Genetic susceptibility to type 1 diabetes

Genomic variants in the vitamin D pathway

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Introduction and objective

Type 1 Diabetes (T1D) is an autoimmune disease which results from the progressive destruction of insulin producing cells, the pancreatic β cells, by auto-reactive T limphocytes, in the pancreas of genetically susceptible individuals. [1]

Vitamin D (Vit D) is known for its role in the bone and calcium metabolism, however it's also involved in the modulation of the immune response. Serum levels of vit D partly depend on diet and sunlight exposure but, genetic factors are also involved.[2]

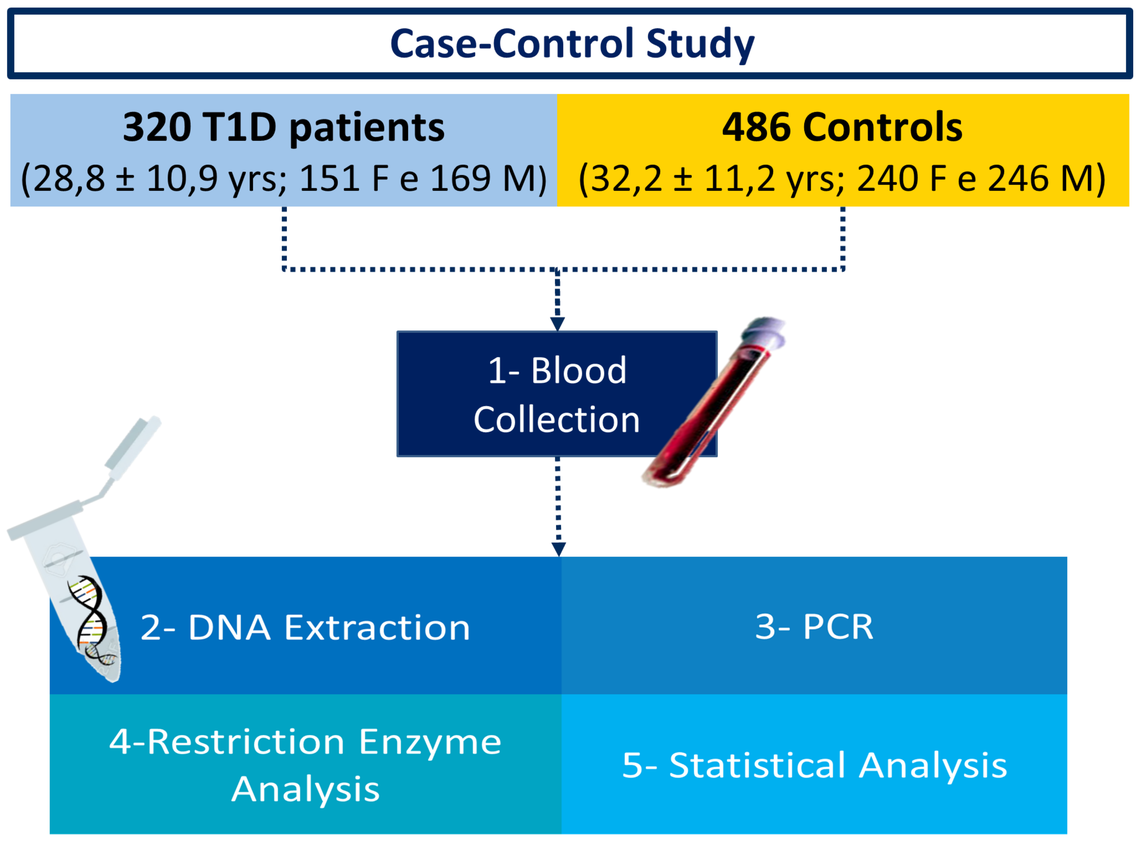
Type 1 Diabetes and Vitamin D

The relationship between the T1D and the Vit D started gain attention with the detection of vitamin D receptor (VDR) in the pancreatic β cells. Suggesting that Vit D has a role upon these cells. [3] Clinical studies showed that T1D patients have lower serum levels of vit D when compared with a control group. Epidimiological studies also report that T1D patients have a higher prevalence of Vit D deficiency. Suggesting that there is a relationship between the levels of VitD and the T1D manifestation. In fact, the supplementation with Vit D seems to reduce the risk for developing T1D. [4]

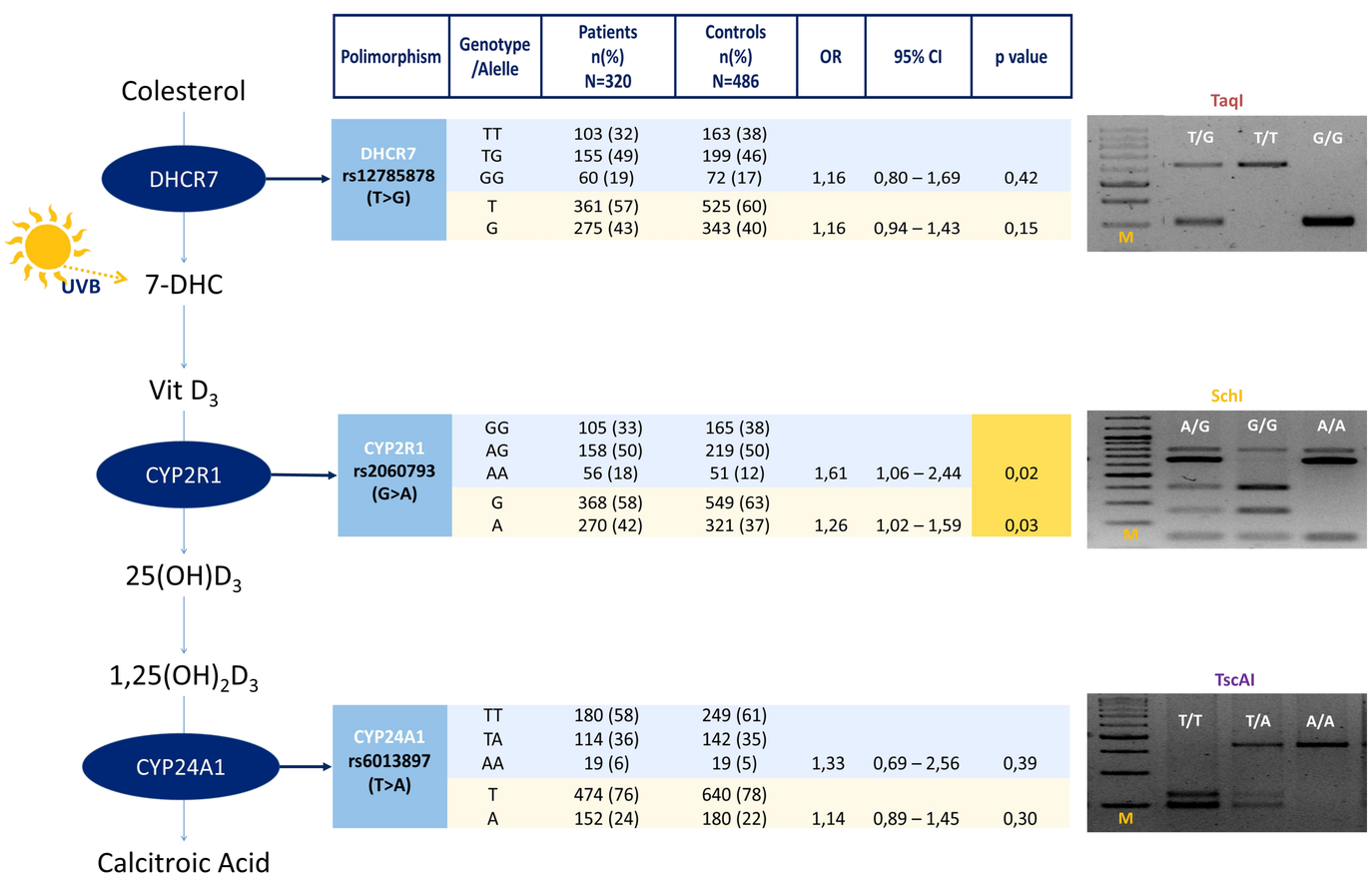
The association between the levels of vit D and the onset of several autoimune diseases were evaluated by a GWAS. Single Nucleotide Polymorphisms (SNP's) in the VDR gene were identified as being associated with the serum levels of Vit D and with the genetic susceptibility to T1D. [5] Latter, SNP's within or near the genes that encode crucial enzymes for the proper function of vit D were also identified as associated with the serum levels of vit D and with the susceptibility for T1D. [6,7] However the SNP's present in the genes of the enzymes of the vit D pathway are poorly explored.

So, the aim of this case-control study was to determine the association between, SNP's located within or near genes that encode crucial enzymes for the synthesis (DHCR7), metabolism (CYP2R1) and degradation (CYP24A1) of Vit D, and the genetic susceptibility to T1D in the Portuguese population

Methods



Results and Conclusions



Polimorphism	Genotype /Alelle	Patients n(%) N=320	Controls n(%) N=486	OR	95% CI	p value
DHCR7 rs12785878 (T>G)	TT	103 (32)	163 (38)			
	TG	155 (49)	199 (46)			
	GG	60 (19)	72 (17)	1,16	0,80 – 1,69	0,42
	T	361 (57)	525 (60)			
	G	275 (43)	343 (40)	1,16	0,94 – 1,43	0,15
CYP2R1 rs2060793 (G>A)	GG	105 (33)	165 (38)			
	AG	158 (50)	219 (50)			
	AA	56 (18)	51 (12)	1,61	1,06 – 2,44	0,02
	G	368 (58)	549 (63)			
	A	270 (42)	321 (37)	1,26	1,02 – 1,59	0,03
CYP24A1 rs6013897 (T>A)	TT	180 (58)	249 (61)			
	TA	114 (36)	142 (35)			
	AA	19 (6)	19 (5)	1,33	0,69 – 2,56	0,39
	T	474 (76)	640 (78)			
	A	152 (24)	180 (22)	1,14	0,89 – 1,45	0,30

We genotype the study population for the three SNP's of interest by using restriction enzymes which cut the DNA in a different manner according to the genotype of the sample.

Next we analysed the differences between the control group and T1D patients, regarding the genotype and allele frequencies. Our results suggest that the CYP2R1 SNP – rs2060793 is associated with T1D in the Portuguese population, where the presence of the allele A increases the risk of developing T1D by approximately 30%

The study suggests that polymorphisms present in the Vit D pathway may contribute to the genetic susceptibility to T1D in the Portuguese population.

Our findings may contribute to a better understanding of the pathogenesis of T1D and of the role of vitamin D in autoimmunity

Figure 2. Results – Scheme of the vitamin D pathway with identification of the enzymes of interest; Analysis of the genotype and allele frequencies between the T1D patients and the control group: N - total number of analysed individuals; n - number of individuals; OR – odds ratio; 95% CI – confidence interval; p value was consider significant when p<0,05 (highlight in yellow); Representative images of the agarose gel with representation of the three possible genotypes for each of the SNP's of interest;

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