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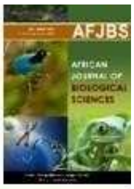

Research Paper
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Association of CAPN10 Gene Variants with Type 2 Diabetes Mellitus Associated and Metabolic Syndrome: A Systematic Review

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder influenced by genetic and environmental factors. CAPN10, encoding the cysteine protease calpain-10, has been identified as a T2DM susceptibility gene. However, conflicting evidence regarding the association of CAPN10 polymorphisms (SNP-43, SNP-19, SNP-63, and SNP-44) with T2DM across diverse populations necessitates further investigation.

Objective: To evaluate the association of CAPN10 polymorphisms with T2DM susceptibility, their prevalence across populations, and their impact on metabolic functions.

Methodology: A systematic review of PubMed, Scopus, Google Scholar, and Embase was conducted to identify case-control, cross-sectional, and genetic association studies on CAPN10 polymorphisms, including (SNP-43, SNP-19, SNP-63, and SNP-44) in T2DM. Study quality was assessed using the Newcastle-Ottawa Scale (NOS).

Results: Fifteen studies from twelve countries, including Tunisia, Mexico, Iran, The United States, China, and Indonesia were analyzed, with sample sizes ranging from 107 to 1,665 participants. SNP-19 (2R/2R genotype) was significantly associated with increased T2DM risk in Tunisians (OR=1.61, 95%CI: 1.20–2.18) and Iranian populations ($P<0.01$). SNP-43 was linked to T2DM in Iranian and Kurdish populations ($P=0.01$) but not in Bangladesh or Poland. SNP-19 was associated with increased waist circumference and triglyceride levels ($P<0.01$). Haplotype 121 was a risk factor for gestational glucose metabolism disorders ($P=0.036$), whereas haplotype 221 was protective ($P=0.042$).

Conclusion: CAPN10 polymorphisms exhibit population-dependent associations with T2DM, with ethnic-specific risk and protective haplotypes suggesting gene-environment interactions. Further large-scale genome-wide association studies are needed to validate these findings and explore therapeutic implications.

Keywords: CAPN10, Type 2 Diabetes Mellitus, Genetic Polymorphisms, Metabolic Traits, Obesity.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and impaired glucose metabolism.[1] T2DM poses a major global health burden, contributing to severe complications, elevated healthcare expenses, and increased mortality rates.[2] The International Diabetes Federation (IDF) predicts that diabetes will affect 700 million people worldwide by 2045, and Pakistan, along with other low- and middle-income nations, holds a significant portion of these cases.[2] T2DM presents a major health problem because it is consistently linked with metabolic syndrome, including central obesity, hypertension, dyslipidemia, and hyperglycemia.[3] Early intervention programs and predictive tools are crucial because metabolic syndrome increases cardiovascular risk and other metabolic complications.[4]

The CAPN10 (Calpain-10) gene, located on chromosome 2q37, encodes a cysteine protease that plays a crucial role in pancreatic β-cell function, insulin regulation, glucose homeostasis, and energy metabolism.[5]. Genetic variations in CAPN10 have been associated with the pathophysiology of T2DM, influencing insulin sensitivity, glucose tolerance, and lipid metabolism.[6] Among these, SNP-43, SNP-63, and SNP-19 polymorphisms have been linked to altered glucose metabolism and an increased risk of diabetes across diverse populations.[7]

Numerous studies have explored the association between CAPN10 polymorphisms and T2DM, but findings remain inconclusive.[8-10] Early research identified SNP-43 as a risk factor in Mexican-American populations.[7] Meanwhile, meta-analyses have confirmed that SNP-43 and SNP-19 enhance insulin resistance and β-cell dysfunction in individuals with a family history of DM.[10] Additionally, CAPN10 variants have been linked to obesity, a key factor of metabolic syndrome, further underscoring their role in metabolic disorders.[11]

Currently, although several mechanisms underlying CAPN10-mediated DM have been proposed, the exact molecular pathways remain unclear and require further investigation across diverse ethnic populations.[10, 12] Therefore, this review aimed to evaluate the association between CAPN10 gene variations, T2DM, and metabolic syndrome, highlighting their potential as predictive markers for disease management and treatment.

METHODS

Protocol: The researchers conducted a systematic review based on the established Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was conducted across PubMed, Embase, Scopus, Google Scholar, and Web of Science to identify studies on the impact of CAPN10 gene mutations on T2DM and metabolic syndrome. This review included observational studies that investigated CAPN10 gene variations in T2DM and metabolic syndrome through cross-sectional, cohort, and case-control designs.

Inclusion and exclusion criteria: All studies included human participants of various ages and sexes, with a particular focus on South Asian demographic groups. The research evaluated the relationship between CAPN10 variants and T2DM, assessing their impact on insulin resistance, glucose tolerance, obesity, and dyslipidemia markers. Only English-language studies published after 2000 were considered to ensure a comprehensive review of recent and relevant research. Although our focus was mainly on South Asian groups, we incorporated data from diverse global populations to enhance the applicability of the findings.

Search and selection: A systematic search strategy was employed using Medical Subject Headings (MeSH) terms and Boolean operators to combine keywords related to CAPN10, T2DM, and metabolic syndrome. The search terms included: ("CAPN10 gene" OR "Calpain-10" OR "CAPN10 polymorphism") AND ("Type 2 Diabetes Mellitus" OR "T2DM") AND ("Metabolic Syndrome" OR "Insulin Resistance"). All references were imported into the EndNote program to remove duplicates. Initially, titles and abstracts were screened to identify eligible studies, followed by full-text reviews. Two independent researchers performed the screening and data extraction processes. Any discrepancies in their findings were discussed until an agreement was reached or a third reviewer was consulted to resolve the remaining conflicts. A tracking log was maintained to document all disagreements and their resolutions between the reviewers.

The research teams used a standardized data extraction form to collect information from the studies, documenting publication dates, objectives, study design methods, populations, genetic data, and measurement outcomes. Additionally, data on potential confounding variables, including age, sex, body mass index (BMI), and lifestyle factors, were gathered alongside the study-specific data points.

The quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluated three key aspects: sample selection, group comparisons, and outcome measurement methods. Two independent reviewers assessed each study for potential bias, and any disagreements were resolved through discussion or consultation with a third reviewer.

The study employed a narrative synthesis approach to integrate key findings, a quality assessment of the included studies, and their methodological weaknesses. Results were reported following PRISMA guidelines, and a PRISMA flow diagram was provided to illustrate the study selection process (Figure 1). The diagram outlines the number of records retrieved from various databases, the removal of duplicates, the application of exclusion criteria during screening, and the final number of studies included in the review (n =15). Figure 1 outlines the identification, screening, eligibility, and inclusion phases of the study selection process.

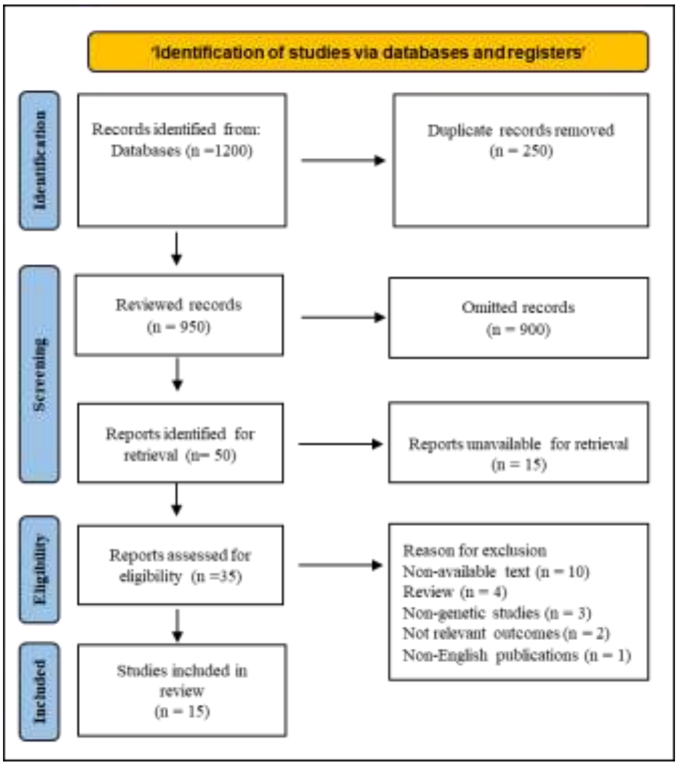

Figure 1: The PRISMA flowchart illustrating the process of study selection.

RESULTS

Overview of Included Studies

This systematic review analyzed 15 studies investigating the association between CAPN10 gene polymorphisms and the risk of developing T2DM and metabolic syndrome (Table 1). The studies employed various observational research designs, predominantly case-control studies, along with a few genetic association and cross-sectional analyses. Sample sizes varied from 107 to 1,665 participants, and the studies were conducted in diverse populations across Tunisia, Mexico, Iran, China, Turkey, South India, Spain, the UK, the USA, Poland, Bangladesh, Finland, Egypt, and Indonesia. Most of the studies focused on CAPN10 polymorphisms UCSNP-43, UCSNP-19, UCSNP-63, and SNP-44.[13-25] Several studies examined the association between these variants and T2DM risk while [13-15, 17, 18, 20-27] others explored their influence on metabolic traits such as BMI, lipid profiles, fasting glucose levels, insulin sensitivity, and glucose metabolism disorders in pregnancy.[16, 19].

Association between CAPN10 Polymorphisms and T2DM

Several studies reported significant associations between CAPN10 polymorphisms and an increased risk of T2DM, although findings varied across different populations. A study conducted in Tunisia found that the UCSNP-19 2R/2R genotype was enriched in T2DM patients, with an increased risk observed in both the 2R/2R (OR = 1.61, 95% CI: 1.20–2.18) and 3R/2R (OR = 1.35, 95% CI: 1.08–1.68) genotypes.[13]

Similarly, a study in Ciudad Juarez, Mexico, found that the homozygous 3R genotype was more frequent in T2DM patients (0.418) compared to controls (0.265), supporting the role of SNP-19 in increasing susceptibility to T2DM.[14] In contrast, a study conducted among the Kurdish ethnic group in Iran reported a significant association between SNP-43 and T2DM, where the A allele was more frequent in T2DM cases (18% vs. 11% in controls, P=0.01). At the same time, SNP-19 and SNP-63 did not show a significant association with diabetes risk.[15] These findings suggest population-specific effects of CAPN10 polymorphisms on T2DM susceptibility.

CAPN10 and Metabolic Traits

Beyond T2DM risk, CAPN10 polymorphisms were also linked to various metabolic traits. A study conducted at Peking University First Hospital in China investigated the role of CAPN10 SNP-19 and SNP-63 in pregnant women with glucose metabolism disorders. The SNP-19 2R/2R genotype and 2R allele were significantly more frequent in affected women than in controls (P=0.012, P=0.006), and individuals with a family history of diabetes showed a significantly higher frequency of SNP-19 2R/2R+2R/3R (P=0.009) and SNP-63 T/T+T/C (P=0.026).[16] Similarly, a study in Turkey found that while SNP-19 and SNP-44 were not significantly associated with T2DM, specific alleles of these polymorphisms were linked to increased BMI in diabetic individuals.[17] A Spanish study also demonstrated that CAPN10 variants were associated with insulin resistance phenotypes, including higher glucose levels after an OGTT and altered HOMA-IR values, while cholesterol levels and blood pressure were influenced by CAPN10 polymorphisms.[19]

Haplotype Analysis and Population Differences

Haplotype analysis provided additional insights into the role of CAPN10 in metabolic dysfunction. A Tunisian study identified a significant enrichment of the 111 haplotype in T2DM patients (Pc = 0.034; OR = 1.22, 95% CI = 1.06–1.41), whereas the high-risk 112/121 diplotype did not show a significant association with diabetes risk in this population.[13] In contrast, a Polish study found that the 121/121 haplotype combination was significantly more frequent in T2DM patients than in controls (17.9% vs. 10.1%, P=0.039), suggesting a population-specific genetic influence.[27] Meanwhile, a genome-wide screen in Mexican Americans and Northern Europeans identified CAPN10 as a diabetes-susceptibility gene, supporting its role in glucose metabolism regulation.[20]

Insulin Sensitivity and Glucose Metabolism

Several studies explored the relationship between CAPN10 polymorphisms and insulin sensitivity. A study in Bangladesh investigated CAPN10 SNP-44 (T>C) polymorphism and found no significant differences in genotype frequencies between T2DM patients and controls, suggesting no direct association with diabetes risk. However, insulin sensitivity (HOMA%S) was significantly lower in T2DM patients compared to controls ($P < 0.001$), and fasting insulin levels were higher ($P < 0.05$).[21] Another study in Pima Indians found that while the UCSNP-43 G/G genotype was not associated with increased T2DM prevalence, it was linked to reduced postabsorptive and insulin-stimulated glucose turnover, suggesting an influence on insulin resistance.[28] Similarly, a study in Mexico identified an association between CAPN10 SNP-19 and metabolic traits, where individuals with del/del and del/ins genotypes had significantly higher waist circumference and triglyceride levels ($P < 0.01$), further implicating CAPN10 in metabolic regulation.[22]

This systematic review highlights the complex relationship between CAPN10 polymorphisms and T2DM across different populations. While certain polymorphisms such as UCSNP-19, UCSNP-43, and SNP-44 have been associated with increased diabetes risk in some populations, their effects are not universally consistent. Haplotype analysis suggests that specific CAPN10 haplotypes may contribute to T2DM susceptibility in a population-specific manner. Furthermore, CAPN10 polymorphisms also appear to influence metabolic traits such as obesity, insulin resistance, lipid profiles, and glucose metabolism. The findings emphasize the need for further large-scale, well-controlled studies to better understand the genetic mechanisms underlying T2DM and metabolic syndrome and to determine how these genetic variations interact with environmental and lifestyle factors.

Table 1: Overview of the studies investigating the association between CAPN10 gene polymorphisms and the risk of developing Type 2 Diabetes Mellitus (T2DM) and metabolic syndrome.

Authors	**Design**	**Sample Size**	**Ethnicity**	**Study Setting**	**Key Findings**
Ezzi et al., 2010 [13]	Case-control	Controls=748 T2DM=917	Tunisian Arab	Population-based	The CAPN10 UCSNP-19 2R allele, 2R/2R genotype (OR 1.61), and 111 haplotype (P=0.034) were associated with increased T2DM risk, while the 112/121 diplotype showed no significant link.
Méndez YL et al., 2014 [14]	Case-control	Controls=64 T2DM=43	Mexican	Population-based	The SNP-19 3R genotype was more frequent in T2DM patients, and the 2R/3R genotype was associated with increased BMI and body measurements in diabetics (P<0.05), suggesting its role in T2DM risk.
Maleki F et al., 2014 [15]	Case-control	Controls=173 T2DM=173	Iran	Population-based	SNP-43 A allele (P=0.01) and GA+AA genotype (OR=1.75, P=0.029) were associated with increased T2DM risk. SNP-19 and SNP-63 showed no direct T2DM association, but SNP-19 (2R/3R+3R/3R) was linked to lower HDL-C (P=0.034), and SNP-63 (CT+TT) to higher LDL-C (P=0.015) in specific groups.
Wu HR et al., 2009 [16]	Case-control	Pregnant women=270 Abnormal glucose tolerance=156 Controls=114	Chinese	Hospital-based	SNP-19 2R/2R genotype (P=0.012), 2R allele (P=0.006), and SNP-63 T/T+T/C (P=0.026) were associated with glucose metabolism disorders, especially in women with a family history of diabetes. Haplotype 121 (P=0.036) increased risk, while haplotype 221 (P=0.042) was protective.
Bayramci et al., 2017 [17]	Case-control	Controls=112 T2DM=125	Turkish	Population-based	No significant association was found between CAPN10 SNP-19, SNP-44, and NR3C1 N363S polymorphisms and T2DM. However, the SNP-19 del-allele, SNP-44 C-allele, and NR3C1 N363S G-allele were identified as risk factors. In T2DM patients, these alleles were also linked to increased BMI.
Bodhini D et al., 2011 [18]	Case-control	Controls=794 T2DM=649	Asian Indian	Population-based	No individual CAPN10 SNP showed a significant association with T2DM, but the 2111 haplotype was significantly more frequent in T2DM cases, suggesting its role in diabetes risk in the South Indian population.
Saez ME et al., 2008 [19]	Cross-sectional	899 individuals	Spanish	Population-based	CAPN10 polymorphisms were associated with insulin resistance (HOMA-IR), post-OGTT glucose, cholesterol levels, and blood pressure. The 1221/1121 haplogroup was under-represented in metabolic syndrome cases, suggesting a protective effect.
Horikawa Y, et al., 2000 [20]	Genetic association study	167 participants	Mexican Americans & Northern Europeans	Population-based	CAPN10 (NIDDM1) was significantly associated with T2DM in Mexican Americans and Northern Europeans, indicating its role in T2DM pathogenesis through a calpain-like cysteine protease pathway.
Evans JC et al., 2001 [26]	Family-based and Case-control	743 sib pairs, parent-offspring trios, case-control groups	British-Irish ancestry	Population-based	SNP-44 C allele was significantly associated with T2DM risk (P=0.033, OR=1.6) in the UK population and confirmed in a UK & Mexican American analysis (P=0.004). T504A, linked to SNP-44 C, may affect protein synthesis or transcriptional regulation.

Baier LJ., 2000 [28]	Genetic association study	158 individuals	Pima Indians	Population-based	UCSNP-43 G/G genotype was not linked to T2DM prevalence in Pima Indians, but in normoglycemic individuals, it was associated with reduced glucose turnover and oxidation, along with lower CAPN10 mRNA expression in skeletal muscle, potentially contributing to insulin resistance and T2DM risk in older individuals.
Malecki MT., 2002 [27]	Case-control	Controls=148 T2DM=229	Polish	Population-based	No significant association was found between CAPN10 SNP-43, SNP-19, and SNP-63 and T2DM. However, the 121/121 haplotype was significantly more frequent in T2DM patients (P = 0.039), suggesting a genetic risk factor, while the 112/121 haplotype showed no association in the Polish population, indicating population-specific effects.
Mir S et al., 2010 [21]	Case-control	Controls=91 T2DM=65	Bangladeshi	Population-based	CAPN10 SNP-44 (T>C) polymorphism showed no significant association with T2DM in the Bangladeshi population. However, T2DM patients had lower insulin sensitivity (HOMA%S, P < 0.001), suggesting that insulin resistance, rather than CAPN10 SNP-44, plays a key role in T2DM development.
Meza-Espinoza et al., 2019 [22]	Case-control	Controls=309 T2DM=289	Mexican	Population-based	CAPN10 SNP-19 showed no significant association with T2DM in Mexican patients. However, it may be linked to metabolic traits associated with obesity in T2DM individuals.
El-Far SW et al., 2022 [23]	Case-Control	Controls=100 T2DM=100	Egyptian	Population-Based	This pilot study found that specific CAPN10 haplotype combinations were significantly associated with an increased risk of T2DM and metabolic syndrome in the Egyptian population.
Tursinawati Yet al., 2020 [24]	Case-Control	Controls=107 T2DM=107	Javanese	Population-Based	CAPN10 SNP-19 (2R/3R and 3R/3R genotypes) was significantly more prevalent in Javanese T2DM patients, suggesting a potential role in T2DM susceptibility in this population.

DISCUSSION

The research examined how CAPN10 genetic variations correlate to T2DM between different population groups. Research indicates that T2DM development risks are elevated among particular populations carrying CAPN10 single nucleotide polymorphisms SNP-19, SNP-43, SNP-63, and SNP-44, although other populations do not demonstrate a significant relationship between these SNPs and T2DM. The findings demonstrated that T2DM genetic predisposition requires consideration of both ethnic backgrounds and environmental conditions that affect the gene-disease relationship.

This review demonstrates that CAPN10 mutations, especially SNP-19 and SNP-43, have a substantial impact on T2DM risk development in particular population groups. Studies from Tunisia and Iran indicated T2DM patients demonstrate a higher occurrence of UCSNP-19 2R/2R genotype (OR = 1.61, 95% CI: 1.20–2.18) which proves a direct link between SNP-19 and diabetes risk.[14] A study on Iranian Kurds showed SNP-43 A allele reached higher frequency among patients with T2DM (18% vs. 11% in controls with P=0.01), and this pattern indicated an elevated risk for T2DM (OR=1.75, 95% CI=1.06–2.89, P<0.029).[14] These findings align with early studies in Mexican Americans, which originally identified CAPN10 as a diabetes susceptibility gene.[22] However, not all studies confirmed this association. A study conducted in Bangladesh found no significant association between SNP-44 (T>C) and T2DM risk, despite observing differences in insulin sensitivity among T2DM patients.[21] Similarly, a Polish case-control study did not find significant differences in allele or genotype distributions between T2DM cases and controls, except for a higher prevalence of the 121/121 haplotype in T2DM patients (P = 0.039).[27] These inconsistencies across studies highlight the possibility that CAPN10 polymorphisms may have population-specific effects influenced by genetic background, lifestyle, and environmental factors.

Several studies included in this review assessed the relationship between CAPN10 polymorphisms and obesity-related metabolic traits, such as BMI, waist circumference, lipid profiles, and insulin resistance.

The Tunisian study found a significant association between the UCSNP-19 2/2 genotype and obesity ($P=0.003$; $OR=2.07$, 95% $CI=1.28–3.33$).[13] Similarly, in a Mexican study, waist circumference ($P<0.01$) and triglyceride levels ($P<0.01$) were significantly higher in individuals with the del/del and del/ins genotypes of SNP-19, suggesting that this variant may contribute to obesity-related metabolic disturbances.[22]. Contrastingly, the Spanish population-based study reported that CAPN10 variants were primarily associated with insulin resistance phenotypes rather than obesity. This study found that CAPN10 polymorphisms influenced glucose levels after an OGTT, HOMA-IR values, and cholesterol levels, but no strong link to BMI was observed.[22] These findings are consistent with those of the UK study, which found no direct association between SNP-43, SNP-19, or SNP-63 and T2DM but identified a significant association between SNP-44 C allele and T2DM risk when combined with a Mexican-American dataset ($P=0.004$).[22]

The relationship between CAPN10 polymorphisms and insulin sensitivity has also been examined in various populations. The Bangladeshi study showed that T2DM patients had significantly lower insulin sensitivity (HOMA%S) compared to controls ($P<0.001$), but SNP-44 (T>C) was not associated with pancreatic β-cell function or insulin secretion.[22] Similarly, a study in Pima Indians found no direct association between SNP-43 G/G genotype and T2DM risk, but G/G homozygotes showed decreased postabsorptive and insulin-stimulated glucose turnover, indicating an impact on insulin resistance rather than direct diabetes risk.[29] These findings suggest that CAPN10 polymorphisms may influence glucose metabolism by altering insulin sensitivity rather than acting as primary risk factors for T2DM.

One of the key findings of this review is the variability in CAPN10 associations across different ethnic groups. The Mexican-American and Finnish studies originally identified CAPN10 as a diabetes susceptibility gene, while subsequent studies in European, Middle Eastern, and South Asian populations have produced inconsistent results.[29] The Tunisian and Iranian studies confirmed significant associations with SNP-19 and SNP-43, whereas the Polish and Bangladeshi studies failed to replicate these findings.[14][14] The UK study also did not find a strong association with SNP-43, SNP-19, or SNP-63, although the SNP-44 C allele was found to increase T2DM risk in a combined analysis with Mexican Americans ($P=0.004$).[26] These discrepancies could be explained by several factors, including differences in genetic backgrounds, linkage disequilibrium patterns, lifestyle factors, and environmental influences. Additionally, haplotype analysis in some populations suggested that specific combinations of SNPs (such as 121/121) may be more predictive of T2DM risk than individual SNPs alone.

The available research about CAPN10 in T2DM and metabolic traits yields important findings, but this review has recognized significant gaps within those studies. Numerous studies included small participant samples, which reduced their ability to find meaningful relationships. The Bangladeshi study with 156 participants and the Polish study with 377 subjects might not have included big enough numbers to uncover minor connections between CAPN10 gene variants and T2DM. The analysis of T2DM risk association with CAPN10 polymorphisms lacks research on their biological impact on T2DM susceptibility through functional studies. Current research lacks evidence on the direct effects of CAPN10 polymorphisms on calpain-10 enzyme activity, pancreatic β-cell processes, and insulin resistance at the molecular level. The absence of functional studies prevents scientists from determining if CAPN10 genetic variations directly cause Type 2 Diabetes or if they correlate with the disease because of regional hereditary elements.

The emergence of population bias presents a problem because researchers have conducted their studies mostly within specific ethnic groups. CAPN10 exhibits robust linkages with type 2 diabetes in North African, Middle Eastern, and Latin American populations, but researchers have not established its importance within European and East Asian groups. The investigation of genetic relationships should focus on establishing results across different population groups using expanded research pools.

CONCLUSION

This systematic review highlights the complex and population-specific role of CAPN10 polymorphisms in T2DM susceptibility and metabolic traits. While certain SNPs (SNP-19, SNP-43, SNP-44) have been linked to T2DM in some populations, others have shown no significant associations. Additionally, haplotype analysis suggests that combinations of CAPN10 polymorphisms may be more predictive of T2DM risk than individual SNPs alone.

Authors' Contributions
Conceptualization: SN, LN, ABAB, SS
Methodology: SN, LN, ABAB, SS
Formal Analysis: SN, LN
Writing, Reviewing, and Editing: SN, LN, ABAB, SS, AI

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