Recent Progress in Genetic Polymorphisms and Diabetic Retinopathy (DR) in Type 1 Diabetes Mellitus (T1DM)

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Abstract

Type 1 diabetes (T1D) is one of the major health burdens worldwide. Diabetes induced diabetic retinopathy (DR) is the most common diabetic eye disease and the leading cause of preventable blindness in working-age adult. Several genetic loci have recently been reported to contribute to the susceptibility of type 1 diabetes induced DR. In order to further understand the genetic influence on the risk of DR in T1D patients, we reviewed and collected the articles from PUBMED for genes that reported by recent genetic studies. At the conclusion of our search, we summarized the publications about relative genetic association studies and summarized the candidate genes, which might relate with DR in T1D patients. Despite the findings of this and other similar, contemporary research projects, many of the special details and underlying mechanisms in this field of study are still, to a great extent, unknown. As a result, future studies are needed to gain a full appreciation regarding the identification of high DR risk in T1D patients.

Keywords: Type 1 diabetes (T1D); Diabetic retinopathy (DR); Genetic; Personalized medicine

Instruction

The epidemic of diabetes has imposed a huge burden on human health worldwide [1]. There are two types of diabetes mellitus, Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). Both T1DM and T2DM can cause many severe complications, such as diabetic ketoacidosis, nonketotic hyperosmolar coma, chronic renal failure and so on [2]. Among these acute and long-term complications, diabetic eye diseases are frequent and serious complications. Diabetic eye disease refers to a group of eye problems occurred in diabetic patients. Diabetic Retinopathy (DR) is the most common diabetic eye disease and the leading cause of preventable blindness in working-age adult [3].

DR affects up to about eighty percent of diabetic patients who have had diabetes for more than ten years. However, the etiology of DR remains complex and poorly understood [4]. Some studies have reported that the duration of diabetes and glycemic levels may be the two major factors contributing to the progression of DR. However, these two major contributors only explained about 11% of the DR risk in total [5]. The remaining susceptibility risk of DR is still unclear. As a typical common complex disease, the DR risk is the result of the interplay between internal factors (genetic and/or epigenetic factors) [6] and external factors (environmental factors) [7]. The suggestive genetic contribution to DR has leaded the researcher to search for risk genes and/or genotypes, using both candidate gene based approaches [8] as well as genome-wide based approaches [9]. Based on the rapid development biotechnologies (e.g., genome-wide SNP chips, next-generation sequencing) and bioinformatics (e.g., integrative network-based computational methods [10-12]), some studies have found potential genetic risk factors contributing to DR in different ethnicities recently.

Majority of the genetic studies and reviewer were focused on DR risk in T2DM patients, which might to some degree due to the higher incidence of T2DM, and/or large numbers of existing T2DM cohorts. However, T1DM also has a high incidence, which varies from about 0.125% in Europe, 0.35% in Scandinavia, to a low of 0.01% in Asian. Besides T2DM, DR is also one of the classical complications of T1DM. Thus, in this review, we explored and summarized the recent studies of DR related risk genes in T1DM patients. The aim of the study is to provide a comprehensive assessment on the association between genetic polymorphism and DR susceptibility in T1DM patients, as well as the prediction ability of these potential biomarkers.

Methods

We searched the relative literatures about genetic polymorphisms and DR susceptibility in T1DM patients through PubMed (http://www.ncbi.nlm.nih.gov), with key words “diabetic retinopathy+SNP” and “diabetic retinopathy+GWAS”. The time period for literature searching was from the first available article to April 2014. Publications meeting the following criteria were including: (1) Patients were diagnosed with T1DM; (2) Patients were diagnosed with DR; (3) The data of DR rate stratified by polymorphisms could be obtained from the original article. The literatures were manually extracted independently by two authors (Q.X and G.S), who were blind to each other. After exaction, all literatures were reviewed and compared by a third reviewer (X.L.X.) and the discrepancies between extractors were discussed and solved with consensus. And the relative studies enrolled T2DM patients have be excluded. Although there were several studies reported the associations between genetics and diabetic retinopathy, most of the studies were based on T2D patients. Thus, after detailed filtration, there were only four studies based on T1D patients remained. All of these four studies were composed of completely T1DM patients, and all of these for studies were used candidate gene based genetic research approaches. The detailed summarized information about these studies was presented in table 1, which included the first author’s name, publication year, ethnicity, sample size, genetic information, SNP information, etc.

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Candidate Genes

CDKN2A/CDKN2B

Fagerholm et al. [13] reported a multi-cohort based study with the sample size up to about 2500 T1DM patients from the UK. They tested the association between nine SNPs and DR risk. These nine SNPs were selected as they had been reported with T2DM risk in genome-wide association studies, including rs7754840 in CDKAL1 gene, rs7756992 in CDKAL1 gene, rs10811661 near to CDKN2A and CDK2B gene, rs1111875 in HHEX gene, rs1470579 in IFG2BP2 gene, rs4420960 in IFG2BP2 gene, rs1801282 in gene, rs13266634 in SLC30A8 gene and rs7903146 in TCF7L2 gene. Among these nine SNPs, they found the rs10811661 was significantly related with severe retinopathy (1673 case vs. 936 controls), with p-value 0.004, odd ratio (OR) 1.37 and 95% confidential interval 1.10 to 1.69. The associated remained after robust correction for multiple testing in the discovery cohort, and in the meta-analysis, the association was remained significant and suggested its prediction abilities.

rs10811661 is located over 100 kb downstream of the closets genes CDKN2A and CDKN2B. Both of these two coding proteins of these two genes are known to function as inhibitors of cyclin-dependent kinase (CDK). These two genes also have several alternative transcripts. One of the transcripts function as a stabilizer of the tumor suppressor protein p53. Thus, these two genes are frequently mutated or deleted in a wide variety of tumors, and are known to be an important tumor suppressor gene. rs10811661, which have been indicated as a risk genotype for T2DM by several studies as well as meta-analysis, is near to another non-coding DNA called ANRIL (also known as CDKN2B-AS1–CDKN2B antisense RNA 1) [14]. It has been suggested that ANRIL is involved in epigenetic silencing of CDKN2A gene. A study in wide-type and CDKN2A-deficient mice models showed that the downstream genes of CDKN2A were not only related with ageing, but also associated with the degree of glomerular disease [15]. Another in vitro study using T1DM mouse models showed that the relative downstream genes of CDKN2A were decreased in these T1DM mouse models [16].

ADORA2A

Charles et al. [17] reported another study in 496 subjects. These participants were from Pittsburgh Epidemiology of Diabetes Complications prospective study of childhood-onset T1D (age less than 17 years old) in the United States. The stereoscopic photographs of the retinal fundus were taken at baseline and biennially for ten years, these clinical records were further used to define DR according to the modified Airlie House system. In this study, two tagging SNPs from ADORA2A gene were tested including rs2236624 and rs4822489. They found a significant association between rs2236624 and DR in a recessive model. The homozygous carried mutated genotype displayed a decreased risk of DR at baseline (OR 0.36 and P 0.04) as well as after ten years (hazard ratio (HR) 0.156, p=0.009). And similar results were found from rs4822489 (OR 0.55, p=0.04). These results were still significant after adjusted potential covariates. This study suggested that the genetic variants of ADORA2A might offer significant protection against DR development in T1DM patients.

ADORA2A gene belongs to the G-protein-coupled receptor superfamily, which is expressed in the basal ganglia, blood vessels, platelets and other tissues in the body. Adenosine is a powerful physiologic mediator which modulates the cellular damage and the resulting tissue injury caused by biologic stressors. But the effects of adenosine are directed by the adenosine receptors (AR). There are two major AR subtypes, ADORA1A have a pro-inflammatory response to tissue injury, while the ADORA2A restricts the inflammation and guards the tissues from further damage [17]. It also has been suggested that the ADORA2A activation decreased the expression of VEGF which is a primary mitogen associated with the development of DR [18]. Some in vitro studies also indicated that the ADORA2A played an essential role in glucose transport, vasodilation, hypoxia, information and might contribute to DR development [19,20].

SUV39H2

Syreeni et al. [21] reported another large study in European using the Finnish Diabetic Nephropathy study (FinnDiane) cohort as a discovery cohort, which included 1167 retinopathy diabetic case, and 1785 non-retinopathy diabetic controls. In this study, they tested 37 tagging SNPs located in the genes and 10 kb both the 3’ and 5’ ends of SETD7 (SET domain containing (lysine methyltransferase) 7), SUV39H1 (suppressor of variegation 3-9 homolog 1) and SUV39H2 (suppressor of variegation 3-9 homolog 2). In this discovery panel, they found three SNPs in SUV39H2 gene significant related with DR (rs17353856, rs7900814, rs12572872). These three SNPs were further replicated in a validation panel, including two cohorts from the European: the Steno cohort (416 DR case vs. 156 controls) and the GoKind U.K. cohort (556 DR case vs. 382 controls). Combined the discovery cohort with the valuation cohort, they found two of these three SNPs were still significant related with DR, rs17353856 (P=0.012 and OR 0.77) and rs12572872 (P-0.013 and OR 0.84). The association between rs17353856 and diabetic retinopathy was confirmed in the meta-analysis of the three studies populations, which indicted the prediction ability of this SNP and T1D induced DR. They present suggestive evidence that the polymorphism within the SUV39H2 gene is associated with DR in T1DM patients.

SUV39H2, suppressor of variegation 3-9 homolog 2, is an enzyme involved in histone methylation and epigenetic silencing, a process determining the regulation of gene expression during keratinocyte differentiation. A loss of SUV39H2 function is predicted to result in delayed differentiation. SUV39H2 catalyzes the addition of methyl groups to the lysine 9 residue of histone 3 (H3K9) and transforms an unmethylated H3K9 into trimethylated H3K9me3. Methylation of H3K9 is a chromatin modification inducing transcriptional silencing and a typical hallmark of heterochromatin. The crystal structure of SUV39H2 has been solved and the catalytically active site for the methyltransferase activity is located within the so-called SET domain. Diseases associated with SUV39H2 including type 1 diabetes, and hypoxia, and its related super-pathways are Signal transduction Activin A signaling regulation [22].
VEGFA

Hussam et al. [23] reported a candidate gene based study in 2007 to explore the genetic risk factors for time to severe retinopathy in Type 1 diabetes. A total of 1369 Caucasian subjects with type 1 diabetes from the Diabetes Control and Complications Trails/Epidemiology of Diabetes Interventions and Complications Study had an average of 17 retinal photographs and ten renal measures over 15 years. The authors studies 18 SNPs in VEGFA gene that represent all r2 larger than 0.64 and tested them for association with time to development of severe retinopathy, three or more step progression of retinopathy, clinically significant macular edema, persistent micro albuminuria, and severe nephropathy. In a global multi-SNP test, there was a highly significant association of VEGFA SNPs with severe retinopathy (P=6.8*, 105). In survival analyses controlling for covariate risk factors, eight SNPs showed significant association with severe retinopathy. The most significant single SNP association was rs3025021 (P=0.0017). Family-based analyses of severe retinopathy provide evidence of excess transmission of C at rs699947 (P=0.029), T at rs3025021 (P=0.013), and the C-T haplotype from both SNPs (P=0.035). This study demonstrates that multiple VEGFA variants are associated with the development of severe retinopathy in type 1 diabetes.

VEGFA is a member of the platelet-derived growth factor/vascular endothelia growth factor family and encodes a protein that is often found as a disulfide linked homodimer. This protein is a glycosylated mitogen that specifically acts on endothelial cells and has various effects, including mediating increased vascular permeability, inducing angiogenesis, vasculogenesis and endothelial cell growth, promoting cell migration, and inhibiting apoptosis. Alternatively spliced transcript variants, encoding either freely secreted or cell-associated isoforms, have been characterized. VEGFA has been shown to stimulate endothelial cell mitogenesis and cell migration. VEGFA is also vasodilator and increases microvascular permeability and was originally referred to as vascular permeability factor.

Personalized medicine

Personalized medicine is a medical model that proposes the customization of healthcare using molecular analysis with medical decisions, practices, and/or products being tailored to the individual patient. In this model, diagnostic testing is often employed for selecting appropriate and optimal therapies based on the context of a patient’s genetic content. The use of genetic information has played a major role in certain aspects of personalized medicine (e.g. pharmacogenomics), and the term was first coined in the context of genetics, though it has since broadened to encompass all sorts of personalization measures. For the past decades, there has been a revolution in human genetics that is having a very significant impact on virtually all specialties of medicine. The new genomic era provides excellent opportunities to identify gene polymorphisms, genetic changes that are responsible for human disease, and to build an understanding of how such changes cause disease. In the clinical arena, it is now possible to utilize the emerging genetic and genomic knowledge to diagnose and treat patients. It is anticipated that such knowledge will revolutionize medical practice result in an advance in personalized medicine. The knowledge of the genetic basis of human disease is ushering a new era in drug development that is focused on targeted drug development. Until now, many studies have investigated that in complex diseases, certain genotypes in some core genes could significantly affect the treatment efficacy, such as diabetes [24,25], seizures [26], cancer [27-31] and so on. Based on these above-mentioned genetic studies, personalized medicine might be a better choice to prevent and treat type 1 diabetes induced DR in the future.

Conclusion

Based on the results of published clinical trials, we have selected several candidate genes that are more likely to have effect on type 1 diabetes induced DR. Confounding variables such as environmental influence and unknown gene-gene interaction do undoubtedly exist. Although several studies reported the associations between genetics and DR, but few published the detailed information regarding threatening retinopathy, diabetic macular edema and proliferative retinopathy. This is one of the major limitations in the current review. However, twin modeling based genetic research might also be used to inspire further exploration of potential biomarkers [7]. Additionally, unidentified associations corresponding to differences in ethnicity, age, study sample sizes, and study-specific methods of analysis do further complicate the situation. Beyond these genetic factors, epigenetics, especially DNA methylation [32,33], should be considered as another potential biomarker which has been suggested contribute greatly to the variance of individual drug response. Additionally, some studies suggested that traditional Chinese medicine [34] may be a good choice treatment for diabetes and its related complications, and paves an opportunity for anti-diabetes treatment.

In conclusion, the complex occurrence of diabetes/its included DR and our current lack of knowledge all prevent us from fully explaining the precise mechanism. Consequently, future studies encompassing larger sample sizes and novel perspectives are called to overcoming current problems. If allowed to transpire, these studies will facilitate a better understanding of the regulatory pathways in diabetes and its induced DR in human beings.

References


