

# Genetic study of the metabolic syndrome in the Moroccan population: a scoping review

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**Abstract.** Complications of metabolic syndrome include cardiovascular disease and type 2 diabetes mellitus for different ethnic populations, which represent a growing public health burden. The identification of genetic factors contributing to the metabolic syndrome is of great interest for the prevention and treatment of cardiovascular diseases in Morocco. This scoping review summarizes the available data on genetic variants associated with metabolic syndrome in the Moroccan population. Electronic searches of PubMed and EMBASE databases were conducted to identify all studies published from January 2000 to 2022, on genetic susceptibility to metabolic syndrome in the Moroccan population. The studies included in this review met the pre-specified inclusion criteria. Studies included in this review matched the requirements for inclusion. Five research targeted genetic variations as their main subject. Data were narratively summarized since the studies were high degree of heterogeneity. There was a total of thirteen polymorphisms in the eight metabolic syndrome susceptibility genes that had different effects and were linked to characteristics in the Moroccan population. There is a clear need to improve our understanding of the genetic causes of the metabolic syndrome. This is the first review to comprehensively and rigorously summarizes the available data on the genetic determinants of the metabolic syndrome, a major contributor to the cardiovascular diseases burden of the Moroccan population.

## 1 Introduction

After controlling many of the world's formerly infectious diseases, non-communicable diseases (NCDs) have become the leading cause of morbidity and mortality not only in developed countries, but also in underdeveloped countries (Coates et al. 2020). Among all these NCDs, metabolic syndrome has been the real burden worldwide (Saklayen, 2018).

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Metabolic syndrome (MetS) is a combination of metabolic risk factors for cardiovascular disease and type 2 diabetes. The principal components of MetS include central obesity, dyslipidemia (increased triglycerides (TG), decreased high-density lipoprotein cholesterol (HDL-C)), increased blood pressure, and increased fasting blood glucose. The presence of three of these risk factors represents a positive diagnosis of MetS (Alberti et al., 2009). The morbidity of MetS is increasing worldwide, making MetS a huge public health burden for many countries (Alberti et al., 2005; Grundy, 2008; Ekelund et al., 2009). MetS is widely estimated to affect a considerable proportion of the world's population, with a reported incidence of 20-25% in the adult population of developed countries (Saklayen, 2018).

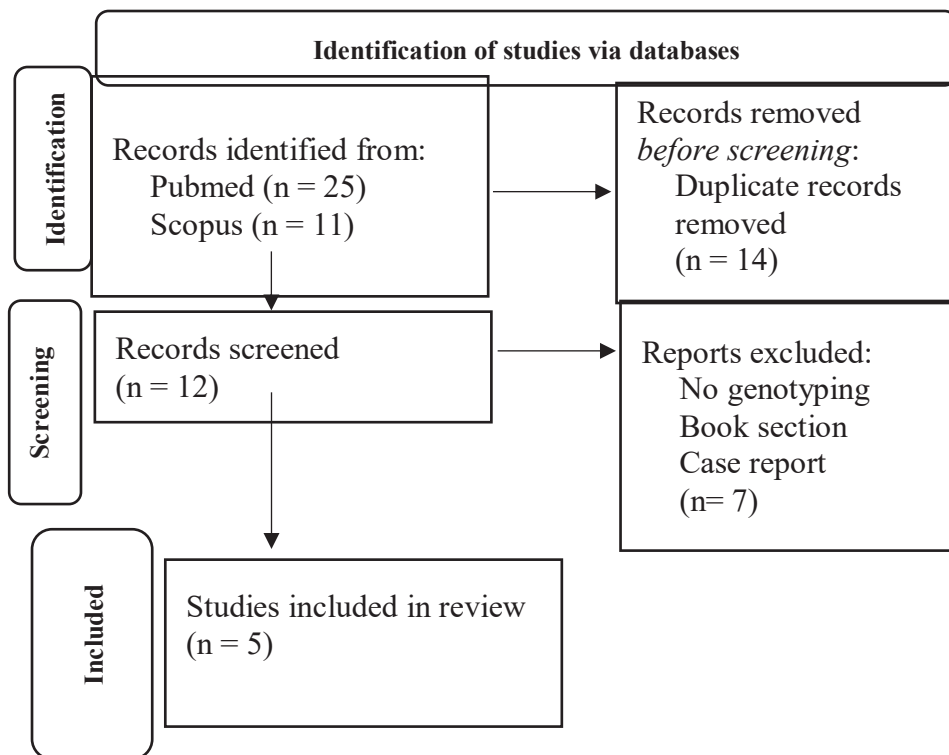
In Morocco, the burden of noncommunicable diseases is high, causing over 75% of all deaths; cardiovascular disease (CVD), diabetes and cancers are among the principal causes of death (57%) (Cahdli et al., 2018). CVD is frequently the leading cause of death worldwide and therefore further studies are important to define the role played by the MetS in this pathology, in order to reduce its heavy negative impact on public health and economic systems. (Fahed et al., 2022). The prevalence of MetS has been estimated in Morocco to be 40.0% (48.0% in women and 31.9% in men) as recently reported by Pengpid & Peltzer (Pengpid and Peltzer, 2020).

The pathogenesis of MetS incorporates several genetic and epigenetic factors (Fathi Dizaji, 2018) that can be linked to insulin tolerance and chronic low-level inflammation. In addition, certain lifestyles such as diet and physical activity, coupled with genetic factors, clearly interact as major contributors to the development of MetS (Fahed et al., 2022). Untreated, MetS is significantly linked to an elevated risk of cardio-vascular disease and type 2 diabetes (Pekgor et al., 2019).

Recently, there has been much interest in a potential genetic contribution to different mechanisms of MetS. Genome-wide linked studies (GWAS catalog) have found many genetic loci involved in different components of MetS (240 associations and 23 studies) (GWAS, n.d). To identify the genetic factors which contribute to the MetS is a great need for the prevention and reduction of the incidence of cardio-vascular disease in Morocco. This systematic review reports the existing data on genetic variants that are linked with the MetS in the Moroccan population.

## **2 Applied Methods for Systematic Review**

The present review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Liberati et al., 2009). An extensive search was conducted on PubMed/Medline and Scopus databases for articles that were published from January 2000 to 2022, using keywords related to MetS (MetS; Morocco; Genetics). Studies were selected based on an initial screening of titles and abstracts. A comprehensive review was performed to exclude research that couldn't meet the eligibility criteria. Inclusion criteria: MetS; Moroccan Genetics and Exclusion criteria: Publications that did not report genetic variants - Case reports - Book section - Review or meta-analysis articles. The search strategy shows the general pattern of the literature search for MetS papers in this systematic review and their inclusion in the final report (Figure 1).



**Fig. 1.** The flow diagram explains the process of article selection

### 3 Literature review and Study Characteristics

Our study strategy (Figure 1 and Methods section) identified five studies that met our inclusion criteria (Table 1) (Ajjemami et al., 2014, 2015; El Yaagoubi et al., 2017; Morjane et al., 2017; Elkhattabi et al., 2018). All studies used the International Diabetes Federation (IDF) definition of MetS. IDF demands as a prerequisite the presence of abdominal obesity in addition to two further criteria: Elevated TG levels or taking lipid-lowering drugs, HDL-C decrease or treatment, high blood pressure  $\geq 130/85$ mmHg or taking antihypertensive drugs, elevated fasting blood glucose  $\geq 100$  mg/dL or treatment for type 2 diabetes.

**Table1.** Genetic polymorphisms reported with metabolic syndrome in Morocco population.

Reference	Population (Patients/Controls)	Used definition	Gene	Polymorphism	Alleles
Ajjemami et al., 2014	176P/105C	IDF	APOC3	SstI (3238C>G) (rs5128)	C/G
Ajjemami et al., 2015	176P/105C	IDF	APOA5	rs2266788	T/C
				rs662799	T/C
				rRs3135506	C/G
				rs2075291	G > T
	177P/139C	IDF	ADCY5	rs11708067	A/G

Lakbakbi El Yaagoubi et al., 2017			APOC 3	rs5128 (C33238C>G)	C/G
			DUSP9	rs5945326	A/G
			G6PC2	rs560887	A/G
			PROX1	rs340874	A/G
			UBE2E2	rs7612463	A/C
Morjane et al., 2017	104P/137C	IDF	HNF1A	rs1169288	A/C
				rs2464196	G/A
				rs735396	T/C
Elkhatabi et al., 2018	50P/50C	IDF	HNF1A	rs1169288	--
				rs2464196	--

## 4 Results

This scoping review summarizes the existing data on genetic variants influencing the risk of developing MetS in the Moroccan population (Table 2).

**Table 2.** Genotypic and allelic distribution for candidate SNPs in Moroccan patients with MetS and control subjects.

Gene	Polymorphisme	Alleles	model	genotype	OR [95% CI]	P-value
ADCY5	rs11708067	A/G		AA vs AG	0.51 (0.28–0.95)	0.034
APOA5	rs 2266788	T/C	--	--	--	--
	rs662799 (-1131)	T/C	Codominant	T//C	10.13 (4.65–22.06)	<0.0001
			Dominant	T//C – C//C	7.82 (3.79–16.14)	<0.0001
	rs3135506 (c.56)	C/G	Codominant	C//G	2.13 (1.05–4.31)	0.035
			Dominant	C//G – G//G	2.07 (1.07–4.03)	0.032
	rs 2075291 (c.553)	G > T				
Haplotype				CCGT	3.223 (1.43; 7.25)	0.00278
				CGGT	8.234 (1.6; 42.5)	0.00534
APOC3	SstI (3238C> G)	C/G	Codominant	[CC vs CG]	4.21 [1.66–10.68]	0.0008
			Dominant	[CC vs CG+GG]	3.83 [1.59–9.19]	0.0010
APOC3	rs5128 (C3238C>G)	C/G	Codominant	[CC vs CG]	4.39 (1.66–11.56)	0,003
			Dominant	[CC vs CG+GG]	3.73 (1.48–9.41)	0,005
DUSP9	rs5945326	A/G		AA vs AG	0.32 (0.17–0.62)	0.001
G6PC2	rs560887	A/G	--	--	--	--
HNF1A	rs1169288	A/C	Codominant	AC	2.15 (1.16–3.97)	0.021
			Dominant	AA	1.77 (1.15–2.72)	0.008

			Log additive model	AA	2.23 (1.26-3.96)	0.006
			Model allelic	AA	2.05 (1.36-3.14)	0.0005
	rs2464196	G/A	Codominant	GA	1.81 (0.93-3.53)	0.040
			Dominant	GG	2.06 (1.11-3.83)	0.020
			Log additive model	GG	1.63 (1.11-2.41)	0.012
			Model allelic	GG	1.52 (1.05-2.20)	0.0272
	rs735396	T/C	--	--	--	--
PROX1	rs340874	A/G	Codominant	(AA vs GG)	2.81 (1.09–7.27)	0.033
			Recessive	(AA+AC VS CC)	2.55 (1.04–6.25)	0.041
UBE2E2	rs7612463	A/C	--	--	--	--

#### 4.1 Genetic association with MetS

In a group of 176 patients and 105 controls from the Moroccan population, the Apolipoprotein A5 (APOA5) gene polymorphism (-1131T>C; C.56C>G; c.553G>T; and C.1259T>C) was investigated (Ajjemami et al., 2015). This study demonstrated a strong association between the APOA5 -1131 T > C polymorphism and MetS in both co-dominant and dominant models. MetS patients and bystanders with the APO A5 variation, c.56 G, had elevated waist circumference and triglyceride levels when compared to those without the variation. The risk of developing MetS was 10.13% higher for those with the APOA5 -1131C genotype in the co-dominant state versus to those with the TT genotype, and in the dominant state, individuals with the CC and TC genotype had a 7.82% higher risk to acquire MetS than those with the TT genotype.

The codominant and dominant models both demonstrated a significant correlation for the APO A5 c.56 C>G polymorphism, with p-values of 0.035 and 0.032, respectively. In the codominant state, carriers of the C>G genotype have a 2.13% increased risk of developing MetS compared to people with the CC genotype, and in the dominant state, carriers of the CG and GG genotype had a 2.07% higher risk of developing MetS compared to people with the CC genotype. No significant correlation between the c.553 G>T and C.1259 T>C polymorphisms of the APOA5 gene and the MetS was discovered in any of the genetic models. In the population of Morocco, the SstI polymorphism is investigated. Two models, codominant and dominant, were used to examine the relationship between the susceptibility to the APOC3 3238C>G polymorphism and the MetS. Nevertheless, for all of the APOC3 SNPs 3238C> G, no correlation was discovered in the codominant-two recessive mode (Ajjemami et al. 2014). Moreover, compared to MetS patients and controls without this mutation, the APOC3 3238G polymorphism was related with heightened levels of TG and LDL (El Yaagoubi et al., 2017). Comparisons of genotype and allelic frequency distributions of the rs5128 (APOC3), rs7612463 (UBE2E2 gene), rs560887 (G6PC2 gene), rs340874 (PROX1 gene), rs5945326 (DUSP9 gene) and rs11708067 (ADCY5 gene) polymorphisms between MetS and non-MetS subjects according to the codominant, dominant, and recessive models are shown in Table 2. Elevated risk of MetS was significantly associated with the single nucleotide polymorphisms rs5128 (APOC3) and rs340874 (PROX1). Two genetic variations, rs5945326 in the DUSP9 gene and rs11708067 in the ADCY5 gene, were

positively correlated with preventing the emergence of MetS. SNPs rs7612463 (UBE2E2) and rs560887 (G6PC2) were not observed to be associated with MetS risk.

Polymorphism in Hepatocyte-Nuclear-Factor1-alpha (HNF1A) gene such as rs1169288 and rs2464196, genotype and allele data are presented in Table 2 The rs1169288, rs2464196, and rs735396 genotypes showed significant relationship with MetS (Morjane et al., 2017). In addition, all four haplotypes (CAC, AAC, AAT, AGT) of these SNPs and rs735396 were also significantly associated with MetS. In contrast, there was no association between rs735396 genotype and MetS. Carriers of the CC and AC genotypes of the HNF1A rs1169288 gene in the co-dominant state had an increased risk (2.54% and 2.15%, respectively) of developing MetS, compared with AA genotype subjects. The same was true for carriers of the AA and GA genotypes of the HNF1A rs2464196 gene in the co-dominant state, who had a 2.64% and 1.81% increased risk of developing MetS, respectively, compared with AA genotype subjects. Association analysis of metabolic traits with the three HNF1A variants shows that there is an association between rs 1169288 and all four traits (holding circumference; systolic blood pressure; impaired fasting glucose; triglycerides) and between rs2464196 and the triglycerides trait, for the rs 735396 trait there is an association with both traits (total cholesterol; HDL).

The gene for apolipoprotein A5 (APOA5) is located on a short arm of human chromosome 11 at region (11q23) and is part of the (APOA1/APOC3/APOA4/APOA5) gene cluster (Pennacchio and al., 2001). Genetic variation in the human APOA5 locus correlates with changes in plasma lipoprotein levels (Van Dijk and al., 2004; Hubacek, 2005; Talmud and al., 2002), and a common APOA5 polymorphism is significantly linked with increased risk of MetS (Yamada and al., 2007; Niculescu and al., 2007). Many single-nucleotide polymorphisms in the APOA5 gene have been linked to the development of MetS, and thus cardio-vascular disease and T2D in different ethnic groups, according to genome-wide association studies (GWAS). In the current study, the APOA5 SNP rs662799 was found to be significant in predicting MetS modulation in a Moroccan population. In addition, the APOA5 rs662799 SNP was found to have a genome-wide significant association with high blood pressure, fasting blood sugar, and HDL. Although the APO A5 rs662799 polymorphism has been widely associated with diabetes risk. The APOA5 rs662799 SNP has been linked to an increased risk of MetS in Greeks (Vasilopoulos and al., 2011), Tunisians (Hechmi and al., 2020) Pakistanis (Fiaz and al., 2019), Caucasians (Maasz et al., 2007) Japanese (Yamada et al., 2007), Taiwanese (Lin and al., 2017; Hsu et al., 2008), Hong Kongese (Ong and al., 2011), Chinese (Xu and al., 2013), and Koreans (Kim et al., 2016; Oh et al., 2020). However, some studies on Caucasian (Grallert and al., 2007; Fallah and al., 2016) and Hispanic (Mattei and al., 2009) populations have shown conflicting results compared to the Moroccan population. Several meta-analyses have also found that the APOA5 rs662799 SNP is linked with an increased risk of MetS in Asians but not in Europeans (Grallert and al., 2007; Mattei and al. 2009; Liu and al. 2012; Xu and al., 2013; Fallah and al. 2016; Kim et al., 2016; Oh and al., 2020). The association between MetS and APOA5 rs3135506 has been obscured. In the population of Morocco, we found a significant linked between the c.56 C>G polymorphism and Increased TG levels and waist circumference. Several studies in other populations have found an relationship between allele "G" of the ApoA5 c.56 C>G polymorphism and TG, Roma population samples (Sumegi et al. 2017), and, in addition, in studies by Maász et al. 2007, the minor G allele at SNP rs3135506 was linked with approximately 50% greater risk of MetS in Caucasian populations (Grallert and al., 2007). In Tunisia's population, SNP rs3135506 is linked to high levels of TG (Chaaba and al., 2005), but no association with TG levels or other elements of the MetS was identified in the study conducted by Kefi et al. 2017. These discrepancies could be explained by ethnically based differences or imbalances related with other genetic factors. The patterns of linkage between SNPs at the APOA5 locus and TG levels differed between

populations; for example, the “CC” genotype of rs2266788 was strongly correlated with increased TG levels and decreased HDL cholesterol levels in Europeans but not in Moroccans (Kraja et al., 2011). The human APOC3 gene encoding ApoC-III is situated on chromosome 11 region 11q23.3 within the APOA5-APOA4-APOC3-APOA1 gene cluster. The rs5128 polymorphism in the 3'untranslated region (UTR) of the APO C3 gene was first identified in 1983 (Rees and al., 1983). The studies which we find in this review found an association between the rs5128 variant and MetS in the population of Morocco. A cross-sectional survey of the Northeast Chinese population found that subjects with the GC genotype of rs5128 had a more advanced risk of MetS than persons with the GG or CC genotypes of rs5128 (Wu et al., 2016). We found that rs5128 was associated with triglyceride and LDL cholesterol concentrations (Ajjemami et al., 2014), but TG associations were absent in the study by El Yaagoubi et al., 2017, but several studies found APOC3 as rs5128 to be linked with increased plasma TG levels (Liu et al., 2010; Qi et al., 2007). A recent meta-analysis of several populations (Indian and US Indians, London Indians, Singaporeans, UK Indians, Singaporean Chinese, London Europeans, UK Europeans, Mexican Americans in San Antonio and multi-ethnic people in Oklahoma) found a major relationship between rs5128 and elevated plasma TG levels and a 3% increase in rs5128 (Goyal et al., 2021). Similarly, a meta-analysis of 19 published studies finds that individuals carrying the rs5128 polymorphism in the APOC3 allele are more likely to develop coronary heart disease (Li et al., 2016).

## 5 Conclusion

This analysis has several limitations. First, it contains only a few research studies with modest sample sizes. Second, ethnic differences are not accounted for in the available research included in this review; therefore, the same SNPs may have different effects by ethnicity (or be associated with one ethnicity but not another). It is also critical to note that the fact that there are different ethnic groups within the Moroccan population makes it difficult to define the population precisely. This suggests that several ethnic-related characteristics, including Linkage Disequilibrium patterns and allelic frequencies, have not been considered in most of the literature. In spite of these shortcomings, this is the first review to completely and rigorously summarize the existing data on the genetic factors of the MetS, a major contributor to the CVD burden of the Moroccan population. As a whole, the impact of genetic variations on the Moroccan MetS was inconsistent, and further research is needed to improve our understanding of the genetic causes of the MetS.

The authors declare that they have no conflict of interest.

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