The Emerging Concept of Genetic Polymorphism in Diabetic Retinopathy

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Abstract

Diabetic Retinopathy (DR) is the leading cause of blindness in the working-age in developed countries. The development and progression of DR are affected by both internal and external risk factors. Recently, the genetic risk factor is heavily studied regarding its association with DR in type 2 diabetic patients. There are some emerging concepts through its essential genetic roles related to DR progression and development. Genetic factors should be highly considered as it may be accountable for around 25-50% of risks in developing DR. several genes are accountable for the progression of DR in the patients with type 2 diabetes mellitus, including Aldose Reductase, Endothelial Nitric Oxide Synthase (eNOS), Receptor for Advanced Glycation Endproducts (RAGE), Vascular Endothelial Growth Factor (VEGF). As the most frequent cause of visual impairment, it is important for people to know more about the genetic risk factors towards DR progression in patients with type 2 diabetes mellitus. In this paper, the author wanted to discuss more the emerging concepts about the association between genetic risk factors and the occurrence of DR in patients with type 2 diabetes mellitus.

Keywords: Diabetes mellitus; Diabetic retinopathy; Genetic polymorphism

Abbreviations: DM: Diabetes Mellitus; DR: Diabetic Retinopathy; SNP: Single Nucleotide Polymorphism; ENOS: Endothelial Nitric Oxide Synthase; RAGE: Receptor for Advanced Glycation Endproducts; VEGF: Vascular Endothelial Growth Factor; AGEs: Advanced Glycation Endproducts; IGF: Insulin-like Growth Factor; AR: Aldose Reductase

Introduction

Diabetes Mellitus (DM) is a metabolic disorder in which the body is unable to maintain the sugar in the blood causing an elevated blood sugar level [1]. Prolonged high blood sugar level may result in vascular complications including macrovascular and microvascular complications [1]. Diabetic retinopathy (DR) is one of the most usual microvascular complications which take place as the leading cause of visual impairment. Recent studies showed that Single Nucleotide Polymorphism (SNP) of some genetic region including Aldose Reductase (AR), Endothelial Nitric Oxide Synthase (eNOS), Receptor for Advanced Glycation Endproducts (RAGE), Vascular Endothelial Growth Factor (VEGF) could be linked in worsening the progression of DR [2-4].

Diabetic Retinopathy

DR is a chronic condition that develops progressively and might be causing a visual impairment through a prolonged state of uncontrolled hyperglycemic condition [5]. It is found that DR is the leading cause of vision loss in patients aged 20 to 74 years old [6]. Some factors may contribute to the formation of DR which can be divided into internal and external factors. Internal factors are the factors that are unable to be modified, including duration of diabetes, age, and genetics [7-10]. Hypertension, dyslipidemia, and hyperglycemic are some external factors that may affect the progression of DR [7,11,12]. several pathways can be surpassed in accelerating the development of DR, such as (DAG)-PKC pathway, polyol pathway, increased VEGF, and insulin-like growth factor (IGF) expressions, accelerated formation of advanced glycation endproducts (AGEs), oxidative stress, and leukostasis [13]. The destruction of vascular endothelial cells or hypoxic cells injury can be induced by the expression of VEGF. Not only does VEGF expression induce more damage to cells, but also triggers angiogenesis and...
disrupts blood-retinal barriers by increasing vascular permeability. These activities stimulate the growth of the endothelial cells resulting in neovascularization. Besides, VEGF expression may induce leukocyte adhesion in retinal endothelial cells resulting in some damages in retinal, retinal bleeding, and visual impairment [14].

Genetic Role in Diabetic Retinopathy

Clinically significant variations in DR onset and severity cannot be entirely explained by acknowledged risk factors like duration of diabetes, glycemic control, or vascular disease comorbid [15]. Some people may have DR even if they have good glycemic control and short duration of DM, while other patients, on the other hand, have poor glycemic control and long duration of DM but still may not develop DR. The chances of developing DR also depend on ethnicity. Reports from various countries show that African and Afro-Caribbean, South Asian, Latin American, have considerably higher recorded rates of DR than European derived people. In other words, Hispanics, people of African descent, and Asians are more susceptible to DR [16-18]. Genetic diversity may define why the incidence and progression of DR differ significantly, even among patients with identical metabolic factors [19]. DR was hypothesized as a complex genetic disease or polygenic diseases that are associated with multiple genetic and environmental factors. These genetic factors are commonly referred to as variants or polymorphism rather than mutations. Variants can be correlated with either increased or decreased risk of disease, whilst polymorphism is generally characterized as a gene variant found in 1% or more of the general population. These variants of genes may interfere with environmental factors in unknown ways [20].

Genes Polymorphism Candidate

Most of the candidate gene studies investigated the genetic variants involved in the development of diabetes or metabolic pathways including polyol pathway, Advanced Glycation End products (AGE), and vascular endothelial growth factor which mediated the angiogenesis in hypoxia. Almost all of the published studies on DR genetics have involved four genes in DR pathogenesis. AR is present in large amounts in retinal pericytes and Schwann cells where it transforms glucose to osmotic sorbitol [21]. The association in AR variation including the polymorphism of rs759853 (-106C/T) has been strongly correlated with 206 Iranian patients with type 2 diabetes but not in 26 Chinese patients with type 2 diabetes. Another association also showed in a meta-analysis of 7,831 patients from 17 studies in Asia, South America, Australia, and Europe reported a substantial correlation between this polymorphism and DR in patients with type 1 diabetes [22,23]. eNOS is important in regulating retinal vascular tone [24]. A meta-analysis of 3,145 patients in nine multi-nation studies reported a significant negative correlation between rs3138808 (4b/s) polymorphism of eNOS and DR in patients with type 1 and type 2 diabetes [25]. RAGE may induce the production of several growth factors and inflammatory cytokines. A meta-analysis that compiled 3,339 patients across seven studies showed a significant relationship between polymorphism of RAGE and DR in patients with type 2 diabetes [26,27]. A significant result was also found in a series of 758 North Indian patients showed a positive association between the homozygous Ser82 genotype of the Gly82Ser polymorphism of RAGE and DR [28]. VEGF was the most studied gene in DR gene polymorphisms. There was four polymorphism of VEGF that has been well studied. The rs833061 (-460C/T) polymorphism showed a positive association with DR in patients with type 2 diabetes in a meta-analysis of 746 Asian patients [29]. In a meta-analysis of 2,402 Asian and European patients [30] and 500 Chinese patients [31] were reported a significant association between rs699947 (-2578C/A) polymorphism and DR in type 2 diabetes patients. Other studies in rs2010963 (-634G/C) polymorphism [32] and rs3025039 (+936C/T) polymorphism [29] also reported a substantial correlation with DR.

Conclusion

As the leading cause of visual impairment, it is important to dig deeper into all the possible aspects related to the occurrence of DR. SNP polymorphism in several genetic promoter regions, such as AR, eNOS, RAGE, and VEGF is thought to be associated with the progression of DR within type 2 diabetes patients. Further studies should be conducted to discover the exact association between this genetic role with DR occurrence.

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