Original Article

Selected Genetic Characteristics of the Vietnamese Minority Living in the Czech Republic

(SNP / genetic analysis / interethnic analysis / nutrigenetics / nutrition)

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Abstract. The aim of this study was to analyse the allelic distribution of selected genes in the Czech and Vietnamese populations. We analysed samples from 94 Vietnamese volunteers and 2,859 Czech population-based subjects (2,559 from the Czechs post-MONICA and 300 volunteers from the South region of the Czech Republic). There were significant differences between the two populations for most, but not all, of the SNPs analysed. In particular, the prevalence of risk alleles in the analysed polymorphisms tended to be lower in the Vietnamese community compared to the Czech population, especially within the *FTO* (rs17817449; associated with obesity risk, P < 0.0001), *TCF7L2* (rs7903146; linked to type 2 diabetes, P < 0.0001) and *ADH1B* (rs1229984; related to alcohol consumption, P < 0.0001) genes. The genotype within the *MCM6/LCT* cluster (rs4988235) associated with lactase persistence was not present in the Vietnamese population. Slight genotype differences were detected for one *HFE* polymorphism (rs1799945 with P = 0.005; but not for rs1800562). Only the genotype frequencies within the *MC4R* and *APOE* genes were almost identical in both populations. We conclude that the Vietnamese population may have a lower genetic predisposition to the non-communicable diseases such as obesity or diabetes mellitus.

Introduction

In recent decades, non-communicable (or "civilization") diseases (especially obesity, diabetes and cardiovascular disease) have not only increased the risk of morbidity and mortality, but they can also impose a significant economic and healthcare burden on society (GBD 2019 Viewpoint Collaborators, 2020). Obesity is associated with a long-term positive energy balance (caloric intake exceeding caloric expenditure). Individuals with similar energy imbalances may have different degrees of obesity. Type 2 diabetes mellitus (T2DM) is characterized by high blood glucose levels, the body's inability to metabolize glucose properly, or a relative lack of insulin combined with insulin resistance. Dyslipidaemia (increased levels of plasma cholesterol and/or triglycerides) is a significant risk factor for atherosclerotic cardiovascular diseases.

These diseases are influenced by environmental factors (mainly dietary habits and physical activity performed) (Budreviciute et al., 2020) as well as by genetic factors (Li et al., 2019). Most of the heritability of these diseases is mediated by single-nucleotide polymorphisms (SNPs).

SNPs in our focus were either selected according to the results of genome-wide association studies (GWAs) (e.g., *FTO* or *TCF7L2*), or the selection was based on the long-time known association with some disease/metabolic disorder (e.g., *APOE* or *HFE*).

The *FTO* (fat mass and obesity-associated) gene encodes a nucleic acid demethylase. This enzyme plays a crucial role in the regulation of post-transcriptional gene

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Abbreviations: ADH1B – alcohol dehydrogenase 1B, APOE – apolipoprotein E, BMI – body mass index, COVID-19 – COrona-VIrus Disease 2019, FTO – fat mass and obesity-associated, GWAs – genome-wide association study, LDL – low-density lipoprotein, MC4R – melanocortin 4 receptor, MCM6/LCT – mini-chromosome maintenance complex component 6/lactase, MONICA – MONItoring on CArdiovascular diseases study, PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism, SNPs – single-nucleotide polymorphisms, T2DM – type 2 diabetes mellitus, TCF7L2 – transcription factor 7 like 2, IHIS CR – Institute of Health Information and Statistics of the Czech Republic, WHO – World Health Organization.

expression, making it influential in various physiological and pathological processes, including the risk of developing obesity and T2DM (Frayling et al., 2007; Kalantari et al., 2016).

The *MC4R* gene is considered to be the second strongest gene associated with body mass index (BMI). It has been associated with increased energy intake and significantly higher BMI and obesity in both children and adults (Xi et al., 2012).

TCF7L2 belongs to the T-cell factor family of transcription factors. SNPs within the *TCF7L2* gene have been associated with an increased risk of developing T2DM (Del Bosque-Plata et al., 2021) and are linked to β-cell dysfunction in response to glucose and insufficient insulin secretion (Gloyn et al., 2009).

There are two apolipoprotein E (*APOE*) SNPs (rs7412, *APOE2* and rs429358, *APOE4*), which are responsible for three APOE isoforms. The amino acid substitutions (Arg158 → Cys, APOE2, and Cys112 → Arg, APOE4) alter the conformation of the protein, leading to differences in the binding affinity to lipoprotein receptors and stability. Consequently, each isoform results in different concentrations of lipoproteins in the blood (Khalil et al., 2021).

Lactase persistence is dominantly inherited and is influenced by several SNPs that regulate the expression of the lactase gene, *LCT*. The key SNP variant, which was in our focus, is the C-13910 → T (rs4988235) exchange. This polymorphism increases the binding affinity of a transcription factor, leading to increased activity of the *LCT* promoter (Anguita-Ruiz et al., 2020).

The *ADH1B* gene, a crucial alcohol-metabolizing enzyme, exists in several allelic forms. We focused on the Arg48His polymorphism, which results in a different NAD^+ binding capacity and affects the level of ethanol oxidation. As a result, carriers of the His allele metabolize alcohol to acetaldehyde more rapidly, leading to acetaldehyde accumulation and contributing to a more severe hangover (Enoch and Goldman, 2001; Edenberg and McClintic, 2018).

Finally, *HFE* plays an important role in regulating the production of hepcidin, a protein that controls iron transport and storage. Variants rs1800562 and rs1800730 make their carriers less sensitive to iron deficiency and anaemia, meaning that they require higher concentrations of transferrin to trigger increased hepcidin production (Barton et al., 2015).

We focused on analysis of the genotype frequencies of the above-mentioned genes potentially associated with an increased risk of non-communicable diseases in the Vietnamese minority living in the Czech region and compared them with the majority Caucasian population.

Material and Methods

Subjects

The Vietnamese population living permanently in the Czech Republic: buccal swabs were collected from 94 adult (38 males and 56 females, aged 18–65 years) unrelated Vietnamese volunteers residing in the Czech Republic, recruited using snowball sampling (Hughes et al., 1995).

The Czech population: data from the Czech population were extracted from the post-MONICA study (1,191 males and 1,368 females, aged 25–64 years) (Cífková et al., 2020) and a study of 300 South Bohemia region residents (150 males and 150 females, aged 18–65 years) (Šedová et al., 2015*)*. All subjects were unrelated, self-reported Caucasian adults.

Ethics

The study received approval from the ethics committees of the Institute of Clinical and Experimental Medicine and Thomayer University Hospital, Prague. All subjects signed an informed consent with the participation in the study.

DNA extraction and genotyping

Buccal samples were collected and placed in tubes 4N6FLOQSwabs (QIAGEN, Hilden, Germany) and stored at –20 °C until further processing. DNA extraction from buccal samples was performed using the Xtreme DNA Kit SME-50, following the manufacturer's (Isohelix, Harrietsham, UK) instructions.

Seven of the nine polymorphisms were genotyped using the PCR-RFLP method in a T100 Thermal Cycler (Bio-Rad, Hercules, CA) (Hubacek et al., 2009, 2023a, 2023b; Rynekrova et al., 2012; Hubácek et al., 2017). The PCR master mix consisted of water, Dream Taq buffer, $MgCl_2$, dNTP, primers and Dream Taq polymerase (ThermoFisher Scientific, Waltham, MA). The oligo sequences and restriction enzymes used are summarized in Table 1. The PCR program consisted of 34 cycles, starting with an initial denaturation at 95 °C for 3 minutes, followed by hybridization at a temperature range of 57 °C to 69 °C for 30 seconds, and the final step was DNA synthesis at 72 °C for 1 minute.

Analysis of the *APOE* SNPs (rs7412 and rs429358) was performed using Taqman SNP Genotyping Assays (assay ID C_904973_10 and C_3084793_20) in the QuantStudioTM 6 Flex Real-Time PCR System, operated with the Quant Studio 6 software (ThermoFisher Scientific).

In cases where the first genotyping had not yielded results, a second attempt was performed. Any samples that remained ungenotyped after two consecutive attempts were classified as missing.

In the majority population, the frequencies of the genotypes of interest were extracted from previously published studies (Hubacek et al., 2009, 2023a, 2023b; Rynekrova et al., 2012; Hubáček et al., 2017).

Statistical analyses

Statistical tools available online (https://www.socscistatistics.com/tests/chisquare2/default2.aspx, accessed 09/2024) were used to compare the genotype/allelic frequencies between the examined populations. Due to the

Table 1. Details of the genotyping methodology for the analysis of SNPs of interest

SNP (Gene)	Oligonucleotides	PCR product	Enzyme	Restriction fragments (bp)	Allele
rs17817449 (*FTO*)	5′ GGG AAG AGG AGG AGA TTG TGT AAC TGG 5′ GAA GCC CTG AGA AGT TTA GAG TAA ATT GGG	198 bp	*Alw*NI	198	G
				99 + 99	T
rs7903146 (*TCF7L2*)	5′ GAA CAA TTA GAG AGC TAA GCA CTT TTT AGG 5′ TGT CCA GGG CCC CTC TAA CCT T	155 bp	*Rsa*I	155	T
				123 + 32	C
rs17782313 (*MC4R*)	5′ AAG TTC TAC CTA CCA TGT TCT TGG 5′ TTC CCC CTG AAG CTT TTC TTG TCA TTT CCT A	137 bp	*Bcl*I	137	C
				107 + 30	T
rs1229984 (*ADH1B*)	5′ AGG GGC TTT AGA CTG AAT AAC CTT GG 5′ AAT CCT GGA TGG TGA ACC ACA CG	92 bp	*Hin*6I	92	A
				65 + 27	G
rs1799945 (*HFE*)	5′ ACA TGG TTA AGG CCT GTT GC 5′ GCC ACA TCT GGC TTG AAA TT	208 bp	*Hin*fI	208	C
				147 + 61	G
rs1800562 (*HFE*)	5′ AAC CTT GGC TGT ACC CCC TG 5′ GCC CAC CCC CTA ACA AAG AG	191 bp	*Rsa*I	191	G
				162 + 29	A
rs4988235 (*LCT*)	5′ GCT GGC AAT ACA GAT AAG ATA ATG GA 5′ CTG CTT TGG TTG AAG CGA AGA	201 bp	*Hinf1*	201	C
				177 + 24	T

high number of gene variability compared, Bonferroni correction was applied, and P values below 0.00625 were considered as significant.

Results

The distributions of genotypes were in agreement with Hardy Weinberg equilibrium both in the Czech Caucasians and in the Vietnamese subjects.

The success rate of genotyping varied, ranging from 75.5 % (rs1800562) to 100 % (both *APOE* variants) within the Vietnamese volunteers and from 94.3 % (rs1800562) to 100 % (rs 17782313 and rs1229984) in the Czech majority population.

When comparing the genotype frequencies between the Czech and Vietnamese populations, significant differences were observed for most of the investigated genes (Table 2).

First, we observed an increased frequency ($P < 0.00001$) of *FTO* risk G allele carriers in the Czech population (42.1 %) compared to the Vietnamese population (16.7 %).

In the case of the *TCF7L2* rs7903146 variant, the T allele ($P < 0.00001$), which is a known risk factor for T2DM, was almost absent in the Vietnamese population (0.6 % compared to 27 % in the Czech population).

The prevalence of the *ADH1B* A allele (rs1229984 polymorphism) was much higher in the Vietnamese (60.8 %) than in the Czechs (5.5 %), with the P value < 0.0001.

Of the *HFE* variants, only rs1799945 showed differences between the studied ethnics. In the Vietnamese population, the frequency of the G allele (7.2 %) was about half of that in the Czech population (14.3 %; $P < 0.005$). Nominal but not significant differences were observed for the second polymorphism (rs1800562). The frequency of the minor A allele was 2.8 % in Czechs and 0.7 % in Vietnamese, respectively.

The rs4988235 variant, linked to lactase persistence, was, as expected, monomorphic in the Vietnamese population, which is in stark contrast to the Czech population, where almost 75 % of the subjects carried at least one mutant allele.

Minor non-significant differences were observed in the genetic variability of the *APOE* gene. A slightly higher frequency of *APOE4/E3* genotypes was found in the Vietnamese population (12.2 % vs 9.7 % in the Czech population).

Finally, *MC4R* genotype frequencies were almost identical in both populations (for more details, see Table 2).

Discussion

This study aimed to investigate the genotype frequency differences in preselected genes between the Czech and Vietnamese populations.

Regional differences in both diet and beverage intake have been influenced by a variety of historical factors, including culture, religion and local availability. In regions where cultural factors or local inhabitants favoured the consumption of certain food, there may have been a selective pressure leading to an advantage for genetic variants that allow better digestion, tolerance or nutritional/energetic utilization (Singh, 2023).

As expected, the largest difference was found in the case of the lactose tolerance mutation, with no mutation carriers detected among the Vietnamese subjects. Lactase persistence refers to the ability to continue digesting lactose into adulthood and is the result of an evolutionary adaptation. The development of dairy farming in Europe around 9,000 years ago led to the genetic adaptation, allowing European populations to be able to con-

Table 2. Comparison of genotype and allelic frequencies of the examined polymorphisms in the Czech and Vietnamese populations

rs17817449 (*FTO*)	**Czech population**		**Vietnamese population**		**P**
	N	**%**	**N**	**%**	
GG	426	17.3	3	3.6	+ G vs TT *0.00001*
GT	1224	49.6	22	26.2	
TT	817	33.1	59	70.2	
G	2076	42.1	28	16.7	*0.00001*
T	2858	57.9	140	83.3	
rs7903146 (*TCF7L2*)					
TT	165	6.5	0	0	+ T vs CC *0.00001*
CT	1042	41.0	1	1.3	
CC	1336	52.5	76	98.7	
T	1372	27.0	1	0.6	*0.00001*
C	3714	73.0	153	99.4	
rs17782313 (*MC4R*)					
CC	128	5.0	3	3.6	+ C vs TT *0.88*
CT	910	35.6	30	36.1	
TT	1521	59.4	50	60.2	
C	1166	22.8	36	21.7	*0.74*
T	3952	77.2	130	78.3	
rs1229984 (*ADH1B*)					
AA	7	0.3	34	38.6	+ A vs GG *0.0001*
AG	266	10.4	39	44.3	
GG	2286	89.3	15	17.1	
A	280	5.5	107	60.8	*0.0001*
G	4838	94.5	69	39.2	
rs1799945 (*HFE*)					
GG	51	2.0	1	1.1	+ G vs CC *0.005*
CG	629	24.6	11	12.2	
CC	1875	73.4	78	86.7	
G	731	14.3	13	7.2	*0.007*
C	4378	85.7	167	92.8	
rs1800562 (*HFE*)					
AA	3	0.1	0	0	AA + AG vs GG *0.15*
AG	124	5.4	1	1.4	
GG	2286	94.5	70	98.6	
A	130	2.8	1	0.7	0.13
G	4484	97.2	141	99.3	
rs4988235 (*MCM6*)					
CC	68	23.6	70	100	*n/a*
CT	146	50.7	0	0	
TT	74	25.7	0	0	
C	282	49.0	158	100	*n/a*
T	294	51.0	0	0	
rs7412 and rs429358 (*APOE*)					
e2/e2	20	0.8	1	1.0	+ *E2* vs *E3E3* vs *+E4* *0.47*
e3/e2	324	12.4	10	10.6	
e3/e3	1787	68.6	60	63.8	
e4/e2	35	1.3	3	3.2	
e4/e3	406	15.6	20	21.3	
e4/e4	33	1.3	0	0	
e2	399	7.7	15	7.9	+ *E2* vs others *0.71*
e3	4304	82.6	150	79.8	
e4	507	9.7	23	12.2	+ *E4* vs others *0.03*

sume milk and dairy products beyond infancy. In general, lactase persistence is less common in Asian populations (Anguita-Ruiz et al., 2020). In lactose-intolerant subjects, consumption leads to various gastrointestinal symptoms (osmotic diarrhoea, abdominal pain, bloating and flatulence). Up to two thirds of the world's population have some degree of lactose intolerance (Ségurel and Bon, 2017).

Within the alcohol dehydrogenase gene (*ADH1B*), the A allele (rs1229984) is more common in the Vietnamese population than in the Czechs. Our findings are consistent with a recent study (Hoang et al., 2022) focusing on alcoholism and alcoholic cirrhosis in the Vietnamese population, which reported a similar A allele frequency of 67.5 %. This allele is responsible for the occurrence of hangover symptoms, including facial flushing, nausea and vomiting. It is likely that the more severe hangover experienced by the A allele carriers contributes to their reduced propensity for alcoholism (Enoch and Goldman, 2001; Edenberg and McClintic, 2018).

Two genes with a strong effect on T2DM development, *TCF7L2* and *FTO*, also show highly significant inter-population differences. Numerous studies, including GWAs, have demonstrated a strong association between a certain variant within these two genes and the risk of T2DM development (for review see Galuška et al., 2022). In both cases, the genetic profile appears to be more favourable in the Vietnamese population. Minor, risky alleles within *TCF7L2* and *FTO* are far less common in Vietnamese subjects. The significantly lower prevalence of the *TCF7L2* and *FTO* risk genotypes in the Vietnamese population may be a contributing factor to the lower prevalence of T2DM in this country (reported as 7.3 % by the Ministry of Health in Vietnam in 2023: http://moh.gov.vn/tin-noi-bat/-/asset_publisher/3Yst7YhbkA5j/content/vitan-nam-hien-ty-le-nguoi-mac-benh-ai-tha-uong-ang-gia-tang-nhanh, accessed 10/2029, or 6 % reported by the WHO in 2017: http://iris.who.int/handle/ 10665/204871) in comparison with the Czech population (10 % as reported by the Institute of Health Information and Statistics of the Czech Republic (IHIS CR) in 2017: https://www.uzis.cz/sites/default/files/knihovna/nzis_rep_2018_K01_A004_diabet_endokrin_2017.pdf., accessed 10/2024 or 10,2 % in 2023 by NZIP: https://www.nzip.cz/data/1769-datove-souhrny-epidemiologie-diabetes-mellitus-dm-v-cr, accessed 10/2024).

This is in contrast with the fact that diabetes in other Asian populations tends to manifest at a younger age, at a lower degree of obesity and at a higher rate with the same degree of weight gain compared to Caucasians (Chan et al., 2009). Additionally, Asians tend to have more visceral fat for the same waist circumference as Europeans. The combination of abdominal fat deposition and lower muscle mass, often referred to as the "metabolically obese phenotype" in normal weight individuals, places Asians at a higher risk of insulin resistance and T2DM. It is likely that other ethnicity-specific genes will play an important role in T2DM development in Asians (Ng et al., 2008; Spracklen et al., 2020; Yanasegaran et al., 2024).

Both genes have rather a regulatory effect on T2DM development – TCF7L2 has been defined as a transcriptional co-factor (Del Bosque-Plata et al., 2021) and FTO acts as a nucleic acid demethylase (Gerken et al., 2007; Jia et al., 2011). This extremely important regulatory effect of *FTO* is reflected in a wide range of other diseases, such as cancer (Li et al., 2022), cardiovascular disease (Xu et al., 2023), renal failure (Hubacek et al., 2012), sepsis (Jabandziev et al., 2024), or even COVID-19 (Hubacek et al., 2024), with which *FTO* variability is associated.

Genetic variations in the *FTO* gene, particularly in intron 1, were originally identified as determinants of BMI and associated with an increased risk of obesity (Frayling et al., 2007; Kalantari et al., 2016, Mahmoud et al., 2022). In Asian populations, this allele increases BMI by an average of 0.25 kg/m² per allele (Qi et al., 2014); in Caucasians, the effect is slightly higher (Day and Loos, 2011).

It is interesting to note that the second strongest genetic determinant of obesity, *MC4R* (polymorphism rs17782313) (Mahmoud et al., 2022), had identical genotype frequencies in both Vietnamese and Czechs in this study.

Hereditary haemochromatosis leads to an excessive absorption of iron from food. It is one of the most common inherited disorders in Europeans. There are several common variants in the *HFE* gene (which codes for a protein that regulates iron absorption in the small intestine), including Cys282Tyr, His63Asp and Ser65Cys. Of these, Cys282Tyr is considered the most relevant, as Tyr282Tyr homozygotes are at increased risk of developing severe haemochromatosis – they have increased iron absorption, leading to iron overload in the body (Feder et al., 1996; Barton et al., 2015).

The spread of these mutations from their probable origins in Celtic regions (Ireland and Wales) to the rest of Europe and, to a lesser extent, other parts of the world can be attributed to population migrations (Simon et al., 1988). Our findings are in agreement with this theory, as the prevalence of *HFE* risk alleles was lower in the Vietnamese population than in the Czech population. Importantly, the allelic frequencies of the *HFE* polymorphisms were similar to those of the Vietnamese population group sampled directly in Vietnam (Pointon et al., 2003).

APOE has three common isoforms: *APOE2*, *APOE3* and *APOE4*. Carriers of the *APOE2* allele are known to have lower levels of low-density lipoprotein (LDL) cholesterol compared to others. *APOE2*/*E2* is known to be associated with type III hyperlipoproteinaemia (Blum, 2016) due to its dysfunctional receptor binding activity. Carriers of the *APOE4* allele may have up to 30 % higher LDL cholesterol levels than carriers of the *APOE2* allele (Bennett et al., 2007).

We observed a slightly increased frequency of the *APOE4* allele in the Vietnamese population. This is con-

sistent with the frequencies observed in other East Asian populations such as Korea, Japan and Malaysia, where the frequency of *APOE4* alleles is typically in the range of 10–12 % (Belloy et al., 2023). *APOE4*, despite being associated with higher LDL cholesterol, may be advantageous in populations where food supply is intermittent or inadequate (Corbo and Scacchi, 1999).

We are aware about the study limitations, requiring confirmation of our results in further studies. First, the sample size of the Vietnamese minority is relatively small. In addition, the "snowball" sampling and some missing data (especially in the case of rs4988235 in *MCM6* and rs1800562 in *HFE*) might introduce some kind of bias. On the other hand, for most polymorphisms, the differences in genotype frequencies are so large (on the level of two orders of magnitude) that it is extremely unlikely that they are the result of type I error. Also, the fact that i/ the genotype frequencies are within the Hardy-Weinberg equilibrium, and ii/ in two cases where SNPs were also analysed in Vietnamese subjects living in Vietnam, the frequencies were almost identical to our sample, further confirms that there is no significant bias in our results.

Despite these points, our results highlight some major differences in the genetic background between the populations and will contribute to a deeper understanding of these variants in a less studied context.

Our results can serve as a valuable tool for tailoring dietary recommendations and guidelines specifically for the Vietnamese population, especially for the Vietnamese community living in the Czech Republic, both for the disease prevention and management of pre-existing health conditions. Analysis of genetic polymorphisms associated with metabolic diseases and their interactions with lifestyle factors could help to understand why certain diseases are more prevalent or less prevalent in different ethnic groups. Understanding the genetic factors that influence metabolic diseases can have important public health implications (Brittain et al., 2017). It may lead to more targeted and personalized approaches to the disease prevention, management and intervention, which can improve the health outcomes and reduce the healthcare costs.

Research in this field highlights the importance of taking into account cross-cultural and inter-ethnic differences when developing lifestyle recommendations (Khoury et al., 2022). What works well for one population may not be as effective for another, and this is particularly important for immigrants, minorities and culturally/ethnically diverse communities. Culturally relevant and personalized dietary advice may be more effective based on the genetic background/predisposition. Our study can serve as a background for future research, particularly in the area of personalized medicine and health interventions. By combining genetic data with lifestyle and dietary information, it is possible to develop more precise and effective strategies to prevent and manage metabolic diseases. This can potentially help to tailor dietary/nutritional recommendations for different ethnic groups, in our case the Vietnamese community in the Czech Republic.

Conflict of interest

There is no conflict of interest.

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