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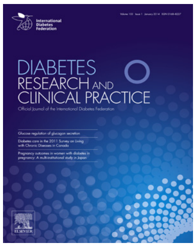

Genetic risk of type 2 diabetes in populations of the African continent: A systematic review and meta-analyses

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ABSTRACT

Background: Type 2 diabetes (T2D) is growing faster in Africa than anywhere else, driven by the dual effects of genetic and environmental factors. We conducted a systematic review and meta-analyses of published studies on genetic markers of T2D in populations within Africa.

Methods: Multiple databases were searched for studies of genetic variants associated with T2D in populations living in Africa. Studies reporting on the association of a genetic marker with T2D or indicators of glycaemia were included. Data were extracted on study design and characteristics, genetic determinants, effect estimates of associations with T2D.

Findings: Overall, 100 polymorphisms in 57 genes have been investigated in relation with T2D in populations within Africa, in 60 studies. Almost all studies used the candidate gene approach, with >88% published during 2006–2014 and 70% (42/60) originating from Tunisia and Egypt. Polymorphisms in *ACE*, *AGRP*, *eNOS*, *GSTP1*, *HSP70-2*, *MC4R*, *MTHFR*, *PHLPP*, *POL1*, *TCF7L2*, *and TNF-α* gene were found to be associated with T2D, with overlapping effect on various cardiometabolic traits. The polymorphisms investigated in multiple studies mostly had consistent effects across studies, with only modest or no statistical heterogeneity. Effect

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sizes were modestly significant [e.g., odd ratio 1.49 (95%CI 1.33–1.66) for *TCF7L2* (rs7903146)]. Underpowered genome-wide studies revealed no diabetes risk loci specific to African populations.

Interpretation: Current evidence on the genetic markers of T2D in African populations mostly originate from North African countries, is overall scanty and largely insufficient to reliably inform the genetic architecture of T2D across Africa.

1. Introduction

The prevalence of diabetes has increased worldwide, including in Africa, where the greatest proportional increase (90%) in the number of diabetes cases is projected to occur by 2030 [1,2]. Type 2 diabetes (T2D) represents more than 90% of diabetes cases in Africa [1,2]. The surge in T2D in Africa has been primarily attributed to environmental factors due to nutrition transition and urbanization that bring about lifestyle changes; however, current understanding of the pathophysiology of T2D in populations within Africa remains elusive. From observations among other populations around the world, it is obvious that T2D has a strong genetic component, as evidenced by a high concordance rate (70%) in monozygotic twins [3] and the over 40% risk of having T2D for an offspring of a T2D patient [4]. Unlike simple monogenic diseases, the pathophysiology of T2D involves most of the time an interaction of several common genetic risk factors of low penetrance with environmental factors. Hitherto, the vast majority of T2D-related risk alleles have been identified through genome-wide association studies, mostly conducted in European Descendants and Asian populations [5]. These findings can hardly be extrapolated to other ethnic groups due to differences in biological traits, cultural practices, and lifestyle habits. Indeed, many common loci originally associated with T2D in Caucasians have not been replicated in non-European populations [6]. Furthermore, Africa is traditionally known to harbor more genetic variations than any other continent [7,8]. It is therefore important to understand the role of genes in populations within Africa as there may be specific genetic susceptibility to T2D in these groups. In addition, studying these populations through genome-wide association and fine mapping has the potential to provide valuable insights into the genetic architecture of type 2 diabetes and further explain geographical differences in prevalence.

This systematic review and meta-analysis synthesizes existing studies on genetic risk inferred by polymorphisms related to T2D among Africa-based populations; and explores the significance of the overall effects of the tested genes and heterogeneity in those effects across regions and major population groupings.

2. Methods

2.1. Data sources

We searched MEDLINE (via PubMed) and EMBASE for articles published until June 2014, without any date or language restriction. We used a combination of relevant search terms presented in appendix pp. 2–3. Two investigators (YYY and MGF) independently identified articles and sequentially (titles, abstracts, and then full texts) screened them for inclusion (Fig. 1). We also scanned the references lists of relevant publications, and identified their citations through the Web of Science. Any disagreements were solved by consensus or review by a third investigator (APK).

2.2. Study selection

We included genetic association studies conducted on African populations residing in the continent, that include diagnosed diabetes and/or markers of glucose homeostasis used as an outcome. Studies had to meet the following criteria: (i) original papers containing independent data, (ii) case-control or cohort, (iii) sufficient data to calculate the odds ratio (OR) with a confidence interval (CI). We excluded duplicate publications; studies conducted exclusively on migrant populations of African descent living outside the continent. Fig. 1 shows the study selection process.

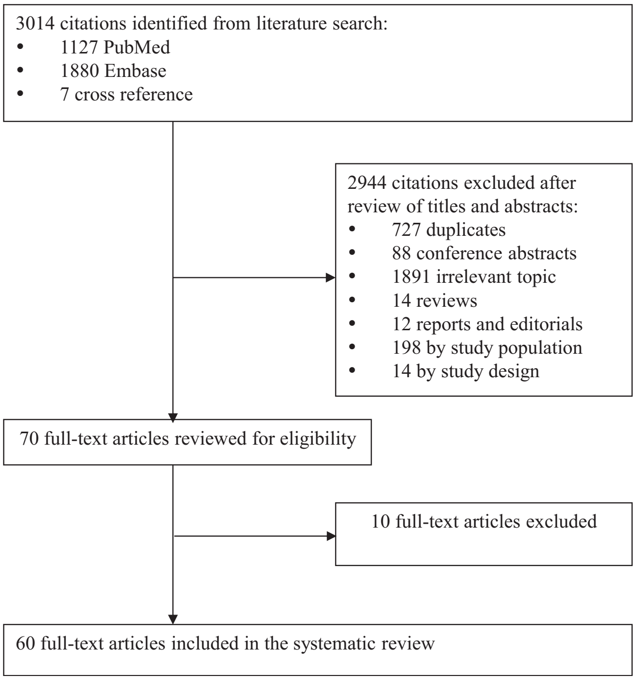

Fig. 1 – Selection process for studies included in the systematic review.