Indian Journal of Genetics and Molecular Research
Volume 1 Number 2, July - December 2012

Genetic Factors in Diabetic Peripheral Neuropathy: From the Known to the Unknown

Kumar Senthil P., MPT*; Adhikari Prabha, MD; Jeganathan, P.S., PhD*****

Abstract

The aim of this letter is directed to exploring the underlying evidence for the role of genetic factors in development of a common microvascular complication of diabetes mellitus (DM), the diabetic peripheral neuropathy (DPN). Genetic factors played a pathogenetic, predisposing role and also a protective therapeutic role in development and amelioration of DPN respectively.

Keywords: Genetic endocrinology; Molecular metabolism; Diabetic neuropathy; Neurobiochemical markers.

Dear Sir,

This letter to editor brings to you and the Indian Journal of Genetics and Molecular Research the warmest best wishes in its maiden effort to provide updated scientific information in the field of Molecular Biology from a wider inter-disciplinary evidence-informed perspective. The aim of this letter is directed to exploring the underlying evidence for the role of genetic factors in development of a common microvascular complication of diabetes mellitus (DM), the diabetic peripheral neuropathy (DPN).

Historically, experimentally induced neuropathy models had utilized genetic polymorphisms and had studied the efficacy of treatments such as Ganglioside (Gorio *et al*, 1984).[1] Initial case-control studies could not find association of genetic factors with DPN and Boulton *et al* (1984)[2] who studied 41 subjects with DPN and 41 DM subjects without PN and compared the acelyator status via HLA-A, B, C and DR antigens, could not find any significant difference between the two groups in the proportion of fast and slow acetylators. The distribution of HLA frequencies was also similar in subjects with and without neuropathy for both Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetic patients.

17 years later, Benjafield *et al* (2001)[3] identified genetic variation in the tumor necrosis factor (TNF) receptor 2 gene (TNFRSF1B)with polymorphism of CA16 allele which was also previously associated with insulin resistance in type 2 diabetes, hypercholesterolemia, coronary artery disease, and essential hypertension. Another study by Strokov*et al* (2003)[4] examined polymorphic markers Ala(-9)Val in SOD2 gene and Arg213Gly in SOD3 gene and their relationship to DPN and found that genes encoding the enzymes Mn-SOD and extracellular superoxide dismutase (EC-SOD) were associated with the pathogenesis of DPN.

More recently, Gazzaruso *et al* (2012)[5]

*Associate professor, PhD Candidate, Dept of Physiotherapy, Kasturba Medical College (Manipal University), Mangalore, India, **Professor, Dept of Medicine, Kasturba Medical College (Manipal University), Mangalore, India, ***Professor, Dept of Physiology, Kasturba Medical College (Manipal University), Mangalore, India.

Corresponding Author: Senthil P. Kumar, Associate professor, Dept of Physiotherapy,Kasturba Medical College (Manipal University),Mangalore-575001, India.

E-mail: senthil.kumar@manipal.edu

studied association of Lipoprotein(a)-Lp(a)- and homocysteine (Hcy) with diabetic foot ulcerations, which were classified according to the presence of peripheral artery disease (PAD) or neuropathy. The study found that high Lp(a) and Hcy levels were associated with the development of vascular diabetic foot (VDF), while low Lp(a) levels appear to be associated with delayed wound healing in patients with neuropathic foot ulcerations.

Genetic factors also played a protective role and Angiotensin-converting enzyme gene single polymorphism was shown to act as a protective genetic biomarker of DPN as demonstrated by Jurado *et al* (2012)[6] who analyzed angiotensin-converting enzyme (ACE) gene polymorphism (D/I) as a genetic marker of risk of developing DPN, and found presence of ACE polymorphism heterozygous genotype D/I in 60.77% which was also independently associated with a decreased risk of DPN. Another study by Walwyn *et al* (2006)[7] investigated the effect of localized nerve growth factor (NGF) expression in a genetic mouse model of progressive diabetic neuropathy, and found that site-specific delivery of NGF initially delayed the appearance of hypoalgesia, which suggested that NGF-based gene therapy would be viable therapeutic option.

Thus genetic factors played a pathogenetic, predisposing role and also a protective therapeutic role in development and amelioration of DPN respectively. Can future controlled clinical trials explore the molecular mechanisms behind use of commonly recommended interventions for DPN?

References

1. Gorio A, Aporti F, Di Gregorio F, Schiavinato A, Siliprandi R, Vitadello M. Ganglioside treatment of genetic and alloxan-induced diabetic neuropathy. *Adv Exp Med Biol.* 1984; 174: 549-64.
2. Boulton AJ, Worth RC, Drury J, HardistyCA, Wolf E, Cudworth AG, *et al.* Genetic and metabolic studies in diabetic neuropathy. *Diabetologia.* 1984; 26(1): 15-9.
3. Benjafield AV, Glenn CL, Wang XL, Colagiuri S, Morris BJ. TNFRSF1B in genetic predisposition to clinical neuropathy and effect on HDL cholesterol and glycosylated hemoglobin in type 2 diabetes. *Diabetes Care.* 2001; 24(4): 753-7.
4. Strokov IA, Bursa TR, Drepa OI, Zotova EV, Nosikov VV, Ametov AS. Predisposing genetic factors for diabetic polyneuropathy in patients with type 1 diabetes: a population-based case-control study. *ActaDiabetol.* 2003; 40(Suppl 2): S375-9.
5. Gazzaruso C, Coppola A, Montalcini T, Baffero E, Garzaniti A, Pelissero G, *et al.* Lipoprotein(a) and homocysteine as genetic risk factors for vascular and neuropathic diabetic foot in type 2 diabetes mellitus. *Endocrine.* 2012; 41(1): 89-95.
6. Jurado J, Ybarra J, Romeo JH, Garcia M, Zabaleta-Del-Olmo E. Angiotensin-converting enzyme gene single polymorphism as a genetic biomarker of diabetic peripheral neuropathy: longitudinal prospective study. *J Diabetes Complications.* 2012; 26(2): 77-82.
7. Walwyn WM, Matsuka Y, Arai D, Bloom DC, Lam H, Tran C, *et al.* HSV-1-mediated NGF delivery delays nociceptive deficits in a genetic model of diabetic neuropathy. *Exp Neurol.* 2006; 198(1): 260-70.