Genetic Determinants of Dyslipidemia in African-Based Populations: A Systematic Review

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Abstract

Identification of genetic/genomic factors contributing to dyslipidemia is of great interest to prevention and reduction of the onset and burden of cardiovascular diseases in Africa. This systematic review summarizes available data on genetic variants associated with dyslipidemia in populations within Africa. A PubMed and EMBASE database search was conducted to identify all studies published until June 2018 on genetic susceptibility to dyslipidemia in African-based populations, excluding familial hypercholesterolemia. All studies on genetic predispositions of dyslipidemia and respecting the preestablished inclusion criteria were included in this systematic review. Because of high heterogeneity, the data were summarized narratively. Twenty-two studies investigated mostly the targeted genetic variants. A total of 51 polymorphisms in 28 susceptibility genes to dyslipidemia have been associated with a particular trait in the African populations, and through variable effects. Most polymorphisms investigated in Northern Africa seemed to have consistent effects on increasing the level of low-density lipoprotein cholesterol (LDL-C), total cholesterol, and triglycerides in patients with diabetes, myocardial infarction, coronary artery disease, and metabolic syndrome. By contrast, only Ser447Ter and C49620T variants were associated with increased LDL-C in sub-Saharan Africa. Despite few studies available in this context in the literature, certain genetic variants were consistently associated with dyslipidemia especially in Northern Africa as highlighted in this analysis. Further data, particularly from genome-wide association studies, would help establish an African-specific reference for genetic susceptibility markers of dyslipidemia.

Keywords: biomarkers, cardiovascular health and disease, dyslipidemia, genetics, genomics, polymorphism, Africa

Introduction

DYSLIPIDEMIA IS A DISEASE characterized by abnormally elevated or decreased levels of lipoproteins causing impaired transport of lipids in blood plasma. The most common forms of dyslipidemia include elevated plasma levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and/or triglycerides (TG), and reduced levels of high-density lipoprotein cholesterol (HDL-C) (Stone et al., 2014). Dyslipidemia represents one of the major risk factors for atherosclerotic cardiovascular disease (CVD),

causing ischemia and damage of the heart, brain, or legs (Stone et al., 2014). It is associated with high morbidity and mortality. For instance, according to the Global Burden of Disease study, 4.4 million deaths and 93.8 million disability-adjusted life-years (DALYs) were attributed to elevated TC in 2016, representing the eighth and seventh leading risk factor in terms of attributable DALYs globally for men and women, respectively (GBD 2016 DALYs and HALE Collaborators, 2017).

The burden of CVD is dramatically rising in African populations, owing to a surge in the prevalence of cardiovascular

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risk factors such as hypertension, diabetes mellitus, and dyslipidemia (WHO, 2014). A recent systematic review and meta-analysis demonstrated high prevalence of dyslipidemia in the general adult population in Africa (Noubiap et al., 2018). This review reports the prevalence of elevated TC (≥ 5.2 mmol/L) as 23.6%, 41.1% for low HDL-C (≤ 1.0 mmol/L), 25.7% for elevated LDL-C (≥ 3.3 mmol/L), and 16.4% for elevated TG (≥ 1.7 mmol/L) in the general population. Much higher prevalence of dyslipidemia is observed in individuals with hypertension, diabetes mellitus, or HIV infection (Noubiap et al., 2018).

Studies performed among African-Americans, Asian-Americans, Mexican-Americans, and non-Hispanic whites revealed significant racial and ethnic differences in dyslipidemia patterns, suggesting strong genetic predispositions to this disease (Franck et al., 2014). Indeed, as most metabolic diseases, dyslipidemia arises from an interplay between genetic and environmental factors.

It is estimated that genetic predispositions may be associated with nearly 50% of dyslipidemia cases (Weiss et al., 2006). Genome-wide association studies (GWAS) identified variants in more than 100 genes that may affect lipoprotein plasma levels (Asselbergs et al., 2012). Variants in these genes may modify phenotypic expression of the disease, explaining the huge clinical variability among patients with dyslipidemia. Furthermore, these genetic variants may also impact response to pharmacologic treatment and therefore be used for risk stratification and personalized therapies (Peters et al., 2011).

Although African populations are the most genetically diverse globally (1000 Genomes Project Consortium, 2015), only few studies have focused on characterizing the genome-wide genetic diversity of these populations, and specifically on determining genetic drivers of cardiometabolic diseases among them (Adebamowo et al., 2017). This systematic review aimed to summarize existing data on the genetic determinants of dyslipidemia including abnormal levels of TC, HDL-C, LDL-C, and TG in populations living in Africa.

Methods Used for Systematic Review

This systematic review is reported in accordance with the preferred reporting items for the systematic reviews and meta-analysis (PRISMA) statement. It does not encompass familial hypercholesterolemia. The epidemiology and genetics of this specific condition in African population will be presented in a dedicated article in future. This is a systematic review using published public data. Therefore, an ethical approval is not required.

Bibliographic search

We searched EMBASE and MEDLINE (through PubMed) databases to identify all relevant articles on the genetics of dyslipidemia in African populations published until June 16, 2018. We used a combination of relevant search terms as presented in the Supplementary Table S1. In addition, the reference list of all relevant articles and reviews were scrutinized to identify additional articles.

Selection of studies

We included all observational studies reporting on the association between any genetic variants and high TC, LDL-

C, TG, or low HDL-C in individuals residing in African countries, or enough data to compute it. To focus on more common dyslipidemia as a complex trait, we excluded (1) studies on familial hypercholesterolemia, as this is clearly defined relatively rare monogenic autosomal-dominant conditions; (2) those presenting an association between genetic polymorphism and lipid profile parameter without quantifying the related risk; and (3) reports on African diaspora and migrants residing outside Africa, who may be exposed to a considerable different environment and dietary habits than populations living in Africa; in addition, it is estimated that African-Americans will have on average 30% genetics background of European ancestry (1000 Genomes Project Consortium et al., 2015).

For studies published in more than one report, the most comprehensive reporting on the largest sample size was considered. Two investigators (J.J.N.N. and H.B.) independently sequentially (titles, abstracts, and then full texts) screened articles for inclusion. Disagreements were resolved through consensus. The detailed selection of the studies is given in Figure 1.

Data extraction, assessment, and synthesis

Three investigators (E.P.M.M., A.D.K., and M.G.-F.) independently extracted data from eligible articles using a preconceived data extraction form. Information collected included the country of the study, study population/subpopulation, sample size, mean age range and proportion of men for cases and controls, genotyping method, gene and polymorphism studied, and the outcome (effects of studied polymorphism on the lipid phenotype).

For matter of simplicity and because of the high heterogeneity between studies, the effect of a genetic variant on a form of dyslipidemia (high TC, LDL-C, TG, or low HDL-C) was reported as increase (+) or decrease (−) if the variant was associated with an increased or reduced risk of the form of dyslipidemia, respectively, and no effect if there was no association (0) between the genetic variant and dyslipidemia. All extracted data were cross-checked for accuracy by a fourth investigator with expertise in the genetics of dyslipidemia (H.B.).

The limited number of eligible studies and the huge heterogeneity between studies pertaining to study populations' characteristics and assessment of association of genetic markers and dyslipidemia inform our decision to perform a narrative synthesis of the collected data.

Results of the Systematic Review

Literature search

We identified 3135 records from PubMed ($n = 2933$) and EMBASE ($n = 202$); after elimination of duplicates ($n = 32$), 3103 records remained. After screening titles and abstracts, we found 2923 records to be irrelevant and excluded them. We assessed full texts of the remaining 180 articles for eligibility, of which 22 were finally included (Abd El-Aziz et al., 2011, 2012, 2014; Abdel Ghany et al., 2017; Abdel-Hamed et al., 2017; Bennouar et al., 2004; Boghdady et al., 2016; Ellman et al., 2015; Elouej et al., 2016a, 2016b, 2016c; Engwa et al., 2018; Fekih et al., 2014; Hooper et al., 2007; Kefi et al., 2017; Khella et al., 2017; Kodogo et al., 2016; Masemola et al., 2007; Mehri et al., 2010; Morjane et al., 2017; Sediri et al., 2011; Sellami et al., 2018) and 158 were excluded with reasons as indicated in Figure 1.

FIG. 1. Preferred reporting items for the systematic reviews and meta-analysis (PRISMA) flow chart.

Populations, genetic assessment, and outcomes

Seventeen of the 22 included studies (72.3%) were conducted in Northern Africa (7 in Egypt, 8 in Tunisia and 2 in Morocco) (Abd El-Aziz et al., 2011, 2012, 2014; Abdel Ghany et al., 2017; Abdel-Hamed et al., 2017; Bennouar et al., 2004; Boghdady et al., 2016; Elouej et al., 2016a, 2016b, 2016c; Fekih et al., 2014; Kefi et al., 2017; Khella et al., 2017; Mehri et al., 2010; Morjane et al., 2017; Sediri et al., 2011; Sellami et al., 2018), whereas only 5 were performed in sub-Saharan African populations (1 in Zimbabweans, 1 in Nigerians, and 3 in South Africans) (Ellman et al., 2015; Engwa et al., 2018; Hooper et al., 2007; Kodogo et al., 2016; Masemola et al., 2007). Most studies were conducted among patients with coronary artery disease, diabetes mellitus, or metabolic syndrome.

The age of participants ranged from 14 to 70 years and the proportion of men from 25% to 88% depending on the populations. A total of 46 polymorphisms (including single-nucleotide polymorphisms (SNPs) and insertion-deletions [Indels]) in 27 different genes were investigated across studies (Table 1). Indels were found mainly in the angiotensin-converting enzyme (ACE) gene, whereas SNPs were found in genes involved in the metabolism of lipoprotein such as apolipoprotein E, apolipoprotein B, lecine cholesterol acyl transferase, and lipoprotein lipase. None of the study was primarily designed to investigate the association between gene polymorphisms and dyslipidemia in general populations, but rather the genetic determinants in specific disease conditions such as coronary artery disease, myocardial infarction, diabetes mellitus, and metabolic syndrome.

Association of genetic markers with TC

According to the studies included in this review, the following gene polymorphisms were associated with the increased level of TC in Egyptian population (Abd El-Aziz et al., 2011, 2012, 2014): *LPL* (HindIII H2H2), *APOC3* [SsTi (S2S2)], *RAS* [ATR1 (Angiotensin II type 1 receptor) polymorphism, AGT (angiotensinogen) polymorphism and *ACE* (Ins16del)], *ABCA1* [rs2230806 (R219K)], *CETP* [rs708272 (TaqIB)], and *LCAT* [rs5923 (4886C/T)]. Similar association was, respectively, observed in Tunisian population with *LRPAP1* (rs762861), *FTO* (rs9939609), and *ACE* (Insdel, I/D) gene polymorphisms (Elouej et al., 2016c; Mehri et al., 2010) and Moroccan population with *ApOE* ($\epsilon 2/\epsilon 3/\epsilon 4$) and *HNF1A* (rs575396) (Bennouar et al., 2004; Morjane et al., 2017).

On the contrary, *APO E* polymorphisms, *LPL* (Ser447Ter), and *ABCC8* (rs1799854) were shown to be associated with reduced concentration of TC in South African, Egyptian, and Nigerian populations (Abd El-Aziz et al., 2011; Engwa et al., 2018; Masemola et al., 2007). No association was observed between polymorphisms of *PON1*, *LDLR*, *ApoB*, *vaspin*, *IL-1A*, *APOA5*, *FTO*, and *VEGFA* genes and TC concentrations (Aldel Ghany et al., 2017; Kefi et al., 2017; Kodogo et al., 2016; Sediri et al., 2011; Sellami et al., 2018) (Table 2).

Association of genetic markers and HDL-C

Renin-angiotensin system (RAS) gene polymorphisms (such as ATR1 polymorphism and AGT polymorphism), *ABCA1* [rs2230806 (R219K)], *CETP* [rs708272 (TaqIB)], *LCAT* [rs5923 (4886C/T)], and *FTO* [rs9939609 (A<T)] gene

TABLE 1. DISTRIBUTION OF GENES AND POLYMORPHISMS INVESTIGATED IN GENETIC ASSOCIATION STUDIES IN DYSLIPIDEMIA IN AFRICA

Gene	Polymorphisms (46)	Studies in Northern Africa	Studies in sub-Saharan Africa
1. <i>ABCA1</i>	rs2230806 (R219K)	1	0
2. <i>ABCC8</i>	C49620T (rs1799854)	0	1
3. <i>ACE</i>	Ins16del (I/D)	2	0
4. <i>ApoA1-CIII-AIV</i>	SacI polymorphisms	1	0
5. <i>APOA5</i>	rs3135506	1	0
1.	Rs651821	1	0
6. <i>Apo B</i>	2488 C>T	0	1
1.	4154 G>A	0	1
7. <i>APOC3</i>	SsTi (S2S2)	1	0
8. <i>APOE</i>	rs 4420638	1	0
1.	$\epsilon 2/\epsilon 3/\epsilon 4$	2	0
9. <i>CD36</i>	rs1761667	1	0
10. <i>CETP</i>	rs708272 (TaqIB)	1	1
11. <i>CILP2</i>	rs 10401969	1	0
12. <i>C20orf152</i>	rs7265718	1	0
13. <i>FTO</i>	rs1421085	1	0
1.	rs8054077	1	0
1.	Rs9939609	2	0
14. <i>HNFI1A</i>	rs1169288 (A>C)	1	0
1.	rs2464196 (G>A)	1	0
1.	rs735396 (T>C)	1	0
15. <i>IL-1A</i>	I/D polymorphism (rs3783553)	1	0
16. <i>INSR</i>	rs 2059807	1	0
17. <i>KLF14</i>	rs 1562398	1	0
18. <i>LCAT</i>	rs 5923 (4886C/T)	1	0
19. <i>LIPC</i>	rs1800588 (514C/T)	0	1
20. <i>LPL</i>	HindIII H2H2)	1	0
1.	rs 328 (Ser447Ter)	1	1
21. <i>LRPAP1</i>	rs762861	1	0
22. <i>PCSK9</i>	rs28362286 (C679X)	0	2
23. <i>PON1</i>	rs854560 (L55M)	1	0
1.	rs622 (Q192R)	1	0
24. <i>RAS</i>	ATR1 polymorphism	1	0
1.	AGT polymorphism	1	0
25. <i>Vaspin</i>	rs2236242	1	0
26. <i>VEGFA</i>	rs1547651	1	0
1.	rs699947	1	0
1.	rs833061	1	0
1.	rs1570360	1	0
1.	rs2010963	1	0
1.	rs25648	1	0
1.	rs833068	1	0
1.	rs833070	1	0
1.	rs3025020	1	0
1.	rs3025026	1	0
27. <i>ZNF664</i>	rs12310367	1	0

AGT, angiotensinogen; ATR1, Angiotensin II type 1 receptor; I/D, Indels.

polymorphisms were associated with a decreased level of HDL-C in Egyptian population (Abd El-Aziz et al., 2012; Boghady et al., 2016; Khella et al., 2017). The same association was observed in Tunisian and Moroccan populations with *LRPAP1* (rs762861) (Elouej et al., 2016a) and *ApoE* $\epsilon 2/\epsilon 3/\epsilon 4$ (Bennouar et al., 2004) gene polymorphisms, respectively.

On the contrary, an increased level of HDL-C was associated with *FTO* (rs8054077), *ACE* Ins16del (I/D) gene polymorphisms in Tunisian population (Elouej et al., 2016c; Mehri et al., 2010), *ApoB* [4154 (G>A)] gene polymorphism in Zimbabweans population (Kodogo et al., 2016), *ApoE* [Apo E polymorphisms ($\xi 2$)] gene polymorphism in South African population (Masemola et al., 2007), *IL-1A* (rs3783553) gene

polymorphism in Egyptian population (Abdel Ghany et al., 2017), *ABCC8* [(C49620T) (rs1799854)] gene polymorphism in Nigerian population (Engwa et al., 2018) and *HNFI1A* [rs735396 (T>C)] gene polymorphism in Moroccan population (Morjane et al., 2017). All the other gene polymorphisms investigated did not seem to have an effect on HDL-C levels (Table 2).

Association of genetic markers with LDL-C

Studies in Egyptian populations (in patients with diabetes, myocardial infarction, and coronary artery disease) showed that *LPL* (HindIII H2H2), *APOC3* [SsTi (S2S2)] (Abd El

TABLE 2. ASSOCIATION OF GENETIC MARKER AND DYSLIPIDEMIA IN SELECTED AFRICAN POPULATIONS

First author (year)	Ethnicity	Study population	Total sample	No. of case/ control	Mean age (case/control)	%Men (case/control)	Genotyping method	Gene	Polymorphism	Phenotype effect		
										TC	HDL	LDL TG
Northern Africa Fekih et al. (2014)	Tunisian	Children and adolescents with type 1 diabetes and healthy controls	219	122/97	14.01 ± 5.3/ 12.86 ± 5.41	62.3/55.7	Multiplex-PCR-RFLP	PON1	rs854560 (L55M) rs622 (Q192R)	0	0	/
Elouej et al. (2016b)	Tunisian	Patients with metabolic syndrome and healthy controls	356	163/193	58.6 ± 9.68/ 53.2 ± 14.88	33.7/25.4	RT-PCR	FTO	rs1421085 rs8054077	0	0	0
Elouej et al. (2016c)	Tunisian	Patients with metabolic syndrome and healthy controls	356	163/193	58.6 ± 9.68/ 53.2 ± 14.88	33.7/25.4	RT-PCR	ZNF664 LRPAP1 CILP2 KLF14 APOE INSR C20orf152 FTO	rs12310367 rs762861 rs 10401969 rs 1562398 rs 4420638 rs 2059807 rs7265718 rs9939609	0	0	0
Elouej et al. (2016)	Tunisian	Patients with metabolic syndrome and healthy controls	685	340/345	56.8 ± 10.14/ 51.6 ± 14.55	25.2/32.6	TaqMan allelic discrimination	FTO		+	0	0
Boghady et al. (2016)	Egyptian	Patients with CAD and healthy controls	147	71/76	55.5 ± 8.6/ 54.0 ± 5.4	63/61	RT-PCR and the allele discrimination	CD36	rs1761667	0	-	+
Bennouar et al. (2004)	Moroccan	Patients with coronary stenosis (>50%) and absence stenosis	250	141/109	50.62 ± 12.08	79.4/47.7	PCR-RFLP	Apo E	ε2/ε3/ε4	+	-	+
Mehri et al. (2010)	Tunisian	Patients with acute myocardial infarction and healthy controls	357	119/238	60.6 (54-68)/ 61.9 (55-69)	60.5/61.9	Allelic specific PCR (I/D)	ACE	Ins16del (I/D)	+	+	+
Abd El-Aziz et al. (2011)	Egyptian	Patients with myocardial infarction and healthy controls	300	200/100	52.9 ± 11.3/ 50.7 ± 9.5	67/64	PCR-RFLP	LPL	HindIII H2H2) Ser447Ter (XX) SstI (S2S2)	+	/	+
Abd El-Aziz et al. (2012)	Egyptian	Patients with PCAD, CAD, and healthy controls	349	116/114/ 119	42.4 ± 70.3/ 68.9 ± 7.1/ 41.9 ± 6.4	77.6/88.9/52.9	PCR-RFLP	APOC3 RAS	ATR1 polymorphism ACE (Ins16del) rs2230806 (R219K)	+	+	+
Abd El-Aziz et al. (2014)	Egyptian	Patients with PCAD and healthy controls	235	116/119	42.4 ± 7.3/ 41.9 ± 6.4	77.6/52.9	PCR-RFLP	ABCA1 CETP LCAT	rs708272 (TaqIB) rs 5923 (4886C/T) Sacl polymorphisms	+	+	+
Sediri et al. (2011)	Tunisian	Patients with myocardial infarction and controls	687	326/361	53.8 ± 8.6/ 51.1 ± 9.5	51 ± 9	PCR-RFLP	ApoA1- CIII-AIV		0	0	0
Abdel Ghany et al. (2017)	Egyptian	Obese individuals and nonobese nondiabetic subjects	224	112/112	40.80 ± 39.60/ 39.52 ± 9.43	/	T-ARMS-PCR	vaspin	rs2236242	0	0	0

(continued)

TABLE 2. (CONTINUED)

First author (year)	Ethnicity	Study population	Total sample	No. of case/ control	Mean age (case/control)	%Men (case/control)	Genotyping method	Gene	Polymorphism	Phenotype effect			
										TC	HDL	LDL TG	
Abdel-Hamed et al. (2017)	Egyptian	Patients with nonalcoholic fatty liver disease and healthy subjects	150	75/75	45.32 ± 1.05/ 44.17 ± 1.14	/	PCR-PAGE	IL-1A	I/D polymorphism (rs3783553)	0	+	0	0
Kefi et al. (2017)	Tunisian	Patients with metabolic syndrome and controls	594	295/299	56.58 ± 8.56/ 52.56 ± 10.09	/	KASPar technology	APOA5	rs3135506 rs651821 rs9939609 (A<T)	0	0	0	+
Khella et al. (2017)	Egyptian	Patients with metabolic syndrome and controls	197	92/105	45.33 ± 9.56/ 44.74 ± 9.67	0	TaqMan SNP Genotyping	FTO		0	0	0	0
Morjane et al. (2017)	Moroccan	Patients with metabolic syndrome and controls	241	104/137	57.59 ± 11.57/ 50.6 ± 10.34	26.97 (26.92/27.00)	KASPar technology	HNF1A	rs1169288 (A>C) rs2464196 (G>A) rs735396 (T>C) rs1547651 rs699947 rs833061 rs1570360 rs2010963 rs25648 rs833068 rs833070 rs3025020 rs3025026 rs3025039	0	0	0	+
Sellami et al. (2018)	Tunisian	Patients with type 2 diabetes and controls	1620	815/805	60.5 ± 7.7/ 60.1 ± 11.5	45.93 (44.4/47.5)	Allelic discrimination method (VIC and FAM labeled)	VEGFA		+	+	0	0
Sub-Saharan Africa	South African (Xhosa)	Healthy black and white women	543	234 White/ 209 black	30/25		PCR-RFLP	CETP	rs708272	0	0	0	0
								LPL	rs328	0	0	+	0
								LIPC	rs1800588 (514C/T)	0	0	0	0
								PCSK9	rs28362286 (C679X)	0	0	0	0
								PCSK9	rs28362286 (C679X)	/	0	0	0
Hooper et al. (2007)	Southern African	Black African women	653	/	24.03 ± 5	/	PCR-RFLP and TaqMan	Apo B	2488 C>T 4154 G>A	0	0	0	0
Kodogo et al. (2016)	Zimbabweans	HIV-infected patients	103	/	40.3 ± 10.1	26.01	RT-PCR	Apo E	Apo E polymorphisms (ε2)	0	+	0	0
Masemola et al. (2007)	South African	Black rural South African	505	/	/	71.9	PCR-RFLP	Apo E		-	+	-	+
Engwa et al. (2018)	Nigerian	Patients with type 2 diabetes and controls	148	73/75	56.87 ± 1.19/ 49.03 ± 1.90	36.49	PCR-RFLP	ABCC8	C49620T (rs1799854)	-	+	+	-

+; increases the risk; -: decreases the risk; 0: no significant effect; /: no data available.

ACE, angiotensin-converting enzyme; CAD, coronary artery disease; FAM, FAM-labeled probe; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCAD, premature coronary artery disease; PCR-PAGE, polymerase chain reaction-PAGE; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RT-PCR, real time-polymerase chain reaction; TC, total cholesterol; T-ARMS-PCR, tetra-primer amplification refractory mutation system-polymerase chain reaction; TG, triglycerides; VIC, VIC-labeled probe.

Aziz et al., 2011), *RAS* [*ACE* (Ins16del)], *ATR1* polymorphism, *AGT* polymorphism (Abd El Aziz et al., 2011), *CD36* (rs1761667) (Bennouar et al., 2004) and *ABCA1* [rs2230806 (R219K)], *CETP* [rs708272 (TaqIB)], and *LCAT* [rs5923 (4886C/T)] were associated with high level of LDL-C. In addition, *LRPAP1* (rs762861) (Elouej et al., 2016a) and *ACE* Ins16del (I/D) (Mehri et al., 2010) in Tunisian population, *LPL* (rs328) in South African (Xhosa) population (Ellman et al., 2015), *ApoE* ($\epsilon 2/\epsilon 3/\epsilon 4$) in Moroccan population (Bennouar et al., 2004), and *ABCC8* rs1799854 (C49620T) in Nigerian population were also associated with increased levels of LDL-C (Engwa et al., 2018).

Only three gene polymorphisms, *LPL* (Ser447Ter), *PCSK9* [rs28362286 (C679X)], and *ApoE* polymorphisms ($\zeta 2$), respectively, in Egyptian, Southern African, and Zimbabweans populations were found to decrease the concentration of LDL-C (Abd El-Aziz et al., 2014; Engwa et al., 2018; Kodogo et al., 2016) (Table 1). No association was found with other gene polymorphisms investigated in this review (Table 2).

Genetic polymorphism associate with TG

LPL (HindIII H2H2), *APOC3* [SsTi (S2S2)] (Abd El-Aziz et al., 2011), *RAS* [*ATR1* polymorphism, *ACE* (Ins16del), *AGT* polymorphism] (Abd El-Aziz et al., 2012), *ABCA1* [rs2230806 (R219K)], *CETP* [rs708272 (TaqIB)], and *LCAT* [rs5923 (4886C/T)] (Abd El-Aziz et al., 2014) gene polymorphisms were associated with high levels of TG in Egyptian population, as well as *LRPAP1*(rs762861) (Elouej et al., 2016c), *ACE* [Ins16del (I/D)] (Mehri et al., 2010), and *APOA5* (rs3135506) (Kefi et al., 2017) gene polymorphisms in Tunisian population; *Apo E* ($\epsilon 2/\epsilon 3/\epsilon 4$) (Mehri et al., 2010) and *HNF1A* [rs1169288 (A>C), rs2464196 (G>A)] (Morjane et al., 2017) in Moroccan population; and *Apo E* polymorphisms ($\zeta 2$) in South African population (Masemola et al., 2007).

On the contrary, *ZNF664* rs12310367 (Elouej et al., 2016a) and *VEGFA* (rs3025026, rs3025039) gene polymorphisms (Sellami et al., 2018) in Tunisian population; *LPL* Ser447Ter (XX) in Egyptian population (Abd El-Aziz et al., 2011), and *ABCC8* [C49620T (rs1799854)] in Nigerian population (Engwa et al., 2018) were associated with decreased levels of TG. For the rest, apart from those where data were not reported, other gene polymorphisms investigated were shown to have no significant effect on the level of TG in African populations according to studies included in this review (Table 2).

Discussion

This systematic review summarizes the available data on genetic variants influencing the risk of developing dyslipidemia in African-based populations. Most included studies used a candidate gene approach. The studies also involved mostly investigations of genetic predisposition of dyslipidemia in specific CVD conditions, and no study was performed in the general populations. Notably very few studies were performed in sub-Saharan African populations.

Some variants were replicated in different populations; for example, *ACE* (Ins16 del), *APOE* ($\epsilon 2/\epsilon 3/\epsilon 4$), *CETP* (rs708272), *FTO* (rs9939609), *LPL* (Ser447Ter), and *PCSK9* (rs28362286) were each investigated in two studies. *ACE* (Ins16del) was investigated in Tunisian (Mehri et al., 2010) and Egyptian population (Abd El-Aziz et al., 2012); Although

this variant was shown to increase the risk of developing dyslipidemia in both populations, DD was the associated genotype in Egyptians, whereas ID genotype was the risk factor in Tunisians population (allele I is the 278-bp insertion and allele D is the deletion variant in intron 16 of the *ACE* gene). Indeed, the *ACE* I/D polymorphisms is a 287-bp insertion/deletion in intron 16 of the *ACE* gene that is associated with lower baseline circulating rates of *ACE* (Rigat et al., 1990).

Established link has already been demonstrated between *ACE* I/D polymorphism and the risk of myocardial infarction and cardiovascular events (Hamelin et al., 2011; Vaisi-Raygani et al., 2010; Zintzaras et al., 2008), microalbuminuria (Pontremoli et al., 2000; Staessen et al., 1997), left ventricular hypertrophy (Petricone et al., 1997), thoracic aortic aneurysm in patients with bicuspid or tricuspid aortic valves (Foffa et al., 2012), pregnancy hypertensive disorders (Chen et al., 2012; Reshetnikov et al., 2015), and hypertensive emergency (Vilela-Martin et al., 2013). Yet, the findings of this study are in line with the above-mentioned investigations. By contrast, the DD genotype of *ACE* was suggested to be associated with coronary artery diseases in Asian Indians (Bhatti et al., 2016).

Association between *ApoE* genotype and plasma lipid was investigated in Moroccan and black rural South African population (Bennouar et al., 2004; Masemola et al., 2007). Interestingly, the allele $\zeta 2$ that is associated with risk of dyslipidemia in Moroccan population showed a protective effect against dyslipidemia in black rural South African population.

Apolipoprotein (apo) E is a multifunctional protein with central roles in lipid metabolism, neurobiology, and neurodegenerative diseases. It is controlled by three codominant alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) that code for three major isoforms (apoE2, apoE3, and apoE4) with different effects on lipid and neuronal homeostasis (Huang and Mahley, 2014). Similar to the results found in the black South African population, a meta-analysis of data from populations in the United States, Asia, and Europe has shown that allele $\epsilon 2$ could be associated with elevated levels of TG and reduced concentrations of TC and LDL-C (Dallongeville et al., 1992).

Although the (rs 9939609) polymorphism in *FTO* gene showed no effects on TG and HDL-C (Kella et al., 2017; Elouej et al., 2016b), it has been associated with increased TC and reduced HDL-C in Tunisians and Egyptian populations, respectively. However, this polymorphism was associated with obesity and type 2 diabetes in a study conducted in Brazil (Steemburgo et al., 2013).

The polymorphism (Ser447Ter) in lipoprotein lipase gene (*LPL*) was shown to reduce TC, LDL, and TG concentrations in Egyptians patients with myocardial infarction (Abd El-Aziz et al., 2011). This suggests that Ser447Ter could have a protective effect against dyslipidemia. However, no significant association was found between this polymorphism and dyslipidemia in South African healthy black and white women (Ellman et al., 2015). Ser447Ter variant is the most common of *LPL* gene. *LPL* is a major rate-limiting enzyme that hydrolyzes TG-rich particles into free fatty acids and glycerol, and it plays a key role in converting very low-density lipoprotein (VLDL) to LDL.

It is well known that *LPL* activity and mass are associated with fluctuation TG and HDL-C levels (Henderson et al., 1999; Rip et al., 2006; Sparkes et al., 1987). Ser447Ter increases the lipoprotein lipase activity and it has consistently

been associated with lower TG and higher HDL-C levels in candidate gene association studies (Huang et al., 2006).

The polymorphism rs708272 (TaqIB) in cholesteryl ester transfer protein (CETP) gene was investigated in Egyptians and South African populations (Ellman et al., 2015; Sediri et al., 2011). It has been associated with dyslipidemia in Egyptians, whereas no effect of this polymorphism was demonstrated in black and white South African women. *CETP* encodes for cholesteryl ester transfer protein, which transfers cholesteryl esters from HDL to apolipoprotein B-containing particles in exchange for TG, thereby reducing the concentration of HDL.

As higher HDL levels are associated with decreased risk of atherosclerosis, the activity of *CETP* is thought to promote development of the disease by reducing HDL levels. The *CETP* TaqIB SNP (rs708272) is the most extensively studied *CETP* polymorphism. A consistent number of investigations have suggested an association between the TaqIB polymorphism of the *CETP* gene, plasma HDL-C levels, and the risk of CVD, but the results are still controversial (Galati et al., 2014; Yilmaz et al., 2005).

In two studies performed in South African population, the polymorphism rs28362286 of Proprotein convertase subtilisin-like/kexin type 9 (*PCSK9*) gene was not associated with dyslipidemia (Ellman et al., 2015; Mehri et al., 2010). However, it has been related to reduce LDL-C concentration in one study (Hooper et al., 2007).

Among studies investigated in one population only, *LRPAP1* (rs762861) in Tunisian (Elouej et al., 2016a), *LPL* (HindIII/H2H2), *APOC3* (SsTi/S2S2), *RAS* (AGT polymorphism/ATR1 polymorphism), *ABCA1* (rs2230806), and *LCAT* (rs 5923) in Egyptians populations (Abd El-Aziz et al., 2011, 2012, 2014) have been associated with dyslipidemia in other populations. Further investigations of the effects of these polymorphisms on lipid profile parameter are needed to obtain more conclusive correlations.

This review has some limitations. First, it includes a limited number of studies, most of which were not designed to primarily investigate the genetic determinants of dyslipidemia, but of other diseases such as coronary artery disease, diabetes mellitus, or metabolic syndrome.

Second, the available included studies were not representative of the whole African populations, with most of the data coming from Northern African populations.

Third, these studies had less substantial sample size compared with studies conducted elsewhere, precluding accurate evaluation of statistical significance.

Fourth, the measures of association were not consistently reported across studies, hence impeding meta-analysis. Despite these limitations, this study is the first review to comprehensively and rigorously summarize the available data on the genetic determinants of dyslipidemia, a major contributor to the burden of CVD in African populations.

In conclusion, the effect of genetic variants on lipid profile parameters identified both in Northern and sub-Saharan Africa was contradictory. Further investigations are needed to elucidate these variable effects. Although dyslipidemia is a major risk factor to CVD and consequentially an important contributor to the burden of disease in African populations, there are still huge knowledge gaps regarding the underlying genetic mechanisms of dyslipidemia in these populations. Efforts are highly needed to expand our knowledge on the

molecular basis of dyslipidemias in Africans using large-scale GWAS, studies of family-based analyses, and gene-environment and gene-gene interactions.

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Authors' Contributions

J.J.N. conceived the study. J.J.N. and A.D.K. performed the literature search. J.J.N., E.P.M.M., H.B., M.G.-F., and A.D.K. selected the studies and extracted the relevant information. J.J.N., E.P.M.M., M.G.-F., and H.B. synthesized the data. J.J.N., E.P.M.M., and M.G.F. wrote the first draft of the article. J.J.N., E.P.M.M., H.B., M.G.-F., A.D.K., and A.W. critically revised successive drafts of the article and approved its final version. All authors have met the ICMJE authorship criteria.

Author Disclosure Statement

The authors declare that no conflicting financial interests exist.

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