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Renal Function and Klotho Gene Polymorphisms among Uygur and Kazak Populations in Xinjiang, China

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Background: The association of genetic polymorphisms of klotho gene with aging has not been thoroughly examined. Previous studies showed that longevity in the Uygurs was considerably greater than in Kazaks in Xinjiang. This study aimed to investigate the difference of renal function and Klotho gene polymorphisms between Kazak and Uygur normal populations in Xinjiang, China.

Material/Methods: A total of 249 Uygur and 386 Kazak clinically normal subjects were included in this study. Four single-nucleotide polymorphisms (*rs1207568, rs564481, rs9527025,* and *rs9536314*) of the klotho gene were genotyped using the ABI SNaPshot method. Estimated glomerular filtration rate (eGFR) was calculated according to the Chinese simplified MDRD equation.

Results: There were significant differences between Kazak and Uygur healthy populations in both allele frequencies and genotype distributions in *rs9527025* and *rs9536314* (*P<0.05*, respectively). When the subjects were divided into 2 groups according to the genotypes of the klotho gene polymorphism, in the *GA+AA* genotype distributions of the *rs1207568*, the differences I serum creatinine and estimated glomerular filtration rate between the Kazak and Uygur groups were statistically significant (*P<0.05*, respectively). In *CC* genotype of *rs564481,* serum creatinine was significantly higher in Kazaks compared with Uygurs (*P<0.05*). In *GG* genotype of *rs9527025*, serum creatinine was significantly higher in the Kazak group compared with the Uygur group (*P<0.05*), as well as in *CG+CC* genotype of *rs9527025* (*P<0.05*). Serum creatinine was significantly higher in the Kazak group compared with the Uygur group in *TT* genotype of *rs9536314* (*P<0.05*), as was *GT+GG* genotype of *rs9536314*. Haplotype analysis indicated that the frequencies of *ACGT, GTGT,* and *GCCG* haplotypes were significantly different between Kazak and Uygur healthy populations (*P=0.04, P=0.018, P=0.000,* respectively).

Conclusions: Significant differences in klotho gene *rs9527025* and *rs9536314* polymorphisms were found between the Uygur and Kazak populations.

MeSH Keywords: Kazakhstan • Pituitary-Adrenal Function Tests • Polymorphism, Genetic

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Background

The klotho gene was first introduced by Kuro-o et al. as an aging suppressor gene in 1997 [1]. Klotho is expressed in multiple tissues and organs, but by far its highest expression is in the kidney. The klotho mutant mouse suffered from multiple disorders, resembling human premature-aging syndromes. The aging phenotype can be reversed by transferring inducible klotho gene. Mice overexpressing klotho have an increase in lifespan of 20% in females and 30% in males [2]. The secreted klotho protein controls multiple ion channels and growth factor signaling pathways, including insulin, IGF-1, and Wnt signaling [3–6]. This signaling activity in tissues shows close association with life span extension and regulates various metabolic processes.

Recent studies have found that the klotho gene is involved in the regulation of aging in human populations [7–9]. In previous studies, more than 10 SNPs in the human Klotho gene have been reported and klotho gene polymorphisms have been extensively associated with the human life span, glucose metabolism, lipid metabolism, serum levels of high-density lipoprotein cholesterol, and uric acid [10–12]. A variant (named KL-VS) of the human Klotho gene, containing 6 SNP sites in complete linkage disequilibrium, was found to be functional; 2 of those SNP sites result in the amino acid substitutions F352V and C370S [13]. Meanwhile, heterozygotes have greater longevity than wild-types in multiple populations, suggesting that the klotho gene affects human life span [13].

Xinjiang is a multi-ethnic populated area, with a total of 47 ethnic groups. The ethnic minority population (non-Han) accounts for about 60%, the most populous of which is the Uygur population, followed by the Kazaks. The present study included Uygur and Kazak populations of Xinjiang, China. Diets of Uygurs and Kazaks are quite different. Among the traditionally nomadic Kazaks in Xinjiang, who have habitually consumed beef, mutton, and dairy products as their staple food, consumption of fresh fruits and vegetables is low. The Uygur dietary staple is bread, with higher consumption of fruits and vegetables than among the Kazaks. We selected Uygur and Kazak populations from the Hetian and Tacheng regions, respectively, in Xinjiang, China. The Hetian region is located in the southernmost tip of the Xinjiang Uygur Autonomous Region, bordering the Taklimakan Desert in the north and the Kunlun Mountains in the south. Tacheng is under the jurisdiction of the Ili Kazak Autonomous State, located in the northwest of Xinjiang, at the north-west end of the Tianshan Mountains, and to the north, it borders on Kazakhstan. Lifestyle and geographical factors may also affect the genetic background. Furthermore, there is no known history or differences in incidence of renal disease in these 2 populations. Based on the above factors, we chose these 2 populations for this study.

Demographic profiles show that Uygurs live longer than Kazaks in Xinjiang [14]. Previous studies reported that the average blood pressure, lipid levels, and arterial stiffness of the Kazak population are significantly higher than those of the Uygur population [15]. To date, there have been few genetic association studies of the klotho gene in healthy populations. Therefore, we performed genotype analyses of 4 SNPs of the klotho gene – rs9536314, rs9527025, rs1207568, and rs564481. We observed the distribution of the klotho gene in Uygur and Kazak populations, as well as the differences in the two ethnic groups.

Material and Methods

Subjects

A total of 635 healthy subjects were enrolled in this study, including 249 healthy Uygur subjects (127 males and 122 females) with an average age of 51.99±11.24 years, age range 30–74 years old and 386 healthy Kazak subjects (198 males and 188 females) with an average age of 49.43±11.50 years, age range 28–70 years old. The Uygur and Kazak populations were from the Hetian and Tacheng regions, respectively, in Xinjiang, China. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University. Written informed consent for research was obtained from the participants.

Healthy adults free from kidney disease, diabetes, hypertension, cancer, rheumatoid disease, history of chronic infection disease, and other diseases were randomly selected. The medical history of each subject was recorded. All subjects underwent physical examination and completed blood tests, including liver function, kidney function, blood lipids, and blood glucose, as well as ECG, carotid artery sonography, and other auxiliary examinations. These indicators were within the normal range in 635 cases of clinically healthy subjects. Data collection was conducted in examination centers at local hospitals in the participants' residential areas.

Epidemiological investigation

All subjects participated in the epidemiological survey and underwent physical examination. They also answered a standardized questionnaire that collected information, including sex, occupation, smoking and drinking habits, medical history, and family history. The body heights and weights of the subjects were measured by a trained technician. The subjects were asked to rest for at least 5 min in the sitting position before their blood pressure was measured by an experienced physician using a mercury sphygmomanometer.

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Biochemical analysis

The serum and plasma collected for measurement were immediately frozen at -80°C until analysis. Preoperative serum fasting blood glucose, blood urea nitrogen, serum creatinine, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured by a Beckman Coulter auto-analyzer (au680, USA) of the First Affiliated Hospital of Xinjiang Medical University Examination Center. Estimated glomerular filtration rate (eGFR) was calculated according to the Chinese simplified MDRD equation [16].

Single-nucleotide polymorphism (SNP) selection and genotyping

Four tSNP sites were selected according to the HapMap database, and the LD degree among different sites (|D'|>0.8, r2>0.3) with a minor allele frequency (MAF) of 15% used as the cut-off after taking SNP functions into consideration.

All blood samples were collected in EDTA tubes and maintained at -80°C until use. Genomic DNA was extracted from the peripheral blood by a QIAamp DNA Blood Mini Kit (QIAGEN Inc., Hilden, Germany) according to the manufacturer's instructions. The polymerase chain reaction (PCR) conditions were as follows: denaturation at 94°C for 4 min, followed by 35 cycles of PCR at 94°C for 30 s, 65°C to 68°C for 30 s, and 72°C for 30 s. The annealing temperatures for rs1207568, rs564481, rs9527025, and rs9536314 were 50°C, 59°C, 61°C, and 58°C, respectively. The obtained digestion products were visualized on a 2% agarose gel, and the PCR product was purified by a PCR purification kit (Qiagen, Mildren, Germany). The klotho gene polymorphism was genotyped using the ABI SNaPshot method (Applied Biosystems, Foster, CA, USA). Briefly, the SNaPshot reaction was carried out in a 10 μL final volume containing SNaPshot Multiplex Ready Mix (5 μL), primer mix (1 μmol/L), and templates (2 μL). The cycling program condition was: denaturation at 96°C for 1 min, followed by 28 cycles of 96°C for 10 s, 50°C for 5 s, and 60°C for 30 s. The extension products were purified by incubation with 1 U of shrimp alkaline phosphatase (Promega, Madison, WI) at 37°C for 60 min. The enzyme was inactivated by incubating the products at 75°C for another 15 min. The purified products (0.5 μL) were mixed with 9 μL of formamide and 0.5 μL of GeneScan-120 LIZ Size Standard (Applied Biosystems) and then separated by capillary electrophoresis (ABI PRISM3130 Genetic Analyzer; Applied Biosystems). The results were analyzed with GeneMapper 4.0 software.

Statistical analyses

Statistical analysis was performed with SPSS for Windows version 17.0 (SPSS, Institute, Chicago, IL, USA). All questionnaire data were double-entered and cross-validated using EpiData version 3.1 (EpiData Association, Odense, Denmark). All data are presented as mean ± standard deviation, and the differences between the Uygur population and the Kazak population groups were assessed by independent-samples t test or Mann-Whitney U test. The genotype distribution was tested for Hardy-Weinberg equilibrium. The comparison of the allele and genotype frequencies between the groups was evaluated by Pearson chi-square test. If the table had cells with a frequency less than 5, Fisher's exact test was used. Linkage disequilibrium (LD) analysis was also performed between polymorphic sites in a locus, to identify "clusters" of highly correlated sites based on LD statistics. We calculated the haplotype frequencies and LD in different groups using the SHEsis software package available online. Correlation analysis was undertaken to test for associations between SNPs and other factors. A $P<0.05$ was considered statistically significant.

Results

Clinical characteristics of the study populations

This study consists of 2 ethnic groups (Uygur: n=249; Kazak: n=386). Clinical data for the Uygurs and Kazaks group is shown in Table 1. Differences in the ratio of females and males and the average age between the Uygur and Kazak groups were not statistically significant. The weight, height, BMI, systolic blood pressure, diastolic blood pressure, serum creatinine, fasting blood glucose, total cholesterol, high-density lipoprotein, and low-density lipoprotein of the Uygur subjects were lower than that of the Kazak subjects. Higher Triglycerides, blood urea nitrogen and estimated glomerular filtration rate were observed in the Uygur subjects when compared with the Kazak populations.

Genotypes and Allele Frequencies of klotho Gene Polymorphisms

Incidence of each genotype and allele in klotho gene were shown in Tables 2 and 3. The genotype distribution of each SNP did not show significant difference from the Hardy-Weinberg equilibrium values for Uygurs and Kazaks (all P>0.05, date not shown). For total participants, the genotype and the allele distribution of rs9527025 differed significantly between the Uygur population and Kazak population (P=0.000 and P=0.000, respectively). Significant differences in the genotype and allele distribution of rs9536314 in klotho were noted between the Kazak population and Uygur population (P=0.000 and P=0.000, respectively). The frequency of rs1207568 allele G was higher in the Kazak population than in the Uygur population (P=0.023). The genotype and allele frequencies of rs564481 polymorphisms had no statistical difference between Uygurs and Kazaks.

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Table 1. Clinical characteristics of study populations.

Variable	Uygur (n=249)	Kazak (n=386)	t/z/χ^2	*P* value
Sex (male/female)	127/122	198/188	0.581	0.943
Age (years)	50.99±11.24	49.43±11.49	1.184	0.426
Weight (kg)	61.70±8.86	72.47±14.44	10.534	0.000
Height (cm)	159.02±7.68	163.52±9.06	6.462	0.000
BMI (kg/m^2)	26.01±3.84	28.73±4.58	3.625	0.000
SBP (mmHg)	118.63±10.02	134.70±14.86	–12.674	0.000
DBP (mmHg)	72.22±7.73	80.53±10.04	–9.896	0.000
BUN (mmol/L)	5.12±1.41	4.90±1.61	–2.701	0.007
Scr (μmol/L)	67.16±13.66	71.82±17.21	3.534	0.000
eGFR (ml/min×1.73 m^2)	126.36±39.66	121.01±35.66	–2.808	0.005
GLU (mmol/L)	4.48±0.77	5.44±0.89	–14.428	0.000
TG (mmol/L)	1.57±0.39	1.19±0.28	–9.151	0.000
TC (mmol/L)	4.27±0.77	5.30±1.06	–12.229	0.008
HDL (mmol/L)	0.84±0.27	1.27±0.36	–14.17	0.000
LDL (mmol/L)	2.59±0.65	3.18±0.87	–8.687	0.000

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; BUN – blood urea nitrogen; Scr – serum creatinine; eGFR – estimated glomerular filtration rate; GLU – fasting blood glucose; TG – Triglycerides; TC – total cholesterol; HDL – high-density lipoprotein; LDL – low-density lipoprotein.

Table 2. Genotype distributions of SNPs of klotho gene in Kazak and Uygur populations.

SNP	Genotype	Uygur n=249		Kazak n=386		χ^2	P
rs1207568	A/A	11	(0.044)	26	(0.067)	4.974	0.083
	A/G	71	(0.285)	134	(0.347)		
	G/G	167	(0.671)	226	(0.585)		
rs564481	C/C	123	(0.495)	191	(0.495)	0.634	0.728
	C/T	108	(0.434)	173	(0.448)		
	T/T	18	(0.072)	22	(0.057)		
rs9527025	C/C	5	(0.020)	2	(0.005)	17.470	0.000
	C/G	54	(0.217)	42	(0.109)		
	G/G	190	(0.763)	342	(0.886)		
rs9536314	G/G	5	(0.020)	2	(0.005)	17.470	0.000
	G/T	54	(0.217)	42	(0.109)		
	T/T	190	(0.763)	342	(0.886)		

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Table 3. Allele distributions of SNPs of klotho gene in Kazak and Uygur populations.

SNP	Allele	Uygur n=249		Kazak n=386		χ^2	P
rs1207568	A	93	(0.241)	186	(0.241)	5.185	0.023
	G	405	(0.823)	586	(0.759)		
rs564481	C	354	(0.711)	555	(0.719)	0.097	0.756
	T	144	(0.289)	217	(0.281)		
rs9527025	C	64	(0.060)	46	(0.060)	18.180	0.000
	G	434	(0.871)	726	(0.940)		
rs9536314	G	64	(0.129)	46	(0.060)	18.180	0.000
	T	434	(0.871)	726	(0.940)		

Table 4. Comparison of renal function in different genotypes of rs1207568 between Kazak and Uygur populations.

	GG			GA+AA		
	BUN (mmol/L)	Scr (μmol/L)	eGFR (ml/min×1.73 m²)	BUN (mmol/L)	Scr (μmol/L)	eGFR (ml/min×1.73 m²)
Kazak	4.88±1.59	72.30±18.37	124.15±32.49	4.93±1.64	71.68±16.77	121.87±36.35
Uygur	5.17±1.51	68.70±19.98	127.68±32.14	5.00±1.19	66.57±14.49	132.07±33.49
t	–1.754	1.814	–1.050	–0.357	2.323	–2.101
P	0.080	0.071	0.294	0.721	0.021	0.037

Table 5. Comparison of renal function in different genotypes of rs564481 between Kazak and Uygur populations.

	CC			CT+TT		
	BUN (mmol/L)	Scr (μmol/L)	eGFR (ml/min×1.73 m²)	BUN (mmol/L)	Scr (μmol/L)	eGFR (ml/min×1.73 m²)
Kazak	4.76±1.43	70.99±18.12	124.82±34.54	5.04±1.76	73.98±17.29	121.64±33.68
Uygur	5.09±1.47	67.19±13.35	129.96±32.87	5.13±1.34	68.74±22.08	128.42±32.47
t	–1.958	2.101	–1.288	–0.468	1.935	–1.754
P	0.051	0.037	0.199	0.640	0.054	0.08

Comparisons of renal function according to the different genotypes of the Klotho SNPs between Kazak and Uygur populations

We divided the subjects into 2 groups according to the genotype distributions of the Klotho gene. The differences in serum creatinine and estimated glomerular filtration rate between the Kazak and Uygur groups were statistically significant in the GA+AA genotype distributions of the rs1207568. However, renal function was not associated with GG genotype group between the 2 groups for (Table 4).

In CC genotype of rs564481, serum creatinine was significantly higher in Kazaks compared with Uygurs. Differences in blood urea nitrogen and estimated glomerular filtration rate were not statistically significant between the Kazak and Uygur groups for CC genotype group (Table 5).

In GG and CG+CC genotype of rs9527025, serum creatinine was significantly higher in Kazaks compared with Uygurs. Blood urea nitrogen and estimated glomerular filtration rate in GG and CG+CC genotypes of rs9527025 were not significantly associated with ethnicity (Table 6).

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Table 6. Comparison of renal function in different genotypes of rs9527025 between Kazak and Uygur populations.

	GG			GG+CC		
	BUN (mmol/L)	Scr (μmol/L)	eGFR (ml/min×1.73 m²)	BUN (mmol/L)	Scr (μmol/L)	eGFR (ml/min×1.73 m²)
Kazak	4.89±1.58	71.79±17.48	123.61±33.05	4.96±1.80	74.05±19.51	120.11±41.69
Uygur	5.13±1.42	68.40±19.60	127.75±30.83	5.04±1.38	66.60±13.25	133.83±37.74
t	–1.691	2.015	–1.391	–0.215	2.259	–1.712
P	0.091	0.044	0.165	0.831	0.026	0.09

Table 7. Comparison of renal function in different genotypes of rs9536314 between Kazak and Uygur populations.

	TT			GT+TT		
	BUN (mmol/L)	Scr (μmol/L)	eGFR (ml/min×1.73 m²)	BUN (mmol/L)	Scr (μmol/L)	eGFR (ml/min×1.73 m²)
Kazak	4.89±1.58	71.79±17.48	123.61±33.05	4.96±1.80	74.05±19.51	120.11±41.69
Uygur	5.13±1.42	68.40±19.60	127.75±30.83	5.04±1.38	66.60±13.25	133.83±37.74
t	–1.691	2.015	–1.391	–0.215	2.259	–1.712
P	0.091	0.044	0.165	0.831	0.026	0.09

Table 8. Klotho haplotype frequencies.

Haplotype	Kazak		Uygur		χ^2	*P*	*OR*	95% (CI)
ACGT	62.93	(0.082)	25.23	(0.051)	4.200	0.04	1.639	1.018–2.639
ATGT	122.97	(0.159)	60.82	(0.122)	3.033	0.081	1.340	0.963–1.865
GCCG	45.90	(0.059)	57.02	(0.114)	12.869	0.000	0.481	0.321–0.723
GCGT	446.11	(0.578)	264.81	(0.532)	1.820	0.178	1.170	0.931–1.469
GTGT	93.99	(0.122)	83.15	(0.167)	5.631	0.018	0.680	0.494–0.936

OR – odds ratio.

Serum creatinine was significantly higher in Kazaks compared with Uygurs in TT and GT+GG genotype of rs9536314. In the TT and GT+GG groups, blood urea nitrogen and estimated glomerular filtration rate were not significantly different between the Kazaks and Uygurs (Table 7).

These was a positive correlation between rs564481 and low-density lipoprotein in Kazak subjects (Spearman r=0.104, P=0.042). There were a positive correlation among rs9527025, rs9536314, and fasting blood glucose in Kazak subjects (Spearman r=0.168 and Spearman r=0.168, P=0.001 and P=0.001, respectively). In the Uygur population, the klotho gene was not associated with other factors. There was no association between the GFR and the genotypes among Uygurs and Kazaks (data not shown).

Haplotype analysis of klotho

We calculated the LD for all marker pairs in each gene. The LD test for all marker pairs in klotho showed strong LD for rs1207568, rs564481, rs9527025, and rs9536314. The results indicated that these 4 SNPs were in 1 LD block with a haplotype frequency. Haplotypes ACGT and GTGT were more frequent in the Kazaks than in the Uygurs (*P*=0.04 and *P*=0.018, respectively). In addition, the frequency of the GCCG haplotype was higher in the Uygurs than in the Kazaks (*P*=0.000). No difference in the other haplotypes was detected between the Kazaks and Uygurs (Table 8).

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Discussion

A previous study showed that the klotho gene was related to aging. The klotho gene is expressed in limited tissues and cell types. The highest expression is observed in distal convoluted tubules in the kidney and choroid plexus in the brain [1]. Klotho-deficient mice display multiple pathologies resembling human aging syndrome – a short life span, arteriosclerosis, hypogonadism, premature thymic involution, skin atrophy, pulmonary emphysema, and neurodegeneration [1]. Masuda et al. [17] reported that the aging phenotype can be reversed in klotho gene-deficient mice by transferring inducible klotho gene. When the klotho gene is no longer induced, the aging phenotype re-appears. This result suggests that klotho is an important anti-aging gene in mice. The tissue-specific *in vivo* expression of klotho was down-regulated during aging. Detection of klotho in the serum of the different populations showed that the concentration of klotho significantly reduces as age increases [18].

The klotho gene encodes a single-pass transmembrane protein. Klotho protein exists in 2 forms: the transmembrane form of klotho expressed primarily in renal tubular cells, and the secreted form circulating in the blood. Transmembrane Klotho is an obligatory co-receptor for fibroblast growth factor 23 (FGF23) and regulates phosphate, calcium, and vitamin D metabolism [19–21]. The secreted Klotho protein can regulate multiple ion channels and growth factor signalling pathways, including insulin/-like growth factor-1, Wnt, and transforming growth factor β1 [3–6]. The discovery of the klotho gene has led to identification of multiple novel endocrine axes mediated by endocrine FGFs and Klothos that regulates various metabolic processes.

Previous studies showed that the decline in renal function with aging is a universal phenomenon [22,23]. However, most studies were based on chronic kidney disease or combined with other risk factors, and there have been few studies of the natural decline of renal function in healthy people. Previous studies have found that blood pressure of Kazaks was higher than Uygurs, primarily due to the higher salt intake of Kazaks compared with Uygurs [15]. In the present study, we found that eGFR levels of Kazaks were lower than in Uygurs. Studies have indicated that the glomerular number and renal function in different ethnic groups were different [24,25].

Healthy Kazaks and Uygurs were selected as participants in this study. Four SNPs in the klotho gene from the Kazak and Uygur populations were genotyped, and the association between klotho and aging was investigated. This study found significant differences in the genotype and allele frequencies of the klotho gene polymorphisms (rs9527025 and rs9536314) between the Kazaks and the Uygurs. Previous studies showed that the heterozygous genotype has a survival advantage over the homozygous genotype in a population of elderly Bohemian Czech subjects [26]. The advantage of the heterozygous genotype was also observed in subjects aged ≥79 years in a study performed in 2 independent populations (Ashkenazi Jewish and Czech) [27]. However, these results were not confirmed in Baltimore Caucasian and Baltimore African-American subjects [28]. A previous study demonstrated that klotho gene mutation may be affected by race and other factors [3,28]. This result may be related to the differences in ethnicity; thus, the genotype distribution in different ethnic groups was different.

This study successfully established haplotypes for the klotho gene from different combinations of the 4 SNPs. The frequencies of ACGT and GTGT (established by rs1207568, rs564481, rs9527025, and rs9536314) were significantly higher in the Kazaks than in the age-matched Uygurs (P=0.04 and P=0.018). However, the frequency of the GCCG haplotype was significantly lower in the Kazaks than in the Uygurs (P<0.000). These results suggest that genetic factors may be involved in the aging process of different ethnicities and that the klotho gene may be associated with aging in different ethnic groups in Xinjiang. The epidemiological survey results of this study showed that the life expectancy of the Kazaks was shorter than that of the Uygurs and that the longevity of the Kazaks was relatively short. The genetic factors in different ethnic groups might have a function in the aging process of the residents in Xinjiang. Previous studies confirmed that genetics is an important factor that affects human longevity [29].

Conclusions

The genetic mutation of Klotho causes multiple aging-related disorders in nearly all organs and tissues. The Klotho protein itself or its metabolites may function as a humoral factor. In conclusion, klotho gene rs9527025 and rs9536314 polymorphisms were significantly different between the Kazak population and the Uygur population. A larger sample size and a more ethnically diverse population are needed to confirm these findings.

Statement

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests

The authors have declared that no competing interests exist.

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