Prevalence of diabetes-associated gene variants and its association with blood glucose levels in the Algarve population, Portugal

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Introduction

Diabetes is one of the leading causes of morbidity and mortality in developed countries. Public health burden as well as economic costs will continue to increase as the prevalence of diabetes is projected to double from the 171 million estimated in 2000 to 366 million in 2030[1]. Type 2 diabetes (T2D) accounts for more than 90% of diabetes cases and results from na impairement in the ability of muscle, fat and liver to respond to insulin , combined with impaired β-cell response to glucose[2]. It is thought to arise from the complex interplay of both genetic and environmental factors. The role of genetics in T2D is stongly indicated by the higher concordance rate of T2D in monozygotic than in dizygotic twins and it has been estimated that 30-70% of T2D risk can be attributed to genetic factors. Transcription factor 7-like 2 (*TCF7L2*), Peroxisome Proliferator-Activated Receptor Gamma (*PPARG*) and Fat and Obesity Associated (*FTO*) genes have been consistently found associated with T2D, and we therefore aimed at identifying their role in T2D in the Portuguese population.

Objectives

The main objectives of this research project were:

• To determine the prevalence of T2D – associated genetic variants previously reported to be associated with T2D in Caucasian populations (*TCF7L2* rs7903146, *PARPG* rs1801282 and *FTO* rs9939609) in the general population;

• To determine its relative contribution to T2D-associated traits.

Materials and Methods

Random sampling of participants was performed based on the National Health System card number of the S. Brás de Alportel Health Centre users, that covers over 99% of the total population. All participants were given a brief description of the objectives of the study, after which they signed a consent form. For each participant, we have measured total glucose levels and collected DNA. In addition, each participant has answered an exhaustive questionnaire including socio-demographic information, health history and lifestyle. Genotyping was performed using MassArray technology. Statistical analysis was performed using the SPSS Software.

Results

The overall participation rate was 36.8%. . In this study, participated 221 individuals (93 men and 128 women) aged 26 to 91 years (mean 57.13). Figure 1 describes the gender (A) and age (B) distribution of the participating individuals.

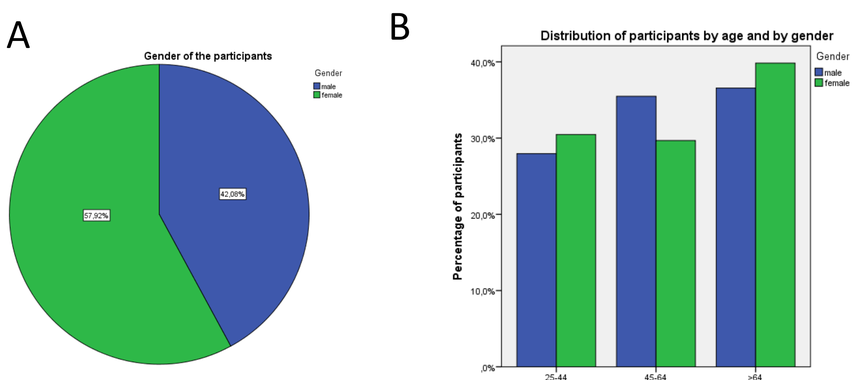

Figure 1. Relative distribution of participants regarding gender (A) and age groups (B).

The descriptive statistics regarding the fasting blood glusose levels of the participants are shown in table 1.

Table 1. Descriptive statistics of thefasting blood glusose levels of the studied population.

	Glucose (mg/dl)					
	N	Mean	95% CI	Median	Minimum	Maximum
Total Population	220,0	104,0	99,2-108,9	97,5	76,0	479,0
Men	92,0	111,5	101,0-122,0	101,0	79,0	479,0
Women	128,0	98,4	95,3-101,4	94,0	76,0	179,0

Overall 39 individuals (17.7%) had blood glucose levels above 110mg/ml (pre-diabetic) and 13 individuals (7.7%) had ablood glucose levels above 126 mg/dl (diabetic). Of the former 38.5% is on specific diabetes medication, whereas the remaining 61.5% are not aware of its (pre)diabetic condition.

We found a significant difference between males and females regarding the fasting blood glucose levels (Mann-Whitney Test P<0.001), with men displaying higher glucose levels than women (Figure 2).

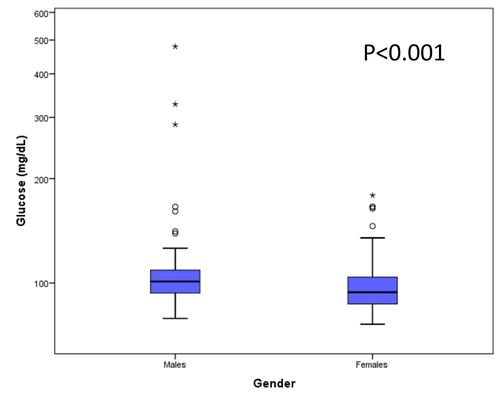

Figure 2. Relative distribution blood glucose levels between males and females.

We have selected and analysed three of the most significant loci previously reported to be associated with T2D in Caucasian populations (*TCF7L2* rs7903146, *PARPG* rs1801282 and *FTO* rs9939609) and performed an association analysis between glucose levels in this population and the selected gene variants. The descriptive statistics are shown in table 2.

Table 2. Descriptive statistics regarding PPARG, TCF7L2 and FTO gene variants.

Gene/SNP	n	Genotype/Allele	n	Freq.(%)	95% CI	HW equilibrium
PPARG	207	CC	170	82,1	76,4 - 87,9	p=0,5351
rs1801282		CG	36	17,4	5 - 29,8	
		GG	1	0,5	0 - 14,1	
		alelle C	376	90,8	87,9 - 93,7	
		alelle G	38	9,2	0 - 18,4	
TCF7L2	206	CC	95	46,1	36,1 - 56,1	p=0,2429
rs7903146		CT	95	46,1	36,1 - 56,1	
		TT	16	7,8	0 - 20,9	
		alelle C	285	69,2	63,8 - 74,5	
		alelle T	127	30,8	22,8 - 38,9	
FTO	206	AA	24	11,7	0 - 24,5	p=0,3744
rs9939609		AT	101	49,0	39,3 - 58,8	
		TT	81	39,3	28,7 - 50	
		alelle A	149	36,2	28,5 - 43,9	
		alelle T	263	63,8	58 - 69,6	

Genotype distribution for all investigated SNPs was in Hardy-Weinberg equilibrium. We found a marginal association between glucose levels and genotypes at the *TCF7L2* locus (Mann-Whitney test *P*=0.045) in females but not in males, with carriers of the T allele displaying higher levels of blood glucose than homozygous for the C allele. This difference is also observed in males, although not reaching significance (Figure 3). No association was found between glucose levels and the other genotyped variants.

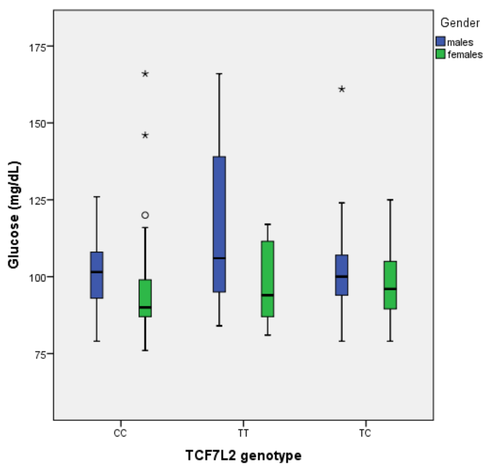

Figure 3. Relative distribution blood glucose levels between males and females.

When we analysed the the blood glucose levels regarding the number of diabetes increased risk alleles carried by each individual, we can observe correlation between the increase in blood glucose levels with the number of risk alleles, although not reaching significance (Figure 4), likely due to the small sample analysed.

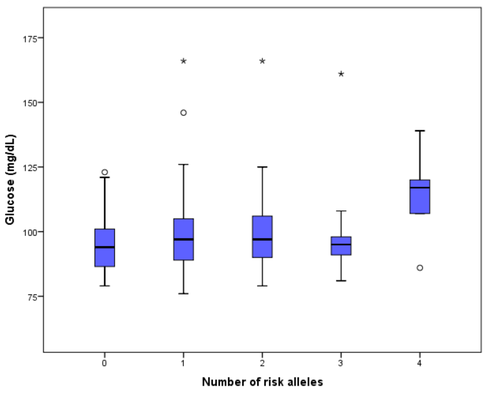

Figure 4. Relative distribution blood glucose levels between males and females.

Conclusions

In the present study, we have found a significant association between the T allele of the *TCF7L2* gene and higher levels of glucose in females. We observe the same trend in the male population although not reaching significance These results suggest that the pathophysiology of the disease may be different between males and females, or that environmental factors are influencing this trait in males, although we can not rule out the possibility of the decreased power of a smaller population in males. We are currently investigating the former hypothesis by increasing our sample size and by analysing lifestyle information provided by the participants in order to evaluate gene-environment interactions influencing glucose levels in the Portuguese population.

References

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