Borneo Journal of Pharmacy
Vol 9 Issue 1 March 2026
Pages 48 – 59

https://journal.umpr.ac.id/index.php/bjop/article/view/7148
DOI: https://doi.org/10.33084/bjop.v9i1.7148
e-ISSN: 2621-4814

Research Article

Identification of Gene Variations Associated with Diabetic Neuropathy Using Bioinformatics Approach

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Keywords:
Diabetes
Hyperglycemia
Neuropathic pain
Single-nucleotide polymorphisms
Variants

Abstract

Diabetic neuropathy is the most common complication of diabetes, experienced by almost 90% of diabetic patients. Pain is one of the most common symptoms of diabetic neuropathy, but the pathophysiologic mechanism of pain is not clearly known. The hypothesis of hyperglycemia toxicity to the development of pain complications has been widely accepted worldwide, but there are still other hypotheses proposed. The basic concept in the management of painful diabetic neuropathy is to exclude other causes of peripheral neuropathic pain, improve glycemic control for prophylactic therapy, and use drugs to reduce pain. Variation data for diabetic neuropathy can be obtained from the Ensembl Genome Browser. Here, genes associated with 26 variants were selected according to Haploreg version 4.2. In addition, protein expression of missense gene variants was examined using the GTEx portal to determine two variants: rs55703767, which encodes the *COL4A3* gene, and rs141560952, which encodes the *DIS3L2* gene. According to data obtained from the Ensembl Genome Browser, the two most prevalent populations for SNP rs55703767, which is linked to the *COL4A3* gene, are in Africa, while SNP rs141560952, which is linked to the *DIS3L2* gene, is most prevalent in Africa, the Americas, East Asia, Europe, and South Asia.

Received: May 16th, 2024
1st Revised: May 21st, 2025
Accepted: December 11th, 2025
Published: March 30th, 2026

INTRODUCTION

According to the International Diabetes Federation, hundreds of millions of people worldwide are affected by diabetes, with diabetic neuropathy standing out as a primary driver of long-term morbidity. Distal symmetrical polyneuropathy (DSPN) represents the most prevalent clinical manifestation of this condition, occurring in more than 90% of affected individuals[1]. This progressive pathology typically compromises the distal toes and feet before advancing proximally to encompass the lower extremities in a characteristic glove-and-stocking distribution, driven by the progressive loss of both somatic and autonomic nerve fibers. The development of foot ulcerations and intractable painful neuropathy constitutes major clinical complications of DSPN, both of which are directly tied to elevated morbidity and mortality rates. Patients frequently delay seeking medical intervention until the onset of neuropathic pain, an exhausting symptom reported by 10% to 26% of the diabetic population[2]. Clinically, diabetic neuropathy remains a highly heterogeneous entity characterized by peripheral sensorimotor and autonomic nerve dysfunction that can remain completely asymptomatic or manifest as debilitating diabetic neuropathic pain.

How to cite: Sultan SF, Novriyanti AP, Rohmah S, Irham LM, Sulistyani N, Ma'ruf M. Identification of Gene Variations Associated with Diabetic Neuropathy Using Bioinformatics Approach. Borneo J Pharm. 2026;9(1):48-59. doi:10.33084/bjop.v9i1.7148

Patients with painful diabetic neuropathy typically describe their symptoms using diverse sensory descriptors, including intermittent or continuous burning, tingling, prickling, numbness, and hypersensitivity to thermal variations or itching, usually initiating in the lower extremities[3]. Because diabetic neuropathy is inherently a diagnosis of exclusion, clinical confirmation demands that alternative etiologies, such as chronic alcohol consumption, vitamin B12 deficiency, neurotoxic chemotherapy, chronic kidney disease, hypothyroidism, malignancies, human immunodeficiency virus (HIV) infection, chronic inflammatory demyelinating polyneuropathy, hereditary neuropathies, and vasculitis, be thoroughly systematically ruled out[4]. Chronic neuropathic pain affects approximately 13% to 26% of patients with diabetes, profoundly disrupting their overall quality of life, sleep architecture, daily functionalities, and emotional well-being. For context, epidemiological surveys underscore that the prevalence of painful polyneuropathy aligns closely with glycemic status, marking about 13.3% in diabetic cohorts, 8.7% in individuals with impaired glucose tolerance, 4.2% in those with impaired fasting glucose, and dropping to just 1.2% among individuals with normal glucose tolerance, with patient weight, advanced age, and peripheral arterial disease serving as key independent risk factors[5].

When presenting clinically, these individuals exhibit mixed sensorimotor involvement affecting both small and large nerve fibers, which initially results in sensory loss, mild impairment of tactile sensation, diminished sensitivity to pressure and vibration, and altered joint proprioception that frequently exacerbates during the night. These debilitating manifestations drastically impact multi-dimensional facets of life, including mood stability, physical mobility, professional productivity, self-esteem, and social recreation[6]. However, despite a wealth of clinical literature investigating diabetic neuropathy, a substantial knowledge gap persists regarding the specific genetic variations that govern the susceptibility, onset, and clinical manifestation of neuropathic pain. Most historical studies have focused narrowly on symptomatic pharmaceutical management and macro-clinical causes, leaving a critical shortage of validated diagnostic and prognostic biomarkers. To bridge this gap and establish a foundational framework for targeted diagnostic tools and personalized therapeutic protocols, this study leverages a rigorous bioinformatics approach to identify and characterize specific genetic variations associated with diabetic neuropathy, focusing explicitly on polymorphism dynamics within the *COL4A3* and *DIS3L2* genes, which may play pivotal roles in the underlying pathophysiology of the condition.

MATERIALS AND METHODS

Materials

The primary materials utilized in this *in silico* study comprised public genomic datasets and open-access bioinformatic repositories. The raw data matrix comprised 26 distinct single-nucleotide polymorphisms (SNPs) associated with diabetic neuropathy, each with its respective chromosomal coordinates, allelic variations, and population-specific minor allele frequencies (MAF). Computational platforms serving as data sources included the Ensembl Genome Browser (Release 112; https://www.ensembl.org/index.html) for population-level allele distributions, the HaploReg v4.2 database (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) for functional genomic annotations, and the Genotype-Tissue Expression (GTEx) portal (https://gtexportal.org/home) for tissue-specific transcriptomic profiles.

Methods

In silico variant identification and baseline mapping

For the bioinformatic data analysis, the operational workflow was systematically partitioned into distinct computational screening stages to evaluate genomic modifiers, as illustrated in the comprehensive pipeline (**Figure 1**). During the initial data preparation phase, the Ensembl Genome Browser was utilized to isolate SNP variants explicitly associated with diabetic neuropathy from the core SNP database. This automated database mining procedure yielded 26 unique SNP variants, from which comprehensive baseline coordinates were collected, including exact chromosomal positions, specific allelic or nitrogenous base substitutions, and population-specific minor allele frequencies across major global reference cohorts encompassing the Americas, Europe, Africa, East Asia, and South Asia.

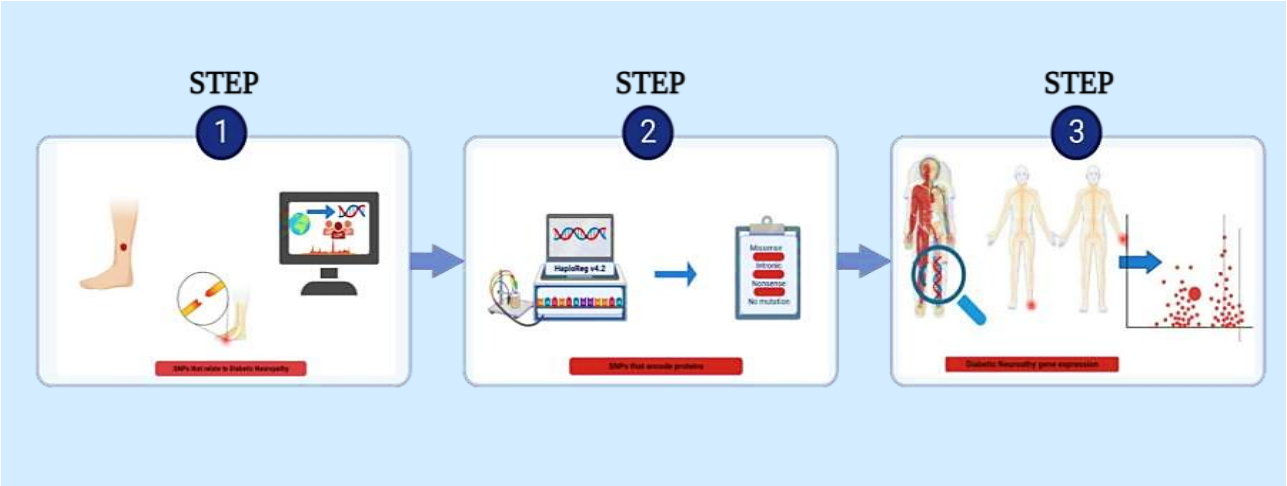

Figure 1. Bioinformatics workflow for identification of genetic variants associated with diabetic neuropathy.

Functional annotation and tissue-specific expression profiling

Following baseline extraction, the HaploReg v4.2 database was executed to map gene annotations and chromosomal localizations corresponding to each diabetic neuropathy variant, thereby identifying functional polymorphisms that directly encode or regulate structural genes. In the subsequent data collection phase, the GTEx portal was leveraged to profile tissue-specific gene expression patterns, specifically screening for functional alterations residing within missense regions among the identified SNP candidates. For downstream high-resolution examination, two specific SNP variants characterized by missense mutations were selected: rs55703767, which alters the *COL4A3* gene, and rs141560952, which alters the *DIS3L2* gene. Finally, automated outputs from the same referenced genome databases were analyzed to evaluate global population frequencies and precise allelic variations characterizing both target loci.

Data analysis

Computational data analysis was performed using a stratified genetic distribution analysis of SNP variant allele frequencies extracted across diverse global ethnic cohorts to assess regional diversity in diabetic neuropathy carriage. Following this population-level assessment, tissue-specific expression profiling was conducted using the GTEx database to systematically quantify and compare transcriptomic abundance of the *COL4A3* and *DIS3L2* genes across a wide range of human tissues. Finally, the mechanistic relevance of these specific genomic variants to the onset and progression of diabetic neuropathy was contextualized by evaluating the biological, molecular, and pathological roles of the target genes through a critical synthesis of current biomedical literature.

RESULTS AND DISCUSSION

A total of 10 SNPs were successfully retrieved from the diabetic neuropathy search queries within the Ensembl Genome Browser to map the precise allele frequencies of target variants across diverse human populations. Among these initial candidates, 2 distinct missense variants were prioritized for detailed downstream evaluation based on their potential structural effects in human tissues: rs55703767, located within the *COL4A3* gene, and rs141560952, located within the *DIS3L2* gene. The baseline tissue-specific expression criteria for the first candidate locus were systematically graphed across multiple anatomical sites to map its physiological baseline, as visualized in **Figure 2**.

The development of focal and segmental glomerulosclerosis (FSGS) in individuals carrying heterozygous *COL4A3* variants exhibits notable phenotypic variability, with only a single family member frequently presenting clinically with proteinuria and advancing FSGS. This clinical heterogeneity is heavily modulated by advancing age, concomitant hypertension, diabetes, obesity, exposure to nephrotoxic agents, or other secondary metabolic factors, though there is currently no direct evidence connecting specific mutation types to the severity of proteinuria in heterozygotes[7]. Because variants of the *COL4A3* gene map directly to chromosome 2, this phenotype is typically inherited in an autosomal recessive pattern[8]. While classic Alport syndrome remains a rare clinical entity accounting for roughly 3% of children diagnosed with end-stage kidney

disease (ESKD), thin glomerular basement membrane (GBM) variants are estimated to affect up to 1% of the global population; these variants are increasingly recognized as primary drivers of renal failure later in life, contributing to chronic kidney disease (CKD) and ESKD at rates up to four times higher than classic Alport presentations[9,10].

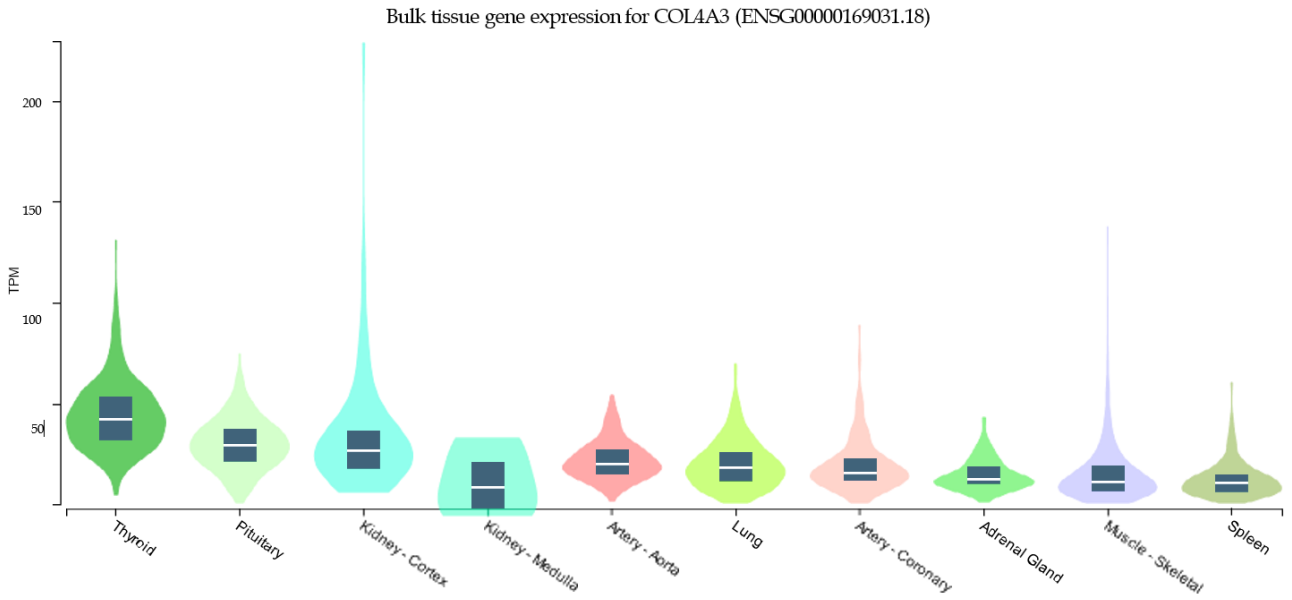

Figure 2. *COL4A3* gene expression in human tissues.

The growing clinical recognition that FSGS, manifesting either with or without accompanying thin GBMs, is explicitly tied to *COL4A3* and *COL4A4* alterations underscores the broad, overlapping phenotype characterizing the Alport syndrome disease family[11]. Consequently, a compelling body of evidence indicates that pathogenic *COL4A3* mutations actively drive the development of FSGS rather than acting as passive genetic modifiers. Pathogenic heterozygous *COL4A3* mutations are highly likely to induce independent FSGS pathology, yet their high baseline prevalence means they may also occur incidentally alongside co-existing etiologies for proteinuria[12]. For instance, patients presenting with concurrent IgA glomerulonephritis and thin basement membrane nephropathy (TBMN) or X-linked Alport syndrome are well documented, and up to 20% of families diagnosed with IgA glomerulonephritis carry pathogenic *COL4A3* variations[13]. In familial cases of focal segmental glomerulosclerosis, most lineages follow an autosomal dominant inheritance pattern, with heterozygous mutations in *COL4A3* accounting for approximately 67% (6 of 9) of mutation-positive cases[14]. Notably, autosomal dominant pedigrees exhibit greater phenotypic variability and incomplete penetrance compared to X-linked lineages, with incomplete penetrance documented in 50% (3 out of 6) of families carrying heterozygous *COL4A3* or COL4A4 variants, which aligns with historical cohort data[15]. Additionally, although no formally published reports of renal cysts linked directly to pathogenic heterozygous *COL4A3* mutations have been reported, separate laboratory registries have confirmed such occurrences, showing no clear correlation between specific variant categories (e.g., null vs. missense mutations) and the likelihood of cyst formation[12].

To compare these structural collagen dynamics with post-transcriptional regulators, the baseline expression profile for the second candidate locus was also mapped across various human tissues, as shown in **Figure 3**. In contrast, only a limited number of empirical studies have directly linked *DIS3L2* dynamics to oncogenesis, and the precise regulatory mechanisms by which *DIS3L2* acts as either a tumor suppressor or an oncogene during carcinogenesis remain open to investigation[16,17]. Experimental knockdowns of *DIS3L2* have been shown to accelerate cell proliferation and cancer cell growth[18]. The expression of the vital cell cycle regulator cyclin D1 rises sharply in cells deficient in *DIS3L2*, whereas it decreases significantly upon *DIS3L2* overexpression; conversely, the expression profiles of key cell cycle inhibitors, including p27[19] and p21[20], increase in cells overexpressing *DIS3L2*. These findings indicate that *DIS3L2* exerts a negative regulatory control over cell cycle progression[21]. Furthermore, recent functional assays indicate that *DIS3L2* actively mediates the inhibitory downstream effects of lncRNA AC105461.1 on colorectal cancer stem-cell-like traits, which are fundamentally tied to tumor maintenance, survival, and macro-metastasis, further supporting a tumor-suppressive role[16].

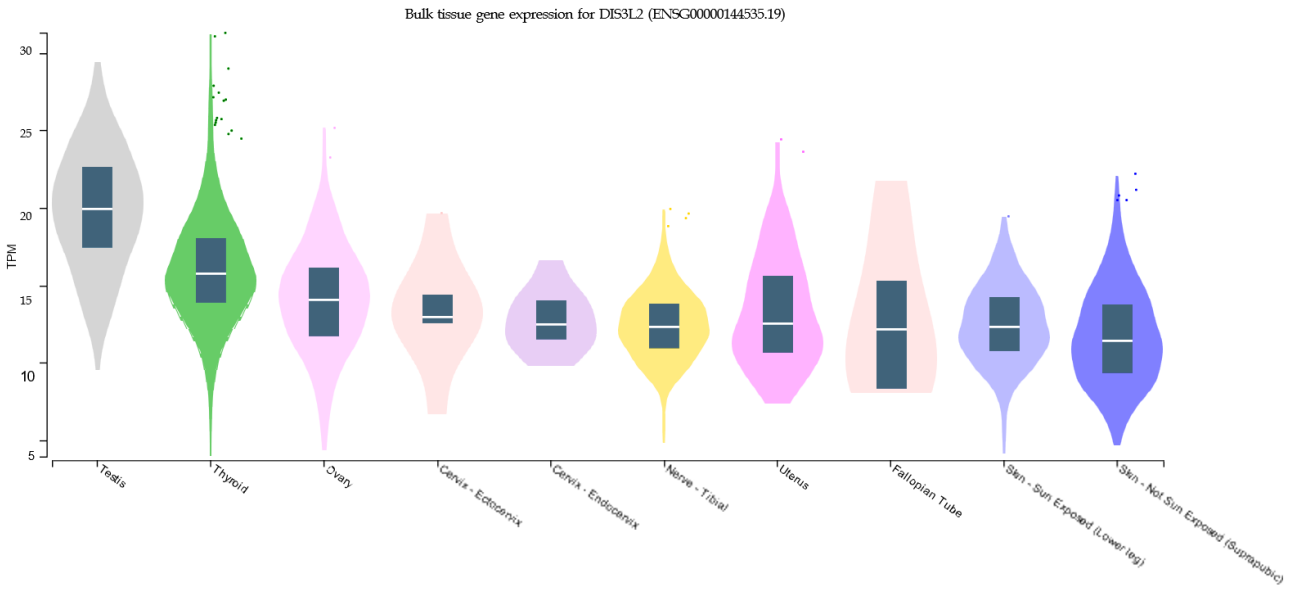

Figure 3. *DIS3L2* gene expression in human tissues.

However, alternative studies show that *DIS3L2* cooperates directly with Lin28 to suppress let-7 microRNA maturation, suggesting a potential oncogenic mechanism, as Lin28 is a characterized oncogene while the let-7 microRNA family acts as a tumor suppressor across multiple human malignancies[22]. It remains highly plausible that *DIS3L2* accelerates pathological progression by driving the targeted downregulation of pre-let-7. This biochemical relationship between *DIS3L2* and the Lin28 oncogene has been thoroughly cross-referenced using the Cancer Cell Line Encyclopedia (CCLE) database, which aggregates genome-wide expression profiles across diverse cancer cell lines[23]. Hierarchical clustering of these transcriptomic profiles revealed elevated expression of TUT4 and *DIS3L2*, along with their downstream target let-7, in Lin28b-positive malignant cells. This pattern is further corroborated by The Cancer Genome Atlas (TCGA) datasets, which confirm a positive correlation between Lin28b and *DIS3L2* expression levels in human hepatocellular carcinoma, shedding light on the potential oncogenic capacity of *DIS3L2* under specific cellular conditions[22].

Additionally, *DIS3L2* has been shown to facilitate the rapid degradation and turnover of aberrant mRNAs in response to severe cellular stressors, including retroviral infection and apoptotic signaling[24,25]. This enables cells to cope with harsh environmental pressures, such as chronic hypoxia and nutrient depletion, both of which are hallmark features of the microenvironment in degenerating tissues and tumors. To adapt to these rigorous microenvironments, cells often implement specialized survival strategies, including altering the expression of long non-coding RNAs (lncRNAs) and their downstream functions[26]. It is highly probable that *DIS3L2* regulates the expression, stability, or metabolic life cycle of these specialized lncRNAs through mechanisms that may operate independently of its standard exoribonuclease activity, granting cells the capacity to proliferate and survive under severe physiological stress. Targeted functional experiments evaluating how *DIS3L2* responds to microenvironmental stressors remain essential to clarify whether it functions predominantly as an inhibitor or a promoter within specific tissue types[27]. While research into the exact role of *DIS3L2* in cellular transformation and structural progression is still developing, emerging evidence suggests that it can act in a dual capacity as either an oncogene or a tumor suppressor, depending on the specific tissue context[16]. Although *DIS3L2* is known to regulate the turnover of specialized disease-associated substrates such as small vault RNAs and Y RNAs, it may also alter disease progression by modulating the metabolic processing of other uncharacterized RNA fractions through cryptic pathways independent of its 3'-5' exoribonuclease activity[27]. In short, the definitive cellular mechanisms of *DIS3L2* remain incompletely elucidated, and future studies must focus on uncovering its uncharacterized biological and physiological roles, particularly its complex interactions in metabolic diseases and tissue degeneration.

To systematically characterize the genetic variants associated with diabetic neuropathy across both the *COL4A3* and *DIS3L2* loci, this study utilized several interconnected genomic databases. The GTEx database was used to evaluate tissue-specific genotypes and baseline transcript abundance in human matrices, leveraging its tools to parse molecular-genomic and phenotypic datasets[28]. Additionally, the Ensembl Genome Browser was utilized as an integrated portal to aggregate high-resolution graphical mappings from OMIM, dbSNP, and the NHGRI GWAS catalogs[29]. Ensembl provides a validated

source of human genome annotation data, reference sequences, transcript models, polymorphisms, and comparative cross-species analyses directly linked to human genetic pathologies[30]. To supplement these findings, the HaploReg database was used to cross-reference GWAS hits with candidate haplotype blocks, cell-type predictions, and regulatory annotations, enabling systematic profiling of non-coding variants. This platform also enabled the direct correlation of disease-linked SNPs with tissue-specific expression quantitative trait loci (eQTL) datasets derived from the GTEx Portal[31].

Our filtering workflow yielded 26 distinct initial SNP variants from these platforms. Functional filtration confirmed that two specific polymorphisms, rs55703767 and rs141560952, encode functional missense mutations within the coding regions of the *COL4A3* and *DIS3L2* genes, respectively. The resulting structural data points, positioning details, base alterations, and broad population-level frequency markers are systematically tabulated and organized in **Table I** for comparative analysis.

Table I. Results for SNP variants, genes, locations, alleles, and population allele frequencies.

SNP	Position	Gene	Location	Allele		Allele frequency (n)				
				Ref	Eff	AFR	AMR	EAS	EUR	SAS
rs55703767	chr2:227256385 (GRCh38.p14)	*COL4A3*	Missense	G	T	G: 0.981 (1297)	G: 0.846 (587)	G: 0.871 (878)	G: 0.788 (793)	G: 0.893 (873)
rs141560952	chr2:232343414 (GRCh38.p14)	*DIS3L2*	Missense	G	-	G: 1.000 (1322)	G: 1.000 (694)	G: 1.000 (1008)	G: 0.996 (1002)	G: 1.000 (978)

Note: Ref: Reference allele; Eff: Effector/Alternative allele; AFR: African; AMR: American; EAS: East Asian; EUR: European; SAS: South Asian; (n): Total sample count per ancestral cohort.

Among these functional candidates collated in the data matrix above, missense variants within the *COL4A3* gene can modify GBM thickness, which may, downstream, alter the susceptibility to or progression of diabetic neuropathy. Interestingly, certain *COL4A3* variants appear to confer protection against diabetic neuropathy. This gene may modulate the baseline production or cellular turnover of core structural GBM components, dynamically altering basement membrane width in response to diabetic complications[32]. However, the precise mechanisms by which these structural adjustments provide tissue protection in a glucose-dependent manner remain unknown. Future mechanical studies are required to establish the exact role of this variant in diabetic kidney and nerve diseases, as uncovering its interaction with chronic glycemia could reveal therapeutic targets across multiple diabetic complications[33].

Concurrently, the *DIS3L2* gene appears to function in a context-dependent manner, acting as a tumor suppressor in some tissue environments and as an oncogenic driver in others. This functional duality likely depends on the specific profile of RNA substrates targeted by *DIS3L2* within that tissue, balancing between classical oncogenes and tumor suppressors. Further biochemical validation of *DIS3L2* expression patterns in clinical specimens will be essential to map its specific role in tissue degeneration[16]. Crucially, characterized mutations in *COL4A3* are responsible for the autosomal recessive form of Alport syndrome (a progressive inherited nephropathy) as well as benign familial hematuria, which is characterized by highly variable GBM width and is considered a milder clinical variant[34]. Furthermore, mutations at this locus have been documented in patients with primary FSGS, leading to proteinuria and progressive renal failure, often accompanied by segmental GBM depletion[27].

The candidate variant displaying the strongest statistical association, rs55703767, represents a common missense mutation in the collagen type IV alpha chain 3 gene (*COL4A3*), which encodes a principal structural component of the glomerular basement membrane. While mutations in *COL4A3* are classically associated with progressive inherited nephropathies such as Alport syndrome, the minor allele of rs55703767 (Asp326Tyr) has unexpectedly shown a protective effect against several manifestations of diabetic microvascular complications, including albuminuria and ESKD. This protective effect correlates with measurable differences in basement membrane width; carriers of this minor allele exhibit significantly thinner baseline GBM before the onset of detectable disease, a structural phenomenon that operates in a glycemia-dependent manner. Other neighboring loci identified within these chromosomal blocks reside within or near genes intimately involved in tissue biology, such as BMP7, *COLEC11*, and *DDR1*[35].

In parallel, *DIS3L2* variants are closely involved in fundamental homeostatic and physiological processes, including regulated cell division, proliferation, differentiation, and apoptosis[36]. The clinical association of *DIS3L2* with Wilms tumor, the most common childhood renal malignancy, is well established, and germline mutations at this locus are known to cause Perlman overgrowth syndrome and markedly elevate Wilms tumor susceptibility[37]. Beyond these classical associations,

accumulating evidence links *DIS3L2* to several other systemic pathologies. The targeted degradation of specific RNA substrates via its core exonucleolytic activity drives its primary biological functions, though *DIS3L2* also appears to operate through pathways independent of its 3'-5' exoribonuclease activity[26].

The specific variant rs141560952 maps directly to *DIS3L2*, which encodes an RNA-binding protein with potent exoribonuclease activity. Structurally, this protein contains two cold-shock domains (CSD) and a single S1 domain, all of which govern RNA binding, alongside a catalytic RNB domain that drives its exoribonuclease function. The 3' polyuridylation of target RNA substrates serves as the primary signal for *DIS3L2*-mediated degradation. Because the enzyme localizes predominantly to the cytoplasm, it selectively recognizes, binds, and degrades cytoplasmic uridylated RNAs, including pre-microRNAs, mature microRNAs, specific mRNAs, and various non-coding RNA species, making it a central player in cytoplasmic RNA surveillance and decay. While it is clearly involved in cell division, proliferation, and apoptosis, its broader systemic implications remain largely unmapped. This highlights the need to catalog the RNA substrates degraded by its exonucleolytic activity alongside its independent non-catalytic pathways to fully understand its role in tissue survival and disease progression[38].

To contextualize how these genetic footprints break down across global reference cohorts, a stratified multi-regional demographic analysis was conducted, as summarized in **Figure 4**. The quantitative metrics compiled across global reference cohorts illustrate a highly stratified, population-specific genetic contribution to *COL4A3* and *DIS3L2* dynamics globally. For the rs55703767 variant, the prevalence of the dominant G allele and alternative T allele demonstrated a notable geographic gradient; European (G: 79% and T: 21%), South Asian (G: 81% and T: 19%), and Admixed American (G: 85% and T: 15%) cohorts displayed lower major allele baseline frequencies compared to the significantly higher fixation rates observed in East Asian (G: 87% and T: 13%) and African (G: 98% and T: 2%) populations. Conversely, the minor allele frequency for the rs141560952(T) variant remains uniformly low or absent across all evaluated regional cohorts, exhibiting absolute or near-absolute fixation of the major allele across African (G: 100% and T: 0%), American (G: 100% and T: 0%), East Asian (G: 100% and T: 0%), European (G: 100% and T: 0%), and South Asian (G: 100% and T: 0%) lineages. This marked homogeneity indicates that the alternative variant is exceptionally rare worldwide, standing in sharp contrast to the distinct lineage-specific divergence observed at the neighboring collagen locus.

Figure 4. Summary of allele frequency analysis on *COL4A3* and *DIS3L2* gene expression in Africa, the Americas, East Asia, Europe, and South Asia.

Genomic verification via the datasets confirms that these regional variations alter individual susceptibility profiles. The high relative frequency of the protective rs55703767 variant within African groups distinguishes it from Western cohorts, where the variant remains less prevalent. Conversely, the uniform global fixation of the major allele for rs141560952 implies that

deviations at this specific exoribonuclease locus are highly evolutionary conserved, minimizing spontaneous background variability across both eastern and western hemispheres.

From a clinical management perspective, emerging studies indicate that targeted interventions can significantly reduce pain scores in patients suffering from diabetic neuropathies. Structured patient education remains an important tool for maximizing glycemic control and preventing the late-stage complications of microvascular disease[1]. Diabetic neuropathy pain is common and causes an immediate, severe decline in a patient's quality of life. Despite this high disease burden, it remains frequently underdiagnosed and undertreated in clinical practice. Disease-modifying therapies capable of directly repairing nerve tissue have yet to be successfully translated into approved clinical treatments[39].

While multiple clinical guidelines and treatment algorithms exist, real-world therapeutic outcomes are often less than satisfactory. Various symptomatic approaches are used to manage neuropathic pain, but few provide robust relief; currently, only three pharmaceutical agents hold formal FDA approval specifically for diabetic neuropathic pain[40]. Future clinical research must focus on establishing optimized combination therapies while exploiting novel molecular pathways to treat pain in diabetic neuropathy.

In conclusion, our bioinformatics pipeline successfully identified key pathogenic variants that may modulate susceptibility to diabetic neuropathy. We propose that these prioritized variants can serve as valuable candidates for future research aimed at validating diagnostic and prognostic biomarkers. However, we acknowledge the inherent limitations of purely *in silico* approaches for evaluating genetic variants in diabetic neuropathy. A primary limitation is that many identified variants reside within non-coding regions or may not represent druggable therapeutic targets. Therefore, downstream clinical validation using patient cohorts is highly recommended to confirm these preliminary findings and gain a clearer understanding of the underlying etiology and functional effects driving diabetic neuropathy.

CONCLUSION

In this study, a comprehensive bioinformatics pipeline leveraging global genomic databases successfully mapped the differential tissue expression profiles of the *COL4A3* and *DIS3L2* genes, highlighting their potential relevance to the genetic architecture of diabetic neuropathy. Recent advances in the utility of GWAS and NGS technologies continue to accelerate the discovery of high-resolution genetic variants linked to complex metabolic and neuropathic disorders. While empirical investigations into the precise hereditary risk factors underlying diabetic neuropathy remain sparse, this study prioritized two distinct missense variants, rs55703767 and rs141560952, which display distinct transcriptomic footprints across human tissue matrices. Demographic evaluation revealed that the alternative effector alleles for rs55703767 and rs141560952 exhibit clear geographical stratification, demonstrating lower baseline frequencies within African (rs55703767 at 2%, rs141560952 at 0%), South Asian (rs55703767 at 11%, rs141560952 at 0%), and East Asian (rs55703767 at 13%, rs141560952 at 0%) populations relative to the higher proportions observed across Admixed American (rs55703767 at 15%, rs141560952 at 0%) and European (rs55703767 at 21%, rs141560952 at 0%) cohorts.

ACKNOWLEDGMENT

The authors express their profound gratitude to all individuals who provided logistical and technical support throughout this study, with particular recognition extended to Universitas Ahmad Dahlan for granting access to the vital resources, facilities, and institutional infrastructure necessary for the successful execution of this research. Additionally, sincere appreciation is due to the academic staff and departmental colleagues whose insightful discussions, administrative facilitation, and collaborative encouragement significantly enhanced the quality and progress of this work.

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DATA AVAILABILITY

The primary datasets generated, compiled, or evaluated during the course of this study are fully incorporated into the body of the published manuscript and its accompanying supplementary materials. Any underlying raw data elements or extended bioinformatics matrices that support the empirical conclusions of this research, but are not explicitly presented within the text, remain accessible from the corresponding author upon receiving a justified and reasonable request.

CONFLICT OF INTEREST

The authors declared no conflict of interest related to this research.

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