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Genetic association of aromatic hydrocarbon receptor (*AHR*) and cytochrome P450, family 1, subfamily A, polypeptide 1 (*CYP1A1*) polymorphisms with dioxin blood concentrations among pregnant Japanese women

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HIGHLIGHTS

- We examined the association of dioxin concentrations with genetic susceptibility.
- Six polymorphisms in genes encoding dioxin-metabolizing enzymes were investigated.
- These six polymorphisms were analyzed in 421 healthy pregnant Japanese women.
- We observed different blood concentrations and TEQs with both *AHR* (rs2066853) and *CYP1A1* (rs4646903).

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ABSTRACT

Dioxins are metabolized by cytochrome P450, family 1 (CYP1) via the aromatic hydrocarbon receptor (AHR). We determined whether different blood dioxin concentrations are associated with polymorphisms in *AHR* (dbSNP ID: rs2066853), AHR repressor (*AHRR*; rs2292596), CYP1 subfamily A polypeptide 1 (*CYP1A1*; rs4646903 and rs1048963), CYP1 subfamily A polypeptide 2 (*CYP1A2*; rs762551), and CYP1 subfamily B polypeptide 1 (*CYP1B1*; rs1056836) in pregnant Japanese women. These six polymorphisms were detected in 421 healthy pregnant Japanese women. Differences in dioxin exposure concentrations in maternal blood among the genotypes were investigated. Comparisons among the GG, GA, and AA genotypes of *AHR* showed a significant difference (genotype model: $P=0.016$ for the mono-*ortho* polychlorinated biphenyl concentrations and toxicity equivalence quantities [TEQs]). Second, we found a significant association with the dominant genotype model ([TT+TC] vs. CC: $P=0.048$ for the polychlorinated dibenzo-*p*-dioxin TEQs; $P=0.035$ for polychlorinated dibenzofuran TEQs) of *CYP1A1* (rs4646903). No significant differences were found among blood dioxin concentrations and polymorphisms in *AHRR*, *CYP1A1* (rs1048963), *CYP1A2*, and *CYP1B1*. Thus, polymorphisms in *AHR* and *CYP1A1* (rs4646903) were associated with maternal dioxin concentrations. However, differences in blood dioxin concentrations were relatively low.

Abbreviations: PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; PCB, polychlorinated biphenyl; TEQ, toxicity equivalence quantity; AHR, aromatic hydrocarbon receptor; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; CYP1A1, cytochrome P450, family 1, subfamily A, polypeptide 1; CYP1A2, cytochrome P450, family 1, subfamily A, polypeptide 2; CYP1B1, cytochrome P450, family 1, subfamily B, polypeptide 1; AHRR, aromatic hydrocarbon receptor repressor; CYP, cytochrome P450; GSTT1, glutathione *S*-transferase θ1; GSTM1, glutathione *S*-transferase μ1; HexCB, Hexachlorinated biphenyl; PenCB, Pentachlorinated biphenyl; TEF, toxicity equivalence factor; SNPs, single-nucleotide polymorphisms; PenCB, pentachlorinated biphenyl; $E_2$17β-estradiol; E_1, estrone; 2-OH-$E_2$2-hydroxyestradiol; 4-OH-$E_2$4-hydroxyestradiol; ERα, estrogen receptor α; TSH, thyroid-stimulating hormone; TSHβ, thyroid-stimulating hormone, β subunit; E_2-ERα, 17β-estradiol-bound estrogen receptor α; T_3, triiodothyronine.

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1. Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs), which are all referred to as dioxins, are persistent endocrine-disrupting chemicals that bioaccumulate as a result of environmental exposure or ingestion of dioxin-containing foods. Adverse health effects of dioxin exposure in humans include the development of serious diseases such as diabetes and cancer and deleterious effects such as an altered immunological response and changes in the expression of receptors and metabolic enzymes (White and Birnbarm, 2009).

Low levels of dioxin exposure in pregnant women can have a significant effect on the developing fetus through circulating blood via the placenta (Miller et al., 2004; Chao et al., 2007). Exposure to high levels of PCDDs plus PCDFs (resulting in a median blood concentration of 168 pg/g lipid) in pregnant women is associated with decreased fundal length and uterine size in 8-year-old girls (Su et al., 2012). Exposure to high levels of PCDDs, PCDFs, and dioxin-like PCBs from dioxin-contaminated rice oil [mean blood concentration of 68.92 toxicity equivalence quantity (TEQ) pg/g lipid], which occurred in the late 1960s (Yusho disease), is associated with lower birth weight (Tsukimori et al., 2012). Additional studies have shown that exposure to low dioxin levels is associated with low birth weight (Tajimi et al., 2005; Sonneborn et al., 2008). One of our previous studies also showed that low prenatal dioxin exposure has a significant negative association with birth weight (Konishi et al., 2009). However, other studies have shown that pregnant women who are exposed to low dioxin levels do not give birth to babies with low birth weight (Longnecker et al., 2005; Nishijo et al., 2008). These conflicting results suggest that maternal genetic susceptibility regarding enzymes involved in dioxin metabolism may play a role.

Dioxins, which include 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), bind the aromatic hydrocarbon receptor (AHR); are metabolized by cytochrome P450 (CYP)1, subfamily A, polypeptide 1 (CYP1A1), polypeptide 2 (CYP1A2), and subfamily B, polypeptide 1 (CYP1B1); and stimulate the transcription suppressor factor AHR repressor (AHRR). Genetic polymorphisms in *AHR*, *AHRR*, and *CYP* modulate the degree of disease risk. For example, a polymorphism in *AHR* (G > A, Arg554Lys, dbSNP ID: rs2066853) is associated with survival in soft-tissue sarcoma (Berwick et al., 2004). A polymorphism in *AHRR* (C > G, Pro185Ala, rs2292596) is associated with endometriosis (Tsuchiya et al., 2005; Kim et al., 2007). A polymorphism in *CYP1A1* (T > C, *Msp*I, rs4646903) is associated with polycystic ovary syndrome (Babu et al., 2004) and lung cancer (Song et al., 2001). A polymorphism in *CYP1A1* (A > G, Ile462Val, rs1048963) is associated with lung cancer (Sugimura et al., 1995). A polymorphism in *CYP1A2* (A > C, *CYP1A2*1F*, rs762551) is associated with squamous cell carcinoma (Singh et al., 2010) and breast cancer (Shimada et al., 2009). Finally, a polymorphism in *CYP1B1* (C > G, Leu432Val, rs1056836) is associated with breast cancer (Shimada et al., 2009). Disease and the effect of exposure concentration are not independent phenomena. First, various polymorphisms may affect dioxin blood concentrations. Second, the exposure concentration may affect the reproductive and immune systems. Third, effects on these systems may lead to increased risk for various diseases.

Exposure to low levels of dioxins may cause reproductive toxicity (Tajimi et al., 2005; Sonneborn et al., 2008; Konishi et al., 2011). Through AHR and the CYP1 family of enzymes, dioxins share a metabolic pathway with polycyclic aromatic hydrocarbons, which are components of cigarette smoke. The risk of fetal growth restriction in pregnant women who smoke during pregnancy is modulated by maternal polymorphisms in *CYP1A1*, glutathione *S*-transferase θ1 (*GSTT1*), and glutathione *S*-transferase μ1 (*GSTM1*) (Delpisheh et al., 2009). Similarly, differences in genetic susceptibility to environmental chemicals in the parental generation may cause adverse health effects in the offspring. Maternal genotypes consisting of *GSTM1* null, a *CYP1A1* (rs1048963) variant, and the combination of *GSTM1* null and a *CYP1A1* (rs4646903) variant are associated with increased risk for low birth weight and premature birth (Sram et al., 2006). Genotypes can modify the effects of environmental factors. Therefore, the genetic susceptibility of pregnant women to environmental chemicals may affect the health status of the next generation.

Our understanding of the association between environmental exposure to chemicals, including dioxins, and its effect on fetal and childhood development years after birth is, however, limited. Dioxin-like PCB (IUPAC No. 126) is ~10,000-fold more potent than non-dioxin-like PCB (IUPAC No.153) in pregnancy. Isomers of these compounds impair learning in young (3-month-old) rats, and the effects are similar in both males and females (Piedrafita et al., 2008). However, the underlying mechanisms in humans remain unclear. In the future, we will investigate the effects of dioxins on developing school-aged children. We also need to examine the associations between dioxin concentrations and polymorphisms in dioxin-metabolizing genes and evaluate the gene–environment interactions. Consequently, here we examined the association of dioxin concentrations in the blood with genetic susceptibility in healthy mothers. The objective of this study was to look for differences in exposure concentrations of dioxins and *AHR* (rs2066853), *AHRR* (rs2292596), *CYP1A1* (rs4646903 and rs1048963), *CYP1A2* (rs762551), and *CYP1B1* (rs1056836) genotypes.

2. Materials and methods

2.1. Study population

From July 2002 through July 2004, we enrolled pregnant women from Sapporo Toho Hospital in Hokkaido, northern Japan, after obtaining their informed consent. Details of the cohort study methods have been reported (Kishi et al., 2011). A total of 514 mothers were registered, but 10 were excluded because of miscarriage, stillbirth, relocation, or voluntary withdrawal from the study before follow-up. Participants completed a self-administered questionnaire after the second trimester of pregnancy regarding dietary habits, alcohol intake, smoking status, caffeine intake, household income, educational level, and medical history. Information from maternal medical records concerning pregnancy complications and parity was obtained. In the present study, 422 complete sets of dioxin congener concentrations and polymorphisms were selected from the 514 registered participants of the cohort study and were used for chemical analysis. However, one sample was excluded from the study because the PCDF concentrations were extremely high and the Smirnoff-Grubbs rejection test was significant. The Institutional Ethical Board for Human Gene and Genome Studies of Hokkaido University Graduate School of Medicine approved the study protocol.

2.2. Sample collection and dioxin analysis

Sample collection has been described in detail elsewhere (Kishi et al., 2011). Analyses of dioxins were performed as described (Todaka et al., 2003). Briefly, a 40-ml blood sample was taken from the maternal peripheral vein during the third trimester. If blood could not be drawn during pregnancy because of anemia, we obtained the blood during hospitalization within a week after delivery. All samples were stored at −80 °C until analysis. PCDD, PCDF, and dioxin-like PCB concentrations in the blood were measured using high-resolution gas chromatography/high-resolution mass spectrometry at the Fukuoka Institute of Health and Environmental Sciences. Sample values below the detection limit were assigned a value of one-half the detection limit to estimate the total dioxin concentration. TEQ values were calculated by multiplying the concentrations of each congener by its toxicity equivalence factor (TEF) value based on the 2006 World Health Organization standards (Van den Berg et al., 2006). We measured the dioxin concentrations in 426 maternal blood samples.

2.3. Genetic analysis

We evaluated six single-nucleotide polymorphisms (SNPs), namely *AHR* (G > A, rs2066853), *AHRR* (C > G, rs2292596), *CYP1A1* (T > C, rs4646903; A > G, rs1048963), *CYP1A2* (A > C, rs762551), and *CYP1B1* (C > G, rs1056836). Genomic DNA was extracted from 400 μl of maternal blood using a Maxwell 16 Instrument (Promega Corporation, Madison, WI, USA). DNA amplifications were performed in batches

in a 96-well microamp reaction plate using validated TaqMan probes for each of the six SNPs on a Gene Amp 9700 thermal cycler (Applied Biosystems, Foster City, CA, USA) with an end-point allelic discrimination assay (Ranade et al., 2001) on a 7300/7500 Real-time PCR System (Applied Biosystems). We randomly selected 20 samples and repeated genotyping to check for genotyping quality. The results were 100% concordant.

2.4. Statistical analysis

Descriptive statistics for pregnant women are expressed as the mean ± standard deviation, as the median (range), or as numbers (percentages). The dioxin and dioxin-like PCB concentrations were lipid adjusted (pg/g lipid) and assumed to have a value equal to half the limit of detection when the levels were below the limit of detection for individual congeners. Associations among dioxin concentrations, TEQ, and genotypes of *AHR* (rs2066853), *AHRR* (rs2292596), *CYP1A1* (rs4646903 and rs1048963), *CYP1A2* (rs762551), and *CYP1B1* (rs1056836) were analyzed with a generalized linear model adjusted for maternal age, maternal height, maternal weight before pregnancy, caffeine intake during pregnancy, alcohol consumption during pregnancy, parity, maternal smoking status during pregnancy, maternal educational level, annual household income, inshore fish intake during pregnancy, deep-sea fish intake during pregnancy, and blood sampling period. *P*-values were calculated for a genotype model, a dominant model, and a recessive model. The dominant model consisted of the following: (AA+AG) vs. GG for *AHR*; (CC+CG) vs. GG for *AHRR*; (TT+TC) vs. CC for *CYP1A1* (rs4646903); (AA+AG) vs. GG for *CYP1A1* (rs1048963); (CC+AC) vs. AA for *CYP1A2*; and (GG+GC) vs. CC for *CYP1B1*. The recessive model was as follows: AA vs. (AG+GG) for *AHR*; CC vs. (CG+GG) for *AHRR*; TT vs. (TC+CC) for *CYP1A1* (rs4646903); AA vs. (AG+GG) for *CYP1A1* (rs1048963); CC vs. (AA+AC) for *CYP1A2*; and GG vs. (GC+CC) for *CYP1B1* (Klein et al., 2010; Qiu et al., 2010; Yu et al., 2012; Xie et al., 2012; Luo et al., 2013).

All statistical analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered significant.

3. Results

Demographic characteristics of the participants are shown in Table 1. The mean age, height, and weight before pregnancy were 30.8 years, 158.2 cm, and 53.2 kg, respectively. The percentages of participants who drank alcohol and smoked during pregnancy were 30.4% and 17.1%, respectively. The majority of participants had 13–16 years of education (55.8%), 3–5 million yen as their annual household income (49.6%), consumed inshore fish 1–2 times/month (49.9%) and deep-sea fish 1–2 times/week (47.7%), and had their blood taken during pregnancy (69.6%).

The distributions of the *AHR* (rs2066853), *AHRR* (rs2292596), *CYP1A1* (rs4646903 and rs1048963), *CYP1A2* (rs762551), and *CYP1B1* (rs1056836) polymorphisms are shown in Table 2. No significant deviation of genotype frequencies from the Hardy-Weinberg equilibrium was detected in the SNPs (data not shown). The *AHR* (G>A), *AHRR* (C>G), *CYP1A1* (T>C, rs4646903; A>G, rs1048963), *CYP1A2* (A>C), and *CYP1B1* (C>G) polymorphisms showed minor allele frequencies of 43.1%, 39.8%, 34.3%, 22.1%, 37.2%, and 13.4%, respectively, among the pregnant Japanese women in this study.

Tables 3 and 4 show the adjusted mean concentrations (with 95% confidence intervals) and TEQs in the generalized linear model for total PCDDs, PCDFs, and dioxin-like PCBs among *AHR* (rs2066853) (Table 3) and *CYP1A1* (rs4646903) (Table 4) polymorphisms for pregnant women in Sapporo, Hokkaido, Japan. Figs. 1 and 2 show the adjusted mean concentrations (Fig. 1) and TEQs (Fig. 2) in the generalized linear model of congeners.

Comparison among GG, GA, and AA of *AHR* (rs2066853) showed a significant difference (genotype model: $P=0.016$ for the mono-*ortho* PCB concentrations and TEQ; $P=0.014$ for the total dioxin concentrations). In addition, we also found a significant association in the dominant genotype model GG vs. (GA+AA): $P=0.047$ for PCDD concentrations; $P=0.028$ for non-*ortho* PCB concentrations; $P=0.022$ for non-*ortho* PCB TEQ; $P=0.004$ for mono-*ortho* PCB concentrations, TEQ, and total dioxin concentrations (Table 3).

A comparison among TT, TC, and CC of *CYP1A1* (rs4646903) showed no significant difference. However, we did find a significant association in the dominant genotype model (TT+TC) vs. CC: $P=0.048$ for PCDD TEQ; $P=0.035$ for PCDF TEQ (Table 4).

In a stratified analysis by congener, concentrations of the dioxins 2,3′,4,4′,5-pentachlorinated biphenyl (PenCB; IUPAC No. 118), 2,3,3′,4,4′-PenCB (IUPAC No. 105), and 2,3′,4,4′,5,5′-hexachlorinated biphenyl (HexCB; IUPAC No. 167) of the *AHR* (G>C, Arg554Lys) genotype model and dominant model showed a significant difference (genotype model [GG vs. GA] and dominant model GG vs. [GA+AA]): $P=0.008$ and $P=0.002$ for 2,3′,4,4′,5-PenCB (IUPAC No. 118) concentration; $P=0.009$ and $P=0.002$ for 2,3,3′,4,4′-PenCB (IUPAC No. 105) concentration; and $P=0.035$ and $P=0.011$ for 2,3′,4,4′,5,5′-HexCB (IUPAC No. 167) concentrations, respectively. Furthermore, 2,3,4,7,8-Pentachlorinated dibenzofuran (PeCDF) concentrations in the *CYP1A1* (T>C, *MspI*) genotype model and dominant model were significantly different (genotype model TT vs. CC and dominant model [TT+TC] vs. CC): $P=0.049$ and $P=0.028$, respectively (Fig. 1). In a stratified analysis by congener, TEQs of the dioxins, 2,3′,4,4′,5-PenCB (IUPAC No. 118), 2,3,3′,4,4′-PenCB (IUPAC No. 105), and 2,3′,4,4′,5,5′-HexCB (IUPAC No. 167) of the *AHR* (G>C, Arg554Lys) genotype model and dominant model were significantly different (genotype model GG vs. GA and dominant model GG vs. [GA+AA]): $P=0.008$ and $P=0.002$

Table 1
Characteristics of the study population in Sapporo, Hokkaido, Japan.

Characteristic	Value ($n=421$)[a]
Maternal age (years)	30.8 ± 4.7
Maternal height (cm)	158.2 ± 5.4
Maternal weight before pregnancy (kg)	53.2 ± 8.8
Caffeine intake during pregnancy (mg/day)	117.3 (1.5–646.3)
Alcohol intake during pregnancy	
Yes	128 (30.4%)
No	293 (69.6%)
Alcohol consumption of the drinkers (g/day)	1.2 (0.3–51.8)
Parity	
Primiparous	204 (48.5%)
Multiparous	217 (51.5%)
Maternal smoking status during pregnancy	
Yes	72 (17.1%)
No	349 (82.9%)
Education level (years)	
≤9	9 (2.1%)
10–12	168 (39.9%)
13–16	235 (55.8%)
≥17	9 (2.1%)
Annual household income (million yen)	
≤3	68 (16.2%)
4–5	209 (49.6%)
6–7	93 (22.1%)
8–10	44 (10.5%)
>10	7 (1.7%)
Inshore fish intake during pregnancy	
Never	20 (4.8%)
1–2 times/month	210 (49.9%)
1–2 times/week	167 (39.7%)
3–4 times/week	23 (5.5%)
Almost every day	1 (0.2%)
Deep-sea fish intake during pregnancy	
Never	12 (2.9%)
1–2 times/month	182 (43.2%)
1–2 times/week	201 (47.7%)
3–4 times/week	25 (5.9%)
Almost every day	1 (0.2%)
Blood sampling period	
During pregnancy	293 (69.6%)
Postpartum	128 (30.4%)

[a] Data are presented as *n* (%), mean ± standard deviation, or median (range).

Table 2
Genotype frequency of *AHR*, *AHRR*, *CYP1A1*, *CYP1A2*, and *CYP1B1* polymorphisms among pregnant women in Sapporo, Hokkaido, Japan.

Genotype	Pregnant women (n = 421) (%)
***AHR* (G>A, Arg554Lys, dbSNP ID: rs2066853)**	
GG	142 (33.7)
GA	195 (46.3)
AA	84 (20.0)
GG+GA	337 (80.0)
GA+AA	279 (66.3)
G allele	479 (56.9)
A allele	363 (43.1)
***AHRR* (C>G, Pro185Ala, dbSNP ID: rs2292596)**	
CC	145 (34.4)
CG	217 (51.5)
GG	59 (14.0)
CC+CG	362 (86.0)
CG+GG	276 (65.6)
C allele	507 (60.2)
G allele	335 (39.8)
***CYP1A1* (T>C, *MspI*, dbSNP ID: rs4646903)**	
TT	176 (41.8)
TC	201 (47.7)
CC	44 (10.5)
TT+TC	377 (89.5)
TC+CC	245 (58.2)
T allele	553 (65.7)
C allele	289 (34.3)
***CYP1A1* (A>G, Ile462Val, dbSNP ID: rs1048963)**	
AA	253 (60.1)
AG	150 (35.6)
GG	18 (4.3)
AA+AG	403 (95.7)
AG+GG	168 (39.9)
A allele	656 (77.9)
G allele	186 (22.1)
***CYP1A2* (A>C, *CYP1A2*1F*, dbSNP ID: rs762551)**	
AA	169 (40.1)
AC	191 (45.4)
CC	61 (14.5)
AA+AC	360 (85.5)
AC+CC	252 (59.9)
A allele	529 (62.8)
C allele	313 (37.2)
***CYP1B1* (C>G, Leu432Val, dbSNP ID: rs1056836)**	
CC	317 (75.3)
CG	95 (22.6)
GG	9 (2.1)
CC+CG	412 (97.9)
CG+GG	104 (24.7)
C allele	729 (86.6)
G allele	113 (13.4)

for 2,3′,4,4′,5-PenCB (IUPAC No. 118) concentration, P = 0.014 and P = 0.002 for 2,3,3′,4,4′-PenCB (IUPAC No. 105) concentration, and P = 0.043 and P = 0.013 for 2,3′,4,4′,5,5′-HexCB (IUPAC No. 167) concentration, respectively. Furthermore, 2,3,4,7,8-PeCDF TEQs of the *CYP1A1* (T>C, *MspI*) genotype model and dominant model were significantly different (genotype model TT vs. CC and dominant model [TT+TC] vs. CC): P = 0.045 and P = 0.028, respectively (Fig. 2).

In contrast, no significant differences were obtained for dioxin concentrations or TEQs among the *AHRR* (rs2292596), *CYP1A1* (rs1048963), *CYP1A2* (rs762551), and *CYP1B1* (rs1056836) polymorphisms (data not shown).

4. Discussion

Recent investigations from the "Hokkaido Study on Environment and Children's Health" have indicated that prenatal exposure to dioxins affects birth weight (Konishi et al., 2009), mental and motor development at the age of 6 months (Nakajima et al., 2006), and otitis media at the age of 18 months (Miyashita et al., 2011). Furthermore, maternal smoking and metabolism-related genes such as *AHR*, *CYP1A1*, *GSTM1*, NADPH dehydrogenase, quinine 1 (*NQO1*), methylenetetrahydrofolate reductase (*MTHFR*), and CYP2 subfamily E polypeptide 1 (*CYP2E1*) affect infant birth size (Sasaki et al., 2006, 2008; Yila et al., 2012).

TCDD is the most toxic of all dioxin compounds. TCDD is used as a standard to evaluate the TEF value of dioxins and dioxin-like congeners to indicate the degree of toxicity. This TEF is determined by the sensitivity of AHR (Van den Berg et al., 1998). Dioxins including TCDD are sensitive to AHR. Although the toxic effects of TCDD have been studied for several decades, the detailed molecular mechanisms are still poorly understood except for the TCDD-mediated transcriptional regulation of AHR and its binding with AHR nuclear translocator (Gim et al., 2010). TCDD accumulates in fatty tissue, stimulates AHR activation, and causes transcription of *CYP1A1*, *CYP1A2*, *CYP1B1*, and *AHRR* (Mimura and Fujii-Kuriyama, 2003). *CYP1A1* is the most potently induced gene following AHR activation (Barouki et al., 2007). CYP1A1 is associated with metabolic activation of hydrophobic molecules such as PCDDs (Ziegler, 1991). The catalytic activities of CYP1B1 overlap with those of CYP1A1 and CYP1A2 (Shimada et al., 1997).

TCDD modulates the induction of DNA strand breaks and poly(adenosine diphosphate ribose) polymerase-1 activation by 17β-estradiol in human breast carcinoma cells by altering CYP1A1 and CYP1B1 expression (Lin et al., 2008). CYP1A1 and CYP1B1 mediate the transformation of 17β-estradiol (E_2)/estrone (E_1) to the biologically active metabolites 2-hydroxyestradiol (2-OH-E_2) and 4-hydroxyestradiol (4-OH-E_2) (Hayes et al., 1996; Martucci and Fishman, 1993; Spink et al., 1997). TCDD enhances the biotransformation of E_2 to 2-OH-E_2 and 4-OH-E_2 in human MCF-7 breast cancer cells (Lavigne et al., 2001). Both 2-OH-E_2 and 4-OH-E_2 induce oxidative damage in purified DNA and break DNA into single strands (Miura et al., 2000; Lin et al., 2003). Cells treated with E_2 and 2-OH-E_2 exhibit a significant decrease in the estrogen-induced response (Gupta et al., 1998).

TCDD mediates estrogen receptor α (ERα) signaling in MCF-7 cells under moderately hypoxic conditions (Seifert et al., 2009). In the mouse uterus and in breast cancer cells, ERα levels are significantly lower after treatment with estradiol plus TCDD than with TCDD alone, indicating that AHR-mediated inhibition occurs by estradiol-induced transactivation. TCDD induces an interaction between AHR and ERα in the presence of estradiol (Wormke et al., 2003).

E_2-ERα inhibits thyroid-stimulating hormone, β subunit (*TSHβ*) expression (Nagayama et al., 2008). Transcriptional repression of *TSHβ* is specific to triiodothyronine (T_3) and its receptor. The proinflammatory cytokine interleukin-1β decreases transcription of the thyroid hormone receptor α gene in liver cells (Kwakkel et al., 2007).

An adequate supply of cerebral T_3 is needed by the fetus. Thyroid hormone-dependent neurodevelopment begins in the second half of the first trimester of pregnancy. The reserves of the fetal gland are low during this period, and thus most of the thyroid hormones needed by the fetus before birth are contributed by the mother (Skeaff, 2011). Effects that are due to a lack of thyroid hormones in pregnant women with poor dioxin-metabolizing enzyme activity may impair fetal brain development and contribute to hypothyroidism in the fetus.

To the best of our knowledge, this is the first study to show different dioxin blood levels in women with both *AHR* (rs2066853) and *CYP1A1* (rs4646903) polymorphisms. Activation mediated by AHR and CYP1A1 is an important mechanism for metabolizing dioxins. The homozygous *AHR* (rs2066853) variant genotype (AA) is associated with significantly lower mRNA expression of *AHR*, *ARNT*, and *CYP1B1* (Helmig et al., 2011). *AHR* AA may thus reduce AHR activity

Table 3
Adjusted means in the generalized linear model of total PCDDs, PCDFs, and dioxin-like PCBs among *AHR* polymorphisms (G > A, Arg554Lys, dbSNP ID: rs2066853) of pregnant women in Sapporo, Hokkaido, Japan.

Model[a]	GG[b]	GA[b]	AA[b]	GA + AA[b]	GG + GA[b]	*P*-value
Concentration (pg/g lipid)						
PCDDs						
Genotype[a]	478.5 (444.1–512.9)	519.7 (490.5–548.9)	526.3 (481.6–570.9)			0.097
Dominant[a]	478.5 (444.1–512.9)			521.7 (497.3–546.0)		0.047*
Recessive[a]			526.3 (481.6–570.9)		502.4 (480.3–524.5)	0.355
PCDFs						
Genotype[a]	19.2 (17.3–21.1)	21.0 (19.4–22.7)	20.2 (17.7–22.7)			0.365
Dominant[a]	19.2 (17.3–21.1)			20.8 (19.4–22.1)		0.189
Recessive[a]			20.2 (17.7–22.7)		20.3 (19.0–21.5)	0.968
Non-*ortho* PCBs						
Genotype[a]	74.6 (67.7–81.5)	83.4 (77.6–89.3)	86.1 (77.2–95.1)			0.079
Dominant[a]	74.6 (67.7–81.5)			84.2 (79.4–89.1)		0.028*
Recessive[a]			86.1 (77.2–95.1)		79.7 (75.3–84.2)	0.216
Mono-*ortho* PCBs						
Genotype[a]	11,266.3 (10,265.9–12,266.8)	13,146.5 (12,297.1–13,995.9)	12,948.9 (11,650.1–14,247.7)			0.016*
Dominant[a]	11,266.3 (10,265.9–12,266.8)			13,087.0 (12,379.6–13,794.4)		0.004*
Recessive[a]			12,948.9 (11,650.1–14,247.7)		12,356.1 (11,709.3–13,003.3)	0.434
Total dioxins						
Genotype[a]	11,838.7 (10,820.5–12,856.9)	13,770.7 (12,906.1–14,635.2)	13581.5 (12,259.1–14,904.3)			0.014*
Dominant[a]	11,838.7 (10,820.5–12,856.9)			13,713.7 (12,993.7–14,433.7)		0.004*
Recessive[a]			13581.5 (12,259.1–14,904.3)		12,958.9 (12,300.1–13,617.0)	0.419
TEQ (pg/g lipid)						
PCDDs						
Genotype[a]	7.003 (6.513–7.493)	7.465 (7.050–7.881)	7.472 (6.837–8.108)			0.323
Dominant[a]	7.003 (6.513–7.493)			7.467 (7.121–7.814)		0.132
Recessive[a]			7.472 (6.837–8.108)		7.271 (6.957–7.585)	0.583
PCDFs						
Genotype[a]	2.505 (2.342–2.668)	2.598 (2.460–2.736)	2.571 (2.359–2.782)			0.696
Dominant[a]	2.505 (2.342–2.668)			2.590 (2.475–2.705)		0.410
Recessive[a]			2.571 (2.359–2.782)		2.559 (2.455–2.664)	0.927
Non-*ortho* PCBs						
Genotype[a]	4.179 (3.769–4.590)	4.809 (4.460–5.157)	4.693 (4.160–5.226)			0.068
Dominant[a]	4.179 (3.769–4.590)			4.774 (4.484–5.064)		0.022*
Recessive[a]			4.693 (4.160–5.226)		4.544 (4.280–4.809)	0.633
Mono-*ortho* PCBs						
Genotype[a]	0.338 (0.308–0.368)	0.394 (0.369–0.420)	0.388 (0.350–0.427)			0.016*
Dominant[a]	0.338 (0.308–0.368)			0.393 (0.371–0.414)		0.004*
Recessive[a]			0.388 (0.350–0.427)		0.371 (0.351–0.390)	0.434
Total dioxins						
Genotype[a]	14.025 (13.056–14.995)	15.267 (14.443–16.090)	15.124 (13.865–16.383)			0.145
Dominant[a]	14.025 (13.056–14.995)			15.224 (14.538–15.910)		0.050
Recessive[a]			15.124 (13.865–16.383)		14.745 (14.121–15.369)	0.604

The generalized linear model was adjusted for maternal age, maternal height, maternal weight before pregnancy, caffeine intake during pregnancy, alcohol consumption during pregnancy, parity, maternal smoking status during pregnancy, maternal educational level, annual household income, inshore fish intake during pregnancy, deep-sea fish intake during pregnancy, and blood sampling period.

[a] Model types are as follows: Genotype, genotype model; Dominant, dominant genotype model; Recessive, recessive genotype model.

[b] 95% CI, 95% confidence interval.

* Statistically significant values ($P < 0.05$).

and decrease metabolism by CYP1. CYP1A1 activity is significantly higher in people with the CYP1A1 (rs4646903) TC or CC genotype (Landi et al., 1994). Dioxin levels may be influenced by CYP1A1 activity or CYP1A1 expression.

In our previous studies, we noted a decrease in birth weight of 231.5 g and 258.8 g with a 10-fold increase in the TEQ levels of total PCDDs and PCDFs, respectively (Konishi et al., 2009). In addition, total PCDD concentrations were significantly negatively associated with Bayley scales of infant development-II mental development index scores at 6 months of age [$\beta = -0.234$ was the point increase in development score per total PCDD level (natural logarithm)] (Nakajima et al., 2006). The odds ratio was 2.50 for otitis media for the 75–100th percentiles of TEQ (3.06–7.77 TEQ pg/g lipid) of total PCDFs increases as compared with the 0–25th percentiles of TEQ (0.64–1.79 TEQ pg/g lipid) (Miyashita et al., 2011). With respect to different polymorphisms, decreases in birth weight and length of 211 g and 1.2 cm, respectively, were noted for infants born to women who smoked during pregnancy with *AHR* (G > A,

Table 4
Adjusted means in the generalized linear model of total PCDDs, PCDFs, and dioxin-like PCBs among *CYP1A1* polymorphisms (T > C, *MspI*, dbSNP ID: rs4646903) of pregnant women in Sapporo, Hokkaido, Japan.

Model[a]	TT[b]	TC[b]	CC[b]	TC+CC[b]	TT+TC[b]	*P*-value[c]
Concentration (pg/g lipid)						
PCDDs						
Genotype[a]	529.8 (499.3–560.3)	497.2 (468.6–525.7)	461.9 (400.6–523.1)			0.097
Dominant[a]			461.9 (400.6–523.1)		512.4 (491.6–533.2)	0.127
Recessive[a]	529.8 (499.3–560.3)			490.9 (465.0–516.7)		0.057
PCDFs						
Genotype[a]	20.8 (19.1–22.5)	20.4 (18.8–21.9)	17.9 (14.4–21.3)			0.324
Dominant[a]			17.9 (14.4–21.3)		20.5 (19.4–21.7)	0.144
Recessive[a]	20.8 (19.1–22.5)			19.9 (18.5–21.3)		0.454
Non-*ortho* PCBs						
Genotype[a]	85.5 (79.4–91.6)	78.6 (72.9–84.3)	74.0 (61.6–86.3)			0.139
Dominant[a]			74.0 (61.6–86.3)		81.8 (77.6–86.0)	0.240
Recessive[a]	85.5 (79.4–91.6)			77.8 (72.6–83.0)		0.061
Mono-*ortho* PCBs						
Genotype[a]	12,748.0 (11,851.9–13,644.0)	12,354.8 (11,517.0–13,192.7)	11,911.9 (10,112.4–13,711.4)			0.666
Dominant[a]			11,911.9 (10,112.4–13,711.4)		12,538.3 (11,928.2–13,148.3)	0.518
Recessive[a]	12,748.0 (11,851.9–13,644.0)			12,275.6 (11,517.7–13,033.5)		0.431
Total dioxins						
Genotype[a]	13,384.0 (12,472.0–14,296.1)	12,951.0 (12,098.2–13,803.8)	12,465.6 (10,634.0–14,297.2)			0.623
Dominant[a]			12,465.6 (10,634.0–14,297.2)		13,153.0 (12,532.0–13,774.1)	0.486
Recessive[a]	13,384.0 (12,472.0–14,296.1)			12,864.1 (12,092.7–13,635.6)		0.394
TEQ (pg/g lipid)						
PCDDs						
Genotype[a]	7.616 (7.183–8.049)	7.225 (6.821–7.630)	6.480 (5.611–7.349)			0.062
Dominant[a]			6.480 (5.611–7.349)		7.408 (7.113–7.703)	0.048*
Recessive[a]	7.616 (7.183–8.049)			7.092 (7.182–8.049)		0.072
PCDFs						
Genotype[a]	2.653 (2.510–2.797)	2.545 (2.411–2.680)	2.267 (1.978–2.555)			0.061
Dominant[a]			2.267 (1.978–2.555)		2.596 (2.498–2.694)	0.035*
Recessive[a]	2.653 (2.510–2.797)			2.495 (2.373–2.617)		0.103
Non-*ortho* PCBs						
Genotype[a]	4.730 (4.363–5.096)	4.496 (4.154–4.839)	4.300 (3.564–5.035)			0.490
Dominant[a]			4.300 (3.564–5.035)		4.605 (4.356–4.855)	0.441
Recessive[a]	4.730 (4.363–5.096)			4.461 (4.152–4.771)		0.273
Mono-*ortho* PCBs						
Genotype[a]	0.382 (0.356–0.409)	0.371 (0.346–0.396)	0.357 (0.303–0.411)			0.666
Dominant[a]			0.357 (0.303–0.411)		0.376 (0.358–0.394)	0.518
Recessive[a]	0.382 (0.356–0.409)			0.368 (0.346–0.391)		0.431
Total dioxins						
Genotype[a]	15.381 (14.521–16.242)	14.638 (13.833–15.442)	13.403 (11.676–15.131)			0.111
Dominant[a]			13.403 (11.676–15.131)		14.985 (14.398–15.571)	0.090
Recessive[a]	15.381 (14.521–16.242)			14.417 (13.688–15.146)		0.095

[a] Model types are as follows: Genotype, genotype model; Dominant, dominant genotype model; Recessive, recessive genotype model.
[b] 95% CI, 95% confidence interval.
* Statistically significant values ($P < 0.05$).

Arg554Lys) GG as compared with those born to women who did not smoke during pregnancy with *AHR* GA + AA. Decreases in birth weight and length of 170 g and 0.8 cm, respectively, were noted for infants born to women who smoked during pregnancy with *CYP1A1* (T > C, *MspI*) TC + CC as compared with those born to women who did not smoke during pregnancy with *CYP1A1* TT. Decreases in birth weight and length of 315 g and 1.7 cm, respectively, were noted for infants born to women who smoked during pregnancy with *AHR* GG, *CYP1A1* TC + CC as compared with those born to women who did not smoke during pregnancy with *AHR* GA + AA, *CYP1A1* TT (Sasaki et al., 2006).

In 82 children aged 6–10 years who were attending schools near an industrial area in Mexico, Sánchez-Guerra et al. (2012) investigated the association among *CYP1A1*2C*, *CYP1B1*3*, *GSTM1*0*, and *GSTT1*0* polymorphisms, urinary 1-hydroxypyrene (1-OHP; a biomarker of polycyclic aromatic hydrocarbon exposure), and DNA adducts. They observed higher urinary 1-OHP concentrations in those with *CYP1A1*2C* AG + GG as compared with those with *CYP1A1*2C* AA (0.23 μmol/mol creatinine for AA vs. 0.45 μmol/mol creatinine for AG + GG).

In human full-term placental trophoblast cultures, after archetype AHR ligands/activators (2,3,7,8-TCDD and

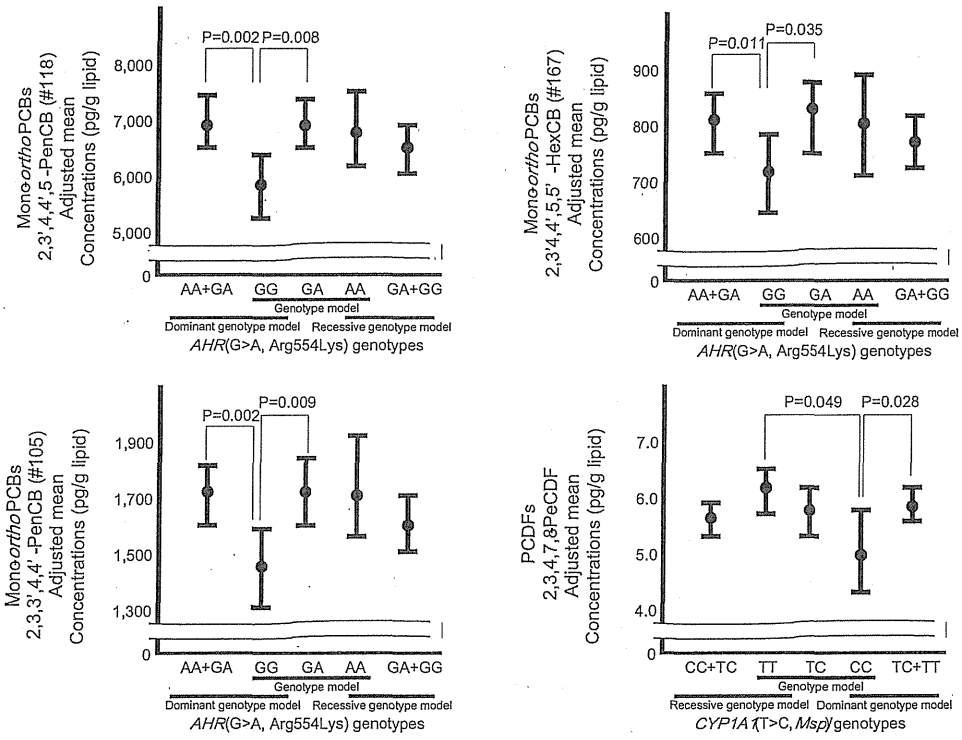

Fig. 1. Concentrations for 2,3',4,4',5-PenCB (IUPAC No. 118), 2,3,3',4,4',-PenCB (IUPAC No. 105), 2,3',4,4',5,5'-HexCB (IUPAC No. 167) and 2,3,4,7,8-PeCDF in the generalized linear model of dioxin congeners among *AHR* and *CYP1A1* polymorphisms of pregnant women in Sapporo, Hokkaido, Japan.
Dots and bars are the adjusted means and 95% confidence intervals, respectively. The means were adjusted for maternal age, maternal height, maternal weight before pregnancy, caffeine intake during pregnancy, alcohol consumption during pregnancy, parity, maternal smoking status during pregnancy, maternal educational level, annual household income, inshore fish intake during pregnancy, deep-sea fish intake during pregnancy, and blood sampling period in the generalized linear model.

3-methylcholanthlene) were added, CYP1A1 mRNA, but not CYP1A2, CYP1B1, AHR, or AHRR mRNA, was significantly induced (Stejskalova et al., 2011). In the present study, dioxin-like PCB concentrations and TEQ were associated with a significant reduction in the frequency of *AHR* (G>A, Arg554Lys) GA+AA as compared with GG. PCDFs were associated with a significant reduction in the frequency of CYP1A1 (T>C, *MspI*) TC+CC as compared with TT. After adjusting for smoking status during pregnancy, changes in dioxin concentrations and TEQ were significantly decreased in association with *AHR* and *CYP1A1* polymorphisms, but not with *AHRR*, *CYP1A2*, or *CYP1B1*. Compared with previous studies by Sasaki et al. (2006), Sánchez-Guerra et al. (2012), and Stejskalova et al. (2011), we observed statistically significant differences only in *AHR* and *CYP1A1*, and not in *AHRR*, *CYP1A2*, or *CYP1B1*, which is similar to the previous three reports. It may be that the chemical effects of tobacco smoke, which include polycyclic aromatic hydrocarbons, are more important confounding factors for *AHR* and *CYP1A1* genotypes in pregnant women who are exposed to low levels of dioxins. However, the importance of associations between the *AHR* (G>A, Arg554Lys) or *CYP1A1* (T>C, *MspI*) genotype and dioxin concentrations in humans remains unclear. In our study, we observed differences of ~1.1-fold in dioxin TEQs and concentrations according to genotypes. Based on our previous study (Konishi et al., 2009), changes in birth weight of about −20 to −25 g (maximum levels) will predict a 1.1-fold increase in the levels of dioxins. For pregnant Japanese women, TEQs of 2,3',4,4',5-PenCB (IUPAC No. 118), 2,3,3',4,4'-PenCB (IUPAC No. 105), and 2,3',4,4',5,5'-HexCB (IUPAC No. 167) showed significant differences in the *AHR* genotypes. The metabolism and pharmacokinetics of 2,3',4,4',5-PenCB (IUPAC No. 118), 2,3,3',4,4'-PenCB (IUPAC No. 105), and 2,3',4,4',5,5'-HexCB (IUPAC No. 167) are unclear in humans, but some mouse studies have been performed. Typically, one dose–response relationship was observed for induction of CYP1A1 and CYP1A2 enzyme activity. The relative potency differs by an order of magnitude in female mice following subchronic exposure to 2,3,3',4,4'-PenCB (IUPAC No. 105) (DeVito et al., 2000). Neither spleen weight nor thymus weight changes, but the liver weight is significantly increased by 2,2',4,4',5,5'-HexCB treatment in pregnant mice (Mattsson et al., 1981).

The TEQ of 2,3,4,7,8-PeCDF showed significant differences for the *CYP1A1* (rs4646903) genotypes. The pharmacokinetics of 2,3,4,7,8-PeCDF have been studied in humans. In Yucheng patients in Taiwan who had been exposed to high levels of 2,3,4,7,8-PeCDF, this dioxin was the greatest contributor to the toxic effects because it accounted for 70% of the total dioxin TEQ in maternal blood (Masuda, 2001). Matsueda et al. (2007) examined the dioxin levels and congener distributions in blood samples of Yusho patients in Japan and normal controls, especially in relation to their respective exposure routes. They reported that the absorptivity and rate of metabolism and elimination for dioxin congeners depend on the exposure source. Further work is needed to confirm these findings for *AHR* and *CYP1A1* in dioxin congener studies in humans, especially in pregnant women, because chronic exposure to low levels of 2,3',4,4',5-PenCB (IUPAC No. 118), 2,3,3',4,4'-PenCB (IUPAC No. 105), 2,3',4,4',5,5'-HexCB (IUPAC No. 167), and 2,3,4,7,8-PeCDF in the environment could be causally confirmed by epidemiological studies.

Although genetic polymorphisms cannot be changed, adverse health effects of dioxins could be prevented by modulating exposure levels, especially among individuals with increased genetic susceptibility, because dioxins may be a modifiable environmental pollutant. For example, one way to reduce dioxin exposure in

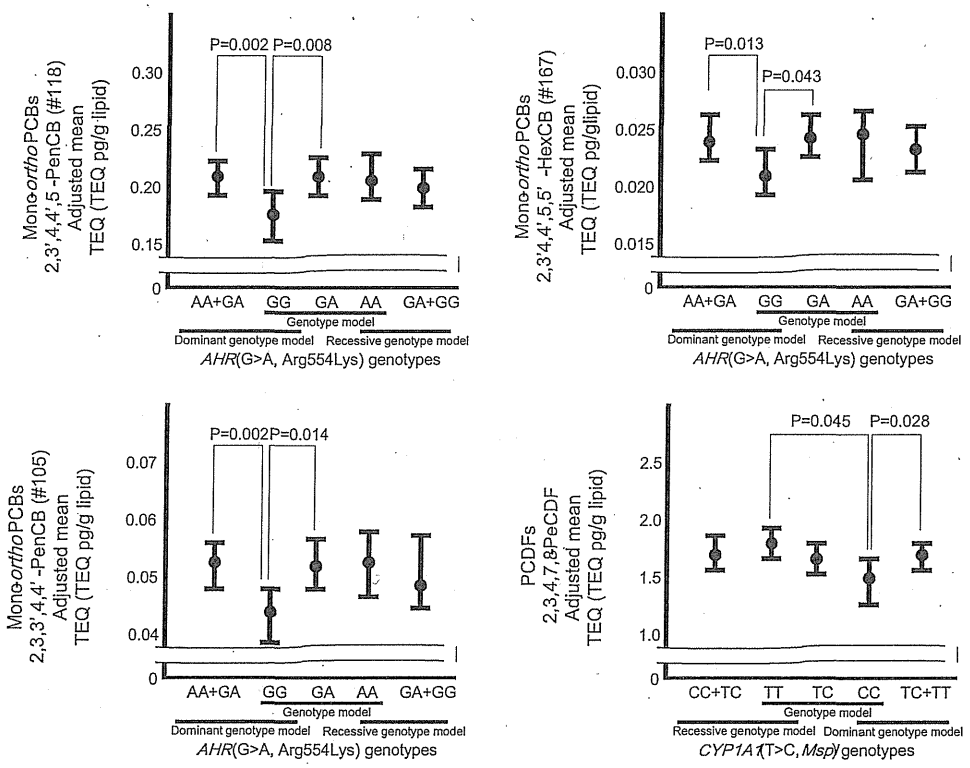

Fig. 2. TEQs for 2,3′,4,4′,5-PenCB (IUPAC No. 118), 2,3,3′,4,4′,-PenCB (IUPAC No. 105), 2,3′,4,4′,5,5′-HexCB (IUPAC No. 167) and 2,3,4,7,8-PeCDF in the generalized linear model of dioxin congeners among *AHR* and *CYP1A1* polymorphisms of pregnant women in Sapporo, Hokkaido, Japan.
Dots and bars are the adjusted means and 95% confidence intervals, respectively. The means were adjusted for maternal age, maternal height, maternal weight before pregnancy, caffeine intake during pregnancy, alcohol consumption during pregnancy, parity, maternal smoking status during pregnancy, maternal educational level, annual household income, inshore fish intake during pregnancy, deep-sea fish intake during pregnancy, and blood sampling period in the generalized linear model.

pregnant women is to minimize consumption of inshore fishes such as horse mackerels and sardines, which contain large quantities of dioxin.

The main strength of this study is that the dioxin concentrations were very accurate because we used highly sensitive methods for dioxin measurement. The present study also has a few limitations. First, we did not measure any metabolites of dioxins or placental AHR and CYP1A1 activity. Some metabolites are produced from one dioxin congener, and distinguishing the metabolites from the congeners was difficult. Thus, we could not measure them. Second, the functional consequences of the Pro/Ala substitution in *AHRR* remain largely unknown. A novel human AHRR complementary DNA that lacks the exon with the Pro185Ala polymorphism represses AHR (Karchner et al., 2009), but further studies are needed to confirm whether this mutation has any functional consequences.

In the present study, differences in dioxin blood concentrations were relatively low. Despite this, partial differences in health effects may exist, depending on the genetic polymorphism. Consequently, further longitudinal cohort studies should be carried out to confirm our findings. Moreover, further studies are also needed to investigate the effects of dioxins on developing school-age children. We are currently following the children of the mother–infant pairs in our study up to school age to determine whether exposure to low levels of dioxins during gestation affects their neurodevelopment, growth or risk of developing allergies. The results are forthcoming. We will also focus our attention not only on dioxin-metabolizing genes but also on the effects of polymorphisms on sex hormone production. Additional molecular and genetic epidemiological studies are needed to further elucidate the effects of both environmental and genetic factors in humans in the current and subsequent generations.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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