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REVIEW ARTICLE

Genetic Component of Type 2 Diabetes in a Mexican Population

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Type 2 diabetes (T2D) is a complex disease caused by the interaction of genetic and environmental factors. In this regard, it has been demonstrated that Hispanics have a greater susceptibility to developing complex diseases like T2D, which has been attributed to their Amerindian component. Mexico has a wide population variety as a result of Amerindian (56–69%), European (26–41.8%) and African (1.8–6%) ancestral components. The stratification of the population has made difficult the study of T2D in the Mexican population. Despite advances, in Mexico the studies in this field are scarce; 9 of 88 *loci* associated with type 2 diabetes by genome-wide association studies (GWAS) in Caucasian populations have been replicated in the Mexican population. Currently, only 19 common variants and two variants of low frequency have been associated with T2D in Mexico. With respect to the private genetic variation in Mexican population, only one haplotype and two genetic variants have been described. This confirms the existence of new genetic variants not yet described, exclusive to the Mexican population, which suggests most likely, that there are more genetic variants to discover. Thus, in the present review we aim to bring together in one place all the studies about T2D in Mexico to understand the contribution of the genetic factors in the susceptibility to developing T2D in a Mexican population.

Key Words: Polymorphisms, Type 2 diabetes, Mexican population, Genetic background.

Introduction

There are different hypotheses that try to explain the rapid increase in the prevalence of chronic degenerative diseases like diabetes, particularly in Western societies. One of these hypotheses arises from the interaction between the environment and genetics during human evolution (1).

During the evolution of man, there were different migrations and environmental phenomena that had exposed societies to intermittent periods of scarcity and abundance. These events, according to Neel's hypothesis, caused the selection of a genotype associated with a thrifty metabolic efficiency and survival (2). However, this genotype in modern societies with a constant supply of food could trigger obesity, hyperinsulinemia and diabetes. Several genes have been identified as candidates for the thrifty genotype, including those that code for proteins involved in insulin and leptin pathways, as well as lipid metabolism. Briefly, the genetic basis of the "thrifty genotype" probably derives from the additive effects of polymorphisms in several sites, instead of just one regulatory abnormality (3). Thus, knowledge of the genetic basis of multifactorial diseases like diabetes is a challenge because as with the thrifty genotype, this disease is caused by the effect of multiple alleles combined in a different way in each population (4). Worldwide, many groups have dedicated their research to identify the genetic component of type 2 diabetes (T2D) to understand the mechanisms involved in the predisposition and development of the disease; however, the genetic underpinnings of disease remain elusive. In Mexico, the study of genetic basis of T2D has become more complicated when population stratification is taken into account. Hence, the aim of the present work was to compile and review all the available information about the contribution of genetic factors in the susceptibility to T2D in Mexican population.

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Type 2 Diabetes in Mexico

Today, diabetes is defined as a group of metabolic diseases characterized by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action or both (5). Before the conquest of Mexico, diabetes existence in the Aztec culture was denoted by Badiano and Florentine Codex where treatment of disease symptoms was explained, although it is important to mention that the term ''diabetes'' as we know it today was unknown (6).

According to the National Health Survey 2012 (ENSANUT 2012), in Mexico, ~1/10 persons is affected with T2D. It is important to mention that these data only reflect subjects previously diagnosed with the disease, but we expect a twofold increase in this number when including newly diagnosed T2D patients. In addition, the prevalence of T2D in younger age groups has increased (25% of diabetes cases in Mexico occurs in young adults <43 years of age), which implies >20 years living with the disease (7,8). In consequence, T2D is found among the leading causes of death, which represents a health burden for the country (9).

Another risk factor for T2D is prediabetes, which is a precedent state of diabetes where glucose homeostasis is impaired (10). According to Guerrero-Romero et al., in Mexico 20−30% of the inhabitants are afflicted with prediabetes, this latter determined as impaired fasting glucose and glucose tolerance according to American Diabetes Association criteria (11,12). In addition, Colorado-Malagon et al. reported that annual progression rate of prediabetes to T2D is 5.9%, whereas in normoglycemic individuals it is 0.6% (12). Thus, the major susceptibility of Mexicans to developing T2D together with the drastic change in lifestyle due to progress have resulted in an increased incidence of this disease.

In search of an answer to the high prevalence of T2D in Mexico, researchers have performed many studies over time and the first studies were focused on epidemiological and clinical data. Later, diet, metabolic and sociocultural risk factors were studied. However, it was not until 1984 when evidence arose of the association of genetic admixture with non-insulin-dependent diabetes mellitus in Mexican Americans, suggesting that the high prevalence of non-insulin-dependent diabetes mellitus found is confined to that part of the population with a substantial native American heritage (Figure 1) (13,14). From this work emerges the investigation of genetic determinants of T2D in Mexican groups, the initial studies involved Mexican-Americans and, later, Mexicans living in Mexico City. All these findings revealed the native American background susceptibility to T2D, suggesting susceptibility differences between ethnic groups (19−24).

Genetic Constitution of the Mexican Population

Since the appearance of the first humans four million years ago until modern man 200,000 years ago, there had been a series of migrations, wars and colonizations that promoted the settlement of inhabitants first in the old continent and later in America (25). Various investigations have shown that the first American settlers date from 13,500 to 14,000 years ago (26). Therefore, it is believed that the first settlers in Mexico were the Olmecs in 1500 B.C., the first great civilization (27).

Later, European colonization of the Americas gave rise to a complex process of race mixture among Native Americans, Spaniards and African slaves, which resulted in a mestizo population (28). Hence, the complex amalgam that characterizes the current Mexican

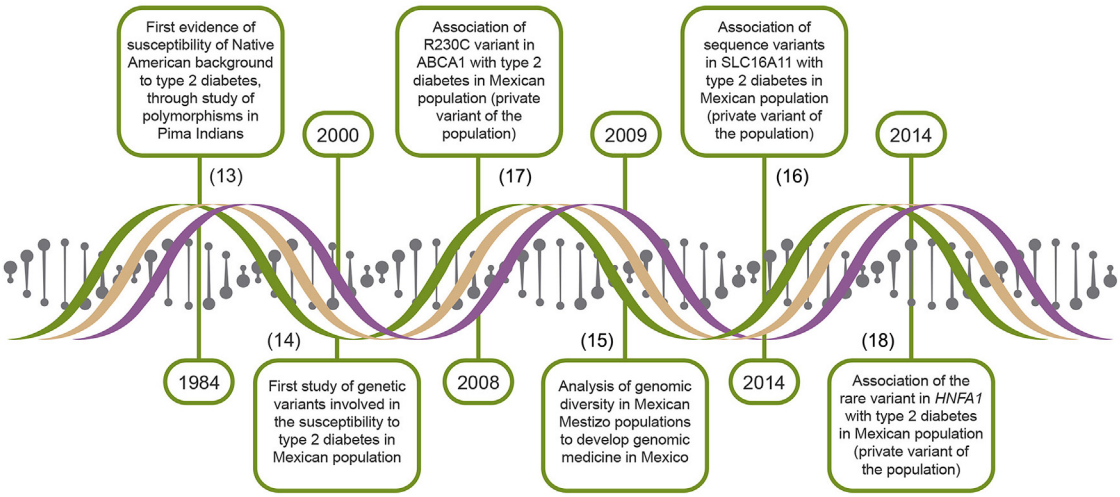

Figure 1. Timeline with the more important events in the study of genetic background of type 2 diabetes in Mexico (13−18). (A color figure can be found in the online version of this article.)