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Review Article

Insights into the molecular underpinning of type 2 diabetes complications

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Abstract

Type 2 diabetes (T2D) complications pose a significant global health challenge. Omics technologies have been employed to investigate these complications and identify the biological pathways involved. In this review, we focus on four major T2D complications: diabetic kidney disease, diabetic retinopathy, diabetic neuropathy, and cardiovascular complications. We discuss advancements in omics research, summarizing findings from genetic, epigenomic, transcriptomic, proteomic, and metabolomic studies across different ancestries and disease-relevant tissues. We stress the importance of integrating multi-omics techniques to elucidate the biological mechanisms underlying T2D complications and advocate for ancestrally diverse studies. Ultimately, these insights will improve risk prediction for T2D complications and inform translation strategies.

Keywords: Type 2 diabetes complications; transcriptomics; epigenomics; proteomics; metabolomics

Introduction

T2D, the most common form of diabetes, is a complex disorder characterized by hyperglycemia [1]. This condition can damage blood vessels, leading to microvascular and macrovascular complications and increased mortality (Fig. 1) [2]. Microvascular complications impact small blood vessels and nerve tissues around organs like the kidneys, retina, and skin, while macrovascular complications affect large blood vessels in the cardiovascular system, potentially causing cardiovascular disease (CVD) and heart failure. The prevalence of complications among individuals with T2D varies between different ancestry populations (Table 1), with estimates highly varying between different studies [3–7]. Studies in European populations show high variability, but the largest Danish study found that individuals of European ancestry generally have lower rates of microvascular complications and higher rates of macrovascular complications compared to those of African ancestry (Table 1) [6]. Another study including individuals from multiple countries shows higher rates of both microvascular and macrovascular complications in Europeans compared to individuals of African and Asian ancestry [3]. In T2D individuals of African ancestry, microvascular complications such as diabetic neuropathy (DN), diabetic retinopathy (DR) and diabetic kidney disease (DKD) are more prevalent than macrovascular complications, with DN being the most common [4]. Various risk factors have been linked to the occurrence of complications including hypertension, smoking, obesity, age, diabetes duration and male gender, summarized in Table 2 [3, 5, 8]. High glycemic levels have been consistently linked to an increased risk of microvascular complications, though it has been shown to have no association with macrovascular complications in multiple studies [6]. The growing prevalence of T2D and its complications, combined with a lack of treatment options, highlights the urgent need to understand their etiology. Collecting data from various molecular levels can enhance our understanding of T2D complications. This review focuses on omics studies of four major T2D complications: diabetic kidney disease (DKD), diabetic retinopathy (DR), diabetic neuropathy (DN), and cardiovascular complications. We cover all major cardiovascular complications but found no relevant studies on cerebrovascular complications.

Genome-wide association studies of T2D complications

Genome-wide association studies (GWAS) of T2D complications have been limited in sample size and statistical power, with few associations being described in non-European populations so far [9]. The genetic associations which have been described mostly correspond to common variants of modest to high effect sizes (Fig. 2, Table 3).

Diabetic kidney disease (DKD)

Persistent hyperglycemia leads to kidney damage in T2D, characterized by a decline in estimated glomerular filtration rate (eGFR) and albuminuria, hallmarks of DKD [10]. A variant near *UMOD*

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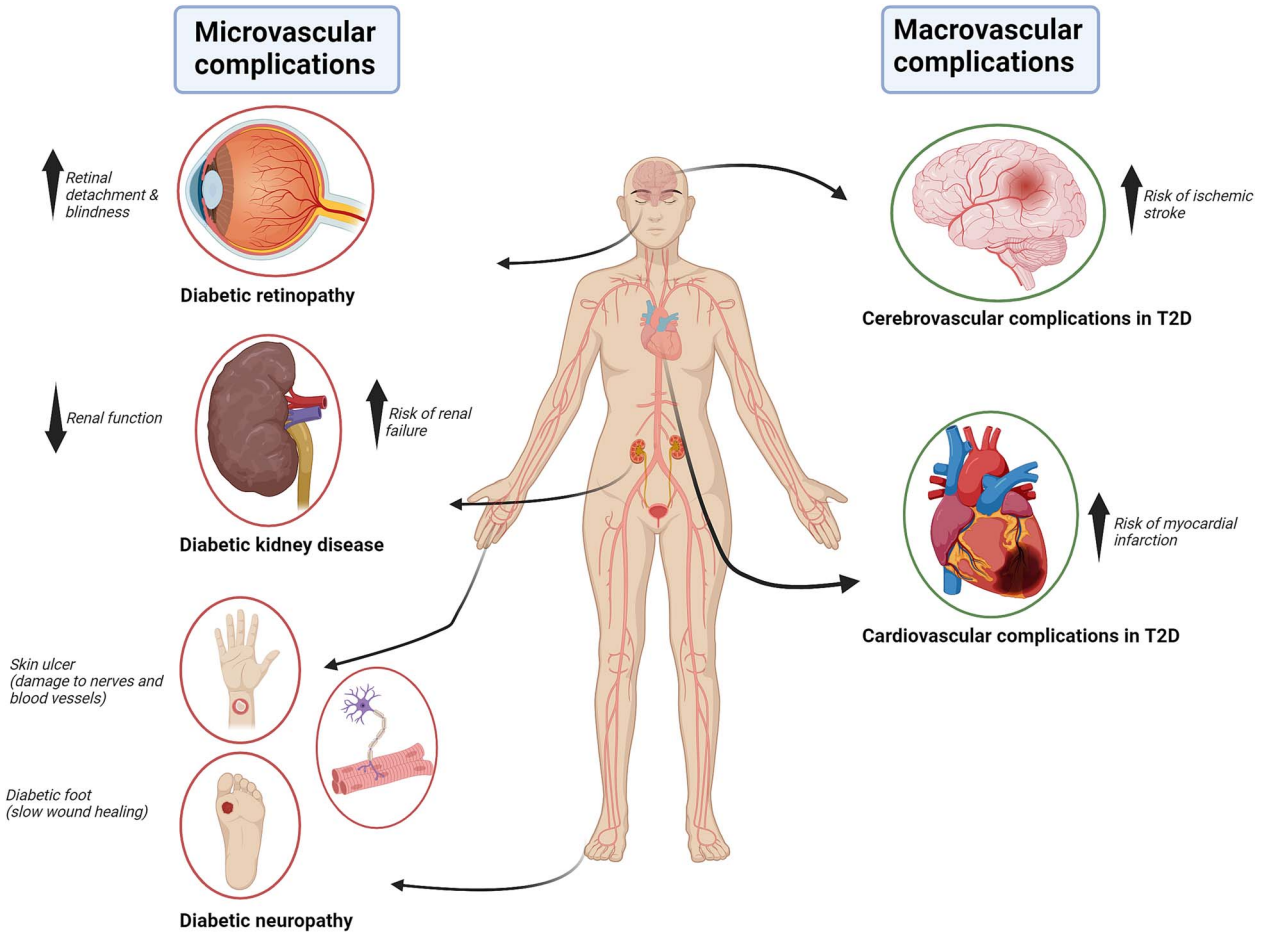

Figure 1. Organs affected by different T2D complications.

Table 1. Prevalence of T2D complications among various ancestry groups.

Prevalence	European ancestry	African ancestry	East Asian ancestry	South Asian ancestry	Hispanic ancestry
DKD	3% (3–35.9%)	13%	10.7% (10.7–28.4%	20.3%	33%
DR	13% (4.9–69%)	15%	14.8% (14.8–23.7%)	16.3%	32.3%
DN	4% (4–83%)	33–48.4%	17.8% (17.8–36.9%)	24.6%	43.1%
CVD	17% (15–72.4%)	1.16%	30.1%	23.3%	29.4%

The prevalence data is sourced from various studies. (References: [3–7])

Table 2. Risk factors associated with T2D complications.

Risk factor	Diabetic kidney disease	Diabetic retinopathy	Diabetic neuropathy	Cardiovascular disease
Smoking	✓	×	✓	✓
Sex	✓	×	×	✓
Obesity	×	×	×	✓
Hypertension	✓	✓	×	✓
Age	✓	×	×	✓
Diabetes duration	✓	✓	✓	✓
Total cholesterol	✓	×	×	✓

× indicates no significant association found (References: [3, 5, 8])

and a variant near *GABRR1* were linked to eGFR decline and microalbuminuria in patients with T2D, respectively [11, 12]. Key pathways underlying DKD and supported by genetics evidence include mechanisms of renal fibrosis, kidney development, blood pressure regulation, and immune response (Fig. 3). *TENM2*, a gene whose expression correlates with higher eGFR and lower renal fibrosis, harbors an intronic variant associated with DKD [13]. Another gene, *DIS3L2*, which is involved in kidney development, was identified in an exome-wide analysis [14]. Similarly, *SCAF8* and *CNKSR3*, involved in transcription and blood pressure regulation, carry intergenic variants linked to DKD across multiple populations [15, 16]. Immune modulation also emerged as an important contributor, with identification of associations for genes like *ERAP2* and *NPEPPS*, both of which regulate immune

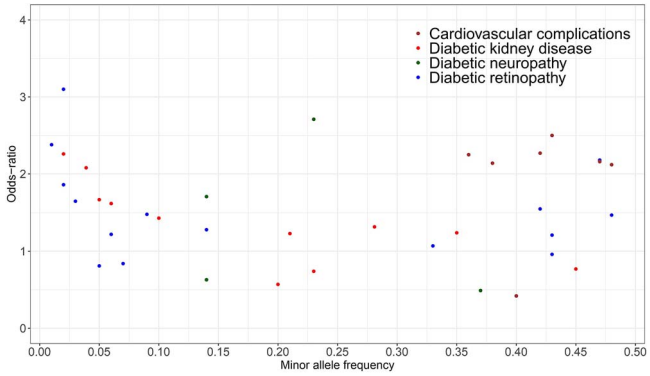

Figure 2. Scatter plot of minor allele frequency against odds-ratio of variants found to be genome-wide significant in T2D complications GWAS.

response [14]. GWAS in non-European populations has revealed ancestry-specific genetic influences, such as an intronic *FTO* variant previously associated with obesity, in Japanese individuals [17, 18]. In African Americans, an intronic *APOL1* variant [19], and a newly identified expression quantitative trait locus in *TRIM27* in Korean individuals further emphasize the diversity of genetic drivers in DKD [20].

Diabetic retinopathy (DR)

DR develops through prolonged exposure to hyperglycemia and is influenced by diabetes duration, as well as high glycemic and blood pressure levels, leading to progressive damage to the retina and the macula [21]. The key pathways include angiogenesis, oxidative stress, and inflammation (Fig. 3). Genetic factors may play a regulatory role in modulating these pathways. For example, in Europeans, a variant near *GRB2*, a gene which activates the MAPK pathway and promotes angiogenesis, was associated with DR, as well as a variant in *NOX4*, with roles in ROS production and neovascularization [22, 23], and Intronic variants of *TCF7L2*, which regulates insulin secretion [24]. Additionally, variants have been identified in genes for which functional mechanisms leading to DR still need to be uncovered, such as *NVL* [25], and *CCDC146* [26]. In individuals genetically similar to African Americans and continental Africans, genetic associations extend to genes including *GOLIM4, WDR72, HLA-B, GAP43/RP11-326J18.1*, and *AL713866.1* [25, 27]. Notably, *WDR72*, which is expressed in the retina, has been linked to HbA1c levels, high glycemic levels, eGFR, and proliferative angiogenesis, highlighting its role in both glucose regulation and retinal damage [28]. Increased oxidative stress also plays a role in DR progression, particularly in African ancestry populations, in which a *G6PD* exonic variant has been associated with reduced *G6PD* levels [24].

Diabetic neuropathy (DN)

DN arises primarily from hyperglycemia-induced vascular and nerve damage. While strict maintenance of glycemic levels can reduce the risk of DN in T1D, this strategy is less effective in T2D, potentially indicating additional biological mechanisms that exacerbate nerve damage [29]. Key pathways implicated in DN include sodium channel regulation, neural signaling and inflammation, with inflammatory pathways being the common thread linking all microvascular complications (Fig. 3). Variants in *MAPK14* intronic regions have been identified in several studies in European populations, highlighting the role of mitogen activated protein kinase pathways in cellular stress response [30]. Further, a variant near *SCN2A*, which regulates sodium channels in neurons, linked to nerve damage, has been associated with DN [31]. Other variants identified near *LOC105371557* and in the 3' UTR of *GYPA*, suggest links to metabolic traits, including obesity, reinforcing its influence on progression to microvascular complications [26, 32].

Cardiovascular complications in T2D

Pathways leading to cardiovascular complications in T2D with genetic evidence from multiple studies include glucose metabolism, oxidative stress, and inflammation, all mechanisms also implicated in microvascular complications (Fig. 3). Evidence of the involvement of these pathways has been found across different populations. GWAS in European, Pakistani, and Egyptian populations identified a variant near *GLUL,* which regulates glutamic acid metabolism, and affects glucose metabolism and oxidative stress [33–37]. Highlighting the role of DNA repair and stress response, associations were found in the intron of *MGMT*, and *CSNK1A1L,* which may contribute to inflammation and cellular damage in cardiovascular complications [38, 39]. Additionally, discovery of a variant near *F5* linked to ischemic stroke, and an intronic variant of *RPS6KA2* associated with stress response in cardiac myocytes, emphasizes the role of blood coagulation in diabetes-related cardiovascular events [40, 41]. An intronic variant of *PDE4DIP* and an intronic variant of *PDE1A* were described in the European and Chinese populations, respectively, both linked to myocardial infarction, further supporting the role of impaired myocardial function in the development of macrovascular complications [26, 42]. A variant near *NAT8* has been associated with eGFR, blood pressure, and renal function, further linking cardiovascular health to kidney function [43–45].

Epigenomics of T2D complications

Epigenomic studies investigate DNA methylation, histone modifications and RNA-mediated mechanisms, which control gene regulation through dynamic tissue-specific mechanisms [46] and can be influenced by environmental factors [47, 48]. To date, no epigenetic associations with cardiovascular complications have been described.

Diabetic kidney disease

DKD involves complex regulatory mechanisms, including DNA methylation, which plays an important role in renal damage, particularly in the progression of albuminuria and declining eGFR [49, 50]. Key differentially methylated sites (DMSs) have been causally linked to eGFR decline using Mendelian randomization, with *COMMD1*, *TMOD1*, and *FHOD1* emerging as significant players in this context [51]. These epigenetic changes are further supported by methylation-associated variants that influence gene expression related to eGFR and kidney fibrosis, notably in *LACTB* and *IRF5*, both of which contribute to kidney function regulation [52]. Evidence from epigenetic studies have also implicated inflammation processes in DKD with reduced methylation of *TNF* in DKD, or hypomethylation of *FOX1* leading to increased inflammation [53–56]. Single cell analysis has revealed alterations in the glucocorticoid receptor signaling within diabetic kidneys, affecting chromatin accessibility. These changes likely modulate localized anti-inflammatory responses, providing further insights into the molecular mechanisms driving DKD [57].

Diabetic retinopathy

Global DNA methylation changes have been found to be predictive of DR and its progression, independently of classical risk factors,

Table 3. Genome-wide significant loci discovered in T2D complications GWAS.

rsid	Closest gene	P-value	Phenotype	No. of cases	No. of controls	Ethnicity	Genomic Position (hg19)	Odds ratio	EAF	Reference
rs13417783[a]	*SCN2A*	7.9×10^{-12}	Diabetic neuropathy	5175	942	European	2:167629849	0.63	0.14	[31]
rs1132787[c]	*GYPA*	3.23×10^{-11}	Diabetic neuropathy	218	382	European	4:145030546	2.71	0.23	[26]
rs522521[c]	*LOC105371557*	5.07×10^{-8}	Diabetic neuropathy	218	382	European	17:15733545	0.49	0.37	[26]
rs80028505[c]	*MAPK14*	2.5×10^{-8}	Foot ulcer in Diabetic Neuropathy	699	2695	European	6:35998388	1.71	0.14	[30]
rs11070992[a]	*WDR72*	4.2×10^{-8}	PDR with T2D	64	227	African	15:53880517	1.28	0.14	[27]
rs1065386[c]	*HLA-B*	4.2×10^{-12}	PDR with T2D	64	227	African	6:31324547	1.21	0.43	[27]
rs10560003[c]	*GAP43/RP11-326 J18.1*	4.2×10^{-13}	PDR with T2D	64	227	African	3:115378465	1.86	0.02	[27]
rs72740408[c]	*AL713866.1*	4.2×10^{-14}	PDR with T2D	64	227	African	1:191105831	1.65	0.03	[27]
rs3095447[c]	*CCDC146*	2.55×10^{-8}	Diabetic retinopathy	203	398	European	7:76764970	2.18	0.47	[26]
rs3913535[c]	*NOX4*	4.05×10^{-9}	Diabetic retinopathy	560	4106	European	11:89096757	1.55	0.42	[23]
rs142293996[c]	*NVL*	2.1×10^{-9}	Diabetic retinopathy	1079	1970	European	1:224448059	2.38	0.01	[25]
rs115523882[c]	*GOLIM4*	5.37×10^{-9}	PDR with T2D	911	941	African American	3:167876205	3.10	0.02	[25]
rs9896052[c]	*GRB2*	4.2×10^{-8}	Diabetic retinopathy	1175	1319	European and Indian	17:73418862	1.47	0.48	[22]
rs1050828[a]	*G6PD*	1.99×10^{-90}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	X:153764217	1.48	0.09	[24]
rs115170237[c]	*MFSD4A*	4.04×10^{-8}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	1:205542207	1.19	0.93	[24]
rs11950268[c]	*TENM2*	2.56×10^{-9}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	5:167252701	0.81	0.05	[24]
rs76624501[c]	*GRHL2*	2.57×10^{-10}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	8:102427724	1.22	0.06	[24]
rs7903146[a]	*TCF7L2*	2.22×10^{-15}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	10:114758349	1.07	0.33	[24]
rs114926776[c]	*FBXW8*	1.56×10^{-8}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	12:117352347	0.84	0.07	[24]
rs7333159[c]	*COL4A1*	4.86×10^{-8}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	13:110900943	1.13	0.87	[24]
rs73995757[c]	*SLC16A5*	4.02×10^{-8}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	17:73089001	1.14	0.89	[24]
rs2076085[c]	*TMPRSS6*	2.48×10^{-8}	Diabetic retinopathy	68 169	129 188	Multi-ancestry	22:37470041	0.96	0.43	[24]
rs13329952[c]	*UMOD*	2.5×10^{-8}	eGFR in T1 and T2D subjects	16 477	NA	Multi-ancestry	16:20366507	−0.0158	0.19	[11]
rs56094641[a]	*FTO*	7.7×10^{-10}	Diabetic kidney disease	2809	5592	Japanese	16:53806453	1.23	0.21	[18]
rs9942471[a]	*GABRR1*	4.5×10^{-8}	Diabetic kidney disease	3345	2372	European	6:89948232	1.24	0.35	[12]
rs12523822[a]	*SCAF8, CNKSR3*	$1.3x10^{-8}$	Diabetic kidney disease	1009	1145	Multi-ancestry	6:154954420	0.57	0.2	[15]
rs72858591[c]	*RND3/RBM43*	$4.5\,4 \times 10^{-8}$	End stage kidney disease in T2D	3432	6977	African American	2:151711452	1.43	0.10	[19]
rs58627064[c]	*SLITRK3*	6.81×10^{-10}	End stage kidney disease in T2D	3432	6977	African American	3:165051826	1.62	0.06	[19]
rs142563193[c]	*ENPP7*	1.24×10^{-8}	End stage kidney disease in T2D	3432	6977	African American	17:77667171	0.74	0.23	[19]
rs142671759[c]	*ENPP7*	5.53×10^{-9}	End stage kidney disease in T2D	3432	6977	African American	17:77706698	2.26	0.02	[19]
rs4807299[c]	*GNG7*	3.21×10^{-8}	End stage kidney disease in T2D	3432	6977	African American	19:2570002	1.67	0.05	[19]
rs9622363[c]	*APOL1*	$1.4\,2 \times 10^{-10}$	End stage kidney disease in T2D	3432	6977	African American	22:36656555	0.77	0.45	[19]
rs72831309[a]	*TENM2*	9.8×10^{-9}	Diabetic kidney disease	4122	13 972	European	5:166978230	2.08	0.039	[13]
rs3128852[c]	*TRIM27*	4.72×10^{-14}	Diabetic kidney disease	2532	8844	Korean	6:29364135	1317	0.281	[20]
rs10911021[b]	*GLUL*	2.0×10^{-8}	CHD with T2D	1517	2671	Multi-ancestry	1:182081960	1.36	0.69	[33]
rs9299870[a]	*MGMT*	9.8×10^{-9}	Cardiovascular mortality with T2D under intensive control of glycemic levels	2667	NA	European	10:131269309	3.58	0.08	[39]
rs57922[a]	*LINC (LINC1335, LINC1333, and LINC1331)*	2.0×10^{-8}	Cardiovascular mortality with T2D under intensive control of glycemic levels	2667	NA	European	5:73577939	2.65	0.48	[39]
rs8000449[c]	*CSNK1A1L*	2.02×10^{-8}	Coronary artery calcification in T2D	1420	NA	European	13:37798358	0.48	0.42	[38]
rs2477088[c]	*PDE4DIP*	6.11×10^{-10}	macrovascular complications with T2D	333	226	European	1:144936353	2.5	0.43	[26]
rs4852954[c]	*NAT8*	1.26×10^{-8}	macrovascular complications with T2D	333	226	European	2:73870010	2.27	0.42	[26]
rs6032[c]	*F5*	2.62×10^{-8}	macrovascular complications with T2D	333	226	European	1:169511555	2.12	0.48	[26]
rs6935464[c]	*RPS6KA2*	3.89×10^{-8}	macrovascular complications with T2D	333	226	European	6:167114208	2.25	0.36	[26]
rs522521[c]	*LOC105371557*	6.95×10^{-10}	macrovascular complications with T2D	333	226	European	17:15733545	0.42	0.4	[26]
rs7236163[c]	*ZNF519*	4.97×10^{-8}	macrovascular complications with T2D	333	226	European	18:14150724	2.14	0.38	[26]
rs3095447[c]	*CCDC146*	4.98×10^{-8}	macrovascular complications with T2D	333	226	European	7:76764970	2.16	0.47	[26]
rs10171703[a]	*PDE1A*	2.4×10^{-8}	CHD with T2D	3596	8898	Chinese	2:183343102	1.21	0.79	[42]

[a]Replicated in same study [b]Replicated in another study [c]Not replicated

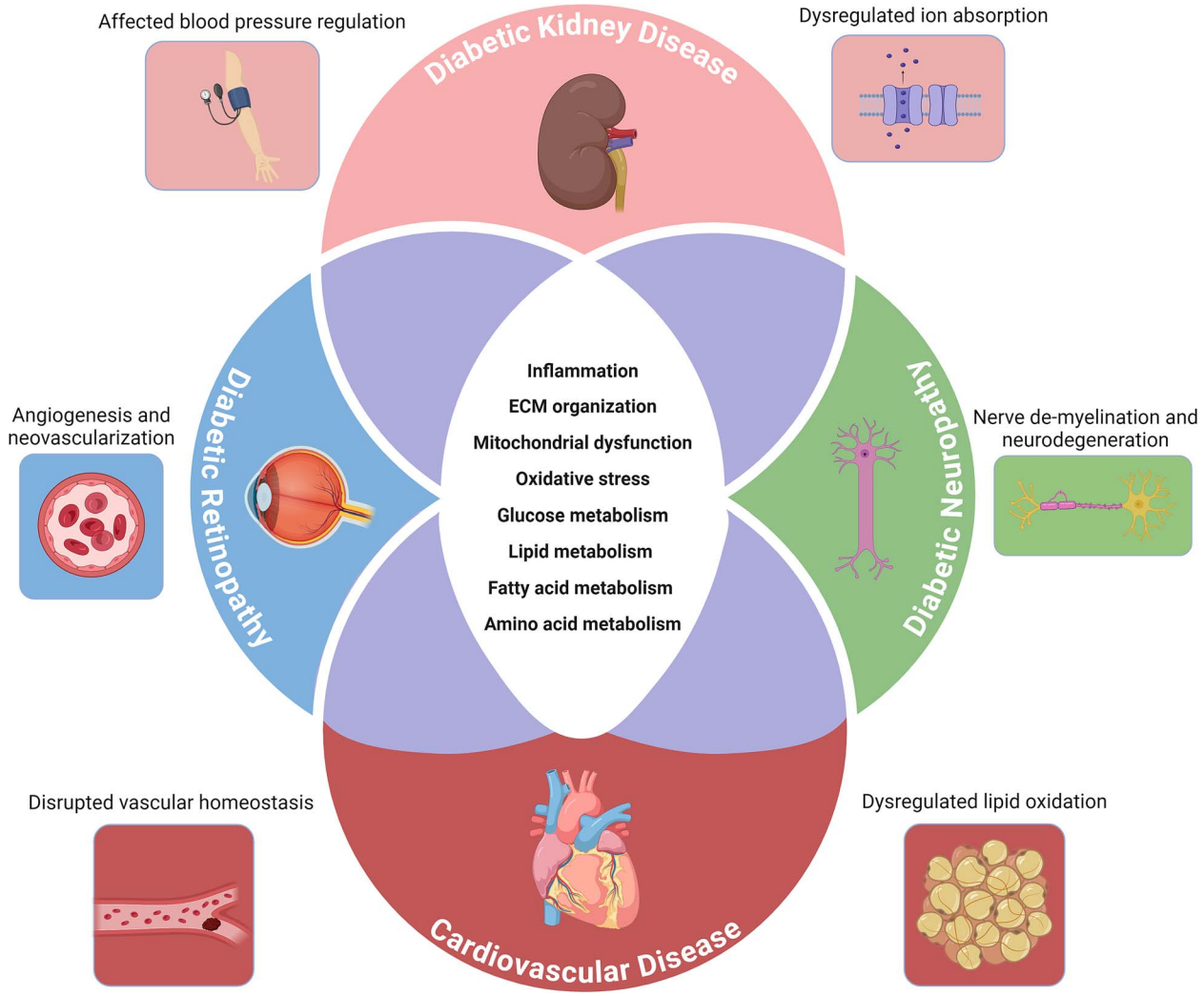

Figure 3. Biological pathways found to be shared between all T2D complications.

underscoring their role in disease pathogenesis [58]. Additionally, epigenetic modifications that affect key pathways involving inflammation, oxidative stress, and vascular damage have been described. For instance, demethylation of two sites in *S100A13* has been shown to activate key inflammatory and stress-related pathways, including *p38 MAPK*, *NFκB*, and RAGE, exacerbating hyperglycemia and promoting vascular damage [59, 60]. The hyperglycemic environment seen in DR leads to elevation of ROS and mitochondrial DNA hypermethylation, which in turn alters mitochondrial gene expression and further contributes to disease progression [61, 62].

Diabetic neuropathy

In DN, disrupted pathways involving nerve myelination, extracellular matrix integrity and insulin signaling are key contributors to nerve damage, for which altered gene expression through DNA methylation has been described [63, 64]. DMSs in genes such as *PLCG2, GNAS, MAPK8IP3, TIMP2, IRS2,* and *ISF-I* are associated with nerve fiber loss, affecting nerve structure and function through impaired myelination and extracellular matrix (ECM) disruption [64]. Additionally, long non-coding RNAs (lncRNAs), such as *LINC00324* and *TUBA4B,* known to modulate DNA methylation and histone modifications, have been described but the affected pathways remain unknown [65]. The interplay between methylation changes and lncRNAs suggests a multilayered epigenetic landscape that contributes to neuropathic complications in T2D.

Transcriptomics of T2D complications

Diabetic kidney disease

DKD is driven by a pro-inflammatory environment, where immune cell infiltration like T-cells, B-cells, plasma cells, and monocytes, as well as upregulation of key inflammatory pathways, play a central role in disease progression [57, 66, 67]. Transcriptomic analyses of kidney biopsies reveal upregulation of *JAK–STAT* and *NFkB* pathways, particularly in late-stage DKD, which contributes to sustained inflammation and tissue damage [68, 69]. *AKIRIN2,* a regulator of *TNF* and *IL-1β* signaling is also upregulated in kidney tissue and correlates with severity of renal fibrosis [13]. Single cell studies provide further insights into functional disruptions in the nephron. Downregulation of sodium, potassium and calcium transporters like *NKA, KCNJ16,* and *NKCC2* in the ascending loop of Henle impairs ion reabsorption, while upregulation of *NKA* in the late distal convoluted tubule leads to increased potassium loss, contributing to electrolyte imbalances commonly seen in DKD [70]. Bulk RNA sequencing of DKD kidney samples reveals broader disruptions in apoptosis,

ECM organization, and amino acid metabolism pathways, further emphasizing the complexity of molecular changes that drive kidney damage and functional decline in DKD [67, 71, 72]. Additionally, early stage DKD is characterized by upregulation of genes such as *RBP4* and *GLP1R*, associated with renal function and protective effects, though these are suppressed in advanced DKD [73].

Diabetic retinopathy

DR is characterized by key pathways involving angiogenesis, neovascularization, inflammation, and vascular damage. Increased vascular permeability and fluid leakage are hallmarks of DR, with angiogenesis playing a central role [74, 75]. Upregulation of *PDGFB*, critical for corneal neovascularization, and downregulation of *ADAMTS4*, an antiangiogenic factor, were found in retinal samples in late DR [76]. Additionally, increased *TTR* expression found in human retinal endothelial cells has been found to protect against neovascularization in DR via lncRNAs [77]. Fibrosis, which contributes to retinal detachment, is associated with upregulation of *POSTN* and *ET* in retinal fibroblasts [78, 79]. Promising therapeutic strategies are emerging from targeting *POSTN* to inhibit neovascularization [79]. Inflammatory pathways also play a crucial role, with upregulation of *ICAM1* and *CD44* antigen in retinal tissue associated with proliferative DR, linking vascular damage and immune response to disease severity [79].

Diabetic neuropathy

DN is driven by a complex interplay between inflammation, metabolic dysregulation, and ECM disruption. In the progression of DN, there is upregulation of inflammation-associated genes such as chemokines, cytokines and interleukins, while pathways involved in glucose metabolism and anti-inflammatory responses, such as PPAR signaling and TNF-α, are downregulated, as seen in nerve biopsy and dorsal root ganglia tissue [80, 81]. This imbalance contributes to neuropathic pain experienced by dorsal root ganglia neurons, a hallmark of DN [81]. Foot ulcers, a major DN sub-phenotype, exhibit a distinct gene expression profile, with healing fibroblasts upregulating anti-inflammatory genes like *CHI3L1* and *TNFAIP6* along with ECM remodeling genes such as *MMP1* and *MMP3* [82]. Additionally, an increase in pro-inflammatory M1 macrophages, characterized by the upregulation of genes like *IL1B, S100A8*, and *S100A9*, highlights the localized pro-inflammatory response critical for wound healing but also underscores the chronic inflammation that hinders recovery in diabetic wounds.

Cardiovascular complications in T2D

CVD in T2D occurs from interlinked pathways that overlap with cardiovascular disease, including lipid, lipoprotein, and glucose metabolism, as well as fatty acid, and bile acid metabolism [83, 84]. Additionally, pathways related to coagulation and inflammation, such as Toll-like receptor, chemokine, MAPK, cytokine, and PDGF signaling, which play crucial roles in vascular damage and atherosclerosis, were found in disease relevant tissues and blood in T2D and CVD [83, 84]. Further insights highlight the role of branched-chain amino acid (BCAA) metabolism and ECM remodeling in cardiovascular complications [83]. Specific genes identified include *HMGCR*, a target for statins, and *CAV1*, linked to hyperglycemia, insulin resistance, and atherosclerosis in mouse models. Other notable genes like *IGF1* and *SPARC* are associated with insulin resistance and coronary artery lesions, while *PCOLCE* and *COL6A2* are involved in ECM regulation [83]. These interlinked pathways highlight the complex molecular landscape of cardiovascular risk in T2D.

Proteomics of T2D complications

Diabetic kidney disease

DKD is marked by proteomic perturbations that reflect underlying pathways of inflammation, fibrosis, and lipid metabolism [85–88]. Circulating biomarkers such as LAYN, ESAM, DLL1, MAPK11, and endostatin are linked to severe DKD, with a role in promoting kidney fibrosis and inflammation [85]. These inflammatory and fibrotic pathways are central to DKD progression, which is also seen in other omics studies [14, 52–56, 68, 69]. Proteomic differences between early and late-stage DKD further underscore these pathways. In late-stage DKD, elevated levels of inflammatory regulators like SERPINA1 and SERPING1 are observed in urine, while fibrosis-related proteins such as COL1A1 and COL3A1 are lower, indicating a pro-inflammatory environment and possible tissue damage [87]. Moreover, glomerulosclerosis, a hallmark of DKD severity, is characterized by upregulation of proteins involved in inflammation (C3, C8, C9) and lipid metabolism, such as ApoE [89]. Overall, these proteomic signatures reflect the muti-factorial nature of DKD, which corroborates the findings reported at other omics levels.

Diabetic retinopathy

As seen in omics studies described previously, the key pathways driving DR involve inflammation, oxidative stress, and ECM remodeling. Elevated levels of interleukins like IL-4 and TNF, along with complement system proteins, and neutrophil signaling molecules have been observed in DR-relevant fluids like tears, vitreous humor, and saliva [90–92]. These inflammatory responses contribute to retinal damage and neovascularization, both hallmarks of DR. Conversely, ADAM10, a key negative regulator of ocular angiogenesis and inflammation, has been found to be downregulated [93]. Oxidative stress is a further major pathway with increased expression of stress response proteins like CALML5, GLUL, CALML3, CTSL, and PDIA3, further exacerbating retinal injury [90]. Retinal homeostasis is also disrupted with proteins such as FGF, PRCP, and AGT, crucial for maintaining retinal health being upregulated in the tear fluid of patients with DR [90]. Finally, ECM-related proteins involved in inflammation and neovascularization like MMP3 and MMP9, are also upregulated in DR, which further contributes to pathological angiogenesis and tissue remodeling [90].

Diabetic neuropathy

Corroborating evidence from previous omics studies, proteomic studies of DN have revealed pathways related to inflammation, neuronal damage, and neurodegeneration. A central aspect is the role of ECM proteins like endostatin, Annexin A3, and tenascin R, which contribute to inflammation and axonal degeneration in neurons from nerve biopsies and dorsal root ganglia, driving DN progression [94]. In parallel, proteins involved in neuronal maintenance like MBP and MPO, show dysregulation, reflecting impaired myelination and exacerbating nerve damage [95]. The dysregulation of pathways observed in DN is further compounded by hyperphosphorylation of eEF2, a key player in RNA binding and protein translation [96]. This promotes endoplasmic reticulum stress, chronic pain, and neurodegeneration, illustrating the complex network of pathways that drive nerve deterioration in DN.

Cardiovascular complications in T2D

Proteomic analyses highlight the role of key pathways like systemic inflammation, insulin resistance, endothelial dysfunction and lipid metabolism in cardiovascular complications of T2D [97]. Inflammatory pathways marked by upregulation of pro-inflammatory cytokines, like TNF-α and IL-1β, are central to the pathogenesis of macrovascular complications [97]. In parallel, insulin resistance contributes to endothelial dysfunction and impaired glucose metabolism, as shows by elevated serum levels of GLP-1, Leptin and C-peptide in individuals with CAD and T2D [97]. Adiponectin, an important regulator of glucose metabolism and vascular health is notably reduced in these individuals, which suggests dysregulation of protective pathways [98]. Proteins associated with vascular health and tissue repair including GDF15, renin, serine protease HTRA1, and EGFR, highlight the complex dynamics of inflammatory and metabolic pathways in cardiovascular complications [98].

Metabolomics of T2D complications

Diabetic kidney disease

As seen in other omics studies, evidence for involvement of several metabolic pathways, inflammation, and vascular dysfunction has been observed in metabolomic studies of DKD. Key metabolites, particularly phenyl compounds like p-cresol sulfate and phenylacetylglutamine in plasma, are known to cause proximal tubular injury in the kidneys, directly connecting them to end-stage DKD and co-occurring cardiovascular complications [99]. These metabolites, along with myo-inositol, pseudouridine, and uric acid show disrupted metabolic environment in patients with advanced DKD, where accumulation of these compounds leads to tissue damage [99]. Serum metabolites involved in the urea cycle also play a crucial role in DKD progression by contributing to systemic inflammation and worsening disease severity [100, 101]. N-acetylneuraminic acid contributes to inflammatory response observed in DKD by binding to the ROCK protein, a regulator of vascular inflammation [102]. Piperidine, similarly linked to both retinal and renal complications, regulates blood flow and vascular resistance, exacerbating damage in multiple tissues [102].

Diabetic retinopathy

As seen before, oxidative stress and inflammation are central to DR progression, with several other metabolic pathways playing key roles. The involvement of purine metabolism in ROS production is evident with elevated levels of guanine, inosine, and hypoxanthine reported in vitreous humor samples in DR, contributing to cellular oxidative stress [103]. Higher plasma levels of asymmetric dimethyl arginine, which inhibits nitric oxide and generates ROS, have been associated with higher DR risk, further emphasizing the role of oxidative stress in DR [104–106]. Conversely, some metabolites, like linoleic and arachidonic acids, may offer protection against DR by maintaining capillary integrity, regulating neovascularization, and reducing retinal inflammation, potentially countering the damaging effects of oxidative stress [107, 108]. Dysregulation of the pentose phosphate pathway (PPP) is crucial in DR pathogenesis, as increased plasma levels of metabolites like 2-deoxyribonic acid, 3,4-dihydroxybutyric acid, erythritol, gluconic acid and ribose have been observed in patients with DR [109]. This metabolic change reflects the oxidative stress characteristic of DR [103, 110]. Further, decreased xanthine levels in the vitreous humor serve as a strong predictor of DR, potentially increasing ROS levels and activating the PPP [103].

Diabetic neuropathy

Key pathways described to be disrupted in DN include lipid metabolism, mitochondrial dysfunction, and vascular circulation, which together contribute to nerve damage and bioenergy imbalance. Increased triglyceride levels in plasma and sural nerve cells are closely linked with DN, suggesting that impaired mitochondrial function and altered nerve bioenergetics can lead to triglyceride accumulation and contribute to the disease [111, 112]. Corroborating this, phospholipids like phosphatidylcholine and phosphatidylethanolamine, essential for mitochondrial function and myelin maintenance, are significantly depleted in patients with DN. This depletion affects myelination in Schwann cells, which require N-acetylaspartic acid for myelin synthesis [96, 113]. Moreover, metabolic byproducts like phenylacetylglutamine, a biomarker of DN, further exacerbate DN by promoting platelet aggregation and thrombosis, thereby impairing peripheral nerve and microvascular circulation [114].

Cardiovascular complications in T2D

Lipid and amino acid metabolism dysregulation are key contributors to macrovascular damage and CVD in T2D, mainly through pathways connected to oxidative stress, mitochondrial dysfunction, and inflammation [115, 116]. Reduced serum levels of phosphatidylcholine, lysophosphatidylcholine, and lysophosphatidylethanolamine have been identified as potential risk factors for CVD in T2D, suggesting impaired lipid metabolism and cell membrane integrity [117]. Low phosphatidylcholine levels, in particular, may indicate myocardial membrane damage, exacerbated by oxidative stress and mitochondrial dysfunction [118, 119]. In parallel, elevated BCAAs (isoleucine, valine, leucine) have been associated with coronary heart disease (CHD) in patients with T2D [120, 121], in line with evidence from transcriptomics studies. BCAAs contribute to cardiovascular risk by promoting oxidative stress and mitochondrial dysfunction, while also activating the mTOR pathway, which accelerates atherosclerosis and increases plasma glucose levels, thus exacerbating coronary vascular damage [122, 123].

Discussion and future directions

We highlight key biological pathways underlying T2D complications, mostly shared across various complication groups. Central pathways include inflammation, vascular damage, metabolism of essential biomolecules, ECM remodeling, and mitochondrial dysfunction. Both pro- and anti-inflammatory pathways are key in complication development, with a critical balance needed for tissue healing. Systemic inflammation exacerbates complication symptoms. Lipid and fatty acid metabolism are key in cardiovascular complications, while purine and amino acid metabolism are crucial for microvascular complications. Overall, these insights offer a deeper understanding of the mechanisms driving T2D complications development. However, research in this field still faces significant limitations which are discussed below, along with recommendations for addressing these challenges. Additional evidence is needed to further validate pathways identified in individual studies, and to better describe and understand the link between genetics and T2D complications.

Despite increasing efforts, small sample sizes remain a bottleneck for genetic discovery in T2D complications, limiting the understanding of their genetic architecture [12]. Given that statistical power in T2D complications studies can be hampered by phenotypic heterogeneity, increasing sample size is a priority. For example, only about 50% of CKD cases in T2D are due to DKD, causing misclassification [124]. This can be mitigated by

considering factors like diabetes duration, absence of DR, sudden proteinuria worsening, or acute renal failure, which suggest non-diabetic renal disease [125].

Moreover, most T2D complication GWAS focus on European populations [12, 25, 31, 33]. Including diverse ancestries is crucial, as shown by a recent multi-ancestry meta-analysis identifying novel T2D-associated loci [126]. Increasing diversity should be considered in all omics studies, as metabolic diversity among ancestral groups is poorly understood and can be influenced by genetic and environmental factors, also affecting disease prevalence, incidence, and mortality [127, 128]. In addition to collecting data from diverse populations, emphasis should be placed on acquiring longitudinal data to track disease-related changes over time.

A major challenge in current GWAS is the lack of interpretability for disease-associated variants, especially in non-coding regions of the genome. Molecular quantitative trait loci (QTL), which describe genetic regulation of molecular traits, can help interpret these signals [129], especially in T2D complications relevant bio-sample/tissues like the vitreous humor and tears in DR or kidney tubules and glomeruli in DKD [130]. Following the identification of molecular QTLs, methods like colocalization and Mendelian randomization analyses can be utilized to understand how molecular traits influence T2D progression to complications [129, 131].

T2D complications often co-occur, independent of known risk factors, indicating shared genetic architecture [132]. DKD biomarkers like macroalbuminuria are associated with increased DR severity [133]. Renal disease with proliferative DR better predicts DKD than DR alone [134], and individuals with T2Dand DN have a higher risk of DR and DKD [135]. Low eGFR and high albuminuria in DKD are independent cardiovascular risk factors in Europeans with T2D [136, 137]. Future studies should aim to identify the biological processes that are upstream of complication development and are shared among different complication groups.

In conclusion, this review summarizes the current research on T2D complications and highlights molecular features across various omics levels. Future studies should expand in sample size and diversity and pursue multi-omics data integration from relevant tissues for a deeper biological understanding. These efforts will likely accelerate drug discovery and improve the prediction of T2D complications, which are increasing in prevalence.

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