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Article

Genetic and Environmental Correlation Analysis of Serum Creatinine Levels in Chinese Twins

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Abstract

Almost all creatinine is excreted by the kidney in individuals. Serum creatinine concentration, a widely used renal function index in clinical practice, can be affected by both genetic and environmental factors, as evidenced by current research exploring the relationship between these factors and kidney function. However, few studies have explored the heritability of serum creatinine in Asian populations. Therefore, we explored the genetic and environmental factors that affect the serum creatinine level in Asian populations. Participants in this study came from the Qingdao Twin Registry in China, and 374 pairs of twins were included, of which 139 pairs were dizygotic twins, whose ages ranged from 40 to 80 years old, and the serum creatinine level ranged from 10 to 126 μmol/L. Structural equation models were constructed using Mx software to calculate heritability, with adjusted covariates being age, sex, and body mass index. The results of heritability analysis showed that ACE was the best fit model. Serum creatinine level is influenced by genetic and environmental factors. The result of heritability was 35.44%, and the influence of shared environmental factors accounted for 52.13%. This study provided the relevant basis for future research on genetic and environmental factors affecting serum creatinine levels in Asian populations.

Keywords: Serum creatinine; heritability; Chinese twins; renal function

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Creatinine is the result of nonenzymatic dehydration of muscle creatine (Borsook & Dubnoff, 1947). Some studies have found that serum creatinine concentration is related to cardiovascular disease (Fried et al., 2003), metabolic syndrome (J. Wang et al., 2015) and type 2 diabetes (Culleton et al., 1999). Almost all creatinine is excreted by the kidneys in individuals, and in today's clinical practice, the serum creatinine concentration is a widely used index of kidney function (Levey et al., 1988; Vidal-Petiot & Flamant, 2017). The impact of decreased renal function extends to nearly all bodily systems, and early identification and intervention in its decrease are very important to slow disease progress, maintain quality of life and improve prognosis (Snively & Gutierrez, 2004). Complex conditions, such as decreased renal function, are usually caused by a combination of environmental and genetic risk factors (Kluwe & Hook, 1980). By studying the factors that cause the changes in serum creatinine levels, we can suggest which ones lead to the decline in renal function (Rakesh Kumar et al., 2021).

The heritability of serum creatinine levels has been explored in several studies, with results ranging from .19 to .59. For a Mexican American study, the inheritance of serum creatinine was only .19 (Arar et al., 2008). In a study from an American population, the heritability estimate was .29 (Fox et al., 2004). In a study of Dutch participants, the estimated heritability was 37% (Zhang et al., 2021). In another European study, the heritability was .44 (Pattaro et al., 2009). In the Australian population, the result was .47 (Whitfield & Martin, 1984). In a study in Sweden, the inheritance of serum creatinine levels was .59 (Arpegård et al., 2015). Currently, there is a lack of exploratory research on the heritability of serum creatinine levels in the Chinese population. Therefore, in this study, 382 pairs of adult twins from Qingdao were selected as research subjects to explore the effects of genetic and environmental factors on serum creatinine level.

Materials and Methods

Research Population

Our study participants came from the Qingdao twin registration system (Xu, Zhang, Tian, Wu et al., 2017), and included 382 pairs of twins from Qingdao city in Shandong province, China. Inclusion criteria for the twin pairs were as follows: age 40 years or above, completed data from all investigations, and signed informed consent form (W. Wang et al., 2018). All subjects used the same questionnaire. The twins completed their physical examination, blood test and questionnaire on the same day. Before researchers investigate the subjects, they must be trained correctly (Xu, Zhang, Tian, Duan et al., 2017). Finally, 374 pairs of twins were used for genetic analysis.

Investigation of Research Content

The demographic characteristics, such as age and sex of the subjects, were obtained from the questionnaire. Information such

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as height and weight of subjects were obtained through physical examination. The serum creatinine level of the subjects was detected by laboratory examination. The subjects were asked to take a sitting position and 10 mL of venous blood was collected. Serum creatinine levels were measured using an automated biochemical analyzer (Liu et al., 2018).

Zygosity Identification

Zygosity identification was by sex, ABO blood group and microsatellite DNA gene scan and genotyping (W. Wang et al., 2020). Twins of different sex are dizygotic and those of the same sex but with different blood types are also dizygotic. If both sex and blood type were the same, the zygosity was further identified using microsatellite DNA gene scanning and genotyping technology (He et al., 2001).

Statistical Analysis

Data entry using EpiData 3.0 software was carried out by two operators at the same time. SPSS 22.0 software was used to calculate the intraclass correlation coefficient (ICC) of serum creatinine levels of the participants. Using Mx software package to build a structural equation model, phenotypic variation can be divided into dominant genetic effect (D), additive genetic effect (A), common or shared environmental effect (C), and unique/nonshared environmental effect (E). If the ICC in the monozygotic twin group was greater than 2 times the ICC in the dizygotic twin group, the ADE model was selected, and if not, the ACE model was selected (Chen et al., 2021).

In the optimal model, heritability (h^2) was considered as the contribution of additive genetic effects to the total phenotypic variation. The best-fit model was determined by a chi-square test of likelihood ratio to compare whether the difference between the full model (ADE or ACE) and its nested models (CE, AE, or DE) was significant. When $p > .05$, it showed that there is no difference between the full model and its nested model, and the parsimonious principle and Akaike's information criterion (AIC) were used for determining the best model. When $p > .05$, we chose the full model. The covariates adjusted in the model were body mass index (BMI; Kashani et al., 2020), age (Karam & Tuazon, 2013), and sex (Sabolić et al., 2007).

Results

Basic Characteristics of Twins

A total of 374 pairs of twins, 359 males and 389 females, aged from 40 to 80, were enrolled in the study. The proportion of female participants was 52%. The median age was 50 years old, and the interquartile range was 11 years old. Serum creatinine levels were between 10 and 126 μmol/L, with a median of 71 μmol/L and interquartile range of 25 μmol/L. Basic characteristics of the twins enrolled in the study are presented in Table 1.

Table 1. Basic characteristics of twins included in the study

Zygosity	*N*	Age (years) *M* (Q)	BMI (kg/m^2) *M* (Q)	Scr (μmol/L) *M* (Q)
All	748	51.722(11)	24.316(4.4)	69.63(24.75)
MZ	470	52.085(11)	24.146(4.2)	68.92(24)
MZ (male)	218	53.339(13.25)	24.101(4.55)	67.5(21)
MZ (female)	252	51(9)	24.185(3.9)	70.14(24)
DZ	278	51.108(11)	24.604(4.6)	70.84(27)
DZ (male)	82	50.732(11.5)	24.26(5.1)	69.63(23)
DZ (female)	78	50.974(11)	24.377(4.05)	73.31(18)
DZ (opposite sex)	118	51.458(10)	24.994(5)	70.05(31.5)

Note: MZ, monozygotic; DZ, dizygotic; *M* (Q), median (interquartile); BMI, body mass index; Scr, Serum creatinine level.

Table 2. Interclass correlation coefficient of serum creatinine levels in monozygotic and dizygotic twins

	Monozygotic twins		Dizygotic twins	
Phenotype	Corr.	(95% CI)	Corr.	(95% CI)
Serum creatinine levels	0.87	(0.82, 0.90)	0.68	(0.58, 0.75)

Note: Corr., interclass correlation coefficient; CI, confidence interval.

Heritability

As shown in Table 2, the ICC of monozygotic twins (rMZ) was .87 (95% CI [.82, .90]), and that of dizygotic twins (rDZ) was .68 (95% CI [.58, .75]). Since 2*rDZ>rMZ, finally the ACE model was fitted.

As shown in Table 3, there were differences between the ACE model and the nested AE model ($p < .05$), thus the ACE model was still selected. Additive genetic effect (A) (i.e., the heritability of serum creatinine levels) accounted for 35.44% (95% CI [21.48, 53.78]), common or shared environmental effect (C) for 52.13% (95% CI [33.72, 65.90]), and unique/nonshared environmental effect (E) for 12.43% (95% CI [9.99, 15.50]).

Discussion

The results of the heritability analysis showed that the ACE model was the best fit model. The heritability result of serum creatinine level was 35.44%, the shared environmental impact accounted for 52.13%, and the nonshared environmental effect accounted for 12.43%.

The heritability of serum creatinine level has been widely studied. A study in Sweden recruited 5635 subjects with an average age of 64.9 years, 55% of whom were women, and the average creatinine level was 77.5μmol/L. The fitting model was the ADE model, and the heredity result of serum creatinine level was 59% (Arpegård et al., 2015). An Australian study of 206 pairs of twins found that the inheritance of serum creatinine was .47 (Whitfield & Martin, 1984). A Danish twin study, fitting the DE model, found heritability in women only, at 44% (Bathum et al., 2004). In a study of British female twins, the participants ranged in age from 18 to 72 years. The heritability result was 37% and the ACE model was fitted; shared environmental factors (C) accounted for 26%, and specific environmental influence accounted for 37% (Hunter et al., 2002). Our research also found the influence of shared environmental factors, but the proportion was higher, and the influence of nonshared environment was lower, which might be due to the influence of different races. In our study, the potential source of shared environmental effects may derive from differences in meat intake or muscle mass. Although our participants came from the same city, differences in economic level and living habits (such as labor intensity) among different families might lead to differences in meat intake or muscle mass.

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Table 3. Model fitting results of the respective proportions of environmental and genetic effects

Phenotype	model	A	C	E	-2LL	*df*	AIC	$\Delta\chi^2$	*p*
Serum Creatinine	ACE*	35.44 (21.48–53.78)	52.13 (33.72–65.90)	12.43 (9.99–15.50)	1700.07	741	218.073		
	AE	87.19 (84.24–89.56)	–	12.81 (10.44–15.76)	1721.16	742	237.158	21.09	<.001
	CE	–	81.68 (77.79, 84.94)	18.32 (15.06, 22.21)	1734.32	742	250.32	34.24	<.001

Note: *Best fit model; A, additive genetic effect; C, common or shared environmental effect; E, unique/nonshared environmental effect; -2LL, 2 times the negative log-likelihood function value; *df*, degree of freedom; AIC, Akaike's information criterion; χ^2, chi-square value.

Some studies have explored the heritability of serum creatinine levels in nontwin populations. A study of 2859 European subjects, including Italian, Dutch and Croatian participants, showed a heritability of .44 for serum creatinine levels (Pattaro et al., 2009). The average age of 1224 participants in the Framingham Heart Study in the United States was 59 years old, and 52% of them were women. The average serum creatinine level was 0.87 mg/dl. The heritability estimate for serum creatinine was .29 (Fox et al., 2004). In a study of 155,911 Dutch participants, of whom 58.1% were women with an average age of 43.1 ± 14.7 years, for serum creatinine, the heritability estimates were 37% (Zhang et al., 2021). The heritability results were different among different studies.

Compared with most other studies on the heritability of serum creatinine, our heritability results were lower. This might be due to the differences among different ethnic groups. In the previous twin studies, most of the people were from Europe and America, while our study focused on the Han ethnic group in northern China. In addition, it might also be related to the age of the research object, the difference of sample size and other factors.

Our research has some shortcomings. Our sample size is small compared to other studies, which is a major limitation, but our study is the first to look at the inheritance of serum creatinine levels in a twin population in China. Twin samples improve study efficiency in studies of complex traits or complex diseases. Second, there are many indicators besides the serum creatinine level that can be used to reflect renal function. At present, each indicator has its own limitations (Filler et al., 2014; Weingart & Wirnsberger, 2021). Many studies use the serum creatinine level to reflect renal function, but some studies also use cystatin C and blood urea nitrogen. Therefore, our conclusion needs further exploration in the future, such as exploring multiple indicators that reflect renal function.

In summary, the results of our study of 373 pairs of adult twins in China showed that the heritability of serum creatinine level was 35%. The influence of shared environmental factors on serum creatinine level accounted for 52%. The serum creatinine level is influenced by genetic and environmental factors. Serum creatinine level tests are widely used in the screening for renal function, and an understanding of the genetic mechanisms underlying these tests may be of value in their interpretation.

Data availability statement. The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

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Ethical statement. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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