Polymorphisms in Gene *UGT1A1* Modify the Association of Prenatal Exposure to Polycyclic Aromatic Hydrocarbons With Congenital Heart Diseases Risk

Jing Tao
National Office for Maternal and Child Health Surveillance of China, Sichuan University
Nana Li
National Office for Maternal and Child Health Surveillance of China, Sichuan University
Zhen Liu
National Office for Maternal and Child Health Surveillance of China, Sichuan University
Ying Deng
National Office for Maternal and Child Health Surveillance of China, Sichuan University
Xiaohong Li
National Office for Maternal and Child Health Surveillance of China, Sichuan University
Fangfang Luo
Meishan maternal and child health care hospital, Sichuan, China.
Yanna Zou
Changyi maternal and child health care hospital
Ping Yu
National Office for Maternal and Child Health Surveillance of China, Sichuan University
Jun Zhu
zhujun028@163.com

National Office for Maternal and Child Health Surveillance of China, Sichuan University

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Abstract

Background: Previous studies have focused on the effect of polycyclic aromatic hydrocarbons (PAHs) exposure on the risk of congenital heart diseases (CHDs), but generated inconsistent conclusions. Genetic susceptibility to PAHs metabolism may modify the exposure-risk relationship.

Methods: Maternal urinary biomarker of PAHs exposure was determined in 357 pregnant women with CHDs fetuses and 270 pregnant women with controls. Maternal genotyping was conducted in *UGT1A1* (rs3755319, rs887829, rs4148323, rs6742078, rs6717546). Unconditional logistic regression was performed to determine the impacts of *UGT1A1* polymorphisms on the risks of CHDs and its subtypes. Generalized multifactor dimensionality reduction (GMDR) was used to analyze the gene-gene and gene-PAHs exposure interactions.

Results: None of the selected *UGT1A1* polymorphisms were independently associated with the risk of CHDs. The interaction between rs4148323 and PAHs exposure was observed to be associated with CHDs ($p<0.05$). Pregnant women with high-levels PAHs exposure and carrying rs4148323 increased the risk of CHDs (GA-AA: aOR =2.00, 95% CI = 1.06-3.79). Moreover, the joint effect of rs4148323 and PAHs exposure was found to be significantly associated with risks of septal defects, conotruncal heart defects and right-sided obstructive malformations.

Conclusions: Maternal genetic variation of *UGT1A1* rs4148323 may modify the impact of prenatal PAHs exposure on CHDs risk. This finding needs to be further confirmed in a larger scale study.

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants that are derived mostly from the incomplete combustion of tobacco, coal and other organic substances[1]. Exposed to PAHs is widespread for human beings through multiple routes such as inhalation of cigarette smoke or polluted air, and ingestion of food containing PAHs[2]. Concern on fetal hazards including congenital defects and intrauterine growth restriction after maternal exposure to PAHs has been raised[3–5].

Congenital heart diseases (CHDs) are among the most common of all human congenital defects. Growing evidences have indicated that PAHs can increase the risk of CHDs. Animal studies have shown that prenatal exposure to PAHs increases the occurrence of CHDs[6, 7]. Some epidemiological studies have also found women with prenatal exposure to PAHs are more likely to have offspring with CHDs such as conotruncal heart defects and septal defects[8], but a population-based study has shown null association[9]. Thus, we hypothesize that genetic variations such as metabolic enzyme gene polymorphisms influencing PAHs may partly be accountable for the inconsistent conclusions.

Some metabolic enzyme genes such as cytochrome P450 1A1 (*CYP1A1*) and uridine diphosphoglucuronosyl transferase 1A1 (*UGT1A1*) have been reported to modulate the metabolism and activation of PAHs[10, 11]. Human studies have also observed that *CYP1A1* and *UGT1A1* gene

polymorphisms significantly affect the concentrations of urinary 1-hydroxypyrene (1-OHP) as a biomarker of polycyclic aromatic hydrocarbons (PAHs) exposure[12, 13]. Moreover, maternal genotypes such as *CYP1B1* polymorphisms have been shown to modify the association between maternal exposure to PAHs and CHDs risk[14]. However, the implications of *UGT1A1* genetic polymorphisms in modulating the impacts of prenatal of PAHs exposure on the risk of CHDs remain undiscovered.

Here we utilized an established case-control study examining the impact of maternal PAHs exposure on the risk of CHDs, where prenatal PAHs exposure was associated with increased risk of CHDs[14]. This study aimed to explore whether maternal *UGT1A1* (rs3755319, rs887829, rs4148323, rs6742078, rs6717546) polymorphisms modified the association of CHDs risk with PAHs exposure.

Materials And Methods

Study participants and data collection

All pregnant women were selected from an established case-control study examining the impacts of maternal PAHs exposures on the risk of CHDs[14]. In brief, cases were having fetuses diagnosed with CHDs (without any extracardiac abnormalities), while controls in the same hospital were having fetuses with no major congenital malformations. Pregnancies with multiple births and fetuses diagnosed with chromosomal aberrations and syndromic diseases were excluded. All CHDs cases were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. CHDs cases based on the anatomic lesions were also classified into six subgroups: septal defects, conotruncal heart defects, left-sided obstructive malformations, right-sided obstructive malformations, anomalous pulmonary venous return, and other heart abnormalities[15]. The well-trained investigators administered a face-to-face interview with each pregnant woman at enrollment. Information on demographic characteristics, living environment, lifestyle habits, maternal reproductive history, maternal illness and drug use history, maternal diet and nutrition were collected by the trained investigators.

PAH exposure assessment

Urine samples from each pregnant woman were collected and stored at − 70°C until analysis. The 1-hydroxypyrene-glucuronide (1-OHPG) in urine is a sensitive exposure biomarker for low-level PAHs exposure[16]. Thus, urinary 1-OHPG concentration was determined using liquid chromatograph system/tandem mass spectrometer mode as described elsewhere[14]. We used urine creatinine (cr) contents to adjust the concentration of 1-OHPG[17]. Moreover, the level of PAHs exposure was categorized into two groups (high and low exposure groups) according to the established the optimal cutoff value of 1-OHPG (0.03μg/g Cr) in our previous study[14].

Polymorphism selection and genotyping

Blood samples from each pregnant woman were collected and stored at − 70°C. Genomic DNA was extracted using a QIAamp^{R} DNA Blood Mini Kit (Qiagen, Cat. No. 51106, Germany). DNA samples were then stored at -80°C before further analysis. In our analysis, selection of single nucleotide polymorphisms (SNPs) in the *UGT1A1* gene was in accordance with the following criteria: (1) previously reported to be significantly associated with some diseases or PAHs metabolism [18–22]. (2) minor allele frequency (MAF) of at least 0.05 in Chinese Han population. Five SNPs (rs3755319, rs887829, rs4148323, rs6742078, rs6717546) were selected in the *UGT1A1* gene.

SNP genotyping was further performed using an improved multiplex ligation detection reaction (iMLDR) technique (Genesky Biotechnologies Inc., Shanghai, China). For quality control, we randomly selected 10% of samples to monitor the reproducibility of the assays, and the concordance was 100%. Five cases and one control failed to be genotyped for *UGT1A1* rs6717546. More detailed information about the studied *UGT1A1* polymorphisms is provided in Additional file Table S1.

Statistical analysis

Descriptive statistics for maternal and fetal characteristics of the study participants were conducted. Parametric and nonparametric methods were respectively used to test the statistical significance for differences in categorical or continuous variables. Deviation from Hardy–Weinberg equilibrium (HWE) expectation in controls was analyzed by chi-square test, and $p < 0.05$ indicated a deviation from equilibrium. We first utilized unconditional logistic regression analysis to investigate the associations of maternal *UGT1A1* polymorphisms with CHDs risk. The associations of *UGT1A1* genotypes with CHDs risk were also stratified by specific CHD subtypes. For genotype comparisons, homozygous wildtype served as the reference group to which heterozygotes and variant homozygotes were compared. Then, testing for gene-gene and gene-PAHs exposure interactions associated with CHDs was performed using generalized multifactor dimensionality reduction (GMDR, version 0.7, University of Virginia, USA), a test that detects and characterizes non-linear interactions among discrete genetic and environmental attributes[23]. Meanwhile, the identified effects of gene-PAHs exposure on the risks of CHDs and its subtypes were further analyzed by logistic regression, in order to obtain the aOR and 95% CI. All logistic regression analyses were adjusted for maternal age (years; continuous), gestational week (weeks; continuous), housing renovation, exposure to a factory or landfill (< 1000 meters), cooking at home (≥ 4 times/week), parental smoking or environmental tobacco smoke (ETS) exposure, maternal alcohol consumption (≥ 1 time(s)/week), and use of folic acid supplements. Two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were calculated using Stata version 14.2 (Stata Corp LP., College Station, United States of America).

Results

Characteristics of participants

A total of 627 pregnant women (357 with CHDs fetuses and 270 controls) were enrolled in our study. Table 1 summarizes maternal and fetal characteristics of the study participants. Data on the environmental characteristics of the cases and controls revealed no significant differences, with the exception of cooking at home and folic acid supplement. Meanwhile, urinary 1-OHPG concentrations were significantly higher in cases ($P < 0.001$). In fetuses with CHDs, septal defects were the most frequent malformations (65.83%), followed by conotruncal heart defects (44.82%) and right-sided obstructive malformations (31.93%).

Table 1
Maternal and fetal characteristics among the study subjects

Characteristic	Controls (n = 270)	Cases (n = 357)	*P* values
Maternal characterisics			
Maternal age (yrs) [a]	29 (26, 32)	28 (25,31)	0.010
Gestational week (week) [a]	23 (18, 25)	25 (23,27)	< 0.001
Housing renovation[b], n (%)	52 (19.26)	79 (22.13)	0.381
Factory or landfill nearby[b], n (%)	37 (13.70)	56 (15.69)	0.489
Cooking at home[b], n (%)	122 (45.19)	203 (56.86)	0.004
Parental smoking or ETS exposure[b], n (%)	155 (57.41)	223 (62.46)	0.200
Maternal alcohol consumption[b], n (%)	8 (2.96)	6 (1.68)	0.282
Folic acid supplements, n (%)	240 (88.89)	297 (83.19)	0.044
Urinary 1-OHPG levels (μg/g Cr)[a]	0.32 (0.06, 0.74)	0.42 (0.15, 0.88)	0.006
Fetal characterisics (CHDs Subgroups)			
Septal defects		235 (65.83)	
Conotruncal heart defects, n (%)		160 (44.82)	
Right-sided obstructive malformations, n (%)		114 (31.93)	
Left-sided obstructive malformations, n (%)		72 (20.17)	
Anomalous pulmonary venous return, n (%)		64 (17.93)	
Other cardiac structural abnormalities, n (%)		102 (28.57)	
ETS = environmental tobacco smoke			
[a] : Distribution was skewness, then Wilcoxon rank sum Z test was used, and described as interquartile range P50 (P25, P75)			
[b] : The exposure was defined from the 3 months before pregnancy to the first trimester			

Association of *UGT1A1* polymorphisms with CHDs

For all five polymorphisms (rs3755319, rs887829, rs4148323, rs6742078, rs6717546) in *UGT1A1*, the distribution of the genotypes conformed well to the Hardy-Weinberg equilibrium (see Additional file Table

S2). No significant association of *UGT1A1* polymorphism with CHDs was found (Table 2). The rs4148323 genotypes with at least one A allele showed an increased risk of right-sided obstructive malformations (see Additional file Table S3), however, it was of borderline significance (aOR = 1.58, 95% CI = 0.95–2.63).

Table 2
Association between maternal *UGT1A1* polymorphisms and the risk of CHDs

Genotype	Controls(n(%))	Cases(n(%))	aOR [a] (95%CI)
rs3755319			
AA	123 (45.56)	152 (42.58)	Ref
A/C-C/C	147 (54.44)	205 (57.42)	1.12 (0.79, 1.58)
rs887829			
CC	214 (79.26)	286 (80.11)	Ref
C/T-T/T	56 (20.74)	71 (19.89)	0.98 (0.64, 1.50)
rs4148323			
GG	193 (71.48)	263 (73.67)	Ref
G/A-A/A	77 (28.52)	94 (26.33)	1.07 (0.73, 1.57)
rs6742078			
GG	212 (78.52)	284 (79.55)	Ref
G/T-T/T	58 (21.48)	73 (20.45)	0.94 (0.61, 1.44)
rs6717546[b]			
GG	117 (43.33)	143 (40.06)	Ref
G/A-A/A	152 (56.30)	209 (58.54)	0.92 (0.66, 1.28)

aOR = adjusted odds ratio, CI = confidence interval

[a] : Adjusted for maternal age, gestational week, housing renovation, factory or landfill nearby, cooking at home, parental smoking or ETS exposure, maternal alcohol consumption, folic acid supplements.

[b] : Five cases and one control failed to be genotyped for *UGT1A1* rs6717546.

Gene-Gene and Gene-Environment Interaction

We used GMDR to screen for the best interaction combination among five polymorphisms of the *UGT1A1* gene (Table 3). A meaningful model involving rs4148323 and PAHs exposure was observed ($p < 0.05$). Overall, the cross-validation consistency of this model was 10/10, and the testing accuracy was 0.5698

(P < 0.05). It indicated that there was a potential interaction between rs4148323 and PAHs exposure influencing CHDs risk. Although *UGT1A1* rs4148323 was not associated with CHDs, pregnant women carrying A allele of rs4148323 had a significantly increased risk of CHDs in the high-levels PAHs exposure (aOR = 2.00, 95% CI = 1.06–3.79) (Table 4). Moreover, women with high-levels PAHs exposure and carrying rs4148323 increased risks of septal defects, conotruncal heart defects and right-sided obstructive malformations (see Additional file Table S4).

Table 3
Gene-gene and gene-PAHs exposure interaction models in CHDs obtained using the GMDR method

Interaction models	TBA1	TBA2	CVC	*P* value
Gene-gene interaction				
SNP1 SNP5	0.5377	0.4487	7/10	0.99
SNP1 SNP3 SNP5	0.5480	0.4314	7/10	1.00
SNP1 SNP3 SNP4 SNP5	0.5599	0.4260	10/10	1.00
SNP1 SNP2 SNP3 SNP4 SNP5	0.5605	0.4197	10/10	1.00
Gene-PAHs exposure interaction				
SNP3 PAHs	0.5711	0.5698	10/10	0.01
SNP3 SNP5 PAHs	0.5753	0.5308	4/10	0.05
SNP1 SNP3 SNP5 PAHs	0.5944	0.5185	10/10	0.38
SNP1 SNP3 SNP4 SNP5 PAHs	0.6060	0.4940	10/10	0.38
SNP1 SNP2 SNP3 SNP4 SNP5 PAHs	0.6069	0.4908	10/10	0.38
SNP1: rs3755319; SNP2: rs887829; SNP3: rs4148323; SNP4: rs6742078; SNP5: rs6717546.				
TBA1: training balanced accuracy; TBA2: testing balanced accuracy; CVC: cross-validation consistency				

Table 4
The interaction between maternal PAHs exposure and *UGT1A1* rs4148323 influencing CHDs based on additive model

rs4148323	PAHs exposure	Controls (n(%))	Cases (n(%))	aOR [a] (95%CI)
G/G	low	41 (15.19)	29 (8.12)	Ref.
	high	152 (56.30)	234 (65.55)	1.74 (0.98, 3.06)
G/A-A/A	low	21 (7.78)	14 (3.92)	0.91 (0.37, 2.22)
	high	56 (20.74)	80 (22.41)	2.00 (1.06, 3.79)
aOR = adjusted odds ratio, CI = confidence interval				
[a] : Adjusted for maternal age, gestational week, housing renovation, factory or landfill nearby, cooking at home, parental smoking or ETS exposure, maternal alcohol consumption, folic acid supplements.				

Discussion

Congenital heart diseases (CHDs) ranks the leading cause of birth defect-related mortality[24]. To date, the etiology of CHDs has not been completely understood. It is widely believed that most CHDs are caused by a complex combination of genetic and environmental factors[25]. Our study investigated an underlying role of *UGT1A1* gene on a previously identified association between PAHs exposure and CHDs risk[14]. In the current study, we found the association of PAHs exposure with CHDs risk was modified by rs4148323 polymorphism in the *UGT1A1* gene.

The uridine diphosphoglucuronosyltransferases (UGTs) belong to a superfamily of metabolizing enzymes participating in detoxifying endogenous and exogenous compounds such as steroid hormones, xenobiotics and drugs[26, 27]. Several polymorphisms in *UGT1A1* gene can affect expression and activity of encoded enzymes[27, 28]. In recent years, several studies have reported the associations of *UGT1A1* gene variations such as rs4148323 and rs887829 with diseases risks, including neonatal hyperbilirubinemia and cancer. Two meta-analysis studies have shown that rs4148323 polymorphism is a risk factor of developing neonatal hyperbilirubinemia in the Asian population, but not in the Caucasian population [21, 29]. For rs887829 polymorphism, one case-control study showed it reduces the risk of neonatal hyperbilirubinemia[18], but no association was observed with risks of endometrial cancer and gallstone[19, 30].

So far, there is limited research evaluating the impact of other *UGT1A1* polymorphisms (rs3755319, rs6742078 and rs6717546) on disease risk. No significant association with progression-free survival or overall survival was observed with rs3755319 polymorphism in irinotecan-treated colorectal cancer patients[31]. As for rs6742078, it reduces the risk of new-onset type 2 diabetes in a Dutch population[20], but increases gallstone risk in German and Indian populations[30, 32]. As for rs6717546, a retrospective

case control study found it is likely a protective factor against neonatal hyperbilirubinemia[18]. However, none of *UGT1A1* polymorphisms was detected to be associated with the risk of CHDs in our study. We speculated that the heterogeneity observed between various diseases may be related to different expression of UGT1A1 in diverse organ sites, and affected by gene-environmental interactions.

The interaction of gene-environment has been investigated to explore the etiology of various diseases in previous studies. A meta-analysis has shown that *UGT1A1* rs4148323 polymorphism increased the risk of severe neutropenia in the low dose of irinotecan (GA + AA vs. GG: OR = 2.66, 95% CI = 1.10–6.45, P = 0.03) [33]. Another study in Japan found the effect of rs4148323 polymorphism on neonatal hyperbilirubinemia is observed in neonates with 5% or greater maximal body weight loss, increasing with the degree of maximal body weight loss[34]. However, a population-based study failed to find the joint effect of *UGT1A1* rs887829 and soy food intake on the risk of endometrial cancer[19]. In our study, we demonstrated that maternal *UGT1A1* rs4148323 was associated with increased CHDs risk in the high-levels PAHs exposure. Thus, it can be speculated that the inconsistency of conclusions of the association between PAHs exposure and CHDs might partly be the role of rs4148323 in the *UGT1A1* gene. Given the relatively limited sample size, our finding is needs to be further confirmed.

Our study had several strengths. The study was the first to evaluate the effect of maternal *UGT1A1* genetic polymorphisms on the risks of CHDs and its subtypes. Secondly, we used 1-OHPG in urine as a quantitative biomarker for estimating prenatal exposure to PAHs. Third, we examined the interactions of gene-gene and gene-PAHs exposure in CHDs by using the method of GMDR. However, several limitations should be noticed. First, limited sample size and multiple comparisons reduced statistical power to evaluate the risk of CHDs with *UGT1A1* genetic polymorphisms and their combination with PAHs exposure. Second, a single spot urine measurement cannot precisely estimate the mother's long-term exposure level. Thus, future studies are needed to collect multiple urine samples. Third, fetal genotypes were not considered, and future studies are needed to investigate the effects of maternal and fetal genotypes, and gene-exposure interaction on the risk of CHDs.

Conclusion

Our study indicates that maternal genetic variation of *UGT1A1* rs4148323 modified the association between PAHs exposure and CHDs. A more comprehensive, larger scale study is needed to further detect other genetic polymorphisms and gene-exposure interactions with respect to CHDs risk.

Abbreviations

PAHs: Polycyclic aromatic hydrocarbons, CHDs: Congenital heart diseases, UGT1A1: Uridine diphosphoglucuronosyl transferase 1A1, 1-OHPG: 1-hydroxypyrene-glucuronide, SNPs: Single nucleotide polymorphisms, GMDR: Generalized multifactor dimensionality reduction, TBA1: Training balanced accuracy , TBA2: Testing balanced accuracy, CVC: Cross-validation consistency, HWE: Hardy–Weinberg equilibrium, aOR: adjusted odds ratio, CI: Confidence interval

Declarations

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Author contributions

Ping Yu, Jun Zhu, Fangfang Luo and Yanna Zou conceived of the study, participated in its design. Zhen Liu, Ying Deng, and Xiaohong Li performed data analyses. Jing Tao and Nana Li drafted the manuscript. All authors approved and agreed to be responsible for all aspects of the work ensuring integrity and accuracy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted under the approval of the Ethics Committee of Sichuan University (No. 2010004) and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

Consent for publication

All authors have read and approved the content, and agree to submit it for consideration for publication in your journal.

Competing interests

The authors declare that they have no competing interests.

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