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Review - Human and Animal Health

Polymorphisms in the SUMO4 Gene Region and Type 1 Diabetes Mellitus in Non-Asian Populations: A Scoping Review

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HIGHLIGHTS

- This scoping review evaluated the SUMO4 and T1D association in non-Asians.
- It is the first study that investigates SUMO4 and T1D association in non-Asians.
- SUMO4 does not appear to affect the risk of T1D in non-Asian populations.

ABSTRACT: Type 1 diabetes mellitus (T1D) is a complex autoimmune disease resulting from pancreatic insulin-producing cell destruction. Numerous studies have investigated the association between the Small Ubiquitin-like Modifier 4 (SUMO4) gene and the risk of T1D development. However, these findings are not consistent, particularly in non-Asian populations. This scoping review aims to comprehensively assess the association between the SUMO4 gene and TD1 in individuals of non-Asian origin. A systematic search of electronic databases was performed, including Web of Science, PubMed, Embase and Scopus. Case-control studies and prospective cohorts that provided relevant information for the association analysis were included. 6,841 articles were initially identified through database searches. After removing duplicates, 3,835 articles remained for screening. Twenty-five studies underwent full-text analysis, with nine being included in the scoping review after 16 were excluded. These studies utilized various genotyping methods, including PCR-ARMS, SSCP, RFLP, and genotyping platforms such as ILMN and SQMN. While some studies reported the male/female ratio, others focused on family studies or diabetic probands. The research was predominantly conducted in North America, Europe, Oceania, and Argentina. Across these studies, no significant evidence

linking SUMO4 SNPs to T1D was found, except for marginal associations or those dependent on high-risk HLA genotype positivity. No significant association was detected between the SUMO4 gene and T1D in non-asian individuals. This finding suggests that polymorphisms in this gene might not play a substantial role in susceptibility to T1D in the investigated population.

Keywords: Diabetes mellitus; insulin-dependent diabetes; SNPs; Euro-descendant; rs237025.

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder mainly characterized by chronic hyperglycemia that affects approximately 537 million people worldwide, aged between 20 and 79 years [1, 2]. This disease is associated with vascular complications that impact the life expectancy of this population, such as diabetic nephropathy, retinopathy, and neuropathy [3]. This illness represents a high-cost burden on healthcare systems worldwid [3].

It can be classified conventionally into several clinical categories, although these are being reconsidered based on genetic, metabolomic, and other characteristics and pathophysiology, type 1 or type 2 diabetes, gestational diabetes mellitus, and other specific types derived from other causes [4].

The type 1 diabetes mellitus (T1D) accounts for about 5% of all diagnoses [5] and stems from a complex interaction between environmental factors, microbiome, genome, metabolism and the immune system [6], which leads to hyperglycemia by autoimmune destruction of insulin-producing pancreatic beta cells [7, 8].

The disorder is understood to be triggered by environmental factors, leading to an autoimmune response in genetically susceptible individuals [7, 9, 10]. The influence of specific genetic loci is critical in the disease development, with the HLA region (Human Leukocyte Antigen) on chromosome 6 [11-13] and the insulin gene (INS) on chromosome 11 contributing to approximately 50% and 10% of the inherited risk for the illness, respectively [11, 14, 15].

Numerous genes have already been linked to the risk of T1D [12, 16-18] and to an increased susceptibility to complications, such as kidney failure or blindness in individuals with uncontrolled glycemic levels [19-21]. However, genetic associations are not uniform, posing a challenge for research into inherited risk of T1D, as the frequencies of several molecular markers vary greatly across different regions of the world [13, 22].

Genes such as *PTPN22* (Protein Tyrosine Phosphatase Non-receptor type 22) and *CTLA*-4 (Cytotoxic T-Lymphocyte Associated Protein 4) have been associated with risk for the disease, especially in Asian populations [23, 24]. Others, such as *MMP*-2 (Matrix Metallopeptidase 2) and *ACE* (Angiotensin I Converting Enzyme), have been associated with complications such as nephropathy and diabetic retinopathy [21, 25].

The gene *SUMO4* (Small Ubiquitin-Like Modifier 4) is located on chromosome 6, within a region linked to susceptibility to T1D, specifically at the IDDM5 locus (Insulin-Dependent Diabetes Mellitus 5) [26, 27]. This gene produces a 95-amino acid protein [27] with the same name [28], which plays a role in modifying post-translational cytosolic proteins (Figure 1) [29], influencing processes such as cell cycle progression and gene transcription [30].

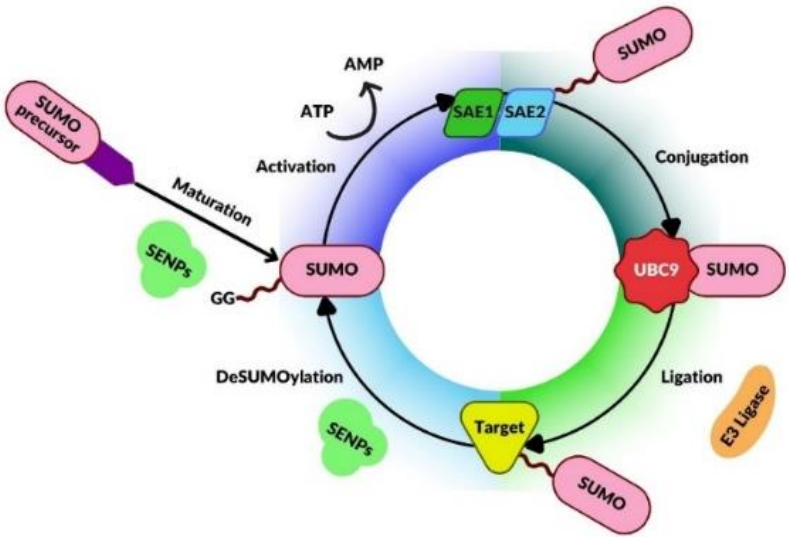

Figure 1. Protein SUMOylation and DeSUMOylation process

SUMOylation and deSUMOylation are finely regulated processes that maintain dynamic equilibrium under physiological conditions. SUMO proteins are initially processed by SUMO-specific proteases, such as SENP, to yield their mature forms. These mature SUMO proteins are then activated by the heterodimeric enzyme complex SAE1/SAE2 in an ATP-dependent manner. The E2 enzyme UBC9 mediates the transesterification reaction, forming a conjugate with SUMO, while SUMO E3 ligases facilitate the transfer of SUMO moieties to target proteins at designated lysine residues, thereby completing the SUMOylation process. Conversely, SUMOylated proteins are deconjugated by SENP, which cleaves the SUMO-protein bond, restoring the target proteins to their unmodified state. This reversible interplay between SUMOylation and deSUMOylation ensures a delicate balance crucial for cellular homeostasis. (Microsoft PowerPoint 2019. Canva. Online version. Available at: https://www.canva.com/.).

This gene has a functional polymorphism, the rs237025, which has been described and studied in many works. It has already been associated with T1D, mainly among East Asian populations [31, 32]. This Single Nucleotide Polymorphism (SNP) promotes the replacement of a methionine amino acid by valine at position 55 of the protein [28], which can lead to increased transcription of genes involved in the immune response [33] such as IL-1α & β (Interleukin 1-alpha & beta), IL-2, 6, 12 Interleukin 2, 6 12), in addition to TNF-α (Tumor Necrosis Factor Alpha) and IL-2Rα (Interleukin 2 Receptor Subunit Alpha) [34].

SNPs, such as rs237025, are the most common form of genetic variation in the human population and are characterized by substituting a single nitrogenous base in DNA in coding or non-coding regions. Their presence can influence susceptibility to diseases, medications response, and other phenotypic aspects. In DM, the genetic component is significant and SNPs can help identify risk variants, and serve as genetic markers of predisposition [35, 36].

These variations can cause amino acids modification in proteins (missense variants) [37] or not if present in coding regions of the genes that are transcribed into these proteins (synonymous variants) [38]. They can also affect the premature termination of transcription (nonsense variants) by placing a stop codon in a different location than the original, resulting in incomplete transcripts and shortened, likely non-functional proteins [39]. Therefore, studying SNPs in complex diseases such as DM can be a valuable strategy for elucidating pathogenic mechanisms that contribute to the risk of developing the disease [40].

However, as in other association studies, mainly involving genes with minor participation in the pathophysiology of the disease, the association of *SUMO4* and its SNPs is not consistent. It is notably significant among Asians but yields dissimilar results among individuals of European descent [[31, 33]. Thus, the objective of this study was to gather and collectively evaluate the available evidence to investigate the association of the *SUMO4* gene and T1D among non-Asians in scoping review research.

RESEARCH DESIGN AND METHODS

Methodology

The scoping review was conducted following the guidelines set by the Joanna Briggs Institute [[41] and the results are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) Checklist [42]. The study protocol was registered on the Open Science Framework (OSF), and additional information can be found using the provided link. https://doi.org/10.17605/OSF.IO/WDTE5

Research Strategy

The study was conducted through a scoping review of the literature in electronic databases of indexed journals, assessed between April and July 2024 and revised in May 2025, after the research question that was defined based on the following question: "*Does the SUMO4 gene contribute to T1D predisposition in non-Asian, Euro-descendant, or mixed-race populations, such as those from the American continent?".*

The research was conducted in four databases - PubMed, Scopus, Web of Science and Embase - without time or language restrictions (Table 1). Each database employed a specific search strategy. Search terms related to *SUMO4* gene, T1D, polymorphisms and diabetes mellitus were combined using the Boolean operators "OR" and "AND". In addition, a manual search was conducted by reviewing the reference lists of the articles that are included in the study, as well as a gray literature search in internet search engines looking for works not detected by the search tools.

Table 1. Research strategies for PubMed, Scopus, Web of Science, and Embase articles

Database	Queries
PubMed	((((((((((polymorphism, genetic[MeSH Terms]) OR (SUMO4[Title/Abstract])) OR ("Small ubiquitin-like modifier 4"[Title/Abstract])) OR (rs237025[Title/Abstract])) OR (A163G[Title/Abstract])) OR (m55v[Title/Abstract])) OR (met55val[Title/Abstract])) OR (SNP[Title/Abstract])) OR ("single nucleotide polymorphism"[Title/Abstract])) OR (polymorphism[Title/Abstract])) AND (((((Diabetes Mellitus, Type 1[MeSH Terms]) OR ("Diabetes Mellitus, Type 1"[Title/Abstract])) OR (T1D[Title/Abstract])) OR (LADA[Title/Abstract])) OR ("Latent autoimmune diabetes of adults"[Title/Abstract]))
Scopus	((TITLE-ABS-KEY ("Diabetes Mellitus, Type 1") OR TITLE-ABS-KEY (t1d) OR TITLE-ABS-KEY (lada) OR TITLE-ABS-KEY ("Latent autoimmune diabetes of adults"))) AND ((TITLE-ABS-KEY (sumo4) OR TITLE-ABS-KEY ("Small ubiquitin-like modifier 4") OR TITLE-ABS-KEY (rs237025) OR TITLE-ABS-KEY (a163g) OR TITLE-ABS-KEY (m55v) OR TITLE-ABS-KEY (met55val) OR TITLE-ABS-KEY (snp) OR TITLE-ABS-KEY ("single nucleotide polymorphism") OR TITLE-ABS-KEY (polymorphism)))
Web of Science	SUMO4 (Topic) or "Small ubiquitin-like modifier 4" (Topic) or rs237025 (Topic) or A163G (Topic) or m55v (Topic) or met55val (Topic) or SNP (Topic) or "single nucleotide polymorphism" (Topic) or polymorphism (Topic) AND "Diabetes Mellitus, Type 1" (Topic) or T1D (Topic) or LADA (Topic) or "Latent autoimmune diabetes of adults" (Topic)
Embase	('diabetes mellitus, type 1':ti,ab,kw OR t1d:ti,ab,kw OR lada:ti,ab,kw) AND 'latent autoimmune diabetes of adults':ti,ab,kw AND sumo4:ti,ab,kw OR 'small ubiquitin-like modifier 4':ti,ab,kw OR rs237025:ti,ab,kw OR a163g:ti,ab,kw OR m55v:ti,ab,kw OR met55val:ti,ab,kw OR snp:ti,ab,kw OR 'single nucleotide polymorphism':ti,ab,kw OR polymorphism:ti,ab,kw

Terms applied to the search strategies of this review in the Pubmed, Scopus, Web of Science and Embase databases. MeSH terms: OR; definition of diabetes: diabetes mellitus, type 1, T1D, LADA, latent autoimmune diabetes of adults; gene/polymorphism: SUMO4, small ubiquitin-like modifier 4, rs237025, A163G, met55val, SNP, single nucleotide polymorphism, polymorphism.

Eligibility criteria

The article selection process consisted of two steps. First, research was conducted in the aforementioned databases. Findings were collected using the Rayyan web platform (https://rayyan.ai/users/sign_in), and duplicates were subsequently identified and removed. During the initial step, only the titles and abstracts of the articles were independently assessed by two reviewers. Articles meeting the inclusion criteria underwent a comprehensive review of their full texts to determine their suitability for inclusion in this review, based on the eligibility criteria. In cases of discrepancies, a third reviewer was consulted. Articles that did not meet the eligibility criteria were excluded from consideration.

We included studies that addressed the research question and involved non-Asian populations of volunteers diagnosed with T1D and LADA. Although previously considered a distinct subtype, Latent Autoimmune Diabetes in Adults (LADA) is now understood to fall within the same spectrum as T1D.

The exclusion criteria adopted were a) research involving participants diagnosed with medical conditions distinct from T1D; b) literature reviews, book chapters, and conference meets; c) that did not describe the origin of the volunteers; and d) preclinical studies.

Data extraction

The investigators gathered pertinent data from chosen articles, analyzed and deliberated the primary outcomes of the studies, examined the findings and underlying trends, and drew relevant insights and conclusions from them. The relevant data from the selected articles and composed a table with all the information collected, such as author, year of publication, experimental design, number of volunteers, country, genotyping technique, markers analyzed and conclusion.

RESULTS AND DISCUSSION

A summary of the scoping review process is presented in the Figure 2, which displays the number of studies evaluated after applying the exclusion/inclusion criteria, until the final selection of works [43-51] whose summary is shown in Table 2.

The search carried out in databases resulted in an absolute number of 6841 articles, which after removing duplicates or ineligibility by automatic marking, was reduced to 3835. After reading the title and abstract and recovering works that were without abstract, the number of works was reduced to 25, of which 9 were finally included in this work and 16 were excluded for deviating from the proposal of this research. No additional study was included through manual search.

Of the studies excluded after reading their content in full, 5 addressed the wrong population (reason 1), 5 were the wrong type of publication (reason 2), 3 presented an experimental design that diverged from the objectives of this investigation (reason 3), 2 had the wrong outcome (reason 4) and 1 was not found (reason 5), as illustrated in Figure 2.

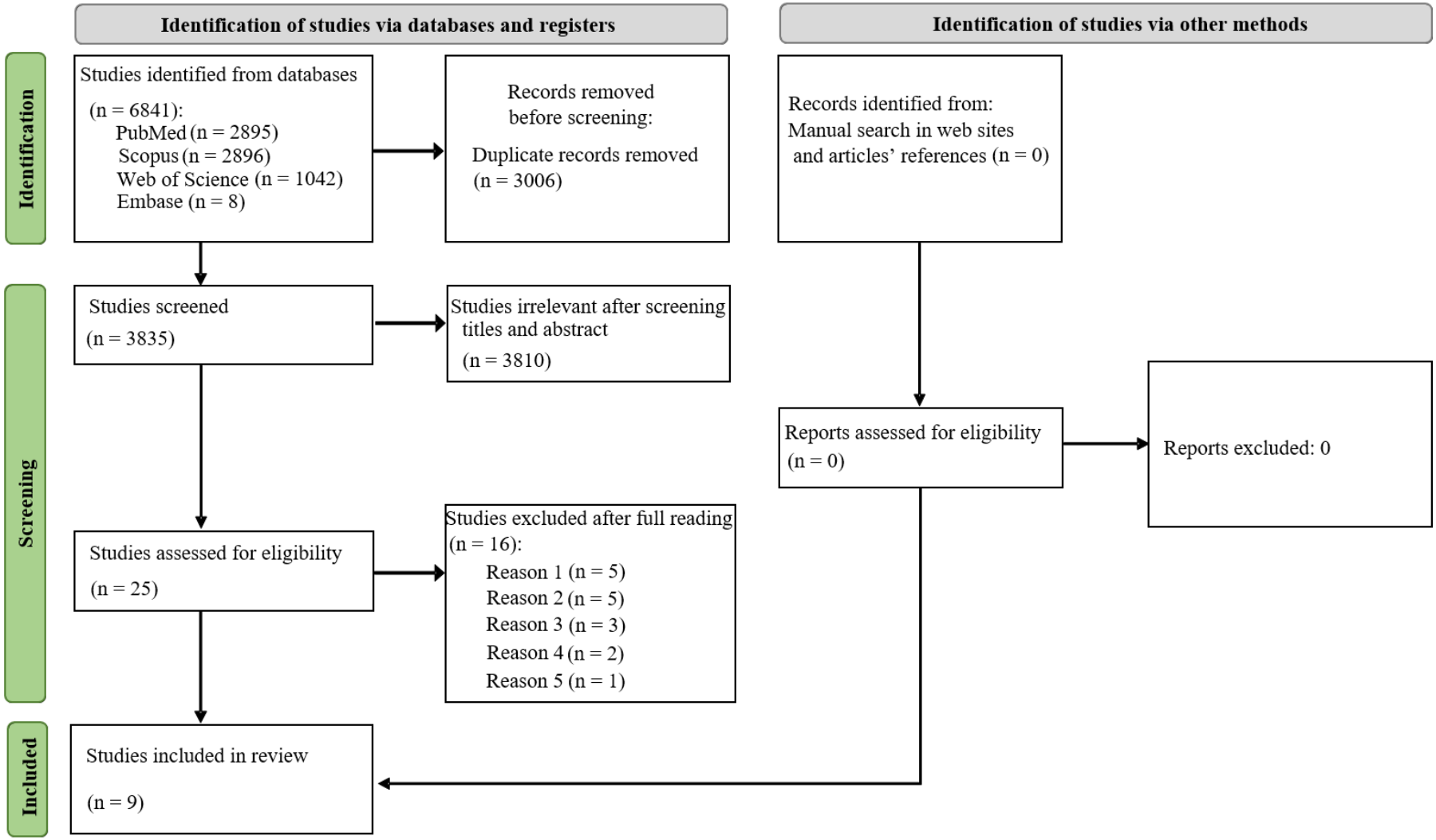

Figure 2. Research and design methods: scoping review process flowchart (42). Stages of the article scoping review process. Inclusion/exclusion criteria and total number of articles analyzed throughout the identification, screening and inclusion stages. Reasons for exclusion of articles in the screening phase: reason 1: wrong population; reason 2: wrong publication type; reason 3: divergent experimental design; reason 4: wrong outcome and reason 5: not retrieved.

Of the articles included, three of them were case-control studies (3/9 – 33.3%), which compare the events of an unaffected population with an affected one, and 6 were of the cohort type (6/9 – 66.6%), where a population was separated and the events observed in that group.

Table 2. Characteristics of the works included in this scoping review

Reference	Design	Volunteers	Country/ Region	SNP	Methods	Results
Caputo *et al*. (2007) [43]	Case-control	n = 62 volunteers with LADA n = 112 volunteers with T1D n = 129 non-diabetic volunteers	Argentina	rs237025	PCR-SSCP	The frequencies of the AA and AG genotypes were similar in the three groups and the frequency of the GG genotype was slightly higher in the control group; however, no significant association was observed in this study**
Howson et al. (2009) [44]	Cohort	n = 2300 families, representing a total of 9682 people.	Europe, North America, and Oceania	- -	*ILMN* and *SQMN*	No association of *SUMO4* with T1D was observed among the 15 genotyped SNPs (minimum P=0.09).
Julier *et al.* (2009) [45]	Cohort	n = 2298 families, representing a total of 11159 people.	Europe, USA, and Oceania	rs237025	*ILMN* and *SQMN*	No association of *SUMO4* alleles with T1D was observed in the study population. Genotypic and allelic frequencies were similar among volunteers in this cohort.**
Kosoy and Concannon (2005) [46]	Cohort	There were 554 families totaling 2604 people, with 1458 of them having T1D.	Europe, and USA	rs237025 rs237027 rs6942381	MGB-eclipse system	No significant evidence of association with T1D was observed for alleles of SNPs rs6942381 (P=0.498), rs237027 (P=0.657) and rs237025 (P=0.778).
Owerbach, Pina and Gabbay (2004) [47]	Cohort	n= 478 families, 256 from USA and 222 from UK.	USA, and United Kingdon	rs237025 rs237027 rs237034 rs237037 rs6942381 rs7896	PCR-SBE	SNPs alleles rs237025 (P≤0.006), rs237027 (P≤0.05), rs237034 (P≤0.006), rs6942381 (P≤0.006) and rs7896 (P≤0.01) were significantly more transmitted to probands with T1D.

Cont. Table 2

Podolsky, Prasad linga-reddy e She (2009) [48]	Cohort	n = 2317 families, with 11250 people in total, of which 5047 had T1D.	Europe, and Oceania	rs12204461 rs7742990 rs9373589 rs9404034 rs2789490 rs237032 rs237025 rs2789488 rs2789489 rs652921 rs366905 rs480034 rs236999 rs513923 rs9485389	*ILMN* and *SQNM*	Only rs236999 showed marginally significant association with T1D in both SNP genotyping platforms, ILMN (P=0.020) and SQMN (P=0.072). SNPs rs366905 and rs480034 showed marginally significant association (P<0.05), in both platforms, with T1D dependent on the positive HLA-DR4 genotype.
Sedimbi *et al.* (2007) [49]	Case-control	n = 673 diabetic volunteers n = 535 non-diabetic volunteers	Sweden	rs237025	PCR-RFLP	The GG genotype was associated with high-risk T1D in HLA-DR3/DR4 positive patients P≤0.0001
Sedimbi *et al*. (2006) [50]	Case-control	n = 46 volunteers with LADA n = 95 volunteers with T1D n = 100 non-diabetic volunteers	Latvia	rs237025	PCR-RFLP	There was no statistically significant difference for the frequencies of the G allele in the control, LADA (P=0.06) and T1D (P=0.09) groups. The comparison of *SUMO4* polymorphism with HLA-DR3 or DR4 positive and negative patients also did not identify any significant association.
Wägner *et al.* (2008) [51]	Cohort	n= 253 families, representing a total of 1097 people.	Denmark	rs237025	ARMS-PCR	The *SUMO4* functional variant was transmitted to 50.9% of affected offspring and 50.5% of unaffected offspring (P=0.767). No association was observed between *SUMO4* SNPs and transmission frequency among affected probands.

PCR-RFLP (Polymerase Chain Reaction - Restriction Fragment Length Polymorphism); PCR-SSCP (Polymerase Chain Reaction - single-strand conformation polymorphism); MGB (Minor Groove Binding); ILMN (Illumina); SQMN (Sequenom); SNP (Single Nucleotide Polymorphism); USA (United States of America); UK (United Kingdom); **Did not demonstrate P value.

Volunteers

Collectively, the sum of volunteers investigated in the selected studies was 37,544 people, including diabetic and non-diabetic individuals, 1752 of them in case-control studies and more than 35,792 in cohort studies.

Of the analyzed studies, two of them separately evaluated individuals with T1D (n = 207) and LADA (n = 108) [43, 50], while the others stated that they evaluated only volunteers with the diagnosis of T1D [44-49, 51].

Of the cohort studies that analyzed families with members with T1D, two of them highlighted the number of diabetic volunteers among all participants (1458 and 5047, respectively) [46, 48], while the others cite the total number of volunteers, without distinguishing between diabetics and controls: 4598 families composed of 20,841 individuals [44, 45]. The study of Owerbach, Pina and Gabbay (2004) cites that 478 families were included, 256 from the USA and 222 from the United Kingdom. However, the study did not specify the total number of volunteers or how many individuals were in each family [47].

Both men and women were analyzed by the works described in this scoping review and those with a case-control study indicate that there was pairing between the samples of volunteers by sex and age. Sedimbi, Luo and Sanjeevi (2007) included in their report a sample with a wide age range of volunteers, ranging from 0 to 35 years of life [49], as well as Sedimbi and coauthors (2006), which reported samples from individuals whose diagnosis ranged from a few months to 18 years of age [50]. Caputo and coauthors (2007) classified the age of the volunteers by diagnosis: LADA patients were diagnosed after age 35, with a mean age of 51.4 years and a standard deviation of 2.6 years, and T1D patients with a mean age at diagnosis of 15 years and a standard deviation of 9.2 years of age [43].

The study of Kosoy and Concannon (2004) reported that in families with affected sibling pairs, none had a sibling with T1D who 29 years was over old. Additionally, in all the families studied, at least one sibling was under the age of 17. [46]. Podolsky, Prasad Linga-Reddy and She (2009), Julier and coauthors (2009), and Howson and coauthors (2009) did not specify the age of the volunteers in their reports [44, 45, 48]. Owerbach, Pina and Gabbay (2004) indicated that the diabetic individuals in his study had an age at onset of the disease equal to or less than 18 years of age, while Wagner and coauthors (2008) study describes that the volunteers received the diagnosis of T1D before the age of 30, but in none of these studies was an average age presented for the population studied [47, 51].

These works were distributed geographically in two main continents: America and Europe, with 3 of them also indicating the participation of volunteers from the pacific. The countries where these volunteers originate from is Sweden [49], Argentina [43], Latvia [50], United States and United Kingdom [47] and Denmark [51]. Large continental extensions are also mentioned, such as Europe, North America and/or Oceania [44-46, 48].

Genotypic frequencies

The genotype frequency of the *SUMO4* gene rs237025 polymorphism among Swedes was 24.2% and 26.3% AA, 52.7% and 51.4% AG, and 23.0% and 22.2% GG, for diabetics and controls, respectively, with a G allele frequency of 49.4% and 47.9% in the same groups and P-value de 0.47 [49].

Among Argentineans, the frequency of the same allele was 48.8% between controls 45.5% for T1D patients and 48.4% for LADA patients [43]. Latvian controls had a frequency of 44.1% when compared to T1D patients and 47.8% when compared to LADA patients, while these patients had 53.1% and 59.7% frequency, respectively, without presenting, in any of these cases, a statistically significant association with the disease [50].

Kosoy and Concannon (2005) observed a frequency of 51.8% of the allele in cases of parental transmission, among families with affected sibling pairs, and the same frequency among families without transmission. Among the children of these families, those affected with T1D had a frequency of 53.2% of the allele and those unaffected of 52.4%, with a P-value of 0.778 and no significant association [46].

Podolsky, Prasad Linga-Reddy and She (2009) investigated 15 SNP markers described in the *SUMO4* gene region. Some of them, such as rs7742990, rs237032, and rs236999, showed a significant P-value in one of the genotyping platforms used in the study ($P < 0.05$), but not in another. This resulted in a marginally significant result only for the SNP rs236999 on the platform Sequenom, with $P = 0.07$. None of the other genotyped polymorphisms, including rs2789488, rs366905, and rs237025, yielded statistically significant results on either of the two platforms. Nonetheless, when investigating the association between T1D and *SUMO4* genotypes and *HLA* genotypes, the rs366905 SNP demonstrated a significant association ($P<0.05$) with T1D and displayed marginal significance based on *HLA* genotypes on both platforms. Furthermore,

rs480034 exhibited a significant association (P<0.05) on both genotyping platforms for both T1D and HLA genotype-dependent T1D [48].

Julier and coauthors (2009) and Howson and coauthors (2009), as well as Wagner and coauthors (2008), did not find evidence of an association between SNPs in the *SUMO4* gene region and T1D (P>0.05). This suggests that any association in non-Asian populations if it exists, may depend on other factors such as sample size or interaction with environmental triggers. This contrasts previous publications that demonstrated an essential role among Asians [44, 45, 51].

Owerbach, Pina and Gabbay (2004) found a statistically significant association for the Met/Val substitution of the rs237025 SNP (P≤0.01), as well as for the rs237027, rs237034, rs6942381, and rs7896 SNPs, but only among probands, indicating that *SUMO4* SNP alleles were significantly more transmitted to volunteers with T1D [47]. All polymorphisms covered in this review are described in Figure 3.

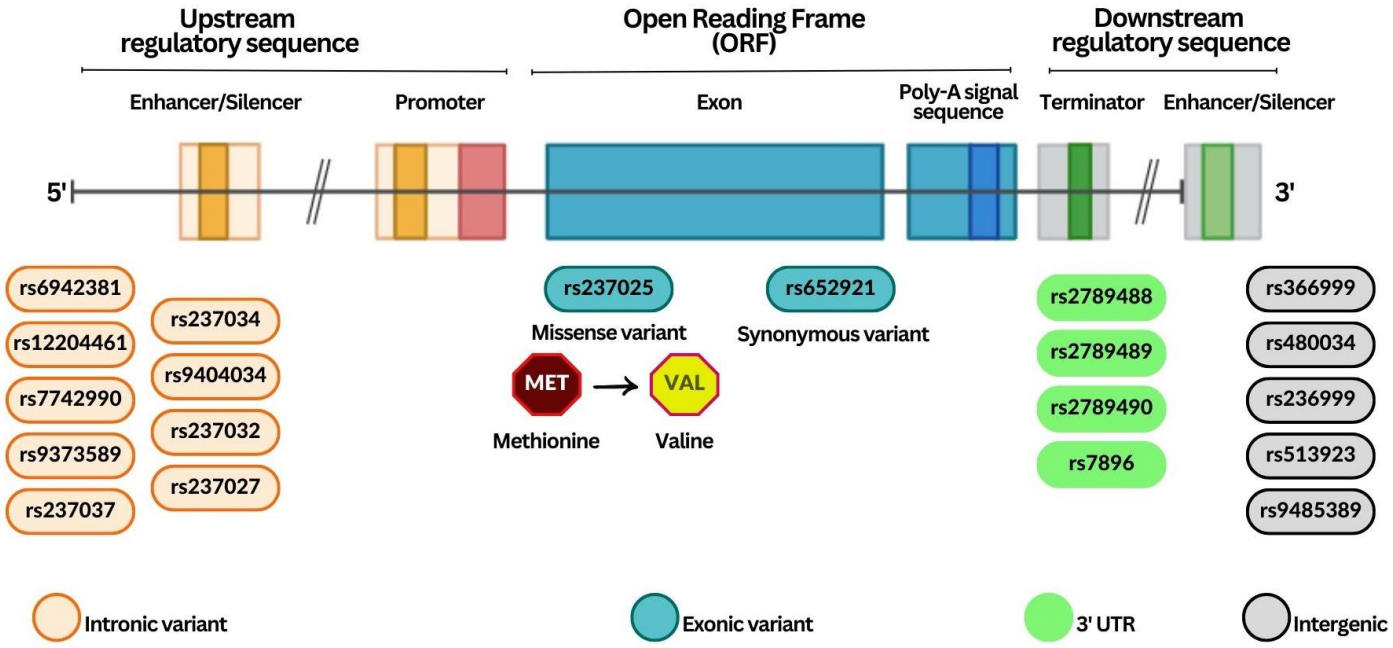

Figure 3. Structure of the SUMO4 gene and location of SNPs present in the gene region covered in this review

The illustration depicts the structure of the *SUMO4* gene and the approximate location of SNPs on chromosome 6. These SNPs are situated in intronic, 3' untranslated region (UTR), and intergenic regions, and have the potential to influence gene transcription. Specifically, the SNP rs237025 is a variation in the gene's exon, causing the substitution of the amino acid methionine with valine at position 55 of the SUMO4 protein, leading to the main functional hypothesis linking the SUMO4 gene with T1D. On the other hand, rs652921 is a variation in the exon that does not result in an amino acid substitution in the protein (synonymous variation). (Microsoft PowerPoint 2019. Canva. Online version. Available at: https://www.canva.com/.).

In T1D, a functional hypothesis supports the rs237025 polymorphism of *SUMO4* as a susceptibility variant was described by GUO and co-workers. In this study, the authors observed a reduction in SUMOylation in the variant with the amino acid valine (V55) in the SUMO4 protein, which caused a 5.5-fold increase in gene-dependent transcription NF-kB [52]. This pathway is critical in several immune-mediated processes and is related to the pro-inflammatory cytokines production, and innate and adaptive immune systems regulation [49, 53].

Aside from the rs237025 SNP, the *SUMO4* gene features additional single nucleotide variation markers. While these markers may not directly alter the protein's amino acid structure, they could still impact transcription or influence pathogenic mechanisms. This could elevate the risk of susceptibility to T1D or reduce the effectiveness of certain therapeutic interventions, akin to the other polymorphisms outlined in this study [43-51].

The scoping review of the *SUMO4* gene in autoimmune diabetes showed that this is a recurrent gene in the investigation of the genetic mechanisms of the disease, although its association in non-Asian populations has not been significant or is controversial [47]. The diverse set of connections inspired the current study. It

was observed that the frequencies of genotypes and alleles remained consistent among the analyzed reports that examined the same gene variations. Minor variations were noted due to varying sample sizes, but these closely matched the descriptions in the databases.

This result shows that the genotyping method used in each investigation did not influence the result, such as PCR-RFLP and PCR-SSCP in case-control studies, because the frequencies described by all of them, in addition to the similarity with other works and databases, are compatible with the Hardy-Weinberg equilibrium, but may have influenced the association with HLA genotypes [43, 49, 50]. Even studies with genotyping platforms such as *Illumina* and *Sequenom* showed homogeneous results among themselves, in addition to describing concern with the level of agreement of the results obtained on each platform, as Podolsky, Prasad Linga-Reddy and She (2009) [48].

The data indicate that *SUMO4* does not play a significant role in the studied populations, showing only a subtle association with T1D among Swedes, but not among Latvians [50]. This association is dependent on HLA-DR3/DR4 positivity and is not observed in isolation, as noted by Sedimbi, Luo and Sanjeevi (2007) [49]. Wang, Podolsky and She (2006) suggested that the lack of association of *SUMO4* with T1D in non-Asian populations may be due to genetic heterogeneity and the potential role of multiple other susceptibility genes in this population. They also highlighted population differences in gene-gene and gene-environment interaction [31].

Potential limitations

The scoping review identified several limitations in the studies. One notable issue was the lack of clarity in identifying and characterizing the volunteers, which raised concerns about the accuracy of diagnosing T1D or LADA and the specificity of the study populations. This could potentially introduce bias and affect the validity of the association between *SUMO4* polymorphisms and T1D.

Another limitation was the variation in genotyping techniques used across the studies, ranging from manual methods like PCR-RFLP and SBE to automated platforms. Notably, studies reporting significant associations between *SUMO4* SNPs and T1D predominantly relied on manual genotyping techniques, which are more susceptible to human error and could result in genotyping inaccuracies and false-positive results.

Additionally, the studies were conducted in diverse geographic regions with varying population characteristics, and not all consistently controlled for population stratification or environmental factors that might influence the genetic association with T1D. Limited sample sizes in several studies also reduce the statistical power to detect subtle associations, potentially leading to marginal or non-significant findings.

Furthermore, the review was limited to non-Asian populations, which restricts the generalizability of the findings and underscores the necessity for further research in more diverse populations to comprehensively understand the role of *SUMO4* polymorphisms in T1D across different ethnic groups.

CONCLUSION

This scoping review showed that there is no significant association between the *SUMO4* gene and T1D in non-Asiatic, indicating that genetic variations in this gene may not play a substantial role in susceptibility to the disease in this specific population. However, further studies are needed to confirm these findings and explore possible interactions with other relevant genetic and environmental factors.

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