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Genetic Risk Factors for Diabetic Peripheral Neuropathy: A Systematic Review

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Abstract

Diabetic peripheral neuropathy (generally called DPN) is the leading cause of neuropathy worldwide. It brings enormous morbidity, affects quality of life and escalates mortality. While genetic factors in the pathogenesis of diabetes are studied extensively, limited literature is available on impact of genetic variants in the development of diabetic peripheral neuropathy which might represent tip of an iceberg. The objective of this article is to comprehensively review the genetic risk factors for diabetic peripheral neuropathy which will help physicians better assess the risk, make preventative measures and tailor the treatment in genetically susceptible individuals.

Keywords: Diabetic peripheral neuropathy; Genetic risk factors; Systematic review

Introduction

Diabetic peripheral neuropathy is one of the most prevalent causes of neuropathy worldwide. It is estimated that it affects approximately half of diabetics and accounts for about three quarters of all diabetic neuropathies [1,2] This debilitating complication causes substantial morbidity, compromises quality of life and increases mortality. The Toronto Consensus Panel on diabetic neuropathy recently defined DPN as a 'symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations resulting from chronic hyperglycemia and cardiovascular risk covariates. Furthermore, patients affected by DPN are susceptible to foot or ankle fractures and ulcerations, depression and lower limb amputation [2,3].

In spite of its healthcare related economic burden, morbidity and detrimental effects on quality of life, there are only limited treatment options and prevention is the key goal [3]. Due to suboptimal results of current interventions, rational therapies are needed to be developed [4]. In order to do so, all potential risk factors ought to be to be identified and treated in a timely manner to prevent it or at least retard the progression of DPN. This article is a comprehensive review of genetic risk factors which influence the incidence of progression of DPN.

Methods

A comprehensive search of literature databases was undertaken including but not limited to Pubmed, Ovid, Embase and Wiley from January 1, 2019 to March 10, 2019. All potential studies were identified and lists of citations were made for removal of duplicate studies. A variety of keywords were used namely, "diabetic peripheral neuropathy", "risk factor", "genetic risk factors", "influence factors" and "gene". After the removal of duplicate studies, abstract assessment process was carried out. Irrelevant studies were removed and a final list was made for full text assessment, a total of fifteen studies were included in the final review. Studies concerning genetic risk factors for diabetic peripheral neuropathy were considered eligible and there were no language restriction imposed (Table 1) [1-8].

Study ID	Country	Year	Study Design	N (M/F)	Gene Discussed
Ji et al. [5]	China	2015	Case control	180 (96/84)	Adiponectin Gene
Wang et al. [6]	China	2012	Case control	251 (124/127)	Methylenetetrahydrofolate reductase gene
Buraczynska et al. [7]	Poland	2016	Case control	1244 (594/650)	Glutathione Peroxidase 1 Gene
Ren et al. [8]	China	2015	Case control	787 (395/392)	Intercellular adhesion molecule-1 gene
Monastiriotis et al. [9]	Greece	2012	Review	N/A	APOE gene
Gupta et al. [10]	India	2017	Case control	650 (N/A)	Aldose reductase gene
Sun et al. [11]	China	2018	Case control	281 (N/A)	CACNA 1A/CACNA 1C/CACNA 1H calcium channel genes
Wu et al. [12]	China	2016	Meta-analysis	N/A	MTHFR and ACE Genes

Yigit et al. [13]	Turkey	2013	Case control	512 (N/A)	MTHFR gene
Inanir et al. [14]	Turkey	2013	Case control	516 (126/390)	Angiotensin-converting enzyme (ACE) Gene
Basol et al. [15]	Turkey	2013	Case control	454 (122/332)	Interleukin 4 Gene
Monastiriotis et al. [16]	Greece	2012	Case control	234 (120/114)	Epsilon4 allele of APOE Gene
Witzel et al. [17]	United Arab Emirates	2015	Review	N/A	Multiple
Papanas et al. [18]	Greece	2007	Case control	190 (104/86)	Alpha2B Adrenoceptor Gene
Stoian et al. [19]	Romania	2014	Case control	174 (87/87)	Vascular Endothelial Growth Factor Gene
Li et al. [20]	China	2014	Meta-analysis	N/A	ACE Gene
Kolla et al. [21]	India	2009	Case control	400 (242/158)	Interferon gamma and Interleukin 10 gene
Tang et al. [22]	United Kingdom	2010	Case control	1155 (N/A)	Glutathione peroxidase-1 Gene

Table 1: Characteristics of studies included.

Literature Review

Genetic factors contribute in the course of diabetic peripheral neuropathy and it might elucidate the variability found in its manifestations. This literature review discovered that mutations in several genes can increase the risk of developing diabetic peripheral neuropathy. A comprehensive list of these genes and associated mutations and polymorphisms is given below [9].

Adiponectin gene

Two adiponectin (ADPN) gene polymorphisms, namely +45T/Gand +276G/T were studies for potential correlation with increased vulnerability for diabetic peripheral neuropathy in type 2 diabetes in a case control study. According to final results, substantial reductions in serum ADPN levels were found in DPN subjects in comparison with non-DPN and normal controls. It was observed that T45G and G276T polymorphisms of ADPN are linked to substantially high risk of developing DPN. TT genotype of +45 T/G polymorphism in DPN group was significantly higher than the normal control group; it signifies that TT genotype might be a high risk factor for DPN. T allele of +45 T/G and + 276G/T polymorphisms frequency was also remarkably higher compared to normal controls, which indicates that T allele poses a higher risk of DPN in type 2 diabetes patients [5].

Methylenetetrahydrofolate reductase gene

The relationship of methylenetetrahydrofolate reductase gene with diabetic peripheral neuropathy is elaborated by multiple studies. A case control study involving 251 subjects was carried out to evaluate the correlation between C677T polymorphism of MTHFR gene and diabetic peripheral neuropathy in Chinese patients.

TT alleles were found to have an odds ratio of 1.732 for development of DPN. It was concluded that C677T polymorphism in methylenetetrahydrofolate reductase could be a risk factor for diabetic peripheral neuropathy in Chinese patients with diabetes. Another study focusing same MTHFR gene C677T mutation was carried out in Turkey [6]. This case control study included a total of 512 participants among which 230 were DPN patients and 282 normal controls. It was observed that CC, CT and TT genotype mutations in C677 T was reported to be 53, 37 and 9.5 percent sequentially. It was ascertained by this study that C677T mutation in MTHFR gene poses high risk for DPN. A meta-analysis study was done to explore the association of C667T mutation of MHTFR gene and DPN. In this study, data from 1720 DPN patients and 1899 healthy controls was analyzed. This meta-analysis concluded that odds ratio for having DPN with C677T mutation is 1.43 in allele model, while it was 1.99 for dominant model. An association between C677T mutation in MTHFR gene and DPN was found by this study [10-13].

Glutathione peroxidase 1 gene

Glutathione peroxidase 1 is a natural anti-oxidant enzyme. It is reported that Pro198Leu mutations in glutathione peroxidase gene are associated with increased susceptibility for DPN in type 2 diabetes. A case control study was carried out in Poland in 2016 to evaluate the relationship of Pro198Leu mutations. This study involved 1244 type 2 diabetics including 594 males and 650 females and 730 normal controls. It was observed that the frequency of T allele of Pro198Leu is remarkably higher in DPN group in comparison with non-DPN group. Odds ratio for developing DPN with T allele was reported as 1.55. Risk was even higher in case of homozygous TT and heterozygous CT reflected by odds ratio of 1.89 and 1.78 respectively. It was ascertained that there was a remarkable relationship between Pro198Leu mutation in glutathione peroxidase gene and risk of DPN in type 2 diabetes [7].

Glutathione peroxidase-1 gene rs1050450 (C>T) mutation and risk of diabetic peripheral neuropathy was explored by a case control study. This study included two different samples of Caucasian subjects. T allele of the GPx-1 rs1050450 (C>T) gene variant was found to have suboptimal enzyme activity. Results revealed that odds ratio for peripheral neuropathy in the T allele carriers in comparison with the CC genotype was 1.61. It was deduced that there is a significant relationship between T allele and development of diabetic peripheral neuropathy [22].

Intercellular adhesion molecule-1 gene

Intercellular adhesion molecule-1 which is an inflammatory cytokine has been associated with diabetic complications. In 2015, a case control study was organized to assess the relationship of its polymorphisms and risk of diabetic peripheral neuropathy in type 2 diabetics hailing from Chinese Han ethnic group. It was a case control

study including 787 subjects. The focus of this study was four genotype distributions namely rs281432, rs1799969, rs5491 and rs5498 in the ICAM-1 gene.

Regarding rs281432, all T2D subjects demonstrated a higher frequency of G allele in comparison with non-diabetic controls when adjusted for age, frequency of this genotype was 0.35 in diabetes subjects while 0.31 in healthy controls with reported odds ratio of 1.2. In terms of rs1799969, significant differences were observed in the frequency of this genotype between subjects with and without DPN with a calculated odds ratio of 3.695 [8].

Apolipoprotein E gene

Apolipoprotein E gene polymorphisms are associated with increased risk of diabetic peripheral neuropathy. A case control study intended to find out the association between epsilon 4 allele of ApoE gene and severity of symptoms of diabetic peripheral neuropathy. This case control study included 234 Greek subjects among which 120 were males and 114 were females. A dramatic fivefold (odds ratio: 5.26) increase in the severity of symptoms of DPN was reported for Epsilon 4 carriers in comparison with non-carriers. Researchers deduced that Epsilon 4 allele is associated with more severe symptoms of DPN [16].

However, in a review study which aimed to identify the association between ApoE polymorphisms and DPN, it was reported that it was uncertain that epsilon 4 allele was linked to this complication [9].

Aldose reductase gene

A case control study was conducted in 2017 on north Indian subjects to evaluate the likelihood that C106T polymorphism is associated with risk of DPN. This study included 650 participants divided in three groups. It was found that C106T genotype was remarkably higher in the DPN group in comparison to non-DPN group with a reported odds ratio of 2.12. It was concluded that C106T genotype of ALR gene is associated with increased vulnerability to develop DPN in north Indians [10].

Calcium channel genes

Different single nucleotide polymorphisms in calcium channel gene are considered to be associated with DPN. A study was conducted in 2018 to identify the association of CACNA 1A, CACNA 1C, and CACNA 1H genes with DPN. This case control study comprised of 281 Chinese subjects. Results showed that CACNA 1A rs2248069 and rsl6030, CACNA 1C rs216008 and rs2239050, and CACNA 1H rs3794619, and rs7191246 SNPs were linked to development of DPN. Moreover, rs2248069, rsl6030, rs2239050, and rs7191246 polymorphisms demonstrated increased vulnerability for DPN. It was ascertained that SNPs in calcium gene were not only related to risk of DPN, but their interactions also influence the outcome [11].

Angiotensin converting enzyme gene

It was proposed by a study carried out in 2013 in Turkey that SNPs in ACE gene are associated with increased risk of DPN. This case control study included 516 subjects and studies ACE gene I/D polymorphism. It was concluded that DD genotype of I/D polymorphism was related to increased susceptibility to develop DPN. With these results, it was deducted that D allele of I/D polymorphism raises the risk of incidence of DPN [14].

A meta-analysis study was carried out to explore the association of ACE gene I/D polymorphism, which analyzed the data from 1720 DPN patients and 1899 healthy controls. This meta-analysis determined that odds ratio for having DPN with I/D mutations was 1.43. Furthermore, it was discovered that ACE I/D mutations were found in the majority of DPN patients belonging to Japan and Pakistan [12].

Another meta-analysis study was conducted to ascertain the relationship of I/D polymorphism of ACE gene. This meta-analysis included a total of seven case control studies comprising of 1316 cases and 1617 controls. Final results revealed that ACE gene I/D polymorphism was related to dramatic increase in risk of DPN with a reported odds ratio of 1.46. Adjusted odds ratio was calculated as 1.84, in subgroup analysis Caucasians showed an odds ratio of 1.32 [20].

Interleukin 4 gene

A study was carried out to assess the relationship of variable number of tandem repeat (VNTR) polymorphism in IL-4 gene with diabetic peripheral neuropathy. This case control study which was carried out in year 2013 in Turkey consisted of 454 Turkish subjects. It was found that frequency of IL-4 gene intron 3 VNTR was dissimilar in DPN group in comparison with control subjects. It was further noticed that frequency of P1 and P2 allele also varied significantly across subjects with DPN and normal controls. It was concluded that intron 3 VNRT of IL-4 gene polymorphism has a significant contribution in the development of DPN in Turkish citizens [15].

Alpha2B adrenoceptor gene

A case control study carried out in Greece in 2007 described that Alpha2B Adrenoceoptor gene polymorphism is linked to increased risk of DPN. This study included 190 participants among them 104 were males and 86 were females. Results of genotyping of I/D allele showed that D allele frequency is found to be significantly higher in patients with DPN when compared with non-DPN subjects. Moreover, it was reported that D allele carriers exhibit a higher neuropathic score which underscore its contribution to severity of symptoms [18].

Interferon gamma and interleukin 10

The relationship of Interferon Gamma and IL-10 with DPN is explained by a case control study conducted in 2009 South Indian suffering from type 2 diabetes. This study involved a total of four hundered patients including 158 females and 242 males. Three most prevalent functional SNPs primarily at the positions on genes of tumor necrosis alpha (TNFa) -308G/A, interferon gamma (IFNc) +874A/T and interleukin (IL) 10 -1082G/A were examined to evaluate the link between these SNPs and DPN in type 2 diabetes. It was concluded that The IFNc +874 A/T polymorphism in patient group indicated the frequency of A/A, A/T and T/T genotype as 33.3%, 47.5 % and 19.2% sequentially. The A/A genotype had demonstrated remarkable association with a reported odds ratio of 2. The IL10 -1082 G/A polymorphism in the patient group has showed the frequency of A/A, of G/A, 21.2% of G/G genotype as 62.6%, 21.2% and 21.2%respectively. A significant association with G/G genotype was found reflected by an odds ratio of 2.9 [21].

Vascular endothelial growth factor gene

The importance of VEGF gene insertion/deletion polymorphism on diabetic peripheral neuropathy is emphasized by a case control study which was conducted in Romania in 2014 on type 2 diabetes patients. This study included 174 patients with equal number of male and female participants. Results indicated that D allele of VEGF gene frequency was found remarkable higher in patients of DPN when compared to normal controls. A strong correlation was proposed between VEGF gene D allele and incidence of DPN in this study [19].

CYBA gene

CYBA gene polymorphism rs4673 has an established relationship with risk of diabetic peripheral neuropathy in type 1 diabetes. This correlation was confirmed by a study focused on juvenile population. It was observed that TT genotype rs4673 was linked to increased risk of diabetic peripheral neuropathy. Odds ratio for this association was reported as 4.997. It was ascertained that there is a remarkable relationship between rs4673 polymorphism in CYBA gene and DPN among type 1 diabetics of Slovak origin [23].

Miscellaneous genes

In addition to above mentioned genes, polymorphisms in genes including AKR1B1, ADRA2B, NOS1AP, NOS3, TLR4, and UCP2 are known to be associated with DPN. A case report has claimed that polymorphisms in ATPase 8, ND1, ND5, and MT-CYB are linked to development of DPN [17].

Discussion

It is obvious that genetic mutations play a noteworthy role in the occurrence and progression of DPN. Identification of these genetic mutations should be followed by structured prospective studies to investigate how these mutations cause or accelerate DPN, and their potential interaction with other risk factors. Knowledge of these genetic variants ought to be applied to individual cases of diabetes to evaluate the risk of DPN, to make plausible preventative strategies and tailor the treatment protocols. More importantly, because these polymorphisms may modulate the therapeutic response, this knowledge should be utilized in the field of Pharmacogenetics for individualized selection of medicine, dosage and route of administration [17].

However, studies included in this review have several limitations. Most of studies included are observational studies which have inherent risk of bias. Sample size is small for most studies and there are significant differences in population and study designs, moreover remarkable heterogeneity exist between studies included in meta-analyses.

Conclusion

It is elucidated that the incidence and course of DPN is influences by genetic factors. Knowledge of genetic risk factors is expected to offer assistance in diagnosis and treatment of diabetic peripheral neuropathy. Genetic risk factors should be taken into consideration for the development of future therapies which may bring promising results.

References

1. Iqbal Z, Azmi S, Yadav R, Ferdousi M, Kumar M, et al. (2018) Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy. Clin Ther 40: 828-849.
2. Singh R, Kishore L, Kaur N (2014) Diabetic peripheral neuropathy: current perspective and future directions. Pharmacol Res 80: 21-35.
3. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, et al. (2010) Diabetic neuropathies: Update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes care 33: 2285-2293.
4. Tesfaye S, Selvarajah D (2012) Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab Res Rev 1: 8-14.
5. Ji ZY, Li HF, Lei Y, Rao YW, Tan ZX, et al. (2015) Association of adiponectin gene polymorphisms with an elevated risk of diabetic peripheral neuropathy in type 2 diabetes patients. J diabetes complications 29: 887-892.
6. Wang H, Fan D, Hong T (2012) Is the C677T polymorphism in methylenetetrahydrofolate reductase gene or plasma homocysteine a risk factor for diabetic peripheral neuropathy in Chinese individuals? Neural Regen Res 7: 2384-2391.
7. Buraczynska M, Buraczynska K, Dragan M, Ksiazek A (2017) Pro198Leu polymorphism in the glutathione peroxidase 1 gene contributes to diabetic peripheral neuropathy in type 2 diabetes patients. Neuromolecular Med 19: 147-153.
8. Ren Z, Ji N, Jia K, Wang L, Gu HF, et al. (2015) Association of the intercellular adhesion molecule-1 gene polymorphisms with type 2 diabetes and diabetic peripheral neuropathy in a Chinese Han population. Genes & Genomics 37: 69-75.
9. Monastiriotis C, Papanas N, Veletza S, Maltezos E (2012) APOE gene polymorphisms and diabetic peripheral neuropathy. Arch Med Sci 8: 583-588.
10. Gupta B, Singh SK (2017) Association of aldose reductase gene polymorphism (C-106T) in susceptibility of diabetic peripheral neuropathy among north Indian population. J Diabetes complications 31: 1085-1089.
11. Sun L, Ma J, Mao Q, Yang YL, Ma LL, et al. (2018) Association of single nucleotide polymorphisms in CACNA 1A/CACNA 1C/CACNA 1H calcium channel genes with diabetic peripheral neuropathy in Chinese population. Biosci Rep 38: 3.
12. Wu S, Han Y, Hu Q, Zhang X, Cui G, et al. (2017) Effects of common polymorphisms in the MTHFR and ACE genes on diabetic peripheral neuropathy progression: a meta-analysis. Mol Neurobiol 54: 2435-2444.
13. Yigit S, Karakus N, Inanir A (2013) Association of MTHFR gene C677T mutation with diabetic peripheral neuropathy and diabetic retinopathy. Mol Vis 19: 1626-1630.
14. Inanir A, Basol N, Karakus N, Yigit S (2013) The importance of association between angiotensin-converting enzyme (ACE) Gene I/D polymorphism and diabetic peripheral neuropathy. Gene 530: 253-256.
15. Basol N, Inanir A, Yigit S, Karakus N, Kaya SU (2013) High association of IL-4 gene intron 3 VNTR polymorphism with diabetic peripheral neuropathy. Journal of molecular neuroscience 51: 437-441.
16. Monastiriotis C, Papanas N, Trypsianis G, Karanikola K, Veletza S, et al. (2013) The epsilon4 allele of the APOE gene is associated with more severe peripheral neuropathy in type 2 diabetic patients. Angiology 64: 451-455.
17. Witzel II, Jelinek HF, Khalaf K, Lee S, Khandoker AH, et al. (2015) Identifying common genetic risk factors of diabetic neuropathies. Front endocrinol 6: 88.
18. Papanas N, Papatheodorou K, Papazoglou D, Kotsiou S, Christakidis D, et al. (2007) An insertion/deletion polymorphism in the alpha2B adrenoceptor gene is associated with peripheral neuropathy in patients with type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 115: 327-330.
19. Stoian A, Bacârea A, Moţăţăianu A, Stoian M, Gliga F, et al. (2014) Vascular endothelial growth factor insertion/deletion gene polymorphism

in patients with type 2 diabetes and diabetic peripheral polyneuropathy. Rom Rev Lab Med 22: 165-172.

20. Li Y, Tong N (2015) Angiotensin-converting enzyme I/D polymorphism and diabetic peripheral neuropathy in type 2 diabetes mellitus: A meta-analysis. J Renin Angiotensin Aldosterone Syst 16: 787-792.
21. Kolla VK, Madhavi G, Reddy PB, Babu SBM, Yashovanthi J, et al. (2009) Association of tumor necrosis factor alpha, interferon gamma and interleukin 10 gene polymorphisms with peripheral neuropathy in South Indian patients with type 2 diabetes. Cytokine 47: 173-177.
22. Tang T, Prior S, Li K, Ireland H, Bain S, et al. (2012) Association between the rs1050450 glutathione peroxidase-1 (C>T) gene variant and peripheral neuropathy in two independent samples of subjects with diabetes mellitus. Nutr Metab Cardiovasc Dis 22: 417-425.
23. Snahnicanova Z, Mendelova A, Grendar M, Holubekova V, Kostkova M, et al. (2018) Association of Polymorphisms in CYBA, SOD1, and CAT Genes with Type 1 Diabetes and Diabetic Peripheral Neuropathy in Children and Adolescents. Genet Test Mol Biomarkers 22: 413-419.