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Genetic Predictors of Type 2 Diabetes in Yakuts

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Abstract

The goal of this study was to investigate the distribution of alleles and genotypes of the *KCNJ11* rs5219, *PPARG* rs1801282, *TCF7L2* rs7903146/rs12255372 SNPs in Yakuts with T2D, in comparison with other ethnic populations.

Methods and Results: The study cohort consisted of 26 Yakut patients diagnosed with T2D (YKT2D). Genotyping of rs5219 *(KCNJ11)*, rs1801282 *(PPARG)*, rs7903146 and rs12255372 *(TCF7L2)* SNPs was performed by pyrosequencing using PyroMark Q48 Autoprep sequencer (QIAGEN).

The genotyping of the studied group of Yakuts did not reveal statistically significant differences between control groups and YKT2D patients with respect to the polymorphic variants of the *KCNJ11*, *PPARG*, and *TCF7L2* genes. The allele frequency analysis of the polymorphisms of the *KCNJ11*, *PPARG*, and *TCF7L2* genes demonstrated a low frequency of the risk T-allele in the *TCF7L2* (rs7903146, rs12255372) in Asian populations, compared to other human populations. We identified three haplotypes [CG (90.5%), TT (6.8%), and TG (2.7%)] in the YKT2D cohort. Also, we observed a strong LD between two SNPs (rs7903146 and rs12255372) of the *TCF7L2* gene in the majority of groups, including YKT2D (D '= 1, LOD = 4.92), except for African populations, where a very weak LD (D '= 0.001-0.435, LOD = 0.0-0.73) was observed.**(International Journal of Biomedicine. 2021;11(3):355-360.)**

Key Words: *KCNJ11* • *PPARG* • *TCF7L2* • type 2 diabetes • single nucleotide polymorphism

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Abbreviations

GWAS, genome-wide association studies**; HWE**, Hardy-Weinberg equilibrium; **KATP,** adenosine triphosphate (ATP)−sensitive potassium channel; **KCNJ11**, potassium inwardly rectifying channel, subfamily J, member 11; **LD**, linkage disequilibrium; **PPARG,** peroxisome proliferator-activated receptor gamma; **SNPs**, single nucleotide polymorphisms; **T2D,** type 2 diabetes; **TCF7L2**, transcription factor-7–like 2.

Introduction

Type 2 diabetes (T2D) is characterized by insulin resistance and/or insufficient insulin production by β-cells.[(1)] T2D is believed to be a polygenic disorder that results from a complex interaction of many genes and environmental factors. SNPs are now well recognized as the most popular molecular markers for genetic studies. SNPs are the most common genetic variation; they occur, on average, once in every 400-1,000 base pairs along DNA.[(2-5)] To date, GWAS

have discovered >600 genetic variants associated with T2D.[6]

Multiple genes and their interactions are involved in the insulin secretion pathway. The glucose-dependent insulin secretion in β-cells of the pancreas is regulated by KATP. KATP is a heteromeric protein, composed of four inward-rectifier potassium ion channel (Kir6.2) tetramers, which form the pore of the KATP channel, as well as sulfonylurea receptor 1 subunits surrounding the pore. Kir6.2 is encoded by the *KCNJ11* gene—a member of the potassium channel genes. Closure of ATP-regulated K+ channels (KATP channels) plays a central role in glucose-stimulated insulin secretion in β-cells.[7] Numerous studies have reported the involvement of SNPs of the *KCNJ11* gene and their interactions in the susceptibility to diabetes. KCNJ11 rs5219 is a common variant in which substitution of C to T replaces glutamate with lysine at position 23 (E23K) in exon 1, causing a decrease of insulin secretion. Among the SNPs in the *KCNJ11* gene, rs5219 is associated with an increased risk for T2D in various populations.[7-9]

The *PPARG* gene is located on chromosome 3p25 and plays a critical role in adipose tissue formation and subcellular metabolism of arterial wall macrophage foam cells. *PPARG* controls insulin sensitivity by transcriptionally stimulating adipocyte-specific genes involved in insulin signaling, lipid accumulation, fatty acid uptake, and glucose uptake. The *PPARG* rs1801282C>G polymorphism, an SNP in exon 2 of PPAR-γ, encodes a proline→alanine substitution at amino acid residue 12. This mutation reduces the transcription of *PPARG*. The *PPARG* rs1801282C>G polymorphism has been extensively investigated and was found to be correlated with the risk of cardiovascular diseases and T2D.[10]

The *TCF7L2* gene is responsible for the synthesis of a transcription factor 7-like 2, which regulates the expression of the proglucagon gene and other genes involved in carbohydrate metabolism. The *TCF7L2* gene is localized on chromosome 10q25.3. The risk T-allele of the *TCF7L2* rs7903146 SNP is associated with increased *TCF7L2* expression, and decreased insulin content and secretion(11). Risk T-allele carriers are further characterized by an elevated plasma proinsulin level and an increased proinsulin-to-insulin ratio suggestive of perturbed proinsulin processing.[11-15] The rs12255372 SNP, located in the intron region of *TCF7L2*, contains a single base G to T transition at position 293. A few epidemiological studies have assessed the relationship between rs12255372 and T2D, but the results of these studies are contradictory.[16-21]

According to previous studies on the Yakut populations, the most significant variants involved in the development of T2D were identified in the *ABCC8* gene (rs1799859 SNP and rs10811661 SNP), *LPL* gene (Int6/PvuII G>A and Int8/Hind3 variants), and *RSTN* gene (CDKN2A/B rs34861192 SNP and rs32119177 SNP). There were no statistically significant differences between the control groups and patients with T2D with respect to the polymorphic variants of the *TCF7L2* and *KCNJ11* genes.[22]

The goal of this study was to investigate the distribution of alleles and genotypes of the *KCNJ11* rs5219, *PPARG* rs1801282, *TCF7L2* rs7903146/rs12255372 SNPs in Yakuts with T2D, in comparison with other ethnic populations.

Materials and Methods

The study cohort consisted of 26 Yakut patients diagnosed with T2D (YKT2D). Exclusion criteria were other types of diabetes, low fasting insulin levels, cancer, heart failure (NYHA class III-IV), concomitant corticosteroid or estrogen treatment, alcoholism, drug addiction, dementia, and serious mental disorders. The reference group was a cohort of different populations without T2D, obtained from the 1000 Genomes Project database and other sources.

Genotyping of rs5219 *(KCNJ11)*, rs1801282 *(PPARG)*, rs7903146 and rs12255372 *(TCF7L2)* SNPs was performed by pyrosequencing using PyroMark Q48 Autoprep sequencer (QIAGEN).

The study was approved by the Ethics Committee of the Center for Personalized Medicine at the Republican Clinical Hospital No. 3. Written informed consent was obtained from each research participant (or the participant's parent/guardian).

Statistical analysis was performed using Microsoft Excel 2010.and PASW Statistics 18. The correspondence of the distributions of genotypes to the expected values at HWE and comparison of the frequencies of allelic variants/genotypes were performed using the chi-square test. Haploview software (ver. 4.2) was used to assess the *TCF7L2* haplotypes and frequencies based on genotyping data and to test the association between alleles and haplotypes of the *TCF7L2* gene.[23] A probability value of $P<0.05$ was considered statistically significant.

Results and Discussion

The results of this study show that the distribution of genotypes for all studied SNPs do not have significant deviations from the HWE. Comparative analysis of allele and genotype frequency distribution in the examined group is presented in Table 1.

Table 1.

Distribution of alleles and genotypes of polymorphisms of genes KCNJ11, PPARG, and TCF7L2 in a group of Yakut patients with T2D

Gene (RefSNP)	Dis	Genotype			Alleles		χ^2	P
		CC	CT	TT	C	T		
KCNJ11 (rs5219)	OF	42.3	46.2	11.5	0.654	0.346	0.010	0.920
	EF	42.8	45.3	12.0				
		CC	CG	GG	C	G	χ^2	P
PPARG (rs1801282)	OF	65.4	30.8	3.8	0.808	0.192	0.002	0.961
	EF	65.2	31.1	3.7				
		CC	CT	TT	C	T	χ^2	P
TCF7L2 (rs7903146)	OF	92.3	7.7	0.0	0.962	0.038	0.042	0.838
	EF	92.5	7.4	0.1				
		GG	GT	TT	G	T	χ^2	P
TCF7L2 (rs12255372)	OF	96.15	3.85	0.00	0.981	0.019	0.010	0.920
	EF	96.19	3.77	0.04				

Dis- distribution, OF- observed frequency, EF- expected frequency

An analysis of the frequency distribution of alleles and genotypes of the *KCNJ11* rs5219 SNP in a sample of YKT2D revealed the predominance of the heterozygous CT genotype (46.2%); the TT genotype (11.5%) was less common. Several meta-analyses and association studies reported a strong association between the r5219 (*KCNJ11 E23K*) and susceptibility to T2D, mainly in Caucasians and in some Asian populations.[24-26] However, some other association studies did not show any association between this polymorphism and susceptibility to T2D.[27]

The study of the *PPARG* rs1801282 showed the prevalence of the CC genotype (65.4%), while the frequency of the GG genotype was 3.8%. The *PPARG* rs1801282C>G polymorphism has been extensively studied and found to correlate with the risk of cardiovascular disease and T2D.[28-31] However, other studies reported contradictory results.[32] For example, it was shown that the Pro12Ala polymorphism protects against diabetes in Caucasians, but not in the South Asian population.[33-34]

The *TCF7L2* rs7903146 SNP was characterized by the prevalence of the CC genotype (92.3%), while the TT

Table 2.

Frequency of risk alleles in KCNJ11, PPARG and TCF7L2 gene polymorphisms in the cohort of Yakuts with T2D and other ethnic populations

Group	Genes and polymorphisms				Reference
	KCNJ11	*PPARG*	*TCF7L2*		
	rs5219	rs1801282	rs7903146	rs12255372	
	T	G	T	T	
YKT2D	34.6 (26)	19.2 (26)	3.8 (26)	1.9 (26)	-
YKTH	33 (348)	15 (348)	5 (348)	Without data	[35]
RUS	43.9 (264)	20.7 (94)	27.6 (201)	16.1 (597)	[27-40]
KGZ	33 (109)	13 (109)	11 (109)	Without data	[36]
JPN	33 (104)	3 (104)	3 (104)	2 (104)	[23]
CDX	22.6 (93)	0.5 (93)	2.2 (93)	1.1 (93)	
GBR	26.4 (48)	12.1 (22)	25.8 (47)	26.4 (48)	
IBS	38.3 (82)	11.7 (22)	39.7 (85)	37.4 (80)	
PEL	32 (85)	26 (85)	14 (85)	11 (85)	
PJL	44 (96)	14 (96)	25 (96)	21 (96)	
STU	30.4 (62)	12.3 (25)	33.8 (69)	22.1 (45)	
MSL	0	0	22.9 (39)	38.8 (66)	
YRI	0	0	24.1 (52)	30.1 (65)	
ACB	5.7 (11)	1.6 (3)	27.6(53)	24.5 (47)	
ASW	13.9 (17)	2.5 (3)	36.1 (44)	27/9 (34)	
ESN	0	0	24.7 (49)	29.3 (58)	

Abbreviations: YKT2D - Yakuts patients with T2D; YKTH - healthy Yakuts without T2D; RUS - healthy Russians; KGZ - healthy Kyrgyz; ACB - African Caribbean in Barbados; ASW - African Ancestry in Southwest US; CDX - Chinese Dai in Xishuangbanna, China; ESN - Esan in Nigeria; GBR - British in England and Scotland; GWD - Gambian in Western Division, The Gambia; IBS - Iberian populations in Spain; JPT - Japanese in Tokyo, Japan; MSL - Mende in Sierra Leone; MXL - Mexican Ancestry in Los Angeles, California; PEL - Peruvian in Lima, Peru; PJL - Punjabi in Lahore, Pakistan; STU - Sri Lankan Tamil in the UK; YRI - Yoruba in Ibadan, Nigeria.

Table 3.

The frequency distribution of TCF7L2 gene haplotypes for two SNPs (rs7903146 and rs12255372) in Yakuts with T2D and other ethnic populations

Group	Haplotype				Linkage disequilibrium (LD)		Reference
	CG	CT	TT	TG	D’	LOD	
YKT2D	90.5	-	6.8	2.7	1.0	4.92	-
JPN	96.6	0.5	1.9	1.0	0.793	5.24	[23]
CDX	97.8	-	1.1	1.1	1.0	2.99	
GBR	73.1	1.1	25.3	0.6	0.971	26.94	
IBS	58.8	1.5	35.0	4.7	0.933	27.02	
PEL	86.5	-	10.6	2.9	1.0	14.89	
MXL	76.5	1.6	17.9	4.0	0.893	12.11	
PJL	74.5	0.5	20.8	4.2	0.966	21.95	
STU	65.0	0.11	20.9	12.9	0.923	13.77	
MSL	49.9	27.2	11.6	11.3	0.193	0.26	
YRI	50.9	25.0	5.1	19.0	0.296	0.27	
ACB	54.7	17.7	6.8	20.8	0.001	0.0	
ASW	45.7	18.2	9.7	26.4	0.039	0.0	
ESN	50.1	25.2	0.41	20.7	0.435	0.73	
GWD	50.5	26.5	10.2	12.8	0.119	0.22	

Abbreviations: (see Table 2).

genotype was not found in the studied group. The *TCF7L2* rs12255372 was characterized by the predominance of the GG genotype (96.1%) and the absence of the TT genotype.

The comparative analysis of risk allele frequencies in *KCNJ11, PPARG,* and *TCF7L2* gene polymorphisms in the studied group and other ethnic populations is presented in Table 2.

The allele frequency analysis showed a low frequency of the risk T-allele of the *TCF7L2* (rs7903146 and rs12255372) SNPs in Asian populations, compared to other ethnic groups (Yakuts without T2D - 3.8% and 1.9%, Kyrgyz - 11%, Japanese - 3% and 2%, Han Chinese from southern regions of China - 2.2% and 1.1%). The frequency of the risk T allele of the *TCF7L2* rs7903146 SNP (3.8%) in the studied YKT2D cohort was similar to the frequency of the T allele in Yakuts without T2D (5%). Probably, the low frequency of the risk T allele in rs7903146, rs12255372 SNPs in Asian populations contributes to the low incidence of T2D.

There was a strong LD between two SNPs (rs7903146 and rs12255372) of the *TCF*7L2 gene (Fig. 1 and Table 3) in almost all groups, including YKT2D (D '= 1, LOD = 4.92), except for African populations, where a very weak LD (D '= 0.001-0.435, LOD = 0.0-0.73) was observed. This is likely due to a high genetic diversity in African populations. This can also indicate that the ancient humans that left the African continent and settled in Europe, Asia, and America went through a strong population decline, the so-called "bottleneck." And our results can indirectly confirm that the division of the human race into Mongoloid and Caucasian races occurred after the exodus from Africa.

The frequency distribution of *TCF7L2* gene haplotypes for two SNPs (rs7903146 and rs12255372) based on all detected variants is presented in Table 3. There are four possible haplotypes CG, CT, TT, and TG for rs7903146 and rs12255372 polymorphisms. We were able to identify three haplotypes [CG(90.5%), TT(6.8%), and TG(2.7%)] in the studied YKT2D group. These haplotypes were also found in the Chinese population and Peruvians. A similar haplotype frequency was observed in Peruvians [CG(86.5%), TT(10.6%), and TG(2.9%)]. We also observed a low frequency of haplotypes with the risk T allele in Yakuts, Chinese and Japanese people, and the absence of a heterozygous CT haplotype in Yakuts and Chinese (Table 3).

In conclusion, the genotyping of the studied group of Yakuts did not reveal statistically significant differences between control groups and YKT2D patients with respect to the polymorphic variants of the *KCNJ11, PPARG,* and *TCF7L2* genes. The allele frequency analysis of the polymorphisms of the *KCNJ11, PPARG,* and *TCF7L2* genes demonstrated a low frequency of the risk T-allele in the *TCF7L2* (rs7903146, rs12255372) in Asian populations, compared to other human populations. We identified three haplotypes [CG(90.5%), TT(6.8%), and TG(2.7%)] in the YKT2D cohort. Also, we observed a strong LD between two SNPs (rs7903146 and rs12255372) of the *TCF7L2* gene in the majority of groups, including YKT2D (D '= 1, LOD = 4.92), except for African populations, where a very weak LD (D '= 0.001-0.435, LOD = 0.0-0.73) was observed.

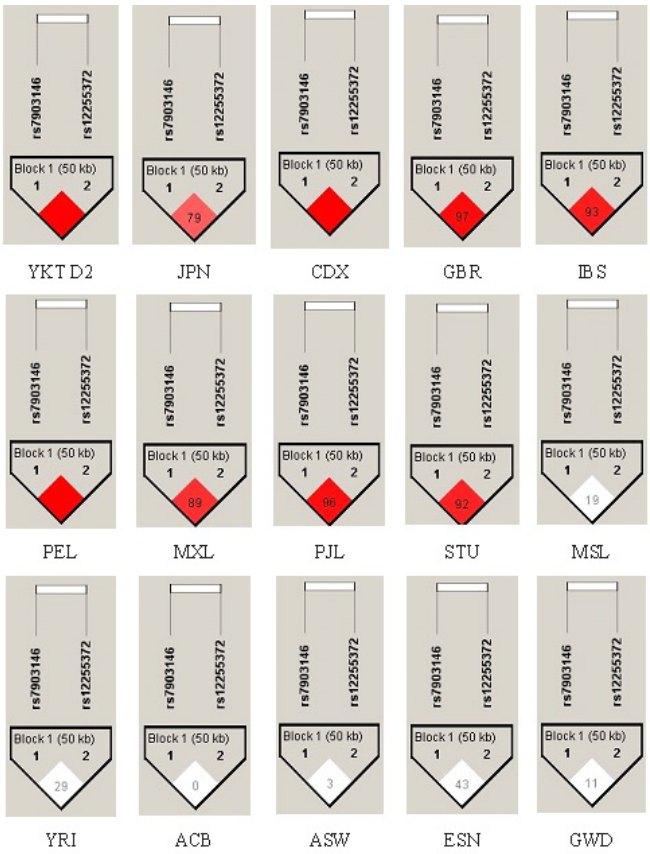

Fig. 1. *LD between the TCF7L2 (rs7903146, rs12255372) SNPs*

The color scheme shows the strength of adhesion between SNPs: bright red – a strong link (D'=1, LOD=2), pink-red – a significant link (D'<1, LOD=2), white – poor link (D'<1, LOD<2).

Abbreviations: YKT2D - Yakuts patients with T2D; ACB - African Caribbean in Barbados; ASW - African Ancestry in Southwest US; CDX - Chinese Dai in Xishuangbanna, China; ESN - Esan in Nigeria; GBR - British in England and Scotland; GWD - Gambian in Western Division, The Gambia; IBS - Iberian populations in Spain; JPT - Japanese in Tokyo, Japan; MSL - Mende in Sierra Leone; MXL - Mexican Ancestry in Los Angeles, California; PEL - Peruvian in Lima, Peru; PJL - Punjabi in Lahore, Pakistan; STU - Sri Lankan Tamil in the UK; YRI - Yoruba in Ibadan, Nigeria.

Competing Interests

The authors declare that they have no competing interests.

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