Review

Genetics of type 2 diabetes in Arabs: What we know to date

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**A B S T R A C T**

Type 2 diabetes (T2D) is among the most challenging health issues of the 21st century and is associated with an alarming rise in the incidence. The Arab population is no exception to this trend. The pathophysiological processes that lead to development of T2D are still unclear, however impairment in insulin secretion and/or action is clearly indicated. T2D is a complex disease with susceptibility being governed by the interaction of multiple genetic and environmental effects. Previous studies indicated that variants in genes encoding the pancreatic β-cell K+ATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) are associated with type 2 diabetes. The common Pro12Ala polymorphism in peroxisome proliferator-activated receptor-γ2 gene (PPAR-γ2) was confirmed in several studies to be associated with type 2 diabetes as well. More recently, studies reported variants within a novel gene, TCF7L2, as a putative susceptibility gene for type 2 diabetes across many ethnic backgrounds around the world. However, studies to date in Arab cohorts remain limited.

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transition in codon 23. Analysis of the E23K variant in several Cau-
casian populations showed that KK homozygosity had a stronger
association with type 2 diabetes relative to KK heterozygosity or
EE wild-type homozygosity [19]. We conducted the only study
investigating an association between T2D risk and the E23K poly-
orphism of KCNJ11 in an Arab population to date. Our study con-
firmed in the Saudi population, association of the E23K allele with
type 2 diabetes as seen in several other populations [16–26].
Whilst association with the K allele was evident, sample size did
not establish whether the risk was recessive in nature and driven
by the KK genotype. Other studies have indicated that associa-
tion could be driven by KK homozygosity [22], however even with
the high consanguinity rate in the Saudi population (~60%) [28] where
recessive effects are likely to be amplified, this was not readily
evident.

Researchers at Decode Genetics reported strong association be-
tween variants in a novel susceptibility gene called TCF7L2 and
type 2 diabetes in Icelandic diabetic patients [29]. TCF7L2 encodes
the transcription factor 7-like 2 [30]. The overexpression of this
gene in human pancreatic β-cells was shown to associate with im-
paired insulin secretion both in vivo and in vitro [31]. This gene re-
ceived attention from many research groups following this report,
and similar studies were replicated in samples from several popu-
lations. Many studies have confirmed the original findings. Sub-
stantial association has been confirmed between variants in
TCF7L2 and type 2 diabetes among broad ethnic backgrounds,
including for example populations of UK [32], Dutch [33], Amish
[34], Finnish [35], Swedish [36], French [37], and US [38,39], Indian
[40], and Japanese [41] origin. It is noteworthy that, as in the origi-
nal report, there was clear evidence of a gene dosage effect, such
that the 10% of individuals with two copies of the susceptibility al-
lele were at almost twice the risk of developing type 2 diabetes
compared to those with only one copy [32,42,43]. Very recently,
lack of association between variants in TCF7L2 and type 2 diabetes
has been reported in Pima Indians and Chinese diabetics [43,44].
In another association study performed in Arabs [45], the authors
reported only a marginal association between rs12255372 and type 2
diabetes risk and no association with rs7903146.

Variants in TCF7L2 have been strongly associated with type 2
diabetes risk [46]. In a Saudi cohort rs12255372 and rs7903146
were not or only weakly associated with T2D. Several studies from
non-European ethnic backgrounds have reported a positive associ-
ation between TCF7L2 variants and T2D. The first, an Indian study,
investigated 3 TCF7L2 variants (rs7903146, rs12255372, and
rs4506565) and reported significant association between all three
SNPs and T2D [40]. In a Japanese study, four TCF7L2 SNPs were ex-
ploried (rs12255372, rs7903146, rs7901695 and rs11196205) and
all four SNPs were found to be significantly associated with T2D,
with rs12255372 showing the strongest association [41]. The third
study was conducted by Cauchi et al. on Moroccans [46]. Signifi-
cant association between rs7903146 variant of TCF7L2 and T2D
risk in this population was concluded. Additionally, positive asso-
ciation was also reported on Indian Asians [47,48], Pakistani
[49], and Afro-Caribbeans [48]. More recently, a surprising lack of
association between TCF7L2 variants and type 2 diabetes was inde-
pendently reported in two non-European populations including
Chinese [43], Pima Indians [44] and in respect to rs7903146 in
Emirati Arabs [45]. In a meta analysis conducted by Cauchi et al.,
the authors reviewed the association of rs7903146 variant with T2D
risk by looking at 27 original published association studies
(including their own), the authors arrived at a pooled OR of 1.46.
There was no overlap between the overall OR and CIs of this
meta-analysis and the upper CI of the Saudi cohort (1.27) [50].
However, there is an overlap with three studies included in this
meta-analysis [38,48,51]. Therefore, even though significant asso-
ciation was not indicated in the Saudi cohort, a weak association
could not be ruled out and justifies a larger replication study in
Arabs.

Given the limited studies conducted in Arabs to date, two points
are clear. Firstly results indicate differences in Arab populations
in relation to genetic risk for T2D. Secondly, data presented in the
literature to date clearly demand replication studies, ideally with
larger numbers to confirm findings reported thus far. Similarly,
further T2D association studies either candidate gene based or gen-
ome-wide are warranted in Arabs and may reveal novel risk loci for
this important global disease.

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