No correlation between the variants of exostosin 2 gene and type 2 diabetes in Burkina Faso population

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Abstract

Recent genome-wide association studies and replication analyses have reported the association of variants of the exostosin-2 gene (EXT2) and risk of type 2 diabetes (T2D) in some populations, but not in others. This study aimed to characterize the variants rs1113132, rs3740878 and rs11037909 of EXT2 and to determine the existence of a possible correlation with T2D in Burkina Faso. It is a case-control study undertaken in Burkina Faso in the city of Ouagadougou at the Hospital of Saint Camille of Ouagadougou from December 2014 to June 2015. It relates to 121 type 2 diabetes cases and 134 non-diabetic subjects. The genotyping of these polymorphisms was done by real-time PCR using the allelic exclusion method with TaqMan probes. The minor allele frequencies (MAFs) was almost identical in diabetic and control subjects for the all three Single Nucleotide Polymorphisms (SNPs) with no statistical significance, p>0.05: rs1113132 (OR=0.89; p=0.82); rs11037909 (OR=0.89; p=0.74) and rs3740878 (OR=1.52; p=0.42). None of the three polymorphisms was associated with the risk of DT2. However, an association between the BMI, age and type 2 diabetes was noted. The variants of EXT2 would not be associated to the risk of T2D in the African black population of Burkina Faso.

Introduction

Type 2 diabetes (T2D) is a public health issue on a worldwide scale characterized by chronic hyperglycemia. In 2017, the number of diabetics in Africa was estimated at approximately 15.9 million with a regional prevalence of 3.1%; in Burkina Faso, this prevalence was estimated to be between 1.3–3.9%.1 In recent years, several genes have been identified as being risk factors for T2D.2,3 In 2007, a genome-wide association study identified multiple novel risk loci for T2D, among them were found Transcription Factor 7 Like 2 (TCF7L2), Solute Carrier Family 30 Member 8 (SLC30A8), Hematopoietically Expressed Homeobox (HHEX) and Exostosin 2 gene (EXT2).2 Hence, many studies have been conducted in various populations relating to some of these genes.4-6 The genome-wide association study conducted in the French population found a genetic association between EXT2 polymorphisms rs1113132, rs3740878, rs11037909, and T2D.2 Thereafter and in the context of different studies these associations were found in some populations such as the Caucasians but not in others such as the Asians, the African-Americans, the North Africans.4,7-11 These contradictory results can be explained by ethnicity which is an important factor in genetic association studies. These results support the need for the replication of these association studies in various populations from different ethnic groups for a better understanding of these mechanisms. Some studies have been conducted on T2D and some candidate genes in Africa12 but to our knowledge, none has focused on EXT2 and T2D in Burkina Faso population nor any other Sub-Saharan African countries. Therefore, the purposes of the present study is to determine the association between the three EXT2 genetics variants and the risk of the T2D within the Burkina Faso population.

Materials and Methods

Study population

It was a case-control study that was carried out from December 2014 to June 2015 in Burkina Faso in the city of Ouagadougou at the Hospital of Saint Camille of Ouagadougou (HOSCO). The study population consisted of 255 subject males and females whose ages ranged from 20 to 88 years old at a rate of 121 diabetic subjects (cases) and 134 non-diabetic subjects (controls). All the subjects were Burkina Faso nationals from several cities of the country. The size and the weight were measured to determine each subject Body Mass Index (BMI).
Results

Study population characteristics

Two hundred and fifty-five (255) subjects were included in this study and consisted of 42.7% (109/255) and 57.3% (146/255) men and women, respectively. The subjects’ ages ranged from 20 to 88 years old with more than 80.8% over 40 years (Table 1). The patients were on average older than the control subjects (54.72±11.35 against 50.90±13.97 years old respectively).

Association analysis

Association case was not observed between studied SNPs (rs1113132, rs11037909, rs3740878) and the risk of developing T2D. Indeed, the minor allele frequencies (MAF) were statistically close between the cases and controls (p>0.05) (Table 2).

The haplotypic analysis of different studied SNPs revealed the existence of linkage disequilibrium between these three variants. The linkage appears stronger between SNPs rs11037909 and rs3740878 (from = 0.86) (Figure 1).

Discussion

In this study, there was no association between the EXT2 variants rs1113132, rs11037909 and rs3740878 and the risk of T2D in the Burkina population. Previous work carried out on the link between the EXT2 SNPs and the T2D reported diverging results according to the ethnicity of the studied populations. The average age of our study population was 54.72±11.35 years for cases and 50.90±13.97 years old for controls which is similar to the study led by Yamógo et al., in which the average age of diabetics was 53.50±3.50 years. This average is similar to the UKPDS study where the average age was 54 years and to that of Nemr study in 2013 (58 6 ± 13.4). This supports the fact that T2D is related to age and usually occurs after 40 years.

Table 1. General characteristics of the study subjects.

|                        | Cases (diabetic) n = 121 | Controls n = 134 | P (χ² test) |
|------------------------|--------------------------|------------------|------------|
| Sex                    |                          |                  |            |
| Men                    | 36 (29.8%)               | 73 (54.5%)       | P < 0.001 |
| Women                  | 85 (70.2%)               | 61 (45.5%)       |            |
| Age                    |                          |                  |            |
| 20 – 40 years          | 14 (11.6%)               | 35 (26.1%)       | P = 0.004 |
| ≥ 40 years             | 107 (88.4%)              | 99 (73.9%)       |            |
| BMI (kg/m²)            |                          |                  |            |
| Underweight            | 4 (3.30%)                | 24 (17.90%)      | P < 0.001 |
| Normal                 | 30 (24.79%)              | 73 (54.48%)      | P < 0.001 |
| Overweight             | 59 (48.76%)              | 31 (15.67%)      | P < 0.001 |
| Obese                  | 28 (23.14%)              | 16 (13.22%)      | P = 0.02  |
| HBP                    |                          |                  |            |
| Presence               | 68 (56.2%)               | -                |            |
| Absence                | 53 (43.8%)               |                  |            |
| Glucose (mmol/l)       | 7.86 ± 3.474             | 3.50 ± 2.449     |            |

BMI: Body Mass Index; underweight (under 18.5 kg/m²), normal (18.5 to 25 kg/m²), overweight (5 to 30 kg/m²), obese (over 30 kg/m²). HBP: High Blood Pressure / Hypertension.

Figure 1. Linkage disequilibrium of EXT2 polymorphisms.
thus explain the divergent results in different studies.\textsuperscript{18,19} However, in our study, a correlation between T2D and BMI was observed. The BMI difference between cases and controls was statistically significant (p < 0.05). Over 71.9% of the patients were overweight or obese with a mean BMI $\geq$ 25kg/m$^2$ or 26.9 $\pm$ 8.4. This result is similar to that of Nemr \textit{et al.} study with 26.8 $\pm$ 4.6 and that of Diyane \textit{et al.}, with 28.1 $\pm$ 4.6.\textsuperscript{20} Finally, in our study we found that over 56.2% of T2D subjects had hypertension, this is comparable to the study conducted by Diyane \textit{et al.} in 2013 where 60% of patients had grade I hypertension.\textsuperscript{20} The haplotype analysis of the three SNPs studied allowed us to demonstrate that in our study population the linkage appears stronger between SNPs rs11037909 and rs3740878 with 86%, for the others, we have 78% between rs1113132 and rs3740878; 55% between rs1113132 and rs11037909.

### Conclusions

This study suggests that polymorphisms of \textit{EXT2} does not play a very decisive role in the development of type 2 diabetes in a black population of Burkina Faso. It would be very important to carry out further studies in our population on a larger cohort while including other genes that are involved in the predisposition to T2D such as \textit{TCF7L2}, \textit{SLC30A8}, and \textit{HHEX}. We believe that understanding the role played by these genes in the T2D pathogenesis will open multiple path for novel therapeutic strategies.

### Limitations

One of the limitations of our study is the size of the study population. We believe that a larger number of cases and controls could have enabled to get a more specific and complete insight on the eventual correlation between T2D and \textit{EXT2} variants on our population.

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### Table 2. Association between \textit{EXT2} and T2D in the study population.

| CHR | SNP | Position (bp) | Genotype | Normal allele | MAF* control | MAF case | OR | P |
|-----|-----|---------------|----------|---------------|--------------|----------|----|---|
| 11  | rs1113132 | 44209979 | CG | C | 0.03358 | 0.03719 | 0.8996 | 0.82 |
| 11  | rs11037909 | 44212190 | TC | T | 0.0709 | 0.07851 | 0.8956 | 0.74 |
| 11  | rs3740878 | 44214378 | AG | A | 0.03731 | 0.02479 | 1.525 | 0.41 |

CHR: Chromosome. *MAF: Minor Allele Frequencies; OR: Odds Ratio (with 95% confidence intervals). SNP: Single Nucleotide Polymorphism.

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