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GENETIC VARIATIONS OF NUTRITION RELATED GENES AND FOOD PREFERENCES IN THE KAZAKHS OF KAZAKHSTAN

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ABSTRACT

The density of taste buds, differences in genes encoding receptors, and other factors affect the on perception of taste and further food preferences. This study aimed to evaluate the association between 24 single nucleotide polymorphisms and food preferences in a Kazakh cohort. A total of 400 subjects were recruited from an outpatient clinic and genotyped for 24 polymorphisms previously described as associated with eating behaviour and food preferences in other ethnic groups. Regression analysis was conducted, adjusting for age and sex.

Associations were detected between rs2290550 polymorphism in phospholipase C-B2 (*PLCB2*), rs34160967 polymorphism in taste 1 receptor member 1 (*TAS1R1*) gene, and rs860170 polymorphism in *TAS2R16* gene and preferences for beef steak, unleavened bread, and sweet tea or coffee, respectively. There was an association between AA haplotype (*TAS2R38*) and a preference for fried potato. The main results of this study are the detection of associations between nutrition-related genes (*BCMO1, PLCB2, TRPV1, TAS1R1,* and *TAS2R*) and food preferences in a Kazakh population.

Keywords: food preferences; genetic variants; Kazakh cohort, polymorphism

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INTRODUCTION

Taste impacts preferences and food consumption and, thus, it may directly affect eating behaviour. The density of taste buds, differences in genes encoding receptors, and other factors affect the on perception of taste and further food preferences. Differences in taste perception and preferences affect food selection, which significantly influences the consumption of nutrients and calories. Humans can differentiate five tastes: sweet, bitter, acid, salty, and umami (savoury), which is described as the taste of glutamate or amino acids and proteins. Studies suggest that preferences for sweet and high-fat foods reduce with high perception of bitter taste [7,10]. This indicates that the

ability to taste bitterness could be connected to the body mass index (BMI), obesity, and risk of cardiovascular diseases, whereas the perception (sensitivity) of sweet taste inversely correlates with BMI [9].

Three widely expressed missense mutations (P49A, A262V, and V296I) were detected in the *TAS2R38* gene, which form haplotypes [4, 1]. (It was demonstrated that two haplotypes of the *TAS2R38* gene affect the perception of bitterness and are significantly associated with the variability of sensitivity to bitterness, preference for saccharose and sweet products, and diabetes mellitus type 2 [14,32]. Bitterness receptor genes *TAS2R5* and *TAS2R16* are substantially associated with alcohol addiction [10,13]. These data suggest that genetic variations in *TAS2R* genes may be involved in the regulation of eating behaviour. Sweet and umami receptors are coded by *taste 1 receptor member* (*TAS1R*) genes. TAS1R2 and TAS1R3 receptors respond to compounds with sweet taste such as sugar, sweeteners, and certain D-amino acids. TAS1R1 and TAS1R3 receptors determine umami taste, which is sensitive to L-amino acids. Genetic differences in sweet taste receptors may affect individual differences in consumption of saccharose and change the diet ration [8]. Despite their variability, sweet and umami tastes have poor genetic characteristics, and it is necessary to determine the genetic variants responsible for differences in these tastes [10,13,8,24,21,22].

Thus nutrition-related genes may change the sense of individual variability in terms of dietary factors and obesity. Nutrition-related genes have mostly been tested in Caucasian populations and, therefore, it is necessary to investigate these genes in other ethnic groups in further studies.

Material and methods

Study subjects. Subjects of Kazakh ethnicity were randomly selected during annual health check-ups conducted at the XXX. Blood samples from 400 study participants were collected according to the study protocol, which was approved by the Ethics Committee of the XXX (No. 1.18.06.2015).

The food questionnaires (FQ) used to evaluate food preferences were based on a food preference checklist used in the study by Pirastu et al. (2012), which was expanded to include regional foods commonly consumed in Kazakhstan. All foods were known to most subjects, but some of the participants had never tasted certain food items. Such responses were treated as missing data, and liking ratings were used as quantitative variables for statistical analyses. 1). Food preferences with > 20% missing data were excluded from the study analysis.

Each participant was informed of the purpose and methods of the study, and they provided written informed consent before participating. The blood samples of individuals who indicated they had an ancestor who was not Kazakh were excluded from the analysis.

Anthropometric indices including weight, height, waist and hip circumferences (WC and HC, respectively), and blood pressure were measured following a standard protocol. Height and weight were measured with the participants wearing light clothes and without shoes. WC was measured at the midpoint between the iliac crest and lowest rib. Hip circumference was measured to the nearest centimetre at the greatest protrusion of the buttocks, just below the iliac crest. The blood pressure was measured in a sitting position with a mercury sphygmomanometer. BMI was calculated as the individuals' body weight in kilograms divided by the square of his or her height in meters.

Characteristics of study population. A questionnaire-based survey was carried out to evaluate food preferences, and the total sample population consisted of 400 subjects (Table 1).

Table 1. Clinical characteristics of randomly sampled Kazakh study population

Parameter	Men	Women
N	103	297
Age, year	30.37 ± 7.68	33.02 ± 10.36
Weight, kg	76.43 ± 15.11	59.70 ± 10.13
Height, cm	175.31 ± 6.65	162.57 ± 5.79
BMI, kg/m^2	24.40 ± 4.97	22.14 ± 3.99
Waist circumference, cm	91.2 5 ± 12.79	76.59 ± 12.74
Hip circumference, cm	101.34 ± 14.44	95.95 ± 8.01
SBP, mmHg	119.61 ± 9.89	109.40 ± 12.87
DBP, mmHg	75.97 ± 7.48	71.58 ± 9.42

Genotyping. DNA was extracted from venous whole blood samples using the salting-out method [15]. There were 24 SNPs of nutrition-related genes genotyped using Biosyntec Genotyping kit (http://www.biosyntec.ru, Novosibirsk, Russian Federation). The analyses were conducted according to the manufacturer's standard protocol. Asymmetric real-time PCR genotyping using TaqMan probes was performed in a final volume of 20 μL containing 10 mM Tris-hydrochloride (HCl, pH 8.9), 55 mM potassium chloride (KCl), 2.5 mM magnesium chloride ($MgCl_2$), 0.01% Tween 20. 2 mM dNTP, 20-100 ng DNA, 1 unit. act. Klentaq DNA polymerase, and solutions of oligonucleotide primers and probes at concentrations of 0.1 mM and 1 mM depending on the primers. The PCR amplification was run on the following schedule: initial denaturation at 96 °C for 3 min; 55 cycles at 96 °C for 6 s, 60 °C for 6 s, and 72 °C for 6 s; melting curve at the interval 30-77 ºC, with a step of 0, 5 ºC, time interval, 5 s per step.

Statistical analysis. The statistical analysis was carried out in R (https://www.r-project.org). The correspondence of the distributions of genotype frequencies to the Hardy-Weinberg equilibrium (HWE) was assessed using the χ^2 criterion (Hardy Weinberg v1.6.1). Own script was used to detect minor alleles for each SNP, then their frequencies were calculated, and the genotype data was recorded according to three genetic models (additive, dominant, and recessive). A linear regression analysis was used to detect associations between polymorphic loci and food preferences (R stats package v3.4.4). After Bonferroni correction the statistical significance threshold was calculated as $p < 0.000035$. However, we chose to report results as $p < 0.001$ because we intended to repeat studies of known food preferences, and not to make clinical claims. Therefore, the borderline results were also important in this study. We confirmed our findings using repeated linear regression analysis with adjustments for potential confounders. Based on literature research we decided to use age, sex, and BMI as potential confounders. The data from the 1000 Genome Project database (phase 3) were used for the comparative analysis of genotype frequencies among the Kazakh and world populations [31]. A Fisher's exact test was performed to make pairwise comparisons of observed genotype frequencies for the Kazakh population with the available genotype frequencies for other populations (R stats package v3.4.4).

RESULTS

We tested 24 common SNPs that were in HWE. The allele and genotype frequencies of the remaining SNPs for the Kazakh population are summarised in Table 2.

Table 2. Allele frequency and distribution of studied single nucleotide polymorphisms (SNPs)

Polymorphism	Gene	a1	a2	MAF	a11	a12	a22
rs2277675	TRPV1	A	G	0.19	232	114	10
rs4595035	TAS2R60	T	C	0.22	213	125	17
rs1376251	TAS2R50	T	C	0.47	97	182	77
rs10772397	TAS2R50	T	C	0.35	147	168	39
rs2227264	TAS2R5	G	T	0.32	166	151	39
rs2599404	TAS2R47	A	C	0.39	138	159	60
rs71443637	TAS2R43	C	T	0.44	107	176	65
rs5020531	TAS2R42	T	C	0.35	118	153	29
rs1404635	TAS2R41	G	A	0.38	144	157	55
rs713598	TAS2R38	G	C	0.5	84	192	81
rs1726866	TAS2R38	C	T	0.47	96	189	72
rs10772420	TAS2R19	G	A	0.38	136	170	49
rs860170	TAS2R16	A	G	0.35	135	134	40
rs2234233	TAS2R1	C	T	0.23	214	116	24
rs4920566	TAS1R2	G	A	0.49	89	181	85
rs34160967	TAS1R1	G	A	0.14	82	23	4
rs2290550	PLCB2	G	T	0.1	276	67	2
rs4988235	MCM6	C	T	0.1	275	59	6
rs2229642	ITPR3	G	C	0.25	193	146	16

rs602662	FUT2	G	A	0.3	175	143	36
rs9939609	FTO	T	A	0.25	197	135	23
rs12934922	BCMO1	A	T	0.28	171	133	26
rs266729	ADIPOQ	C	G	0.28	172	128	28
rs1229984	ADHIB	G	A	0.27	192	131	30
Notes: 1 a1- allele 1; 2 a2- allele 2; 3 maf - minor allele frequency; 4 a11 - homozygous for allele 1; 5 a12 - heterozygote; 6 a22 -homozygous for allele 2; 7 na -not applicable, number of missed genotypes							

We also performed a comparative analysis of the differences in genotype frequencies between the Kazakh population and populations represented in the 1000 Genome Project database and divided them into following groups: African (Yoruba in Ibadan, Nigeria; Luhya in Webuye, Kenya; Gambian in Western Divisions in the Gambia; Mende in Sierra Leone; Esan in Nigeria; Americans of African Ancestry in South West USA; African Caribbeans in Barbados), American (Mexican Ancestry from Los Angeles USA; Puerto Ricans from Puerto Rico; Colombians from Medellin, Colombia; Peruvians from Lima, Peru), East Asian (Han Chinese in Beijing, China; Japanese in Tokyo, Japan; Southern Han Chinese; Chinese Dai in Xishuangbanna, China; Kinh in Ho Chi Minh City, Vietnam), European (Utah residents with Northern and Western European ancestry, USA; Toscani, Italy; Finnish, Finland; British in England and Scotland; Iberian, Spain), and South Asian (Gujarati Indian from Houston, Texas; Punjabi from Lahore, Pakistan; Bengali from Bangladesh; Sri Lankan Tamil from the UK; Indian Telugu from the UK). Significant differences in allele frequencies were found between Kazakhs and representatives of other ethnic groups for a large number of SNPs (Table 3). For the African populations, allele frequencies of 22 out of studied 24 SNPs were significantly different from those of the Kazakh population. Allele frequencies of 19 SNPs were significantly different between Europeans and the Kazakhs. For Asian populations, allele frequencies of 11 out of 24 SNPs were significantly different compared to those of the Kazakh population. For American populations, allele frequencies of 16 SNPs were significantly different between the Kazakh and the American populations.

Table 3. Comparative analysis of genotype frequencies between the Kazakh population (present study) and other ethnic populations (1000 Genome Project data)

	Fisher's exact test (*p*-value)																								
SNPs	ACB	ASW	ESN	GWD	LWK	MSL	YRI	CLM	MXL	PEL	PUR	CDX	CHB	CHS	JPT	KHV	CEU	FIN	GBR	IBS	TSI	BEB	GIH	ITU	PJL	STU
rs2277675	2.62E-47	6.65E-24	4.11E-53	NA	2.66E-46	1.58E-47	2.11E-57	0.001178	0.185229	1.83E-09	3.33E-07	0.296612	0.548724	0.683356	0.832405	0.737989	0.00516894	0.2753077	0.2994092	0.097238	0.003448	0.000588	1.10E-06	0.00524 1	0.461726	0.002103
rs45950 35	1.36E-10	4.29E-14	1.88E-12	4.20E-09	1.08E-14	1.28E-19	1.39E-09	2.79E-36	3.20E-29	6.09E-52	5.08E-37	8.92E-56	1.71E-55	1.43E-60	3.48E-61	2.73E-56	4.95E-21	4.97E-31	4.38E-25	2.65E-27	1.93E-31	4.03E-42	1.23E-41	7.46E-43	2.75E-34	1.07E-45
rs13762 51	9.92E-35	5.11E-18	3.00E-32	2.58E-43	2.65E-37	4.80E-37	2.13E-40	0.00326	0.290214	2.81E-05	2.41E-05	1.91E-05	1.27E-09	6.58E-07	8.11E-11	9.21E-10	1.73E-06	5.35E-05	2.33E-07	0.000184	0.020454	0.172782	0.004405	0.786519	0.236529	0.00116
rs10772 397	5.60E-27	1.72E-14	1.11E-30	1.42E-43	1.17E-31	4.16E-44	1.01E-28	0.852843	0.516298	0.100047	0.000426	0.235952	0.00395	0.042794	0.000490	0.0002907	0.38109152	0.3257373	0.8250989	0.6630 31	0.8136 71	0.9113 53	0.2618 54	0.1347 49	0.2180 98	0.1334 54
rs22272 64	0.345264	0.168366	2.50E-05	4.66E-06	0.017873	1.12E-05	0.033778	7.68E-07	4.14E-08	1.77E-11	3.00E-06	1.57E-20	2.27E-23	1.44E-20	1.18E-19	4.47E-16	0.00276534	0.0036979	0.0274085 6	5.25E-07	0.000129	0.000539	0.040639	0.037148	0.029063	0.0004949
rs25994 04	0.301191	0.931357	3.88E-01	8.21E-01	0.250239	6.78E-02	0.421999	0.308932	0.257033	0.000129	0.768232	6.20E-06	3.23E-06	3.46E-05	1.98E-06	1.80E-09	0.00133976	1.62E-05	0.0002410 1	0.101941	0.389797	0.030082	7.00E-08	0.132062	0.006374	1.17E-05
rs71443 637	4.02E-29	1.14E-13	4.61E-38	8.57E-37	1.30E-35	1.23E-38	3.64E-36	1.57E-09	2.65E-10	7.72E-10	1.18E-05	1.04E-21	2.32E-31	5.08E-28	1.17E-33	2.21E-24	3.79E-08	2.97E-20	5.92E-11	9.66E-09	2.20E-08	6.70E-12	1.03E-08	8.64E-15	1.41E-09	2.42E-17
rs50205 31	7.46E-06	1.67E-01	1.14E-09	1.09E-09	2.82E-10	1.55E-14	0.000192	2.78E-18	3.68E-09	1.71E-10	3.95E-06	6.49E-19	7.70E-26	2.09E-21	1.61E-27	1.68E-26	1.75E-10	1.82E-21	1.55E-13	2.19E-11	1.75E-13	6.37E-12	1.12E-17	2.03E-08	2.08E-15	1.21E-20
rs14	1.3	3.8	1.3	4.0	1.6	9.0	5.4	0.0	0.1	0.1	0.0	3.4	0.0	0.7	0.3	0.01	0.30	2.6	0.00	0.0	0.0	0.2	0.0	0.0	0.1	0.0

04635	9E-20	4E-09	6E-29	4E-35	9E-25	2E-26	7E-29	10662	22741	94672	02921	7E-07	78331	51471	48146	1097	104423	9E-05	447346	2525	0162	33844	53707	38408	58488	22413
rs71359 8	1.77E-01	4.58E-01	6.21E-01	4.18E-02	7.51E-01	3.72E-01	0.533649	0.237112	0.001342	4.10E-18	0.192972	3.96E-07	1.89E-05	1.66E-05	0.075192	1.74E-09	0.00826281	0.0034022	0.01747891	0.24352	0.139596	6.84E-06	0.023664	7.47E-06	2.81E-05	5.36E-07
rs17268 66	1.13E-03	2.47E-04	3.38E-04	1.20E-01	7.32E-05	3.57E-02	0.000016	0.037888	0.003051	5.00E-18	0.000504	1.48E-05	0.000465	0.000487	0.229239	1.76E-07	0.02552	0.0003621	0.01755516	0.653344	0.545227	2.18E-06	0.014519	5.24E-06	8.94E-05	9.61E-09
rs10772 420	6.01E-01	9.63E-01	7.71E-01	9.44E-01	6.32E-01	1.28E-01	0.658088	0.278664	0.243272	3.51E-05	0.508349	1.81E-05	5.04E-05	2.60E-06	4.14E-09	0.00011591	1.03E-06	0.00015348	0.37083	0.167711	0.021766	2.52E-07	0.375235	0.027542	4.99E-05	
rs86017 0	1.21E-10	1.04E-07	4.09E-19	6.55E-27	2.23E-17	3.48E-18	1.43E-24	0.008003	0.582444	8.73E-05	0.009166	0.001212	0.004232	0.006959	0.065865	0.000168	0.054893	0.5099723	0.14914526	0.962483	0.461022	0.607169	0.746584	0.949084	0.536973	0.752815
rs22342 33	8.00E-16	2.32E-06	5.86E-12	2.48E-09	1.67E-08	9.97E-11	2.29E-19	0.002451	0.009211	5.55E-05	0.026061	4.97E-05	0.009549	0.003818	0.002192	1.34E-06	0.12434658	0.0554792	0.08054332	0.005964	0.001017	0.296819	0.266396	0.153165	0.513508	0.036919
rs49205 66	8.56E-11	7.68E-05	2.04E-13	1.27E-14	2.14E-15	4.25E-16	7.17E-14	4.79E-05	0.001026	7.10E-08	0.715779	0.015378	0.003157	0.331261	0.033063	0.011121	7.95E-05	0.1046229	3.32E-06	0.001205	0.001788	0.604253	0.112679	0.064174	0.148927	0.653718
rs34160 967	9.51E-02	3.60E-01	3.40E-03	1.93E-03	1.54E-03	1.85E-01	0.003459	0.022262	0.082174	6.78E-05	0.409778	0.000356	6.37E-05	0.00036	2.13E-08	0.00436 0	0.46012 44	0.4042985	0.64979 24	0.487369	0.016949	0.616311	0.470531	0.806044	0.018945	0.927808
rs22905 50	3.60E-13	3.40E-07	1.55E-13	4.11E-19	2.14E-06	8.95E-14	1.03E-09	0.000106	0.147804	0.309844	0.013787	1.01E-06	1.72E-06	7.14E-09	0.030099	2.99E-05	0.00066 21	0.0003917	5.25E-06	1.43E-05	0.000159	0.400189	0.146398	0.354637	0.297115	0.021888
rs49882 35	3.91E-01	8.95E-02	1.06E-07	1.98E-06	1.06E-07	9.09E-07	1.92E-08	5.74E-09	0.000237	0.838365	0.000267	2.08E-07	6.01E-08	3.11E-08	3.98E-08	1.06E-07	9.72E-52	9.60E-38	1.01E-45	7.60E-23	0.703794	0.251542	0.136255	0.149691	1.37E-06	0.076147
rs22296	6.50E-	1.02E-	7.64E-	1.27E-	4.30E-	3.63E-	3.14E-	0.0005	0.0682	0.0591	2.84E-	2.92E-	1.26E-	3.56E-	0.0140	4.61	3.54	7.89E-	1.15	1.49E-	1.75E-	0.002	0.1609	0.2620	0.0114	0.1896

42	38	26	36	52	39	38	46	71	69	73	11	07	05	08	57	E-09	E-13	05	E-17	14	14	27	71	45	55	48
rs60 2662	8.40E-07	6.11E-05	8.43E-10	2.11E-05	2.23E-03	7.96E-02	3.95E-10	0.0 81907	0.4 88415	4.34E-05	2.70E-13	1.87E-23	4.33E-21	4.79E-26	9.06E-26	5.06E-23	2.47E-11	0.3 21372 3	1.94E-05	0.0 00479	4.48E-06	0.2 04542	0.3 83569	0.1 94954	0.0 05991	0.0 33504
rs99 396 09	4.81E-09	3.57E-05	1.41E-07	2.87E-07	1.85E-13	3.98E-10	7.81E-12	0.0 63463	0.6 80675	4.02E-07	0.0 04283	0.0 09044	0.0 06596	0.0 00566	0.0 55195	0.77 855 498	2.48E-06	0.0 00276 8	0.00 16473 1	0.0 00999	9.73E-08	0.5 77114	0.9 66615	0.3 42169	0.7 25119	0.0 57729
rs12 934 922	6.03E-05	0.0 04420	1.63E-06	5.83E-17	1.90E-09	2.60E-07	6.42E-11	0.0 03281	0.6 24556	0.4 57785	0.1 22879	0.0 00196	9.60E-05	2.43E-06	0.0 00223	4.62E-07	0.00 89818 5	4.25E-06	0.00 08649 9	7.79E-06	2.25E-05	0.3 12589	0.0 24933	0.1 23987	0.3 19648	0.9 38978
rs26 672 9	9.81E-06	5.45E-05	1.18E-06	4.50E-12	7.83E-06	3.94E-08	1.07E-07	0.2 91408	0.5 57218	0.7 78022	0.0 35334	0.0 52474	0.1 05693	0.4 71562	1.00	0.29 667 2	0.76 779 913	0.1 96911 6	0.24 92231	0.4 47124	0.3 50514	0.4 82724	0.4 54565	0.8 569	0.8 34887	0.9 11186
rs12 299 84	8.12E-18	7.72E-14	1.80E-21	3.23E-24	1.80E-21	7.88E-19	3.32E-23	2.3 44E-08	2.4 88E-05	1.02E-15	5.40E-11	4.24E-17	2.53E-26	3.31E-31	1.31E-29	7.50E-19	3.28E-17	1.80E-21	2.98E-18	2.70E-10	6.22E-12	7.49E-15	7.51E-16	9.49E-18	1.10E-12	2.34E-20

Notes: YRI - Yoruba in Ibadan, Nigeria; LWK - Luhya in Webuye, Kenya; GWD - Gambian in Western Divisions in the Gambia; MSL - Mende in Sierra Leone; Esan in Nigeria; ASW - Americans of African Ancestry in South West USA; ACB - African Caribbeans in Barbados; MXL - Mexican Ancestry from Los Angeles USA; PUR - Puerto Ricans from Puerto Rico; CLM - Colombians from Medellin, Colombia; PER - Peruvians from Lima, Peru; CHB - Han Chinese in Beijing, China; JPT - Japanese in Tokyo, Japan; CHS - Southern Han Chinese; CDX - Chinese Dai in Xishuangbanna, China; KHV - Kinh in Ho Chi Minh City, Vietnam); CEU - Utah residents with Northern and Western European ancestry, USA; TSI - Toscani, Italy; FIN - Finnish, Finland; GBR - British in England and Scotland; IBS - Iberian, Spain; GIH - Gujarati Indian from Houston, Texas; PJL - Punjabi from Lahore, Pakistan; BEB - Bengali from Bangladesh; STU - Sri Lankan Tamil from the UK; ITU - Indian Telugu from the UK; NA: data not available from the 1000 Genome Project

Participants were requested to evaluate certain products using a scale of 9 to 0 (9 - like extremely, 7 - like, 5 - neutral, 3- do not like but had to consume, 1 - dislike, 0- never tasted). The regression analysis was used to detect genetic associations with taste preferences. Table 4 shows results of regression analysis.

Table 4. Significant associations between studied SNPs and food preferences

Polymorphism/ gene	Phenotype	*Beta*	*p*-value	N	Model
rs1726866 *TAS2R38*	Black pepper	-0,731	0,00056	341	REC
rs2227264 *TAS2R5*	Sorbet	-1,203	0,00094	341	REC
rs2277675 *TRPV1*	Tonic	-0,871	0,00098	338	ADD
rs2290550 *PLCB2*	Beef steak	-6,677	7,50133E-07*	330	REC
rs34160967 *TAS1R1*	Unleavened bread (lavash, flat cake)	-1,082	0,00021	107	ADD
rs34160967 *TAS1R1*	Unleavened bread (lavash, flat cake)	-1,219	0,00067	107	DOM
rs4595035 *TAS2R60*	Sea products	-2,441	0,00098	340	REC
rs860170 *TAS2R16*	Tea or coffee	1,331	0,00021	293	REC
Notes: 1 *Beta* – allele effect direction; 2 Significance level p = 0,001; 3 *- Bonferroni correction; 4 N – number of samples; 5 REC – recessive model, ADD – additive model, DOM – dominant model					

According to Table 4, eight associations were found between polymorphisms of experimental genes and taste preferences in various genetic models. The strongest association was between rs2290550 in *PLCB2* gene and preference for beef steak. An association was found between the recessive model and negative coefficient beta, indicating that homozygous carriers of the alternative allele (TT) preferred to eat less beef than GG and GT carriers did. It is worth noting that this association was the only one that passed the Bonferroni correction. The rest of the results showed borderline associations that were also interesting to our study. The rs2227264 polymorphism was associated with a preference for sorbet with a negative correlation in the recessive model, rs2277675 polymorphism was associated with low preference for tonic in the additive model, and rs1726866 polymorphism was associated with a preference for "black pepper" with a negative correlation in the recessive model. The *TAS1R1* gene polymorphism *(*rs34160967) was an association with a low preference for unleavened bread in the additive and dominant models. The rs4595035 polymorphism was negatively associated with a preference for seafood, and rs860170 polymorphism was positively associated with preference to tea or coffee.

These results were reported without any adjustment for potential confounders. However, based on the stepwise regression analysis we concluded that age and sex could be potential confounders for food taste preferences (data is not shown). Therefore, we repeated the regression analysis with adjustments for age and sex, and the results are shown in Table 5.

Table 5. Significant associations between studied SNPs and food preferences after adjustment for potential confounders

Polymorphism/ gene	Phenotype	*Beta*	*p*-value	N	Model
rs12934922 *BCMO1*	Fresh-water fish: bream, pike perch, pike, etc.	-1.413	00.00092	306	REC
rs1726866 *TAS2R38*	Oatmeal	-0.548	0.00069	330	ADD
rs2290550 *PLCB2*	Beef steak	-6.954	2.76757E-07*	320	REC
rs34160967 *TAS1R1*	Unleavened bread (lavash, flat cake)	-1.168	0.00014	101	ADD
rs34160967 *TAS1R1*	Fried potatoes	-1.306	0.00023	96	ADD
rs34160967	Unleavened bread	-1.329	0.00048	101	DOM

TAS1R1	(lavash, flat cake)				
rs860170 *TAS2R16*	Tea or coffee	1.317	0.00018	285	REC
Notes: 1 Beta - allele effect direction; 2 Significance level p = 0.001; 3 *- Bonferroni correction; 4 N – number of samples; 5 REC – recessive model, ADD – additive model, DOM – dominant model.					

As is evident from Table 4, adjusting for potential confounders revealed the associations between rs2290550 polymorphism in *PLCB2* and a preference for beef steak; rs34160967 polymorphism in *TAS1R1* gene and preference for unleavened bread; and rs860170 polymorphism in *TAS2R16* gene and preference for tea or coffee. However other associations were not statistically significant (rs1726866, rs2227264, rs2277675, and rs4595035). Except for rs860170, all polymorphisms showed negative associations. It should be noted that the association between the rs2290550 polymorphism and a "beefsteak preference" phenotype passed the Bonferroni correction. The rs860170 polymorphism in the *TAS2R16* gene was positively associated with "tea or coffee" preference. In addition, after adjustment for potential confounders, supplementary associations were revealed between rs12934922 polymorphism in *BCMO1* and "fish"; rs1726866 polymorphism in *TAS2R38* and "oatmeal"; and rs34160967 polymorphism in *TAS1R1* and "fried potato" (Table 6).

Table 6. Taste status of *TAS2R38* haplotypes

Haplotype	Designation in terms of the study	P49A rs713598	V262A rs1726866	[1296V]	Taste status
AV[I]	AV	G	T	[A]	Non-tasters, if homozygote
AA[V]	AA	G	C	[G]	Small effect on non-tasters status, when homozygote is AVI/AAV
PV[I] PA[V]	PV PA	C C	T C	[A] [G]	Unknown Tasters, if homozygote or heterozygote

Then, regression analysis was carried out to detect associations between BMI and the studied SNPs, and the association results did not meet the assigned level of significance (p = 0.001, data not shown).

Two SNPs (rs713598 and rs1726866) were used to construct haplotypes. We observed that the frequencies for haplotypes CC, GT and GC were 49.52%, 45.82% and 4.11% accordingly. The haplotype test revealed that GC haplotype is associated with higher preference for fried potato (p = 0.00034), while CC haplotype was related to lower distaste for bacon (Table 7)

Table 7. Association between haplotypes of *TAS2R38* and food preferences

Phenotype	Model	rs713598	rs1726866	Haplotypes	Haplo index	Frequency	*P*-value
Fried potato	REC	G	C	AA	3.58	0.04	0.00034
Note: REC - recessive model							

DISCUSSION

Kazakhs are a Turkic-speaking, native population of Kazakhstan. They comprise a significant population in contiguous areas in China, Russia, Uzbekistan, Turkmenistan, Kyrgyzstan, and Mongolia. It is well known that meals are important elements of material culture, being the carrier of ethnic specifics. The historically formed food system of Central Asian nomads is based on a balance of meal and milk products slightly supplemented with plant products (wild and cultivated plants and vegetables), hunting and fishing products, which were not always available to all groups of the nomadic population.

History clearly shows that various cultures have certain food systems that were developed and established based on local conditions and the availability of certain food items. For instance, coastal populations obviously mainly consumed fish and cattle farmers preferred meat. However, all these differences have been subject to adaptation and have been modified by outside societal influences. Objective practices have been established as a result of changes in lifestyle, globalisation, and urbanisation. Thus, universal food items such as salads, yoghurts, snacks, and fast food, have gradually become part of the daily dietary lifestyle of Kazakhs, particularly those who live in big cities.

A number of studies based on historical and genetic data have suggested that the Kazakh population was formed as a result of admixture of European and Asian populations [27]. Comparative analysis of allelic frequencies of the studied SNPs showed significant differences between the Kazakh population and the majority of other population groups from the 1000 Genome project database. These results indicate that the genetic profile of the Kazakh population has its own unique identity in terms of the studied variants.

Currently, many genes have polymorphisms that are associated with the development of metabolic disorders. It has been determined that food components can cause epigenetic changes in humans [3]. In addition, many studies have demonstrated the association of certain genes related to adiposis and diabetes mellitus type 2 with certain food items [16]. The gustatory system regulates perception, and five different types of taste receptors have been identified: sweet, bitter, acid, salty, and umami. Recent studies indicate that fat could be the sixth taste modality [2]. It is commonly known that sweet taste indicates the caloric content of food and umami perception allows the identification of foods with high protein content. Furthermore, salty taste is assumed to indicate the level of sodium and other mineral substances in the organism while an acid taste safeguards against the consumption of spoiled food items or unripe fruits and vegetables. In addition, bitter taste prevents the consumption of toxic or poisonous compounds and is considered a warning of the presence of harmful compounds. Certain products such as fruits and vegetables contain some bitter compounds, which could be phytonutrients. Diets with a high content of phytonutrients contribute to low cardiovascular and cancer risks. Individuals with an intensive perception of bitter compounds would avoid consuming bitter foods, thus increasing their risk of these diseases [18].

Food preference assessment is used for the evaluation of penchants or antipathy to certain food items. Food preferences are influenced by many factors such as organoleptic features (taste, texture, smell, and appearance), and individual factors, namely age, sex, ethnic background, BMI, and health condition [21, 22, 18]. (Taste varies both within and between populations, and this could be influenced by genetic variants of taste receptor families [10, 32, 13, 8, 29, 24 28, 12 19, 6, 34, 11].

The strongest association in this study was detected between the phospholipase C-B2 (*PLCB2*) gene and a low preference for beef (p = 2.76757E-07*). PLCβ2 is expressed in a subset of receptor cells in the taste buds and is involved in the transduction of sweet, bitter, and umami stimuli. This gene is also expressed in olfactory epithelia, particularly in cells that use phosphatidylinositide signal transduction and comprise nearly 5% of all olfactory cells [11]. It should be noted that a negative association between rs2290550 polymorphism and a “beefsteak preference” phenotype was proven after adjustment for age and sex in the recessive model. The negative correlation indicates that a less frequent allele is related to low preference for the tested food. It is important to note that meat plays a major role in Kazakh food culture. Therefore, many members of the Kazakh population would be expected to have the G allele, making them more susceptible to liking beef.

The rs34160967 polymorphism of the *TAS1R1* gene is associated with a low preference to unleavened bread and fried potatoes. *TAS1R* genes encode heterodimeric receptors that mediate umami (hTAS1R1 + hTAS1R3) and sweet (hTAS1R2 + hTAS1R3) tastes. According to a previous study by Rawal *et al.* [25], polymorphism of the *TAS1R1* gene is associated with differences in taste intensity. Our results demonstrated a negative association of this polymorphism with unleavened bread. In addition, *GNAT3* gene is highly coexpressed with *TAS1R* and a gene product, i.e. alpha G protein subunit, signal taste molecule, is involved in sweet, bitter, and umami transduction. Recently Choi *et al.* [5] showed that *TAS1R* genes modulate the perception of sweet and umami tastes and regulating metabolism. These genes showed significant association of their polymorphisms with eating behaviour and susceptibility to stomach cancer among Korean men. The association between TAS1R and fried potatoes cannot be easily explained. Functional studies would be required to clarify the results.

The association between rs2277675 (transient receptor potential cation channel subfamily V member 1 [*TRPV1*]) polymorphism and preference to tonic was detected. The *TRPV1* gene encodes an ion channel that is activated by various chemical stimuli, such as capsaicin and active chilli ingredients, certain lipids. *TRPV1* transcription product participates in various biological processes, including regulating heart rate, mechanical and thermal hyperalgesia, and psychic anxiety [11]. Studies suggest that this gene is responsible for the metallic taste of sweeteners, or at least the antipathy to sweeteners [26]. Most tonics include sweeteners, and the results agree with the global data. However, after adjustment for age and sex, the association did not achieve the significance level (p > 0,001).

Sweet, umami, and bitter substances activate various G protein-coupled receptors (GPCR). For example, receptor cells expressing T2R receptors of the GPCR family are required for the perception of bitter compounds. Currently, genomic databases provide a list of 43 *TAS2R* genes that determine bitter taste [13].

The results showed that a polymorphism *(*rs2227264) in the *TAS2R5* gene was negatively associated with sherbet; a polymorphism (rs860170) in *TAS2R16* gene was positively associated with a preference for tea and coffee; and polymorphism (rs4595035) in *TAS2R60* gene was negatively associated with a preference for seafood. *TAS2R16* gene has also been associated with alcohol addiction in other

studies [33]. These data prove that the mentioned genetic variants are involved in the regulation of eating behaviour.

TAS2R38 gene codes a seven-transmembrane G protein-coupled receptor that controls the ability to taste glucosinolates, a family of bitter-tasting compounds. *TAS2R38* gene analysis determines the level of perception of bitter tastes. Different grade of sensitivity may affect the selection of certain food items. Many natural antioxidants and drugs have bitter tastes. Our research showed that rs1726866 polymorphism was associated with antipathy to black pepper in the recessive model; however, after corrections for age and sex, a statistically significant association was observed between the polymorphism and antipathy to oatmeal in the additive model. Other studies have also proven the association of *TAS2R38* gene polymorphism with a bitter taste, namely vegetables in the *Brassica* family of plants [10]. According to studies bitter taste is positively associated with cream or high-fat milk.

There are three missense mutations that result in three replacements of amino acids in P49A, A262V, and V296I codons. These polymorphisms form several haplotypes - PAV (PTC-phenylthiocarbamide sensitive allele) and AVI (PTC-insensitive allele) that are widespread among them. In addition, bitter taste, sex, and creamy consistency are considered significant predictors of preference for high-fat products [18]. Thus, our results showed a positive association between the AA haplotype with a preference for fried potatoes. No statistically significant association was observed between the *TAS2R38* gene haplotypes and BMI. These results agree with those of other studies that did not reveal associations between the *TAS2R3*8 gene haplotypes and BMI [30] while another study proved that PTC phenotypes were associated with BMI and waist circumference (WC) and high-risk factors of cardiovascular diseases [18].

Some limitations of this study should be acknowledged. Only a limited number of SNPs (24) could be analysed in our cohort, and a relatively limited sample population of Kazakhs was investigated. Another possible limitation of our study might be the fact that no Bonferroni correction was applied to avoid a type 1 error due to multiple comparisons. If Bonferroni's correction was applied to *p*-values obtained in our study, the thresholds of significance for each comparison would be 0.000035. After the correction, only the rs2290550 polymorphism would have been associated with low preference for "beefsteak".

CONCLUSION

The main results of this study were the detection of associations between nutrition-related genes (*BCMO1, PLCB2, TRPV1, TAS1R1,* and *TAS2R*) and food preferences. Many studies have proved the existence of other factors affecting the selection of food items, which may negatively or positively influence health, such as biological (other candidate genes), environmental, and socio-cultural factors.

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ҚАЗАҚСТАНДАҒЫ ҚАЗАҚТАРДЫҢ ТАМАҚТАНУЫ МЕН ТАҒАМДЫҚ ТАЛҒАМЫНА БАЙЛАНЫСТЫ ГЕНДЕРДІҢ ГЕНЕТИКАЛЫҚ ӨЗГЕРІСТЕРІ

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ТҮЙІН

Бұл зерттеу қазақстандық когорттағы 24 бірнуклеотидті полиморфизм мен тағамдық артықшылық арасындағы байланысты бағалауға бағытталған. Амбулаториялық клиникадан барлығы 400 адам қабылданды және бұрын басқа этникалық топтардағы тамақтану тәртібі мен тамақтану әдеттерімен байланысты деп сипатталған 24 полиморфизмге генотиптелді. Жасы мен жынысы бойынша түзетілген регрессиялық талдау жасалды.

C-B2 (PLCB2) фосфолипазасындағы rs2290550 полиморфизмі, 1 дәм сезу рецепторының 1 геніндегі (TAS1R1) rs34160967 полиморфизмі және TAS2R16 геніндегі rs860170 полиморфизмі анықталған және сиыр еті стейктері, жаңа піскен нан және тәтті шайға немесе кофеге қатысты артықшылықтар арасындағы сәйкесінше бірлестіктер табылды. AA (TAS2R38) гаплотипі мен қуырылған картоптың артықшылығы арасындағы байланыс табылды. Осы зерттеудің негізгі нәтижелері тамақтанумен байланысты (BCMO1, PLCB2, TRPV1, TAS1R1 және TAS2R) гендер мен Қазақстан халқының тағамдық қалауы арасындағы қауымдастықтарды анықтау болып табылады.

Негізгі сөздер: ұнататын тағамы, генетикалық нұсқалар, қазақстандық когорта,полиморфизм.

ГЕНЕТИЧЕСКИЕ ИЗМЕНЕНИЯ ГЕНОВ, СВЯЗАННЫХ С ПИТАНИЕМ И ПИЩЕВЫМ ПРЕДПОЧТЕНИЕМ У КАЗАХОВ КАЗАХСТАНА

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АБСТРАКТ

Плотность вкусовых сосочков, различия в генах, кодирующие рецепторы, и другие факторы влияют на восприятие вкуса и дальнейшие пищевые предпочтения. Данное исследование было направлено на оценку связи между 24 однонуклеотидными полиморфизмами и пищевыми предпочтениями в казахстанской когорте. В общей сложности 400 человек были набраны из амбулаторной клиники и генотипированы на 24 полиморфизма, ранее описанные как связанные с пищевым поведением и пищевыми предпочтениями в других этнических группах. Был проведен регрессионный анализ с поправкой на возраст и пол.

В результате были обнаружены ассоциации между полиморфизмом rs2290550 в фосфолипазе C-B2 (PLCB2), полиморфизмом rs34160967 в гене рецептора 1 вкуса 1 (TAS1R1) и полиморфизмом rs860170 в гене TAS2R16 и предпочтениями в отношении говяжьего стейка, пресного хлеба и сладкого чая или кофе, соответственно. Обнаружена связь между гаплотипом AA (TAS2R38) и предпочтением жареного картофеля. Основными результатами этого исследования являются выявление ассоциаций между генами, связанными с питанием (BCMO1, PLCB2, TRPV1, TAS1R1 и TAS2R), и пищевыми предпочтениями у населения Казахстана.