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Review

Recent advances in exploring the genetic susceptibility to diabetic neuropathy

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ABSTRACT

Diabetic polyneuropathy and cardiovascular autonomic neuropathy are common and disabling complications of diabetes. Although glycaemic control and cardiovascular risk factors are major contributory elements in its development, diabetic neuropathy recognizes a multifactorial influence and a multiplicity of pathogenetic mechanisms. Thus genetic and environmental factors may contribute to its susceptibility, each with a modest contribution, by targeting various metabolic and microvascular pathways whose alterations intervene in diabetic neuropathy pathogenesis. This review is aimed at describing major data from the available literature regarding genetic susceptibility to diabetic neuropathies. It provides an overview of the genes reported as associated with the development or progression of these complications, i.e. *ACE, MTHFR, GST, GLO1, APOE, TCF7L2, VEGF, IL-4, GPX1, eNOS, ADRA2B, GFRA2, MIR146A, MIR128A*.

The identification of genetic susceptibility can help in both expanding the comprehension of the pathogenetic mechanisms of diabetic nerve damage and identifying biomarkers of risk prediction and response to therapeutic intervention.

Contents

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1. Introduction

Diabetic neuropathy is a common complication of diabetes. While estimates vary, depending on the methods and criteria used to diagnose diabetic neuropathy, it is generally held that at least 50% of all diabetic patients will develop neuropathy in their lifetime [1,2]. The neuropathies developing in patients with diabetes are known to be heterogeneous for their symptoms, pattern of neurological involvement, course, risk covariates, pathologic alterations, and underlying mechanisms [3,4]. The most common neuropathies are diabetic polineuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) [1,2].

Both these diabetic neuropathies can entail disabling consequences like neuropathic pain, foot ulceration and amputation, diabetic gastroparesis, postural hypotension, and cistopathy. Moreover, they are burdened with negative impact on quality of life and health related costs [5] and associated with increased morbidity and mortality [1,6,7].

DPN has recently been defined by the Toronto Expert Panel on Diabetic Neuropathy as a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates [6]. Age, diabetes duration, glycaemic control, hypertension and smoking (these last two mainly in type 1 diabetes) are the major risk factors, while new and less strong clinical correlates or predictors are obesity, body mass index (BMI), waist circumference, hypoinsulinemia in type 2 diabetes, low levels of C peptide in type 1 diabetes, metabolic dyslipidemia, and cardiovascular disease including peripheral arterial disease [2,8,9].

CAN is the other common form among diabetic neuropathies. The prevalence of confirmed CAN (based on at least two abnormal cardiovascular heart rate test results) in unselected people with type 1 and type 2 diabetes is around 20%, but figures as high as 65% are reported with increasing age and diabetes duration [7]. Established risk factors for CAN are glycaemic control in type 1 diabetes, and a combination of hypertension, dyslipidaemia, obesity and glycaemic control in type 2 diabetes [7].

Although CAN often coexists with DPN, there is no totally parallel behavior between the two forms. In type 2 diabetes their development may diverge and their response to therapeutic interventions may differ [10].

The pathogenesis of DPN and CAN have not been completely understood. There is a common view that these complications are multifactorial diseases caused by complex interactions between a variety of genetic and environmental factors. Given the large inter-individual variability in terms of clinical manifestations and severity of DPN and CAN, it has been suggested that genetic factors may influence the natural course of the disease.

The aim of this review is to focus the attention on the recent findings about the genetic component of these common complications of diabetes, DPN and CAN. Below we give an overview of the genes that have been found associated with the development or progression of these diabetic complications (Table 1).

2. Searching strategy

The scientific publications were identified from the international web database PubMed. We selected the papers that investigated the association of genetic variants with the diabetes complications, focusing our attention in particular on diabetic neuropathy. We included articles published between September 2006 and May 2015. We performed the research using the following key words: diabetes mellitus/type 2 diabetes, polymorphism, diabetes complications, genetic susceptibility to diabetes, diabetic polineuropathy/DPN, peripheral neuropathy and cardiovascular autonomic neuropathy/CAN. We excluded the papers that investigated any kind of neuropathy not related to diabetes or other kinds of diabetes complications, as well as papers that did not identify any association. Furthermore we repeated the research focusing our attention on the identified genes. We included all observational population-based studies, which were conducted as case-control, cohort and cross sectional analysis, or as meta-analysis. In addition, we excluded animal studies, clinical trials, short communications, letters to editor, dissertations and in vitro studies. References of all selected articles were investigated.

3. *ACE* gene

Angiotensin-converting enzyme (*ACE*) is a component of the renin–angiotensin system that converts Angiotensin I to