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Research Paper

Highlighting the Role of Neurofilament Light and Medium Polypeptides in Peripheral Diabetic Neuropathy

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ABSTRACT

Introduction: Diabetes mellitus is a chronic disease caused by insulin uptake or deficiency. Side effects of diabetes are numerous, according to the severity of the disease. Diabetes could harm the peripheral nerves, with chronic pain leading to nerve damage known as diabetic neuropathy (DN). Signs and symptoms of DN are sharp pains, numbness, and tingling. Distal symmetric polyneuropathy is the most common nerve injury during DN. Accordingly, this study screens candidate genes related to sural nerve DN (SDN) to find the critical ones.

Methods: Gene expression data from diabetic patients with and without progressive sural nerve neuropathy (GSE24290) were included in the analysis. GEO2R was applied to the first step analysis to find the significantly differentially expressed genes (DEGs). The queried significant DEGs, along with their first 100 neighbors, were included in a network using the Cytoscape software. The network was analyzed using the Cytoscape network analysis application, and the central nodes were identified.

Results: A total of 26 significant DEGs that were extracted from the gene expression profiles, plus 100 first neighbors, were interacted to form the network. *INS*, *ALB*, *AKT1*, *APP*, *SNAP25*, *NEFL*, *GFAP*, *IL6*, *NEFM*, *TNF*, *MAPT*, *GAP43*, and *MBP* were identified as 13 hubs of the network. *NEFL* and *NEFM* were highlighted as the queried hub genes. Insulin, as the top hub node, was determined among all interacted genes (the queried and added genes).

Conclusion: *INS*, *NEFL*, and *NEFM* are key genes in DN, which are involved in metabolism regulation and intracellular transportation into axons and dendrites, respectively.

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Highlights

• *INS*, *ALB*, *AKT1*, *APP*, *SNAP25*, *NEFL*, *GFAP*, *IL6*, *NEFM*, *TNF*, *MAPT*, *GAP43*, and *MBP* are the critical dysregulated genes in diabetic neuropathy.

• *NEFL* and *NEFM* genes along with INS are the possible biomarkers for diabetic neuropathy.

• Metabolism regulation and intracellular transportation into axon and dendrites are the dysregulated biological terms in diabetic neuropathy.

Plain Language Summary

Diabetes is a major challenge in medicine. The diabetic patients suffer from insulin uptake or deficiency. There are numerous side effects for diabetes progression such as peripheral nerves damage or diabetic neuropathy (DN). One essential method to detect the molecular mechanisms of diseases is gene expression analysis. Exploring the dysregulated genes provide appreciated knowledge of progression and possible treatment of diseases. In this research, gene expression analysis of DN by using network analysis led to the introduction of a few genes that are involved in DN. Findings showed that *INS*, *ALB*, *AKT1*, *APP*, *SNAP25*, *NEFL*, *GFAP*, *IL6*, *NEFM*, *TNF*, *MAPT*, *GAP43*, and *MBP* were the critical dysregulated genes in DN. More investigation showed that *NEFL* and *NEFM* genes were two important dysregulated genes in DN. These two genes can be considered as possible drug targets or diagnostic biomarkers. Findings suggest that metabolism regulation and intracellular transportation into axons and dendrites are two critical biological terms in DN. Since the introduced genes and biological terms were identified via a theoretical investigation, the use of experimental data in future research can confirm the results.

1. Introduction

The well-known factor in the incidence of diabetes mellitus is deregulated metabolic pathways and genetic predispositions (Merchant & Klein, 2007), a disease that a vast majority of people worldwide are living with. Diabetic neuropathy (DN) is one of the most common complications of diabetes, observed in 50% of patients (Dyck et al., 1987). This disorder is a long-term complication in type I diabetic patients and, conversely, in type II diabetic individuals (Dyck et al., 1987). Initial classification of DN includes sensorymotor neuropathy and autonomic neuropathy (Boulton, 2007). DN is characterized by several processes, including progressive loss of peripheral axons, decreasing sensation, and pain feeling (Callaghan et al., 2012). The detection of DN is accompanied by irreversible damage caused by the disease (Tesfaye et al., 2010). Patients may show only one or all three types of neuropathies. Distal symmetrical neuropathy (DSN) is the most common kind of neuropathy (Bennett et al., 2014). DN can manifest as motor impairment (Ness et al., 2013), latent cardiac ischemia (Gupta & Pandit, 1992), situational hypotension (Sundaram et al., 1986), vasomotor impairment (Aso et al., 1997), increased sweating, bladder dysfunction (Gaur et al., 2000), and sexual dysfunction (Koutsojannis & Hatzilygeroudis, 2004). Careful monitoring of blood sugar and daily food care are key to preventing DN (White et al., 1981). The variety of complications from diabetes reflects the wide range of damages. The lack of knowledge about the cause of post-diabetes complications, such as DN, has increased our distance from understanding the mechanism of the disease (Shilubane & Potgieter, 2007).

Recently, biomarker discovery from the body fluids of diabetic individuals to improve the management of the patients has been implemented as an attractive approach. They use proteomic techniques as a powerful tool with high accuracy in this regard (Pasinetti et al., 2006). Although Western blot and immunohistochemistry were used for protein quantification in pathological and normal tissues; however, their inherent ability to process some proteins at a time is a part of technical limitations (Singh et al., 2009). Proteomics techniques could solve this problem by analyzing thousands of proteins quantification simultaneously. In addition, proteomics could provide information about protein structure and protein-protein interactions (Orme et al., 2010). Proteomics, with the assistance of system biology, could explore the network interaction between proteins to understand the pathophysiology of diseases (Langley et al., 2013). Most of the proteomic studies for protein quantification

about DN were done using 2D-PAGE (Niederberger & Geisslinger, 2008b). It is possible to separate thousands of proteins with the 2D-PAGE technique, but the limitation to abundant and soluble proteins is inevitable (Bantscheff et al., 2007).

Meanwhile, most of the proteins in the nervous system are hydrophobic and membrane receptors (Wetterhall et al., 2011) and mass spectrometry-based proteomics could rapidly identify both heavy and low-abundant hydrophilic and hydrophobic proteins. Treatment of DN is still a challenging task. The molecular mechanism for DN is still unclear, and there are many different hypotheses about the origin of the disease (Negi et al., 2011). Genes and protein databases such as GEO are useful sources to find key genes and proteins related to DN (Li et al., 2016). Cytoscape software and STRING database are useful tools to investigate and screen the set of genes and proteins which are related to the DN (Jian & Yang, 2020; Yu et al., 2019). Numerous studies have been performed on neuropathic pain in animal models, and due to its diverse origins, changes in protein levels depend on the pain model and the time of its development. Nevertheless, several proteomic overlapping models are defined for protein expression changes and their role in neuropathic pain (Niederberger & Geisslinger, 2008a). Fundamentally categorized proteins for neuropathic pain, arranged based on their physiologic functions, as proteins related to homeostasis, neuronal functions, chaperons and heat shock proteins, proteins related to neurodegeneration and apoptosis, immune system related and signaling proteins, and neurodegenerative and regenerative proteins (Niederberger & Geisslinger, 2008a). Inhibition of the tumor necrosis factor (TNF) pathway may cause DN progression in animal models (Omote et al., 2014).

Another study revealed that changes in ion channel functions and energy metabolism that are related to axon-glia interaction may cause DN development (Li et al., 2016). Chen et al. reported that “nucleotide-binding oligomerization domain like receptor 3” (NLRP3) activation mediated by signaling of ATP-P2X4 may cause inflammation related to DN (Chen et al., 2013). In vivo research suggested that knocking down micro-ribonucleic acid (RNA), miR-29c, and miR-27a could reduce DN progression (Wu et al., 2016). Scientists introduced miR-21 and miR-29 as biomarkers of DN progression (Chien et al., 2016). Demyelination is an early pathological aspect of peripheral DN (PDN) with precedes axon degeneration (Dyck & Tracy, 2018). Molecular biology of demyelination could help find biomarkers of PDN. Systematic research has investigated the relationship between the molecules that are involved in the PDN. In a study, gene expression in different DN patients was compared and concluded that the intervention genes, which are involved in DN, were associated with lipid metabolism and inflammatory reactions (Hur et al., 2011). A study based on network analysis using weighted gene databases related to DN introduced genetic differences between progressive and non-progressive types of DN (Langfelder & Horvath, 2008). Annotation methods as gene ontology or mapping genes and proteins, are helpful instruments for understanding and gaining a better view of biological features of the interest sets of proteins in DN (Doncheva et al., 2022).

The identification of interventional biomarkers in the development of diabetes and subsequently DN can help us to identify the contradictory and diverse factors of diabetes-related diseases to assist in treating them. In this study, we use existing data to try to find the key genes involved in the development of DN of the sural nerve via network analysis.

2. Materials and Methods

The gene expression dataset GSE24290 was downloaded from Gene Expression Omnibus (GEO) as a secondary study, which included 35 samples from patients with progressive and non-progressive sural nerve DN (SDN). The GSM597469-85 as non-progressive sural nerve and GSM597451-68 as progressive sural nerve samples were selected to analyze. The samples were statistically matched via GEO2R software. The distribution of gene expression profiles in the matched samples was median median-centered pattern. A total of 250 top-score genes (based on P) were selected to calculate the difference between progressive and non-progressive SDN groups via GEO2R. The 26 significant DEGs among the 250 DEGs were identified based on $P<0.05$ and FC >1.5 as cutoff criteria. The network was constructed by the 26 DEGs plus 100 first neighbors from the STRING database by Cytoscape software 3.7.2. The network analyzer application of Cytoscape was used to analyze the network. Central parameters, such as degree, betweenness centrality, closeness, and stress, were determined for the elements of the network. Meanwhile, 10% of the top nodes based on degree value were selected as hub nodes. The first 10 neighbors of the queried potent hub node were identified from the STRING database.

3. Results

As shown in Figure 1, a total of 17 control samples (non-progressive sural nerve neuropathy) gene expression profiles matched with 18 progressive sural nerve neuropathy samples. There were aligned midpoints, demonstrating that the samples were comparable.

Among 250 top-score genes, 26 genes (FC ≥1.5 and P<0.05) were identified as significant DEGs (Table 1).

The network, including 26 DEGs plus 100 first neighbors, was constructed. The analyzed network based on degree value is shown in Figure 2.

The 13 hub nodes were determined and tabulated in Table 2. Among the 13 hubs, only 2 nodes are queried genes named *NEFL* and *NEFM*. The first 10 neighbors of *NEFL* (as the potent queried hub nodes) as an interactome are shown in Figure 3.

4. Discussion

This study represents a critical advancement toward identifying a specific set of genes whose expression levels are closely associated with the onset and progression of SDN. By analyzing gene interactions within known cellular pathways, we could identify common elements in this complicated network to yield novel insights into disease pathogenesis and therapeutic targets to identify potential DN biomarkers. Proteomics is a suitable screening tool for extracting a large amount of data to identify biomarkers related to PDN. A proteomic research, for example, suggested serum apolipoprotein C1 precursor for detecting and classification of DN (Tang et al., 2011). Our initial analysis of data sets classified as progression of DN. The reported data related to DN were screened by PPI network analysis to trace key related elements. The samples, including progressive and non-progressive DN, were matched as equal boxplots demonstrated in Figure 1 and statistically comparable. A total of 26 significant genes were selected considering restricted conditions for further investigations (Table 1). As shown in Table 1, the two overexpressed genes were *GJB6* and *CCL26*, respectively. The *GJB6* gene, or gap junction protein beta 6, as the highest over-expressed gene (Log FC=1.4), provides instructions for making a protein named gap junction beta 6 or connexin 30. Its related pathways are gap junction trafficking and vesicle-mediated transport (Nahili et al., 2008). *GJB6* upregulation in progressive DN is associated with fatty acid homeostasis and glucose homeostasis, which is confirmed by our results (Zhou & Zhang, 2019). *GJB3* is an important paralog of this gene and is expressed in peripheral and auditory nerves, which could cause peripheral nerve neuropathy and auditory impairment (López-Bigas et al., 2001). The second overexpressed one was *CCL26* or C-C motif chemokine ligand 26, which is a protein-coding gene involved in *PEDF*-induced signaling and *AKD* signaling. Gene ontology related to this gene has

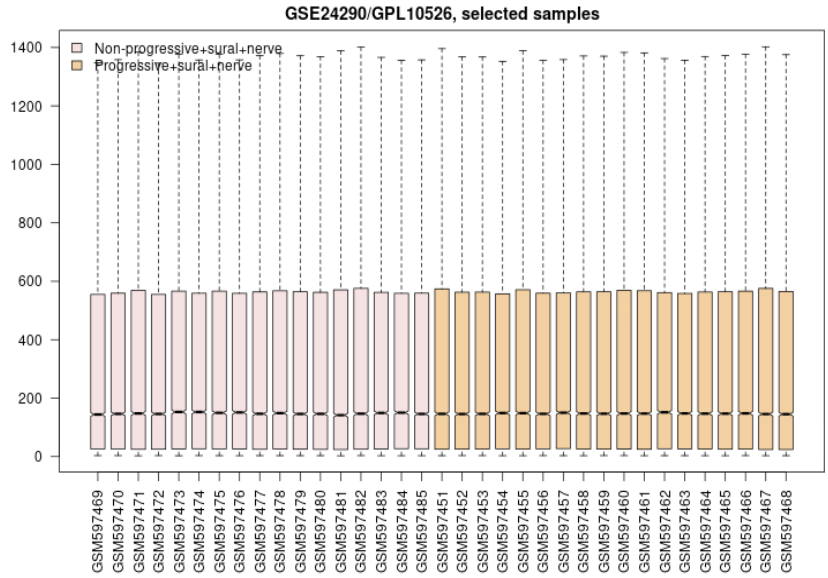

Figure 1. A total of 17 ribonucleic acid profiles of non-progressive SDN (pink color) and 18 progressive SDN (orange color) matched via boxplot illustrations

Notes: The vertical axis revealed normalized gene expression amounts.

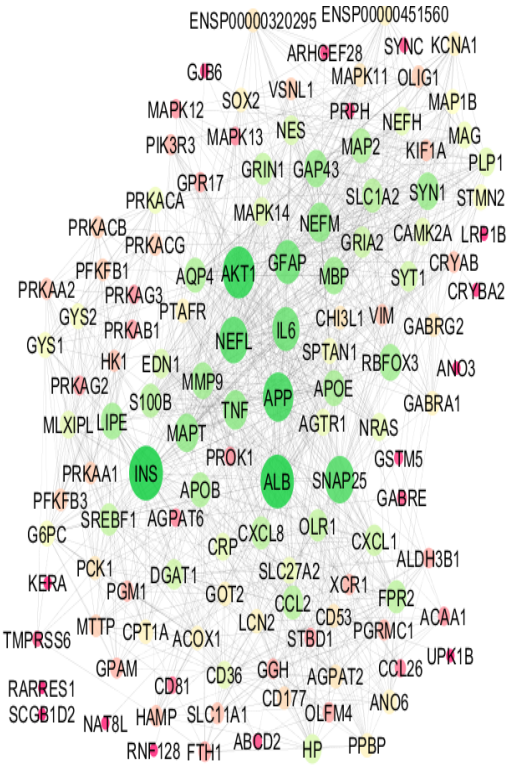

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Figure 2. Protein–protein interaction network of SDN

Note: The node's degree value determines the network layout. The node size corresponds to a higher value of degree, and the color change from red to green indicates an increment of degree value.

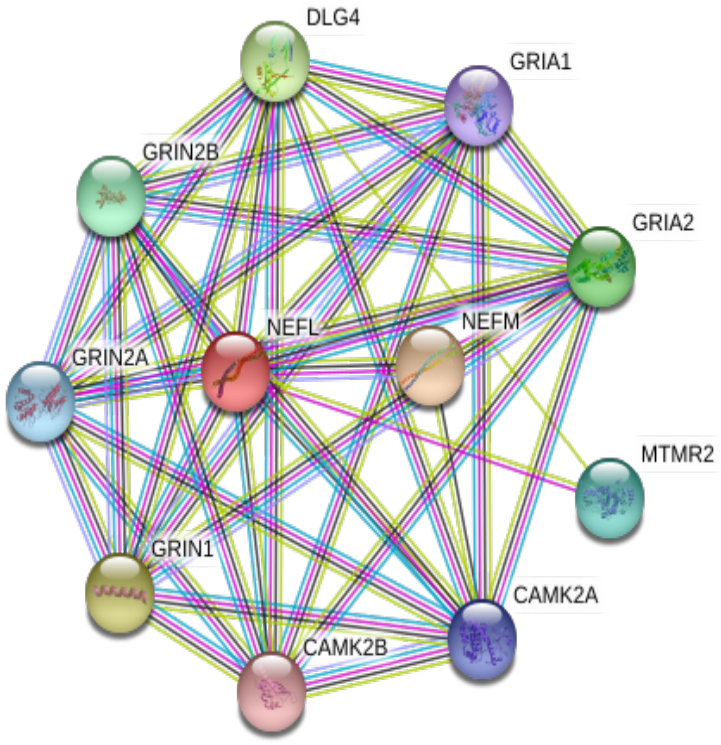

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Figure 3. *NEFL* (the potent queried hub node) related to the 10 first neighbors

Table 1. A total of 26 significantly differentially expressed genes, including 16 up-regulated differentially expressed genes, which are characterized by positive logFC, and 10 down-regulated differentially expressed genes identified with negative logFC

Row	Gene Symbol	Gene Title	LogFC	P
1	*GJB6*	Gap junction protein beta 6	1.40	0.005
2	*CCL26*	C-C motif chemokine ligand 26	1.24	0.002
3	*HAMP*	Hepcidin antimicrobial peptide	1.01	0.009
4	*SCGB1D2*	Secretoglobin family 1D member 2	0.84	0.008
5	*NEFM*	Neurofilament, medium polypeptide	0.82	0.010
6	*RNF128*	Ring finger protein 128, E3 ubiquitin protein ligase	0.81	0.001
7	*GSTM5*	Glutathione S-transferase mu 5	0.81	0.001
8	*VSNL1*	Visinin like 1	0.77	0.000
9	*UPK1B*	Uroplakin 1B	0.75	0.001
10	*CRYBA2*	Crystallin beta A2	0.72	0.014
11	*NEFL*	Neurofilament, light polypeptide	0.71	0.009
12	*OLIG1*	Oligodendrocyte transcription factor 1	0.70	0.004
13	*RARRES1*	Retinoic acid receptor responder 1	0.66	0.004
14	*OLFM4*	Olfactomedin 4	0.66	0.006
15	*OLR1*	Oxidized low-density lipoprotein receptor 1	0.64	0.001
16	*KERA*	Keratocan	0.61	0.002
17	*MTTP*	Microsomal triglyceride transfer protein	-0.61	0.012
18	*GABRE*	Gamma-aminobutyric acid type A receptor epsilon subunit	-0.64	0.007
19	*PROK1*	Prokineticin 1	-0.65	0.011
20	*NAT8L*	N-acetyltransferase 8 like	-0.77	0.013
21	*GPAM*	Glycerol-3-phosphate acyltransferase, mitochondrial	-0.82	0.015
22	*LRP1B*	LDL receptor related protein 1B	-0.85	0.013
23	*ABCD2*	ATP binding cassette subfamily D member 2	-0.90	0.016
24	*ANO3*	Anoctamin 3	-0.93	0.013
25	*PFKFB1*	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1	-1.03	0.010
26	*GYS2*	Glycogen synthase 2	-1.05	0.014

Note: Dysregulation is determined in the patients relative to the control samples.

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chemokine activity, and an important paralog of this gene is *CCL2*, which enhances microglial activation, leading to increased expression of receptor CCR2, suggesting an important role of chemokine *CCL2* and its receptor CCR2 in the development of neuropathic pain (Kwiatkowski & Mika, 2014). On the other hand, two lower-expressed genes were *GYS2* and *PFKFB1*, respectively. *GYS2* is involved in glucose metabolism, and its expression is decreased in diabetic patients, which conforms to our findings (Nilsson et al., 2014). The *GYS2* gene provides instructions for making liver glycogen synthase, an enzyme produced in the liver to form glycogen from glucose monomers. *GYS2* plays a role

Table 2. Selected 13 hub nodes for SDN

Row	Genes	Description	K	BC	CC	Stress
1	*INS*	Insulin: Insulin decreases blood glucose concentration. It increases cell permeability to monosaccharides, amino acids, and fatty acids. It accelerates glycolysis, the pentose phosphate cycle, and glycogen synthesis in the liver.	52	1.00	0.62	13640
2	*ALB*	Serum albumin: Serum albumin, the main protein of plasma, has a good binding capacity for water, $Ca^{(2+)}$, $Na^{(+)}$, $K^{(+)}$, fatty acids, hormones, bilirubin, and drugs. Its main function is the regulation of the colloidal osmotic pressure of blood.	51	0.67	0.62	11604
3	*AKT1*	V-akt Murine Thymoma Viral Oncogene Homolog 1: AKT1 regulates many processes, including metabolism, proliferation, cell survival, growth, and angiogenesis. AKT is responsible for the regulation of glucose uptake. AKT is also thought to be one mechanism by which cell proliferation is driven.	49	0.84	0.61	12110
4	*APP*	Amyloid beta (A4) precursor protein: N-APP binds TNFRSF21, triggering caspase activation and degeneration of both neuronal cell bodies (via caspase-3) and axons (via caspase-6), endogenous ligands.	46	0.55	0.59	7884
5	*SNAP25*	Synaptosomal-associated 25 kDa protein: t-SNARE, involved in the molecular regulation of neurotransmitter release, may play an important role in the synaptic function of specific neuronal systems.	44	0.73	0.59	7754
6	*NEFL*	Neurofilament, light polypeptide: Neurofilaments usually contain three intermediate filament proteins, namely L, M, and H, which are involved in the maintenance of neuronal caliber.	43	0.29	0.55	4664
7	*GFAP*	Glial fibrillary acidic protein: GFAP, a class-III intermediate filament, is a cell-specific marker that, during the development of the central nervous system, distinguishes astrocytes from other glial cells.	40	0.19	0.57	5314
8	*IL6*	B-Cell Stimulatory Factor 2: Cytokine with a wide variety of biological functions. It is a potent inducer of the acute phase response. Plays an essential role in the final differentiation of B-cells into Ig- secreting cells Involved in lymphocyte and monocyte differentiation.	40	0.24	0.58	5734
9	*NEFM*	Refer to the description of NEFL.	35	0.08	0.49	2136
10	*TNF*	TNF ligand superfamily member 2: Cytokine that binds to TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR. It is mainly secreted by macrophages and can induce cell death in certain tumor cell lines.	35	0.11	0.56	3640
11	*MAPT*	Microtubule-associated protein Tau: Promotes microtubule assembly and stability, and might be involved in the establishment and maintenance of neuronal polarity.	34	0.11	0.55	3636
12	*GAP43*	Axonal membrane protein GAP-43: This protein is associated with nerve growth. It is a major component of the motile “growth cones” that form the tips of elongating axons. Plays a role in axonal and dendritic filopodia induction.	33	0.00	0.54	2040
13	*MBP*	Myelin membrane encephalitogenic protein: The classic group of MBP isoforms (isoform 4-isoform 14), are with PLP the most abundant protein components of the myelin membrane in the central nervous system. They have a role in both its formation and stabilization.	33	0.06	0.54	3102

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Note: The genes are sorted by degree value. The values of degree (K), betweenness centrality (BC), closeness centrality (CC), and stress are represented in columns 4-7, respectively.

in the denosine monophosphate (AMP)-activated protein kinase (AMPK) signaling pathway in PDN (Zhou & Zhang, 2019). *PFKFB1* (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1) is a protein-coding gene, and one of its related pathways is glucose metabolism. Signaling pathway of AMPK in progressive and non-progressive DN is significantly enriched with *PFKFB1* and other genes as *PPARG* and *SDC*. Network analysis suggested *AMPK* and *PPAR* pathways may be implicated in DN, confirmed by our results (Li et al., 2016). Table 2 demonstrates the identified hubs that are ranked and tabulated based on degree value. Myelin formation is the result of the circumferential wrapping of Schwann cells’ cytoplasm, and it is particularly enriched with cholesterol and saturated long-chain fatty acids (Saher et al., 2011). Some researchers believed that diabetic hyperglycemia leads to malfunction in differentiation and re-differentiation of Schwann cells in accompany with myelin damage (Sango et al., 2011). New myelin formation after Schwann cells malfunction could be difficult and may cause DN progression (Cinci et al., 2015). As it is depicted in Table 2, a total of 13 nodes of the constructed network were highlighted as hub genes. Among the hub nodes (*INS*, *ALB*, *AKT1*, *APP*, *Snap25*, *NEFL*, *GFAP*, *IL6*, *NEFM*, *TNF*, *MAPT*, *GAP43*, and *MBP*), there are 11 first neighbors. According to the assumptions in Table 2, there are two queried hubs among the introduced hubs, including *NEFL* and *NEFM*.

According to Table 2, *INS* gene centrality is accompanied by degree 52, which is more than the other 12 genes. *INS* gene expression dysregulation following diabetes and hyperglycemia plays a critical role in disease progression. As it is shown in Table 2, *INS* is the potent bottleneck and is also characterized by the highest values of closeness centrality and stress. Further findings were obtained from roles of *NEFM* and *NEFL* as the only queried hub genes in progression of disease based on published documents, *NEFL* and *NEFM* encode the neurofilament proteins, and mutation of them leads to Charcot Mariye neuropathy and peripheral nerve neuropathy (Jordanova et al., 2003). Neurofilaments are intermediate filament type IV heterodimers composed of three different heavy, intermediate, and light chains, and they functionally maintain the neural caliber because neurofilaments comprise an exoskeleton (Abe et al., 2009). They may play a role in intracellular transportation into axons and dendrites. *NEFL* encodes light chain neurofilament protein. A mutation of this gene could cause disorders of peripheral nerves characterized by neuropathy (Drew et al., 2015). As it is demonstrated in Figure 3, *NEFL* and *NEFM* are linked with edges together, and the other 9 neighboring genes can be considered as the other related genes that have a significant impact on progressive DN incidence.

5. Conclusion

NEFL and *NEFM* play a critical role in the progression of DN, and more in vitro and in vivo investigations are needed to assess the specificity and sensitivity of these two highlighted differentially expressed genes in progressive DN. The investigation may result in *NEFL* or *NEFM* as biomarkers of DN.

Ethical Considerations

Compliance with ethical guidelines

This article is a data-analysis with no human or animal sample.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interests.

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