

IS HLA THE CAUSE OF THE HIGH INCIDENCE OF TYPE 1 DIABETES IN THE CANARY ISLANDS? RESULTS FROM THE TYPE 1 DIABETES GENETICS CONSORTIUM (T1DGC)

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Background and aims

The incidence of childhood-onset type 1 diabetes in the Canary Islands is the highest described so far in Spain (Carrillo et al 2000, Belinchón et al 2008, N´ovoa et al 2016), and one of the highest worldwide.

Our aim was to assess high-risk and protective HLA DRB1-DQA1-DQB1 haplotype distribution in the Canarian families included in the T1DGC, compared with the rest of Spain

Materials and methods

The T1DGC is an international effort to study the genetics and pathogenesis of type 1 diabetes. It included more than 3300 families with type 1 diabetes worldwide. Spain provided 149 of these families, of whom 42 were from the Canary Islands Tenerife and Gran Canaria.



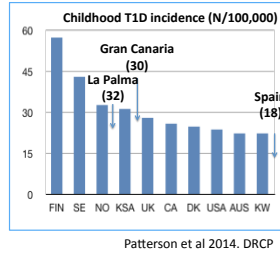
HLA was genotyped centrally in Malmo, Sweden (J Carlson et al), using a PCR-based, sequence-specific oligonucleotide probe system and read with specific software (SCORE)

A deterministic algorithm (alleHap) was developed in the environment R, to impute HLA haplotypes (Medina-Rodríguez N et al. <https://cran.r-project.org/web/packages/alleHap/index.html>). Based on previous T1DGC results in Caucasian population, risk and protective haplotypes were identified. The distribution of protective, high-risk and other haplotypes were compared in the (first two) affected siblings and unaffected parents in the Canarian and non-Canarian Spanish families (chi-squared).

Risk HLA haplotypes	Protective HLA haplotypes
DRB1*0301-DQA1*0501-DQB1*0201 (DR3)	DRB1*0403-DQA1*0301-DQB1*0302
DRB1*0401-DQA1*0301-DQB1*0302 (DR4)	DRB1*0701-DQA1*0201-DQB1*0303 (DR7)
DRB1*0402-DQA1*0301-DQB1*0302 (DR4)	DRB1*1101-DQA1*0501-DQB1*0301 (DR11)
DRB1*0404-DQA1*0301-DQB1*0302 (DR4)	DRB1*1104-DQA1*0501-DQB1*0301 (DR11)
DRB1*0405-DQA1*0301-DQB1*0302 (DR4)	DRB1*1301-DQA1*0103-DQB1*0603
	DRB1*1303-DQA1*0501-DQB1*0301
	DRB1*1401-DQA1*0101-DQB1*0503 (DR6)
	DRB1*1501-DQA1*0102-DQB1*0602 (DR2)

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Spain: 149 Families



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Results

Complete unambiguous haplotypes were obtained and compared in Canarian (74 siblings with type 1 diabetes and 70 non-diabetic parents) and non-Canarian subjects (162 siblings with type 1 diabetes and 139 non-diabetic parents).

HLA haplotype distribution

Siblings with diabetes	Canary Islands	Rest of Spain
Risk haplotypes (%)	72.3	72.5
Protective haplotypes (%)	2.7	1.2
Other haplotypes (%)	25.0	26.2

p= 0.55

Parents without diabetes	Canary Islands	Rest of Spain
Risk haplotypes (%)	47.9	51.4
Protective haplotypes (%)	9.2	13.7
Other haplotypes (%)	42.9	34.9

p= 0.19

Parents without diabetes	Canary Islands	Rest of Spain
DRB1*0301-DQA1*0501-DQB1*0201 (%)	20.1	30.0
DRB1*0401-DQA1*0301-DQB1*0302 (%)	7.5	2.9
DRB1*0402-DQA1*0301-DQB1*0302 (%)	8.2	8.3
DRB1*0404-DQA1*0301-DQB1*0302 (%)	3.0	5.1
DRB1*0405-DQA1*0301-DQB1*0302 (%)	8.2	5.4
DRB1*0403-DQA1*0301-DQB1*0302 (%)	0.7	1.8
DRB1*0701-DQA1*0201-DQB1*0303 (%)	0	0
DRB1*1101-DQA1*0501-DQB1*0301 (%)	0	1.1
DRB1*1104-DQA1*0501-DQB1*0301 (%)	0	0.7
DRB1*1301-DQA1*0103-DQB1*0603 (%)	5.9	3.6
DRB1*1303-DQA1*0501-DQB1*0301 (%)	0.7	1.1
DRB1*1401-DQA1*0101-DQB1*0503 (%)	0.7	0.4
DRB1*1501-DQA1*0102-DQB1*0602 (%)	0.7	0

Conclusion

According to this family-based study, the high incidence of childhood-onset type 1 diabetes in the Canarian population does not seem to be explained by higher-risk class II HLA haplotypes.

Other genetic and /or environmental factors may account for the high incidence of type 1 diabetes in the Islands

This family-based sample, however, is not necessarily representative of sporadic type 1 diabetes