Genetic Studies on Diabetic Microvascular Complications: Focusing on Genome-Wide Association Studies

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Diabetes is a common metabolic disorder with a worldwide prevalence of 8.3% and is the leading cause of visual loss, end-stage renal disease and amputation. Recently, genome-wide association studies (GWASs) have identified genetic risk factors for diabetic microvascular complications of retinopathy, nephropathy, and neuropathy. We summarized the recent findings of GWASs on diabetic microvascular complications and highlighted the challenges and our opinion on future directives. Five GWASs were conducted on diabetic retinopathy, nine on nephropathy, and one on neuropathic pain. The majority of recent GWASs were underpowered and heterogeneous in terms of study design, inclusion criteria and phenotype definition. Therefore, few reached the genome-wide significance threshold and the findings were inconsistent across the studies. Recent GWASs provided novel information on genetic risk factors and the possible pathophysiology of diabetic microvascular complications. However, further collaborative efforts to standardize phenotype definition and increase sample size are necessary for successful genetic studies on diabetic microvascular complications.

Keywords: Diabetes; Microvascular complication; Retinopathy; Nephropathy; Neuropathy; Genome-wide association study; Genetics

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that can result in multiple long-term micro- and macrovascular complications. Microvascular complications include retinopathy, nephropathy and neuropathy. Diabetes is well known as the leading cause of blindness, end-stage renal disease (ESRD) and limb amputation. In Korea, approximately 18.6% of diabetic patients have retinopathy, 27.3% albuminuria, and 33.5% diabetic neuropathy [1]. In a nationwide survey in 2012, diabetes accounted for 50.6% of new-onset ESRD in Korea [2]. Microvascular complications significantly affect the quality of life and impose a major burden on the healthcare system and economy.

The development of microvascular complications is related to several environmental risk factors, including duration of diabetes, degree of hyperglycemia, blood pressure, and dyslipidemia. In the landmark U.K. Prospective Diabetes Study, which enrolled newly diagnosed type 2 diabetes mellitus (T2DM) patients, participants randomized to intensive glucose control (median hemoglobin A1c [HbA1c] 7.0%) had a 25% reduc-
The advances in genotyping technology and publicly available databases of reference genomes and human genetic variations, including the International HapMap project [15], have contributed to understanding the genetic risk factors of common metabolic disorders using GWASs. In GWASs, hundreds of thousands or more of single-nucleotide variants are genotyped and tested for association with a disease or a continuous trait in several hundred or more subjects [16]. GWASs do not rely on previous knowledge and thus, are free from bias. Recently, GWASs have increased the number of genetic markers to more than one million by imputation methods and the sample size has increased to more than one hundred thousand by using meta-GWASs. The first successful GWAS on T2DM was published in 2007 [17]. Since then, at least 77 confirmed genetic loci for T2DM have been identified, [18] providing a better understanding of diabetes pathophysiology and there are ongoing efforts to use this genetic information in risk prediction and tailoring of individualized therapy [19]. In parallel, attempts have been made to unravel the genetic risk factors for diabetic microvascular complications using GWASs. In this article, we reviewed the recent GWASs on diabetic retinopathy, nephropathy and neuropathy and discussed their limitations and future directives.

**DIABETIC RETINOPATHY**

Diabetic retinopathy is clinically defined by the retinal microvascular lesions in diabetic patients and broadly classified into nonproliferative diabetic retinopathy (NPDR) and PDR. Diabetic macular edema can result in moderate visual loss and can be present at any stage of diabetic retinopathy, although more common in advanced retinopathy. The gold standard for classification of diabetic retinopathy severity is derived from the Early Treatment of Diabetic Retinopathy Study [20]. Diabetic retinopathy increases as the duration of diabetes increases. According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy in T2DM patients, diabetic retinopathy is present in 20% of patients at the time of diagnosis, which increases to 60% to 85% after 15 years [21]. Whether the pathophysiology of retinopathy differs between type 1 diabetes mellitus (T1DM) and T2DM remains unknown. All heterogeneity factors—including the severity, duration, and type of diabetes—should be considered to understand the genetic risk factors for diabetic retinopathy.

Currently, five GWASs on diabetic retinopathy have been published. The first GWAS performed included 283 Mexican-American T2DM retinopathy patients and controls (Table 1)
## Table 1. Genome-Wide Association Study on Diabetic Retinopathy

| Study            | Ethnicity     | Diabetes type | Design                                | Sample size, n | Covariates                      | Platform                    | SNP ID            | Gene            | Risk allele | RAF | OR     | P value    |
|------------------|---------------|---------------|---------------------------------------|----------------|---------------------------------|-----------------------------|---------------------|-----------------|-------------|-----|---------|------------|
| Fu et al. (2010) | Mexican       | T2DM          | Single stage GWAS                     | 103            | Age, sex, diabetes duration, HbA1c | Affymetrix GeneChip 100K   | rs2300782         | CAMK4          | A            | 0.32 | 2.64   | 6.04×10^-7 |
|                  | American      |               |                                       | 183            |                                 |                             | rs10519765         | FMN1            | G            | 0.71 | 3.33   | 6.21×10^-4 |
| Huang et al. (2011) | Taiwanese     | T2DM          | Single stage GWAS                     | 174            | Diabetes duration, HbA1c        | Illumina Human-Hap550      | rs2811893         | MYSM1          | T            | 0.63 | 1.50   | 3.09×10^-7 |
|                  |               |               |                                       |                |                                 |                             | rs1737646          | Intergenic KIAA0825 | A   | 0.05 | 1.16   | 4.25×10^-7 |
|                  |               |               |                                       |                |                                 |                             | rs12219125         | A               | 0.96 | 3.63   | 2.99×10^-10 |
|                  |               |               |                                       |                |                                 |                             | rs4838605          | PLXDC2          | T            | 0.09 | 1.62   | 9.29×10^-9  |
|                  |               |               |                                       |                |                                 |                             | rs4462262          | ARHGAP22        | C            | 0.09 | 1.58   | 1.87×10^-9  |
|                  |               |               |                                       |                |                                 |                             | rs2038823          | Intergenic HS6ST3 | C             | 0.94 | 1.54   | 9.21×10^-8  |
|                  |               |               |                                       |                |                                 |                             |                   |                 | 0.96 | 2.33   | 4.68×10^-11 |
| Grassi et al. (2011) | Caucasian    | T1DM          | Meta-analysis of two GWAS             | 973            | No adjustment                   | GoKinD: Affymetrix GeneChip 5.0 | rs476141          | LOC339529       | A            | 0.51 | 1.37   | 1.20×10^-7 |
|                  |               |               |                                       |                |                                 | EDIC: Illumina Human-Hap550 | rs13064954         | Intergenic LEKR1/CCNL1 | G   | 0.04 | 1.02   | 7.10×10^-7  |
|                  |               |               |                                       |                |                                 |                             | rs9866141          | Intergenic RBFOX1     | T             | 0.04 | 1.02   | 8.80×10^-7  |
|                  |               |               |                                       |                |                                 |                             | rs4787008          | Intergenic HS6ST3 | C             | 0.17 | 1.47   | 6.40×10^-7  |
| Sheu et al. (2013) | Taiwanese, Hispanic | T2DM         | Two stage GWAS and follow-up genotyping | 826            | Age, sex                        | Illumina OmniExpress     | rs4668142         | Intergenic Intergenic | T   | 0.41 | 1.60   | 3.60×10^-4  |
|                  |               |               |                                       |                |                                 |                             | rs2380261          | UCHL3           | T            | 0.43 | 1.50   | 2.00×10^-4  |
|                  |               |               |                                       |                |                                 |                             | rs9543976          | Intergenic UCHL3   | G             | 0.30 | 1.60   | 7.40×10^-4  |
| Awata et al. (2015) | Japanese     | T2DM          | Three stage GWAS and follow-up genotyping | 837            | Sex, diabetes duration, HbA1c  | Affymetrix GeneChip 6.0 | rs9362054         | RP1-90L14.1     | T             | 0.29 | 1.36   | 1.70×10^-4 |
|                  |               |               |                                       | 1,149          |                                 |                             |                   |                 |           |       |        |            |

SNP, single nucleotide polymorphism; RAF, risk allele frequency in controls; OR, odds ratio; T2DM, type 2 diabetes mellitus; GWAS, genome-wide association study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DR, diabetic retinopathy; HbA1c, hemoglobin A1c; T1DM, type 1 diabetes mellitus; DME, diabetic macular edema; GoKinD, Genetics of Kidneys in Diabetes; EDIC, Epidemiology of Diabetes Interventions and Complications. 

OR are from dominant model and P values are from the lowest among six genetics models.
DIABETIC NEPHROPATHY

Diabetic nephropathy is clinically defined as an increase in urinary albumin excretion and a decrease in kidney function. Classification of diabetic nephropathy using the Kidney Disease: Improving Global Outcomes group criteria is based on estimated glomerular filtration rate (eGFR) and the degree of proteinuria. The eGFR is generally calculated using the Modification of Diet in Renal Disease formula and is divided into five stages. The degree of proteinuria is used for substaging diabetic nephropathy. The eGFR reflects the current kidney function and proteinuria reflects the extent of pathological kidney damage. Proteinuria is a hallmark of diabetic nephropathy and precedes the decline in kidney function, but is not a prerequisite in some cases. A large body of evidence indicates that treatments to prevent or delay its progression should include intensive glycemic and blood pressure control. In the Action in Diabetes and Vascular Disease (ADVANCE) trial, intensive glucose control resulted in the risk reduction for microalbuminuria (30 to 300 mg/g), macroalbuminuria (>300 mg/g) and ESRD, by 9%, 30%, and 65%, respectively [27]. In the pivotal study of Diabetes Control and Complications Trial (DCCT), intensive glucose control in T1DM patients resulted in 39% reduced occurrence of microalbuminuria [28]. However, 25% of participants in the intensive treatment group eventually developed microalbuminuria during the 6.5-year follow-up period. Therefore, individual variations in the risk of diabetic nephropathy exist and genetic factors likely play an important role.

Consequently, efforts have been made to understand the genetic risk factors for diabetic nephropathy. Nine GWASs on diabetic nephropathy have been published (Table 2) [29-37]. The first large-scale genotyping of more than 80,000 gene-based single nucleotide polymorphisms was performed in 2005 by Shimazaki et al. [29] in 920 Japanese T2DM patients. They identified an intronic variant, rs741301, of the engulfment and cell motility 1 (ELMO1) gene to be significantly as-

[22-26]. Fu et al. [22] found two potential loci in the introns of calcium/calmodulin-dependent protein kinase IV (CAMK4) and formin 1 (FMN1) genes. Huang et al. [23] reported a GWAS on T2DM diabetic retinopathy including 749 Taiwanese patients and found seven independent loci with potential significance ($P < 1.0 \times 10^{-6}$). However, they reported the lowest $P$ value among the six genetic models (genotype, allele, trend, additive, dominant, and recessive) and did not adjust for multiple comparisons. The third study is the largest GWAS conducted to date and is a meta-analysis of two GWASs, Genetics of Kidneys in Diabetes (GoKinD) and Epidemiology of Diabetes Interventions and Complications (EDIC) studies [24]. This study by Grassi et al. [24] involved 2,829 European subjects with T1DM. The most significant variant was rs476141 located in a long non-coding RNA (LOC339529) in chromosome 1 with $P$ values of $1.20 \times 10^{-5}$. The study by Sheu et al. [25] used a two-stage GWAS with follow-up genotyping in an independent population. Although they found three potential genetic variants in stage 1 GWASs in Taiwanese subjects, these findings were not replicated in the Hispanic population. The latest GWAS on diabetic retinopathy was a three-stage design performed by Awata et al. [26] in Japanese subjects. Among the eight variants that were followed-up to the third stage, none reached a genome-wide significance threshold. The most significant variant was located in RP1-90L14.1, a long non-coding RNA gene, with a $P$ value of $1.70 \times 10^{-5}$ in the meta-analysis of the three-stage results.

Overall, three studies were performed with Asian subjects, one with Mexican-American and one with European subjects. One study included T1DM patients and the remaining four studies included T2DM patients. The earliest two studies performed by Fu et al. [22] and Huang et al. [23] were single-stage GWASs with a small sample of fewer than 1,000 subjects. The findings were not replicated in an independent cohort using a different genotyping method. The majority of the genetic variants reported from the five studies did not pass the conventional significance threshold of $P < 5.0 \times 10^{-8}$, except for several variants in the study by Huang et al. [23]. However, the latter study reported the best $P$ value among various genetic models and did not correct for multiple comparisons. None of the genetic variants reported overlapped among the five studies; however, cases and controls were defined differently, which could be a crucial point when performing a genetic study. Regarding case groups, several studies included subjects with either NPDR or PDR, whereas others included only subjects with PDR. Regarding the control group, only in the study by Sheu et al. [25] the subjects were limited to those with a diabetes duration of more than 8 years without any diabetic retinopathy. The heterogeneity in study design and relatively small sample sizes could explain the inconsistencies in the genetic variants identified in the five GWASs on diabetic microvascular complications. A clear and rational definition of cases and controls is necessary to enhance genetic contrast as well as a large sample size to ensure sufficient statistical power.
| Study               | Ethnicity | Trait | Diabetes type | Design                                      | Diagnostic criteria                                                                 | Sample size, n | Covariates | Platform | SNP ID          | Gene                  | Risk allele | RAF   | OR       | P value          |
|---------------------|-----------|-------|---------------|---------------------------------------------|--------------------------------------------------------------------------------------|----------------|------------|----------|----------------|-----------------------|-------------|-------|---------|------------------|
| Shimazaki et al.    | Japanese  | DN    | T2DM          | High-throughput genotyping with follow-up genotyping | Cases: diabetic retinopathy, ACR ≥ 300 µg/mg, or ESRD                                | 560           | None       | Illumina  | rs741301 | ELMO1                  | G          | 0.30  | 2.67    | 8.00×10⁻⁶      |
| Hamon et al.        | Indian    | ESRD  | T2DM          | Pooled DNA GWAS and validation genotyping   | Cases: ESRD                                                                          | 105           | -          | Affymetrix | rs2648875 | PYT1                   | A          | 0.53  | 2.97    | 1.80×10⁻⁴      |
| Pezzolesi et al.    | European  | DN    | T1DM          | Two stage GWAS and follow-up genotyping    | Cases: ACR ≥ 300 µg/mg or ESRD, diabetes duration ≥ 15 years, ACR < 20 µg/mg        | 820           | Sex        | Illumina  | rs39075  | CHN2                  | G          | 0.61  | 1.43    | 6.50×10⁻⁷      |
| Craig et al.        | European  | ESRD  | T1DM          | Pooled DNA GWAS and validation genotyping  | Cases: ESRD                                                                          | 462           | None       | Affymetrix | rs1749824 | ZME1                  | T          | 0.40  | 1.47    | 8.10×10⁻⁴      |
| McDonough et al.    | African   | DN    | T2DM          | Two stage GWAS and follow-up genotyping    | Cases: ESRD                                                                          | 1,674         | Admixture  | Affymetrix | rs769051 | P53       | C          | 0.29  | 1.28    | 2.20×10⁻⁴      |
| Sandholm et al.     | European  | DN    | T1DM          | Two stage GWAS meta-analysis and follow-up genotyping | Cases: macroalbuminuria or ESRD, diabetes duration ≥ 15 years, no evidence of kidney disease | 4,409         | Age, sex   | Illumina  | rs2437854 | RGM4/MCTP2             | C          | 0.04  | 1.8     | 2.00×10⁻⁴      |
| Sandholm et al.     | Finnish   | ESRD  | T1DM          | Sex-specific analysis of GWAS              | Cases: ESRD                                                                          | 688           | Age, diabetes duration | Illumina  | rs4972593 | SPD/CDCA7               | A          | 0.14  | 1.81    | 3.85×10⁻⁴      |
| Sandholm et al.     | Finnish   | Albumin excretion site | T1DM          | Two stage GWAS and follow-up genotyping   | Excluding ESRD                                                                       | 5,675         | Sex, age at diabetes onset, diabetes duration | Illumina  | rs2410601 | PCS3/H2D4A             | G          | 0.42  | 1.08    | 3.85×10⁻⁴      |
| Germain et al.      | European  | DN    | T1DM          | Two stage GWAS                            | Cases: ACR ≥ 300 µg/mg or ESRD, diabetes duration ≥ 15 years, normoalbuminuria        | 1,503         | Age, sex   | Illumina  | rs326934 | SORBS1                | T          | 0.67  | 1.2     | 0.009           |

SNP, single nucleotide polymorphism; RAF, risk allele frequency in controls; OR, odds ratio; DN, diabetic nephropathy; T2DM, type 2 diabetes mellitus; ACR, albumin to creatinine ratio; ESRD, end-stage renal disease; GWAS, genome-wide association study; T1DM, type 1 diabetes mellitus.
associated with diabetic nephropathy. *In vitro* experiments suggested its role in the overaccumulation of extracellular matrix proteins and progression of glomerulosclerosis. Subsequently, a GWAS by Hanson et al. [30] used pooled DNA and validated the top signals using individual genotyping in 207 Pima Indian T2DM ESRD cases and controls. A variant in plasmacytoma variant translocation (*PVT1*) gene was suggestively associated with ESRD.

The first standard GWAS on diabetic nephropathy was published in 2009 by Pezzolesi et al. [31] and included the GoKinD study participants. They used two-stage GWAS with follow-up genotyping in 1,705 T1DM cases and controls. The four loci having a potential association signal of $P<1.0 \times 10^{-5}$ included FERM domain containing 3 (*FRMD3*), cysteinyltRNA synthetase (*CARS*), chimerin 2 (*CHN2*), and carboxypeptidase (*CPVL*). The rs1888747 variant in *FRMD3* and rs451041 variant in *CARS* showed associations with time to onset of diabetic nephropathy in an independent cohort of DCCT/EDIC study with $P<0.05$. Craig et al. [32] reported a GWAS using pooled DNA of 932 T1DM GoKinD participants. They reported suggestive loci for ESRD on zinc finger, MIZ-type containing 1 (*ZMIZ1*) and musculin (*MSC*) genes as well as the association signals in six previously reported genetic loci of diabetic nephropathy ($P\leq0.0006$). A relatively large-scale GWAS involving 3,393 African-American T2DM subjects was performed by McDonough et al. [33] in 2011. However, it was uncommon for African-Americans to have normal albuminuria after a diabetes duration of 10 years and the authors used nondiabetic controls for the control group. Therefore, analysis was performed to discriminate association signals between T2DM-associated ESRD, T2DM and all-cause ESRD using additional genotyping in African-Americans. Although none of the genetic variants reached genomewide significance, several genes—including SAM and SH3 domain containing 1 (*SASH1*), ribosomal protein S12 gene (*RPS12*), and LIM kinase 2 (*LIMK2*)—were suggested as strong candidates for diabetic nephropathy in T2DM patients.

As previous studies were not fully powered for GWAS and the phenotype definition was different, a collaborative effort was made to conduct the Genetics of Nephropathy: An International Effort (GENIE) study on T1DM diabetic nephropathy [34]. This study was performed in two stages by Sandholm et al. [34]. In the first stage, a GWAS was meta-analyzed in three cohorts with a sample size of 5,783 subjects. In the second stage, *de novo* genotyping was performed in 5,873 participants from nine cohorts. The study was adequately powered and two variants were found associated with ESRD in AF4/FMR2 family, member 3 (*AFF3*) and in the intergenic region between repulsive guidance molecule family member A (*RGMA*) and multiple C2 domains, transmembrane 2 (*MCTP2*) that reached a genome wide significance threshold of $P<5.0 \times 10^{-8}$. In a GWAS on Finnish Diabetic Nephropathy study and GENIE consortium, Sandholm et al. [35] identified a gender-specific variant, rs4972593, which was associated with the risk of T1DM ESRD only in females. A GWAS was also conducted on urinary albumin excretion rate in 5,675 T1DM patients. This study identified rs2410601 in the intergenic region between pleckstrin and Sec7 domain containing 3 (*PSD3*) and SH2 domain containing 4A (*SH2D4A*) as the most significantly associated with albumin excretion rate ($P=3.85 \times 10^{-8}$) [36].

Among the nine GWASs, six included participants of European origin and one study each of Japanese subjects, Pima Indians and African-Americans. Only three studies were performed on T2DM, and the remaining six on T1DM subjects. Most of the studies included both ESRD and macroalbuminuria groups as cases. Only a few studies, including those from the GENIE consortium, had sufficient statistical power for GWAS and most of the earlier studies were limited in terms of sample size. Genetic variants in earlier reports, such as in *ELMO1*, were analyzed in subsequent studies and an association with diabetic nephropathy was confirmed in several, but not all, studies. Whether the pathophysiology of diabetic nephropathy differs between T1DM and T2DM patients remains unknown. Nonglycemic factors, such as insulin resistance and dyslipidemia, in T2DM may modulate the development of diabetic nephropathy and certain genetic risk factors could be involved in this process. Most of the well-powered GWASs were performed on T1DM patients and the genetic variants of diabetic nephropathy in T2DM patients should be elucidated.

**DIABETIC NEUROPATHY**

Diabetic peripheral neuropathy is classified as generalized symmetric polyneuropathies and focal and multifocal neuropathies [38]. Diabetic sensorimotor polyneuropathy is one of the most common complications in diabetic patients with an estimated lifetime prevalence of up to 50% [38]. In 2009, the Toronto Consensus Panel on Diabetic Neuropathies updated its definition and diagnostic criteria for diabetic polyneuropathy [39]. Diagnosis of distal symmetric polyneuropathy is categorized into possible, probable, confirmed, and subclinical, according to the certainty based on symptoms and signs. The
confirmation of neuropathy requires typical symptoms, signs, and positive nerve conduction studies.

Currently, only one GWAS on neuropathic pain in diabetic patients has been published (Table 3) [40]. Using the Genetics of Diabetes Audit and Research Tayside (GoDARTS) study, Meng et al. [40] performed a GWAS on 3,063 T2DM patients. The case control status was defined based on the prescription of medications frequently used for diabetic sensorimotor polyneuropathy, including duloxetine, gabapentin, pregabalin, capsaicin, and lidocaine patch. In a single-stage GWAS without follow-up genotyping, rs17428041 located in the intergenic region between the GDNF family receptor alpha 2 (GFRA2) and docking protein 2 (DOK2) was potentially associated with neuropathic pain ($P = 1.77 \times 10^{-7}$). In addition, the narrow sense heritability of diabetic neuropathic pain was 11%, excluding the effect of gene-gene and gene-environment interactions. Further studies are required to replicate this finding and to identify additional genetic variants of diabetic neuropathy.

**CONCLUSIONS**

During the past several years, the identification of genetic risk factors for diabetic microvascular complications has improved. However, most of the studies were not fully powered for GWASs, with the exception of the GENIE study. Therefore, most of the results associated with the genetic risk factors were below the genome-wide significance threshold and inconsistent among studies. In addition, the definition of cases and controls differed, thereby introducing significant heterogeneity. Based on the findings reported, these genetic association results should be validated in other populations. In addition, a collaborative effort to harmonize phenotype definitions and to increase sample size is necessary.

Whether certain microvascular complications are caused by specific genetic risk factors, or common genetic risk factors are shared by different microvascular complications should be clarified. Additionally, a possible difference in genetic risk factors for microvascular complications between T1DM and T2DM patients should be explored. Whether confirmed genetic variants for T1DM or T2DM *per se* have significant effects on the development of microvascular complications remains unclear. Finally, a metabolic memory or legacy effect, as shown by the DCCT/EDIC trial, should be considered; this might be mediated by epigenetic change. Compared to T2DM, genetic studies on diabetic microvascular complications are still in the early stages and have further challenges to overcome. Further genetic studies of microvascular complications will enhance understanding of their pathogenesis and facilitate the development of effective preventive and therapeutic measures.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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