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REVIEW

Recent progress in the genetics of diabetic microvascular complications

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Abstract

Diabetic complications including diabetic nephropathy, retinopathy, and neuropathy are as major causes of morbidity and mortality in diabetes individuals worldwide and current therapies are still unsatisfactory. One of the reasons for failure to develop effective treatment is the lack of fundamental understanding for underlying mechanisms. Genetic studies are powerful tools to dissect disease mechanism. The heritability (h^2) was estimated to be 0.3-0.44 for diabetic nephropathy and 0.25-0.50 for diabetic retinopathy respectively. Previous linkage studies for diabetic nephropathy have identified overlapped linkage regions in 1q43-44, 3q21-23, 3q26, 10p12-15, 18q22-23, 19q13, 22q11-12.3 in multiple ethnic groups. Genome-wide association studies (GWAS) of diabetic nephropathy have been conducted in several populations. However, most of the identified risk loci could not be replicated by independent studies with a few exceptions including those in *ELMO1*, *FRMD3*, *CARS*, *MYO16/IRS2*, and *APOL3-MYH9* genes. Functional studies of these genes revealed the involvement of cytoskeleton reorganization (especially non-muscle type myosin), phagocytosis of apoptotic cells, fibroblast migration, insulin signaling, and epithelial clonal expansion in the pathogenesis of diabetic nephropathy. Linkage analyses of diabetic retinopathy overlapped only in 1q36 region and current results from GWAS for diabetic retinopathy are inconsistent. Conclusive results from genetic studies for diabetic neuropathy are lacking. For now, small sample sizes, confounding by population stratification, different phenotype definitions between studies, ethnic-specific associations, the influence of environmental factors, and the possible contribution of rare variants may explain the inconsistencies between studies.

Key words: Microvascular complications; Nephropathy; Retionopathy; Neuropathy; Diabetes

Core tip: Most risk genetic loci identified by genome-wide association studies (GWAS) for diabetic nephropathy could not be replicated by independent studies with a few exceptions including those in *ELMO1, FRMD3, CARS, MYO16/IRS2*, and *APOL3-MYH9* genes. These findings highlighted the importance of cytoskeleton reorganization, phagocytosis of apoptotic cells, fibroblast migration, insulin signaling, and epithelial clonal expansion in the pathogenesis of diabetic nephropathy. Conclusive results from GWAS for diabetic retinopathy and diabetic neuropathy are currently lacking.

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INTRODUCTION

The prevalence of diabetes mellitus is increasing globally, especially in developing countries[1]. This surge of diabetes mellitus prevalence poses a serious threat to the public and diabetic complications are ranked as major causes of morbidity and mortality worldwide. Several common mechanisms underlying these microvascular complications including the polyol pathway, advanced glycation end products pathway, protein kinase C pathway, the hexosamine pathway, and cytokines such as nuclear factor-κB, tumor growth factor-β, and vascular endothelial growth factor are well described and the unifying mechanism of superoxide production have been proposed[2]. Nevertheless, therapies targeting these pathways have not been very successful[3-5]. One of the reasons is the lack of fundamental understanding for underlying mechanisms.

Genetic studies provide a powerful tool to the understanding of disease mechanism. Previous family linkage analyses have successfully identified mutations responsible for high-penetrating monogenetic disease. Some discoveries, for example, the identification of *PCSK9* mutation through linkage analyses in hypercholesterolemic families, have resulted in major breakthroughs in therapy[6,7]. However, family linkage analysis is generally not adequately powered to detect genetic loci of complex disease. Over the last few years, the advent of genome-wide association studies (GWAS) have launched a great leap toward the genetic basis of complex diseases such type 2 diabetes mellitus, cancers, and psychiatric diseases. Intriguingly, many of the identified genetic loci were not previously considered to be related to these diseases and the discoveries indeed illuminated important pathophysiological pathways to these complex diseases. Diabetic microvascular complications are complex traits influenced by both environmental and genetic factors, and compelling evidences indicate that diabetic microvascular complications are heritable[8-12]. Here in this review, we only summarized the progress in the genetics for diabetic microvascular complications.

GENETICS STUDIES OF DIABETIC NEPHROPATHY

Linkage studies of diabetic nephropathy

The heritability (h^2) of diabetic nephropathy (DN) defined by reduced glomerular filtration rate (GFR) or albuminuria was estimated to be 0.3-0.44 in multiple Caucasian diabetic populations[8-10]. Previous linkage studies have repeatedly identified linkage region in 1q43-44, 3q21-23, 3q26, 10p12-15, 18q22-23, 19q13, 22q11-12.3 in multiple ethnic groups (Figure 1, Table 1)[13-24]. However, these linkage regions usually spanned over megabases and therefore exact locus or risk gene is unclear. In contrast, the resolution of linkage disequilibrium mapping (also called association mapping) is much higher than linkage studies. The distinction between linkage and association mapping is that family linkage mapping use the small amount of recombination events that occurs in each generation within a pedigree to localize a chromosomal region, which usually contains hundreds of genes; while population-based case-control association mapping uses large amount of recombinations that occurred during the evolutional history of a population to locate the risk loci, which generally did not extend over a few genes. However, population-based case-control association studies are susceptible to the population stratification and independent replication is essential to confirm the result of association studies.

Association studies of DN in type 2 diabetic patients

Several GWAS of DN have been conducted in several ethnic populations (Table 1, Figure 1). *ELMO1* (the engulfment and cell motility 1 gene) was first found to be associated with diabetic nephropathy in a GWAS in Japanese 2 diabetic patients (546 DN cases and 334 type 2 diabetic controls)[25]. Replication studies in the GoKinD collection (558 DN cases and 820 type 2 diabetes controls)[26], two African American cohorts [1136 end-stage renal diseae (ESRD) diabetes cases and type 2 diabetic 1160 controls][27], a Chinese population (123 DN cases and 77 type 2 diabetic controls)[28], and a Caucasian GWAS (547 ESRD and 549 type 1 diabetic controls)[29] confirmed this finding although the risk SNPs are not exactly the same with those reported in the original Japanese population (intron 16-20 in original Japanese GWAS, intron 16-20 in GoKinD, intron 13 in African Americans, intron 18 in Chinese). In a large meta-analysis of the GENIE

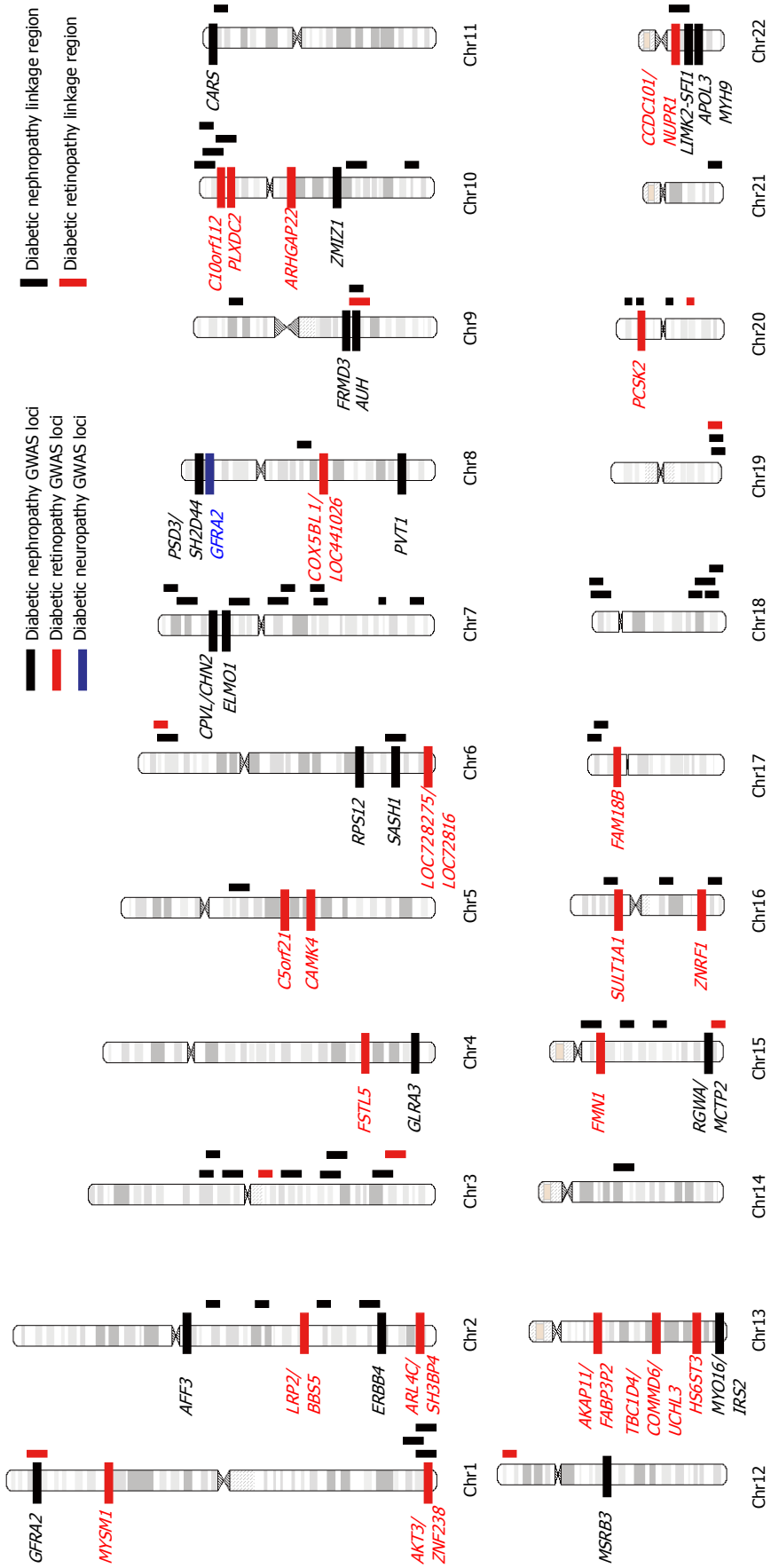


Figure 1 Genetic risk loci for diabetic nephropathy, retinopathy, and neuropathy indentified through genome-wide linkage (vertical bar) and association scans (horizontal bar). GWAS: Genome-wide association study; Chr: Chromosome.

consortium (including UK-ROI, FinnDiane, and GoKinD US) involving 2966 DN cases and 3399 type 1 diabetic controls, an expanded investigation of the *ELMO1* locus yielded only nominal associations with DN[30]. Furthermore, another replication studies in Pima Indians of Arizona involving 248 DN cases and 524 diabetic controls found significant association of SNPs in intron 13 but the associations were in the opposite direction from those observed in African Americans[31], and another study in 455 Mexican-American patients with DN and 437 controls failed to replicate the association[32].

A GWAS in Pima Indians comparing 105 diabetic ESRD and 103 controls identified plasmacytoma variant translocation (*PVT1*), an lncRNA gene, was associated with DN in type 2 diabetic patients[33]. Another large GWAS in an initial set of 965 African American type 2 diabetic patients with ESRD and 1029 controls without type 2 diabetes or kidney disease and further replication studies in 1246 type 2 diabetic patients indentified *SASH1* (SH3 Domain Containing 1), *RPS12* (ribosomal protein S12), *AUH* (AU RNA binding protein/enoyl-CoA hydratase), *MSRB3* (methionine sulfoxide reductase B3), *LIMK2* (LIM domain kinase 2)-*SFI1* (Sfi1 homolog, spindle assembly associated),

Table 1 Genome-wide linkage studies for diabetic nephropathy and retinopathy

Ethnicity and sample size	Type of diabetes	Phenotype definition	Linkage region (LOD score or *P*-value or MLS)	Ref.
Diabetic nephropathy				
954 African American, 781 American Indians, 614 European American, 1611 Mexican Americans (FIND)	1 + 2	Estimated GFR	10p12.31[1] (LOD: 2.16), 1q43[1] (2.26), 2q31.3 (1.91), 3p12.1 (2.19), 7q11.22 (2.19), 10p14[1] (2.16), 15q12 (2.84), 20q11.11[1] (3.34)	[13]
218 African American, 335 American Indians, 119 European American, 469 Mexican Americans (FIND)	1 + 2	Urine ACR	7q21.3 ($P = 8.6 \times 10^{-5}$), 10p15.3[1] (1.29×10^{-5}), 14q23.1 (7.8×10^{-4}), 18q22.3[1] (2.17×10^{-3})	[14]
3972 Americans (African American, American Indians, European American, Mexican Americans) (FIND)	1 + 2	DN defined by macroalbuminuria or ESRD, ACR	DN: 1q43[1] (LOD: 2.00), 6p24.3 (2.84), 7p21.3 (2.81), 10p15.1[1] (2.10), 11p15.3 (2.28), 15q21.1 (2.04) ACR: 2q22.3 (2.04), 3p13 (2.76), 7q21.2 (2.96), 16q13 (2.31), 22q12.3[1] (2.29)	[23]
882 American (African American, American Indians, European American, Mexican Americans) (FIND)	1 + 2	eGFR	1q43[1] (LOD: 1.87), 7q36.1 (4.23), 8q13.3 (2.75), 15q22.3 (2.08), 18q23.3 (1.40)	[24]
100 United States sibling pairs (Joslin Study on Genetics of Diabetic Nephropathy)	1	Proteinuria or ESRD	1q44[1] (MLS: 1.6), 2q14.1 (2.1), 3p13 (0.6), 5q14.2 (2.7), 10q26.1 (2.4), 17p13.1 (1.9), 19q13.43[1] (3.1), 20p12.1 (1.8)	[15]
63 extended United States families (Joslin Study on Genetics of Diabetic Nephropathy)	2	GFR	2q33.3 (LOD: 4.1), 10q23.31 (3.1), 18p11.22 (2.2)	[19]
556 Finnish, Danish, and French (FinnDiane)	1	Macroalbuminuria or ESRD	3q21-25[1] (LOD: 0.76), 6p21 (2.31), 9p21.2, 16p12, 19q13[1] (1.61), 22q11 (2.78)	[16]
83 Finnish sibling pairs	1	Macroalbuminuria or ESRD	3q21.3-23[1] (MLS: 2.67)	[21]
18 Turkish family + 101 sibling pairs of Pima India	2	Macroalbuminuria	18q22.3-23[1] (max LOD:6.14)	[17]
201 Pima India sibling pairs	2	Macroalbuminuria or ESRD	3q26.1[1] (LOD: 1.48), 7q32.3 (2.04), 20p12.3 (1.83)	[18]
206 African American sibling pairs	2	ESRD	3q13.3[1] (LOD: 4.55), 7p21.1 (3.59), 18q22.1[1] (3.72)	[22]
691 West African	2	GFR	7p12.2 (LOD: 1.84), 16q24.1 (3.56), 17p13.2 (2.08)	[20]
Diabetic retinopathy				
282 Mexican American sibling pairs	2	Non-proliferative DR and proliferative DR	3q12.3 (LOD: 2.41), 12p13.31 (2.47), 20q13.12 (4.47), 6p24.1 (2.28), 15q26.3 (2.53), 19q13.42 (2.21)	[45]
725 Pima Indian sibling pairs	2	Worse eye score	1p36.13 (LOD: 3.1)	[46]
210 Pima Indian sibling pairs	2	Hemorrhage, microaneurysm, and proliferative DR	3q26.31 (LOD: 1.36), 9q22.33 (1.46)	[18]

[1]Overlapped region. MLS: Maximum LOD score; DN: Diabetic nephropathy; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; ACR: Albumin-to-creatinine ratio; DR: Diabetic retinopathy.

APOL3 (apolipoprotein L, 3), and *MYH9* (myosin, heavy chain 9, non-muscle) genes as risk loci[34]. Among them, the association of *MYH9* risk variants has been replicated in another study involving 1963 European Americans diabetic patients[35]. Compelling evidence demonstrated that *APOL3-MYH9* gene clusters are also associated with non-diabetic nephropathy including focal segmental glomerulosclerosis and hypertensive nephropathy in African American as well as other ethnic populations[36-38].

Association studies of DN in type 1 diabetic patients

A large GWAS in a initial set of 820 DN cases and 885 type 1 diabetic controls in the GoKinD study and a replication set of 1304 participants in the Diabetes Control and Complication Trial/Epidemiology of Diabetes Control and Complication (EDIC) identified *FRMD3* (FERM domain containing 3), cysteinyl-tRNA synthase (*CARS*), carboxypeptidase, vitellogenic-like (*CPVL*)/chimerin 2, and intergenic region at 13q33.3 between *MYO16* and insulin receptor substrate 2 (*IRS2*) associated with DN[39]. Interestingly, another genome-wide linkage analysis and regional association fine mapping in 1007 general Mongolian also identified SNPs in the *FRMD3*, glycine amidinotransferase, and spermatogenesis associated 5-like 1 genes associated with estimated glomerular filtration rate[40]. A family-based candidate-gene association study involving 798 type 2 diabetic members in the Joslin Study of Genetics of Nephropathy replicated the association of SNPs in the *FRMD3*, *CARS*, and 13q33.3 between *MYO16* and *IRS2* genes[41]. Another GWAS in 547 Caucasian ESRD cases and 549 type 1 diabetic controls identified *ZMIZ1* (zinc finger, MIZ-type containing 1) gene is associated with DN[29]. This study also observed significant association of 13q33 variant near the *MYO16/IRS2* genes[29]. However, in a large replication study of 1535 Japanese type 1 and 2 diabetic patients, only variants in 13q33.3 between *MYO16/IRS2* gene but not those in *FRMD3*, *CPVL/CHN2*, or *CARS* are significantly associated with DN[42]. Furthermore, a large meta-analysis of the GENIE consortium (UK-ROI, FinnDiane, and GoKinD US) involving 2966 type 1 diabetic cases with DN and 3399 type 1 diabetes controls failed to replicate the association between SNPs in the *FRMD3*, *CARS*, and 13q33 loci near *MYO16*

Table 2 Genome-wide association studies for diabetic nephropathy, retinopathy, and neuropathy

Patients	Ethnic	Case	Control	Gene	Ref.	Replication studies	Non-replication studies
Diabetic nephropathy							
T2DM	Japanese	459 DN	242	*ELMO1*[1]	[25]	26, 27, 28, 29, 30	31, 32
T2DM	European	105 ESRD	102	*PVT1*	[33]		
T2DM	African American	965 ESRD	1029	*SASH1, RPS12,AUH, MSRB3, LIMK2-SKI1, APOL3-MYH9*[1]	[34]	35	
T1DM	Caucasian (GoKinD, DCCT/EDIC)	820 ESRD	885	*FRMD3*[1], *CARS, CPVL/CHN2*, 13q3 between *MYO16/IRS2*[1]	[39]	40, 41, 42	42, 30
T1DM	Caucasian	547 ESRD	549	*ZMIZ1*	[29]		
T1DM	GENIE (UK-ROI, FinnDiane, GoKinUS) + 9 follow-up studies	Stage 1: 4315 ESRD Stage 2: 1880 ESRD	Stage 1: 8568 Stage 2: 6656	*AFF3, RGMA/MCTP2, ERBB4*	[43]		
T1DM	Caucasian (FinnDiane + 7 follow-up studies)	5675 T1DM Urine albumin excretion rate		*PSD3, SH2D4A*	[44]		
Diabetic retinopathy							
T1DM	Caucasian (GoKinD and EDIC)	2829 PDR and macular edema	1856	*AKT3/ZNF238, LEKR1/CCNL1, KRT18P34/VEPH1, A2BP1*	[47]		
T2DM	Taiwanese	174 NPDR and PDR	575	*MYSM1, FSTL5, C5orfF21, PLXD2, ARHGAP22, HS6ST3*	[48]		
T2DM	Taiwanese	437 PDR	570	*TBC1D4-COMMD6-UCHL3, LRP2-BBS5*, and *ARL4C-SH3BP4*	[49]		
T2DM	Mexican-American	103 severe DR	183	*CAMK4, FMN1* genes	[50]		
Diabetic neuropathy							
United Kingdom	United Kingdom (GoDART)	572 diabetic neuropathic pain	2491	*GFRA2*	[51]		

[1]Loci that could be replicated in independent studies. T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; DN: Diabetic nephropathy; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy.

and *IRS2* genes[30].

A recent huge meta-analysis involving 4315 type 1 diabetic nephropathy and ESRD cases and 8568 type 1 diabetic controls of the GENIE consortium and subsequent replication analyses in 9 independent cohorts (1880 cases and 6656 controls) revealed risk SNPs in the *AFF3* (AF4/FMR2 family, member 3) and *ERBB4* (v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4) genes and an intergenic SNP between *RGMA* (repulsive guidance molecule family member a)/*MCTP2* (multiple C2 domains, transmembrane 2) genes[43]. Another large GWAS for 24-h urine albumin excretion rare in type 1 diabetic patients including an initial set of 1925 patients (FinnDiane) and 3750 additional patients from 7 follow-up studies (Steno Diabetes Center, Italian individuals from the Milano region, Umea Diabetes Study from Sweden, Scania Diabetes Registry, NFS-ORPQ, UK-ROI) identified the strongest signal from the *PSD3* (pleckstrin and Sec7 domain containing 3)/*SH2D4A* (SH2 domain containing 4A) genes[44].

Collectively, current data from GWAS are not very consistent and only genetic loci in the *ELMO1*, *FRMD3*, *APOL3-MYH9*, *CARS*, and 13q33 between *MYO16* and *IRS2* genes have been successfully replicated in independent studies.

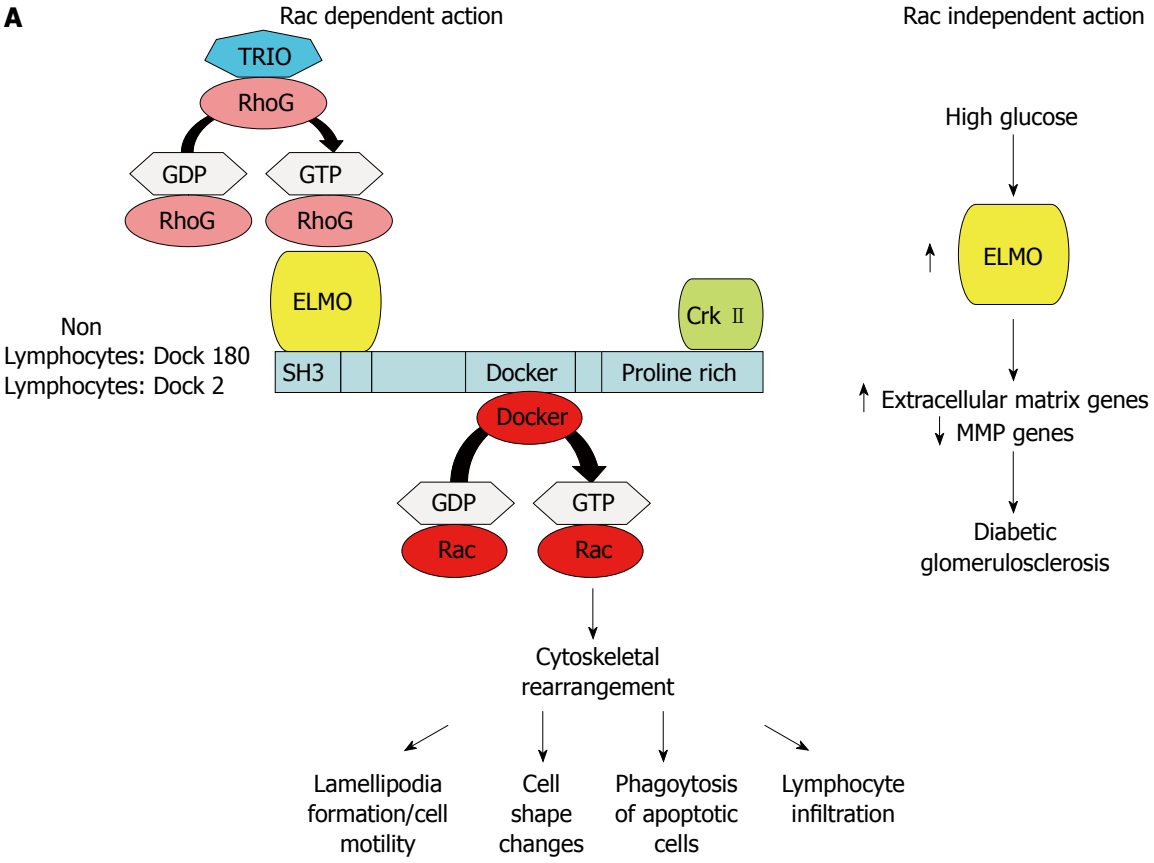
GENETIC STUDIES OF DIABETIC RETINOPATHY

Linkage studies of diabetic retinopathy

The heritability of diabetic proliferative retinopathy is estimated to be 0.25-0.50 in Caucasian populations[11,12]. Previous results of three family linkage analyses for diabetic retinopathy (DR) are summarized in Table 1 and Figure 1[18,45,46]. However, the only overlapped region is 1q36 between Pima Indians (LOD: 3.1) and Mexican Americans (LOD: 1.24) studies[45,46].

Association studies of DR

Four GWAS of DR have been published till now (Table 2, Figure 1). A large meta-analysis of GWAS in the GoKinD and EDIC cohorts involving 2829 cases of severe diabetic retinopathy defined by proliferative retinopathy and macular edema and 1856 type 1 diabetic controls identified several possible loci including intergenic SNPs between *AKT3/ZNF238, LEKR1/CCNL1, KRT18P34/VEPH1* and SNP in the *A2BP1* genes with *P*-value less than 10^{-6}[47]. After excluding cases with concomitant nephropathy to identify DR-specific genes, SNPs in the intergenic region between *LOC728275/LOC728316,* the *CCDC101/NUPR1/SULT1A2/SULT1A1* gene clusters, the *FAM18B*,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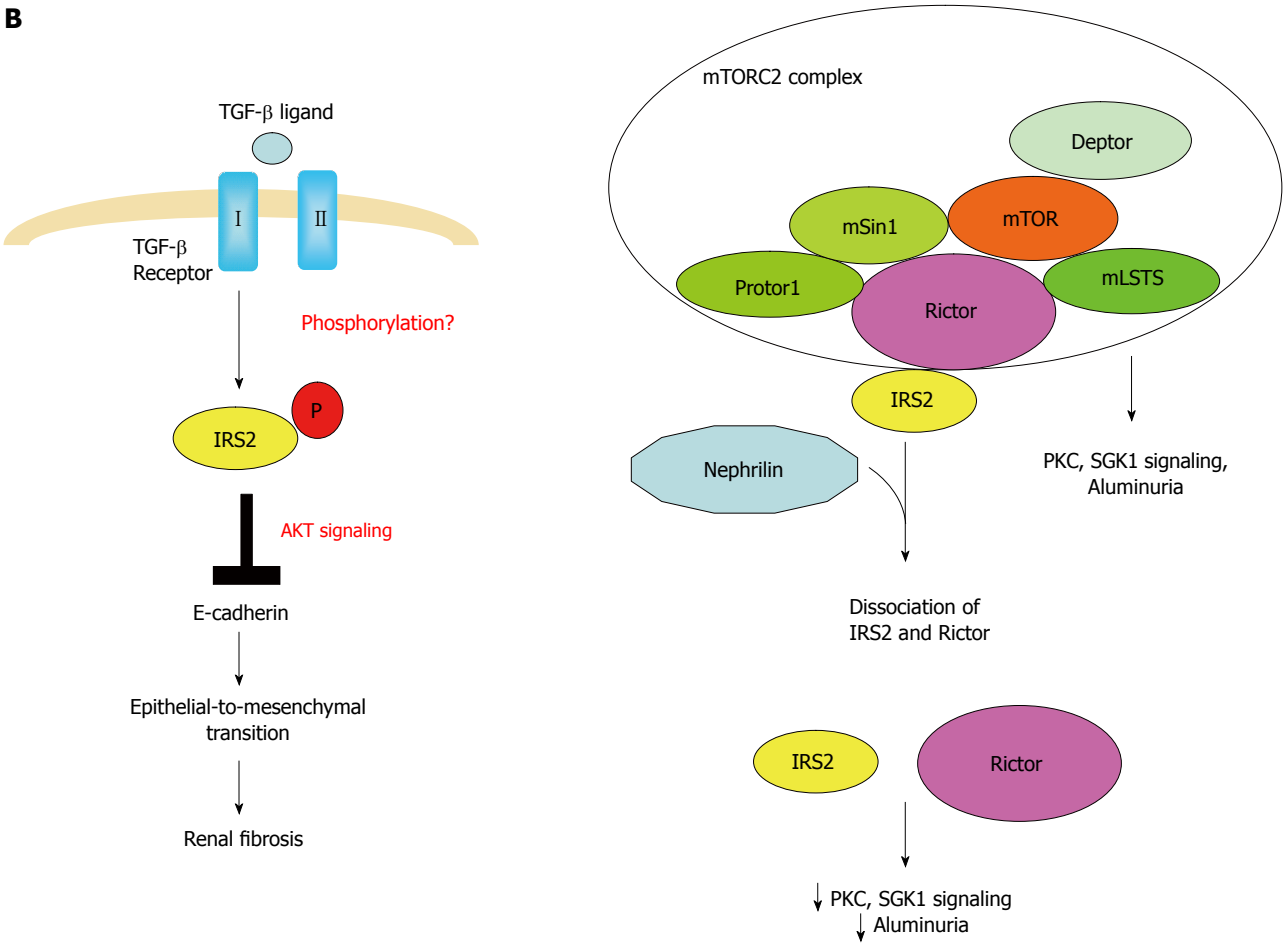
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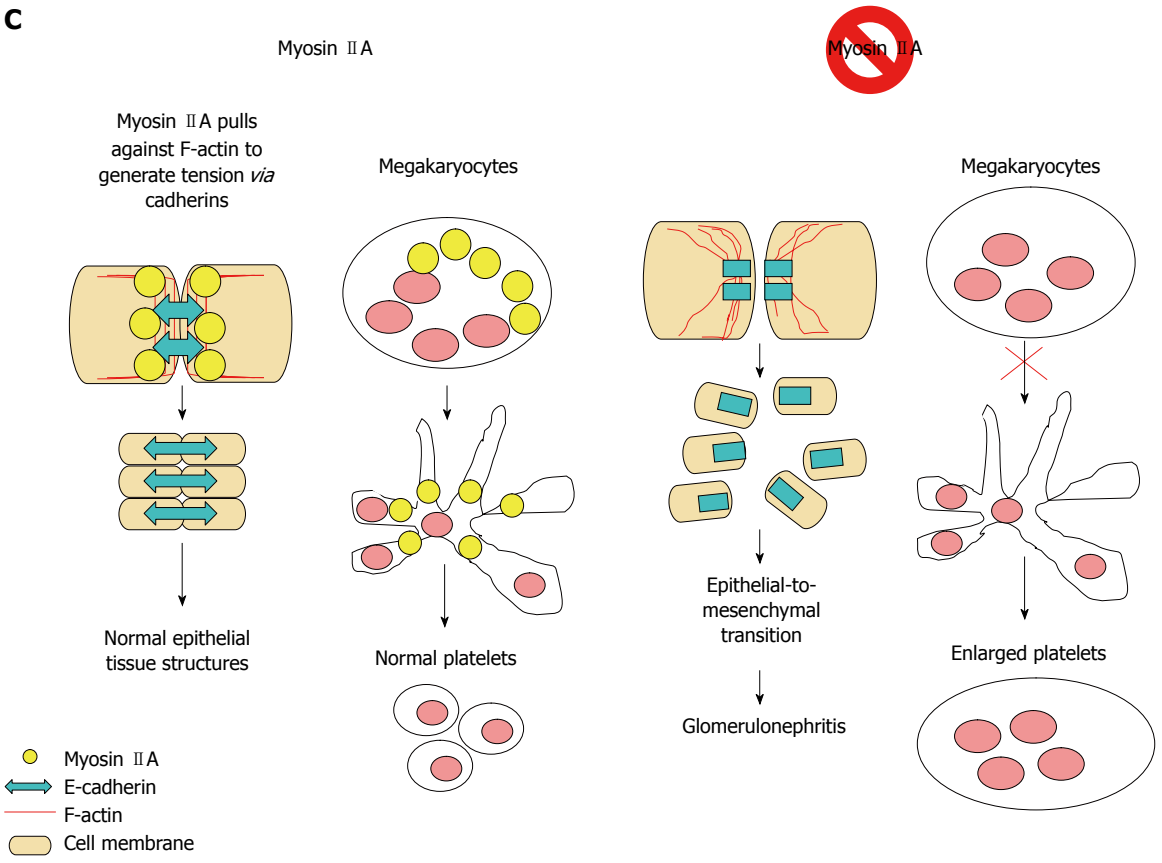

Figure 2 Possible molecular mechanisms. Possible molecular mechanisms by which ELMO1 (A), IRS2 (B), and MYH9 (C) regulate diabetic nephropathy. TRIO: Triple functional domain (PTPRF interacting); RhoG: Ras homolog family member G; GDP: Guanosine diphosphate; GTP: Guanosine triphosphate; MMP: Matrix metalloproteinases; Crk Ⅱ: V-Crk Avian Sarcoma Virus CT10 Oncogene Homolog Ⅱ; TGF-β: Transforming growth factor beta; AKT: Protein kinase B; mLSTS: Mammalian lethal with SEC13 protein 8; mTOR: Mammalian target of rapamycin; mTORC2: Mammalian target of rapamycin complex 2; mSin1: Mammalian SAPK interacting protein; PKC: Protein kinase C; SGK1: Serum- and glucocorticoid-induced kinase 1.

AKAP11/FABP3P2/TNFSF11 gene cluster, and intergenic region between *COX5BL1/LOC441026, ZNRF1, PCSK2, C10orf112* genes were found to be associated with DR[47]. A GWAS for DR involving 174 Taiwanese type 2 diabetic non-proliferative and proliferative retinopathy cases and 575 controls identified several genetic loci with *P*-value less than 10^{-6}, including *MYSM1, FSTL5, C5orfF21, PLXD2, ARHGAP22*, and *HS6ST3*[48]. Another GWAS in Taiwanese identified three risk loci in *TBC1D4-COMMD6-UCHL3*, *LRP2-BBS5*, and *ARL4C-SH3BP4* genes in the initial set of 437 cases of proliferative retinopathy and 570 type 2 diabetic controls. However, none of them were replicated in another 585 Hispanic diabetics[49]. A smaller GWAS comparing 103 Mexican-American type 2 diabetics with severe retinopathy and 183 type 2 diabetics identified suggestive signals in the *CAMK4* and *FMN1* genes[50]. However, the results from these 4 GWAS did not overlap with each other.

GENETIC STUDY OF DIABETIC NEUROPATHY

There was no heritability estimation for diabetic neuropathy in human and no family linkage study for diabetic neuropathy. Only GWAS comparing 572 diabetic neuropathic pain cases defined by treatment for diabetic neuropathic pain and positive monofilament test and 2491 diabetic controls in the Genetics of Diabetes Audit and Research Tayside (GoDARTS) identified potential signals from *GFRA2* gene[51] (Table 2, Figure 1).

PHYSIOLOGICAL INSIGHT FROM GENETIC STUDIES

The *ELMO1* gene encode for a signaling molecule involved in phagocytosis of apoptotic cells[52,53], fibroblast migration[52,54,55], cytoskeleton reorganization[56], and lymphocyte infiltration[57] through interaction with DOCK2 and DOCK180 (Figure 2A). *ELMO1* expression was found to be elevated in cells cultured under high glucose conditions and in the kidney of diabetic mice, but was weakly detectable in tubular and glomerular epithelial cells in normal kidney[25].

The *FRMD3* gene encodes for a member of the protein 4.1 superfamily. *FRMD3* has been demonstrated to be silenced in lung cancer tissue in genomic screening. *FRMD3* overexpression in different epithelial cell lines decreased clonal expansion, indicating *FRMD3*

as a potential tumor suppressor gene[58]. The *CARS* encodes for a cysteinyl-tRNA synthetase, which is a frequent gene fusion partner of anaplastic lymphoma kinase found in anaplastic large-cell lymphoma and inflammatory myofibroblastic tumor[59,60]. However, the link between *FRMD3* or *CARS* and diabetic nephropathy is currently poorly understood.

The 13q33 risk loci lie between the *MYO16* and *IRS2* genes. The *MYO16* gene encodes a novel unconventional myosin with divergent tails that is presumed to bind to membranous compartments and interact with actin filaments. *MYO16* has also been shown to be expressed during brain development and regulate neuronal morphogenesis through interaction with protein phosphatase and modulation of phosphoinositide 3-kinase signaling[61]. A GWAS for autism has identified risk loci within an intergenic region between the *MYO16* and *IRS2* genes[62]. A genome-wide linkage study and regional fine mapping for schizophrenia[63] and another GWAS of the Framingham Heart Study for pulse pressure[64] have identified *MYO16* as risk loci, indicating *MYO16* may play pleiotropic functions.

The *IRS2* gene encodes for an adaptor protein that interacts directly with the insulin receptors and the insulin-like growth factor Ⅰ receptor and is a key mediator of insulin signaling. IRS2 was expressed in renal epithelial and tubular cells. Deletion of *Irs2* causes reduced kidney size and reduced glomerular number in mice[65]. A study of transcriptome and metabolome profiles of the primary cultured inner medullary collecting duct cells grown in hyperosmolar culture medium identified IRS2 levels to be significantly altered[66]. IRS2 expression in kidney tubules has also been shown to be elevated nine fold in human diabetic nephropathy patients[67]. Transforming growth factor (TGF)-β1 is the primary cytokine shown to induce fibrosis. IRS2 has been shown to mediate TGF-β1 signals in kidney epithelial cells[68]. IRS2 has also been shown to interact with nuclear complex of rictor to regulate albuminuria in diabetic mice[69] (Figure 2B).

Mutations in MYH9 results in a familial autosomal dominant syndrome characterized by a variety of clinical features, including macrothrombocytopenia, deafness, nephritis, and cataract[70]. GWAS also identified common *MYH9* polymorphism as risk loci for non-diabetic nephropathy including focal segmental glomerulosclerosis and hypertensive nephropathy[36,27]. *MYH9* encodes the non-muscle myosin heavy chain 9, which, with other subunits, forms myosin Ⅱ. Myosin Ⅱ is a motor protein that binds actin to regulate cellular motility. *MYH9* is expressed in the podocytes, as well as in mesangial cells and arteriolar and peritubular capillaries in kidneys[71]. Classical deletion of *Myh9* in mice results in embryonic lethality due to loss of cell-cell adhesion and loss of cell movement during gastrulation. Podocyte-specfic deletion of *Myh9* in C57BL/6 mice results in susceptibility to experimental doxorubicin hydrochloride glomerulopathy[71]. Several strains of *Myh9* knockin mice showed macrothrombocytopenia, premature cataract formation, kidney abnormalities, including albuminuria, focal segmental glomerulosclerosis and progressive kidney disease, and mild hearing loss[72,73] (Figure 2C).

LIMITATIONS AND PROSPECTIVE

The major limitation of family linkage studies is their low resolution and power to detect variants with small effects, especially for complex genetic diseases. GWAS is a hypothesis-free and unbiased tool with finer resolution and greater power to detect risk loci. However, false positivity often results from population admixture or stratification in GWAS. Therefore, independent replications are essential for genetic association studies. However, current results from GWAS are not consistent since most identified loci are not reproducible except for a few genes such as *ELMO1*, *CARS*, *FRMD3*, *MYO16/IRS2*, and *APOL3/MYH9*. Small sample sizes, different phenotype definitions between studies, population-specific associations, and strong influence of environmental factors (medications, co-morbidities) may explain the failure of GWAS for diabetic complications. While GWAS are usually designed for common variants, rare variants with intermediate effects within should also be pursued with next-generation sequencing. The interaction with environmental factors should also be taken into account.

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