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# Genetics, Environment, and Diabetes-Related End-Stage Renal Disease in the Canary Islands

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*Aims:* Type 1 and type 2 diabetes, complicated with renal disease, have a significantly higher incidence in the Canary Islands than in mainland Spain and other European countries. Present-day Canarian inhabitants consist of a mixed population with North African indigenous and European colonizer ancestors who have rapidly evolved from a rural to an urban life style. The aim of this work was to assess the possible role of genetic and environmental factors on diabetes-related end-stage renal disease incidence in the Canary Islands. *Results:* For both types of diabetes there is an ethnic susceptibility increased by diabetes family history. Whereas the Y-chromosome does not play a significant role, mitochondrial DNA (mtDNA) haplogroup differences point to a maternal origin for this ethnic predisposition, confirming susceptible and protective effects for haplogroups J and T, respectively. In addition, urban life style seems to be an additional risk factor for type 1 diabetes. *Conclusions:* The maternal ethnic predisposition to diabetes complicated with kidney disease detected in the Canary Islands signals mtDNA and X-chromosome markers as the best candidates to uncover the genetic predisposition to this disease.

## Introduction

The incidence of diabetes mellitus is increasing worldwide, causing a heavy social and economic burden. This problem is particularly acute in the Canary Islands as its population shows a high rate of incidence of type 1 diabetes (Carrillo Dominguez, 2000), a prevalence of type 2 diabetes in the highest European range (de Pablos-Velasco *et al.*, 2001; Boronat *et al.*, 2005), and a disproportionately high incidence of diabetes-related end-stage renal disease (ESRD) compared with the rest of Spain (Cabrera de Leon *et al.*, 2009; Lorenzo and Boronat, 2010; Lorenzo *et al.*, 2010). In the Canary Islands, around 16% of the diabetes patients are of type 1 and 84% of type 2 (de Pablos-Velasco *et al.*, 2005). As in the majority of screenings, in both types, prevalence in men is significantly higher than in women (Carrillo Dominguez, 2000; Boronat *et al.*, 2005; Cabrera de Leon *et al.*, 2009), and the risk of inheriting diabetes from an affected mother is greater than that from an affected father (Boronat *et al.*, 2005). Combined type 1 and type 2 diabetes mellitus-ESRD incidence in the Canary Islands, 180–185 patients per million population (PMP) is significantly higher than in other Spanish regions ranging from 125 to 130 PMP (Ceballos *et al.*, 2005).

Both genetic (Florez *et al.*, 2003) and environmental (Berdanier, 2001) risk factors enhance susceptibility to diabetes. As the mitochondria play a central role in oxidative stress, control of insulin secretion, and glucose metabolism, the search for association between mitochondrial DNA (mtDNA) variants and susceptibility to diabetes has been the focus of numerous studies. For instance, the presence of the A3243G mtDNA transition in a large pedigree was consistently associated with maternally transmitted type 2 diabetes and deafness (van den Ouweland *et al.*, 1992), as was the resistance of individuals with the mtDNA C5178A transversion to type 1 diabetes in Japan (Okada *et al.*, 2000). However, these types of associations appear to be restricted to particular cases. In other instances, different mtDNA backgrounds seem to partially explain the different ethnic or geographic predispositions to diabetes (Tajima *et al.*, 2004). This could be one of the causes to explain the fact that the mtDNA T16189C transition has been consistently associated with type 2 diabetes susceptibility in Asia (Park *et al.*, 2008) but only sporadically in Europe (Poulton *et al.*, 2002; Chinnery *et al.*, 2005), or that some specific Western Asian mtDNA haplogroups, such as J, seem to confer susceptibility to type 2 diabetes in Finns (Mohlke *et al.*, 2005) and Caucasian-Brazilians (Crispim *et al.*, 2006), but

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this trend could not be detected in other large European samples (Saxena *et al.*, 2006; Chinnery *et al.*, 2007; Benn *et al.*, 2008). In this regard, it seems pertinent to point out that the present-day Canarian inhabitants represent a mixed population made up by pre-Hispanic natives of North African origin and mainland colonizers from the Iberian Peninsula (Flores *et al.*, 2001). Undoubtedly, other factors, such as family history, must be taken into account as was recently demonstrated in a study on patients of Jewish origin, in which the presence of the mtDNA haplogroup J1 was found to be significantly under-represented in patients without diabetic ancestors compared to patients having diabetic parents (Feder *et al.*, 2009).

In the Canary Islands, age, central obesity, serum triglycerides, and family history of diabetes were, previously (de Pablos-Velasco *et al.*, 2001; Boronat *et al.*, 2005), independently associated with type 2 diabetes in both sexes. The aim of the present study was to assess, in the Canarian population, the effect of several environmental and genetic risk factors such as age, ethnicity, rural versus urban style of life, family history of diabetes, and uniparental Y-chromosome and mtDNA polymorphic backgrounds in type 1 and type 2 diabetes patients complicated with chronic renal disease compared with healthy controls.

## Materials and Methods

### Subjects

Patients previously found to have type 1 (83) and type 2 (184) diabetes with chronic renal disease stage IV (Kidney Disease Outcomes Quality Initiative guidelines) were recruited from health centers in different islands, as were the age-matched nondiabetic controls (288). The three cohorts consisted of unrelated subjects. Age, sex, place of residence, and geographic origin of all their known ancestors were recorded for all subjects, as well as family diabetic histories for the type 1 and type 2 diabetes cohorts. Subjects living in agricultural areas with fewer than 30,000 inhabitants were considered of rural style of life, and those others who lived in service centers with more than 30,000 inhabitants were considered of urban style of life. Only subjects with all known ancestors of Canarian origin were considered as ethnically Canarian. The study design was approved by the Clinical Investigation Ethics Committee (CEIC) of the Universitary Hospital of Canaries, and all subjects gave their written informed consent.

### Molecular analysis

As it is well known that the pre-Hispanic inhabitants of the Canary Islands had a North African origin (Flores *et al.*, 2001; Santos *et al.*, 2010), the North African indigenous Y-chromosome M81 binary marker was analyzed by restriction fragment length polymorphism (RFLP) as previously mentioned (Flores *et al.*, 2003). This marker has been recently detected in Canarian aborigine remains (Fregel *et al.*, 2009a). The mtDNA A3243G polymorphism was screened by RFLP following the protocol of Zhong *et al.* (2000) but omitting the radioactive labeling step. The mtDNA hypervariable segment I was amplified and sequenced for both complementary strands with the Big Dye Terminator Cycle sequencing kit (Applied Biosystems) and analyzed on an Applied Biosystems 3100 DNA analyzer. Primers and conditions were already described (González *et al.*, 2006). mtDNA sequences were aligned with the revised Cambridge Reference Sequence (CRS) using CLUSTAL and mutations identified by the three last digits of their position in the reference sequence (Anderson *et al.*, 1981). The haplotypes obtained were sorted into mtDNA haplogroups following the updated nomenclature proposed by van Oven and Kayser (2009). When necessary, haplogroup assignation was confirmed using haplogroup diagnostic RFLP analysis as detailed previously (Rando *et al.*, 1999). We have considered mtDNA Canarian pre-Hispanic founder types those haplotypes defined as such by Rando *et al.* (1999). However, the CRS was omitted as it is as common in the Canary Islands as in any Iberian Peninsula population. The majority of the supposed founder types have been recently detected in Canarian aborigine remains (Maca-Meyer *et al.*, 2004; Fregel *et al.*, 2009b).

### Statistical analysis

Comparison of the frequencies of discrete variables between type 1 and type 2 diabetes cases and with controls were performed using Chi-square or Fisher exact tests. To evaluate the association of type 1 and type 2 diabetes with other risk factors, logistic regression models were used. All statistical analyses were performed with the SPSS package (PASW statistics 18).

## Results

### Diabetic nephropathy progression

The mean period from the diagnostics of type 2 diabetes complicated with renal disease to the initiation of dialysis in our cohort was $5.0 \pm 3.33$ years.

### Family history

The frequency of type 2 diabetes patients with diabetes-positive family history (59%) is significantly greater ($p < 0.001$) than that of the type 1 diabetes group (32%), but this is mainly due to those with affected maternal ancestors ($p < 0.001$), as paternal histories are not significantly different between groups ($p = 0.185$).

### Age

Supplementary Table S1 (Supplementary Data are available online at www.liebertonline.com/gtmb) shows that although all patients suffered chronic renal disease stage IV, all the type 2 diabetes patients were above 40 years old, while 30% of the type 1 diabetes were under this age ($p < 0.001$). However, within this age limit, the frequency of type 1 diabetes patients with diabetes parental family history (11%) was significantly smaller ($p = 0.043$) than those without affected parents (36%).

### Gender

It can be deduced from Supplementary Table S1 that only in the type 2 diabetes cohort was the number of affected men (61%) marginally ($p = 0.053$) greater than that of women compared to controls (52%). This male susceptibility reaches statistical significance ($p = 0.042$) when only type 2 diabetes patients without diabetes affected parents, represented by 64% of men, are compared to controls.

### Ethnicity

The fraction of diabetes patients with all known ancestors of Canarian origin (92%) was significantly greater ($p = 0.003$) than that of controls (84%), with a similar tendency in both types (Supplementary Table S1). Furthermore, this ethnic susceptibility is mainly due to patients who have a positive diabetes family history ($p = 0.002$).

### Lifestyle

From Supplementary Table S1 it can be deduced that the type 1 diabetes group has a significantly greater ($p = 0.005$) proportion of patients of urban origin (66%) than the type 2 diabetes group (45%) and controls (46%). However, when examining their diabetes family history it is suggested that all the significance is due to the majority urban origin of the type 1 diabetes patients who lack diabetes affected ancestors (71%) as those with diabetes parents have an urban frequency (44%) similar to that found in the type 2 diabetes and control groups. On the contrary, in the type 2 diabetes cohort, patients of urban origin with healthy parents (39%) are significantly ($p = 0.031$) less frequent than those with affected (55%) parents.

### Uniparental molecular markers

The Y-chromosome-specific North African binary marker M81 showed similar frequencies in type 1 diabetes (11%), type 2 diabetes (11%), and control (12%) groups (Supplementary Table S1). The mtDNA A3245G mutation was not found in this survey. The mtDNA T16189C polymorphism was less frequent in the type 1 diabetes group (11%) than in controls (18%) and significantly ($p = 0.021$) less frequent than in the type 2 diabetes group (23%). Supplementary Table S1 shows the mtDNA haplotypic composition of each experimental and control cohort, with the respective frequencies of the Canarian founder haplotypes being shown. Total founders frequency in the type 1 diabetes group (31%) is significantly greater than in type 2 diabetes (20%) and in controls (20%), with probability values of $p = 0.046$ and $p = 0.038$, respectively. This difference is mainly due to the frequency of founders (33%) in type 1 diabetes patients without diabetes-affected parents. Table 1 shows the mtDNA haplogroup distribution in type 1 diabetes, type 2 diabetes, and control groups. Haplogroup U with the North African–specific U6 subgroup excluded is significantly ($p = 0.033$) less frequent in the type 1 diabetes cohort (6.0%) than in controls (14.9%), whereas haplogroup J is significantly ($p = 0.037$) less frequent in the latter (8.0%) than in the former (15.7%). These tendencies also hold when the type 1 diabetes patients are compared with type 2 diabetes patients with probability values of $p = 0.018$ and $p = 0.027$ for J and U, respectively. In relation to the type 2 diabetes group, only haplogroup T is significantly ($p = 0.037$) more abundant in controls (13.9%) than in type 2 diabetes patients (7.6%). The same tendency is observed for the frequency of haplogroup T in type 1 diabetes (8.4%) although it did not reach any significance. However, when the global frequency of haplogroup T in diabetes patients is compared to that in controls, the significance increases ($p = 0.023$) accordingly. Finally, when the diabetes family history is taken into account, it is observed that the haplogroup J excess in the type 1 diabetes cohort is mainly due to patients with diabetes affected parents ($p = 0.039$).

Table 1. Mitochondrial, Haplogroup Distribution, Founder Haplotypes, and T16189C Transition Carriers in Controls (288) and Type 1 (83) and Type 2 (184) Diabetes Patients

| *Haplogroups* | *Controls* | *T 1* | p-*value* | *T 2* | p-*value* |
|---|---|---|---|---|---|
| H | 100 (34.7) | 25 (30.1) | 0.435 | 65 (35.3) | 0.893 |
| R(xH,UK,JT) | 12 (4.2) | 5 (6.0) | 0.476 | 12 (6.5) | 0.256 |
| U(xU6) | 43 (14.9) | 5 (6.0) | 0.033 | 29 (15.8) | 0.807 |
| U6 | 37 (12.8) | 16 (19.3) | 0.140 | 25 (13.6) | 0.817 |
| J | 23 (8.0) | 13 (15.7) | 0.037 | 12 (6.5) | 0.554 |
| T | 40 (13.9) | 7 (8.4) | 0.188 | 14 (7.6) | 0.037 |
| N(xR) | 11 (3.8) | 6 (7.2) | 0.191 | 7 (3.8) | 0.993 |
| M | 4 (1.4) | — | 0.280 | 3 (1.6) | 0.832 |
| L | 18 (6.3) | 6 (7.2) | 0.749 | 17 (9.2) | 0.227 |
| FU | 59 (20.5) | 26 (31.3) | 0.038 | 37 (20.1) | 0.921 |
| 16189 | 53 (18.4) | 9 (10.8) | 0.104 | 42 (22.8) | 0.242 |

*p*-value of the $\chi^2$ test between type 1 and type 2 with controls. The number in parentheses gives the percentage of the given value.

### Multiple regression analysis

When multiple regression analyses are performed using as independent variables the significant risk factors detected for each diabetes type (Tables 2 and 3), it is shown that urban lifestyle seems to be the best predictor for type 1 diabetes, with frequency of haplogroup U playing only a marginal protective role (Table 2). In relation to type 2 diabetes, Canarian ethnicity is the best predictor, while belonging to haplogroup T has a significant protective effect, and being male suggests a marginal susceptibility (Table 3).

## Discussion

Some of the studied factors seem to affect both types of diabetes in a similar way. So, the absence of association of the Y-chromosome North African M81 marker discards any specific male ethnic predisposition for both diabetes types. Most importantly, there is a significant ethnic predisposition

Table 2. Multiple Logistic Regression Analysis for the Association Between Markers and Diabetes Risk Factors for Type 1 Diabetes

| *Determinants* | *Adjusted OR* | *95% CI* | p-*value* |
|---|---|---|---|
| Sex | 1.214 | 0.727–2.026 | 0.459 |
| Mt189 | 0.679 | 0.307–1.501 | 0.339 |
| CAN | 1.827 | 0.765–4.364 | 0.175 |
| FU | 1.538 | 0.847–2.793 | 0.157 |
| hg_U(xU6) | 0.423 | 0.155–1.155 | 0.093 |
| hg_J | 1.528 | 0.701–3.334 | 0.287 |
| hg_T | 0.548 | 0.227–1.324 | 0.181 |
| RU | 0.397 | 0.234–0.673 | 0.001 |

Mt189, mtDNA T16189C SNP; CAN, Canarian origin; FU, carriers of mtDNA Canarian prehispanic founder haplotypes; hg_U(xU6), carriers of U mtDNA haplotypes (except U6); hg_J, carriers of J mtDNA haplotypes; hg_T, carriers of T mtDNA haplotypes; RU, individual living in rural areas; OR, odds ratio; CI, confidence interval.

Table 3. Multiple Logistic Regression Analysis for the Association Between Markers and Diabetes Risk Factors for Type 2 Diabetes

| *Determinants* | *Adjusted OR* | *95% CI* | p-*value* |
|---|---|---|---|
| Sex | 1.459 | 0.995–2.137 | 0.053 |
| Mt189 | 1.285 | 0.789–2.092 | 0.314 |
| CAN | 2.376 | 1.246–4.531 | 0.009 |
| FU | 0.995 | 0.605–1.636 | 0.985 |
| hg_U(xU6) | 1.001 | 0.573–1.748 | 0.998 |
| hg_J | 0.803 | 0.377–1.710 | 0.570 |
| hg_T | 0.469 | 0.243–0.907 | 0.025 |
| RU | 1.034 | 0.706–1.516 | 0.862 |

of the native Canarian Islanders to suffer from diabetes, a tendency that is reinforced in those patients with diabetes affected parents. On the contrary, the similar protective effect of the mtDNA haplogroup T carriers is stronger in those type 1 and type 2 diabetes patients who lacked a positive diabetes family history. There are also factors that behave differently in each type. To begin with, maternal diabetes-positive history is significantly greater in the type 2 diabetes than in the type 1 diabetes group. Lifestyle has also an opposite effect as the type 1 diabetes incidence is stronger in urban centers, whereas that of type 2 diabetes is more prevalent in rural villages. This difference increases when patients of each type, lacking affected parents, are compared. Finally, we have detected that the mtDNA polymorphism T16189C is significantly less frequent in the type 1 diabetes group than in the type 2 diabetes group, which might be interpreted as if it could confer a protective effect only to type 1 diabetes. In contrast to some studies (Poulton *et al.*, 2002), but in agreement with others (Chinnery *et al.*, 2005), we have not found any significant positive association of this polymorphism with type 2 diabetes.

It is well known that type 1 diabetes has a significant earlier age of onset than type 2 diabetes. However, in the Canary Islands, this difference is mainly due to the type 1 diabetes patients who have affected parents, pointing to a hereditary predisposition also reflected by the fact that the haplogroup J susceptibility to type 1 diabetes is mainly due to the same subgroup of patients with affected parents. On the contrary, haplogroup U, excluding the North African type U6, seems to have a protective influence. Furthermore, the Canarian-specific predisposition to type 1 diabetes is confirmed by the fact that Canarian founder haplotypes are more prevalent in these patients, with special importance in those that lack a family diabetes history, than in controls. It is precisely this subgroup that is more susceptible to the illness when they shift to an urban lifestyle, in principle, pointing to a strong gene–environment interaction.

With regard to type 2 diabetes, Canary Islanders, carrying fewer mtDNA haplogroup T haplotypes, living in rural villages and being men are the most susceptible group. In addition, these factors have a stronger incidence in those type 2 diabetes patients without diabetes-affected parents.

However, before suggesting a direct relationship among the associated variables and diabetes, some confounding factors must be evaluated. For instance, we have found that type 1 diabetes is more prevalent in urban and type 2 diabetes in rural centers, but that could be explained as a secondary effect of the different age onset of both types and the well-known demographic differences between rural and urban areas, with the former having a significant excess in the elder and the latter in the younger age segment. However, when correcting for age differences between areas, a significant excess of type 1 diabetes patients in urban centers still persists ($p = 0.045$), pointing to a specific environmental predisposition, which is reinforced by the fact that it is mainly the cohort of patients without affected parents who are the most prevalent in urban centers.

In a similar way, there are previous studies suggesting a direct relationship among the associated molecular mtDNA markers and diabetes. So, haplogroup T has also been found to significantly protect against type 2 diabetes in a very distant Russian population study (Buikin *et al.*, 2008). Haplogroup J showed a trend toward association with type 2 diabetes in Finns (Mohlke *et al.*, 2005) and JT in Caucasian-Brazilians (Crispim *et al.*, 2006). Furthermore, it is subclade J1 that seems to confer susceptibility to the same illness in Jewish patients with diabetes-affected parents (Feder *et al.*, 2009). In a similar way, haplogroup U has been positively associated with type 2 diabetes in an aged Finnish cohort (Niemi *et al.*, 2003). However, in our opinion, it is more appropriate trying first to explain the specific associations found in the Canary Islands as an indirect consequence of the global predisposition of native Canarians to diabetes when compared to residents from the Iberian Peninsula. At the mtDNA level, the main characteristic that differentiates Canarians from peninsular Iberians is that the North African haplogroup U6 is significantly ($p < 0.0001$) more abundant in the former (16%) than in the latter (2%), which is extendable to a greater prevalence of founder lineages in Canarian natives (Santos *et al.*, 2010). The counterpart is that other haplogroups have to be more abundant in the Iberian Peninsula than in the Canarian natives. Precisely, this is the case for haplogroup T ($p < 0.001$) and marginally so for haplogroup U excluding U6 ($p = 0.055$) although this trend does not hold for haplogroup J ($p = 0.764$). Consequently, the haplogroup T and U deficits in the type 1 and type 2 diabetes cohorts might be better explained by the significant excess in both patient groups of native Canarians compared to controls. Indeed, this is the case for U but not for T because its frequency in native diabetes (8.5%) is still significantly smaller ($p = 0.029$) than in native controls (13.9%). So, haplogroup J and the T16189C polymorphism and haplogroup T might be, respectively, genuine susceptible and protective variants. However, the fact that these associations are not consistently found in all the populations studied (Chinnery *et al.*, 2005, 2007; Saxena *et al.*, 2006; Benn *et al.*, 2008) seems to point to statistical errors or to hidden associations with still unknown genetic and/or environmental conditions.

In summary, in the Canary Islands, urban lifestyle, interacting with a native Canarian background, evidenced by an excess of founder mtDNA haplotypes, seems to be the most evident risk factors for type 1 diabetes with chronic renal disease that, in addition, has an earlier onset in those patients with affected parents. For type 2 diabetes with chronic renal disease, again Canarian ethnicity is the most evident hereditary risk factor with rural lifestyle and male gender involved in secondary predisposition.

The study of this ethnically mixed Canary Islands population has served to discard several molecular markers as

direct causes of this complex illness, and to point to future studies in search of the true genetic factors involved in the ethnic susceptibility detected here.

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### Author Disclosure Statement

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