REVIEW

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Impact of Genetic Polymorphisms on Bortezomib-Induced Peripheral Neuropathy in Multiple Myeloma: A Systematic Review and Bioinformatics Analysis

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Abstract

Background: Bortezomib, a 26S proteasome inhibitor, has become a cornerstone in the treatment of multiple myeloma. However, its use is limited by a common and potentially serious adverse effect, bortezomib-induced peripheral neuropathy (BIPN), which manifests in 30-60% of multiple myeloma patients primarily as a sensory, distal, axonal neuropathy, often with pain, numbness, tingling, and in some cases, motor involvement, which can lead to dose reductions, therapy discontinuation, or long-term morbidity. BIPN is associated with genetic predisposition, and several studies suggest that single-nucleotide polymorphisms (SNPs) may contribute to the protective or increased risk effects of BIPN. This study aimed to investigate the genetic basis of BIPN in multiple myeloma. **Methods:** A qualitative systematic review was conducted to determine unique SNPs with significant association with BIPN. The search was performed using PubMed, Embase, Scopus, Web of Science, Google Scholar, Cochrane Library, ScienceDirect, and ClinicalTrials.gov. The risk of bias analysis was conducted following the Q-Genie protocol. The included SNPs were computationally analyzed using Gene Ontology enrichment, KEGG, and PPI network analyses to determine pathways implicated in BIPN. SNPnexus analysis was applied, including SIFT and PolyPhen-2 functional prediction, evolutionary conservation, epigenetic regulatory mapping, significant biological pathways, and population allele frequencies. **Results:** From a total of 9 studies, 48 SNPs increase the risk of BIPN, while 21 are protective. Computational analyses revealed that SNP-associated BIPN genes are implicated in xenobiotic response, detoxification, signal transduction, and inflammatory pathways. SIFT and PolyPhen-2 identified some variants with a potential impact on protein function. Several SNPs are conserved, which reflects their functional roles. Allele frequencies are distinct, with some SNPs being rare and others showing uneven distribution across populations. **Conclusions:** Genetic variants probably play a significant role in the development of BIPN. The findings provide a mechanistic framework for predictive genotyping and personalized therapeutic strategies to mitigate BIPN in multiple myeloma patients.

Keywords: multiple myeloma- bortezomib- bortezomib-induced peripheral neuropathy- genetic polymorphism

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Introduction

Multiple myeloma is a hematological malignancy characterized by clonal proliferation of plasma cells in the bone marrow, leading to anemia, bone defects, renal disease, and immunodeficiency [1]. Over the last 20 years, the survival rate of multiple myeloma patients has significantly increased due to the introduction of proteasome inhibitors, including bortezomib. Bortezomib, a reversible 26S proteasome inhibitor, impairs intracellular proteolysis and promotes apoptosis of malignant cells; thus, it is a pillar in the multiple myeloma treatment [1].

Although the therapeutic effect of bortezomib is highly valued, bortezomib has been reported to be highly prone to adverse effects, with the most clinically critical being bortezomib-induced peripheral neuropathy (BIPN) [2]. BIPN causes severe, bilateral, sensorimotor neuropathy, which frequently causes delays in treatment, dose adjustments, or withdrawal, which reduces the effectiveness and efficacy of treatments and affects patient quality of life. It has been reported that BIPN can occur in up to 30-60 percent of patients using bortezomib, and a high proportion of them may develop moderate to severe neuropathic symptoms [3].

The pathophysiology of BIPN is not fully comprehended but is thought to be a complicated combination of

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oxidative stress impact, mitochondrial errors, endoplasmic reticulum stress, and neurotrophic signaling disturbance, a key mechanism involves mitochondrial dysfunction in dorsal root ganglia neurons, leading to impaired ATP production and increased reactive oxygen species (ROS), which trigger oxidative stress and neuronal damage [4]. Bortezomib-induced inhibition of the ubiquitin-proteasome system causes the accumulation of misfolded proteins in neurons, resulting in endoplasmic reticulum stress, activation of the unfolded protein response (UPR), and neuronal apoptosis. This cellular stress particularly affects sensory neurons due to their long axons and high metabolic demand [5].

Different incidences and severity in patients imply that individual genetic predisposition may contribute to the development of BIPN [6–8]. Current research has examined the role of single-nucleotide polymorphisms (SNPs) in BIPN predisposition. Polymorphisms in genes involved in drug metabolism, nerve repair, and inflammatory pathways have been suggested [6, 9]. These SNPs are located in genes involved in drug transport and metabolism, neurodevelopment and repair, and immune regulation. Awareness of these genetic mechanisms may pave the way for tailored therapeutic approaches to minimize neurotoxicity.

Considering the clinical significance and the lack of clear understanding regarding the mechanisms of BIPN, a systematic review was conducted to collate the evidence addressing genetic variance regarding BIPN. Bioinformatics analyses were also performed, in addition to qualitative synthesis, to strengthen the results and clarify possible implicated biological pathways. This integrative approach seeks to identify predictive genetic markers, clarify underlying mechanisms, and inform future research directions for personalized medicine in multiple myeloma treatment.

Materials and Methods

Study protocol and registration

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards. The protocol was pre-registered for inclusion in the International Prospective Register of Systematic Reviews (PROSPERO: CRD420251061928). The review systematically identifies and synthesizes studies examining the association between SNPs and BIPN in multiple myeloma patients. It qualitatively identifies significant SNPs related to PN, either negatively or positively, determines gaps in the current literature, and suggests directions for future research.

Source of data and search strategy

In the search strategy, the PECO framework was followed: (P) the target population includes patients receiving bortezomib either as monotherapy or in combination; (E) the exposure of interest is the presence of specific genetic polymorphisms; (C) for comparison, the control group includes patients who received bortezomib-based treatment regimens and did not develop peripheral neuropathy or only exhibited mild or subclinical symptoms (grade 0-1); and (O) the main outcome of interest is the occurrence of BIPN of grade 2 or higher. The search was conducted using PubMed, Embase, Scopus, Web of Science, Google Scholar, Cochrane Library, ScienceDirect, and Clinical Trials. Each database was searched using relevant keywords and Boolean operators using the following formula, ((Bortezomib OR Velcade OR "proteasome inhibitor") AND (peripheral neuropathy OR neuropathy OR neurotoxicity OR "chemotherapy-induced neuropathy" OR "drug-induced neuropathy" OR "sensory neuropathy" OR "autonomic neuropathy" OR polyneuropathy) AND (multiple myeloma OR myeloma OR "plasma cell dyscrasia" OR "hematologic malignancy") AND (SNP OR "single nucleotide polymorphism" OR "genetic polymorphism" OR "genetic variant" OR "genetic susceptibility" OR pharmacogenetics OR pharmacogenomics OR "genome-wide association study" OR GWAS OR "candidate gene study" OR "inherited polymorphism" OR "genetic predisposition" OR "molecular markers" OR biomarker OR "genetic variation" OR "pharmacogenetic biomarkers")).

Eligibility criteria

The studies in the English language that met the following criteria were included: case-control, cohort studies (prospective or retrospective), cross-sectional, clinical trials, pharmacogenetics studies, and genome-wide association studies that explore the relationship between genetic polymorphism and peripheral neuropathy caused by bortezomib-based treatment. Studies involving multiple myeloma patients aged 18 years or older, of any ethnic origin, race, or gender, treated with bortezomib either as monotherapy or in combination with other drugs, reported significantly associated SNPs with either increased risk or protective effects. The exclusion criteria consisted of review articles, systematic reviews or meta-analyses, abstracts, posters, animal studies, and case reports without extractable data, studies that had not examined the association between genetic polymorphisms and adverse effects, studies that lacked data on genetic polymorphisms or did not specify bortezomib as part of the treatment regimen, and studies that examined neuropathy caused by non-bortezomib-based protocols.

Data extraction

The screening process was done through two distinct stages. The initial stage involved screening titles and abstracts, which was done using Rayyan (https://www.rayyan.ai/), a tool that facilitates screening. Studies that met the inclusion criteria advanced to the second stage, which is the full-text screening stage, where the study was evaluated in terms of eligibility. Three reviewers utilized an Excel sheet to extract data from the eligible studies, and any conflicting assessments during the screening process were handled through consensus. The collection of data involved: article details (first author name, publication year, and study design), sample size, ethnicity, genotyping method, and therapy protocol. The treatment duration information was also included. Three reviewers performed independent extraction of all genetic markers, which included genes, SNPs, alleles, and SNP types that existed

in the main text, figures, and tables. Supplementary materials were also reviewed to ensure completeness. The reference SNP (rs) number for every SNP was retrieved directly from the studies. Allele and SNP type information was extracted when reported, or retrieved from NCBI resources when absent. In exploratory GWAS, only validated and reported polymorphisms with either protective or risk effects related to BIPN in MM patients were included. Unlike GWAS, other clinical studies had no such limitations. We selected significant and associated SNPs based on their odds ratios (OR), hazard ratios (HR), and risk ratios (RR), considering statistical significance at a 95% confidence interval and p-value < 0.05. Significantly associated SNPs mentioned in the main text were also considered.

Risk of bias assessment

The methodological quality and risk of bias in the included genetic studies were assessed using the Q-Genie tool (Quality of Genetic Association Studies). This tool contains 11 criteria covering aspects such as study rationale, selection and definition of the outcome of interest, group comparability, technical classification of the exposure, non-technical classification of the exposure, other sources of bias, sample size and power, a prior planning of analyses, statistical methods and control for confounding, testing of assumptions and inferences for genetic studies, and appropriateness of inferences drawn from results. Each item was scored on a 7-point Likert scale (1 = poor, 3 = good, 5 = very good, and 7 = excellent), following Q-Genie guidelines. Studies with a control group were categorized as low quality (≤35), moderate quality (36-45), or high quality (>45) based on their total scores [10]. Three independent assessments were performed, and discordances were resolved by consensus. To create the risk of bias assessment figure, three R packages were used: ggplot2, readxl, and dplyr.

Gene ontology analysis

Gene ontology enrichment analysis of SNP-associated genes was performed using an over-representative analysis (ORA) and a genome protein-coding reference set on WebGestalt (http://www.webgestalt.org/process.php). In this study, the biological process, cellular component, and molecular function were focused on, and the findings were represented as bar and bubble plots and then interpreted accordingly. The selection criteria for SNP-associated genes submitted to the server for analysis were ORA query, FDR < 0.05, and the Benjamini-Hochberg method for multiple test adjustment. The visualization was built using ggplot2 in R. Data with P<0.05 are selected and presented.

KEGG pathway enrichment analysis

SNP-associated BIPN genes were analyzed for the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway using Database for Annotation, Visualization, and Integrated Discovery (DAVID version 6.8; https://david.ncifcrf.gov/tools.Jsp), a set of functional annotation tools. SNP-associated genes were submitted to the server for analysis as a query in DAVID with Homo Sapiens and FDR < 0.05 as selection criteria. KEGG analysis was utilized because this study is a systematic review that synthesizes SNPs reported across multiple independent studies with heterogeneous populations, study designs, and statistical models, precluding the use of rank-based SNP enrichment methods that require uniform GWAS statistics. The visualization was created in R using the ggplot2 package to represent significantly enriched KEGG pathways, with a P-value < 0.05. Modified Fisher's exact test was used to analyze data, and Benjamini-Hochberg FDR was applied for multiple testing correction.

Construction of protein-protein interaction network

The protein-protein interaction (PPI) network of SNP-associated genes was analyzed and constructed using Search Tool for the Retrieval of Interacting Genes/Proteins (STRING version 12.0; https://string-db.org/). SNP-associated genes were uploaded based on the settings selection of "Homo sapiens" model, medium FDR stringency < 0.05, and 0.4 confidence for the interaction between the targets. The network nodes represent proteins, and the edges reflect the SNPs-associated protein–protein interactions. The interaction network generated in STRING incorporated multiple evidence types, including text-mining, experiments, databases, co-expression, neighborhood, gene fusion, and co-occurrence. Furthermore, Cytoscape software was utilized to visualize the network based on a hierarchical layout.

Functional annotation of genetic polymorphisms

This research focused on analyzing 69 retrieved unique SNPs through the SNPnexus tool (https://www.snp-nexus.org/v4/), a comprehensive web-based tool for the functional annotation of genetic variants. The tool analyzes variants by accepting input via genomic coordinates, dbSNP, or a chromosome region. SNPs were submitted for analysis by selecting the GRCh38/hg38 human genome assembly. Through SNPnexus, each variant to multiple gene models was mapped, including RefSeq, Ensembl, UCSC, Vega, and AceView. The tool created associations between gene models and each variant to demonstrate potential functional consequences involving coding changes, such as synonymous and non-synonymous mutations, intronic regions, UTR, splice sites, and upstream and downstream effects. The tool exhibits the potential impact of non-synonymous coding variants on protein function through the integration of SIFT and PolyPhen predictive scores. In addition, the tool integrated data from references to disease associations from ClinVar and COSMIC databases. The tool enables users to access results through functional consequence sorting and allele frequency and phenotypic relevance sorting options, while also providing filtering functions. This comprehensive annotation provided an enhanced explanation regarding the potential biological impact of the examined SNPs. This test presented functional biological pathways of SNPs-associated genes [11].

Genomic evolutionary rate profiling and PHAST conservation annotation

The genomic evolutionary rate profiling (GERP) test

predicts the evolutionarily conserved SNPs at a nucleotide "Base RS Score" or across a region "Element RS Score" by comparing expected versus observed substitutions. Phylogenetic Analysis with Space/Time models (PHAST) was also conducted to select conservation speed and probability of SNPs by comparing genomes across multiple species (multiple species alignment). Both GERP and PHAST are important for measuring the conservation rate among specific elements or regions. This analysis was conducted using the SNPnexus tool.

Exome gnomAD analysis

Allele frequencies for exonic variants were collected from gnomAD exomes, a large public reference set as provided by SNPnexus annotations, to document variant prevalence across global populations and specific subgroups. Exome-wide allele frequencies analysis among 8 global populations was performed to identify fundamental heterogeneity and variants distributed across specific populations. The following populations were included in the analysis: African/African American (AFR), Admixed American (AMR), Ashkenazi Jewish (ASJ), East Asian (EAS), Finnish (FIN), Non-Finnish European (NFE), other populations (OTH), South Asian (SAS).

Epigenetic regulatory functions of genetic polymorphisms

Regulatory and epigenomic context was assigned by intersecting SNP coordinates with ENCODE via SNPnexus outputs to capture DNase hypersensitivity, histone-mark peaks, chromatin states, and transcription-factor motif alterations; variants overlapping active promoters/enhancers or high regulatory scores were flagged as candidate regulatory SNPs.

Statistical analysis

Data analyses and visualizations were performed using the R programming language version 4.3.3. A p-value threshold of < 0.05 was considered statistically significant.

Results

Eligible studies characterizations

The initial screening included 1,508 studies, which were then reduced to 1,149 studies after removing duplicate articles. A total of 9 studies were finally included in the study from the full screening studies (48) according to the inclusion criteria (Figure 1A). The included studies were focused on the significant correlation between BIPN and SNPs in multiple myeloma patients. Different types of study designs existed in the included studies, such as case-control, prospective cohort, GWAS, and pharmacogenetic studies across various regions, with most being European [6–9,12–16]. In addition, therapy protocols included either bortezomib alone or in combination, as well as varied genotyping methods (Table 1). Each included study highlighted the PN and non-PN groups and sample sizes.

Treatment duration and exposure across included studies

Treatment exposure and timing of BIPN were variably reported across the nine included studies. Broyl et al. (2010) clearly defined treatment duration (three 21-day induction cycles; around 9 weeks), distinguished early- versus late-onset BIPN, and reported median time to BIPN (42 days) and cumulative dose at onset, thereby inherently controlling for exposure within the induction phase. On the contrary, Campo et al. (2016) and Campo et al. (2018) classified cases by BIPN severity but did not report the number of cycles, cumulative dose, total duration, or onset timing, and treatment exposure was not adjusted for. Corthals et al. (2011) reported median time to BIPN onset (around 6-7 weeks) but did not include cycle number or cumulative dose as covariates, nor stratify analyses by onset timing.

Favis et al. (2010) is an exception: cohorts differed markedly in exposure; VISTA allowed up to nine 6-week cycles (up to 52 doses), while IFM 2005-01 allowed four 3-week cycles (up to 16 doses), and the authors explicitly used time-to-event methods (Cox proportional hazards) and cumulative-dose-to-onset endpoints (with baseline covariates) to account for treatment duration/exposure in the genetic analyses; the paper therefore considered duration and cumulative dose directly and compared cohorts with different exposure schedules.

Magrangeas et al. (2016) described different induction regimens between cohorts but did not adjust genetic analyses for cycles, duration, or cumulative dose, defining cases by severity only. Min et al. (2024) reported clinical covariates but did not include treatment duration or cumulative dose in analyses. Zhang et al. (2024) applied a minimum cycle requirement in eligibility ($\geq$3 cycles unless stopped early due to BIPN) but did not analyze or adjust for variation in cycles or dose. Zhou et al. (2023) reported cumulative dose differences between BIPN and non-BIPN patients, yet did not adjust genetic comparisons for this exposure.

Overall, only Favis et al. formally modelled treatment duration/exposure, while most studies either incompletely reported or did not adjust for exposure, a key consideration when interpreting genetic associations given the dose- and time-dependent nature of BIPN. The frequent absence of duration adjustment underscores the common scope of pharmacogenetic studies, which prioritize the discovery of hereditary susceptibility variants over the analysis of treatment dose-response relationships.

Quality assessment

The quality of data in the nine eligible studies was evaluated using the Q-Genie tool, which comprises 11 questions and a quality assessment score on a 7-point Likert scale ranging from poor (1) to excellent (7). Overall, the quality of all studies was high (scores > 45), with one study evaluated as moderate (scores from 36 to 45), as shown in Figure 1B. All included studies have a control group, which makes them eligible for this scoring scale.

Polymorphisms associated with BIPN

SNPs significantly associated with BIPN were retrieved from the included studies. The total number of significantly associated SNPs that increase the risk of BIPN (grades 2-4) was 49 (48 unique SNPs and 1

Table 1. Characteristics of the Included Studies Related to the SRignificant Association between BIPN and SNPs.

No.	Author and year	Study design	Ethnicity	Genotyping method	Therapy protocol	Sample size			Reference
						Total	PN	Non-PN	
1	Broyl et al. [6]	Case-control study	European	Affymetrix Targeted Genotyping custom panel.	PAD, 1 cycle of BZ	160	13	147	[6]
					PAD, 2-3 cycles of BZ	129	49	80	
2	Campo et al. [12]	Case-control study	German	Illumina Human OmniExpress arrays.	BZ	646	102	544	[12]
3	Campo et al. [13]	GWAS	German	Illumina Human OmniExpress arrays	PAD, PAd, VCD	646	102	544	[13]
4	Corthals et al [14]	Pharmacogenetic study	European	Affymetrix Targeted Genotyping custom panel	Discovery: VD	238	72	166	[14]
					Validation: PAD, BZ	231	69	162	
5	Favis et al. [9]	Pharmacogenetic study	Caucasian (Europe, North America)	Nuclear SNPs: Illumina iSelect custom chip. Mitochondrial SNPs: SNPlex/PCR-LDR.	VISTA: VMP	139	76	67	[9]
					IFM 2005-01: VD	212	51	161	
6	Magrangeas et al. [15]	GWAS	European	Affymetrix SNP 6.0 arrays, Birdseed (exploratory), and CRLMM v2 (replication).	Exploratory Cohort (IFM): VD, 4 cycles of BZ	469	155	314	[15]
					Replication Cohort (HOVON): VD, 3 cycles of BZ	114	40	74	
7	Min et al. [7]	GWAS	South Korean	Discovery cohort: Infinium Global Screening Array-24 v3.0 BeadChip.	VD, VMP, VTD	185	86	99	[7]
				Validation cohort: MassArray system (Agena Bioscience).					
8	Zhang et al. [8]	Case-control study	Chinese	Next-generation sequencing (NGS) with a custom panel (233 drug metabolism-related genes).	VD, VTD, VRD	204	115	89	[8]
9	Zhou et al. [16]	Prospective cohort study	German	Sanger sequencing	BZ	88	29	59	[16]

PAD, bortezomib, doxorubicin (Adriamycin), dexamethasone; BZ, bortezomib; GWAS, genome-wide association study; PAD, bortezomib, doxorubicin (Adriamycin), dexamethasone; PAd, bortezomib, liposomal doxorubicin, dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VD, bortezomib, dexamethasone; VMP, bortezomib, melphalan, prednisone; VTD, bortezomib, thalidomide, dexamethasone; VRD, bortezomib, lenalidomide (Revlimid), dexamethasone.

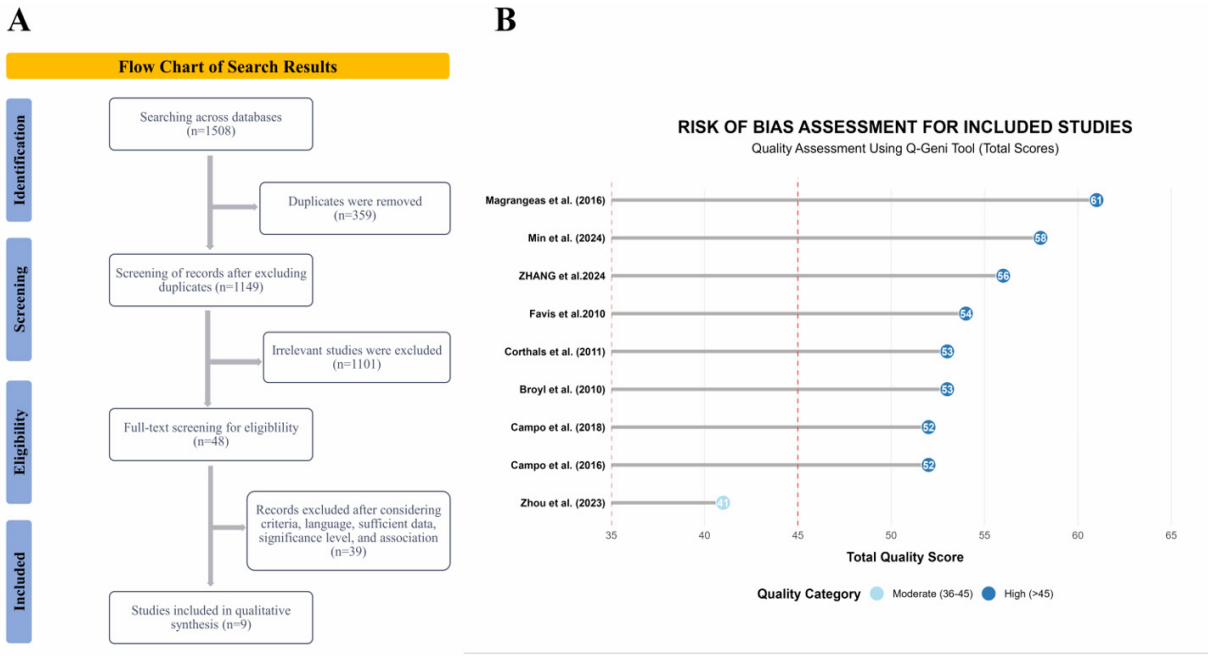

Figure 1. PRISMA Flow Chart of Search Results and Included Studies, and Risk of Bias Assessment for Included Studies Using the Q-Geni Tool

repeated). The OR and p-values were mentioned in all included studies, except for the article by Zhou et al. (2023), in which the authors stated that SNPs are associated with increased susceptibility to BIPN. Moreover, the findings indicate 21 SNPs associated with decreased risk of BIPN (protective). These SNPs were presented in multiple genes; however, few were identified as loci, chromosomes, or parts of genes, such as (8.3 kb 5′ of NFATC1, LOC105373177, Chr7:54151514, LOC729254, Chr21:19036091, LOC105374754, Chr21:24697514, and LOC105373727). Furthermore, these SNPs occurred as single or multiple alleles and represented distinct types, such as intronic, coding non-synonymous, 5′-UTR, or missense variants. The PKNOX1 rs2839629 SNP was reported in two studies, Zhou et al. 2023 and Magrangeas et al. 2016, both of which associated it with an increased risk of BIPN. Intron represents the most common allele type among the included SNPs. Tables 2 and 3 provide a detailed description of all included polymorphisms.

Gene ontology, KEGG enrichment analyses, and protein-protein interaction network

Gene ontology enrichment analysis showed that SNPs are located in multiple genes possessing distinct biological processes, cellular components, and molecular functions. The SNP-associated BIPN genes are significantly related mostly to biological regulation, response to stimuli, and metabolic processes (Figure 2A). Regarding the cellular component's roles, the genes involved in multiple functions, such as endomembrane and nuclear synthesis, the SNP-associated BIPN genes play critical roles in metabolic pathways, including xenobiotic, hormone, and lipid pathways. Other genes are associated with wound healing, response to stimuli or radiation, and regulatory processes (Figure 2B).

KEGG pathway enrichment analysis of the included genes revealed five highly enriched pathways (Fold Enrichment (FE) $\geq$ 5.0) that dominate the outcomes, indicating robust biological correlation with particular disorders. For example, ABCC1, MTHFR, and ALOX12 are highly integrated in antifolate drug resistance, and CASP9 and NFATC1 correlate with HIV-1 infection. Furthermore, the findings revealed one moderately enriched pathway (FE $\geq$ 2.0) involved in cancer pathways, such as CASP9, END, and DCC. The significance of KEGG pathway enrichment, p-value, gene count, and FE is represented in Figure 2C.

The PPI network of SNP-associated BIPN genes is constructed using the STRING database, and the criteria include medium FDR stringency < 0.05 and 0.4 confidence for the target interaction. The network nodes exhibited proteins, and edges reflected the BIPN protein-protein interactions. The SNP-associated BIPN gene regulatory network is densely connected, and its characteristics are 49 nodes, 42 edges, 1.71 average node degree, 0.416 average local clustering coefficient, 22 expected number of edges, and 6.36e-05 PPI enrichment p-value, indicating a strong interconnectedness among the encoded proteins (Figure 3A). These findings suggest overlapped biological pathways implicated in BIPN.

Biological pathways analysis by SNPnexus

Analysis of significant pathways for the SNP-associated BIPN genes was performed by SNPnexus. Eighteen biological pathways related to SNPs were identified. The highest percentage of SNPs is particularly located in genes related to immune system function, signal transduction, and metabolism, and some genes have various roles, such as PSMB4, PSMB1, ATM, and BTRC (Figure 3B).

Table 2. Significantly associated SNPs Implicated in Increasing the Risk of BIPN in Multiple Myeloma Patients

No.	Author and year	Gene	SNP	Allele	Type of SNP
1	Broyl et al. [6]	*RDM1*	rs2251660	A>C, G*	Coding non-synonymous
2		*CASP9*	rs4646091	T>C*	Intron
3		*ALOX12*	rs1126667	A>C, G, T*	Coding non-synonymous
4		*ALOX12*	rs434473	A>C, G*	Coding non-synonymous
5		*LSM1*	rs7823144	G>A*	Intron
6		*ERCC4*	rs1799800	G>A, T*	Intron
7		*ERCC4*	rs1799801	T>C*	Coding synonymous
8		*IFNGR2*	rs1059293	C>A, T*	Untranslated, intron
9		*ERCC3*	rs2276583	G>A, C*	Locus
10		*MRE11A*	rs10501815	C>A*	Intron, TagSNP
11	Campo et al. [12]	*PSMB4*	rs7172	G>A, C, T*	Coding synonymous
12		*MED20*	rs2274578	C>G*	5′-UTR
13		*F2*	rs3136516	G>A*	Intron
14		*8.3 kb 5′ of NFATC1*	rs9954562	C>T*	NP
15	Campo et al. [13]	*Near TENM3*	rs6552496	A>C	Intergenic linked to enhancer regions
16		*Near THBS4*	rs12521798	G>A	Intergenic linked to enhancer regions
17		*CDH13*	rs8060632	C>A	Intron
18		*DCC*	rs17748074	G>A	Intron
19	Favis et al. [9]	*CTLA4*	rs4553808	A>G	Flanking 5′ UTR
20		*PSMB1*	rs1474642	A>G	Intron
21		*CTSS*	rs12568757	A>G	Intron
22		*GJE1*	rs11974610	G>A	Flanking 5′ UTR
23		*DYNC1I1*	rs916758	A>G	Intron
24	Magrangeas et al. [15]	*PKNOX1*	rs2839629	G>A	3’ UTR
25	Min et al. [7]	*LOC105373177*	rs6520592	T^>C	Intron
26		*Chr7:54151514*	rs11238298	C^>T	NP
27		*LOC729254*	rs6708269	G^>A	Intron
28		*LINC01593*	rs7574949	A^>G	NP
29		*PLEKHG1*	rs1492577	T>C^	Intron
30		*Chr21:19036091*	rs6517852	A>G^	NP
31		*LINC02331*	rs2884439	T>G^	Intron
32		*SMOC2*	rs2342645	T>G^	Intron
33		*LOC105374754*	rs2418495	C>A^	Intron
34		*Chr21:24697514*	rs2829271	A>G^	NP
35		*Chr15:66896240*	rs12593557	G>A^	NP
36		*ASIC2*	rs9902778	A>G^	Intron
37		*LOC105373727*	rs4144827	T^>A	2 KB upstream variant
38		*ASIC2*	rs1490895	A>G^	Intron variant
39		*P4HA3*	rs3741132	G>A^	Stop gained
40	Zhang et al. [8]	*MTHFR*	rs1801131	T>G^	Exon region
41		*MTHFR*	rs1801133	G^>A	Exon region
42		*MTHFR*	rs17421511	G>A^	Intron
43		*EPHX1*	rs1051740	T^>C	Exon region
44		*MME*	rs2016848	G>A^	Intron
45		*ALDH1A1*	rs6151031	GCTins/G GCTins/G+G/G	2 KB upstream variant
46		*HTR7*	rs1935349	C>T^	Intron
47		*CYP2A6*	rs8192720	G>A^	Exon region
48	Zhou et al. [16]	*PKNOX1*	rs2839629	G>A^	3’ UTR
49		*PKNOX1-CBS*	rs915854	C>T^	Intergenic region

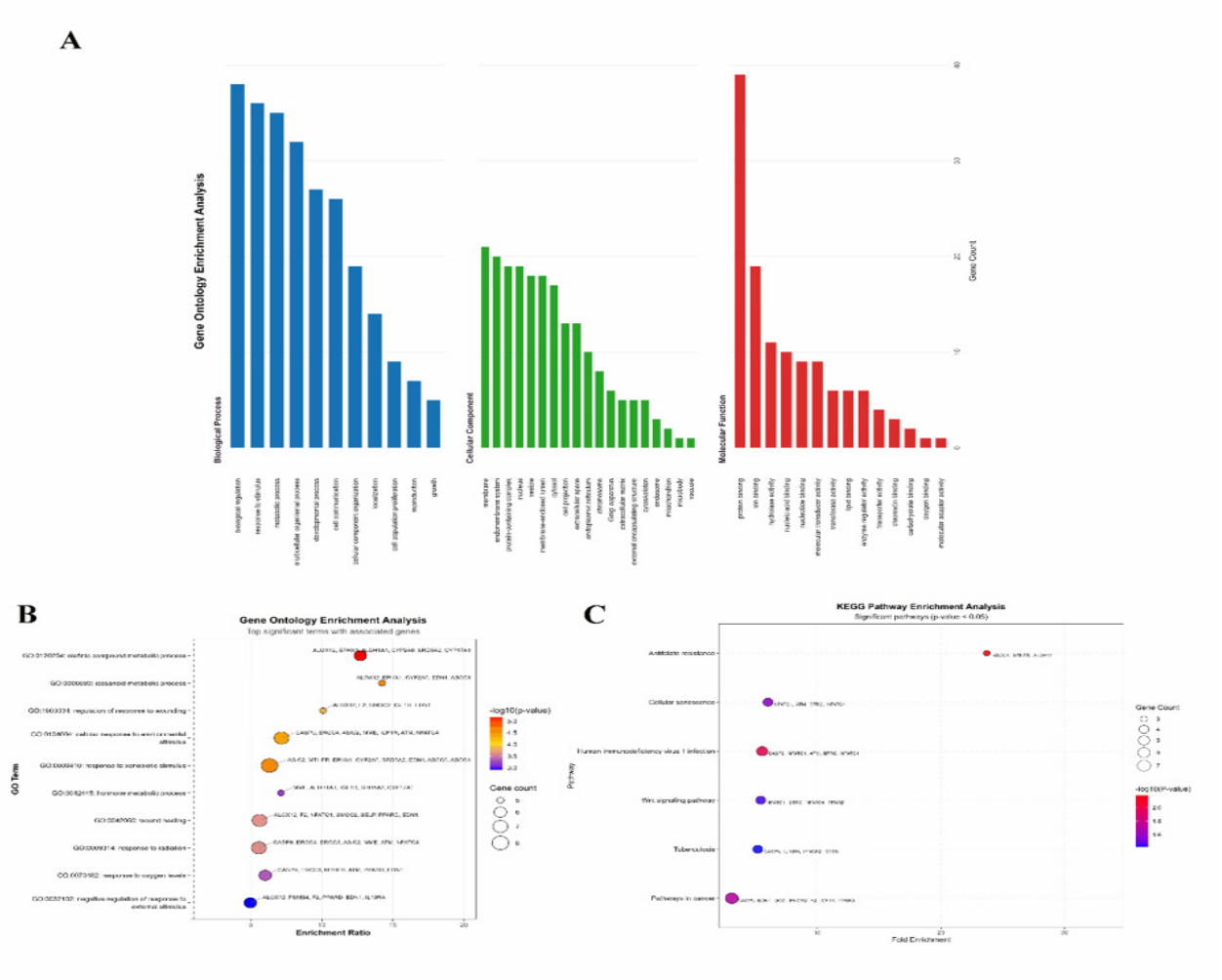

Figure 2. Gene Ontology and KEGG Enrichment Analyses of SNPs Associated with BIPN in Multiple Myeloma. (A) Biological process categories, cellular component categories, and molecular function categories. (B) Gene ontology enrichment analysis. (C) KEGG pathway enrichment analysis. Data with a P-value > 0.05 were included.

Functional impact prediction of SNPs

SNPnexus was utilized to analyze the included SNPs, which were subsequently scored using SIFT and PolyPhen-2 algorithms. SIFT indexing identified a total of 52 SNP variants as "Tolerated," which are unlikely to cause changes in protein function, and 15 SNPs as "Deleterious," which are likely to affect protein function. The analysis included multiple transcripts for the same SNP. In addition, some SNPs were identified as tolerated and deleterious, such as rs1801133 and rs1029871, but in different transcripts (Figure 3C).

PolyPhen-2 indexing identified 24 SNPs with no potential impact termed as "Benign", 4 SNPs may cause an impact on protein function termed as "Possibly Damaging", and 14 SNPs are more likely to affect protein structure/function termed as "Probably Damaging" (Figure 3D). Both tests help in identifying the possible impact of SNPs on the BIPN in multiple myeloma patients by recognizing their hosted genes and roles. More details about SNPs and their functional impacts are found in the supplementary files.

GERP and PHAST conservation analysis

GERP test estimates the evolutionarily conserved SNPs at a nucleotide "Base RS Score" or across a region "Element RS Score" by comparing expected versus observed substitutions. The findings identified strong functional constraint SNPs (Base RS score >2) in a highly conserved functional element across mammalian evolution, such as rs1801131, rs4151060, and rs4722266, indicating that these elements are significant for gene function and mutations at these regions are less likely to occur, as they are conserved by natural selection. Higher Element RS Scores for SNPs refer to strong conservation across regions. The test also detected fast-evolving SNPs (Base RS score < 0), such as rs1545981 and rs1126667. However, the Element RS score for both SNPs was high, indicating that the broader genomic region, such as an exon or regulatory element, is highly or moderately conserved evolutionarily. This suggests that the specific nucleotide where the SNP is located is not constrained, implying that the site itself may be fast-evolving or poorly aligned, potentially due to local sequence divergence rather than selective pressure (Table 4).

PHAST was also utilized to identify conservation speed and probability of SNPs by comparing genomes across multiple species (multiple species alignment). The higher score means likely function or regulatory

Table 3. Significantly Associated SNPs Involved in a Protective Role from the BIPN in Multiple Myeloma Patients

No.	Author and year	Gene	SNP	Allele	Type of SNP
1	Broyl et al. [6]	*IGF1R*	rs1879612	T>C*	Intron
2		*NEK4*	rs1029871	G>A, C, T*	Coding non-synonymous
3		*SRD5A2*	rs2300697	C>T*	Intron
4		*ATM*	rs189037	G>A*	Locus, untranslated
5		*ATM*	rs664677	C>A, T*	Intron
6		*ATM*	rs664982	C>A, G, T*	Intron
7		*SELP*	rs6131	C>A, T*	Coding non-synonymous
8		*PTPRN2*	rs1130499	C>G. T*	Coding non-synonymous
9		*STK31*	rs4722266	G>A*	Coding non-synonymous
10		*PPARD*	rs2267668	G>A, C*	Intron
11	Campo et al. [12]	*IL17RD*	rs1545981	A>G*	Coding synonymous
12		*EDN1*	rs5370	G>T*	Missense variant
13		*BTRC*	rs4151060	G>T*	Missense variant
14		*IL10RA*	rs2229113	A>G, T*	Missense variant
15		*NFATC4*	rs2228233	C>G, T*	Coding synonymous
16		*ABCC6*	rs8058696	G>C, T*	Coding synonymous
17		*ABCC1*	rs2384937	T>C*	Intron
18		*ABCC1*	rs35604	G>A*	Intron
19	Corthals et al. [14]	*CYP17A1*	rs619824	G > T	3' UTR
20	Favis et al. [9]	*TCF4*	rs1261134	A>T	intron
21	Min et al. [7]	*Chr6:6664684*	rs201015	C>T^	NP

N>N, reference allele>alternative allele; *, alleles derived from NCBI; ^, protective allele; NP, not reported.

Table 4. GERP of SNPs Implicated in BIPN

SNP ID	Chromosome	Region Start	Region End	Element RS Score	Base RS Score
rs1801131	Chr1	11794371	11794542	179.7	2.78
rs1801131	Chr1	11796198	11796399	186.2	2.78
rs1051740	Chr1	225831901	225831961	78.2	2.75
rs4151060	Chr10	101538290	101538377	164.4	3.67
rs1126667	Chr17	6999299	6999469	130.3	-5.67
rs1545981	Chr3	57105852	57106010	196.5	-7.51
rs4722266	Chr7	23754309	23754491	527.5	4.46

Chr, chromosome; RS, rejected substitution

significant regions. The findings indicate one highly conserved SNP (600-1000), 4 moderately to highly conserved SNPs (400-599), and 7 SNPs with a likely low conservation rate (< 400) (Table 5).

Both GERP and PHAST are important for measuring the conservation rate among specific elements or regions. If the GERP test shows low conservation, and the PHAST test shows high conservation, for instance, rs1545981 (Base RS Score = -7.51, and PHAST score = 407), this means that the region across species is conserved; nevertheless, the particular SNP may evolve more rapidly or suggest other evolutionary mechanisms.

Exome gnomAD analysis

Exome-wide allele frequencies analysis among 8 global populations was performed to identify fundamental heterogeneity and variants distributed across specific populations. SNPnexus returns the eight gnomAD exome population bins because it reflects how gnomAD organizes and reports allele frequencies: gnomAD groups samples into broad genetic-ancestry clusters (AFR, AMR, EAS, NFE, and SAS) plus two important founder/subgroup bins (FIN, ASJ) and an "OTH" category for samples that cannot be confidently assigned. These ancestry labels are derived from genetic-similarity analyses (principal-component clustering and related quality control) rather than self-reported labels, so the bins represent major continental ancestries and some historically distinct founder populations whose allele spectra can differ markedly.

Overall, the alleles for the included SNPs are distributed unequally. Some SNPs are not distributed among all populations, such as rs434473; however, specific SNPs exist in high percentages among populations, such as rs2229113, rs1545981, and rs35604. Additionally, some SNPs exhibit a distinct pattern; for example, rs1801133 revealed inverted allele patterns, where the alternate

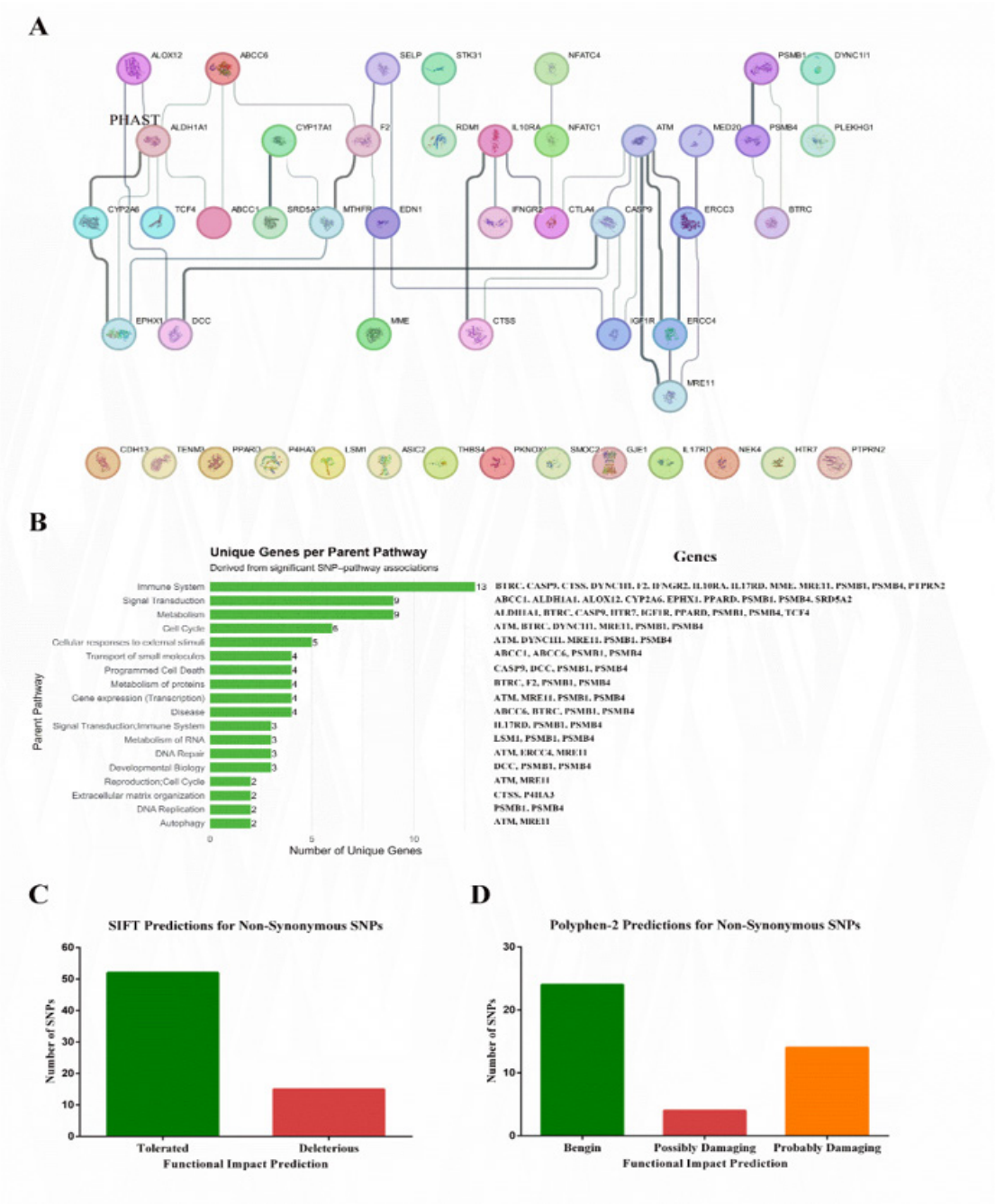

Figure 3. PPI Network, Gene-Pathways Analysis, and STIF and Polyphen-2 Prediction of SNPs Associated with BIPN in Multiple Myeloma. (A) PPI network with medium FDR stringency < 0.05 and 0.4 confidence for the target interaction. (B) Unique genes per parent pathway. (C) STIF prediction for non-synonymous SNPs. (D) Polyphen-2 prediction for non-synonymous SNPs. Data with a P-value > 0.05 were included.

allele (A) was rare in AFR populations (10.8%) but predominant in AMR (50.3%) and ASJ (50.3%) groups. Extreme disparities were observed for rs7172, which exists in high frequency in NFE (82.2%) compared to EAS (22.1%), while rs2229113 was roughly fixed in EAS (99.7%) but variable elsewhere (62.2-86.6%) (Table 6). These results highlight population stratification in human genetic variation.

Epigenetic regulatory functions of BIPN-associated SNPs

To estimate how epigenetic variation might participate in BIPN, SNPnexus was utilized to examine annotated regulatory variants, particularly those active in neurons and glial cells. Most variants are found in bipolar neurons that overlap both activating marks (H3K4me1, H3K27ac) and repressive marks (H3K36me3, H3K9me3). For instance, CTLA4 rs4553808 exhibits a repressive H3K27me3 mark, while variants such as rs17421511 and rs1059293 are located in DNase I hypersensitive regions that bind to transcription factors such as SP1, YY1, and MAX. Many variants are found in elements essential for the glial support of astrocytes. Multiple variants lie within gene bodies distinguished by H3K36me3, others in enhancers distinguished by H3K4me1 and H3K27ac (including rs7172), and a group in CCCTC-binding factor (CTCF)-bound or DNase I-accessible

Table 5. PHAST Conservation Annotation of SNPs Implicated in BIPN

SNP ID	Chromosome	Region Start	Region End	LOD Score	Score
rs1801131	Chr1	11794418	11794420	16	268
rs1801133	Chr1	11796305	11796322	204	520
rs1051740	Chr1	225831931	225831936	58	395
rs4151060	Chr10	101538332	101538349	194	515
rs2228233	Chr14	24369959	24369964	57	394
rs1799801	Chr16	13948101	13948112	56	392
rs2251660	Chr17	35925510	35925583	259	543
rs6517852	Chr21	19036076	19036105	24	308
rs1029871	Chr3	52763541	52763618	647	634
rs1545981	Chr3	57105944	57105949	65	407
rs4722266	Chr7	23754399	23754410	52	385
rs7823144	Chr8	38170668	38170678	21	295

Chr, chromosome; LOD, log-odds score

regions. A single variant (rs9902778) highlighted by the H3K9me3 in astrocytes may impact genes responsible for neuroinflammation.

Finally, some variants are located in neural progenitor cells that overlap promoters and enhancers carrying H3K4me1/3 mark and DNase I sites, and smaller clusters of repressive H3K27me3 and insulator CTCF regions. These results imply that the risk of developing BIPN in certain individuals may be affected by genetic variants that modify the functioning of enhancers and promoters in neurons and glial cells. Specifically, two SNPs, rs7172 (located on chromosome 1) and rs189037 (located on chromosome 11), are situated within extensive CpG islands, suggesting that they could potentially influence DNA methylation and impact genes associated with nerve regeneration, defenses against oxidative stress, or inflammation. These variants are promising candidates for additional studies aimed at understanding and possibly predicting which individuals will experience neuropathy following bortezomib therapy. The row data for epigenetic and chromatin regulation are found in the supplementary files.

Discussion

Bortezomib remains a cornerstone of multiple myeloma therapy protocols due to its proteasome-suppressing effect; however, its clinical utility is often limited by the development of peripheral neuropathy, which affects 30-60% of treated patients [2, 3]. Genetic polymorphisms have emerged as key modulators of patient susceptibility to drug-induced neurotoxicity, presenting a potential approach to personalize treatment and mitigate toxic adverse effects. Despite numerous genetic association

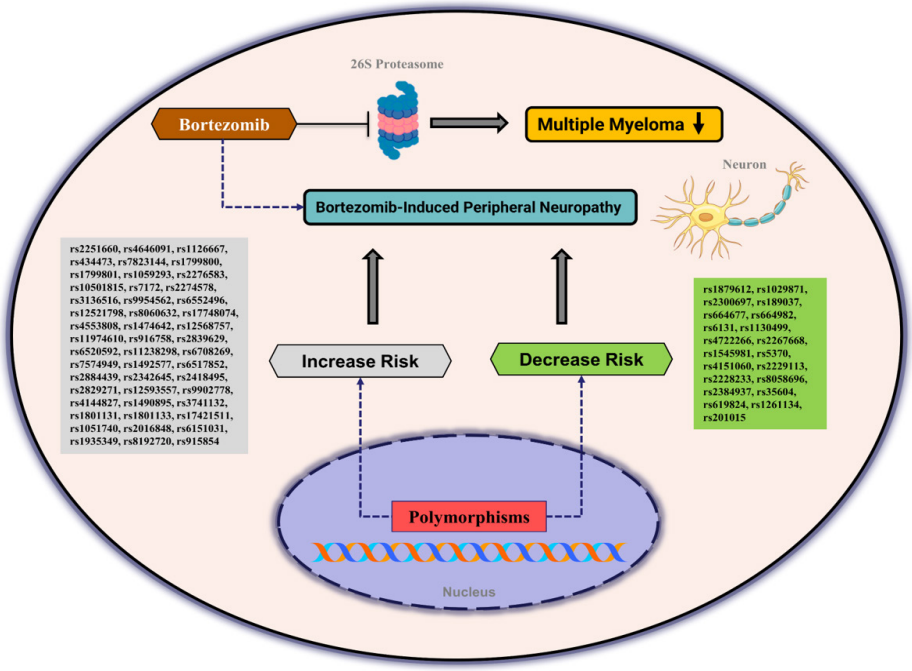

Figure 4. Graphical Representation of the Genetic Polymorphisms Associated with BIPN in Multiple Myeloma. This illustration was created using PowerPoint.

Table 6. Exome-Wide Allele Frequencies of SNPs Implicated in BIPN Analysis among 8 Global Populations.

SNP ID	REF Allele	ALT Allele	AFR Frequency	AMR Frequency	ASJ Frequency	EAS Frequency	FIN Frequency	NFE Frequency	OTH Frequency	SAS Frequency
rs1801131	T	G	0.158215	0.15941	0.15941	0.21977	0.319412	0.318632	0.296284	0.411648
rs1801133	G	A	0.107591	0.502717	0.502717	0.290475	0.230734	0.339593	0.329749	0.14512
rs7172	G	A	0.359373	0.396534	0.396534	0.220892	0.772664	0.821932	0.724633	0.687814
rs6131	C	T	0.323486	0.09324	0.09324	0.216143	0.200767	0.189772	0.197971	0.249853
rs1051740	T	C	0.178172	0.39321	0.39321	0.461283	0.30114	0.296773	0.307429	0.352355
rs4151060	G	T	0.009167	0.020352	0.020352	None	0.030317	0.047353	0.033887	0.008427
rs3741132	G	A	0.268678	0.148957	0.148957	0.285589	0.330773	0.161996	0.168651	0.237915
rs2229113	A	G	0.804509	0.866233	0.866233	0.996628	0.621741	0.682059	0.727867	0.73794
rs2228233	C	T	0.378341	0.481196	0.481196	0.460066	0.279596	0.272015	0.314462	0.410523
rs1799800	G	A	0.162327	0.138718	0.138718	0.234704	0.22107	0.278112	0.264407	0.248526
rs1799801	T	C	0.172656	0.232903	0.232903	0.240157	0.235487	0.294486	0.292333	0.313492
rs35604	G	A	0.870043	0.775437	0.775437	0.790368	0.837909	0.826678	0.796155	0.611828
rs8058696	G	C	0.349778	0.469939	0.469939	0.158616	0.446338	0.489872	0.444426	0.261499
rs1126667	A	G	0.667262	0.698611	0.698611	0.509842	0.669889	0.580347	0.586184	0.546063
rs434473	A	C	None	None	None	0.000054	None	None	None	None
rs434473	A	G	0.187339	0.231408	0.231408	0.482873	0.329557	0.418835	0.396934	0.447552
rs2251660	A	C	0.433169	0.257795	0.257795	0.212864	0.141979	0.147583	0.180098	0.261026
rs8192720	G	A	0.028271	0.004316	0.004316	0.191279	0.033785	0.003776	0.01459	0.00427
rs1029871	G	C	0.14668	0.529261	0.529261	0.424523	0.404139	0.401229	0.37961	0.204021
rs1545981	A	G	0.765714	0.906764	0.906764	0.502943	0.935934	0.896715	0.887855	0.960882
rs5370	G	T	0.190007	0.147537	0.147537	0.28072	0.190049	0.214587	0.219218	0.401816
rs4722266	G	A	0.20314	0.396759	0.396759	0.175123	0.147445	0.140662	0.172543	0.268264
rs1130499	C	T	0.441039	0.508986	0.508986	0.49891	0.296324	0.292442	0.331534	0.278337

REF, reference allele; ALT, alternate allele; AFR, African/African American; AMR, Admixed American; ASJ, Ashkenazi Jewish; EAS, East Asian; FIN, Finnish; NFE, Non-Finnish European; OTH, other populations; SAS, South Asian.

studies, a cohesive systematic synthesis of risk and protective SNPs and their functional consequences has been lacking. In the present study, the literature on genetic studies of polymorphism association with BIPN in multiple myeloma patients was systematically reviewed, and a functional bioinformatics analysis was also conducted on the resulting significantly associated SNPs so that the genetic drivers of BIPN can be clarified and a foundation for genotype-guided management strategies can be laid.

A total of 9 studies were included in the systematic review, GWAS, case-control, prospective cohort, and pharmacogenetic studies. Six studies were conducted on Europeans, and 3 studies on South Koreans, Chinese, and Caucasians (Europeans and North Americans) [6–9,12–16]. Notably, the outcomes identified 69 unique SNPs associated with BIPN, 21 protective SNPs related to a decreased risk of BIPN, and 48 risk SNPs implicated in the development of BIPN, where susceptibility arises from an inherited impairment in neuronal resilience mechanisms under proteasome suppression. Furthermore, 8 of the studies were of high quality, with 1 study of moderate quality.

This systematic review and integrative bioinformatics analysis propose BIPN as a polygenic pharmacogenomic adverse drug reaction, driven by the convergence of metabolic pathways, neuroinflammation, DNA damage response, neurodevelopmental signaling pathways, immune response, and cellular signal transduction. The highest functional scores emerge from pathways regulating bortezomib metabolic clearance and detoxification, including xenobiotic response and olefinic and icosanoid metabolic pathways, highlighting the risk effect of phase I/II enzyme (CYP2A6, EPHX1, and ALDH1A1) polymorphisms in Chinese [8] and the protective effect of ABC transporters in Germans [12]. These variants modulate intraneuronal drug exposure and may impair or enhance detoxification pathways. CYP2A6 rs8192720 may negatively modify bortezomib metabolic clearance, whereas polymorphisms that decrease EPHX1 and ALDH1A1 activity impair the removal of harmful epoxides and aldehydes biosynthesized under bortezomib-induced oxidative stress. The subsequent accumulation of reactive metabolites amplifies mitochondrial and endoplasmic reticulum impairment in dorsal root ganglia, triggering sensory neuron destabilization and axonal degeneration, features of BIPN [17, 18]. The reported presence of the EPHX1 rs1051740 variant in neurons and astrocytes was proposed to have possible consequences for neuropathy [8]. A comprehensive analysis of mouse brains has also exhibited that EPHX1 is involved in the cerebral metabolism of epoxyeicosatrienoic acids, which could overlap with neuronal signal transmission [19]. A prior study of Japanese epilepsy patients carrying an EPHX1 diplotype in rs1051740 showed increased plasma carbamazepine-diol/carbamazepine-epoxide ratios, presenting a rationale for future therapeutic interventions. This ratio could provide insights into vulnerability to BIPN in multiple myeloma patients [20, 21].

Olefinic and icosanoid metabolism also involves ALOX12 in metabolizing lipid-derived neurotoxins. ALOX12 participates in neuropathy development by provoking axonal degeneration, inflammation, and pain signaling. In rat models with nerve injury, ALOX12 expression is remarkably increased in the dorsal root ganglia and spinal cord. Mice deficient-Alox12/15 demonstrate mitigated optic nerve degeneration following crush injury compared to wild-type controls, suggesting a direct role for 12/15-LOX activity in axonal breakdown [22]. Furthermore, selective suppression of spinal 12-LOX through intrathecal delivery of inhibitors such as baicalein or CDC mitigates inflammation-induced tactile allodynia, demonstrating that ALOX12-derived metabolites (including 12-HETE and hepoxilins) contribute to the development of neuropathy [23]. In spinal cord injury models, ALOX12 knockout mice reveal decreased glial stimulation, inflammation (via NF-κB signaling), and apoptosis, supporting a neuroprotective influence of ALOX12 inhibition [24]. These data indicate that ALOX12-mediated lipid peroxidation contributes to axonopathy and neuroinflammation, and that both ALOX12 genetic deletion and pharmacological suppression can decrease neuropathy. The functional bioinformatics analysis suggests that ABCC1 variants (rs2384937 and rs35604) and ABCC6 rs8058696 gain-of-function in Germans could enhance efflux of oxidative byproducts or bortezomib metabolites from peripheral neurons, potentially reducing intracellular BIPN.

Defects in the MTHFR folate metabolism gene may worsen nucleotide repair under proteotoxic stress. The researchers also found that the likelihood of BIPN was higher in patients with reduced levels of MTHFR transcripts before bortezomib treatment. The alteration in MTHFR activity via polymorphisms can lead to disruption of methionine biosynthesis, minimizing the level of S-adenosine methionine, which can cause nerve myelin damage and affect the serum homocysteine level, and also stimulate Ca2+ homeostasis imbalance resulting from bortezomib. Elevated serum homocysteine level has a direct cytotoxic effect on the nervous system, which causes neuropathy [25]. On the other hand, clearance and genomic stability can be improved by protective ATM and ABC transporter alleles, marking detoxification as a dominant factor of BIPN risk.

Bortezomib stimulates a calcium-NFAT-cytokine axis in the dorsal root ganglia, leading to a self-sustaining inflammatory cascade. Calcium-NFAT-cytokine signaling in dorsal root ganglia may be implicated in BIPN in multiple myeloma. Proteasome suppression via bortezomib stimulates endoplasmic reticulum stress, dysregulating calcium release and stimulation of transient receptor potential channels (TRP), which elevate cytosolic Ca^{2+}. This calcium overload can promote the phosphatase calcineurin, enhancing NFAT dephosphorylation and nuclear translocation. Although direct evidence is limited, NFAT is known to drive pro-inflammatory cytokine expression, including TNF-α and IL-1β, in neurons, probably intensifying neuroinflammation and axonal damage in BIPN [26–29]. The evolutionarily constrained protective rs2228233 variant (NFATC4) might lead to reduced NFATC4 activation or altered function, affecting nuclear translocation or DNA-binding capacity, thus

weakening transcription of pro-inflammatory cytokines in dorsal root ganglia neurons or glial cells [30]. After optic nerve injury, NFATC4 is transiently upregulated in retinal ganglion cells. Genetic deletion of NFATC4 remarkably promotes retinal ganglion cell survival, preserves retinal function, and slows axonal degeneration by inhibiting pro-apoptotic signaling. Restoration of NFATC4 into knockout mice reverses these protective effects, firmly establishing NFATC4 as a key regulator whose blockage offers a potential neuroprotective approach for optic neuropathies [31].

HIV infection pathway (CASP9, NFATC1, ATM, BTRC, and NFATC4) spotlights immune cell infiltration. In autoimmune neuropathy, T cell-derived IFN-γ acts on macrophage IFNGR2, stimulating TNF-α production and sensitizing nociceptors; thus, modulation of the IFN-γ/IFNGR2 signaling axis may mitigate TNF-α secretion and microglial activation, presenting a therapeutic opportunity to balance neural regeneration with inflammatory pathology [32]. The findings indicate that apoptosis is triggered by CASP9 rs4646091 risk variants; however, the rs5370 T allele in EDN1 enhances ET-1 stability and expression under stress. Although ET-1 induces vasoconstriction, Asn198 carriers show enhanced microvascular adaptability, maintaining vasa nervorum perfusion during bortezomib treatment and thus protecting dorsal root ganglia neurons from ischemia-driven oxidative damage and BIPN [33].

IL10RA rs2229113 protects from BIPN in Germans; however, the mechanism is still not defined. A previous study suggests that the G330R substitution in the IL10RA has been demonstrated as a loss-of-function allele, impairing IL-10 signaling via STAT3, increasing rheumatoid arthritis and systemic lupus erythematosus susceptibility [34]. Therefore, the rational effect should be an inflammatory effect; however, rs2229113 protects from BIPN in Germans. A previous study also proposed a model of balancing selection, where heterozygous carriers of certain IL10RA missense or nonsense variants acquire a selective advantage against Schistosoma japonicum infection as their modestly decreased IL-10 signaling results in a more substantial protective immune response against parasites. Nevertheless, when these same alleles are homozygous, IL-10 signaling falls below a critical threshold, unleashing unregulated inflammation in the gut and manifesting as early-onset, monogenic inflammatory bowel disease [35]. Similar to its heterozygote advantage in parasitic infection, the rs2229113 variant may protect against BIPN by tuning down IL-10 signaling just enough to hinder maladaptive neuroimmune interplay without inducing intense inflammation. This hypothesized mechanism should be tested. Another possible explanation is based on the SIFT prediction that the rs2229113 variant is tolerated, suggesting that this variant does not affect the function of the protein, resulting in an effective, balanced immune response without provoking an uncontrollable pro-inflammatory reaction that leads to BIPN.

The bioinformatics analysis for response to radiation and cellular senescence with functional insights into mitochondrial ROS generation shows a cohesive ATM-Caspase axis driving BIPN. 26S proteasome inhibition by bortezomib increases mitochondrial ROS, resulting in DNA double-strand breaks that involve ATM-dependent repair pathways [36]. In Schwann cells, protective ATM alleles (rs189037, rs664677, and rs664982), which represent high phastCons scores, enhance p53-mediated repair, preserving genomic integrity and counteracting neuropathic damage [37]. However, risk polymorphisms in CASP9 diminish this resilience by shifting the cell-fate balance toward apoptosis [38]. GERP-constrained sites in CASP9 emphasize the evolutionary significance of its apoptotic functions. A recent study exhibited that lysosomal dysfunction in Schwann cells triggered by bortezomib is implicated in the BIPN. Thus, improved lysosomal function in Schwann cells can be a promising strategy for BIPN treatment [39].

BTRC has been shown to ubiquitinate phosphorylated NFKBIA, targeting it for degradation and thus activating NF-κB. The missense SNP rs4151060 is located within BTRC, which is involved in the NF-κB activation mechanism [40]. Although it is a gain-of-function, BTRC rs4151060 is a protective variant in Germans, perhaps by the neuroprotective functions of residual NF-κB after bortezomib treatment, preserving neuronal health, synapse growth, and plasticity [41]. In addition, SIFT and Polyphen-2 models suggest that this variant is tolerated and benign, respectively. Therefore, the results suggest oxidative stress and genomic maintenance as interlinked nodes in BIPN development and propose that stratification by ATM, CASP9, and BTRC genotypes could inform neuroprotective strategies in proteasome-inhibitor therapy. KEGG enrichment for Wnt signaling and axon guidance demonstrates DCC as a key mediator of netrin-dependent axonal regrowth, whereas IGF1R rs1879612 amplifies PI3K/Akt-driven neurotrophic signaling, enhancing survival and repair of peripheral neurons under proteasome-inhibitor stress [42]. DCC rs17748074 likely promotes BIPN risk by disrupting DCC-mediated netrin-1 signaling, crucial for axon maintenance in sensory neurons, by altering intronic enhancer activity, downregulating DCC transcription by impairing Maf/Nkx3_4/Pax2 binding [13].

The protective SRD5A2 rs2300697 variant also provides neuroprotection via androgen-mediated pathways, whereas PPARD variants may modulate lipid metabolism to support membrane integrity during regeneration [43, 44]. ASIC2 constitutes a component of heteromeric proton-gated sodium channels with ASIC1/3 in sensory neurons, modifying pH sensitivity by elevating activation thresholds and delaying desensitization; thus, accelerating acid-stimulated neuronal excitability under mild acidosis. Peripheral inflammation, including that activated by cytotoxic agents, augments ASIC2A expression, leading to central sensitization and mechanical hyperalgesia [45, 46]. Risk variants in ASIC2 probably sensitize pH-gated nociceptors, and MME (neprilysin) loss-of-function polymorphisms disrupt the degradation of pain-modulating neuropeptides such as substance P, directly shaping the sensory phenotype of neuropathy [47]. Harmonizing with mitochondrial ROS-ATM-Caspase axis and BTRC/NF-κB inflammatory regulation, ASIC2

pain-modulating variants support a polygenic landscape in which both repair capacity and nociceptive sensitivity combine to define BIPN risk and severity.

The CYP17A1 rs619824 variant is related to steroid hormone biosynthesis and protects Europeans from BIPN [14]. Whereas PKNOX1 rs2839629, a homeobox transcription factor playing a key role in gene regulation during development, cell differentiation, and DNA repair, increases the risk of BIPN [15,16]. On the contrary, CYP17A1 rs619824, PKNOX1 rs2839629, IL10RA rs2229113, PSMB1 rs1474642, PSMB4 rs7172, IL17RD rs1545981, F2 rs3136516, CTLA4 rs4553808, NFATC4 rs2228233, ABCC1 rs35604/rs2384937, ABCC6 rs8058696, EDN1 rs5370, BTRC rs4151060, TCF4 rs1261134, NFATC1 rs9954562, and MED20 rs2274578 are not significant in South Koreans [7]. In addition, multiple variants in non-coding elements and genomic locations are implicated in increasing the risk of BIPN in various populations, such as LOC105373177, Chr7:54151514, LOC729254, LINC01593, Chr21:19036091, LINC02331, LOC105374754, Chr21:24697514, Chr15:66896240, and LOC105373727, suggesting a regulatory function of these genomic elements. However, the Chr6:6664684 rs201015 variant is observed to decrease the BIPN risk in South Koreans. The readouts regarding population allele frequencies illuminate genetic determinants of BIPN variations. BTRC rs4151060 is rare in South Asians (MAF=0.008) but common in Europeans (MAF=0.047), while the highly conserved NEK4 rs1029871 demonstrates purifying selection, indicating critical roles in microtubule stability [48].

Variants like ALOX12 rs1126667 disrupt enzyme function, amplifying inflammation in ancestry-specific patterns [6]. The findings hypothesize a model in which inherited deficits in xenobiotic metabolism and efflux amplify the consequences of primary proteasome inhibition; synchronous predisposition to neuroinflammation and apoptosis exacerbates neuronal injury; compromised DNA repair and elevated oxidative stress hinder effective recovery; and suboptimal neurodevelopmental signaling limits regenerative potency. Protective variants may counterbalance these hits by improving drug clearance, repairing DNA damage, and reducing inflammatory responses. These genetic outcomes establish a framework for precision-guided alleviation of BIPN and the design of novel neuroprotective interventions. By incorporating both susceptibility alleles, for instance, CYP2A6 rs8192720, EPHX1 rs1051740, and CASP9 rs4646091, and protective polymorphisms, such as ABCC1 rs2238476, ATM rs189037, and IL10RA rs2229113, into a genotyping panel, clinicians may prospectively stratify multiple myeloma patients according to inherent neurotoxicity risk, hence optimizing proteasome-inhibitor selection and individualized dosing protocols.

Key risk variants like MTHFR rs1801131 (SAS: 41.2%, FIN: 31.9%) and PSMB4 rs7172 (NFE: 82.2%, FIN: 77.3% vs. EAS: 22.1%) exhibit ancestry-biased frequencies, perhaps clarifying increased BIPN rates in Europeans and South Asians due to disrupted drug metabolism and proteasome dysfunction, while protective SNPs like ABCC6 rs8058696 (AMR/ASJ: 47.0%) improve bortezomib efflux and demonstrate elevated occurrence in admixed populations. While protective alleles such as SELP rs6131 are enriched in Africans (AFR: 32.3%), Black/African American patients experience disproportionately elevated BIPN incidence [49]. This is likely due to co-inherited risk variants such as RDM1 rs2251660 (AFR: 43.3%) and CYP2A6 rs8192720 that surpass protective SELP anti-inflammatory effects. Other factors may include clinical comorbidities such as high prevalence of diabetes and APOL1 renal risk variants, nephrotoxic alleles, decreasing bortezomib clearance, and lengthening neurotoxic exposure [50, 51].

East Asians, such as the Chinese in our analysis, face compounded vulnerability from high-MTHFR burden and partially low ABCC6 frequency; East Asians are protected by low PSMB4 prevalence but challenged by CYP2A6 rs8192720, reducing bortezomib metabolism; and Europeans, such as Germans, balance the high risk of PSMB4/MTHFR variants with robust ABCC6/IL17RD protection. These variants' distribution variations, mediated through drug transport (ABCC6), inflammation (IL10RA rs2229113), and DNA repair (ATM and ERCC4) pathways, highlight the necessity for ethnically dosing adjustment approaches and functional validation of protective mechanisms (such as SELP's anti-inflammatory action) to decrease BIPN across different populations, as indicated in pharmacogenomic studies. However, the current synthesis is restricted by cohort heterogeneity, predominance of European variant discovery, and reliance on a computational functional approach. To overcome these challenges, comprehensive verification using CRISPR-engineered allelic series in iPSC-derived sensory neuron models is recommended [52]. Additionally, the translation of these polygenic determinants into effective, mechanism-based neuroprotective strategies will require prospective, multiethnic clinical trials with real-time genotyping, the development of polygenic risk scores, systematic investigations of drug-gene interactions, and integrated multi-omics biomarker profiling.

Lineage-specific chromatin data propose allele-dependent regulatory variation in BIPN risk. In sensory neurons, the co-location of over half the neuro-focused SNPs with an active enhancer (H3K4me1), transcriptional elongation (H3K36me3), and accessible chromatin (DNase I) marks indicates that these variants may fine-tune the expression of genes essential for nociceptive signaling and axonal maintenance through SP1 or YY1 binding. The presence of repressive marks (H3K9me3 and H3K27me3) at various sites, most notably CTLA4 rs4553808, further implies that SNP-dependent shifts in polycomb-mediated silencing could adjust neuronal gene expression under stress conditions [53]. In astrocytes, localization of polymorphism variants to CTCF-defined insulators and H3K27ac-marked enhancers points to potential disruption of glial support functions and neuroinflammatory regulation, consistent with emerging evidence that astrocyte epigenetics modulates chemotherapeutic nerve injury [54]. The mapping of risk PSMB4 rs7172 and protective ATM rs189037 to high-density CpG islands further increases the likelihood that

genotype-driven methylation modifications could impact DNA repair, oxidative stress responses, or cytokine expression in both neurons and glia. These data suggest that epigenetic dysregulation, through alterations in enhancers, promoters, and insulators, may be a key mechanistic link between inherited SNPs and the variable onset or severity of BIPN, warranting allele-specific chromatin and methylation experiments in peripheral nerve models.

In conclusion, BIPN exemplifies a polygenic pharmacotoxic phenotype in which variants regulating xenobiotic metabolism, inflammatory signaling, DNA repair, neurotrophic support, and epigenetic regulatory processes modulate neuron cell resilience to proteasome suppression. Protective alleles facilitate enhanced detoxification, genomic maintenance, and anti-inflammatory responses, whereas risk polymorphisms predispose to oxidative stress, immunogenic activation, and apoptotic loss (Figure 4). This integrative model establishes a foundation for the development of genotype-guided dosing approaches, targeted prophylactic regimens, and novel neuroprotective therapeutics. A recurrent limitation across these pharmacogenetic and GWAS studies is incomplete or inconsistent accounting for treatment exposure (number of cycles, cumulative dose, or follow-up time). Genetic association tests typically compare cases defined by severity to controls without harmonizing or adjusting for the amount of neurotoxic exposure; because BIPN risk is dose- and time-dependent, unequal exposure or variable follow-up can confound SNP associations. Time-to-event or cumulative-dose analyses (used by Favis et al.) mitigate this bias by explicitly modelling exposure, but such approaches are uncommon in the reviewed literature. Consequently, reported genetic risk loci should be interpreted cautiously and ideally validated in cohorts where exposure is measured and either adjusted for or used to perform time-to-event (hazard) analyses. Future research should aim to experimentally validate the functional effects of the highlighted polymorphisms using neuronal models or clinical cohorts to strengthen causal inferences. Expanding genetic analyses to diverse, multi-ethnic populations will decrease the current European-centric biases and enhance the generalizability of the results. Eventually, applying advanced systems biology approaches will unravel the crosstalk between overlapping biological pathways and define the polygenic basis of BIPN.

Conflict of Interests

Author Contribution Statement

Nadeen S. Sultan: Screening, data extraction, data synthesis and analysis, manuscript writing and revision, visualization, risk of bias analysis, and bioinformatics analysis. Ahmed S. Alhallaq: Conceptualization, screening, data extraction, data synthesis and analysis, manuscript writing and revision, visualization, risk of bias analysis, bioinformatics analysis, and overall project supervision. Mohammed S. Alhallaq: Screening, data extraction, data synthesis, and manuscript writing.Heba Mohammed Arafat: Risk of bias assessment and manuscript revision. Sadeen Eid: Screening and manuscript writing. Ashraf Jaber Shaqaliah: Manuscript revision and overall project supervision.

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Ethical Approval

This article is a systematic review supported by bioinformatics analysis and does not require ethical approval.

Availability of Data

All data generated or analyzed during this study are included in this published article or the supplementary materials.

Conflict of Interests

The authors declare no conflict of interest.

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