BMC Endocrine Disorders

RESEARCH

Open Access

Polymorphic variants and risk of diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: systematic review and meta-analysis

Daniella Vinelli-Arzubiaga[1], Carmen Elizabeth Suasnabar Campos[1], María Cristina Laso-Salazar[2] and Hugo Abarca-Barriga[1,2*]

Abstract

Background Neuropathy is a frequent complication of diabetes mellitus, a disease that is growing exponentially worldwide. Genetic research has emerged as an important tool for better understanding its predisposition, although a systematic synthesis of existing evidence is needed to better comprehend its association. The objective of this review was to determine the association between polymorphic variants identified through massive genomic testing and the risk of peripheral diabetic neuropathy in patients with type 2 diabetes mellitus.

Methods Inclusion criteria were case-control, cohort, and cross-sectional studies examining polymorphic variants and diabetic neuropathy (DNP) risk in type 2 diabetes, studies using GWAS, EWAS, or microarray for identifying genetic polymorphisms, studies involving adults, and articles in English or Spanish. Exclusion criteria included case reports, case series, ecological studies, editor letters, reviews, or secondary studies and conference abstracts. Exhaustive search in PubMed, Scopus, and Web of Science databases, using keywords. Risk of bias was determined through Newcastle-Ottawa scale. A qualitative synthesis of the results was performed (frequency), including meta-analysis where applicable (forest plot and funnel plot).

Results The searching strategy identified 370 studies, from which 7 were chosen for the systematic review, included 9478 participants. The quality of the studies was mostly good, but a significant heterogeneity in methods was found. We identify a significant association between peripheral neuropathy and plenty of single nucleotide variants (SNVs). Just the SNV rs10555080 in the gene *THEG5* showed a higher likelihood of neuropathy (OR:1,34; IC 95%: 1,19 – 1,49).

Discussion This study faced limitations due to heterogeneity in DNP definitions, genotyping methods, and a focus on white and Arab populations, limiting generalization. Only English and Spanish articles were included, potentially excluding relevant research in other languages. Multiple SNVs were identified through genomic testing that were associated with peripheral diabetic neuropathy in patients with type 2 diabetes mellitus; however, the SNVs were not similar between studies.

*Correspondence:
Hugo Abarca-Barriga
hugo.abarca@urp.edu.pe

Full list of author information is available at the end of the article

Trial registration This research received no funding and was registered in PROSPERO (ID CRD42024505256).
Keywords Genetic polymorphism, Diabetic neuropathies, Genetic association studies

Background

Diabetes mellitus (DM) is a chronic disease that has become increasingly prevalent in the last decades, and it is estimated that around 79% of affected persons with this condition reside in low and middle income countries [1]. In Latin America, studies also show an increase in the prevalence of DM, being Mexico, Haiti, and Puerto Rico the most affected regions [2].

Neuropathies are a set of clinical syndromes belonging to microvascular complications developed by diabetic patients, characterized by their variable presentation in symptoms, pattern of neurological involvement, risk factors, and mechanisms that produce them [3]. Half of diabetic neuropathy (DN) cases present in its most typical form as distal symmetric polyneuropathy (DSP), which is a frequent type of diabetic peripheral neuropathy (DPN). DSP arises in a context of metabolic dysfunction and can manifest in around 10–15% recently diagnosed people with type 2 DM, and 50% of patients with 10 years of disease [4, 5].

The estimated prevalence of DPN in the world is 31,5% in patients with type 2 DM patients with type 2 DM n patients with type 2 DM [6]. It is characterized by variable clinical expressions, ranging from asymptomatic to the presence of painful neuropathic discomfort, diabetic foot, Charcot arthropathy, and non-traumatic lower limb amputations. Therefore, early detection and prevention are of vital importance [7, 8].

While type 2 DM is a disease with multifactorial inheritance and various environmental risk factors, such as poor glycemic control, hypertension, cardiovascular disease, depressive symptoms, among others [9, 10], the importance of genetic factors cannot be overlooked. In recent years, genetic polymorphism research has emerged as an important tool for understanding the pathways of genetic predisposition that increase the risk of DPN, providing valuable information to guide the development of more personalized, preventive and therapeutic approaches in the management of this diabetic complication [11].

Although multiple previous studies have found various types of polymorphisms associated with the risk of type 2 DM and its complications [12–14], the intrinsic complexity of DPN and the heterogeneity of individual studies, along with the use of new technologies, emphasize the need of a systematic synthesis of the existing evidence. This is necessary to establish consistent and robust patterns in the underlying genetic relationship, an area where research is currently lacking. Therefore, this article aims to determine the association between polymorphic variants identified through genomic testing and the risk of DPN in patients with type 2 DM.

Methods

This study is a systematic review, registered in PROSPERO (ID CRD42024505256) and IBR (INICIB) (ID PG 264 2023) [15]. Protocol can be requested to Universidad Ricardo Palma. We included all case-control, cohort, and cross-sectional analytical studies that evaluated the association between polymorphic variants and the risk of DPN in patients with type 2 DM, studies that had used genomic testing such as Genome-wide association study (GWAS), Exome association study (EWAS), or Microarray to identify genetic polymorphisms, and studies conducted in adults, published in English or Spanish. We excluded case reports, case series, ecological studies, letters to the editor, review articles, secondary studies and conference summaries.

Information source

A comprehensive search was conducted in the databases PubMed, Scopus and Web of Science.

Search strategy

This search was conducted using terms and combination of the following keywords: “Diabetes Mellitus; Peripheral Nervous System Diseases; Diabetic Neuropathies”; “Genome-Wide Association Study”; “Exome Sequencing”; “Oligonucleotide Array Sequence Analysis” (Supplementary material 1).

Studies selection

Articles identified through the database search up to January 23rd of 2024 were transferred to the program Rayyan (https://rayyan.qcri.org), and duplicated articles were eliminated. The authors of this study conducted an independent and blind initial review of the titles and abstracts of the articles, which allowed the selection of those that met the inclusion and exclusion criteria. A third reviewer, a medical genetics specialist, solved any discrepancies that arose and took responsibility for making the final decision.

The first reviewers individually read and reviewed the full text of each study included in the process. The same way, when discrepancies arose regarding the inclusion or quality of a study, the third reviewer was included. Once the research articles from various databases were selected, a thorough review of their bibliography sources and the studies referred to in those articles was performed. This process aimed to detect possible new

studies that may not have been considered in the initial search. Additionally, an exhaustive review of the articles citing the selected studies was carried out using the search engine provided by Google Scholar (https://scholar.google.com/). The inclusion and evaluation of these studies followed the methodology previously described.

Data collection process

The reviewers performed independently the extraction and verification of required data of each study included in the process. Similarly, when discrepancies arose, the third reviewer was involved in the process. We utilized Rayyan, a web-based tool designed to streamline the screening and selection process of systematic reviews. Rayyan helped in managing and categorizing the studies during the data extraction process, ensuring a more efficient review. At last, the data collected was registered in a sheet of Microsoft Excel 2019.

Data items

The extraction of relevant data from each study was carried out, including information about the authors, year of the study, country, study design, number of participants, sex, age (median or mean), ethnicity (ethnic background of participants), diabetic neuropathy, type of polymorphic variant studied, diagnostic technology used (GWAS, EWAS or microarray analysis).

Bias risk assessment

Bias risk assessment in the selected studies was conducted by the reviewers independently, and discrepancies were resolved with the intervention of the third reviewer. To evaluate the quality of the studies, the Newcastle-Ottawa Scale [16] was used for case control studies, as well as its adaption for analytical cross-sectional studies made by Modesti et al. [17]. This scale consists of three categories: selection, comparability, and ascertainment for the case control studies; and selection, comparability, and outcome for cross-sectional studies. A score was assigned to each category based on the specific characteristics of each study. The study quality was considered good when it obtained from 7 to 9 points, acceptable when it obtained 5 to 6 points, and bad when it obtained from 0 to 4 points [18]. This process guaranteed a rigorous assessment of the methodological quality of the studies included in the review.

Effect measures

The odds ratio (OR) value between the polymorphic variants and DNP, along with their respective 95% confidence intervals and *p* values.

Data processing and analysis technique

During the qualitative analysis of the systematic review, a careful reading of all collected studies was conducted, providing a detailed description of clinical and methodological characteristics present in the included studies. Additionally, the strengths and weaknesses inherent to each study were identified. We also paid attention to the structure of the studies, considering their potential to bias their results, and we explored the relationship between the characteristics of the studies and the reported outcomes.

A meta-analysis was conducted when at least two studies evaluating the same SNVs were found in the systematic review. As the variables in this study were categorical in nature, the OR was calculated as a summary measure, along with 95% confidence intervals, considering the association significant when the *p*-value was less than 0,05. For the analysis, Stata v.14 software was used, while Excel was employed for graphical representation.

Reporting bias assessment

Publication bias was determined through heterogeneity between studies, evaluated with the I^2 index, considering that a value less than 40% indicates little variability between studies.

Regarding incomplete Data Reporting, we reviewed the completeness of data in each study, flagging those with missing or unclear results and considering their impact on the synthesis.

We reached out to study authors for additional data or clarification to address missing information and reduce bias.

Sensitivity analyses were performed to evaluate how missing data affected overall conclusions.

We assessed study quality using established criteria like the Newcastle-Ottawa Scale to identify potential reporting biases.

Certainty assessment

We employed the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework to assess the overall certainty of the evidence for each outcome. This framework evaluates evidence based on study design, risk of bias, inconsistency, indirectness, and imprecision.

Results

370 published studies were identified using the search formula in the following databases: Pubmed (75), Scopus (116) and Web of Science (179). After removing 173 duplicate studies recognized by the Rayaan program, 197 publications were evaluated by title and abstract, with 179 publications being excluded for not meeting the required criteria. Subsequently, the whole text of the

18 remaining articles was analyzed, and 12 articles were excluded (Supplementary material 2). Articles were identified from citations of the included articles, and one was excluded due to the study design. Finally, seven articles were included in the systematic review (Fig. 1).

Characteristics of the studies

The publication period of the seven studies included in this systematic review goes from 2013 to 2023, identifying four case control studies and three prospective cross-sectional studies. The studied population was predominantly white and Arab; only the study by Margolis et al. [19] evaluated genetic variants associated with peripheral neuropathy in African American population.

Regarding the methodology of the studies, heterogeneity was observed in the definition of DPN. Only the study by Tang et al. [20] defined the presence of DPN using the Michigan neuropathy screening instrument (MNSI), a validated instrument for the diagnosis of this condition.

Results of individual studies

Additionally, heterogeneity was found in the evaluation of genetic variants regarding the genotyping method and the number of SNVs. A total of 66 SNVs in various genes were identified and studied for their association with DPN (Supplementary material 3).

Bias risk assessment

Four articles were evaluated using the NOS tool for case control studies, and three articles were assessed using the NOS tool modified by Modesti et al. [17] for cross-sectional studies. However, due to the number of studies (< 10) it was not possible to assess the risk of publication bias using the funnel plot [21]. In general, the evaluation of the articles showed that they were of "good quality", only the article by Margolis et al. [19] showed "acceptable quality" (Table 1).

A possible bias in this article is the focus on the study by Tang et al. This occurred because of the methodological robustness of the study. It was the only one that used a validated instrument to define DPN. Also, it got the highest quality evaluation score, which was "Very good quality". However, this emphasis might underestimate the contribution of the other 6 studies. The heterogeneity of the studies limited the ability of comparing and integrating the data in the metanalysis. This highlights the need of future research to standardize diagnostic criteria, have high quality methodological designs and reduce bias in the systematic reviews.

Meta-analysis

Two studies that evaluated the association of the SNV rs1963645 of the gene *NOS1AP* and DPN were included, however, due to the heterogeneity in both studies, the article by Margolis et al. [19], was not considered for the

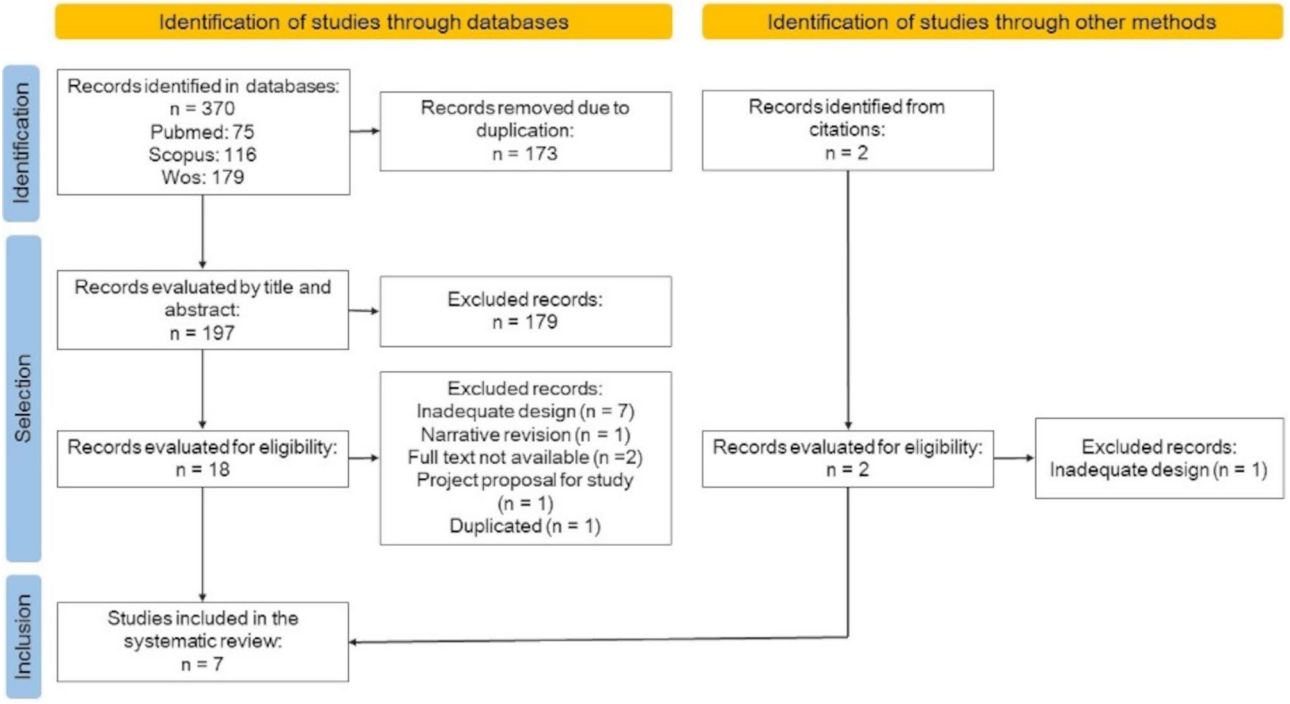

Fig. 1 Flowchart for the selection of studies on polymorphic variants in patients with neuropathy in type 2 diabetes mellitus

Table 1 Assessment of the quality of case-control and cross-sectional studies using the Newcastle-Ottawa scale

Case-control studies											
Authors and years	**Selection**				**Comparability**		**Exposition**			**Score**	**Judgement**
	Is the case definition appropriate? (1)	**Representativeness of the cases (2)**	**Selection of controls (3)**	**Definition of controls(4)**	**The study controls for the most important factor (5)**	**The study controls for any additional important factor(s) (6)**	**Determination of exposure (7)**	**Same method of determining cases and controls (8)**	**Non-response rate* (9)**		
Meng et al. 2015 [22]	--	☆	☆	☆	☆	☆	☆	☆	NA	7	**Good quality**
Meng et al. 2015 [23]	--	☆	☆	☆	☆	☆	☆	☆	NA	7	**Good quality**
Chehadeh et al. 2021 [24]	--	☆	☆	☆	☆	☆	☆	☆	NA	7	**Good quality**
Ustinova et al. 2021 [25]	--	☆	☆	☆	☆	☆	☆	☆	NA	7	**Good quality**

Cross-sectional studies									
	Representativeness of the sample (10)	**Size of the sample (11)**	**Not surveyed (12)**	**Determination of exposure (risk factor) (13)**	**The study controls for the most important factor (14)**	**The study controls for any additional factor (15)**	**Outcome assessment (16)**	**Statistical analysis (17)**		
Margolis et al. 2013 [19]	☆	--	--	☆	☆	--	☆☆	--	6	**Acceptable quality**

Table 1 (continued)

	Cross-sectional studies									
	Representativeness of the sample (10)	**Size of the sample (11)**	**Not surveyed (12)**	**Determination of exposure (risk factor) (13)**	**The study controls for the most important factor (14)**	**The study controls for any additional factor (15)**	**Outcome assessment (16)**	**Statistical analysis (17)**		
Tang et al. 2019 [20]	☆	☆	☆	☆☆	☆	☆	☆☆	☆	10	**Very good quality**
Mansour et al. 2023 [26]	☆	☆	☆	☆	☆	☆	☆☆	☆	9	**Very good quality**

1. Is the case definition appropriate? A star was assigned to studies that had some form of independent validation

2. Representativeness of the cases: A star was assigned to studies with a representative case series

3. Selection of controls: A star was assigned if their control series was community-based

4. Definition of controls: A star was assigned if controls did not have a history of DPN

5. The study controls for the most important factor: A star was assigned if adjustment has been made, methodological or statistical, for the most important covariate

6. The study controls for any additional important factor(s): A star was assigned if adjustment has been made, methodological or statistical, for other covariates

7. Determination of exposure: A star was assigned if the study mentions that they had a safe registry and/or a structured interview where the participant is unaware of their case/control status

8. Same method of determining cases and controls: A star was assigned if the study mentions the same method

9. Non-response rate (*): In the studies considered for this systematic review, surveys were not used, so "none of the above" (NA) was selected

10. Representativeness of the sample: A star was assigned to studies that had adequate representation of the target population

11. Size of the sample: A star was assigned to studies with a justified and satisfactory sample size

12. Not surveyed: A star was assigned if comparability was established between the characteristics of surveyed and not surveyed, and the response rate was satisfactory

13. Determination of exposure: Two stars were assigned if the dependent variable has been measured with a validated instrument, and one star if it is not a validated instrument but is available or described

14. The study controls for the most important factor: An adjustment has been made, methodological or statistical, for the most important covariate

15. The study controls for any additional factor: An adjustment has been made, methodological or statistical, for other covariates.

16. Outcome assessment: Two stars were assigned if the study mentions an independent blind assessment or if its records are linked, and one star if it was self-reported

17. Statistical analysis: A star was awarded if the study mentions whether subjects from different outcome groups are comparable, according to the study's design or analysis, and confounding factors are controlled

analysis results due to its atypical values, obtaining an OR of 0,84 (IC 95%: 0,75 – 0,93; $p <= 0{,}0001$) (Fig. 2A).

On the other hand, when conducting the meta-analysis of the study by Tang et al. [20], the association between DPN and several SNVs in their cohorts BARI2D and ACCORD was evaluated. A significant association was found between DPN and SNP rs13417783 of the gene *XIRP2* (OR: 0,63; IC 95%: 0,54 – 0,71), rs11073752 of the gene *WBSCR17* (OR: 0,75; IC 95%: 0,66 – 0,84), rs60770880 of the gene *NTRK3* (OR: 0,77; IC 95%: 0,68 – 0,85), rs1202660 of the gene *LOC101–927,394* (OR: 0,77; IC 95%: 0,68–0,85), and rs9948095 of the gene *IMPA2* (OR: 0,73; IC 95%: 0,63 – 0,83), which suggests a lower likelihood of DPN with the presence of these

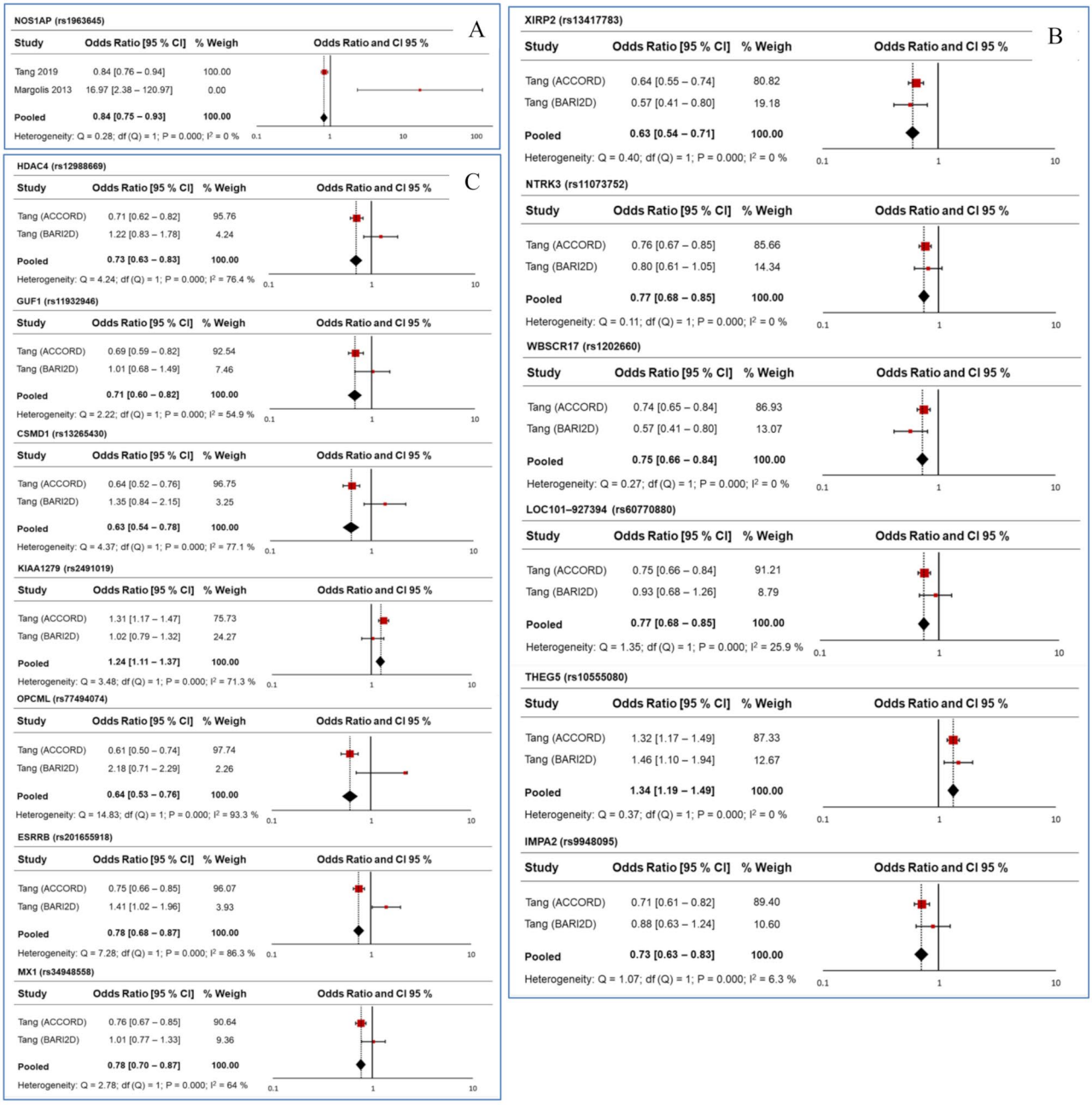

Fig. 2 **A**. Forest plot diagram showing the association between the SNV of *NOS1AP* (rs1963645) and DPN. **B**. Forest plot diagram of heterogeneous studies of SNVs associated with DPN, revealing an association between the *THEG5* gene and DPN. Conversely, polymorphisms in *XIRP2*, *IMPA2*, *LOC101927394*, and *WBSCR17* appear to act as protective factors against the development of DPN. **C**. Forest plot diagram for studies on SNVs associated with DPN. Protective SNVs include *HDAC4*, *GUF1*, *CSMD1*, *OPCML*, *ESRRB*, and *MX1* genes. The SNV associated with DPN is *KIAA1279*. Heterogeneity Test Statistic (Q); Degrees of Freedom (df); Heterogeneity (I^2)

genetic variants. However, the SNV rs10555080 of the gene *THEG5* showed an OR of 1,34 (IC 95%: 1,19 – 1,49), indicating a higher likelihood of DPN (Fig. 2B).

Additionally, the association of DPN with other SNVs of the study by Tang et al. [20], was evaluated, where a significant association was found with the SNV rs12988669 of the gene *HDAC4* (OR: 0,73; IC 95%: 0,63 – 0,83), rs11932946 of the gene *GUF1* (OR: 0,71; IC 95%: 0,60 – 0,82), rs13265430 of the gene *CSMD1* (OR: 0,66; IC 95%: 0,54 – 0,78), rs2491019 of the gene *KIAA1279* (OR: 1,24; IC 95%: 1,11 – 1,37), rs77494074 of the gene *OPCML* (OR: 0,64; IC 95%: 0,52 – 0,76), rs201655918 of the gene *ESRRB* (OR: 0,77; IC 95%: 0,68 – 0,87), rs34948558 of the gene *MX1* (OR: 0,78, IC 95%: 0,70–0,87). Although all these associations were significant ($p < 0{,}0001$), considerable heterogeneity was observed between the studies, with I [2] values over 40% (Fig. 2C).

Reporting biases

The overall assessment of the risk of bias due to missing results is rated as moderate to high. This assessment is based on the exclusion of studies with atypical values and the presence of moderate to high heterogeneity across several syntheses, which suggest a considerable risk of bias from missing results. While this risk is partially mitigated in analyses where findings are consistent across the included studies, the potential for publication bias continues to be a significant concern (Supplementary material 4).

Certainty of evidence

The certainty of the evidence for the association between genetic variants and diabetic peripheral neuropathy (DPN) varies across outcomes. For the association with the SNV rs1963645 of the *NOS1AP* gene, the certainty is rated as low due to the exclusion of studies with atypical values and the resulting high risk of bias and imprecision. The evidence for SNVs in the BARI2D and ACCORD cohorts shows a moderate level of certainty. Despite significant associations, moderate heterogeneity affects the confidence in these findings. The association of SNV rs10555080 of the *THEG5* gene with DPN is rated as moderate due to consistent results across studies but limited data. Additional SNVs from the Tang et al. study show a low to moderate certainty due to considerable heterogeneity and potential reporting biases. Overall, the evidence is characterized by moderate to high risk of bias due to missing results and heterogeneity, impacting the overall confidence in the findings.

Protein interaction analysis

Finally, all genes whose polymorphisms showed significant association with DPN in the articles included in this systematic review were enter into the STRING CONSORTIUM 2023 platform, which is a database that collects information on protein-protein interactions and creates association networks between functional proteins. Among the studies reviewed, identified significant associations with *XIRP2*, *CSMD1*, *PPARA*, *EDN1*, and *NOS1*. Using STRING, a functional relationship was found between *XIRP2* and *CSMD1*, and alternatively between *PPARA*, *EDN1* and *NOS3*. This finding highlights potential protein-protein interactions that may underlie the molecular mechanism contributing DPN (Fig. 3).

Discussion

The results of this review suggest a significant association between several genetic variants and DPN. However, most of the included studies focused on white patients. Similarly, Vujkovic et al. [27], mention that, despite large disparities in the prevalence and severity of type 2 DM complications, most studies have been conducted in patients of European or Asian ancestry.

Chehadeh et al. [24] report that, prior to their study in the Arab population, the SNV rs4496877 in the *NOS3* gene had not been reported as associated with DPN. Therefore, while the evidence supports significant association between genetic variants and DPN, the of ethnic diversity in the studies available is still a limitation.

Regarding the risk of bias, even though most studies demonstrated good quality, significant differences were found in case definitions. This variability in DPN diagnosis has also been mentioned by Chicharro-Luna et al. [28], who reported that various criteria exist for diagnosing DPN, making this a complex diagnosis that should not be diagnosed solely on monofilament testing. Additionally, the American Diabetes Association (ADA) recommends using 3 clinical tests to diagnose DPN, assessing long and small fiber function from distal to proximal [4].

Regarding the association between SNVs and DPN, the Italian Society of Diabetology (ISD) stated in 2017, that research on these genetic determinants that could influence on the presentation and development of diabetic neuropathies was in its early stages, and that there was still insufficient evidence to use these genetic markers to evaluate the risk of DN in patients [29]. Therefore, the results of this study allow us to expand the current knowledge about the genetics of DPN, although, as mentioned before, there is still need for additional research.

To further understand the genetic factors that contribute to DPN, it is essential to evaluate different genes involved in various biological processes that take place in the neuronal signaling and the pathophysiology of DPN. One of these genes is the *NOS1AP* gene, which encodes a protein that binds to Neuronal nitric oxide synthase (NOS1), that is involved in neuronal signaling

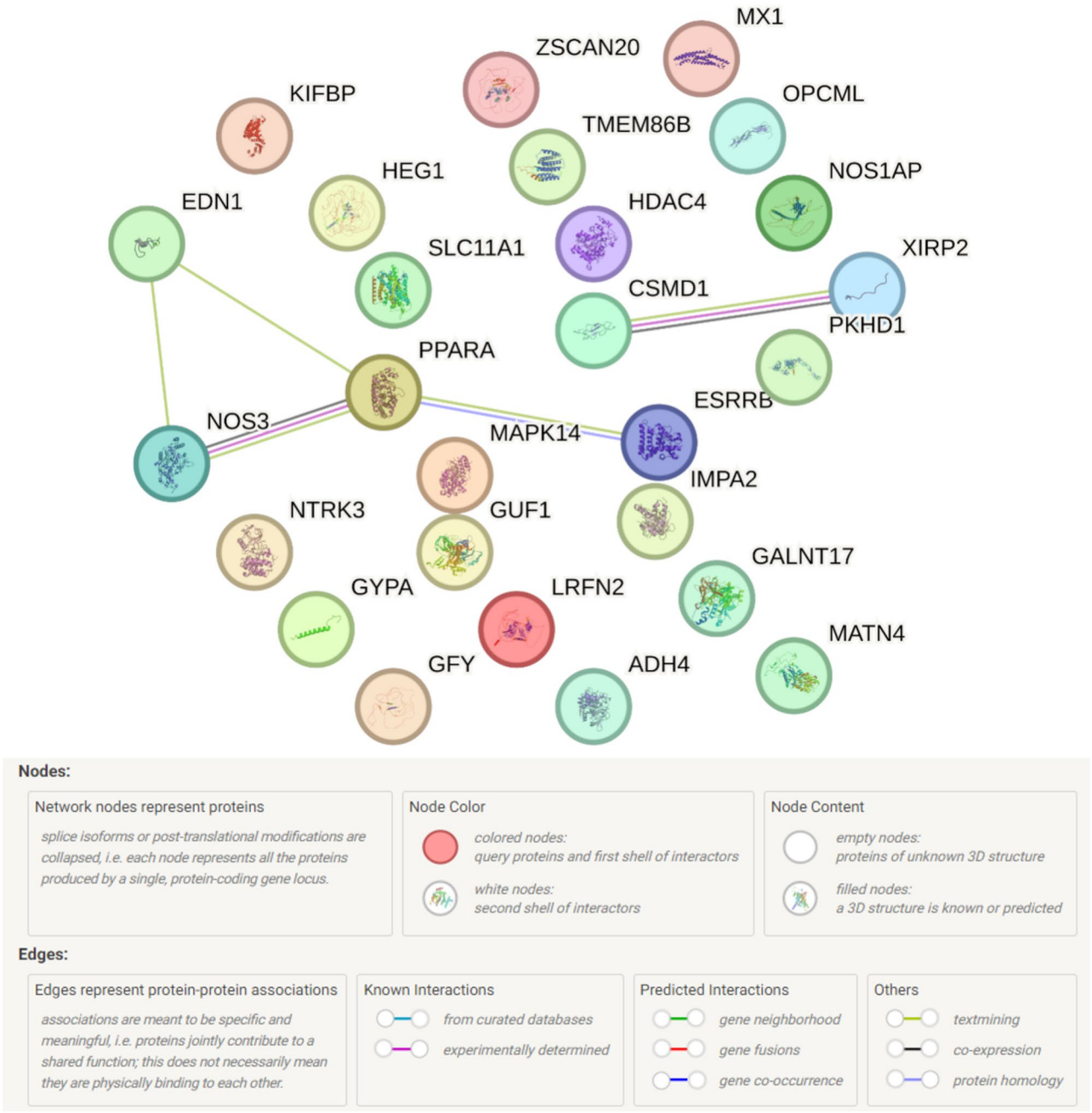

Fig. 3 Diagram representing the network of protein interactions

and neurotransmission [30]. Margolis et al. observed four variants in the *NOS1AP* gene associated with an increased risk of lower extremity amputation in diabetic patients. Two of these variants were linked to a higher risk of loss of protective sensation [31], suggesting a potential association between this gene and DPN.

On the other hand, the *NOS3* gene encodes the enzyme nitric oxide synthase, which is responsible for producing nitric oxide in the vascular endothelium [32]. This gene has been evaluated through PCR in other studies, showing an association with DPN [33]. This is consistent with the results obtained in the study by Chehadeh et al. [24], in which new technologies were used for the genomic analysis in diabetic patients. The influence of this gene in DPN could be due to excessive production of highly reactive compounds in diabetics due to hyperglycemia. This could lead to oxidative stress, mitochondrial dysfunction,

and direct damage to proteins, lipids, and nucleic acids in nerve cells [34].

The *XIRP2* gene is involved in the formation of cardiac muscle tissue, organization of cellular connections, and development of the heart wall [35]. The association of the SNV rs7595556 in this gene with neuronal networks had recently been observed in Mexican Americans, and it was also mentioned that it could be related with metabolic characteristics, such as DN [36]. However, before the study by Tang et al. [20], this gene had not been evaluated in DPN or type 2 DM. This could be attributable to the inherent complexity of multifactorial diseases such as DPN and type 2 DM, which could have led to some genes being overlooked in previous studies.

The gene *NTKR3* encodes tyrosine kinase neurotrophic receptors, which are membrane receptors that, when they bind neurotrophins, they phosphorylate themselves and members of the MAPK pathway. These receptors play a crucial role in the development of proprioceptive neurons, responsible of detecting the position of the body [37]. In this regard, the genetic variants affecting tyrosine kinase receptors may influence DN by affecting myelination of the peripheral nervous system and the response to key neurotrophins in the neuronal development. These variants could alter the ability of the Schwan cells to form myelin, which would contribute to neuronal dysfunction [38]. However, their relationship with peripheral neuropathy has not been previously studied.

The gene *WBSCR17*, officially known as *GALNT17*, encodes the enzyme N-acetylgalactosaminyltransferase 17, which transfers N-acetyl-D-galatosamin residues to serine or threonine in protein receptors; additionally, it has been suggested that it could have an important role in membrane traffic [39].

In this context, it should be noted that, in the case of DPN, alterations in glycosylation can affect the function of proteins in peripheral nerves; in addition, type 2 DM is associated with metabolic changes, including abnormal protein glycosylation [40, 41]. Therefore, although there is no definitive evidence, the *GALNT17* gene could be related to peripheral DN through its function in protein glycosylation and its expression in nerves.

The gene *IMPA2* encodes the enzyme inositol monophosphatase 2, which catalyzes the dephosphorylation of inositol monophosphate, converting it into inositol, and plays a crucial role in phosphatidylinositol signaling [42]. In diabetic patients, a deficit of myo-inositol is observed in the nerves due to inhibition of sodium dependent myo-inositol absorption and significant alterations in the polyol pathway [43]. Additionally, the activity of the ATPase Na/K enzyme, vital for nerve impulse conduction, decreases when myo-inositol levels are low [43]. Likewise, the decrease in nitric acid and the deficient production of glutathione due to NADPH depletion can affect vasodilation and increase reactive oxygen species, damaging endothelial cells function [44].

On the other hand, an association has also been found between intergenes, such as *LOC101–927,394* and *THEG5*, and DPN. Intergenic regions are DNA segments located between genes that do not code for proteins and constitute most of the genome. It is known that intergenic DNA regulates the expression of nearby genes, often containing enhancer DNA sequences, which can activate the expression of discrete sets of genes at distances of several thousand base pairs [45]. Changes in protein bound to enhancers can reprogram gene expression and affect cellular phenotype [45].

Some polymorphisms in these intergenic regions could increase individual susceptibility to developing DPN, by interacting with environmental and metabolic factors. In this sense, Guo et al. [46] explored the relationships between HbA1c, DNA methylation, and gene expression patterns by integrating epigenomic and transcriptomic data. They found that 44% of these genetic variations were in intergenic regions. Similarly, a recent study found an association between five SNVs that increased the risk of DPN, located in an intronic region of the genes [47]. Therefore, although more research is needed, polymorphisms and intergenic regions may affect DPN by modulating the expression of genes related to nervous system function and metabolic response.

Studies of genes involved in metabolic diseases and their complications are an active and evolving area of genetics, and understanding the involved polymorphisms could help design personalized therapeutic strategies for patients with DPN, since current treatments often failed to stop or reverse DPN development in type 2 DM patients [48]. For example, it has been shown that limiting the number of free radicals produced by oxidative stress, supplementation with alpha lipoic acid in combination with epalrestat or methylcobalamin clearly improves these latter medications, reduces adverse events, and accelerates nerve conduction, interpreted as improvement in neuropathic symptoms [49, 50].

This study did not find articles reporting the association between CNVs and DPN using genomic tests. However, the study by Latini et al., [51] analyzed the variants in the number of copies of mitochondrial DNA (mtDNA) in the presence of the rs3746444 polymorphism of the gene *MIR499A* and its association with DPN; finding that the variant homozygous genotype was associated with a significant reduction in the number of mtDNA copies, which was especially notable in DPN patients ($p = 0{,}009$). In this regard, Gamazon and Stranger [52] mention that transcriptome studies will continue to reveal functional consequences of CNVs, making it relevant to improve structural variation maps in the genome to better understand their impact on gene expression.

Due to the inclusion of only two studies per analysis, a conventional sensitivity analysis by excluding studies was not feasible and had limited interpretability. Typically, sensitivity analyses are performed to assess the robustness of the findings by systematically excluding individual studies; however, with only two studies, this approach would leave a single study, precluding meaningful statistical evaluation. The quality of the included studies ranged from acceptable to very good.

Heterogeneity, measured by I [2], varied from 0 to 93%, suggesting considerable variability in some analyses. This could be attributed to methodological differences or variations in study populations. While a formal statistical assessment of potential biases (e.g., publication and selection bias) was not possible due to the limited number of studies, a qualitative evaluation was conducted. The findings should therefore be interpreted with caution, acknowledging the limitations imposed by the small sample size and heterogeneity. Additional studies are needed to allow for a more robust sensitivity analysis and to enhance the reliability of the pooled estimates.

Finally, it should be mentioned that a limitation of this study was the heterogeneity observed in the definition of DPN among the analyzed studies, making comparability of results difficult. Similarly, the heterogeneity in the methodology used for genotyping polymorphism and the number of variants studied should be taken into consideration. Some of the studies did not adequately adjust for confounding factors such as age, sex, duration of diabetes, and glycemic control, potentially biasing the associations found in this study. On the other hand, studies with atypical values, high heterogeneity and incomplete data were excluded, which could affect the final results. Another limitation was that most of the included studies focused on white and Arab populations, limiting the generalization of the results to other ethnic populations. Lastly, this study only considered articles in English or Spanish, so there may be other relevant research in other languages, such as Chinese, so it would be important to consider studies in other languages for future reviews. None of the included studies explored Copy Number Variants (CNVs), which could have an important role in DPN risk, and could have an important impact in the conclusions of this study.

For future reviews, we recommend expanding the search strategy to include publications in other languages other than English and Spanish, unpublished studies and grey literature, which would provide a broader dataset for analysis and additional insights. Additionally, we would encourage including more studies with standardized diagnostic criteria and genotyping methods to obtain more comparable results.

In conclusion, the studies evaluating the association between polymorphic variants and the risk of DPN in patients with type 2 DM showed significant heterogeneity in their methodology, differing in the genotyping method used and the number of single nucleotide variants evaluated. Additionally, only one study used a validated instrument to measure DPN, however, the quality of the studies was overall good, as only one study showed acceptable quality. To date, 66 SNVs identified through genomic testing have been reported to be associated with the risk of DPN in type 2 diabetic patients, of which only some showed a significant association, but no CNVs identified through genomic testing have been reported to be associated with DPN.

Further research is required on the association between polymorphic variants and the risk of DPN in patients with type 2 DM. Identifying an association with specific polymorphisms could lead to personalized treatment for type 2 DM. Additionally, it may eventually be possible to create risk profiles that include these polymorphisms, along with other known factors such as glycemic control or other comorbidities. Moreover, understanding the molecular mechanisms affected by these polymorphisms could drive the development of new therapies. Finally, routine genetic testing could be implemented in clinical settings to assess risk and inform patients about their genetic risk of developing this diabetes complication.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01897-1.

Supplementary Material 1

Acknowledgements

The authors have no acknowledgments.

Author contributions

HAB served as the principal investigator and contributed to the conceptualization of the study. DVA and CESC were responsible for drafting the manuscript, performing data analysis, and participating in data collection. All authors provided ongoing input throughout the process and contributed to the editing and review of the manuscript. HAB, DVA, and CESC were involved in the data analysis and interpretation. Each author reviewed and approved the final version of the manuscript.

Funding

The present research has not received specific funding from public sector agencies, commercial sector or non-profit organizations.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate

This research was approved by Institutional Review Board of *Universidad Ricardo Palma* (*Instituto de Investigaciones en Ciencias Biomédicas*). Consent no participate is not applicable. The study was conducted in accordance with Declaration of Helsinky.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Author details
[1]Instituto de Investigaciones de Ciencias Biomédicas, Universidad Ricardo Palma, Avenida Benavides, Lima 5440, Perú
[2]Instituto Nacional de Salud del Niño-Breña, Lima, Perú

Received: 9 August 2024 / Accepted: 7 March 2025
Published online: 14 March 2025

References

1. Cho NH, Shaw JE, Karuranga S, Huang Y, Da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271–81. https://doi.org/10.1016/j.diabres.2018.02.023
2. Avilés-Santa ML, Monroig-Rivera A, Soto-Soto A, Lindberg NM. Current state of diabetes mellitus prevalence, awareness, treatment, and control in Latin America: challenges and innovative solutions to improve health outcomes across the continent. Curr Diab Rep. 2020;20(11):62. https://doi.org/10.1007/s11892-020-01341-9
3. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, et al. Diabetic neuropathy. Nat Rev Dis Primers. 2019;5(1):41. https://doi.org/10.1038/s41572-019-0092-1
4. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American diabetes association. Diabetes Care. 2017;40(1):136–54. https://doi.org/10.2337/dc16-2042.
5. Albers JW, Pop-Busui R. Diabetic neuropathy: mechanisms, emerging treatments, and subtypes. Curr Neurol Neurosci Rep. 2014;14(8):473. https://doi.org/10.1007/s11910-014-0473-5
6. Sun J, Wang Y, Zhang X, Zhu S, He H. Prevalence of peripheral neuropathy in patients with diabetes: a systematic review and meta-analysis. Prim Care Diabetes. 2020;14(5):435–44. https://doi.org/10.1016/j.pcd.2019.12.005
7. Hicks CW, Selvin E. Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. Curr Diab Rep. 2019;19(10):86. https://doi.org/10.1007/s11892-019-1212-8
8. Selvarajah D, Kar D, Khunti K, Davies MJ, Scott AR, Walker J, et al. Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention. Lancet Diabetes Endocrinol. 2019;7(12):938–48. https://doi.org/10.1016/s2213-8587(19)30081-6
9. Lu Y, Xing P, Cai X, Luo D, Li R, Lloyd C, Sartorius N, Li M. Prevalence and risk factors for diabetic peripheral neuropathy in type 2 diabetic patients from 14 countries: estimates of the INTERPRET-DD study. Front Public Health. 2020;8:534372. https://doi.org/10.3389/fpubh.2020.534372. PMID: 33194943; PMCID: PMC7606804.
10. Morales EV, Ramos ZGC, Rico JA, Ledezma JCR, Ramírez LAR, Moreno ER. Sedentarismo, Alimentación, obesidad, Consumo de alcohol y Tabaco Como factores de Riesgo Para El desarrollo de diabetes Tipo 2. J Negat No Posit Results. 2019;4(10):1011–21. https://doi.org/10.19230/jonnpr.3068
11. Jankovic M, Novakovic I, Nikolic D, Mitrovic Maksic J, Brankovic S, Petronic I, et al. Genetic and epigenomic modifiers of diabetic neuropathy. Int J Mol Sci. 2021;22(9):4887. https://doi.org/10.3390/ijms22094887.
12. Witka BZ, Oktaviani DJ, Marcellino M, Barliana MI, Abdulah R. Type 2 diabetes-associated genetic polymorphisms as potential disease predictors. Diabetes Metabolic Syndrome Obes. 2019;12:2689–706. https://doi.org/10.2147/DMSO.S230061.
13. Zhao Y, Zhu R, Wang D, Liu X. Genetics of diabetic neuropathy: systematic review, meta-analysis and trial sequential analysis. Ann Clin Transl Neurol. 2019;6(10):1996–2013. https://doi.org/10.1002/acn3.50892.
14. Wu S, Han Y, Hu Q, Zhang X, Cui G, Li Z, et al. Effects of common polymorphisms in the MTHFR and ACE genes on diabetic peripheral neuropathy progression: a meta-analysis. Mol Neurobiol. 2017;54(4):2435–44. https://doi.org/10.1007/s12035-016-9823-4
15. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160. https://doi.org/10.1136/bmj.n160
16. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. 2021 [citado 20 de octubre de 2023]. Disponible en: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
17. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. PLoS ONE. 2016;11(1):e0147601. https://doi.org/10.1371/journal.pone.0147601
18. McPheeters ML, Kripalani S, Peterson NB, Idowu RT, Jerome RN, Potter SA et al. Thresholds for quality assessment. En: Closing the Quality Gap: Revisiting the State of the Science. Agency for Healthcare Research and Quality (US); 2012 [citado 29 de febrero de 2024]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK107322/
19. Margolis DJ, Gupta J, Thom SR, Townsend RR, Kanetsky PA, Hoffstad O, et al. Diabetes, lower extremity amputation, loss of protective sensation, and neuronal nitric oxide synthase associated protein in the chronic renal insufficiency cohort study. Wound Repair Regeneration. 2013;21(1):17–24. https://doi.org/10.1111/j.1524-475x.2012.00866.x
20. Tang Y, Lenzini PA, Pop-Busui R, Ray PR, Campbell H, Perkins BA, et al. A genetic locus on chromosome 2q24 predicting peripheral neuropathy risk in type 2 diabetes: results from the ACCORD and BARI 2D studies. Diabetes. 2019;68(8):1649–62. https://doi.org/10.2337/db19-0109
21. Fernandez Chinguel JE, Zafra Tanaka JH, Goicochea Lugo S, Peralta CI, Taype Rondan A. Aspectos básicos sobre La lectura de revisiones sistemáticas y La interpretación de meta-análisis. Acta Med Peru. 2019;36(2):157–69.
22. Meng W, Deshmukh H, Donnelly L, Torrance N, Colhoun H, Palmer C, et al. A genome-wide association study provides evidence of sex-specific involvement of Chr1p35.1 (ZSCAN20-TLR12P) and Chr8p23.1 (HMGB1P46) with diabetic neuropathic pain. EBIOMEDICINE. 2015;2(10):1386–93. https://doi.org/10.1016/j.ebiom.2015.08.001
23. Meng W, Deshmukh H, van Zuydam N, Liu Y, Donnelly L, Zhou K, et al. A genome-wide association study suggests an association of Chr8p21.3 (GFRA2) with diabetic neuropathic pain. Eur J Pain. 2015;19(3):392–9. https://doi.org/10.1002/ejp.560.
24. Chehadeh S, Sayed N, Abdelsamad H, Almahmeed W, Khandoker A, Jelinek H, et al. Genetic variants and their associations to type 2 diabetes mellitus complications in the united Arab Emirates. Front Endocrinol. 2022;12(751885):1–15. https://doi.org/10.3389/fendo.2021.751885.
25. Ustinova M, Peculis R, Rescenko R, Rovite V, Zaharenko L, Elbere I, et al. Novel susceptibility loci identified in a genome-wide association study of type 2 diabetes complications in population of Latvia. BMC Med Genom. 2021;14(1):18. https://doi.org/10.1186/s12920-020-00860-4
26. Mansour A, Mousa M, Abdelmannan D, Tay G, Hassoun A, Alsafar H. Microvascular and macrovascular complications of type 2 diabetes mellitus: exome wide association analyses. Front Endocrinol (Lausanne). 2023;14(1143067):1–11. https://doi.org/10.3389/fendo.2023.1143067.
27. Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. Nat Genet Julio De. 2020;52(7):680–91. https://doi.org/10.1038/s41588-020-0637-y
28. Chicharro-Luna E, Pomares-Gómez FJ, Ortega-Ávila AB, Coheña-Jiménez M, Gijon-Nogueron G. Variability in the clinical diagnosis of diabetic peripheral neuropathy. Prim Care Diabetes. 2020;14(1):53–60. https://doi.org/10.1016/j.pcd.2019.05.008
29. Buzzetti R, Prudente S, Copetti M, Dauriz M, Zampetti S, Garofolo M, et al. Clinical worthlessness of genetic prediction of common forms of diabetes mellitus and related chronic complications: a position statement of the Italian society of diabetology. Nutr Metabolism Cardiovasc Dis. 2017;27(2):99–114. https://doi.org/10.1016/j.numecd.2016.08.005
30. National Institutes of Health. NOS1AP nitric oxide synthase 1 adaptor protein [Homo sapiens (human)]. Gene-NCBI. 2024 [citado 9 de marzo de 2024]. Disponible en: https://www.ncbi.nlm.nih.gov/gene/9722#summary
31. Margolis DJ, Gupta J, Thom SR, Townsend RR, Kanetsky PA, Hoffstad O, Papdopoulos M, Fischer M, Schelling JR, Mitra N. Diabetes, lower extremity amputation, loss of protective sensation, and neuronal nitric oxide synthase associated protein in the chronic renal insufficiency cohort study. Wound

Repair Regen. 2013;21(1):17–24. Epub 2012 Dec 10. PMID: 23228162; PMCID: PMC3667959.
32. National Institutes of Health, Gene-NCBI. NOS3 nitric oxide synthase 3 [Homo sapiens (human)]. 2024 [citado 9 de marzo de 2024]. Disponible en: https://www.ncbi.nlm.nih.gov/gene/4846
33. Shah V. Endothelial nitric oxide synthase gene polymorphism and the risk of diabetic neuropathy in Asian Indian patients with type 2 diabetes. J Diabetes Metabolism. 2013;4(2):1–7. https://doi.org/10.4172/2155-6156.1000243
34. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865):813–20. https://doi.org/10.1038/414813a
35. National Institutes of Health. XIRP2 xin actin binding repeat containing 2 [Homo sapiens (human)]. National Library of Medicine. 2024 [citado 7 de marzo de 2024]. Disponible en: https://www.ncbi.nlm.nih.gov/gene/129446#summary
36. Colmenarez M, Silzer T, Royall DR, Palmer RF, Barber R, Phillips N. δ' is for dementia: genomic architecture of the latent variable Δ homolog (dEQ) in Mexican Americans and non-Hispanic Whites. Alzheimer's Dement. 2020;16(S3):e044205. https://doi.org/10.1002/alz.044205
37. National Institutes of Health. NTRK3 neurotrophic receptor tyrosine kinase 3 [Homo sapiens (human)]. Gene-NCBI. 2024 [citado 7 de marzo de 2024]. Disponible en: https://www.ncbi.nlm.nih.gov/gene/4916#summary
38. Cosgaya JM, Chan JR, Shooter EM. The neurotrophin receptor p75NTR as a positive modulator of myelination. Science. 2002;298(5596):1245–8. https://doi.org/10.1126/science.1076595
39. National Institutes of Health. GALNT17 - polypeptide N-acetylgalactosaminyltransferase 17 (human). Gene-NCBI. 2024 [citado 9 de marzo de 2024]. Disponible en: https://pubchem.ncbi.nlm.nih.gov/gene/GALNT17/human
40. Wada R, Yagihashi S. Role of advanced glycation end products and their receptors in development of diabetic neuropathy. Ann N Y Acad Sci. 2005;1043:598–604. https://doi.org/10.1196/annals.1338.067
41. Smith S, Normahani P, Lane T, Hohenschurz-Schmidt D, Oliver N, Davies AH. Pathogenesis of distal symmetrical polyneuropathy in diabetes. Life (Basel). 2022;12(7):1074. https://doi.org/10.3390/life12071074
42. National Institutes of Health, Gene-NCBI. IMPA2 inositol monophosphatase 2 [Homo sapiens (human)]. 2024 [citado 9 de marzo de 2024]. Disponible en: https://www.ncbi.nlm.nih.gov/gene/3613#summary
43. Clements RS. Diabetic neuropathy—new concepts of its etiology. Diabetes. 1979;28(6):604–11. https://doi.org/10.2337/diab.28.6.604
44. Singh R, Rao HK, Singh TG. Neuropathic pain in diabetes mellitus: challenges and future trends. Obes Med. 2020;18:100215. https://doi.org/10.1016/j.obmed.2020.100215
45. Yadav ML, Mohapatra B, Intergenic J, Shackelford T, editores. Encyclopedia of animal cognition and behavior. Cham: Springer International Publishing; 2017 [citado 9 de marzo de 2024]. pp. 1–5. Disponible en: https://doi.org/10.1007/978-3-319-47829-6_64-1
46. Guo K, Eid SA, Elzinga SE, Pacut C, Feldman EL, Hur J. Genome-wide profiling of DNA methylation and gene expression identifies candidate genes for human diabetic neuropathy. Clin Epigenet. 2020;12(1):123. https://doi.org/10.1186/s13148-020-00913-6
47. Tordai DZ, Hajdú N, Rácz R, Istenes I, Békeffy M, Vági OE, et al. Genetic factors associated with the development of neuropathy in type 2 diabetes. Int J Mol Sci. 2024;25(3):1815. https://doi.org/10.3390/ijms25031815
48. Bondar A, Popa AR, Papanas N, Popoviciu M, Vesa CM, Sabau M, et al. Diabetic neuropathy: a narrative review of risk factors, classification, screening and current pathogenic treatment options. Experimental Therapeutic Med. 2021;22(1):1–9. https://doi.org/10.3892/etm.2021.10122
49. Sawangjit R, Thongphui S, Chaichompu W, Phumart P. Efficacy and safety of mecobalamin on peripheral neuropathy: a systematic review and meta-analysis of randomized controlled trials. J Altern Complement Med. 2020;26(12):1117–29. https://doi.org/10.1089/acm.2020.0068
50. Xu Q, Pan J, Yu J, Liu X, Liu L, Zuo X, et al. Meta-analysis of methylcobalamin alone and in combination with lipoic acid in patients with diabetic peripheral neuropathy. Diabetes Res Clin Pract. 2013;101(2):99–105. https://doi.org/10.1016/j.diabres.2013.03.033
51. Latini A, Borgiani P, Benedittis GD, D'Amato C, Greco C, Lauro D, et al. Mitochondrial DNA copy number in peripheral blood is reduced in type 2 diabetes patients with polyneuropathy and associated with a MIR499A gene polymorphism. DNA Cell Biol. 2020;39(8):1–6. https://doi.org/10.1089/dna.2019.5326
52. Gamazon ER, Stranger BE. The impact of human copy number variation on gene expression. Brief Funct Genomics. 2015;14(5):352–7. https://doi.org/10.1093/bfgp/elv017

Publisher's note