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Study on the relationship between KCNQ1 gene–environment interaction and abnormal glucose metabolism in the elderly in a county of Hechi City, Guangxi

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Abstract

This study aimed to understand the potassium voltage-gated channel KQT-like subfamily, member 1 gene polymorphism in a rural elderly population in a county in Guangxi and to explore the possible relationship between its gene polymorphism and blood sugar. The 6 SNP loci of blood DNA samples from 4355 individuals were typed using the imLDRTM Multiple SNP Typing Kit from Shanghai Tianhao Biotechnology Co. The data combining epidemiological information (baseline questionnaire and physical examination results) and genotyping results were statistically analyzed using GMDR0.9 software and SPSS22.0 software. A total of 4355 elderly people aged 60 years and above were surveyed in this survey, and the total abnormal rate of glucose metabolism was 16·11 % (699/4355). Among them, male:female ratio was 1:1·48; the age group of 60–69 years old accounted for the highest proportion, with 2337 people, accounting for 53·66 % (2337/4355). The results of multivariate analysis showed that usually not doing farm work (OR 1·26; 95 % CI 1·06, 1·50), TAG ≥ 1·70 mmol/l (OR 1·19; 95 % CI 1·11, 1·27), hyperuricaemia (OR 1·034; 95 % CI 1·01, 1·66) and BMI ≥ 24 kg/m^2 (OR 1·06; 95 % CI 1·03, 1·09) may be risk factors for abnormal glucose metabolism. Among all participants, rs151290 locus AA genotype, A allele carriers (AA+AC) were 0.70 times more likely (0.54 to 0.91) and 0.82 times more likely (0.70 to 0.97) to develop abnormal glucose metabolism than CC genotype carriers, respectively. Carriers of the T allele at the rs2237892 locus (CT+TT) were 0.85 times more likely to have abnormal glucose metabolism than carriers of the CC genotype (0.72 to 0.99); rs2237897 locus CT gene. The possibility of abnormal glucose metabolism in the carriers of CC genotype, TT genotype and T allele (CT + TT) is 0·79 times (0·67–0·94), 0·74 times (0·55–0·99) and 0·78 times (0·66, 0·92). The results of multifactor dimensionality reduction showed that the optimal interaction model was a three-factor model consisting of farm work, TAG and rs2237897. The best model dendrogram found that the interaction between TAG and rs2237897 had the strongest effect on fasting blood glucose in the elderly in rural areas, and they were mutually antagonistic. Environment–gene interaction is an important factor affecting abnormal glucose metabolism in the elderly of a county in Hechi City, Guangxi.

Keywords: **Abnormal glucose metabolism: Elderly population: Gene–environment interaction: Interaction model: SNP**

Abbreviations: IFG, impaired fasting blood glucose; IGR, impaired glucose regulation; IGT, impaired glucose tolerance; KCNQ1, potassium voltage-gated channel KQT-like subfamily member 1; NCD, non-communicable diseases; T2DM, type 2 diabetes mellitus; UA, uric acid.

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Donglan County, Hechi City, Guangxi is a well-known hometown of longevity. It is located in the northwest of Guangxi Zhuang Autonomous Region, south of the Yunnan-Guizhou Plateau, and in the middle reaches of the Hongshui River Basin. According to the results of the seventh national census released by the National Bureau of Statistics: in 2020, the number of people aged 60 years and over in the country was 264·02 million, accounting for 18·70 %. Among them, the population of 65 years and over was 190·64 million, accounting for 13·50 %. The population has reached a new high. In Donglan County, the proportion of people over 60 years old accounted for 21·15 %, while those over 65 years old accounted for 16·12 %[1]. The proportion of people over 60 years old and over 65 years old was higher than the national average[2]. Studies have shown that genetic polymorphisms in the Zhuang population in Donglan County are related to longevity and may affect human ageing and lifespan through an unknown mechanism.

Non-communicable diseases (NCD) are the most common cause of long-term disability and premature death worldwide[1]. Despite a slowdown in the rate of increase in the incidence of NCD in some developed countries, the global disease and economic burden of NCD remains substantial due to the rising incidence of NCD in developing countries[2]. Globally, chronic diseases affect the health of many citizens and lead to reduced quality of life, and more than two-thirds of deaths each year are caused by chronic diseases. Problems related to chronic diseases, especially obesity and diabetes, are expected to rise rapidly in the coming years, especially in developing countries[3].

The disease burden has shifted from premature death to long-term disability in some high-income countries, and premature mortality from NCD is also rising rapidly in low- and middle-income countries, and these transitions have imposed a severe socio-economic burden globally[4].

It is estimated that there are about 300 million chronic disease patients in China, and the mortality caused by chronic diseases accounts for 86·00 % of the mortality of all diseases. Among all ageing countries, China is the country with the largest total population, and the harm of chronic diseases to the living standards of the elderly should be a cause for concern.

According to the latest estimates and projections from the International Diabetes Federation, the global number of adults with type 2 diabetes mellitus (T2DM) is expected to increase by 51 %, from 463 million in 2019 to 702 million in 2045[5].

Fasting glucose level is a feature of elevated blood glucose and may be a strong predictor of T2DM when elevated in non-diabetic patients. Genome-wide association analysis conducted by some scholars for non-diabetic patients found that SNP was related to fasting glucose[6].

Genetic factors, environmental exposures and behavioural factors may account for the growing burden of NCD. Although genome-wide association studies of different ethnic groups or populations have identified some common genetic variants for chronic diseases, given the diversity of causes of NCD, the associated common variants are not entirely suitable for Chinese people, especially rural populations in China's ethnic minority areas[7].

Chronic diseases or NCD are growing exponentially in developing countries, with high rates of mortality and disability, adding to the overall disease and social burden[8]. Diabetes (diabetes mellitus) is a metabolic disorder. There are about 285 million patients in the world. It is estimated that by 2030, the number of diabetic patients will increase by about 50·00 %. Impaired glucose regulation (IGR) includes three types: impaired fasting blood glucose (IFG), impaired glucose tolerance (IGT) and IFG with IGT (IFG/IGT)[9]. IGR refers to the metabolic state between normal glucose stability and diabetes. IGR is commonly referred to as prediabetes or non-diabetic hyperglycaemia and represents a high risk of T2DM[10]. Studies have shown that more than 50 % of IGR patients will develop T2DM and have an increased risk of CVD and cardiovascular death within 10 years if they do not make lifestyle changes or interventions, particularly weight loss and increased physical activity[11]. Lifestyle, environment and genetic factors, especially the interaction between the latter two, are the current causes of abnormal glucose metabolism.

In a recent study of the research group, we used the Illumina Infinium® Global Screening Array gene chip to perform a genome-wide association analysis on the blood glucose phenotypes of 1040 rural elderly people in Donglan County and found that the potassium voltage-gated channel KQT-like subfamily, member 1 (KCNQ1) gene SNP sites rs1057128, rs151290, rs163184, rs2237892, rs2237897 and rs231361 may be related to the glucose metabolism of this population.

Is the KCNQ1 gene possibly related to abnormal glucose metabolism in this population? So, we intend to analyse the blood glucose levels and related risk factors of 4355 elderly people in the three townships with the highest proportion of people aged 60 years and over in Donglan County.

Methods

Data collection

From August 2016 to July 2017, Wuchuan, Sanshi and Donglan in Donglan County, Hechi City, Guangxi Province, were selected as the study sites. The number of people aged 60 years and above in these three townships accounted for the total number of people in the townships and ranked among the top three in Donglan County. A total of 4475 elderly data were collected, and 120 data missing due to unqualified questionnaires, and physical examination data were excluded. Finally, 4355 valid data were obtained. Inclusion criteria: Those aged ≥ 60 years old, permanent residents of the above three towns (Wuzhuan Town, Sanshi Town and Donglan Town) and those who voluntarily join the study. Exclusion criteria: Those who do not agree to participate in this study by themselves or their family members and those whose physical condition is unstable during the investigation, such as those with mental illness, Alzheimer's, etc., who cannot communicate normally.

Preparation of the questionnaire

The self-designed questionnaire was prepared on its own on the basis of a large amount of literature. Experts in epidemiology, nutrition, labour hygiene and environmental hygiene were invited to participate in the review, and the questionnaire was revised again after the pre-survey was completed so that the questionnaire was suitable for the local rural elderly population.

Preliminary investigation

A total of 300 elderly people aged 60 years and above in Wuchuan Township, Donglan County, Hechi City, Guangxi Province, were selected as the study subjects of the pre-survey. During the pre-survey process, the possible problems of various workflows and contents were recorded in detail and adjusted in time to ensure that the follow-up work could be carried out smoothly. The questionnaire survey is completed by doctoral and master students in preventive medicine who have been trained by experts. The physical examination is completed by a doctor who has obtained the corresponding physician qualification certificate. At the end of the survey, the questionnaire will be reviewed uniformly, and the questionnaires will be checked for omissions and vacancies.

Genotyping

A total of six SNP locus in the KCNQ1 gene were selected for exploration. These six locus were all explored by genome-wide association analysis in the previous work of our group and found to be potentially associated with fasting blood glucose: rs1057128, rs151290, rs163184, rs2237892, rs2237897 and rs231362. The IML DRTM multi-SNP typing kit from Shanghai Tianhao Biotechnology Co., Ltd was used to type six SNP loci in blood DNA samples of 4355 individuals.

PCR Primers:

rs231362R: CCATCTGAAAGCCACTGAGTCTGA
F: AAGAGCAGGGCGAGCTGTGTAG
rs2237897R: AGACCCTGGGCCTTGGTCAC
F: CAATGTTGAGGGACGGAGGTG
rs2237892R: GGTGCTAAGGACCCAACAGGTG
F: AGAGCAAGGGTAGGTGCCTCTG
rs163184R: CAGCTTGTCAATGTGGGGAGGT
F: GCAGCTCTCCCAAAGCAGTCAG
rs151290R: ACAGCCTCAGAGCAGGCAAAGT
F: CAGCCGTTCCTGCTTCCTACTG
rs1057128R: ACCTCCTCTGCAGCTCCTTGAT
F: GGAACCAGGCTTATGCCATCAC

Statistical analysis

The Hardy–Weinberg law of genetic equilibrium was used to test whether the genotype frequencies of the study populations met genetic representativeness at $P > 0{\cdot}05$. Frequency and constitutive ratios were used to describe the qualitative data, and the χ^2 test or Fisher's exact probability method was used to compare genotype frequencies and allele frequencies between the two groups; mean (standard deviation) or median (Q1, Q3) was used to describe the qualitative data, and *t* test, ANOVA and rank-sum test were used for between-group comparisons of qualitative data. Multifactor dimensionality reduction and multifactor logistic regression were used to compare the site–site and gene–environment interactions of SNP in the KCNQ1 gene.

Results

A total of 4355 elderly people participated in this survey, of which 1757 (40·34 %) were males and 2598 (59·66 %) were females; the 60–69 years old age group accounted for the highest proportion, with 2337 people accounting for 53·66 % (2337/4355); followed by 60–69 years old, with 1610 people, accounting for 37·0 % (1610/4355); and with 408 people aged 80 years and above, accounting for 9·37 % (408/4355). There were 3656 people with normal glucose metabolism and a total of 699 people with abnormal glucose metabolism, and the rate of abnormal glucose metabolism was 16·05 % (699/4355). The factors with statistically significant differences between the normal and abnormal glucose metabolism groups were sex, education level, ethnicity, whether to do agricultural work and whether to drink alcohol ($P < 0{\cdot}05$), as shown in Table 1.

The comparison between groups found that the proportion of cooking methods in the abnormal group was higher than that in the normal group, 19·74 % (138/699) and 16·11 % (589/3656), respectively. The proportion of using animal oil for cooking in the abnormal group was lower than that in the normal group, 86·55 % (605/699) and 89·85 % (3285/3656), respectively. The proportion of daily consumption of vegetables was higher than that of the normal group, which were 74·68 % (522/699) and 69·61 % (2545/3656), respectively. There were significant differences in the above indicators between the two groups ($P < 0{\cdot}05$).

The proportions of abdominal obesity reflected by systolic blood pressure, diastolic blood pressure, TAG, uric acid (UA), creatinine, BMI, waist-hip ratio and bone mineral density in the abnormal glucose metabolism group were higher than those in the normal group. The differences in the above indicators between the two groups were statistically significant ($P < 0{\cdot}05$).

Analysis of influencing factors of abnormal glucose metabolism

The unconditional logistic regression method was used to explore the possible influencing factors of abnormal glucose metabolism. Among them, whether glucose metabolism is abnormal was taken as the dependent variable, and the factors that are meaningful in univariate analysis were taken as independent variables which include sex, ethnicity, WHR, BMI, bone density, alcohol consumption, daily consumption of dark vegetables, animal fats, cooking methods, farm work, systolic blood pressure, diastolic blood pressure, TAG, UA, creatinine and grip strength. The assignment of each variable is shown in Table 2. The results of multivariate analysis showed that farm work (OR (95 % CI) = 1·26 (1·06, 1·50)), TAG (OR (95 % CI) = 1·19 (1·11, 1·27)), UA (OR (95 % CI) = 1·03 (1·01, 1·66)) and BMI (OR (95 % CI) = 1·06 (1·03, 1·09)) are possible influencing factors of abnormal glucose metabolism (Table 2).

Table 1. Comparison of demographic characteristics and relevant clinical indicators between normal and abnormal glucose metabolism groups (Numbers and percentages; mean values and standard deviations)

	Total (*n* 4355)		Normal group (*n* 3656)		Abnormal group (*n* 699)			
Factors	*n*	%	*n*	%	*n*	%	χ^2/t	*P*
Demographic characteristics (*n*, %)								
Sex							24·64	< 0·01
Male	1757	40·34	1416	38·73	341	48·78		
Female	2598	59·66	2240	61·27	358	51·22		
Education level							31·88	< 0·01
Elementary school and below	3492	80·18	2945	80·55	547	78·25		
Junior high school and above	863	19·81	1410	38·57	152	21·75		
National							7·42	0·03
Han	444	10·20	353	9·66	91	13·02		
Zhuang	371	8·52	3137	85·80	575	82·26		
Others	199	4·57	166	4·54	33	4·72		
Doing farm work							15·43	< 0·01
Yes	2807	64·45	2402	65·70	405	57·94		
No	1548	35·55	1254	34·30	294	42·06		
Drinking							29·18	< 0·01
Yes	1064	24·43	837	22·89	227	32·47		
No	3291	75·57	2819	77·11	472	67·53		
Dietary status								
Cooking methods							5·57	0·02
Boiled/steamed/stewed	3628	83·30	3067	83·89	561	80·26		
Fried	727	16·69	589	16·11	138	19·74		
Cooking with animal oil							6·70	0·01
No	465	10·68	371	10·15	94	13·44		
Yes	3890	89·32	3285	89·85	605	86·55		
Eating vegetables every day							7·23	0·07
No	1288	29·58	1111	30·39	177	25·32		
Yes	3067	70·42	2545	69·61	522	74·68		
			Mean	SD	Mean	SD		
Related clinical indicators								
SBP (mmHg)			140·09	22·65	143·80	23·83	–3·94	< 0·01
DBP (mmHg)			80·17	13·15	82·32	14·04	–3·74	< 0·01
TAG (mmol/l)								
n			1·03		1·22		–8·92	< 0·01
%			0·74		0·78			
UA (μmol/l)			320·62	113·91	355·16	126·10	–6·73	< 0·01
Cr (μmol/l)			67·66	24·92	70·33	29·73	–2·24	0·03
GLU (mmol/l)			4·54	0·59	7·26	2·91	–24·88	< 0·01
			n	%	*n*	%		
WHR (≥ 0·9)			1553	42·47	346	49·49	11·23	0·01
BMI (≥ 24 kg/m^2)			827	22·62	222	31·76	26·81	< 0·01
BMD (g/cm^3) (T ≤ –2·5)			852	23·30	177	25·32	26·16	< 0·01

SBP, systolic blood pressure; DBP, diastolic blood pressure; UA, uric acid; Cr, creatinine; WHR; waist-hip ratio; BMD, bone mineral density.

Characteristics of polymorphic distribution

Hardy–Weinberg equilibrium test for study population. The Hardy–Weinberg equilibrium test was performed on the KCNQ1 gene SNP loci rs1057128, rs151290, rs163184, rs2237892, rs2237897 and rs231362 in the abnormal glucose metabolism group and the normal group by using HWE software, all of which met the Hardy–Weinberg equilibrium rule ($P > 0·05$). It indicates that the samples selected in this study are representative of the population, and their gene frequency can be used as a representative of population gene distribution, as shown in Table 3.

Comparison of genotype and allele frequency of each SNP in KCNQ1 gene. It can be seen from Table 4 that in the genotype distribution of each SNP locus of the KCNQ1 gene in the normal blood sugar group and the abnormal group, the differences in the genotype distribution of the three locus rs151290, rs163184 and rs2237897 were statistically significant ($P < 0·05$). The allele frequency distribution of rs151290, rs163184, rs2237892 and rs2237897 was statistically significant ($P < 0·05$).

Correlation analysis between different gene models of KCNQ1 gene SNP loci and abnormal glucose metabolism. After adjusting for sex and age, unconditional logistic regression analysis was used to explore the association between different models of genotypes of each SNP locus of the KCNQ1 gene and abnormal glucose metabolism. The results showed that for the rs151290 locus, the CC genotype was used as the reference

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Table 2. Logistic regression analysis of influencing factors of abnormal glucose metabolism (Odds ratios and 95 % confidence intervals)

Factors	B	S.E.	Wald	*P*	OR	95 % CI
Sex	–0·26	0·13	4·22	0·04	0·77	0·60, 0·99
TAG	0·17	0·03	24·56	< 0·01	1·19	1·11, 1·27
Uric acid	0·03	0·01	6·04	0·01	1·03	1·01, 1·06
BMI	0·05	0·02	13·64	< 0·01	1·06	1·03, 1·09
Doing farm work	0·23	0·09	6·69	0·01	1·26	1·06, 1·50
Constant	–3·50	0·50	50·88	< 0·01		

Table 3. Hardy–Weinberg equilibrium genetic law test for six SNP in normal and abnormal glucose metabolism groups (Numbers and percentages)

Genotype	Normal group				Abnormal group			
	n	%	χ^2	*P*	*n*	%	χ^2	*P*
rs1057128								
AA	263	7·19			38	5·44		
AG	1374	37·58	0·93	0·63	253	36·19	0·02	0·99
GG	2019	55·22			408	58·37		
rs151290								
AA	586	16·03			88	12·59		
AC	1777	48·61	0·18	0·91	332	47·50	0·24	0·89
CC	1293	35·37			279	39·91		
rs163184								
GG	559	15·29			134	19·18		
GT	1691	46·25	0·90	0·64	336	48·07	0·17	0·92
TT	1406	38·46			229	32·76		
rs2237892								
CC	1636	44·75			341	48·78		
CT	1634	44·69	0·28	0·87	298	42·63	0·08	0·96
TT	386	10·56			60	8·58		
rs2237897								
CC	1651	45·16			358	51·22		
CT	1619	44·28	0·07	0·97	280	40·06	0·15	0·93
TT	386	10·56			61	8·73		
rs231362								
AA	30	0·82			9	1·29		
AG	599	16·38	< 0·01	1·00	124	17·74	0·32	0·85
GG	3027	82·80			566	80·97		

group, the AA genotype and the A allele carrier (AA + AC) group were statistically associated with abnormal glucose metabolism, and the OR (95 % CI) values were 0·70 (0·54, 0·91) and 0·82 (0·70, 0·97), respectively. For the rs163184 locus, the TT genotype was used as the reference group; the GT genotype, the GG genotype and the G allele carrier (GT + GG) group were all statistically associated with abnormal glucose metabolism; and the OR (95 % CI) values were 1·21 (1·01, 1·45), 1·46 (1·16, 1·85) and 1·27 (1·07, 1·58). For the rs2237892 locus, the CC genotype was used as the reference group, the T allele carrier (CT + TT) group was statistically associated with abnormal glucose metabolism, and the OR (95 % CI) values were 0·85 (0·72, 1·00). For the rs2237897 locus, the CC genotype was used as the reference group; the CT genotype, TT genotype and T allele carrier (CT + TT) were statistically associated with abnormal glucose metabolism; and the OR (95 % CI) values were 0·79 (0·67, 0·94),0·74 (0·55, 0·99) and 0·78 (0·66, 0·92), as shown in Table 5.

Table 4. Genotype and allele frequency distribution of six SNP loci in the KCNQ1 gene (Numbers and percentages)

Locus	Genotype and allele	Normal group		Abnormal group		χ^2	*P*
		n	%	*n*	%		
rs1057128							
	AA	263	7.19	38	5.44	3.97	0.14
	AG	1374	37.58	253	36.19		
	GG	2019	55.22	408	58.37		
	A	1900	25.99	329	23.53	3.70	0.05
	G	5412	74.02	1069	76.47		
rs151290							
	AA	586	16.03	88	12.59	8.00	0.02
	AC	1777	48.61	332	47.50		
	CC	1293	35.37	279	39.91		
	A	2949	40.33	508	36.34	7.82	0.01
	C	4363	59.67	890	63.66		
rs163184							
	GG	559	15.29	134	19.17	11.04	< 0.01
	GT	1691	46.25	336.	48.07		
	TT	1406	38.46	229	32.76		
	G	2809	38.42	604	43.20	11.29	< 0.01
	T	4503	61.58	794	56.80		
rs2237892							
	CC	1636	44.75	341	48.78	4.90	0.09
	CT	1634	44.69	298	42.63		
	TT	386	10.56	60	8.58		
	C	4906	67.10	980	70.10	4.84	0.03
	T	2406	32.90	418	29.90		
rs2237897							
	CC	1651	45.16	358	51.22	8.99	0.01
	CT	1619	44.28	280	40.06		
	TT	386	10.56	61	8.87		
	C	4921	67.30	996	71.24	8.38	< 0.01
	T	2391	32.70	402	28.76		
rs231362							
	AA	30	0.82	9	1.29	2.32	0.31
	AG	599	16.38	124	17.74		
	GG	3027	82.80	566	80.97		
	A	659	9.01	142	10.16	1.84	0.18
	G	6653	90.99	1256	89.84		

The relationship between KCNQ1 locus-locus and site-environment and abnormal glucose metabolism. The interaction between four environmental factors (doing farm work, BMI, UA, TAG) and six loci (rs1057128, rs151290, rs163184, rs2237892, rs2237897 and rs231362) of KCNQ1 gene was analysed by GMDR software, and it was found that the cross-validation agreement of the model by TAG alone was 10/10, and the cross-validation of the two-locus model consisting of BMI and TAG and the three-locus model consisting of farm work, TAG and rs2237897 were 9/10. Due to the three-site model composed of doing farm work, TAG and rs2237897, the test equilibrium was higher than that of the model composed of other sites and the model's $P < 0{\cdot}05$; therefore, the optimal interaction model was a three-locus model composed of doing farm work, TAG and rs2237897, as shown in Table 6.

The best model ring diagram shows that there are two combinations of high-risk factors in the CC genotype (wild type, left panel) at rs2237897. Combination 1: Usually not doing farm work and the combination of normal and high TAG. Combination 2: Usually doing farm work and the combination

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Table 5. Correlation analysis between different models of six SNP loci in KCNQ1 gene and abnormal glucose metabolism (Numbers and percentages; odds ratios and 95 % confidence intervals)

		Normal group		Abnormal group				
Locus	Genotype	*n*	%	*n*	%	*P*	OR	95 % CI
rs1057128								
	GG	2019	55·22	408	58·37		1	
	AG	1374	37·58	253	36·19	0·34	0·92	0·77, 1·09
	AA	263	7·19	38	5·44	0·07	0·72	0·50, 1·03
	GG	2019	55·22	408	58·37		1	
	AA + AG	1637	44·78	291	41·63	0·15	0·89	0·75, 1·05
rs151290								
	CC	1293	35·37	279	39·91		1	
	AC	1777	48·61	332	47·50	0·09	0·86	0·72, 1·03
	AA	586	16·03	88	12·59	0·01	0·70	0·54, 0·91
	CC	1293	35·37	279	39·91		1	
	AA + AC	2363	64·63	420	60·09	0·02	0·82	0·70, 0·97
rs163184								
	TT	1406	38·46	229	32·76		1	
	GT	1691	46·25	336	48·07	0·04	1·21	1·01, 1·45
	GG	559	15·29	134	19·17	< 0·01	1·46	1·16, 1·85
	TT	1406	38·46	229	32·76		1	
	GT + GG	2250	61·54	470	67·24	< 0·01	1·27	1·07, 1·51
rs2237892								
	CC	1636	44·75	341	48·79		1	
	CT	1634	44·69	298	42·63	0·11	0·87	0·73, 1·03
	TT	386	10·56	60	8·58	0·06	0·76	0·56, 1·02
	CC	1636	44·75	341	48·79		1	
	CT + TT	2020	55·25	358	51·21	0·05	0·85	0·72, 1·00
rs2237897								
	CC	1651	45·16	358	51·22		1	
	CT	1619	44·28	280	40·06	< 0·01	0·79	0·67, 0·94
	TT	386	10·56	61	8·73	0·04	0·74	0·55, 0·99
	CC	1651	45·16	358	51·22		1	
	CT + TT	2005	54·84	341	48·78	< 0·01	0·78	0·66, 0·92
rs231362								
	GG	3027	82·80	566	80·97		1	
	AG	599	16·38	124	17·74	0·39	1·10	0·89, 1·36
	AA	30	0·82	9	1·29	0·20	1·638	0·77, 3·48
	GG	3027	82·80	566	80·97		1	
	AA + AG	629	17·20	133	19·03	0·27	1·12	0·91, 1·38

Table 6. Models for analysing locus-locus and locus-environmental factor interactions by GMDR method

Model	Training bal. acc	Testing bal. acc	CV consistency	Sign test	*P*
TAG	0·56	0·56	10/10	10	< 0·01
BMI/TAG	0·57	0·56	9/10	10	< 0·01
Doing farm work/TAG/rs2237897	0·58	0·57	9/10	10	< 0·01

of high TAG. In combination with the CT + TT genotype (mutant type, right picture) at rs2237897, the combination of abnormal TAG and normal non-farm work and farm work are high-risk factors (see Fig. 1.)

As can be seen from the interaction tree, locus rs2237897 in the best model is closest to TAG, and their interaction is relatively strong but antagonistic, as shown in Fig. 2.

Discussion

Abnormal glucose metabolism includes IGR and diabetes[12]. IGR is an intermediate metabolic state between normal blood glucose and diabetes, including IGT and IFG[9]. In this study, the inclusion criteria for abnormal glucose metabolism in the elderly were fasting blood glucose ≥ 5·6 mmol/l and diabetic patients with normal fasting blood glucose after taking hypoglycaemic drugs, including impaired fasting blood glucose and diabetic patients. Some scholars believe that people in a state of impaired fasting blood glucose have significantly decreased islet β-cell function parameters and insulin sensitivity parameters and increased insulin resistance parameters[13]. The progression from prediabetes to diabetes is associated with the following risk factors: age, genetic factors, obesity, dyslipidaemia, hypertension, hyperglycaemia and plasma insulin levels and poor beta

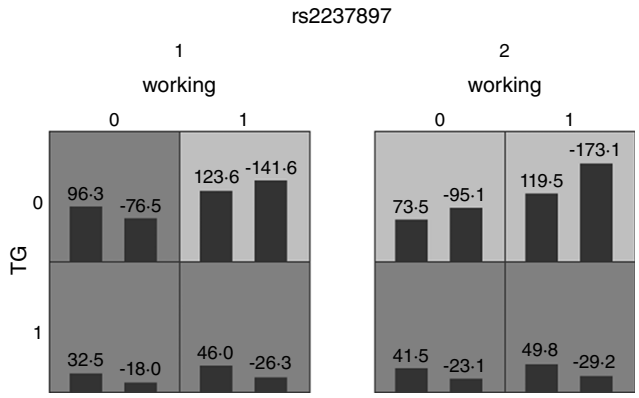

Fig. 1. Ring diagram of the best model.

cell function, smoking, alcohol consumption, sedentary life and physical inactivity way[14]. If patients with IFG pay attention to diet, exercise, lifestyle and other aspects, their blood glucose may gradually return to the normal level; on the contrary, if they do not control in daily life, they may develop diabetes[15]. Dysglycemia is prevalent in the Chinese population. Obesity and dyslipidaemia are important predictors of diabetes and IFG. Regular physical activity and fruit and vegetable intake may be favourable factors for maintaining normal blood glucose level[16].Our study found that farm work, TAG, UA and BMI may be the influencing factors of fasting blood glucose levels in a rural elderly population in a county in Hechi City, Guangxi, which is similar to the above conclusion. However, whether it is possible to reduce blood sugar through lifestyle changes requires continued follow-up observation to verify.

Some studies have confirmed that FPG level is highly heritable in Chinese population, and some gene variants are involved in regulatory domains, functional genes and biological pathways regulating FPG level. These results provide important directions for further research on the mechanism of glucose metabolism homeostasis[17].The study by Jana V *et al.*[18] found that in the Dutch population, genotype variants of three KCNQ1 gene loci (rs151290, rs2237892 and rs2237895) were significantly associated with T2DM, and rs151290 had the strongest correlation. A meta-analysis of the association between the KCNQ1 polymorphism and the risk of T2DM found that the polymorphisms of KCNQ1 gene (rs2237892, rs2283228, rs2237895, rs151290 and rs2074196) may be the susceptibility factors for T2DM, especially in Asian population[19]. In a cohort study of 3210 Chinese Han population, Qibin Qi *et al.*[20] found that KCNQ1 gene SNP rs2237892, rs2237895 and rs2237897 were closely associated with T2DM, IFG and combined IFG/T2DM. Among the Kazakh people, gene KCNQ1 loci rs2237892 and rs7756992 were statistically correlated with glucose metabolism, blood lipid profile and BMI in patients with T2DM in the population[21]. The results of this study suggest that the polymorphisms of KCNQ1 gene loci rs151290, rs2237892 and rs2237897 may be associated with the risk of abnormal glucose metabolism in rural elderly people in a county in Guangxi. It is consistent with the above conclusion. It is suggested that the effect of KCNQ1 gene polymorphism on glucose metabolism may be irrespective of ethnic and geographical differences.

In our study, with the CC genotype as the reference, the AA genotype of rs151290 was associated with a reduced risk of abnormal glucose metabolism, and with the C allele as a reference, the A allele was associated with a reduced risk of abnormal glucose metabolism. It is consistent with the results of a meta-analysis of 6696 diabetic patients and 7151 controlled studies, which concluded that the locus rs151290 in KCNQ1 had a population-attributable risk rate of 6·83 %, and the risk allele C was associated with T2DM in the global population associated with increased risk[22]. Many researchers have concluded that the KCNQ1 locus rs2237892 is associated with the risk of T2DM. Zhang Wanling *et al.*[23] found that when the TT genotype of rs2237892 was used as the reference, both CT and CC genotypes were associated with increased risk of T2DM, and when the T allele was used as the reference, the C allele was associated with an increased risk of T2DM. In the Chinese Han population, some scholars[24] verified the association between rs2237892 of the KCNQ1 gene and T2DM, and its risk allele C-specific OR (95 % CI) was 1·37 (1·19–1·69).

Lee *et al.*[25] also found that the C allele of KCNQ1 rs2237892 was significantly associated with T2DM in the Korean population. The above studies of domestic and foreign researchers all believe that with the T allele as a reference, the C allele is associated with an increased risk of T2DM. In this study, taking the CC genotype as a reference, the T allele carriage of rs2237892 was associated with a reduced risk of abnormal glucose metabolism, consistent with the above findings. The site rs2237897 in the KCNQ1 gene has been reported to be involved

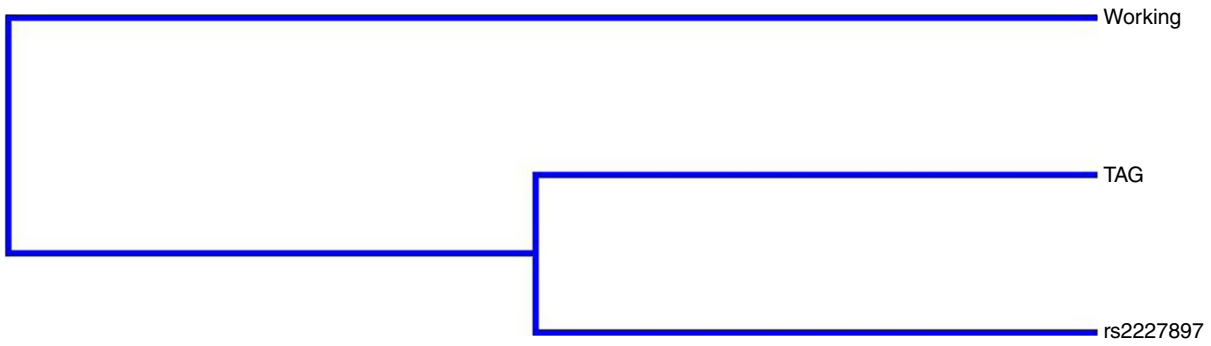

Fig. 2. Tree diagram of the best model.

in acute insulin and c-peptide responses following arginine stimulation. The independent effect test showed that the rs2237897 variant had the strongest correlation with T2DM. Li Yiping *et al.*[26] found in their study of Chinese population that the rs2237897T allele in KCNQ1 is a protective allele for T2DM. In this study, taking the CC genotype as a reference, the T allele carriage of rs2237897 was associated with a reduced risk of abnormal glucose metabolism. Among them, the risk of T2DM in individuals with CT and TT genotypes was 0·79 and 0·74 times that of individuals with CC genotype, respectively. Individuals with alleles were 0·78 times more than individuals with CC genotypes, indicating that taking the C allele as a reference, the T allele carrying was associated with a reduced risk of abnormal glucose metabolism, which was consistent with the above conclusions.

Most disease effects are the result of a series of dynamic interactions under the combined action of genes and environmental factors. When changes in genetic or environmental factors disrupt the overall homeostasis, disease-related effects may appear[27]. Identifying environment-specific genetic effects is a key challenge in understanding complex trait diseases[28]. Among the numerous diseases that humans face, environment–gene interactions have been widely discussed, but only a few interaction patterns have been replicated[29]. A gene–environment interaction study of T2DM risk in older adults in their 50s showed an interaction between environmental factors and genetic variation in T2DM risk, suggesting that physical activity participation, diet, alcohol consumption, smoking and socio-economic status may increase or decrease the effect of different SNP on blood glucose[30]. In our study, by using multifactor dimensionality reduction to investigate the effect of gene and environment interaction on fasting blood glucose levels in rural elderly population, the optimal interaction model was found to be composed of farm work, TAG and rs2237897. In the three-point model, the high-risk group in this model has an increased risk of abnormal glucose metabolism compared with the low-risk group, and its OR (95 % CI) = 2·07 (1·60, 2·68); in addition, the tree model also showed the relationship between TAG and rs2237897. The interaction effect had the strongest effect on fasting blood glucose in the rural elderly population, and they were mutually antagonistic.

Conclusions

Environment–gene interactions are possible factors influencing glucose metabolism abnormalities in elderly people in a county of Hechi City, Guangxi, China. Polymorphisms of KCNQ1 gene loci rs151290, rs2237892 and rs2237897 may be associated with the risk of abnormal glucose metabolism. The interaction effects between whether or not to do farm work, TAG and KCNQ1 locus rs2237897 had the greatest impact on abnormal glucose metabolism in a rural elderly population in this county.

There were some limitations in this study

The relationship between the specific locus polymorphism and environmental interaction of the gene KCNQ1 obtained in this study and abnormal glucose metabolism has not been verified in other populations and will be verified from multiple perspectives in other populations in the future.

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S. C.: conceptualisation, methodology, software, data management, writing – manuscript preparation; C. H.: formal analysis, visualisation, investigation; H. L.: resource and data management; Y. L.: resources, writing – original manuscript; J. C.: data management, writing – reviews and editing; T. L.: investigation and verification; X. L.: investigation and method; B. L.: surveys, resources; Y. W.: investigation, formal analysis, J. T.: investigation and supervision, Z. Z.: supervision, project management, funding acquisition, J. Q.: supervision, project management, funding acquisition.

The authors declare that there is no competing interest.

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