Association of cytochrome P450 2C19 *2 and *3 variants with type 2 diabetes mellitus in Chinese population

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Background: Cytochrome P450 2C19 is a very important drug metabolizing enzyme. Meanwhile, CYP2C19 involved in the biosynthesis and metabolism of steroids, cholesterol, and other lipids. The current study aimed to estimate the association of CYP2C19 genotype with the risk of type 2 diabetes.

Methods: A total of 226 patients with glycometabolism disorder (GMD) and 349 volunteers with normal glucose metabolism (NGM) were genotyped for the CYP2C19 *1/*2/*3 using a BaiO^{TM} gene microarrays system.

Results: CYP2C19 double mutation genotype (*2/*2, *3/*3, *2/*3) in the type 2 diabetes group are significantly higher than those in the GDWD group (χ^2=12.729, P=0.000). CYP2C19 double mutation genotype was also an independent risk factor for type 2 diabetes (OR 4.960, 95% CI: 1.928–12.760, P=0.000).

Conclusions: It shows that double mutation genotype may be related to the type 2 diabetes susceptibility. Double mutation genotype was an independent risk factor for type 2 diabetes, and the risk of type 2 diabetes is five times higher than wild type and single mutation genotype. Furthermore, GMD cases with CYP2C19 double mutation genotype have a higher probability to deteriorate into type 2 diabetes.

Keywords: Diabetes mellitus; CYP2C19; genotype

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Introduction

According to the latest report from the International Diabetes Federation, 415 million people worldwide suffer from diabetes and this number is projected to rise to 642 million by the year of 2040 (1). Types 2 diabetes is the most common diabetes type characterized by high blood glucose. As a chronic metabolic disorder, it represents the leading cause of macrovascular and microvascular complications including cardiovascular disorders, kidney failure, blindness and lower limb amputation. Although the knowledge in the pathophysiological process of diabetes mellitus has greatly accumulated in recent years, the cellular and molecular mechanisms underlying its genetic pathogenesis remain very limited (2).

Growing evidence are suggesting that a combination of genetic and environmental factors contribute to the development of type 2 diabetes. In recent years, genetic factors including receptors and key enzymes are being frequently researched (3). Of particular interest is the cytochrome *P450* gene superfamily involved in drug metabolism as well as synthesis of cholesterol, steroids and other lipids (4). As its major isoform, CYP2C19 acts

on 10–15% of drugs in current clinical use, including proton pump inhibitor, platelet aggregation inhibitor, and anti-depressants (5). CYP2C19 also has the capacity of metabolizing polyunsaturated fatty acids (6). Due to its pivotal role in lipid metabolism and proton transfer in mitochondria, CYP2C19 could be a potential candidate for treating type 2 diabetes. *CYP2C19* gene consists of 9 exons spanning approximately 90 kb and encodes a protein of 490 amino acids. Approximately 30 variant alleles of CYP2C19 have been identified thus far. Several mutations on *CYP2C19* gene have been well documented, such as wild-type allele *1, and mutant alleles *2, *3, *4, *5, *6, *7 and *8. The *1 allele is the wild-type allele that encodes full length of CYP2C19 enzyme. The *2 and *3 alleles are the most common variants and result in a complete loss of enzymatic activity (7,8). However, the relationship of these CYP2C19 variants with type 2 diabetes are not yet well understood. In the present study, we attempted to investigate the association of CYP2C19 polymorphisms with type 2 diabetes in the Chinese population.

Methods

Patients

This study was conducted from 2012 to 2015 at The General Hospital of Western Theater Command. Overall, 575 participants were enrolled in this study, including 226 cases of glycometabolism disorder (GMD) and 349 cases of healthy control with normal glucose metabolism (NGM) (432 males, 143 females; mean age 70±14 years). Among the GMD patients, 62 of them were diagnosed with type 2 diabetes. Subjects with family history of diabetes or coronary heart disease were 10.78% and 58.26%, respectively. Blood samples were collected for further biochemical analysis. Diagnosis of type 2 diabetes mellitus and cardiovascular disordersare made according to WHO diagnostic criteria. The study was approved by the institutional review board of The General Hospital of Western Theater Command and written informed consent was taken from all participants.

Measurements and blood sample collection

The CYP2C19 genotype and biochemical measurements, including total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Cystatin C, fasting blood-glucose (FBG), were performed in accordance with the recommendations proposed by national center for clinical laboratories. Genomic DNA was isolated from whole blood samples using a commercially available DNA isolation kit (TaKaRa, China) according to the manufacturer's instruction. Then the gene site *1, *2 and *3 were enriched by the PCR method. Finally, the PCR amplification products were hybridized by gene microarrays method. CYP2C19 variants measurements were performed based on single nucleotide polymorphism microarrays (9).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were reported as counts and percentages. Analyses of *t*-tests and chi-square tests were used to examine the differences between control and disease group. Multivariate logistic regression analysis was used to identify independent predictors of type 2 diabetes. Analyses were performed using SPSS version 19.0 statistical software. A value of $P<0.05$ (two-tailed) was considered significant difference (10). The P value is accurate to three decimal places using SPSS (11).

Result

A total of 575 participants' CYP2C19 genotypes were performed based on gene microarray (BaiO, Shanghai), and biochemical measurements based on biochemical reaction from Beckman Coulter platform.

Clinical and biochemical characteristics of participants

The clinical profile of the GMD group and the NGM group are summarized in *Table 1*. As expected, the fast blood glucose, a key criterion of diabetes, was significantly higher in GMD group in comparison with NGM group. Deregulation of lipid metabolism is also a common clinical symptom of type 2 diabetes. Hence, the major lipids, TG was dramatically increased in GMD group, while HDL-C was reduced in GMD group. No significant difference of TC, LDL-C, and Cystatin C were observed between two groups.

No association of CYP2C19 genotypes with GMD

The levels of TG, HDL-C, Cystatin C, fasting blood-glucose (FBG) were significantly higher in GMD group than in NGM group. However, the association of CYP2C19 genotypes between GMD and NGM group was analyzed

Table 1 Clinical information and CYP2C19 genotype frequency in the GMD and NGM group

Variable	GMD group (n=226)	NGM group (n=349)	t/χ^2 value	P
Male (%)	76.1	74.5	0.008	0.928
Age (years)	71±14	68.74±13.27	2.309	0.021
Coronary heart disease (%)	61.0	56.4	0.121	0.728
TC (mmol/L)	4.186±1.241	4.139±1.253	–0.102	0.919
TG (mmol/L)	1.664±1.184	1.418±0.725	2.596	0.010
HDL-C (mmol/L)	1.110±0.310	1.146±0.263	–2.097	0.036
LDL-C (mmol/L)	2.519±0.986	2.409±1.001	0.898	0.370
Cystatin C (mg/L)	1.291±0.786	1.165±0.502	2.410	0.016
FBG (mmol/L)	8.126±3.068	5.128±0.502	16.71	0.000
CYP2C19 *1/*1 (%)	42.0	40.2	0.009	0.926
CYP2C19 *1/*2 (%)	38.9	38.3	0.000	0.984
CYP2C19 *1/*3 (%)	7.1	6.8	0.002	0.961
CYP2C19 *2/*2 (%)	6.0	8.7	0.717	0.397
CYP2C19 *3/*3 (%)	0.0	0.3	0.000	1.000
CYP2C19 *2/*3 (%)	5.0	3.8	0.085	0.771

CYP, cytochrome P450; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; GMD, glycometabolism disorder; NGM, normal glucose metabolism.

and showed no association of any CYP2C19 genotypes (*1/*1, *1/*2, *1/*3, *2/*2, *3/*3, *2/*3) between the two groups. In *Table 1*, the P value of *t*-test for all genotypes was over 0.05.

*CYP2C19 genotype (*2/*3) is associated with type 2 diabetes*

Further, the genotypes of CYP2C19 between the type 2 diabetes group and the GMD without diabetes (GDWD) group were compared. As shown in *Table 2*, CYP2C19 genotype *2/*3 was found to be significantly higher in the type 2 diabetes group than GDWD group (χ^2=4.888, P=0.009). Statistically significant difference of CYP2C19 genotype *2/*3 was also observed between the type 2 diabetes group and the NGM group (χ^2=4.888, P=0.000), suggesting that individuals with CYP2C19 *2/*3 mutation may confer a higher risk of developing type 2 diabetes in future.

Double mutation of CYP2C19 genotypes are highly associated with type 2 diabetes

While the frequencies difference of CYP2C19 wild-type (*1/*1; χ^2=2.097, P=0.148) and single mutation genotype (*1/*2 and *1/*3; χ^2=1.309, P=0.235) revealed no association between the type 2 diabetes group and the GDWD group. Double mutation (*2/*2, *2/*3 and *3/*3; χ^2=12.729, P=0.000) had striking differences between the two groups (*Table 3*).

Double mutation of CYP2C19 genotypes are independent risk factor for type 2 diabetes

Remarkably, as shown in *Table 4*, multivariate logistic regression analysis confirmed CYP2C19 double mutation genotype (*2/*2, *3/*3, *2/*3) as an independent risk factor for type 2 diabetes [odds ratio (OR): 4.960, 95% confidence interval (CI) 1.928–12.760; P=0.000]. Individuals with double mutations appeared to have fivefold increase in their type 2 diabetes risk. Similarly, FBG (OR 1.173; 95% CI, 1.024–1.344; P=0.021) and low-density lipoprotein cholesterol (OR 0.718; 95% CI, 0.531–0.972; P=0.032) were also independent risk factors for type 2 diabetes. Age, coronary heart disease, TC, TG, HDL-C, LDL-C in wild type and single mutation genotype were not associated with the type 2 diabetes.

Table 2 Clinical information and CYP2C19 genotype frequency in the type 2 diabetes and GDWD group

Variable	Type 2 diabetes (n=62)	GDWD group (n=164)	t/χ^2 value	P
Male (%)	67.7	78.7	0.393	0.53
Age (years)	71±12	72±15	–0.601	0.548
Coronary heart disease (%)	59.60	64.02	0.000	0.997
TC (mmol/L)	4.442±1.302	4.091±1.207	1.884	0.061
TG (mmol/L)	1.704±1.149	1.649±1.2	0.757	0.310
HDL-C (mmol/L)	1.110±0.250	1.11±0.33	–0.73	0.942
LDL-C (mmol/L)	2.754±1.017	2.432±0.964	2.181	0.300
Cystatin C (mg/L)	1.152±0.377	1.343±0.888	–1.62	0.106
FBG (mmol/L)	7.317±2.629	8.417±3.16	–2.387	0.018
CYP2C19 *1/*1 (%)	35	45	2.097	0.148
CYP2C19 *1/*2 (%)	33.9	40.9	1.164	0.281
CYP2C19 *1/*3 (%)	6.5	7.3	0.000	0.984
CYP2C19 *2/*2 (%)	11	4	3.534	0.060
CYP2C19 *3/*3 (%)	0	0	0.000	1.000
CYP2C19 *2/*3 (%)	13	2	4.888	0.009

CYP, cytochrome P450; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; GMD, glycometabolism disorder; NGM, normal glucose metabolism; GDWD, glycometabolism disorder without diabetes.

Table 3 Frequencies of the CYP2C19 genotype in the type 2 diabetes and GDWD group

Variable	Type 2 diabetes (n=62)	GDWD group (n=164)	χ^2 value	P
Wild type				
CYP2C19 *1/*1 (%)	35	45	2.097	0.148
Single mutation			1.309	0.235
CYP2C19 *1/*2 (%)	33.9	40.9		
CYP2C19 *1/*3 (%)	6.5	7.3		
Double mutation			12.729	0.000
CYP2C19 *2/*2 (%)	11	4		
CYP2C19 *3/*3 (%)	0	0		
CYP2C19 *2/*3 (%)	13	2		

CYP, cytochrome P450; GDWD, glycometabolism disorder without diabetes.

To further validate the association between CYP2C19 double mutation genotype and type 2 diabetes, the association of CYP2C19 double mutation with both cardio cerebrovascular disease and type 2 diabetes were analyzed. As shown in *Figure 1*, the frequency of CYP2C19 double mutation genotype was dramatically higher in type 2 diabetes (24.2%) than its corresponding nondiabetic control (10.27%) in cardio cerebrovascular disease patients (χ^2=6.945, P=0.008). Convincingly, no significant difference was detected in the wild type and single mutation, demonstrating the specificity of double mutation with type 2 diabetes.

Table 4 Multivariate logistic regression analysis of independent risk factor for type 2 diabetes

Independent risk factor	95% CI	P	OR
Age	0.986–1.027	0.547	1.006
Coronary heart disease	0.663–1.507	0.997	0.999
TC	0.623–1.012	0.062	0.794
TG	0.755–1.226	0.756	0.962
HDL-C	0.391–2.749	0.941	1.037
LDL-C	0.531–0.972	0.032	0.718
Cystatin C	0.900–2.596	0.116	1.528
FBG	1.024–1.344	0.021	1.173
Wild type (*1/*1)	0.371–1.162	0.148	0.656
Single mutation (*1/*2, *1/*3)	0.410–1.264	0.720	0.253
Double mutation (*2/*2, *3/*3, *2/*3)	1.928–12.760	0.000	4.960

FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; OR, odds ratio; CI, confidence interval.

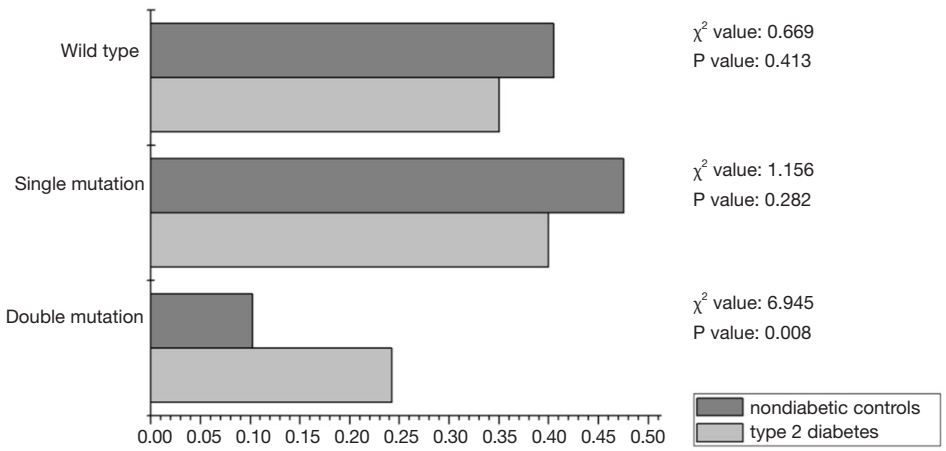

Figure 1 Comparative analysis of double mutant genotypes in patients with cardio cerebrovascular disease. The genotype frequencies of CYP2C19 mutations (wildtype, single mutation, double mutations) were compared between type 2 diabetes and non-diabetic control in patients who also suffered cardio cerebrovascular disease by chi-square tests.

Discussion

There are 35 alleles found in the Chinese populations (*2, *3, *8, *11, *13, *14, *16, *19, *23, *27, *29, *31, *33, *34, *36 to *56). *2 and *3 are the main variants among all of CYP2C9. However, the mutation frequency of *2 and *3 is very low (about 2%) in Asian. So CYP2C19 become a focus in this study.

The gene has polymorphisms of some isoforms of CYPs that associated with type 2 diabetes in certain populations. Examples the CYP2C8*3, CYP2C9*2, CYP3A4, CYP2C19*2 and CYP1B1*2 polymorphisms were associated with risk to type 2 diabetes in Indian, Japanese, Mexican and Saudi populations (12,13). Furthermore, the polymorphism CYP2C19*2 has been described to be associated with susceptibility to metabolic syndrome in south Portuguese population.

CYP2C19 is located within a cluster of cytochromes *P450* genes on chromosome 10q24, which contains nine exons and eight introns (14). The gene encodes a 490-aa

long protein of approximately 56 kDa, which is a member of the cytochrome P450 superfamily of enzymes. CYP2C19 is a clinically significant drug-metabolizing enzyme and its genotyping and phenotyping information have the potential to improve drug safety and efficacy (15). At least 27 variant alleles for CYP2C19 have been identified, with the most extensively described being CYP2C19*2, CYP2C19*3 in Chinese population (16).

CYP2C19*2 has been shown to be a G681A transition exon 5 of wild-type CYP2C19*1. This variant results in a wrong reading frame and produces a truncated protein. The CYP2C19*3, on the other hand, involves a G636A variant in exon 4, that encode a premature stop codon and a truncated protein (17). In clinical application, six CYP2C19 genotypes (CYP2C19*1/*1, *1/*2, *1/*3, *2/*2, *2/*3 and *3/*3,) have been observed in 99% of Chinese population. In the present study, double mutations of CYP2C19 (*2/*2, *2/*3 and *3/*3) are highly associated with type 2 diabetes, suggesting that the normal function of CYP2C19 may be required for proper glucose metabolism.

According to earlier studies, the frequency of CYP2C19 genotypes was variable among populations. For example, the frequencies of six CYP2C9 genotypes were 43.5%, 42.9%, 0.3%, 12.7%, 0.6% and 0.0% in South Asia, while the genotype frequencies were 44.9%, 41.1%, 4.7%, 7.0%, 1.8% and 0.6% in Southeast Asia (18). In this study, the genotype frequencies of CYP2C19 in Chinese population were 41.6%, 38.9%, 7.0%, 7.8%, 4.5% and 0.2%, respectively. Consistent with their findings, our results reiterated a great difference in the genotype frequencies of CYP2C19 from different regions of Asia.

Previously, it has been documented that CYP2C19 is associated with the occurrence of coronary heart disease and stroke. A positive association between diabetes mellitus and vascular dementia was also established (19). Here our work further demonstrated that CYP2C19 double mutation genotype is specifically related to type 2 diabetes, but not cardio cerebrovascular disease. This was confirmed by a comparative analysis of double mutant genotypes in cardio cerebrovascular disease patients with the type 2 diabetes patients showing a significant higher frequency of double mutant genotypes. Multivariate logistic regression analysis also indicated that the CYP2C19 double mutation genotype is an independent risk factor for type 2 diabetes, and individuals are 5-fold more likely to develop type 2 diabetes. We therefore propose that CYP2C19 double mutation is a specific genotype related to increased type 2 diabetes susceptibility in Chinese.

Indeed, type 2 diabetes mellitus results from the interaction between genetic and environmental factors, leading to heterogeneous and progressive pancreatic β-cell dysfunction (20). In particular, glucocorticoids are known to exert deleterious effects on the glucose metabolism, leading to a wide range of alterations from insulin resistance to diabetes. Under stress condition, glucocorticoids also regulate cytochrome P450 family (21). Since CYP2C19 expression is regulated by constitutive and rostane receptor (CAR) involved in glucocorticoids synthesis, it is reasonable to propose that there are certain interactions between CYP2C19 double mutant genotypes and type 2 diabetes through some of these receptors in charge of cholesterol regulation and bile acid.

Conclusions

Taken together, the association between CYP2C19 double mutation genotype and type 2 diabetes was strikingly significant; suggesting that double mutation genotype directly translates into higher type 2 diabetes susceptibility. As an independent risk factor for type 2 diabetes, individuals with double mutation genotype are also five-fold more susceptible to develop type 2 diabetes, as compared with those with the wild-type or single mutation genotype. Furthermore, GMD patients with CYP2C19 double mutation genotype are most likely to deteriorate into type 2 diabetes. Hence, the potential role of CYP2C19 polymorphism in the development of type 2 diabetes underscores the importance of genomics towards preventing this growing epidemic.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2019.08.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of The General Hospital of Western Theater Command and written informed consent was taken from all participants.

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