TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 599-606
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doi:10.3906/sag-1510-92

Association of the *CETP* gene TaqIB and D442G polymorphisms with essential hypertension in the Chinese Mongolian population

Shudong NIU[1,*], Xiaoming TAO[2,*], Jingping LI[1], Yongyue LIU[3], Jian WANG[3], Mingyu CONG[1], Keyong ZHANG[1], Wenyu ZHOU[2], Changchun QIU[1,2,]**

[1]Basic Medical Science College, Qiqihar Medical University, Qiqihar, Heilongjiang, P.R. China
[2]National Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing, P.R. China
[3]Department of Epidemiology, Tongliao Center for Disease Control and Prevention, Tongliao, Inner Mongolia Autonomous Region, P.R. China

Received: 21.10.2015 • **Accepted/Published Online:** 02.10.2016 • **Final Version:** 18.04.2017

Background/aim: This study aimed to explore the associations of the cholesteryl ester transfer protein (*CETP*) gene TaqIB and D442G polymorphisms with essential hypertension (EH).

Materials and methods: In this case-control study, 883 hypertensive patients and 1044 normal controls were randomly selected from the Mongolian population of China. Polymerase chain reaction (PCR) and direct sequencing of PCR products were used to identify the genotypes. Haplotype analysis was performed by estimating the haplotype frequencies using the online SHEsis package.

Results: The distribution frequency of the B2-G haplotype was significantly lower in the EH group than in the control group (0.7% vs. 1.9%, P = 0.001, OR = 0.359 [0.188–0.689]). Subjects with the B2B2 genotype showed significantly lower levels of total cholesterol (TC) ($P < 0.05$). When subgrouped by sex, male subjects with the B2B2 genotype showed significantly increased high-density lipoprotein cholesterol and decreased TC levels ($P < 0.05$), and those with the B2 allele showed significantly lower triglyceride levels as compared to the subjects with the B1B1 homozygote ($P < 0.05$).

Conclusion: TaqIB and D442G polymorphisms of the *CETP* gene did not independently affect the risk of developing EH in the Chinese Mongolian population, while the B2-G haplotype obviously decreased the susceptibility to EH. The B2 allele could alter the blood lipid level and reduce the risk of developing cardiovascular diseases.

Key words: Cholesteryl ester transfer protein gene, essential hypertension, polymorphism, Mongolian population

1. Introduction

The human cholesteryl ester transfer protein (*CETP*) gene is a 25-kb gene with 16 exons and 15 introns located at 16q12-21. Previous studies have shown that polymorphisms at multiple sites of the *CETP* gene are strongly associated with cardiovascular diseases including atherosclerosis, stroke, and coronary heart disease (1,2). Most studies on the effects of *CETP* polymorphisms on cardiovascular risk factors have been about the associations with levels of serum lipids, including triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) (3,4). However, whether the susceptibility of another major risk factor, essential hypertension (EH), would be affected by these variants has not been widely investigated.

The Mongolian population in the Inner Mongolia Autonomous Region has a high prevalence of 20.22% for EH, ranking third among the 56 official ethnicities in China. Their relatively isolated subsistence tradition and low population mobility endow them with a relatively stable genetic background, which could effectively reduce the potential for genetic admixture and make them an ideal population for studying the genetic associations of complex diseases such as EH. In the present study, subjects from the Mongolian population were selected to evaluate the associations of TaqIB and D442G polymorphisms in the *CETP* gene with EH by logistic regression after adjustment for age, sex, body mass index (BMI), smoking, drinking, and serum lipid level. The effects of the two polymorphisms on serum lipid levels were assessed

* These authors contributed equally to this work.
** Correspondence: niushudong1970@126.com

to give better insight into the relation between *CETP* polymorphisms and cardiovascular diseases.

2. Materials and methods

2.1. Subjects

The present study was approved by the Ethics Committee of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. Written informed consent was obtained from all the subjects. Thirty-two unincorporated villages of Kezuohou Tribe, Tongliao, Inner Mongolia Autonomous Region were selected as the study sites. Mongolian subjects above 40 years, with no history of miscegenation in at least three generations and permanently residing in the villages, were selected. Questionnaire investigations and physical examinations were performed. Finally 883 hypertensive patients (including 453 males and 430 females) and 1044 normal controls (including 372 males and 672 females) were included.

2.2. Inclusion criteria for hypertensive patients

Hypertension was diagnosed according to the diagnostic criteria issued by the WHO/ISH in 1999. Patients with the following features were included: 1) absence of consanguinity at enrollment; 2) onset of hypertension before the age of 60 years; 3) systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg; 4) free from secondary hypertension, diabetes, and liver or renal diseases according to clinical and biochemical examinations; and 5) absence of pharmacological treatment for hypertension for >95% of EH patients.

2.3. Inclusion criteria for the controls

Nonrelated subjects above 45 years old with normal blood pressure (SBP of <130 mmHg, DBP of <80 mmHg) and free from diabetes and liver/renal diseases were recruited. The controls were matched for age, sex, and ethnicity with EH patients from the same region.

2.4. Anthropometry

Blood pressure was measured according to the international standard methods using a desktop mercury sphygmomanometer. For each subject, blood pressure was measured three times and mean values were calculated for the study. BMI was calculated as weight (kg) divided by height squared (m^2). The waist-to-hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm).

2.5. Blood collection and biochemical examinations

For each subject, 5 mL of fasting venous blood was collected into a 10-mL anticoagulant tube (containing 1 mL of 2% EDTA-Na_2) for biochemical examinations and the extraction of genomic DNA. Enzymatic methods (Automatic Biochemical Analyzer ERBA XL-300, ERBA Diagnostics Mannheim GmbH, Mannheim, Germany) were used to measure the plasma levels of total cholesterol (TC), TG, HDL-C, and LDL-C.

2.6. Genomic DNA extraction and genotyping

Centrifugal column kits (TIANamp Blood DNA Midi Kit, TIANGEN Biochemical Technology Co., Ltd., Beijing, China) were used to extract genomic DNA from leukocytes. The DNA was then dissolved in TE solution (OD: 260/280 ≥ 1.80), divided into aliquots, and stored at –20 °C until required. Polymerase chain reaction (PCR: MyCycler Thermal Cycler, Bio-Rad, Hercules, CA, USA) was used for the amplification, and the PCR products were directly sequenced (BGI LifeTech Co., Beijing, China) to identify the genotypes of TaqIB and D442G. The primers for the PCR are listed in Table 1.

2.7. Statistical analyses

SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used for database management and statistical calculations. Continuous data are shown as mean ± SD. A two-tailed $P < 0.05$ was accepted as statistically significant. Anthropometric and biochemical indices were compared between the EH and control subjects using the two-sample t-test. For data with skewed distributions, arithmetic square root transformation was performed before the statistical analyses. Hardy–Weinberg equilibrium was checked by comparing the observed and expected genotype frequencies by chi-square test. Differences

Table 1. PCR primer sequences of polymorphic sites for genotyping of the studied polymorphisms in *CETP* gene.

Locus	Primer sequence
TaqIB	F: 5 `CAC TAG CCC AGA GAG AGG AGT GCC 3' R: 5 `CTG AGC CCA GCC GCA CAC TAA3'
D442G	F: 5 `TCA TGA ACA GCA AAG GCG TGA GCC TCT CCG 3' R: 5'AGC CAA GCT GGT AGA GGC CCC TCT GTC TGT 3'

F, forward primer; R, reverse primer.

in categorical data of genotype and allele distributions between the EH and control subjects were examined by chi-square test. Logistic regression was used to adjust the confounding factors and investigate the associations between the genotypes and blood pressure or blood lipids. Haplotype analysis was performed by estimating the haplotype frequencies using the online SHEsis package. The haplotype frequencies were compared between patients and controls using the chi-square test.

3. Results

3.1. Baseline characteristics

The demographic and clinical characteristics of the study population are presented in Table 2. EH patients had higher levels of BMI, WHR, SBP, DBP, TC, TG, and LDL-C compared with the control subjects ($P < 0.01$). In contrast, the control subjects had higher HDL-C levels compared with the EH patients ($P < 0.05$).

3.2. Genotype and allele distributions of studied polymorphisms between EH and control subjects

All three genotypes of the TaqIB polymorphism (B1B1, B1B2, B2B2) were distributed in both the EH and control groups; however, no subject in the EH group or the control group was found with the GG genotype of D442G. The frequencies of the genotypes and alleles of the TaqIB and D442G polymorphisms were not significantly different between the EH and control groups ($P > 0.05$; Table 3). After being stratified by sex or analyzed by binary logistic regression, still no statistical difference between the two groups was found after adjusting for age, sex, BMI, smoking, drinking, and lipid level.

3.3. TaqIB and D442G haplotype distributions between EH and control subjects

Distributions of haplotypes of TaqIB and D442G were analyzed to detect the association between polymorphism combinations and EH risk (Table 4). We found that the frequencies of all four haplotypes were higher than 1%. However, the frequency of the B2-G haplotype in the EH group was significantly lower than that in the control group (0.7% vs. 1.9%, $P = 0.001$, OR = 0.359 [0.188–0.689]).

3.4. Correlation between genotype and blood lipid level

The blood lipid levels were stratified according to the 2007 Chinese guidelines on prevention and treatment of dyslipidemia in adults (5). Normal blood lipid level was evaluated as 0 while an abnormal level was evaluated as 1. Binary regression was then performed to investigate the associations between the genotypes of TaqIB and D442G polymorphisms and blood lipid levels. As shown in Table 5, in the overall sample, subjects with the B2B2 genotype had lower TC levels ($P < 0.05$) compared with the others. For male subjects, the HDL-C level was significantly higher ($P < 0.05$), while the TC level was significantly lower ($P < 0.01$) in subjects with the B2B2 genotype. In addition, subjects with B2B2 or B1B2 genotypes had significantly lower TG

Table 2. Demographic and anthropometric characteristics and biochemical measurements of the study population.

Characteristics	Controls (n = 1044)	EH (n = 883)	P
Age (years)	42.29 ± 11.36	52.09 ± 12.15	<0.01
Smoking (%)	42.0	48.4	<0.01
Drinking (%)	25.8	45.8	<0.01
BMI (kg/m^2)	21.69 ± 3.12	23.03 ± 3.78	<0.01
WHR (cm/cm)	0.85 ± 0.06	0.89 ± 0.07	<0.01
SBP (mmHg)	112.77 ± 8.94	153.05 ± 23.92	<0.01
DBP (mmHg)	75.20 ± 6.13	96.72 ± 10.84	<0.01
TC (mmol/L)	3.56 ± 1.06	3.99 ± 1.21	<0.01
TG^S (mmol/L)	0.97 ± 0.3	1.16 ± 0.46	<0.01
HDL-C^S (mmol/L)	0.98 ± 0.31	0.95 ± 0.18	<0.05
LDL-C (mmol/L)	1.94 ± 0.90	2.15 ± 1.01	<0.01

EH: essential hypertension; BMI: body mass index; WHR: waist-hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.
^{S} Expressed raw data were adjusted by arithmetic square root transformation.
Data values are expressed as means ± standard deviation.
P-value was estimated by two-sample t-test.

Table 3. Distribution of genotypes and alleles of each polymorphism of *CETP* in the essential hypertensive and normotensive subjects.

Locus	Genotype (%)	Control (n = 1044)	EH (n = 883)	χ^2	P
TaqIB	B1B1	326 (31.2)	303 (34.3)	2.658	0.265
	B1B2	553 (53.0)	457 (51.8)		
	B2B2	165 (15.8)	123 (13.9)		
	B1	1205 (57.7)	1063 (60.2)	2.433	0.119
	B2	883 (42.3)	703 (39.8)		
D442G	DD	980 (93.9)	843 (95.5)	2.399	0.121
	DG	64 (6.1)	40 (4.5)		
	GG	0 (0)	0 (0)		
	D	2024 (96.9)	1726 (97.7)	2.333	0.127
	G	64 (3.1)	40 (2.3)		

EH: Essential hypertensive patients; χ^2: chi-square.
Genotype and allele data are expressed as number (%).
P was calculated by the χ^2 test with a 3 × 2 contingency table for genotype distribution and 2 × 2 contingency table for allele distribution.

Table 4. Haplotypes and frequencies of the *CETP* gene in essential hypertensive and normotensive subjects

TaqIB - D442G	Controls	EH	χ^2	P	OR (95% CI)
B1-D	1180 (56.5)	1035 (58.6)	1.716	0.190	1.089 (0.958–1.239)
B1-G	25 (1.2)	28 (1.6)	1.063	0.303	1.329 (0.772–2.288)
B2-D	844 (40.4)	691 (39.1)	0.668	0.414	0.947 (0.832–1.078)
B2-G	39 (1.9)	12 (0.7)	10.347	0.001	0.359 (0.188–0.689)

EH: Essential hypertensive patients; CI: confidence interval; OR: odds ratio; χ^2: chi-square.
Haplotype data are expressed as number (%).
P was calculated by the χ^2 test with a 4 × 2 contingency table.

levels compared with those with the B1B1 genotype ($P < 0.05$). For female subjects, no significant difference was found among the subjects carrying different genotypes. No significant difference in blood lipid levels was found among the subjects carrying different D442G genotypes in the overall sample or after being stratified by sex.

4. Discussion

Hypertension and dyslipidemia (including low HDL-C and high LDL-C, TC, and TG) are the major risk factors for cardiac-cerebral vascular diseases (6), which is the leading cause of death for humanity. They often coexist in an individual and interact with each other in the development of cardiac-cerebral vascular diseases. Prospective epidemiological studies have shown that the risk of developing cardiovascular diseases is not only dependent on the severity of the individual risk factors, but also, or even more greatly, dependent on the varieties of the risk factors coexisting in the subjects. The varieties and severity of the risk factors together affect the risk of developing cardiovascular diseases, which is called the comprehensive risk of multiple risk factors. Among the multiple risk factors, the pathogenic effects of EH are substantially higher than other factors (7). As the only known protein with reverse cholesterol transport functions, CETP has been widely studied in regards to the effects on lipid transport and the components of lipoprotein. Meanwhile, a study on CETP inhibitors found that polymorphisms of *CETP* might be associated with EH risk (8). Thus, effects of *CETP* polymorphism on EH risk became another concern regarding the association of CETP with cardiovascular risk.

Table 5. Correlation of the TaqIB polymorphism in the *CETP* gene with serum lipid and lipoprotein levels.

	B1B1	B1B2	B2B2	P[b]
Total				
HDL-C[s] (mmol/L)	0.95 ± 0.19	0.96 ± 0.18	0.97 ± 0.18	0.050
LDL-C (mmol/L)	1.98 ± 1.03	2.08 ± 0.94	1.92 ± 0.87	0.357
TC (mmol/L)	3.69 ± 1.25	3.78 ± 1.11	3.66 ± 1.03	0.025
TG[s] (mmol/L)	1.07 ± 0.43	1.04 ± 0.38	1.02 ± 0.34	0.126
Male				
HDL-C[s] (mmol/L)	0.90 ± 0.36	0.93 ± 0.36	0.98 ± 0.36	0.016
LDL-C (mmol/L)	2.04 ± 1.11	2.04 ± 0.95	1.86 ±0.85	0.120
TC (mmol/L)	3.83 ± 1.40	3.80 ± 1.19	3.68 ± 0.99	0.007
TG[s] (mmol/L)	1.18 ± 0.50	1.10 ± 0.44	1.06 ± 0.36	0.028
Female				
HDL-C[s] (mmol/L)	0.96 ± 0.18	0.97 ± 0.17	0.97 ± 0.17	0.599
LDL-C (mmol/L)	1.94 ± 0.96	2.10 ± 0.93	1.97 ± 0.89	0.878
TC (mmol/L)	3.56 ± 1.13	3.77 ± 1.06	3.64 ± 1.07	0.840
TG[s] (mmol/L)	0.99 ± 0.35	0.99 ± 0.32	0.98 ± 0.33	0.964

HDL-C: High-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.
Data values are expressed as mean ± standard deviation.
[s] Expressed raw data were adjusted by arithmetic square root transformation.
[b] Binary logistic regression adjusted for age, sex, BMI, and smoking and drinking status.

4.1. Ethnic differences of TaqIB and D442G polymorphisms

Multiple studies have shown that polymorphisms at the promoter, introns, exons, and 3'-regulatory region of the *CETP* gene could be associated with the expression and lipid-transporting activity of CETP, the structure and functions of lipoprotein, and the risk of cardiovascular diseases (3).

The TaqIB (rs708272) polymorphism is a G/A variant at nucleotide 277 of the first intron, which results in the disappearance of the enzyme recognition site of TaqIB (namely the B2 allele). The allele containing the TaqI endonuclease site is called B1, while the allele without the restriction site is called B2. The variant is widely spread in various ethnicities. Its frequency is about 0.42 in white Americans (9), 0.39 in Japanese subjects (10), and 0.42 in Taiwanese subjects (11). In the present study, we found that the frequency of TaqIB polymorphism is 0.41 in the Chinese Mongolian population. The D442G (rs2303790) polymorphism is an A/G variant at nucleotide 55 of the 15th exon, which results in the replacement of Asp at the 422nd amino acid of CETP by Gly. Most of the individuals with this variant are carrying heterozygous DG; the D442G polymorphism is mainly found in the Asian population, and no study has reported this polymorphism in Caucasians from Europe or America. Among Asians, the Japanese have the highest frequency of 8% (12), while the frequency in the Chinese Han population is about 2% (13). The present study showed that the frequency of the D442G polymorphism in the Chinese Mongolian population is 4.8%.

Table 6. Linkage disequilibrium parameters of TaqIB and D442G polymorphisms.

D'	Controls (n = 1044)		EH (n = 883)	
	TaqIB	D442G	TaqIB	D442G
TaqIB	-	0.224	-	0.390
D442G	0.224	-	0.390	-

4.2. Effects of TaqIB and D442G polymorphisms on blood lipid levels

Prospective population studies have identified a low level of HDL-C or a high level of LDL-C as an independent predictor of cardiovascular risk. According to the literature, most of the *CETP* polymorphisms are associated with decreased transport activity and concentrations of

CETP, increased levels of HDL-C, and, in some cases, synchronously decreased levels of LDL-C, which have been manifested in studies of polymorphisms including TaqIB, D442G, I405V, and –629C > A (14). Thus, it is commonly accepted that genetic variations in the human *CETP* gene are associated with a reduction in cardiovascular risk when accompanied by both an increase in the level of HDL-C and a decrease in the level of LDL-C. TaqIB is the most investigated polymorphism to date and the conclusions are generally consistent that subjects with the B2 allele have increased plasma HDL-C levels, decreased CETP activity, and a decreased risk of having a cardio-cerebrovascular event (3). Nevertheless, the association between TaqIB polymorphism and HDL-C level has ethnic variations and sex differences according to epidemiological studies (15,16) and could be affected by multiple environmental factors (17). Several large-scale studies showed that the association between the TaqIB polymorphism and plasma HDL-C level is only found in male subjects (16,18), which is consistent with our study results. We found that male subjects carrying the B2B2 genotype had significantly higher HDL-C and decreased TC levels ($P < 0.05$), and those with the B2 allele had significantly lower TG levels as compared with the subjects with the B1B1 homozygote ($P < 0.05$). No statistical difference in blood lipid levels was found among the female subjects carring different genotypes. These sex differences might be linked to the regulating effect of estrogen on the expressions of hepatic lipase (*HL*) and *CETP* genes in females (19, 20). However, the impact of ethnic variation and subject stratification on the difference between males and females cannot be ruled out so far.

Previous studies suggested that the D442G polymorphism is located near the lipid transportation active center, and thus could reduce CETP activity and consequently increase the HDL-C level (12,21). However, the effects of D442G polymorphism in the development of cardio-cerebrovascular diseases are still controversial (13,22). In the present study, no significant difference in blood lipid levels was found between the DD and DG genotypes, which might be affected by the relatively small sample size and the unique dietary habits of the Mongolian population (high-fat diet) that could result in gene - diet interactions (23,24).

4.3. Effects of TaqIB and D442G polymorphisms on EH risk

In single-locus analysis, no association was found between TaqIB or D442G polymorphism and EH risk. As the associations between genotypes and phenotypes of *CETP* could be affected by factors including smoking, drinking, BMI, plasma lipid level, age, and sex (17), the present study adjusted the above factors in binary regression analyses. However, the results still showed no significant difference in the distribution frequencies of the alleles and genotypes of TaqIB and D442G polymorphisms between the control and EH groups, suggesting that neither TaqIB or D442G could independently affect the risk of developing EH in the studied population.

Hypertension is believed to be a complex polygenic disorder resulting from multiple genes/loci and decreased TC; each has a mild effect independently or through interactions. In the studies on the association between a single locus and EH risk, the effect of the single variant could be diluted or masked by other loci with which it was in linkage disequilibrium. The findings of the present study showed that there was weak linkage disequilibrium between these two polymorphisms in both the EH and the control groups (Table 6), which is in line with previous studies (12). Thus, we detected the combined effect of TaqIB and D442G on the susceptibility to EH by haplotype analysis. The results showed that subjects with the B2-G haplotype had significantly decreased risk of developing EH ($P = 0.005$), and thus the B2-G haplotype might be a protective factor for EH. The mechanisms of association between *CETP* polymorphisms and reductions in blood pressure could not be expounded fully, and the following factors may be involved. First, *CETP* polymorphisms resulting in low CETP levels expressed in endothelial cells could exert a protective modulating effect on endothelial function. Second, the changing lipoprotein profiles and increased HDL-C could play a role against atherosclerosis and conserve arterial wall distensibility (8).

The findings above showed that haplotype analyses of the *CETP* gene could be more efficient in identifying the associations between polymorphisms of *CETP* and EH. However, B2-G is not a widely distributed haplotype; the application value for general comprehension of the pathogenesis of EH was limited. More polymorphic sites should be included in further research on the effects of polymorphic combinations on the association between *CETP* gene and EH risk.

In recent years, the CETP inhibitor has become a hotspot of new drug development for cardiovascular diseases based on the abundant evidence that genetically low CETP levels provide significant lipid modulation effects and cardiovascular protection. Multiple basic and clinical studies have shown that applying CETP inhibitors could increase the HDL-C level and decrease the LDL-C level; however, whether the application of CETP inhibitors could reduce the risk of developing atherosclerosis or the incidence of cardiovascular diseases is still under debate. In regard to the intervention effects of CETP inhibitor on the major risk factors, hypertension and dyslipidemia, the associations between the lipid-regulating effects of the CETP inhibitor and the genotypes of the *CETP* polymorphisms have been reported, but the associations of

the *CETP* gene polymorphisms with blood pressure levels are still unclear (8,25). Therefore, the associations between *CETP* polymorphisms and lipoprotein/hypertension are not only involved in the mechanisms of cardiovascular diseases but also could provide important evidence for the clinical application of CETP inhibitors.

Due to the ethnic heterogeneity of EH, a relatively genetically homogeneous population is optimal for study subjects. In the present study, all the recruited individuals were of Mongolian origin with the same geographical location subjected to the same environmental factors such as living status, dietary habits, and lifestyles. The combined effects of genetic and geographic stability that yielded conclusive results is the main advantage of our study. The second advantage is that the blood pressure values of the control subjects were all below 130/80 mmHg, which could exclude selection bias and reduce the possible susceptibility to hypertension in controls.

Further study, expanding the ranges of the polymorphic sites, performing haplotype analyses, investigating the interactions among multiple sites, and measuring the transport activity of CETP simultaneously, could give better insight into the associations between *CETP* polymorphisms and the risk of cardiovascular diseases.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (grant number: 31440054), the American Chinese Medical Foundation (grant number: 96-657), and Major Scientific Research Projects of Beijing (grant number: 700400).

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