, the first lane shows the product from size-standard sample; for other lanes, C and T indicate the product from PCR.

4693C genotype of the *CD38* gene, and the remaining 5.2% had a lower-cADPR synthesizer 4693T genotype. Mothers with the 4693T genotype (6/63) had a statistically significant increased risk of admission to the NICU versus those with the 4693C genotype (0/53) ($P = 0.02105$ in Table 2). The ratio of the C/T genotype in the mothers whose babies were admitted to the NICU was significantly higher than that in the control (including female volunteers) group ($P = 0.00101$). None of the subjects in the study population had a T/T genotype.

3.2.2. OXTR (rs2254298)

The majority (57.4%) of the study population had a G/G genotype of the *OXTR* gene. The remaining 35.0% had an A/G genotype, and 7.6% had an A/A genotype. However, we found no correlation between the SNP rs2254298 within the OXTR gene and the risk of admission to the NICU (Fig. 2 and Table 3).

4. Discussion

Pregnancy and parturition involve an intricate biochemical and molecular interplay between the mother and fetus [5]. Incomplete knowledge of theses complex, time-varying processes has hampered the study of PBT. An investigation of static markers, such as sequence variants, may help to predict the risk of PTB/admission to the NICU.

In this study, we used a candidate gene approach to better understand the genetic factors contributing to PTB/NICU admission. Previous studies have identified some polymorphisms possibly associated with PTB/NICU admission, but they have mainly focused on immune-related and inflammatory genes, such as the interleukin (IL)-1 receptor antagonist, interferon γ, coagulation factor II, IL-12A, colony-stimulating factor 2, interferon γ receptor 2, killer cell immunoglobulin-like receptor, IL-4, IL-13, IL-6, tumor necrosis factor α, and monocyte chemoattractant protein-1 [16–19]. The present study was undertaken to explore the contribution of genetic variations in another functionally relevant pathway, the CD38–cADPR pathway, to the etiology of PTB/NICU admission, given the important role of constituents of the pathway in oxytocin signaling [8].

The SNP (rs1800561 (4693C>T): R140W) of *CD38* was first reported in Japanese [15] (allele frequency, 0.035) and Han Chinese (allele frequency, 0.01) but not in European or African control populations in an online SNP database. In a recent study of Polish Caucasians, the same SNP was detected in three of 500 healthy controls, yielding an allele frequency of 0.003, and 21 W140 carriers were found among

Table 2
Allele frequencies of CD38 (rs1800561) in control subjects and mothers with their babies in NICU admission.

	C/C	C/T	*P* value
Control mothers	53	0	0.02105 vs NICU mothers
Control (female total)	184	2	0.00101 vs NICU mothers
NICU mothers	57	6	

Table 3
Allele frequencies of oxytocin receptor (rs2254298) in control subjects and mothers with their babies in NICU admission.

	G/G	G/A	A/A	*P* value
Control mothers	33	17	3	0.212 vs NICU mothers
Control (Female total)	111	64	12	0.144 vs NICU mothers
NICU mothers	30	25	8	

439 B-cell chronic leukemia patients (frequency, 0.024) [20]. An Italian study found one carrier among 25 healthy controls (frequency, 0.02) [21]. A study of autism spectrum disorder found 68 carriers of the C/T genotype among 1384 Japanese subjects (frequency, 0.025) and among five of 150 Koreans subjects (frequency, 0.017) in autism spectrum disorder research [22]. In this study, we found eight carriers of the C/T genotype among 249 Japanese females (allele frequency, 0.016), indicating that the *CD38* polymorphism is more common among Asians than Caucasians.

The amino acid substitution can cause severe perturbations of the predicted protein structure/enzymatic activity in comparison with wild-type R140 ((human; R141 in macaque, R133 in bovine, R148 in canine, R116 in *Aplysia kurodai*, R116 in *Aplysia californica*), Q140 (chimpanzee; Q137 in *Xenopus laevis*), K145 (pig; K138 in rabbit), G143 (rat; G144 in mouse), H142 (chicken; H93 in alligator), and D121 (seabass)) CD38/ADP-ribosyl cyclase(s) (Fig. 3). In fact, in our previous experiment using CHO cells, the W140-CD38 protein showed only one third of ADP-ribosyl cyclase activity of wild-type (R140) CD38 [15]. Moreover, social amnesia was not rescued by local re-expression of human W140-CD38 in the hypothalamus of the *Cd38*-null mice, whereas local re-expression of human R140-CD38 rescued social amnesia [8]. Taken together, these observations indicate functional abnormality of W140-CD38 or insufficient functioning of the protein.

The CD38–cADPR signaling system has been shown to play an essential role not only in glucose-induced insulin secretion [10–12] but also in OXT secretion [8]. We also studied the *OXTR* SNP (rs2254298). The *OXTR* gene SNP, rs2254298, has been reported to be associated with several human diseases, mainly neurological/psychological diseases, such as communication difficulties, depression and anxiety, disorders of emotional empathy, social cognition, autism spectrum disorder, and Asperger syndrome [23–25]. We found no correlation between the *OXTR* SNP (rs2254298) and the risk of NICU admission (Table 3). Therefore, the increased risk of NICU admission/PTB in mothers with the *CD38* SNP (rs1800561 (4693C>T): R140W) may be independent of the OXT–OXTR pathway, at least the *OXTR* SNP (rs2254298).

In contraction of the myometrium during delivery, cADPR signaling was reported to play an essential role in oxytocin-induced Ca^{2+} transients in human myometrium cells [26]. The mRNA and protein levels of CD38 were reported to be increased in uterine smooth muscle obtained from term rats compared to preterm (14–17 days of gestation) rats [27], suggesting that the CD38–cADPR signaling is important for oxytocin-induced myometrium contraction for delivery. Therefore, it is quite possible that mothers with the *CD38* SNP (rs1800561 (4693C>T): R140W) have lower cADPR-producing activity in uterine

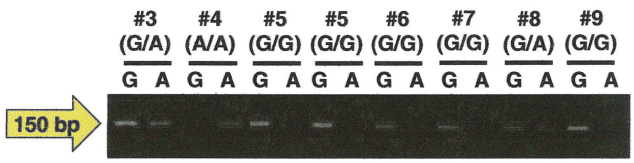

Fig. 2. Representative genotyping pattern of *OXTR* polymorphism (rs2254298) by allele-specific PCR. For each sample, two PCR reactions were performed and run side by side on agarose gel. A 150-bp band indicated the presence of the allele; amplification failure indicated the absence of the allele. In the gel, G and A indicate the product from PCR.

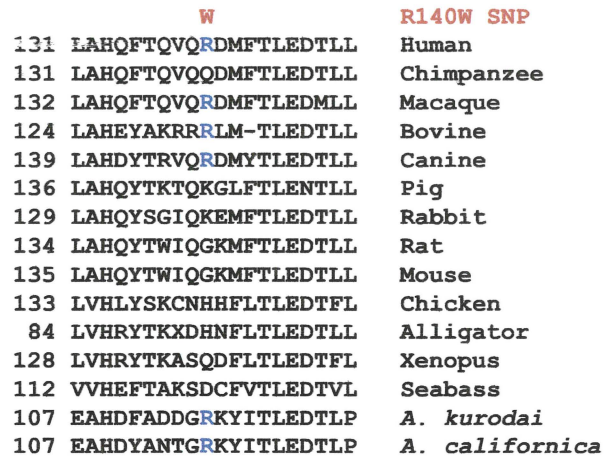

Fig. 3. Amino acid sequences of cADPR synthesizing enzymes (CD38 and its homologues). Conversion of R at 140th amino acid of human CD38 among different species. Amino acid sequences were obtained through accession numbers BAA18966 (human), JAA17667 (chimpanzee), AAT36330 (macaque), DAA28387 (bovine), NP_001003143 (canine), NP_001230812 (pig), NP_001076152 (rabbit), NP_037259 (rat), CAJ18593 (mouse), ADQ89191 (chicken), XP_006278685 (alligator), BAL72804 (Xenopus), CBN82130 (seabass), BAA06284 (*Aplysia kurodai*), and NP_001191476 (*Aplysia californica*).

smooth muscle and therefore show lower oxytocin-induced Ca^{2+} transients and reduced lower uterine smooth muscle contraction, in addition to lower levels of oxytocin secreted from hypothalamus/pituitary. These factors may possibly explain the increased risk of NICU admission in mothers with the *CD38* SNP (rs1800561 (4693C>T): R140W), as well as the reduced oxytocin secretion seen in *CD38*-null mice [8].

In addition to the SNP (rs1800561 (4693C>T): R140W) of *CD38*, autoantibodies against CD38 were reported to be associated with human diseases, such as diabetes and Graves' disease, in Asians and Caucasians [28,29]. With regard to PTB/NICU admission, it is quite possible that not only the *CD38* SNP but also autoantibodies against CD38 could be a risk factor. Therefore, SNPs and/or autoantibodies of components of the CD38-cADPR system other than CD38, such as the FK506-binding protein 12.6 and ryanodine receptor Ca^{2+} channel [10,30], may be related to PTB/NICU admission.

5. Conclusions

The CD38 rs1800561 (4693C>T) genotype in pregnant women could be a sensitive genotype for NICU admission/PTB.

Conflict of interest statement

The content of this article is solely the responsibility of the authors. The authors declare that there is no conflict of interest.

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