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CUBN GENE POLYMORPHISMS AND SUSCEPTIBILITY TO TYPE 2 DIABETES VERSUS TYPE 1 DIABETES: A SYSTEMATIC REVIEW

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Abstract

The CUBN gene polymorphisms have been implicated in the pathogenesis of diabetes mellitus, encompassing both type 1 diabetes and type 2 diabetes. Nevertheless, the outcomes have been erratic.

We conducted a comprehensive review to examine the connections. The literature was obtained from PubMed, ISI Web of Science, EmBase, and Scopus databases. The systematic review of the relationships between CUBN gene polymorphisms and diabetes risk identified 8 studies based on the search technique and inclusion criteria. Every single study that was considered used a case-control methodology. There was no study that was not considered to be of "high" or "medium" quality. The CUBN gene polymorphism in type 2 diabetes was the subject of five investigations involving 54,0970 patients and 435,312 controls.

The CUBN gene polymorphism in type 1 diabetes was the subject of three studies including 19,660 patients and 388,374 controls. The majority of the research were conducted in European communities, with one study specifically focusing on American groups.

Finally, the investigations varied in the platform utilized for genotyping or sequencing. While the study uncovers a new connection between the CUBN gene polymorphism and type 1 diabetes, the specific mechanism by which this polymorphism increases the chance of developing diabetes requires additional exploration.

The results offer fresh perspectives on the genetic structure of albuminuria and emphasize specific genes and pathways that can be targeted to prevent kidney damage associated with type 2 diabetes.

Our findings suggest that the CUBN gene may play a significant role in the genetic vulnerability to diabetes in individuals of European and American descent. Nevertheless, the generalizability of these findings to other ethnic groups remains unknown due to the previously documented significant variations in the genetic structure of CUBN gene between European and African populations

Keywords: *. CUBN gene, diabetes mellitus, genetic polymorphism, systematic review.*

Introduction

Severe vascular complications can cause major injury and death in people with diabetes mellitus (DM), a prevalent chronic condition. The immune system attacks and destroys the pancreatic beta cells in type 1 diabetes mellitus (T1D). Although they only account for about 5-10% of all diabetes cases

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globally, T cells are the principal culprits in this disease [*Roep B et al., 2021*]. Type 2 diabetes mellitus (T2D), affecting 90-95% of patients with diabetes, arises from inadequate insulin production in response to insulin resistance [*Galicia-Garcia U et al., 2020*]. Both types of diabetes can be influenced by environmental factors such as location, body mass index, food choices, and level of physical activity. Nevertheless, hereditary susceptibilities play a significant role in both forms of DM [*Polychronakos C, Li Q, 2011; Colberg S et al., 2016*].

Cubilin (CUBN) is a 460-kDa protein found in the plasma membrane and expressed in many different organs, such as the proximal tubules of the kidneys, the placenta, the lining of the intestines, and maybe even the thymus [*Christensen E, Nielsen R, 2007*]. Endocytosis of the complex 25(OH)D3-DBP is completely reliant on the membrane proteins megalin and *CUBN gene* in the kidney, which is responsible for producing the vast majority of systemic 1,25(OH)2D3 [*Christensen E, Birn H, 2001; Willnow T, Nykjaer A, 2002*]. Steroid hormones are thought to penetrate cells only through passive diffusion across the plasma membrane. Recent research has discovered an endocytic pathway that is responsible for delivering the steroid 25-hydroxyvitamin D3 to the kidney [*Nykjaer A et al., 1999*]. This discovery resulted in a revised understanding that endocytosis may have a significant impact on the specific targeting and absorption of steroid hormones by different types of cells.

The importance of *CUBN gene* in the 25(OH)D3-DBP complex's endocytic route has recently been highlighted by additional research. New research shows that when dogs and humans both lose a functional *CUBN gene*, 25(OH)D3 is lost in urine and plasma levels of 25(OH)D3 and 1,25(OH)2D3 drop [*Nykjaer A et al., 2001*]. Previous research on the possible functions of these common single nucleotide polymorphisms (SNPs) in T1D and T2D has yielded contradictory findings; thus, we performed a revised meta-analysis to draw a more solid conclusion regarding the importance of the associations between the four common polymorphisms in the *CUBN gene* and susceptibilities to T1D and T2D.

Material and methods

This investigation followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, encompassing literature searching, inclusion and exclusion criteria, data extraction, quality evaluation, and statistical analysis [*Moher D et al., 2010*]. Ethical approval was unnecessary as we did not conduct any experiments involving human volunteers or animals.

Search strategy: A comprehensive search was performed in PubMed, ISI Web of Science, Scopus, Cochrane Library, and Embase Data. The main search terms and Medical Subject Headings (Mesh) utilized were: ("type 2 diabetes mellitus" OR "NIDDM" OR "type 1 diabetes mellitus" OR "IDDM" OR "diabetes mellitus") AND ("cubilin" OR "CUBN") AND ("polymorphisms" OR "single nucleotide polymorphism" OR "SNP" OR "variation"). The search approach employed a synthesis of the chosen keywords to identify all possible articles. The investigations utilized Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) and allelic discrimination technique employing Taq-Man Real-time PCR to determine the genetic makeup of the four CUBN gene polymorphisms. In addition, the original and review articles were analyzed for cross-references in order to find possible publishing. Only the study with the largest sample size was taken into account if multiple articles were published using the same study data. The literature search was updated on February 29th, 2024.

Inclusion and Exclusion criteria: The inclusion criteria were employed to ascertain the studies that were incorporated. (1) An unpublished study; (2) research that compares a group of individuals with a particular condition (cases) to a group without the condition (controls) or a study that tracks a group of individuals over a period of time; (3) a study that examines the links between specific variations in the *CUBN gene* and the likelihood of developing T1D or T2D; and (4) a study that offers sufficient data to compute the odds ratio (OR) along with a 95% confidence interval. The analysis excluded studies that met the following criteria: (1) being confined to case reports or review papers; (2) including cases with other disorders, such as osteoporosis or coronary heart disease; or (3) relying on pedigree data for the study.

Data extraction: The findings of each inquiry are as stated below: The following contains the necessary information: The necessary data comprises the following: (1) the name of the primary author, (2) the year of publication, (3) the country of origin, (4) the ethnicity of the study population, (5) the gender distribution and mean age of participants in both the case and control groups, (6) the average age at which symptoms appeared in the case group, (7) the distribution of genotypes in both the case and control groups, and (8) the p value for the Hardy-Weinberg equilibrium test in the control group. Further information is required. Two authors conducted separate evaluations of each paper to assess their suitability for inclusion. We engaged in extensive deliberation until we achieved unanimity on all issues.

Quality assessment: To assess the methodological rigor of the studies included in the analysis, two reviewers employed the Newcastle-Ottawa Scale. The Newcastle-Ottawa Scale consists of nine aspects: Selection, Comparability, and Exposure. The rating scale ranges from zero to nine stars, with studies scoring 0-3, 4-6, or 7-9 categorized as low, moderate, or high-quality, respectively [*Stang A, 2010*].

Statistical analysis: This research looked at the associations between polymorphisms in the *CUBN gene* and the likelihood of getting type 1 or type 2 diabetes. Pooled odds ratios (ORs) with 95% confidence intervals were calculated using a multiplicative genetic model. Z tests were used to determine whether the combined odds ratios (ORs) were statistically significant. For statistical purposes, a p-value below 0.05 was considered important. Using the Q-statistic and the I^2-statistic, we checked for study heterogeneity [*Higgins J et al., 2003*]. The pooled odds ratios were calculated using either the random-effects model (Der Simonian-Laird technique) or the fixed-effects model (Mantel-Haenszel method) [*Dettori J et al., 2022*], depending on the existence ($p < 0.10$) or absence ($p \geq 0.10$) of heterogeneity. A meta-regression analysis was conducted using maximum likelihood estimation to investigate the potential sources of heterogeneity among studies. An investigation was conducted to examine subgroups based on ethnicity. A sensitivity analysis was conducted by systematically deleting one study at a time to assess the robustness of the findings. The Begg's funnel plot, which is a scatter plot of the effect size plotted against the sample size, was created to visually identify any bias or systematic heterogeneity [*Begg C, Mazumdar M, 1994*]. Egger's test was used to evaluate publication bias, with statistical significance set at $p<0.05$. The data was analyzed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

RESULTS

Characteristics of the studies: You can see all the processes we took to search the literature in figure. The characteristics of the studies are listed in table 1. The systematic review of the relationships between *CUBN gene* polymorphisms and diabetes risk identified 8 studies based on the search technique and inclusion criteria. Every single study that was considered used a case-control methodology. There was no study that was not considered to be of "high" or "medium" quality. The *CUBN gene* polymorphism in T2D was the subject of five investigations involving 54,0970 patients and 435,312 controls (Table 1). The *CUBN gene* polymorphism in T1D was the subject of three studies including 19,660 patients and 388,374 controls (Table 1). The majority of the research were conducted in European communities, with one study specifically focusing on American groups. Finally, the investigations varied in the platform utilized for genotyping or sequencing, as indicated in table 1. Most of the research employed Next-Generation Sequencing technology, with six investigations. Among these, two studies utilized various forms of Genome-Wide Association research (GWAS), two studies employed RFLP-PCR, and one study used Exome-Wide Association investigations (ExWAS).

CUBN gene polymorphism and T1D: First selected study showed that shed light on the genetic architecture of genes and pathways that are targets for preventing kidney disease associated with diabetes [*Ahluwalia T et al., 2019*]. Data from 33,985 European-ancestry people (15,872 with and 18,113 without diabetes) and 2605 Greenlanders were used in a two-stage exome-wide association research to discover coding variations. They found an uncommon missense mutation (A1690V) in the *CUBN gene* that is related with T1D as a continu-

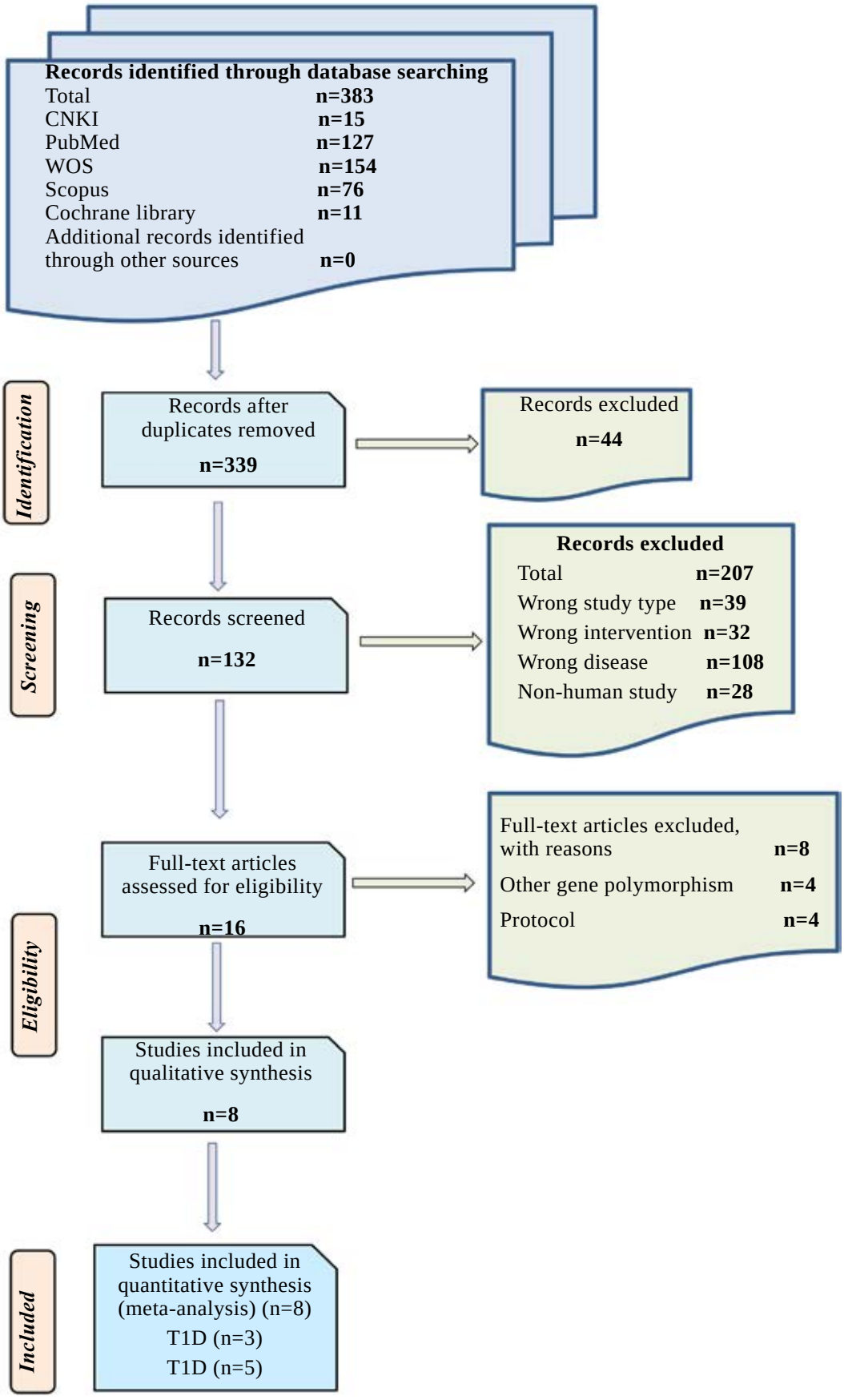

Figure 1: Selection of articles for inclusion in the study

TABLE 1

Summary of selected studies related to *CUBN* gene polymorphisms in type 1 diabetes (T1D) and type 2 diabetes (T2D)

Study ID, Country	Ethnicity	Population		Age		Genotyping Method	Findings	Quality Score
		Case	Control	Case	Control			
T2D								
Greece (Tsekmekidou et al., 2020)	Euro.	716	542	68.93 ± 9.53	73.53 ± 7.15	RFLP-PCR	SA	8
Germany (Albert et al., 2019)	Euro.	39, 17.97	178, 82.0	66.5	68	Taq-Man	NA	7
Mix Europe (Ahluwalia et al., 2019)	Euro.	15,872	18,113	68.1 ±7.7	48.6 ±13.7	ExWAS	SA	7
Mix Europe (Uglebjerg et al., 2023)	Euro.	31,155	370,061	30.77 ± 5.70	27.10 ± 4.50	GWAS	SA	8
USA (Ma et al., 2016)	USA	529	535	61.6±10.5	49.0±11.9	AXIOM	SA	8
Mix Europe (Teumer et al., 2016)	Euro.	5,825	4,6061	57	56.5	GWAS	SA	8
T1D								
Mix Europe (Ahluwalia et al., 2019)	Euro.	15,872	18,113	23.1 ±9.9	48.6 ±13.7	ExWAS	SA	8
Mix Europe (Uglebjerg et al., 2023)	Euro.	3,588	370,061	29.40 ± 4.80	27.10 ± 4.50	GWAS	SA	8
Germany (Ramos-Lopez et al., 2010)	Euro.	200	200	11.5 ± 4.51	13.23 ± 4.16	RFLP-PCR	SA	7

NOTES: *AXIOM, Affymetrix Axiom Biobank Genotyping Array; GWAS, Genome-wide association study;* ExWAS, *Exposome-wide association study; RFLP-PCR, restriction fragment length polymorphism-PCR,* Significant association -SA,No association NA

ous measure in the combined European population (rs141640975, p= 1.3×10^{-11}). In a separate study, researchers used four *CUBN* missense variants in T1D populations from several European cohort studies and non-diabetic individuals from the UK Biobank – to conduct a genetic association-based linear regression analysis [*Uglebjerg N et al., 2023*]. The strong correlations between diabetes and the four *CUBN* missense variations (rs141640975, rs144360241, rs45551835, rs1801239) point to *CUBN*'s multifaceted function and highlight the need for additional research into the potential role of CUBN in the future of diabetes-related problem personalization. Using RFLP-PCR, the third study that was chosen genotyped people with T1D as well as healthy controls for five polymorphisms that were found within the *CUBN gene* [*Ramos-Lopez E et al., 2010*]. While the study uncovers a new connection between the *CUBN gene* polymorphism and T1D, the specific mechanism by which this polymorphism increases the chance of developing diabetes requires additional exploration (Table 2). ***CUBN gene* polymorphism and T2D:** In the first selected study [*Tsekmekidou X et al., 2020*], to determine the role of *CUBN gene* variations in the heritability of T2D, genotyped this gene in 716 individuals diagnosed with the disease and 542 healthy controls of Greek descent. The findings from their study suggest that the *CUBN gene* may have a significant role in the genetic vulnerability to T2DM in the Greek population. Ma J. et al. (2016) examined data from next-generation exome sequencing (NGES) to investigate the impact of genetic variations in the *CUBN gene* on the risk of T2D and diabetes-associated kidney complications in black Americans. They showed that evidence for genetic association exists between a *CUBN gene* variant with the risk of T2D and diabetes-associated kidney complications in populations with recent African ancestry. Teumer A. et al. (2016) performed functional studies after GWAS and independent replication in up

Table 2

Associations for the *CUBN gene* polymorphism and diabetes

Study Id, Databases	SNP (rsID)	Genotype (Number)					
		Diabetes			Control		
T1D							
Mix Europe [*Ahluwalia, TS, et al*., 2019] AFTEREU cohort	rs1801239	CC (10)	CT (146)	TT (698)	CC (4,033)	CT (68,575)	TT (297,244)
UK-ROI cohort		CC (15)	CT (193)	TT (851)	CC (4,033)	CT (68,575)	TT (297,244)
GENESIS cohort		CC (17)	CT (259)	TT (1048)	CC (4,033)	CT (68,575)	TT (297,244)
Mix Europe [*Ahluwalia, TS, et al*., 2019] AFTEREU cohort	rs141640975	AA (0)	AG (8)	GG (846)	AA (0)	AG (101)	GG (289)
Germany [*Ramos-Lopez, E, et al*., 2010]	rs3740165	AA (52)	AG (88)	GG (60)	AA (10)	AG (101)	GG (89)
	rs2796835	GG (0)	GC (0)	CC (200)	GG (0)	GC (0)	CC (200)
	rs1801233	AA (12)	AG (188)	GG (0)	AA (6)	AG (194)	GG (0)
	rs3740168	CC (0)	CG (7)	GG (193)	CC (0)	CG (2)	GG (198)
	rs1801229	GG (9)	GA (7)	AA (184)	GG (4)	GA (0)	AA (196)
T2D							
Germany [*Albert, C, et al*. 2019]	rs1801239	CC (2)	CT (8)	TC (22)	CC (2)	CT (27)	TC (133)
Mix Europe [*Ahluwalia, TS, et al*., 2019]	rs141640975	AA (1)	AG (66)	GG (3,806)	AA (1)	AG (152)	GG (9,270)
Mix Europe [*Ahluwalia, TS, et al*., 2019] DiaGene cohort	rs1801239	CC (3)	CT (1,681)	TT (0)	CC (4)	CT (1465)	TT (0)
Rotterdam cohort		CC (15)	CT (209)	TT (798)	CC (11)	CT (198)	TT (698)
ANDIS cohort		CC (89)	CT (1,653)	TT (7,625)	CC (3,937)	CT (64,572)	TT (291,240)
UKBB cohort		CC (153)	CT (2,839)	TT (11,888)	CC (3,937)	CT (64,572)	TT (291,240)

to 5,825 European ancestry diabetics and up to 46,061 non-diabetic individuals to gain insight into a CUBN gene variant associated with the risk of T2D and diabetes-related kidney complications. They observed several intriguing signals among persons with diabetes, and gene-by-diabetes interactions were confirmed for variations in the *CUBN gene*. Albert C. et al. (2019) examined the correlation between genetic variations in functional polymorphisms of matrix metalloproteinase and CUBN gene with the occurrence of diabetic nephropathy, end-stage renal disease, and cardiovascular disease in Caucasian individuals with T2D. The findings suggest that CUBN-SNPs may have an impact on the likelihood of developing T2D, diabetic nephropathy, or end-stage renal disease. Ahluwalia T.S. et al. (2019) conducted an exome-wide association study using a two-step strategy consisting of a discovery stage and a replication stage to detect coding variations. The study contained data from 33,985 adults of European descent, consisting of 15,872 persons with diabetes and 18,113 individuals without diabetes. Additionally, data from 2605 Greenlanders were also included. The investigation has identified a scarce coding variation in the *CUBN gene* linked to albuminuria in diabetic and non-diabetic patients. These genes have been linked to malfunction in the kidneys and heart. The results offer fresh perspectives on the genetic structure of albuminuria and emphasize specific genes and pathways that can be targeted to prevent kidney damage associated with T2D (Table 2).

DiscussionVitamin D plays a crucial role in various biological processes, including regulating the immune system, modulation of insulin secretion, and enhancing insulin resistance [*Lemire J, 2000; Pittas A, et al., 2007*]. These processes are closely related to the development of diabetes mellitus and are susceptible to the effects of different gene polymorphisms such as CUBN gene [*Akhlaghipour I et*

al., 2022]. To address the conflicting findings of previous research with limited sample sizes, we conducted a systematic study to elucidate the relationship between CUBN gene polymorphisms and the likelihood of developing T1D and T2D. As far as we know, this is the initial comprehensive evaluation examining the connection between variations in the *CUBN gene* and both T1D and T2D. Our analysis indicates a strong association between a specific variation in the CUBN gene and the likelihood of developing both T1D and T2D, particularly among individuals of European descent.

The findings of our study indicate that there is an association between the *CUBN* polymorphisms (namely rs1801239, rs141640975, and rs1801239) and T2D. These intronic variations have not been previously associated with T2D. However, it is still uncertain if these variations result in an altered function of the protein that is encoded. There has been no exploration of the relationship between *CUBN* and T1D. However, variations in the genes involved in the vitamin D pathway are linked to T1D and impact the levels of 25(OH)D3 or their mRNA expression. Furthermore, compelling data indicates that early-life Vitamin D supplementation decreases the likelihood of developing T1D. Therefore, future studies should investigate the precise molecular processes linking these SNPs with T1D and T2D. In a study, researchers primarily examined the influence of the rs3740165 polymorphism in the *CUBN gene* on the likelihood of developing T1D in the German population. This is significant because other genes in the vitamin D cascade have been linked to T1D. Based on their data, the researchers found that *CUBN* polymorphism was more common in individuals with T1D compared to the healthy control group. Therefore, the CUBN gene could contribute to the susceptibility of T1D. The data from another study, when paired with our results, may indicate that *CUBN* polymorphisms play a role in the development of dysglycemia, regardless of the specific type of diabetes [*Ramos-Lopez E et al., 2010*]. Contrary to what we observed, the authors were unable to demonstrate a correlation between rs3740165 or other SNPs and concentrations of 25(OH)D or 1,25(OH)2D [*Krasniqi E et al., 2021*].

It is still necessary to determine whether the connections revealed in the previous investigations are causal [*Ma J et al., 2016; Teumer A et al., 2016; Ahluwalia TS et al., 2019*]. Based on the cumulative evidence, it is possible to hypothesize that mutations in the *CUBN gene* play a role in the genetic predisposition to different types of diabetes and associated complications.

LIMITATIONS

Our review has some limitations. The recruitment of study participants was limited to two prominent European diabetes centers, resulting in a restricted number of people enrolled. Furthermore, the diagnosis of T2DM in the various studies included primarily relied on fasting plasma glucose and hemoglobin A1c levels. Participants were not assessed using the Oral Glucose Tolerance Test, considered the most sensitive approach for diagnosing diabetes [*Association, AD,* 2020]. Third, our review did not evaluate the impact of gene-gene and gene-environment interactions on the development of DM, as there was insufficient data available from the papers included in our study.

CONCLUSION

Our findings suggest that the *CUBN gene* may play a significant role in the genetic vulnerability to DM in individuals of European and American descent. Nevertheless, the generalizability of these findings to other ethnic groups remains unknown due to the previously documented significant variations in the genetic structure of *CUBN gene* between European and African populations. Our data suggest that there may be an indirect impact of dysregulation in vitamin D metabolism on the development of DM. Furthermore, due to our restricted sample size and the highly variable nature of the CUBN gene region, it is not possible to draw a definitive conclusion. However, this work is the first to establish a connection between a variation of the CUBN gene and T1D and T2D. Additional research is necessary to reproduce our results and elucidate the intricate underlying mechanisms.

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