Open Journal of Hematology

ROSS Science Publishers

Mini Review

OPEN ACCESS

Genomic markers associated with insulin resistance and Type 2 Diabetes in African Americans: A review.

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Published: 2nd March, 2017 Accepted: 2nd March, 2017
Received: 10th January, 2017

Open Journal of Hematology, 2017, **8**-2

Keywords: Genomics, biomarkers, diabetes, African ancestry, genomic markers

ABSTRACT

Purpose: *Personalized medicine is exponentially advancing. In order to optimize an individual's healthcare, their individual genetic makeup, as well as environmental profiles, need to be quantified. The prevalence of type 2 diabetes among African Ancestry is alarmingly high within northwester North Carolina, with preliminary studies indicating that levels are even higher than the general U.S. population. Our overall goal is to identify genetic markers that are linked to type 2 diabetes and insulin resistance within this population.*

Materials and Methods: *A literature review was conducted to determine which genomic markers have been associated with type 2 diabetes and insulin resistance with the African population.*

Results and Conclusions: *Thirteen studies reported genomic markers that have been associated with type 2 diabetes within the African Ancestry. A compilation of these genomic markers are presented within this review.*

BACKGROUND

Type 2 diabetes mellitus is the seventh leading cause of death in the United States [1]. Patients with type 2 diabetes are insulin resistant and suffer the effects of hyperglycemia along with secondary effects that include high blood pressure, cardiovascular disease, stroke, blindness, and increased risk of cancer, placing these individuals at greater risk for all of the leading causes of death. It is estimated that 29.1 million people are affected by this disease and the rate of diabetes is estimated to 53.1 million people by 2025 [2]. The total estimated cost of diabetes in the United States in 2012 was 245 billion dollars [3]. Although type 2 diabetes affects all ethnicities, Hispanics, Native Americans, and African Ancestry (AA) are most vulnerable. Thirteen point two million non-Hispanic blacks are affected by diabetes in the United States. The risk for diabetes in AAs is 77 percent higher than non-Hispanic white Americans [4]. This indicates an overwhelming need for research that can ease the health and financial burden that this disease places on the AA population.

On January 20, 2015, President Obama announced the Precision Medicine Initiative® [5]. Precision medicine is an emerging method for disease prevention and treatment that considers individual variations in genes, environment, and

lifestyle. This initiative proposes to generate evidence-based practice needed to translate the notion of precision medicine into clinical practice. Studies have identified a genetic predisposition among AA for insulin resistance, but further studies are necessary to substantiate this claim. The aim of this project is to identify common genetic markers found in AA populations with type 2 diabetes.

METHODS

To identify eligible studies, a search was conducted within the PUBMED database for English language articles published at any point in time. Key words included genome-wide association study, single nucleotide polymorphism(s), African American, African Ancestry, non-Hispanic blacks, type 2 diabetes, diabetes, adult-onset diabetes, and non-insulin dependent diabetes. Reference lists from articles retrieved from search engines were searched by hand.

Initially, the titles and abstracts of all the articles were reviewed to determine eligibility, then the full text of the articles that met eligibility were assessed. Studies included in this review met the following criteria: quantitative study, assessments of type 2 diabetes as opposed to type 1 diabetes, and inclusion of African American population. Studies were included regardless of study type or quality. However, methodological issues were addressed throughout the review in order for the reader to weigh the outcomes of each study accurately.

A manual data extraction tool was used to pull out pertinent data from the articles. The data extracted included the purpose statement, study design, sample characteristics and size, country of origin, journal, findings, and limitations. Then a matrix of all the articles included in the review was developed.

FINDINGS

The total number of articles resulting from the electronic and manual search was 30. After reviewing each article based on duplication and inclusion criteria, the final number of research reports identified was 13 studies, as referenced in Table 1. The earliest study was published in 2007 and the latest in 2014. Six of the articles reported only genes associated with type 2 diabetes within the AA population. Four of the articles reported on single nucleotide polymorphisms associated with type 2 diabetes in AAs. Finally, three of the twelve studies reported on both genomic markers. Additionally, almost all of the studies (n=12) were conducted in the United States, with one conducted in Canada.

Human genome studies have identified association among AA and type 2 diabetes. In a genome-wide association study involving African Americans, Elbein et al. found evidence that chromosome 2 is linked to the development of type 2 diabetes [6]. Alternatively, Jeff et al. identified 13 single nucleotide polymorphism correlated with genes TCIRG1, CHKA, and ALDH3B1 on chromosome 11 and type 2 diabetes in AA populations [7]. Landberg et al. noted that three of the 32 genome-wide associated search (GWAS)-derived single nucleotide polymorphisms (SNPs) showed nominally significant association with type 2 diabetes in the AA cohort [8]. Two of the replicated SNPs were rs864745 in JAZF1 gene and rs10490072 in BCL11A gene. Additionally, Leak et al. reported that type 2 diabetes was observed among 4 SNPs: rs2021785, rs1609659, rs4814597, and rs2269023, while Long revealed that seven of 29 SNPs examined were associated with type 2 diabetes risk, including rs6769511 of the IGF2BP2 gene, 2 SNPs in the WFS1 gene (rs4689388 and rs1801214), rs7903146 of the TCF7L2 gene, and 3 SNPs in the KCNQ1 gene (rs231362, rs2237892, and rs2237897) [9, 10]. Notably, the association for rs7903146 reached significance in the GWAS. Among SNPs determined by other researchers to be genome-wide significant, Palmer et al. found a single SNP, rs7560163, reaching genome-wide significance with 4 other SNPs associated with type 2 diabetes-rs7542900, rs4659485, rs2722769, rs7107217; these may represent novel loci that contribute to Type 2 Diabetes [11].

Although type 2 diabetes affects all ages, genders, and ethnicities, some groups are more vulnerable than others, such as Hispanics, Native Americans, and African Ancestry (AA). More than 13 million non-Hispanic blacks are affected by diabetes in the United States. The risk for diabetes in AA is 77 percent higher than non-Hispanic white Americans [12]. Studies have identified genetic association among AA and type 2 diabetes. For example, Keaton et al. suggested that there are

ethnic-specific differences in genetic architecture underlying type 2 diabetes, and that these differences complicate the understanding of how risk allele load impacts disease susceptibility [13]. Cheng et al. noted that there were two potential loci for type 2 diabetes, but concluded that no single gene is sufficient to explain a large portion of the observed population difference in risk of diabetes since there undoubtedly is a complex interplay [14]. Research has shown that AA populations with diabetes mellitus have specific genes that those without the disease do not contain (Table 1). For example, Bressler et al. found rs1421085C to be protective against diabetes in AAs while Grant et al. found rs3751812 to be the only SNP conferring risks to the AA population [15, 16]. Long et al. found rs7903146 to have genome-wide significance for diabetes in AAs [10]. Other studies involving type 2 diabetes and African Americans have been performed, as well, that indicate that other genes may be important to the disease or issues associated with the disease [17, 18, 19] (Table 1).

Table 1:

Author	Genes	SNPs	# of Subjects	Findings
Bressler 2010		rs1421085 C allele	670 cases and 2,780 non-cases in African-American	SNP providing Protection against diabetes
Cheng 2012	12p13.31 (LOD=4.0) 13q14.3		2,373 with type 2 diabetes and 4,648 without	Two potential loci for diabetes in AAs
Dastani 2012	ADIPOQ IRS1 on 2q36.3 and at 6q24.1		4,232 African Americans, N=1,776 Asians, and N=29,347 European	Reached genome-wide significance for metabolic disease
Elbein 2009	Chromosome 2 Chromosome 13p Chromosome 18p TCF7L1, VAMP5, VAMP8, CDK8, INSIG2, IPF1, PAX8, IL18R1, MAP4K4		580 AA families 1344 individuals 5914 SNPs	Chromosome 2 had strongest signal for T2DM Chromosome 13p linked to T2DM and age of dx Chromosome 18p linked to age of dx
Grant 2008		rs3751812	18 Caucasian obese children (BMI 95th percentile) 2,270 Caucasian controls (BMI 95th percentile) 578 AA obese children 1,424 AA control	Only SNP conferring significant diabetes risk in AA
Jeff 2014	TCIRG1, CHKA, ALDH3B1		1,563 African Americans	AAs associated with T2DM
Keaton 2014	ADAMTS, TCF7L2, and ZFAND6		1,990 African Americans (n= 963 T2D cases, n= 1,027 controls) 1,644 European Americans (n= 719 T2D cases, n= 925 controls)	Genes correlating AAs with risk of T2DM
Langberg 2012	JAZF1; BCL11A	rs864745 rs10490072	1496 AA	Significant association between T2D and AAs
Leak 2007		rs2021785 rs1609659 rs4814597 rs2269023	380 unrelated AA individuals with T2DM and end-stage renal disease (T2DM–ESRD), 278 AA controls 96 European Americans (EA) and 120 Yoruba Nigerian (YRI) controls	Association of SNPs with T2DM in AAs
Long 2012	IGF2BP2 WFS1 TCF7L2 KCNQ1	rs6769511 rs4689388 rs1801214 rs7903146 rs231362 rs2237892 rs2237897	African Americans (1,554 cases and 2,734 controls)	Associated with T2D risk Notably, the association for rs7903146 reached the GWAS significance
McCormack 2013	PPARG IGF2BP2 JAZF1 TCF7L2	rs1801282 rs4402960 rs86745 rs7903146 rs7560163 rs12255372 rs1421074	AA populations	rs1421074 C allele for obesity in AA may protect against T2DM ; rs7903146 higher risk for T2DM for AA; High-risk T allele at rs12255372 associated with reduced beta cell sensitivity to glucose in response to changes in peripheral insulin sensitivity; GWAS significance with T2DM is rs7560163

Palmer 2012		rs7560163 rs7542900 rs4659485 rs2722769 rs7107217	965 AA with T2DM and end-stage renal disease compared to 1029 controls	Rs7560163 was found to have genome-wide significance The latter 4 were found to be associated with T2DM
Sale 2009	123-124 cM 44-45 cM 78cM f		521 AA	Linkage peaks on chromosome 14 at 123-124 cM detected for T2DM and for later age of dx; Two linkage peaks on chromosome 7 at 44-45 cM and 78cM for T2DM and earlier onset 14q appears to reduce age of disease onset

DISCUSSION

AA have nearly twice the prevalence of type 2 diabetes than European-Americans (EA) [7]. Multiple genome-wide studies have shown that there are SNPs present in AA with the disease when compared to EA as well as SNPs present more often in AA with type 2 diabetes than those without the disease. There are also SNPs that correlate with protecting AA from type 2 diabetes. SNPs that has been shown in more than one study to correlate with a genome-wide significance for type 2 diabetes in AA is rs7903146 [10, 18]. Another SNP found to have genome-wide significance for AA with type 2 diabetes is rs7560163. These and other SNPs found more often in populations with type 2 diabetes should be a focus in personalizing treatments for the disease and serving patients on a case by case basis. For example, patients who carry a gene that correlates with higher risk can be made aware of that risk and learn to improve their lifestyles and dietary habits with the goal of preventing the diagnosis altogether. Alternatively, for individuals who have already developed the disease, those with a particular SNP associated with type 2 diabetes may respond better to a specific treatment regimen over another.

However, there are challenges to personalized medicine that include processing large amounts of data, understanding the overall impact of the various SNPs, correlating genotypes with phenotypes, and understanding how treatments can be optimized based on this information [20]. It is clear that more research needs to be carried out, with consideration of these challenges, to determine which treatment approaches would better serve type 2 diabetes patients with each of the at-risk SNPs. It may be that patients with one SNP are better approached using lifestyle changes while another may require medications and more extensive interventions. There is little to no research published that delves into optimal treatments for each SNP found to correlate significantly with the disease.

There are also ethical concerns over the use of individual genomes being used in personalized medicine [21, 22]. Many people are not comfortable with sharing this private information and have fears of losing confidentiality. Just as subjects participating in genome research need to be assured that they will have complete privacy after consenting, so do patients whose SNPs are used in personalized medicine [22]. The benefits of personalized medicine could be extensive as long as patient confidentiality is not placed at risk. Benefits should not put a patient at-risk for being turned away by insurance companies, for example. Fears such as these were addressed in the Genetic Information Nondiscrimination Act of 2008 [23]. This act protects Americans against discrimination from both insurance companies and employers. Furthermore, consent must be obtained when research involving the genome is used. Researchers must explain how information will be used and indicate how confidentiality will be maintained. Insurance companies may not use genomic information to set premiums or determine eligibility just as employers may not use it to hire, fire, determine salaries, or decide on promotions.

FUTURE PERSPECTIVE

Multiple SNPs have been shown to be correlated with AA at risk for type 2 diabetes. This information may be useful to individuals for understanding risk factors for the disease as well as medical practitioners who are treating these patients. However, most patients with type 2 diabetes or with the hereditary risk, do not know which SNPs they carry that put them at risk. This

information could allow people to improve their lifestyles before the disease is in full swing. Another key missing piece is understanding what treatments or preventions may best serve those with a particular SNP. There have been little to no advances made in science toward reaching this goal. Thus, more research is necessary so that links can be made between high-risk genes and receiving the necessary treatment to avoid the condition altogether or reduce the symptoms.

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