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REVIEW

The metabolic effects of APOL1 in humans

María M. Adeva-Andany[1] · Raquel Funcasta-Calderón[1] · Carlos Fernández-Fernández[1] · Eva Ameneiros-Rodríguez[1] · Matilde Vila-Altesor[1] · Elvira Castro-Quintela[1]

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Abstract

Harboring apolipoprotein L1 (APOL1) variants coded by the G1 or G2 alleles of the *APOL1* gene increases the risk for collapsing glomerulopathy, focal segmental glomerulosclerosis, albuminuria, chronic kidney disease, and accelerated kidney function decline towards end-stage kidney disease. However, most subjects carrying APOL1 variants do not develop the kidney phenotype unless a second clinical condition adds to the genotype, indicating that modifying factors modulate the genotype–phenotype correlation. Subjects with an APOL1 high-risk genotype are more likely to develop essential hypertension or obesity, suggesting that carriers of APOL1 risk variants experience more pronounced insulin resistance compared to noncarriers. Likewise, arterionephrosclerosis (the pathological correlate of hypertension-associated nephropathy) and glomerulomegaly take place among carriers of APOL1 risk variants, and these pathological changes are also present in conditions associated with insulin resistance, such as essential hypertension, aging, and diabetes. Insulin resistance may contribute to the clinical features associated with the APOL1 high-risk genotype. Unlike carriers of wild-type APOL1, bearers of APOL1 variants show impaired formation of lipid droplets, which may contribute to inducing insulin resistance. Nascent lipid droplets normally detach from the endoplasmic reticulum into the cytoplasm, although the proteins that enable this process remain to be fully defined. Wild-type APOL1 is located in the lipid droplet, whereas mutated APOL1 remains sited at the endoplasmic reticulum, suggesting that normal APOL1 may participate in lipid droplet biogenesis. The defective formation of lipid droplets is associated with insulin resistance, which in turn may modulate the clinical phenotype present in carriers of APOL1 risk variants.

Keywords Focal segmental glomerulosclerosis, Collapsing glomerulopathy, Kidney disease, Vascular disease, albuminuria · Interferon · HIV1 infection · COVID-19 · Autophagy

Abbreviations

AA-DHS	African American Diabetes Heart Study
AASK	African American Study of Kidney Disease and Hypertension
APOL1	Apolipoprotein L-1
ARIC	Atherosclerosis Risk in Communities study
BMI	Body mass index
CARDIA	Coronary Artery Risk Development in Young Adults
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease-epidemiology collaboration
CHS	Cardiovascular Health Study
COVAN	Coronavirus-associated nephropathy
COVID-19	Coronavirus 2019 disease
CRIC	Chronic Renal Insufficiency Cohort
CVD	Cardiovascular disease
ESKD	End-stage kidney disease
eIF2α	α Subunit of the eukaryotic initiation factor-2
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HEK	Human embryonic kidney
HIV1	Human immunodeficiency virus
HIVAN	Human immunodeficiency virus-associated nephropathy
HOMA-IR	Homeostasis model of assessment-insulin resistance
JHS	Jackson Heart Study
MDRD	Modification of Diet in Renal Disease

✉ María M. Adeva-Andany
madevaa@yahoo.com

[1] Nephrology Division, Internal Medicine Department, Hospital General Juan Cardona, c/ Pardo Bazán s/n, 15406 Ferrol, Spain

MESA	Multi-Ethnic Study of Atherosclerosis
MIND	Memory and Cognition in Decreased Hypertension
MVP	Million Veteran Program
PKR	Protein kinase R
REGARDS	Reasons for Geographic and Racial Differences in Stroke
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SAVI	Stimulator of interferon genes-associated vasculopathy with onset in infancy
SLE	Systemic lupus erythematosus
SPRINT	Systolic Blood Pressure Intervention Trial
STING	Stimulator of interferon genes
T2D	Type 2 diabetes
TORC1	Target of rapamycin complex-1

Introduction

In 1997, human apolipoprotein L was identified as circulating in plasma associated with high-density lipoproteins (HDL) [25]. Subsequent research uncovered several highly homologous apolipoprotein L proteins encoded by genes clustered at the long arm of chromosome 22 (22q12.1–13.1). Among them, human apolipoprotein L1 (APOL1) was first reported in connection with the defense against trypanosomiasis. The G0 allele of the *APOL1* gene encodes wild-type APOL1, a protein that protects the host against infection caused by *Trypanosome brucei* and *Trypanosome evansi* [107]. *Trypanosome brucei* rhodesiense has evolved to inactivate wild-type APOL1. In turn, some African populations affected by endemic trypanosomiasis have developed variants of APOL1 (coded by the G1 and G2 alleles) that block APOL1 inactivation by Trypanosome brucei rhodesiense. Heterozygous carriage of either G1 or G2 variants protects the host against this parasite. Due to positive selection, G1 or G2 alleles virtually only exist in some human African groups and are absent in European or Asian populations [38, 102]. In addition to some *Trypanosome* species, APOL1 alleles G1 and G2 may participate in the defense against other pathogens. In a meta-analysis of four prospective cohorts, including 2066 African Americans with human immunodeficiency virus (HIV1) infection, carriage of two APOL1 variants (G1 or G2) was associated with a reduced risk for opportunistic infections [3]. The beneficial impact of APOL1 variants (G1 or G2) on the immune response to some infections may become a disadvantage among kidney allograft recipients. In a prospective observational cohort, kidney allograft recipients carrying a single copy of either G1 or G2 alleles experienced more acute cellular rejection episodes and worse long-term graft survival compared to G0/G0 recipients, independent of African ancestry [114].

In addition to the effects of APOL1 variants on the immune system, biallelic carriage of these alleles predisposes to kidney disease and cardiovascular disease (CVD). Homozygous or compound heterozygous subjects with two copies of either G1 or G2 alleles (G1/G1, G1/G2, or G2/G2) endure an increased risk for kidney diseases [104], such as hypertension-attributed nephropathy [38], focal segmental glomerulosclerosis (FSGS) [38], and collapsing glomerulopathy associated with viral infections, including HIV-1 [57] and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Fig. 1) [58]. The detrimental effect of APOL1 risk variants on cardiovascular risk has not been universally found and might be partially mediated by kidney disease [41, 47, 49]. In addition to the G1 and G2 alleles present in some African populations, genetic variants of APOL1 that may have a deleterious effect on kidney function have been identified in European population groups. In 1489 kidney transplantation patients and 2559 healthy controls, the prevalence of a 55-base pair APOL1 deletion was higher in the patients compared to the controls [46].

APOL1 expression is widespread in normal human tissues. APOL1 mRNA has been detected predominantly in

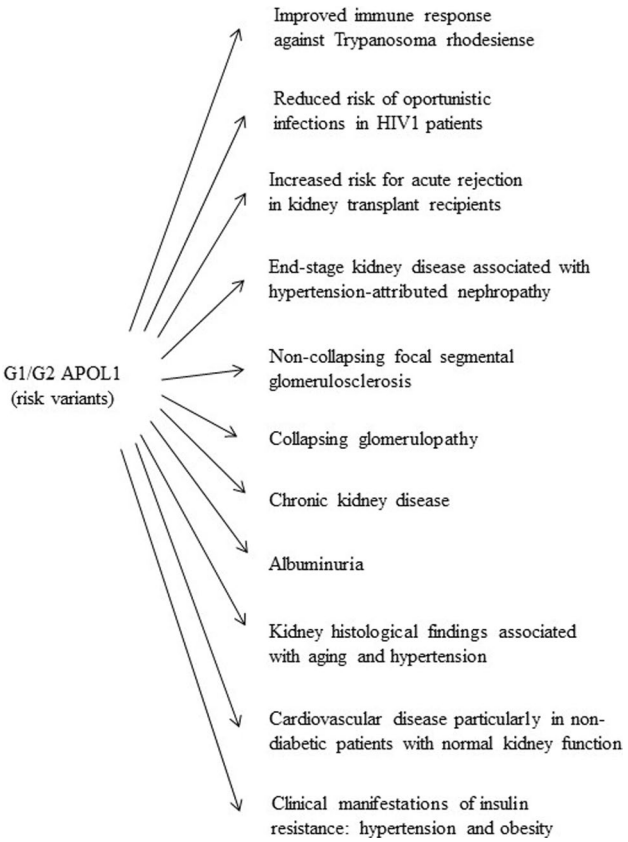

Fig. 1 Clinical associations of APOL1 variants (G1/G2). APOL1 variants associate with enhanced immune response, kidney disorders, and clinical manifestations of insulin resistance

the placenta, lung, liver, spleen, and prostate. Lower expression is identified in the kidney, heart, and pancreas [26, 79, 86]. In human vascular tissue, APOL1 expression has been detected in endothelial cells [68, 69, 79] and vascular smooth muscle cells [68, 69]. In normal human kidneys, APOL1 has been localized to glomerular endothelial cells, podocytes, and tubular cells [68, 69].

Approximately 12–13% of the African population harbors two APOL1 risk alleles, and about 40–47% carry one APOL1 risk variant. Bearing APOL1 variants G1 or G2 increases the risk of some kidney disorders but is not sufficient to cause the clinical phenotype associated with APOL1 risk alleles. Most carriers of APOL1 variants do not develop clinical disease unless an additional condition takes place, such as interferon upregulation due to viral infection or systemic lupus erythematosus (SLE). Therefore, genetic or environmental factors may interact with APOL1 risk alleles to elicit the clinical phenotype [21, 83]. The presence of modifying genes has been investigated in genome-wide association studies [24, 62]. In African American patients with nondiabetic end-stage kidney disease (ESKD), single nucleotide polymorphisms in *NPHS2* (podocin), serologically defined colon cancer antigen 8 (*SDCCAG8*), and near bone morphogenetic protein 4 (*BMP4*) may interact with APOL1 risk alleles to elevate the risk of nondiabetic ESKD [24]. However, no single nucleotide polymorphism showed significant interaction with APOL1 risk variants capable of modifying the rate of ESKD in two African American cohorts that included a total of 2650 ESKD cases and 1656 controls, either in individual genome-wide association studies or in a meta-analysis, suggesting that gene interactions do not contribute substantially to the clinical expression of APOL1 variants [62]. Similarly, nongenetic modifying factors of the relationship between APOL1 and chronic kidney disease (CKD) progression have not been found in a cohort of 693 participants in the African American Study of Kidney Disease and Hypertension (AASK) followed for 7.8 years. Investigated variables included age, gender, smoking status, education, income, obesity, systolic blood pressure, baseline glomerular filtration rate (GFR), total cholesterol, HDL-c, hematocrit, serum uric acid, serum phosphorus, calcium/phosphate product, net endogenous acid production, urinary urea nitrogen, urinary sodium, and potassium excretions, intact parathyroid hormone, 25-hydroxy vitamin D, and fibroblast growth factor 23. None of them modified the association between APOL1 genotype and CKD progression (doubling of serum creatinine or incident ESKD) [11].

Pathogenic mechanisms underlying the development of kidney disease in carriers of the APOL1 high-risk genotype are not fully understood. Carriers of APOL1 risk variants may experience a greater degree of insulin resistance, which in turn may contribute to APOL1-associated kidney disease. The differential intracellular location of wild-type APOL1 (lipid droplet) versus APOL1 risk variants (endoplasmic reticulum) may contribute to clarifying the cause of insulin resistance among individuals harboring APOL1 risk variants.

Lipid droplets are lipid storage organelles derived from the endoplasmic reticulum. Neutral lipids such as triglycerides and cholesterol esters are initially deposited and clustered within the endoplasmic reticulum. A nascent lipid droplet subsequently detaches from the endoplasmic reticulum and enters the cytoplasm. The proteins involved in the separation of the emergent lipid droplet from the endoplasmic reticulum are not fully known. Wild-type APOL1 is located in the lipid droplet, whereas mutated APOL1 remains positioned on the endoplasmic reticulum, suggesting that normal APOL1 may participate in the detachment of the emergent lipid droplet from the endoplasmic reticulum and may thus contribute to the normal formation of the lipid droplet. Accordingly, lipid droplet generation is impaired among carriers of APOL1 risk variants. The defective generation of lipid droplets has been associated with insulin resistance [16]. Observational studies show that carriers of APOL1 risk variants develop more frequently essential hypertension [81] and obesity [82] compared to noncarriers, suggesting that individuals with an APOL1 high-risk genotype may endure more severe insulin resistance. Accordingly, clinical and histopathological manifestations of insulin resistance in the kidney are remarkably similar to the clinical phenotype associated with APOL1 risk variants, namely albuminuria, CKD, faster CKD progression, glomerulomegaly, FSGS, and arterionephrosclerosis [106]. In addition, plasma APOL1 levels are increased in patients with more pronounced insulin resistance compared to those who are more insulin-sensitive [19, 84].

In this review, we summarized information concerning the effect of APOL1 risk variants on clinical diseases and the potential impact of insulin resistance on the clinical phenotype related to APOL1 risk variants.

Association between *APOL1* genotype and kidney disease

Clinical investigations reveal that subjects harboring two copies of the APOL1 risk variants (G1 or G2) experience a higher risk of FSGS, collapsing glomerulopathy, albuminuria, CKD progression, and ESKD compared to carriers of one or zero copies of these APOL1 variants.

Association between APOL1 genotype and focal segmental glomerulosclerosis

Case–control studies indicate that harboring two APOL1 risk variants increases the risk of FSGS compared to the carriage of zero or one of these alleles [38, 57]. Furthermore, APOL1-associated FSGS occurs earlier and progresses to ESKD more rapidly compared to FSGS in patients with no APOL1 risk alleles [57]. Likewise, the prevalence of FSGS in carriers of the APOL1 high-risk genotype (two-risk alleles) with HIV1 infection and non-HIVAN pathology is higher compared to patients with no APOL1 risk variants (76% versus 12%) (Table 1) [30].

Association between APOL1 genotype and collapsing glomerulopathy

In 1986, the first description of collapsing glomerulopathy was reported in six African American patients who presented with nephrotic syndrome and rapid progression to ESKD [109]. Collapsing glomerulopathy develops primarily among patients with African ancestry in the setting of

Table 1 Studies that examined the relationship between apolipoprotein L1 genotype and focal segmental glomerulosclerosis/collapsing glomerulopathy

Reference	Type of study	Number of subjects	Population group	Main result
Association between APOL1 genotype and focal segmental glomerulosclerosis				
Genovese et al. [38]	Case–control	205 FSGS, 180 controls	AA subjects	APOL1 high-risk genotype (2 risk variants) associates with an increased risk of FSGS
Kopp et al. [57]	Case–control	385 FSGS, 383 controls	AA/European American	FSGS occurs earlier and progresses more rapidly to ESKD in carriers of 2 APOL1 risk variants, compared to noncarriers
Association between APOL1 genotype and collapsing glomerulopathy in patients with interferon upregulation				
Markowitz et al. [73] and Nichols et al. [83]	Case series	11 interferon-treated patients, 7 with APOL1 genotype	AA subjects that required interferon therapy	Seven interferon-treated patients with collapsing glomerulopathy carried APOL1 high-risk genotype (100%)
Larsen et al. [64]	Retrospective observational study	26 SLE patients with collapsing glomerulopathy	AA patients with SLE	Carriage of APOL1 risk variants increases the risk of collapsing glomerulopathy in patients with SLE
Abid et al. [1]	Case report	One patient with SAVI	14-month-old AA patient	Case report of a patient with APOL1 high-risk genotype (G1/G2), SAVI, and collapsing glomerulopathy
Association between APOL1 genotype and human immunodeficiency virus-associated nephropathy				
Kopp et al. [57]	Case–control	54 HIVAN patients, 237 controls	AA subjects	APOL1 high-risk genotype (two risk variants) increases the risk for HIVAN compared to APOL1 low-risk genotype
Association between APOL1 genotype and coronavirus-associated nephropathy				
May et al. [75]	Retrospective	107 COVAN patients	AA/Hispanic	APOL1 high-risk genotype is present in 91.7% of patients with COVAN
Kudose et al. [58]	Retrospective	17 COVAN patients	AA/Caucasian	APOL1 high-risk genotype is present in 94% of patients with COVAN
Masset et al. [74]	Case report	Patient with COVAN and active lupus nephritis	AA subjects	Case report of collapsing glomerulopathy in a female patient heterozygous for APOL1 risk variants (G2/G0) with COVID-19 and active lupus nephritis

Abbreviations: *AA*, African American; *APOL1*, apolipoprotein L1; *CKD*, chronic kidney disease; *COVAN*, coronavirus-associated nephropathy; *ESKD*, end-stage kidney disease; *FSGS*, focal segmental glomerulosclerosis; *HIV1*, human immunodeficiency virus; *HIVAN*, HIV1-associated nephropathy; *SAVI*, stimulator of interferon genes-associated vasculopathy with onset in infancy; *SLE*, systemic lupus erythematosus

upregulated interferon secretion or exogenous interferon therapy [83]. Glomerular ischemia may lead to collapsing glomerulopathy in sickle cell disease, thrombotic microangiopathy, and diabetes [94]. On light microscopy, kidney biopsy specimens show a striking loss of patency in glomerular capillary loops. Collapsed capillary loops are wrapped by swollen and hypertrophic podocytes that contain vacuoles and hyaline droplets. The number of epithelial cells within the Bowman's capsule is increased, which may lead to pseudo-crescent formation. Tubulointerstitial damage is prominent and includes tubular dilatation, the formation of tubular microcysts, interstitial edema, and an interstitial inflammatory infiltrate. Immunofluorescence studies are typically negative or show nonspecific glomerular staining for IgM, C3, and C1q in collapsed segments and mesangial areas. Electron microscopy reveals tubuloreticular aggregates (called interferon footprints) in endothelial cells (Table 2) [70, 96, 99, 112].

APOL1 high-risk genotype (biallelic carriage of G1 or G2 variants) associates with an increased risk of collapsing glomerulopathy, particularly in the setting of interferon upregulation. Elevated interferon production occurs in several acquired and inherited clinical conditions, including viral infections (such as HIV1 and SARS-CoV-2), SLE, hemophagocytic syndrome, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), and Aicardi-Goutières syndrome. These conditions and exogenous interferon therapy predispose to collapsing glomerulopathy, particularly in patients harboring two APOL1 risk alleles (Fig. 2) [1, 29, 83].

Pathogenic mechanisms underlying interferon-related collapsing glomerulopathy in patients with APOL1 high-risk genotypes have not been defined, but interferon increases markedly the expression of APOL1 in a variety of human cells, including endothelial cells and podocytes [27].

APOL1 genotype and collapsing glomerulopathy in the setting of exogenous interferon administration

In 2010, a series of eleven patients that developed collapsing glomerulopathy during treatment with interferon-α, interferon-β, or interferon-γ for various disorders (malignant melanoma, hepatitis C virus infection, multiple sclerosis, and idiopathic pulmonary fibrosis) was reported. Ten

Table 2 Histopathological characteristics of collapsing glomerulopathy

• Light microscopy:
- Segmental to global severe glomerular collapse
- Swollen and hypertrophic podocytes that contain intracellular vacuoles
- Increased number of epithelial cells that may lead to glomerular pseudo-crescents
- Marked interstitial inflammation and acute tubular injury
- Tubular dilatation and tubular microcysts formation
- Interstitial fibrosis and tubular atrophy are not remarkable
• Immunofluorescence microscopy: negative or unspecific
• Electron microscopy:
- Retraction and wrinkling of the glomerular basement membrane
- Podocyte foot processes effacement
- Endothelial tubuloreticular aggregates (interferon footprints)
- No electron-dense deposits are identified
• Viral particles:
- In patients with HIV1, viral particles are identified in glomerular epithelial cells and tubular cells
- No direct kidney infection has been demonstrated so far in patients with SARS-CoV-2 infection

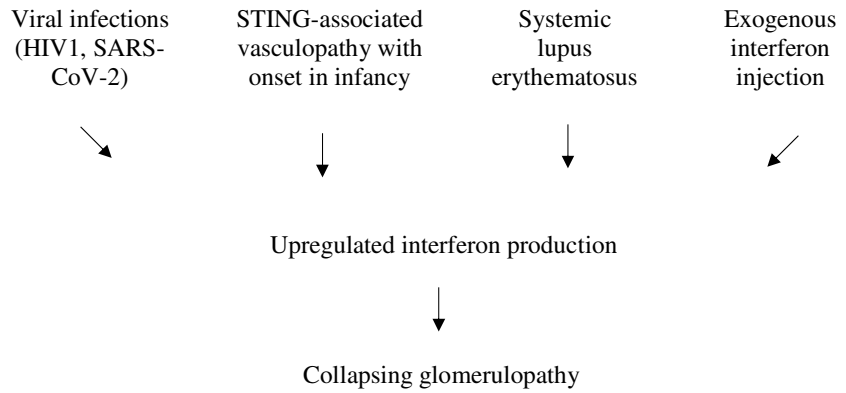

Fig. 2 Patients with APOL1 high-risk genotype may develop collapsing glomerulopathy during exogenous interferon administration or endogenous interferon upregulation

of the eleven patients were African Americans. All of them presented with proteinuria and kidney function decline. A kidney biopsy revealed typical features of collapsing glomerulopathy. In addition, arteriosclerosis and arteriolosclerosis with hyalinosis were identified in most biopsies [73]. In 2015, the APOL1 genotype was analyzed in archival renal biopsy tissue from eleven patients. Seven yielded adequate samples and were genotyped. All of them carried the APOL1 high-risk genotype, suggesting that this genetic background may facilitate the development of interferon-associated collapsing glomerulopathy [83].

APOL1 genotype and collapsing glomerulopathy in the setting of viral infections

Collapsing glomerulopathy has been consistently reported in association with HIV-1 and SARS-CoV-2 infections, particularly in African American patients carrying APOL1 high-risk genotype.

APOL1 genotype and collapsing glomerulopathy in the setting of HIV1 infection Kidney disease in the setting of HIV-1 infection is predominantly related either to active, untreated viral infection or to insulin resistance associated with sustained interferon secretion and/or antiretroviral therapy. The respective histological pictures are collapsing glomerulopathy (HIV1-associated nephropathy (HIVAN)) and kidney manifestations of insulin resistance such as FSGS (in the setting of insulin resistance-related glomerular hyperfiltration), diabetic kidney disease, or hypertension-attributed nephropathy (arterionephrosclerosis). An association between the carriage of APOL1 risk variants and worse renal outcomes in HIV-1 patients has been documented [7, 8, 30, 89, 111, 113].

Collapsing glomerulopathy was commonly identified among African American patients with untreated active HIV-1 infection and was termed HIVAN. The extensive use of anti-retroviral therapy dramatically reduced HIVAN frequency. In kidney biopsies from patients with HIVAN, HIV1 DNA and mRNA have been identified within podocytes, glomerular parietal epithelial cells, and tubular epithelial cells, suggesting that the kidney epithelium constitutes a target for HIV-1 infection. In addition, circularized viral DNA has been detected, denoting active replication of the virus in renal epithelia [8].

An indirect indication that APOL1 variants G1 or G2 were a risk factor for HIVAN was first provided by the simultaneous absence of HIVAN and these APOL1 variants in Ethiopian patients with HIV1 infection. In HIV-1-infected patients of Ethiopian descent, the susceptibility to HIVAN is similar to that of White subjects, which is strikingly less than that reported for other African populations harboring APOL1 risk variants [104]. In a subsequent case–control study, carriage of two APOL1 risk alleles was associated with a greater risk of developing HIVAN compared to patients with HIV-1 infection homozygous for the G0 allele [57].

APOL1 genotype and collapsing glomerulopathy in the setting of SARS-CoV-2 infection (coronavirus disease 2019) Patients with SARS-CoV-2 infection, the cause of coronavirus disease 2019 (COVID-19), have a number of risk factors for developing kidney disease, including viral infection, cytokine outbursts, kidney hemodynamic changes, and nephrotoxic medications. Patients with COVID-19 may develop collapsing glomerulopathy, which has been named coronavirus-19-associated nephropathy (COVAN). Like HIVAN, COVAN targets predominantly African Americans and has been attributed to active viral infection and/or cytokine response to SARS-CoV-2, with enhanced secretion of type I interferon among other cytokines. COVAN's clinical features are usually acute kidney injury and proteinuria. The histological pattern corresponds to collapsing glomerulopathy with endothelial tubuloreticular aggregates (interferon footprints) [63, 88]. Unlike HIVAN, SARS-CoV-2 viral particles or viral RNA have not been conclusively identified in the glomerular or tubular cells of patients with COVAN [9, 76]. Retrospective clinicopathological investigations, case reports, and a small series of patients with COVAN indicate that biallelic carriage of APOL1 variants G1 or G2 is a risk factor for developing the disease. Most patients (91%) with COVAN are African Americans and carry an APOL1 high-risk genotype (91.7–94%), suggesting that mutated APOL1 predisposes to COVAN [37, 55, 58, 63, 70, 75, 88, 96, 112]. Collapsing glomerulopathy has been described in an APOL1 heterozygous (G2/G0) female patient of African ancestry with active lupus nephritis and COVID-19, suggesting that carrying one APOL1 risk allele may predispose to COVAN when other causative factors are present, such as SLE-associated interferon upregulation [74].

APOL1 genotype and collapsing glomerulopathy in the setting of other conditions that feature excessive interferon production (such as systemic lupus erythematosus, macrophage activation syndrome, and congenital disorders)

Patients with SLE experience persistent interferon secretion [22, 42] and an increased expression of genes regulated by interferon (interferon signature) that may participate in the pathogenesis of the disease [72, 90]. The APOL1 high-risk genotype increases the susceptibility to collapsing glomerulopathy in the setting of SLE. In a retrospective study that identified 26 cases of collapsing glomerulopathy among 546 renal biopsies from African Americans with SLE, carriage of one or two APOL1 risk variants conferred higher odds of developing SLE-associated collapsing glomerulopathy [64].

Collapsing glomerulopathy is also the most frequent histological pattern observed in African American patients with kidney disease in the setting of the hemophagocytic syndrome (macrophage activation syndrome or hemophagocytic lymphohistiocytosis). This disease is characterized by the infiltration of the bone marrow and other organs by activated macrophages that secrete massive amounts of interferon and other cytokines. APOL1 has not been genotyped in African American patients with this disease so far [103].

SAVI is a congenital disorder due to gain-of-function mutations in the gene *TMEM173*, which encodes STING. Patients with SAVI endure constitutive activation of STING that leads to endogenous, unregulated overproduction of type I interferon. The disease is clinically characterized by severe cutaneous vasculopathy and interstitial lung disease that start during infancy [66]. Collapsing glomerulopathy has been reported in an African American patient with SAVI at the age of 14 months. APOL1 genotyping demonstrated compound heterozygosity for the G1 and G2 variants [1].

Collapsing glomerulopathy has also been reported in a 15-year-old female with Aicardi-Goutières syndrome, a monogenic type 1 interferonopathy that usually presents with neurologic manifestations. The patient did not carry the APOL1 G1 and G2 alleles [29].

Relationship between APOL1 genotype and albuminuria

The APOL1 high-risk genotype is very consistently associated with albuminuria in cross-sectional and longitudinal investigations, independent of confounding. A cross-sectional association between carriage of two APOL1 risk variants (recessive inheritance) and urinary albumin excretion has been identified in several trials, including the Dallas Heart Study [36], the Atherosclerosis Risk in Communities (ARIC) study [31], the Systolic Blood Pressure Intervention Trial (SPRINT) [35, 61], the SPRINT-Memory and Cognition in Decreased Hypertension (MIND) [34], the AASK [12], the African American Diabetes Heart Study (AA-DHS) [33], the Coronary Artery Risk Development in Young Adults (CARDIA) study [44], and the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study [43]. Carriers of the APOL1 high-risk genotype are more likely to have both albuminuria and higher urinary albumin excretion rates compared to individuals with the APOL1 low-risk genotype (one or zero risk variants). Similarly, among 90 African Americans with proteinuria ≥ 0.5 g/day in the Nephrotic Syndrome Study Network (NEPTUNE), patients with the APOL1 high-risk genotype (two-risk alleles) show a 52% increase in the level of proteinuria (urine protein-to-creatinine ratio) compared to patients with the low-risk genotype. In addition, the APOL1 high-risk genotype is associated with a 69% reduction in the probability of complete remission of the primary glomerulopathy, independent of the histopathologic diagnosis (predominantly minimal change disease, FSGS, and membranous nephropathy) [95]. Likewise, a cross-sectional association between the APOL1 high-risk genotype and proteinuria has been observed at baseline in a prospective cohort study that recruited 100 Ghanaian patients with SLE [5]. A strong and independent longitudinal association of APOL1 risk genotype and albuminuria has been documented in the CHS. African Americans with APOL1 high-risk genotype (two allelic variants) had two-fold higher levels of urinary albumin excretion rate compared to subjects with a low-risk genotype over a follow-up period of 13 years [80].

Association between APOL1 genotype and kidney function impairment

The APOL1 high-risk genotype is associated with ESKD, CKD (estimated GFR of < 60 ml/min/1.73 m^2) and faster progression of CKD to ESKD, in a variety of population groups, including patients with diabetes.

Observational investigations reveal an independent association between the APOL1 high-risk genotype and ESKD in different population groups (Table 3) [31, 38, 87, 104]. The first correlation between the APOL1 genotype and kidney disease was documented in a case–control study that compared the APOL1 genotype in 1,030 African Americans with ESKD attributed to hypertension and 1,025 control subjects. The presence of two APOL1 risk alleles (recessive model) versus zero risk alleles associated with a marked increase in the rate of hypertension-attributed ESKD suggests that the APOL1 high-risk genotype contributes to elevating the risk for ESKD [38]. An association between APOL1 high-risk genotype and incident ESKD, regardless of diabetes status, has been observed in prospective cohorts that recruited a variety of population groups, including patients with diabetes, such as the ARIC study, the AASK, and the Chronic Renal Insufficiency Cohort (CRIC). African Americans with the APOL1 high-risk genotype experience a higher risk of incident ESKD independently of other factors compared with patients with zero/one risk alleles [31, 40, 87]. Accordingly, cross-sectional analyses show that carriage of the APOL1 high-risk genotype (two allelic variants) is associated with an earlier age at dialysis initiation compared to patients with one to zero APOL1 risk variants after adjustment for confounding [49, 52]. The higher risk of ESKD associated with the APOL1 high-risk genotype has been documented in patients with HIV1 infection or SLE as well [5, 6, 30, 32].

Likewise, a consistent association between the APOL1 high-risk genotype and CKD and accelerated kidney function decline towards ESKD has been documented in several population groups by most observational studies. A few

Table 3 Studies that investigated the relationship between apolipoprotein L1 genotype and end-stage kidney disease

Reference	Type of study	Number/follow-up	Population group	Main result
Genovese et al. [38]	Case–control	2055 (patients and controls)	AA subjects	APOL1 high-risk genotype (2 risk alleles) associates with a marked increase in the rate of hypertension-attributed ESKD
Tzur et al. [104]	Case–control	109 whole genome sequences	African/European ancestry	APOL1 high-risk genotype is strongly associated with ESKD
Foster et al. [31]	Prospective cohort (ARIC)	3067/19.7 years	AAs from the general population	APOL1 high-risk genotype (2 risk alleles) increases the risk for incident ESKD in subjects from the general population
Grams et al. [40]	Prospective cohort (ARIC)	3067/22.6 years	AAs from the general population	The association between APOL1 high-risk genotype (two risk alleles) and incident ESKD in the ARIC persist with longer follow-up
Parsa et al. [87]	Prospective cohort (AASK)	693/9 years	AA subjects	APOL1 high-risk genotype associates with increased risk for incident ESKD in nondiabetic patients with hypertension-attributed CKD
Parsa et al. [87]	Prospective cohort (CRIC)	2955/4.4 years	Caucasian and AAs patients with CKD	The association between APOL1 high-risk genotype and incident ESKD is independent of diabetes status
Ito et al. [49]	Community-based cohort (JHS)	1959	AAs from the general population	APOL1 high-risk genotype associated with earlier age at dialysis initiation
Kanji et al. [52]	Cross-sectional	407	Nondiabetic AAs with ESKD	Patients with the APOL1 high-risk genotype (2 copies of the G1 risk allele) initiate chronic hemodialysis at a younger age
Relationship between APOL1 genotype and ESKD in patients with SLE and HIV1 infection				
Freedman et al. [32]	Case–control	1389 (cases and controls)	AAs with SLE	APOL1 risk variants strongly impact the risk of SLE-associated ESKD
Blazer et al. [6]	Retrospective cohort	113/1.5 years	As patients with SLE	Patients with APOL1 high-risk genotype and SLE-associated nephropathy have an increased risk for incident ESKD
Blazer et al. [5]	Prospective cohort	100/12 months	Ghanaians with SLE	APOL1 high-risk genotype (two risk variants) increases the risk for ESKD in patients with SLE
Fine et al. [30]	Prospective cohort	98/310 person-years	HIV1 AAs with non-HIVAN pathology	APOL1 high-risk genotype (two risk alleles) increases the risk for incident ESKD in patients with HIV1 infection and non-HIVAN pathology on kidney biopsy

Abbreviations: *AA*, African American; *AASK*, African American Study of Kidney Disease and Hypertension; *APOL1*, apolipoprotein L1; *ARIC*, Atherosclerosis Risk in Communities study; *CRIC*, Chronic Renal Insufficiency Cohort; *CKD*, chronic kidney disease; *ESKD*, end-stage kidney disease; *HIV1*, human immunodeficiency virus; *HIVAN*, HIV1-associated nephropathy; *JHS*, Jackson Heart Study; *SLE*, systemic lupus erythematosus

trials failed to find evidence of such a relationship, particularly in patients with diabetes [23, 35, 80]. The reason for the discrepancy is unclear, but the assessment of kidney function is usually performed with formulas to estimate GFR that may differ among the studies. In patients with diabetes, serum creatinine-based formulas, such as the Modification of Diet in Renal Disease (MDRD), may underestimate the rate of CKD, as insulin resistance-associated sarcopenia in these patients lowers serum creatinine levels and tends to spuriously elevate the serum creatinine-based GFR estimate.

Cross-sectional analyses from the Dallas Heart Study, the Jackson Heart Study (JHS), the SPRINT, the SPRINT-MIND, the Million Veteran Program (MVP), the AASK, and the AA-DHS-MIND reveal a consistent association of the APOL1 high-risk genotype (carriage of two risk alleles) and prevalence of CKD (estimated GFR < 60 ml/min/1.73 m^2) in comparison with APOL1 low-risk (harboring less than two risk variants) in diverse population groups, such as the general population, patients with hypertension, and patients with diabetes (Table 4) [4, 12, 34, 36, 49, 61]. In the JHS, the robust relationship between APOL1 risk variants and CKD remained after adjusting for diabetes status [49]. Furthermore, APOL1 risk variants predicted a greater rate of kidney function decline in patients with CKD attributed to essential hypertension across blood pressure targets [65]. Similarly, among African Americans with proteinuria ≥ 0.5 g/day, the APOL1 high-risk genotype (two risk alleles) is associated with a lower estimated GFR [95]. A cross-sectional association between the APOL1 high-risk genotype and accelerated progression of kidney failure [32] and lower estimated GFR [5] has also been reported in patients with SLE.

Longitudinal studies such as the ARIC, the MVP, the AASK, and the CRIC reveal that carriage of two APOL1 risk variants is an independent risk factor for the development of incident CKD and faster kidney function decline, compared to an APOL1 low-risk genotype (one or zero risk alleles) in a variety of population groups, including patients with diabetes (Table 5) [4, 31, 40, 87].

The ARIC study followed 3067 African Americans from the general population free of CKD for a median observation period of 10.2 years. Carrying two APOL1 risk alleles was independently associated with an increased risk of incident CKD and faster progression to ESKD after accounting for confounding variables. In addition, the detrimental effect of the APOL1 high-risk genotype on kidney function was comparable among patients with and without diabetes [31]. The relationship between the APOL1 high-risk genotype and CKD in African Americans from the general population was confirmed with a longer follow-up period (22.6 years), although the rate of kidney function decline was variable [40].

In the MVP, a retrospective cohort study from the Veteran Affairs Health Care System, the APOL1 high-risk genotype was strongly associated with incident renal disease among 30,903 African Americans with normal kidney function at baseline over a mean follow-up period of 12.5 years [4]. Similar results were obtained in two multicenter prospective cohorts, the AASK (nondiabetic patients with hypertension-attributed CKD) and the CRIC (patients with CKD, 45.5% with diabetes). Patients with the APOL1 high-risk genotype had a higher risk of renal outcomes over the follow-up period (9 years in the AASK and 4.4 years in the CRIC). Regardless of diabetes status, African Americans with two high-risk variants in the APOL1 gene experience an increased risk for CKD progression, even those with well-controlled blood pressure [87].

A meta-analysis of ten cohort studies confirms the prospective association between the APOL1 high-risk genotype and the incidence and progression of CKD. Accordingly, kidney function decline was steeper in patients with an APOL1 high-risk genotype compared to low-risk patients, although the decrement in estimated GFR was variable between trials [50].

Comparable findings have been observed in patients with SLE or HIV-1 infection. Longitudinal trials in patients with SLE show that APOL1's high-risk genotype is associated with accelerated kidney function decline compared to patients with one or no risk variants [5, 6]. Likewise, a longitudinal study shows that HIV-1 patients with two APOL1 risk variants have a faster decline in kidney function compared with those with low-risk genotypes [30].

Kidney pathological phenotype associated with APOL1 high-risk genotype

The carriage of the APOL1 high-risk genotype is associated with a pathological phenotype in the kidney. Autopsy findings reveal that carriers of APOL1 risk variants exhibit more severe pathologic changes associated with aging and hypertension, such as arterionephrosclerosis, glomerulomegaly, and nephron loss, compared to bearers of the low-risk genotype [45, 47]. In an autopsy study that collected kidney tissue from 159 African Americans and 135 Caucasians without kidney disease, arterionephrosclerosis was absent or very mild before age 35 for both races. After 35 years of age, glomerulosclerosis and arteriosclerosis were independently related to aging and hypertension. In addition, APOL1's high-risk genotype (two risk variants) magnified these lesions [47]. Accordingly, histopathologic examination of kidney specimens obtained at autopsy revealed a higher percentage of sclerotic glomeruli in African American subjects carrying two APOL1 risk alleles compared with African American individuals harboring a low-risk genotype [18]. Among African Americans with proteinuria, APOL1 high-risk genotype (two-risk alleles) is associated with more

Table 4 Cross-sectional studies that examined the association between apolipoprotein L1 genetic variation and chronic kidney disease

Reference	Type of study	Number of subjects	Population group	Main result
Friedman et al. [36]	Population-based cohort (Dallas Heart Study)	2867	General population, > 50% AAs	APOL1 high-risk genotype (2 risk alleles) increases the risk for MDRD-estimated GFR < 60 ml/min/1.73 m^2 in nondiabetic patients
Ito et al. [49]	Population-based cohort (JHS)	1959	General population, AAs	APOL1 high-risk genotype (2 risk alleles) increases the rate of CKD regardless of diabetes status
Langefeld et al. [61]	Randomized clinical trial (SPRINT)	2571	Nondiabetic AAs with hypertension	APOL1 high-risk genotype is associated with prevalent CKD (estimated GFR < 60 ml/min/1.73 m^2, calculated with the CKD-EPI equation)
Chen et al. [12, 10]	Prospective cohort (AASK)	693	AAs with hypertension and CKD	Carriers of 2 APOL1 risk variants and hypertension-attributed CKD have lower mean GFR (measured by iothalamate clearance)
Bick et al. [4]	Retrospective cohort (MVP)	30,903	AAs	APOL1 high-risk genotype associates with a higher prevalence of CKD (estimated GFR < 60 ml/min/1.73 m^2) at baseline
Lipkowitz et al. [65]	Case–control (data from the AASK)	675 cases and 618 controls	AAs with hypertension and CKD	APOL1 high-risk genotype (2 risk variants) is strongly associated with CKD in nondiabetic AASK participants compared to controls
Freedman et al. [34]	Cross-sectional (AA-DHS-MIND)	483	AAs with diabetes	APOL1 high-risk genotype (2 risk variants) associates with kidney disease in patients with diabetes
Freedman et al. [34]	Randomized clinical trial (SPRINT-MIND)	2568	Nondiabetic AAs with hypertension	APOL1 high-risk genotype (2 risk alleles) associates with lower estimated GFR, calculated with the 4-variable MDRD equation
Sampson et al. [95]	Nephrotic Syndrome Study Network	90	AAs with proteinuria ≥ 0.5 g/day	APOL1 high-risk genotype (2 risk alleles) associates with a 17 ml/min/1.73 m^2 lower estimated GFR
Cross-sectional association between APOL1 high-risk genotype and CKD in patients with SLE				
Freedman et al. [32]	Case–control	1389	AAs with SLE	Patients with APOL1 high-risk genotype and SLE endure ESKD 2 years earlier
Blazer et al. [5]	Prospective cohort	100	Ghanaians with SLE	Patients with APOL1 high-risk genotype and SLE show lower estimated GFR at baseline

Abbreviations: *AA*, African American; *AA-DHS-MIND*, African American Diabetes Heart Study-Memory and Cognition in Decreased Hypertension; *AASK*, African American Study of Kidney disease and Hypertension; *APOL1*, apolipoprotein L1; *CKD*, chronic kidney disease; *CRIC*, Chronic Renal Insufficiency Cohort; *EPI*, epidemiology collaboration; *JHS*, Jackson Heart Study; *GFR*, glomerular filtration rate; *MVP*, Million Veteran Program; *SLE*, systemic lupus erythematosus; *SPRINT*, Systolic Blood Pressure Intervention Trial

Table 5 Longitudinal trials that investigated the association of apolipoprotein L1 genetic variation, chronic kidney disease, and progression of chronic kidney disease

Reference	Type of study	Number/follow-up	Population group	Main result
Foster et al. [31]	Prospective population-based cohort (ARIC)	3067/12.2 years	AAs from the general population	APOL1 high-risk genotype (2 risk alleles) increases the risk for CKD and for faster progression to ESKD, regardless of diabetes status, in subjects from the general population
Grams et al. [40]	Prospective population-based cohort (ARIC)	15,140/22.6 years	AAs from the general population	African American subjects with and without APOL1 high-risk genotype demonstrate variable rates of kidney function decline
Bick et al. [4]	Retrospective cohort (MVP)	30,903/12.5 years	AAs from the Veteran Affairs Health Care System	APOL1 high-risk genotype is strongly associated with incident renal disease (estimated GFR < 60 ml/min/1.73 m^2, renal replacement therapy, or a kidney transplant)
Parsa et al. [87]	Prospective cohort (AASK)	693/9 years	Nondiabetic AAs with hypertension and CKD	APOL1 high-risk genotype (2 risk alleles) increases the risk of rapid CKD progression to ESKD, even in patients with well-controlled blood pressure, regardless of diabetes status
Parsa et al. [87]	Prospective cohort (CRIC)	2955/4.4 years	Caucasians and AAs with CKD, 45% diabetes	APOL1 high-risk genotype is strongly associated with faster progression of CKD to ESKD among patients with diabetes
Jagannathan et al. [50]	Systematic review and meta-analysis	53,976/10 years	Subjects from 10 prospective cohort studies	APOL1 high-risk genotype associates with increased incidence of CKD and faster loss of kidney function in a meta-analysis of 10 cohorts
Longitudinal association between APOL1 genotype and CKD in patients with SLE or HIV1 infection				
Blazer et al. [6]	Retrospective cohort	113/1.5 years	AAs patients with SLE	APOL1 high-risk genotype associates with accelerated progression of kidney failure to ESKD in patients with SLE
Blazer et al. [5]	Prospective cohort	100/12 months	Ghanaian patients with SLE	APOL1 high-risk genotype (2 risk alleles) confers increased risk for progressive kidney disease in patients with SLE
Fine et al. [30]	Prospective cohort	98/310 person-years	HIV1 AAs with non-HIVAN pathology on kidney biopsy	APOL1 high-risk genotype (2 risk variants) is associated with a higher risk for progression to ESKD, faster decline of kidney function, and incident ESKD in HIV1 patients with non-HIVAN

Abbreviations: *AA*, African American; *AA-DHS-MIND*, African American Diabetes Heart Study-Memory and Cognition in Decreased Hypertension; *AASK*, African American Study of Kidney disease and Hypertension; *APOL1*, apolipoprotein L1; *ARIC*, Atherosclerosis in Communities study; *CKD*, chronic kidney disease; *CRIC*, Chronic Renal Insufficiency Cohort; *ESKD*, end-stage kidney disease; *HIV1*, human immunodeficiency virus; *HIVAN*, HIV1-associated nephropathy; *JHS*, Jackson Heart Study; *MVP*, Million Veteran Program; *SLE*, systemic lupus erythematosus; *SPRINT*, Systolic Blood Pressure Intervention Trial

severe interstitial fibrosis and tubular atrophy on kidney biopsy samples compared to the low-risk genotype [95].

In vitro effects of wild-type and mutated APOL1 in the kidney

The function of wild-type APOL1 and the consequences of its mutation in the human kidney are largely unknown (Table 6). Kidney organoids derived from human induced pluripotent stem cells [67] and human podocyte cell models that replicate in vitro the function of mutated APOL1 [27] have been developed to investigate the mechanisms underlying APOL1-related kidney disease and assess potential therapies. In human podocyte cell lines, APOL1 overexpression leads to podocyte detachment. This effect is genotype-independent, such that the proportion of detached podocytes increases to the same degree in either G2/G2 or G0/G0 podocytes following APOL1 upregulation [27]. Wild-type APOL1 contributes to stabilizing adherens junctions by binding to CD2AP, a constituent of these cellular linkage sites. Consequently, silencing of wild-type APOL1 causes instability of adherens junctions and thinning of the actin cytoskeleton in human podocyte cell lines. In contrast, G1 or G2 APOL1 proteins fail to bind to CD2AP, and podocytes expressing G1 or G2 APOL1 proteins show disrupted adherens junctions and an attenuated actin cytoskeleton, similar to the silencing of G0 APOL1 protein (Fig. 3) [60]. Likewise, the expression of a mutated APOL1 reduces cellular adherence and actin filaments in podocyte cell lines

Table 6 Effects of apolipoprotein L1 (APOL1) on human podocyte cell lines

Effects of APOL1 on human podocytes	Wild type (G0) APOL1	Mutated (G1 or G2) APOL1
Binding to CD2AP, a protein associated with adherens junctions	G0 APOL1 binds to CD2AP	Mutated APOL1 does not bind to CD2AP
CD2AP level in podocyte cell lines	Normal	Adaptive CD2AP upregulation
Adherens junctions	Normal, stable, and solid adherens junctions	Abnormal, unstable, and loose adherens junctions
Effect of overexpression of APOL1 on podocyte adhesion sites	G0 APOL1 overexpression does not reduce podocyte adhesion sites	G2 APOL1 overexpression reduces podocyte adhesion sites
Effect of overexpression of APOL1 on podocyte detachment and loss	G0 APOL1 overexpression induces podocyte detachment and loss	G2 APOL1 overexpression induces podocyte detachment and loss
Interaction with the actin cytoskeleton	G0 APOL1 interacts with the actin cytoskeleton	Interaction with the actin cytoskeleton is impaired for mutated APOL1 proteins
Actin cytoskeleton	G0 APOL1 podocytes show normal actin cytoskeleton	Mutated APOL1 podocytes show disorganized and attenuated actin filaments
Expression of nephrin and podocin	G0 podocyte cell lines show normal expression of nephrin and podocin	Mutated APOL1 podocytes show reduced expression of nephrin and podocin

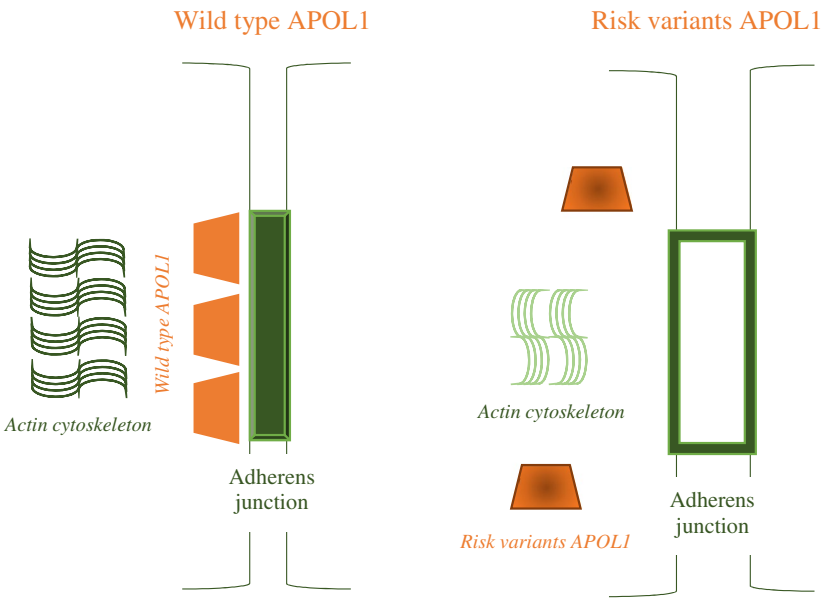

Fig. 3 Effect of APOL1 on cellular junctions and the actin cytoskeleton. Wild-type APOL1 contributes to maintaining the normality of adherens junctions and the actin cytoskeleton, while risk variants of APOL1 associate with loose adherens junctions and reduced actin cytoskeleton

established from G1/G2, G1/G1, or G2/G2 patients suffering from FSGS or HIVAN [105]. Accordingly, human G2/G2 podocytes exhibit adaptive upregulation of CD2AP and attenuation of the actin cytoskeleton, compared with G0/G0 podocytes. After APOL1 overexpression, G2/G2 podocytes exhibit fewer adhesion sites compared to G0/G0 podocyte cell lines [27]. Overexpression of either G1 or G2 APOL1 protein reduces the expression of nephrin and podocin in human podocyte cell lines whereas no change in these proteins follows overexpression of wild-type APOL1 (G0) [110].

Association between APOL1 genotype and cardiovascular disease

The carriage of two APOL1 risk variants has been associated with increased risk for clinical events and pathological features of vascular disease compared with the APOL1 low-risk genotype. However, this association has not been universally observed, and it could be partly mediated by the strong relationship between the APOL1 high-risk genotype and impaired kidney function/albuminuria in some population groups.

A cross-sectional association between the APOL1 high-risk genotype and prevalent CVD has been observed in participants of the JHS (a population-based trial that recruited subjects from the general population) and the Women´s Health Initiative study (a randomized controlled trial that followed 161,808 postmenopausal healthy women to analyze the effect of postmenopausal hormone therapy). Subjects with two copies of APOL1 risk alleles had an increased risk for CVD independent of traditional CVD risk factors. Participants in the Women's Health Initiative study had normal kidney function, suggesting that the increased cardiovascular risk associated with the APOL1 high-risk genotype is not mediated by kidney disease in this population [49]. Likewise, a cross-sectional association between the carriage of one or more APOL1 risk variants and prevalent atherosclerotic CVD has been observed in patients with SLE after adjustment for risk factors including ESKD [6]. However, no cross-sectional association between APOL1 genetic variation and prevalent CVD has been identified in other studies or a meta-analysis that included eight cohorts [41].

A longitudinal association between the APOL1 high-risk genotype and incident CVD has been identified in the CHS, the REGARDS study, and the MVP trial, particularly among nondiabetic subjects and individuals with normal kidney function [4, 43, 80].

The CHS recruited older subjects (≥ 65 years) from the general population and found an association between the APOL1 high-risk genotype (two risk variants) and incident myocardial infarction after adjustment for kidney function (GFR estimation based on serum cystatin C) [80]. The REGARDS study enrolled subjects from the general population and found no difference in the risk of incident CVD (stroke or coronary heart disease) related to the APOL1 genotype in the whole study population. However, the APOL1 high-risk genotype (two risk variants) was independently associated with incident CVD in nondiabetic subjects and participants with normal kidney function. In nondiabetic individuals, this association is driven by ischemic stroke events, particularly those related to small vessel disease [43]. Likewise, the MVP study found a retrospective association of the APOL1 high-risk genotype with incident CVD in subjects with normal kidney function compared to those with no risk alleles [4]. Conversely, the Multi-Ethnic Study of Atherosclerosis (MESA), the SPRINT, and the AASK find no longitudinal association between APOL1 genotype and incident CVD among African Americans from the general population (MESA), nondiabetic patients with hypertension (SPRINT), and patients with CKD attributed to hypertension (AASK). The small number of events in some studies may have limited the power to detect an association between the APOL1 risk variants and CVD [10, 12, 35]. In a meta-analysis that included 21,305 African Americans from eight cohorts, individuals carrying two APOL1 risk variants had a similar risk of incident CVD compared to subjects with zero or one risk allele over a mean follow-up of 8.9 years in fully adjusted analyses that accounted for kidney function [41].

Investigations that examine the influence of the APOL1 genotype on arterial calcification have yielded inconsistent results [10, 13, 33, 44, 49]. In the JHS, APOL1 high-risk status is associated with reduced coronary artery calcification in African Americans compared to the general population. Subjects with two APOL1 risk variants have lower coronary artery calcification, which has been associated with an increased risk of plaque instability and clinical coronary events [49]. In the AA-DHS, the effect of the APOL1 genotype on arterial calcification varies according to the localization of the artery. While harboring one APOL1 high-risk variant (dominant model) is associated with lower carotid calcification, this APOL1 genotype has no effect on aortic calcification and only a marginal effect on coronary artery calcium content [33]. No association between APOL1 genetic variation and arterial calcification has been found in the CARDIA study, the MESA study, or the Predictors of Arrhythmic and Cardiovascular Risk in the ESKD cohort study, such that APOL1 risk status is not associated with coronary artery calcification in subjects from the general population or patients with ESKD in these trials [10, 13, 44].

Regarding cerebrovascular disease, the AA-DHS-MIND finds less severe intracranial small vessel disease among participants with APOL1 risk variants (in additive genetic models) [34].

Autopsy findings show an association between the APOL1 high-risk genotype and coronary artery atherosclerosis. In an autopsy study that included 764 African Americans from the CVPath Sudden Death Registry, carriers of two APOL1 risk alleles demonstrated larger necrotic cores in coronary plaques compared with noncarriers, suggesting that the APOL1 high-risk genotype predisposes to the development of unstable coronary artery disease. Accordingly, patients harboring two APOL1 risk alleles had an increased risk of coronary thrombosis due to plaque rupture compared to noncarriers [18]. Likewise, fibrous intima-media thickness in kidney interlobular arteries was greater in carriers of two APOL1 risk variants compared to low-risk genotypes in an autopsy study that included subjects from the general population without kidney disease [47].

Relationship between insulin resistance and APOL1

As mentioned, the genotype–phenotype correlation in bearers of APOL1 risk variants is not straightforward, as most of them do not develop the clinical disease unless another condition combines with the genetic background. Several pieces of information suggest that insulin resistance may be involved in the relationship between APOL1 genetic variation and the clinical phenotype of mutated APOL1. First, essential hypertension [81] and obesity [82] occur more frequently in subjects with an APOL1 high-risk genotype compared to low-risk subjects, suggesting that carriers of APOL1 risk variants may experience more severe insulin resistance than noncarriers. Second, the kidney phenotype associated with mutated APOL1 and the kidney consequences of insulin resistance are strikingly similar (albuminuria, CKD, faster CKD progression, glomerulomegaly, FSGS, and arterionephrosclerosis) [106]. Third, patients with increased plasma APOL1 levels show more pronounced insulin resistance than those with lower circulating APOL1 [19, 84]. Fourth, wild-type APOL1 is a component of the lipid droplet, while APOL1 risk variants stay sited on the endoplasmic reticulum. Defective detachment of the lipid droplet from the endoplasmic reticulum compromises the biogenesis of these organelles and impairs normal triglyceride accumulation, which has been associated with insulin resistance [16]. Fifth, conditions associated with interferon upregulation, such as SLE and viral infections, typically feature worse kidney outcomes in patients with the APOL1 high-risk genotype. Interferon triggers APOL1 overexpression [83, 115] and promotes insulin resistance [56], which may contribute to explaining the clinical manifestations associated with the APOL1 high-risk phenotype under these conditions. Sixth, clinical disorders that feature insulin resistance are usually associated with reduced protein synthesis and increased protein degradation to ensure energy supply to tissues. APOL1 overexpression may contribute to facilitating these processes by suppressing the kinase target of rapamycin complex-1 (TORC1) and inducing phosphorylation of the eukaryotic initiation factor-2 on its α subunit (eIF2α) [20, 85, 108].

Carriers of APOL1 risk variants develop essential hypertension and obesity more frequently than noncarriers

Individuals harboring APOL1 risk alleles G1 or G2 develop components of the metabolic syndrome (the clinical manifestation of insulin resistance), such as essential hypertension and obesity, more frequently than subjects without these variants, implying that carriers of APOL1 risk variants can be more insulin-resistant than noncarriers. A number of studies, including the Dallas Heart Study, the AASK, the CRIC, the SPRINT, the MESA, and the MVP, show very consistently that subjects with the APOL1 high-risk genotype (carriage of two risk alleles) have a higher prevalence of hypertension compared to individuals with one or zero risk variants in varied African American population groups [4, 10, 35, 36, 87]. In addition, carriage of APOL1 risk alleles is associated with higher blood pressure values and a younger age at diagnosis of hypertension over a mean follow-up period of 3.6 to 7.6 years among a total of 9203 African Americans from Mount Sinai´s BioMe biobank (discovery cohort) and three replication cohorts (Vanderbilt BioVU, Northwestern NUgene, and BioMe replication). The age of hypertension diagnosis was 2 to 5 years earlier in subjects harboring two copies of G1 or G2 [81].

Similarly, harboring one or two risk variants in the APOL1 gene is independently and robustly associated with a higher body mass index (BMI) and may partially explain the increased rate of obesity among African Americans compared to European Americans [35, 82]. In cross-sectional analyses of 11,930 African American participants in the Genetic Testing to Understand and Address Renal Disease Disparities (GUARDD) study, the JHS, and the BioMe Biobank, BioVU, NU-gene cohorts, carriage of one or two APOL1 risk variants is independently associated with obesity both in recessive and additive models. Individuals carrying one or two APOL1 risk variants are more likely to be obese than wild-type homozygotes (G0/G0). In a recessive model, bearers of two APOL1 risk variants have a 0.58 kg/m^2 higher BMI than subjects carrying one or zero risk alleles. In an additive model, each risk variant increases BMI by 0.36 kg/m^2 [82]. Likewise, the APOL1 high-risk genotype is associated with greater BMI in the SPRINT, such that participants with two APOL1 risk alleles show a higher BMI than subjects with one or two risk variants [35].

The kidney phenotype associated with the APOL1 high-risk genotype shares similarities with clinical complications of insulin resistance

Biallelic carriage of APOL1 risk variants is associated with kidney manifestations of insulin resistance, such as albuminuria, CKD, glomerulomegaly, FSGS (in the setting of glomerular hyperfiltration), and arterionephrosclerosis (the pathological correlate of hypertension-associated nephropathy) [47, 106]. As mentioned, several studies, including the Dallas Heart Study, the AASK, the CRIC, the SPRINT, the MESA, and the MVP, show very consistently that carriers of two copies of the APOL1 risk variants have a higher prevalence of albuminuria and greater values of albuminuria when compared to individuals with one or zero risk variants in varied African American population groups [4, 10, 35, 36, 87]. In addition, carriers of two APOL1 risk alleles have a higher prevalence of CKD compared to noncarriers [4, 35, 36]. Furthermore, the carriage of two APOL1 risk variants is associated with greater nephron loss and increased glomerular volume associated with aging [45] and increases the risk for arterionephrosclerosis [47] and FSGS [38, 57]. Likewise, the APOL1 high-risk genotype (two risk variants) is associated with an increased risk of FSGS in African Americans with HIV-1 infection (Fig. 4) [30].

Association between plasma level of APOL1 and insulin resistance

Cross-sectional and longitudinal studies reveal an independent association between the plasma level of APOL1 and more severe insulin resistance and a consequently higher risk for new-onset type 2 diabetes (T2D) [19, 84]. In a cross-sectional study that recruited 126 nondiabetic volunteers and 36 T2D patients, circulating levels of APOL1 were increased in participants with more pronounced insulin resistance, independent of confounding variables. Subjects with higher plasma APOL1 had greater waist circumference and BMI, higher serum insulin levels, and more severe insulin resistance-associated dyslipidemia (higher levels of triglycerides and lower HDL-c) compared with participants with a lower APOL1 level. Accordingly, circulating APOL1 demonstrates a positive correlation with homeostasis model assessment-insulin resistance (HOMA-IR) values, and participants with elevated plasma APOL1 levels show higher HOMA-IR and lower adiponectin levels. Likewise, circulating APOL1 is increased in subjects with the metabolic syndrome, regardless of diabetes or obesity status [84]. Consistently, plasma APOL1 levels are independently associated with increased risk for incident T2D in an ancillary analysis of the prospective observational trial Innovation Thérapeutique-Diabète (IT-DIAB). In this study, 307 participants with glucose intolerance were followed for a median period of 5 years to ascertain the association between plasma APOL1 concentration and the incidence of new-onset T2D. After adjustment for confounding variables, the plasma level of APOL1 was positively associated with a higher risk for incident T2D [19].

Similarly, the plasma level of APOL1 correlates strongly and independently with the plasma levels of glucose and triglycerides among 137 participants in the HDL Atherosclerosis Treatment Study (patients with coronary artery disease, reduced HDL-c, and hypertriglyceridemia), suggesting that increased plasma APOL1 associates with more pronounced insulin resistance. Patients with hyperglycemia had mean APOL1 levels > 50% higher than normoglycemic subjects (13.2 µg/ml versus 8.3 µg/ml). In contrast, circulating APOL1 is not associated with the progression of coronary artery disease in this population, suggesting that plasma APOL1 may be a marker of vascular injury rather than a causative factor [2].

Interferons promote insulin resistance and trigger APOL1 overexpression

As mentioned, collapsing glomerulopathy develops predominantly in subjects with the APOL1 high-risk genotype when interferon levels are increased either through exogenous

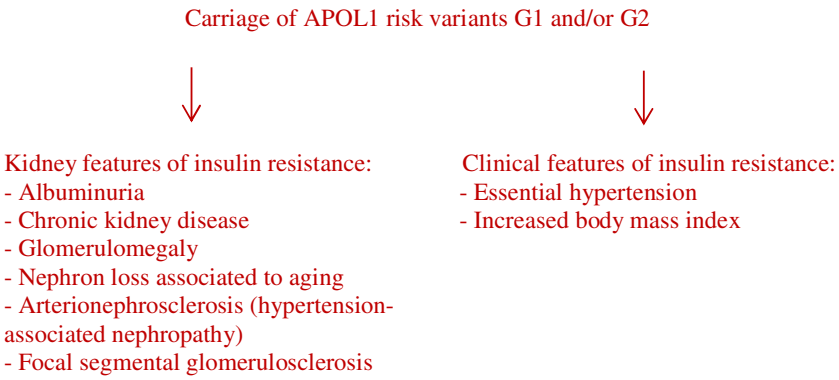

Fig. 4 Carriers of APOL1 risk variants manifest clinical features of insulin resistance

injection or endogenous upregulation. Interferons are molecules that participate in the immune and metabolic responses against infections or abnormal host DNA, promoting both insulin resistance and the expression of genes involved in the immune response (interferon signature) [90, 97]. Type I interferons are produced by many cell types and include interferon-α and interferon-β. The production of type I interferon is activated by foreign (bacterial or viral) DNA or aberrant self-DNA located in the cytosol. There are several DNA sensors in human cells, including STING, that activate interferon secretion in response to anomalous DNA (foreign DNA or self-DNA abnormally located). Interferon synthesis elicited by aberrant self-DNA can play a role in the pathogenesis of autoimmune diseases such as SLE. Type II interferon (interferon-γ) is generated predominantly by immune cells. Type III interferon comprises several interferon-λ (IFNL) isoforms that are primarily produced by epithelial cells and some immune cells, such as macrophages and dendritic cells. Interferons promote insulin resistance and therefore both infections and SLE typically feature this metabolic adaptation. In addition, interferon triggers marked APOL1 overexpression in human cells [21, 59, 83, 102, 115].

Interferons induce insulin resistance

Clinical studies indicate that interferon elicits insulin resistance. Compared to placebo, interferon-α injection in healthy subjects increases plasma glucose and plasma insulin levels and induces insulin resistance, as evaluated by insulin clamps and oral and intravenous glucose tolerance tests. In addition, injection of interferon-α causes an acute rise in circulating counterregulatory hormones such as glucagon, cortisol, and growth hormone [56]. Similarly, recombinant interferon-α therapy for two weeks worsens insulin resistance (assessed by euglycemic hyperinsulinemic clamp) and impairs oral glucose tolerance in patients with chronic active hepatitis C, suggesting that long-term interferon administration may maintain an insulin-resistant status [48]. Furthermore, an interferon signature characterizes the whole blood transcriptome profile of insulin-resistant subjects, highlighting the association between interferon and insulin resistance. The Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) study was a prospective observational trial that investigated the whole blood transcriptome profile in participants with an elevated risk of T2D. Insulin resistance was characterized by a unique whole blood transcriptome profile typified by higher expression of interferon-stimulated genes and lower expression of genes involved in remodeling of the actin cytoskeleton [51]. Furthermore, in the Chennai Urban Rural Epidemiology study, serum levels of interferon-γ are increased among Asian Indian patients with metabolic syndrome compared to subjects without clinical insulin resistance. Additionally, circulating interferon-γ shows a positive association with HOMA-IR values and a negative association with serum adiponectin in this population [98].

Consistently, conditions associated with interferon upregulation, such as infections and SLE, feature insulin resistance. Activation of the immune system during microbial invasion or autoimmune disorders requires a continuous energy supply to immune cells to achieve an immune response. This metabolic adjustment is implemented by insulin resistance. Infections are associated with an increment in both fasting plasma insulin levels and HOMA-IR values. In patients with diabetes, infection-associated insulin resistance typically worsens glycemic control. Clinical observational studies show that patients with HIV-1 infection [7] or COVID-19 [14] endure prolonged insulin resistance and a subsequent increased risk for new-onset T2D. In a prospective cohort study that followed 505 HIV-1 nondiabetic patients aged ≥ 50 years for 7.25 years, the prevalence of either T2D or insulin resistance was very high (46%) at the end of the study, and the incidence of T2D was higher than in the general population (1.2/100 patient-years) [7]. Likewise, SARS-CoV-2 infection intensifies insulin resistance and predisposes to new-onset T2D 6 months after the acute infection. In a prospective study that followed 64 nondiabetic patients with COVID-19 for 6 months, insulin resistance (assessed by HOMA for β-cell function) was more severe at follow-up compared with baseline values [14].

Similarly to infections, SLE is associated with enhanced interferon secretion and insulin resistance. Compared to healthy controls, insulin resistance and the prevalence of metabolic syndrome, diabetes, and hypertension are higher in patients with SLE (adults and children) compared to healthy subjects [39, 77, 78, 92, 101]. Furthermore, the fasting plasma level of glucagon and the glucagon response to a meal tolerance test are increased in SLE patients compared to healthy subjects [77]. In a retrospective longitudinal cohort that enrolled 1498 patients with SLE, adherence to antimalarials conferred protection against incident T2D over a median follow-up of 4.62 years, suggesting that reduction of interferon secretion (due to less active disease) improves insulin resistance in patients with SLE [93]. Additionally, patients with SLE experience elevated cardiovascular risk that is unexplained by traditional risk factors and may be attributed to insulin resistance. Among SLE patients, insulin resistance associates with subclinical vascular injury, such as increased arterial stiffness and carotid and coronary intima-media thickness [39, 78]. Likewise, patients with other conditions that feature increased interferon levels also experience vascular disease unexplained by conventional cardiovascular risk factors. Patients with HIV-1 infection endure an increased risk of myocardial infarction and cerebrovascular events that may be attributed to more severe insulin resistance [7]. Gain of function mutations in STING are associated with cutaneous vasculopathy [66]. Most patients

with collapsing glomerulopathy following interferon therapy show arteriosclerosis and arteriolosclerosis with hyalinosis in kidney biopsy samples, suggesting that vascular damage is associated with this condition [73].

Interferons elicit APOL1 Overexpression in human cells

In addition, to promote insulin resistance, interferons markedly intensify APOL1 expression in diverse human cell lines and human kidney organoids. Interferon-β enhances APOL1 expression in human podocyte cell lines, while interferon-γ increases APOL1 expression in endothelial cells, macrophages, podocytes, glomerular parietal epithelial cells, and human embryonic kidney (HEK) cell lines [21, 59, 83, 102, 115].

In human primary macrophages and monocyte-derived macrophages isolated from healthy blood donors, interferon-γ triggers the expression of APOL1, although, in the basal state, these cells do not express APOL1. In contrast to the potent effect of interferon-γ, interferon-α prompts only slight APOL1 expression in these cells [102].

In human umbilical vein endothelial cells and endothelial cells at other locations, interferons heighten the expression of APOL1 mRNA and protein. Like in human macrophages, interferon-γ has the most potent effect on boosting APOL1 overexpression, followed by interferon-β and interferon-α. In endothelial cells, interferon-γ increased 200-fold the expression of APOL1 mRNA. In addition, interferons induce the appearance of new APOL1 transcripts that are undetectable under resting conditions [83, 115].

Interferon-γ induces APOL1 expression in human glomerular parietal epithelial cells and HEK cell lines, although in the basal state, these cells lack APOL1 [59].

APOL1 is expressed in normal human podocytes, but interferon-γ magnifies the expression of the protein and induces the appearance of new APOL1 transcripts in these cells [59, 83]. Likewise, interferon-β induces APOL1 overexpression in human podocytes carrying either wild type (G0/G0) or G1 variant (G1/G1) [21].

The upregulation of APOL1 induced by interferon has been confirmed in human kidney organoids derived from induced pluripotent stem cells homozygous for APOL1 G0 or G2 alleles (G0/G0 or G2/G2). APOL1 is highly upregulated in response to interferon-γ. Furthermore, interferon-γ-induced APOL1 overexpression is greater in APOL1 high-risk genotype organoids (G2/G2) compared with wild-type (G0/G0) kidney organoids [17].

The biological significance of the remarkable effect of interferon augmenting APOL1 expression in human cells remains to be fully understood, but it might suggest that APOL1 can mediate some effects of interferon.

In carriers of APOL1 risk variants, impaired lipid droplet biogenesis may contribute to causing insulin resistance

Wild-type and risk variants of the APOL1 protein show different intracellular locations. In varied human cell lines, including human podocytes, HEK-293 cells, human cervical carcinoma (HeLa) cells, and human liver (Huh7) cells, wild-type APOL1 (G0) localizes predominantly to lipid droplets, while the risk variants G1 and G2 localize primarily to the endoplasmic reticulum. The formation of lipid droplets involves the separation of the nascent lipid droplet from the endoplasmic reticulum. Mutated APOL1 proteins remain stationary on the endoplasmic reticulum while wild-type APOL1 moves with the emergent lipid droplet into the cytoplasm, suggesting that APOL1 may be implicated in lipid droplet biogenesis by contributing to the detachment of the lipid droplet from the endoplasmic reticulum. Supporting this notion, human podocytes expressing APOL1 risk variants G1 or G2 exhibit a reduced number of lipid droplets per cell and a diminished size of these intracellular organelles compared to podocytes expressing wild-type APOL1 [16]. These findings have been replicated in human kidney organoids derived from induced pluripotent stem cells that express wild-type APOL1 (G0/G0) or an APOL1 high-risk genotype (G2/G2). Human kidney organoids with the APOL1 high-risk genotype exhibit fewer lipid droplets compared to wild-type APOL1 organoids, highlighting the functional importance of the intracellular position of the APOL1 protein [17]. While wild-type APOL1 allows the adequate formation of lipid droplets, the presence of mutated APOL1 leads to the abnormal generation of these organelles (manifested as a reduction in their size and number). Defective lipid droplet formation hinders triglyceride deposition in the normal storage site and has been consistently associated with insulin resistance. Mutations in genes encoding several lipid droplet-associated proteins cause severe insulin resistance, including *BSCL2* (seipin) [71], caveolin-1 (*CAV1*) [53], and cell death-inducing DNA fragmentation factor-α-like effector C (*CIDEC*) [91].

APOL1 reduces protein synthesis and activates autophagy

Insulin resistance is a metabolic response to a variety of clinical conditions (including infections) that, when driven by glucagon, includes a catabolic state with protein synthesis reduction. Protein synthesis may be attenuated by suppression of TORC1 or phosphorylation of eIF2α (Fig. 5). TORC1 and the eukaryotic initiation factor-2 participate in the regulation of protein metabolism. Activation of TORC1 promotes protein synthesis. In contrast, inhibition of TORC1

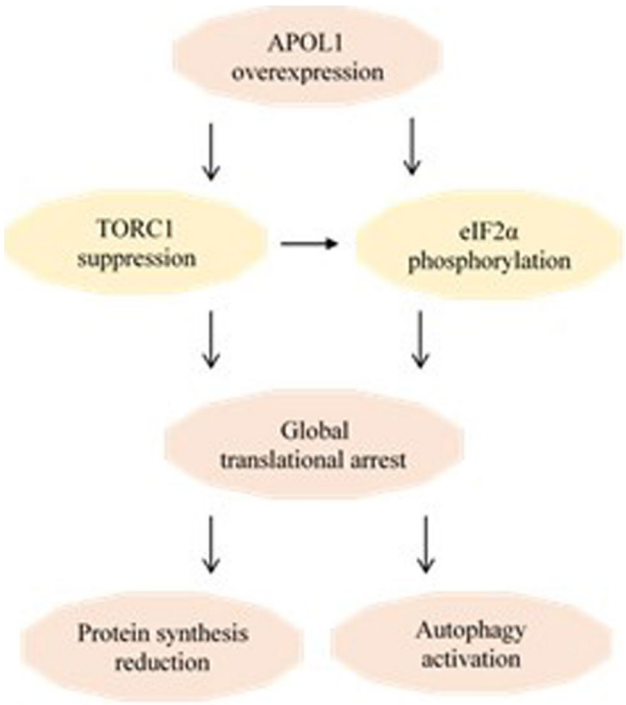

Fig. 5 APOL1 reduces protein synthesis by suppressing target of rapamycin complex-1 (TORC1) and inducing phosphorylation of the eukaryotic initiation factor-2 on its α subunit (eIF2α)

or phosphorylation of eIF2α by specific kinases, such as protein kinase R (PKR), suppresses protein synthesis [54, 100]. TORC1 and eIF2α cooperate to regulate protein synthesis and degradation, such that TORC1 inhibition leads to eIF2α phosphorylation and the consequent cessation of protein translation, reduction of protein synthesis, and autophagy initiation. During viral infections, the host experiences global translational arrest that can be reversed by TORC1 activation, suggesting that TORC1 attenuation occurs during viral infections and contributes to reducing protein synthesis [100].

APOL1 may contribute to implementing protein synthesis reduction and the initiation of catabolic pathways (autophagy). Upregulation of APOL1 by interferon suggests that this protein may be an effector of the metabolic effects of interferon.

APOL1 risk variants induce eIF2α phosphorylation. In HEK-293 cell lines, heterozygous overexpression of APOL1 risk variants (G0/G1 or G0/G2) induces eIF2α phosphorylation compared with overexpression of wild type APOL1 (G0/G0). In turn, eIF2α phosphorylation reduces protein synthesis [20, 85]. PKR mediates eIF2α phosphorylation that follows overexpression of APOL1 risk variants. In HEK293FT cells, overexpression of mutated APOL1 increases PKR phosphorylation markedly, unlike overexpression of wild-type APOL1. Accordingly, silencing of APOL1 risk variants reduces PKR phosphorylation compared to APOL1 wild-type. Furthermore, in glomeruli from patients with FSGS that carry two APOL1 risk alleles, PKR phosphorylation is increased [85].

Additionally, APOL1 overexpression may suppress TORC1 in human cell lines. APOL1 is a lipid-binding protein with a high affinity for phosphatidic acid. Phosphatidic acid activates TOR in HEK-293 cell lines [28]. It has been proposed that overexpression of APOL1 may bind phosphatidic acid, thus reducing the amount of this compound available to activate TORC1. In turn, TORC1 inactivation promotes eIF2α phosphorylation and facilitates autophagy initiation [60, 108, 115].

Overexpression of either wild-type or allelic variants of APOL1 reduces protein synthesis and induces autophagy in human cell lines, such as colorectal adenocarcinoma cells and hepatoma cells [15, 20, 85, 108]. This effect is more intense in cell lines (HEK293FT) expressing APOL1 risk alleles compared with the G0 variants [85]. Accordingly, autophagic pathways are more active in carriers of APOL1 risk alleles compared to noncarriers [16, 95]. In human podocytes and human kidney organoids derived from induced pluripotent stem cells, the recruitment of APOL1 to the lipid droplet is associated with a reduction in autophagy compared to values corresponding to its placement in the endoplasmic reticulum [17].

Summary

Human APOL1 protein is widely expressed in human tissues, circulates in plasma associated with HDL, and normally facilitates immune defense against infections, particularly trypanosomiasis. The G0 allele of the *APOL1* gene codes the wild-type protein, while the G1 and G2 alleles code APOL1 variants. Harboring mutated APOL1 increases the risk of focal segmental glomerulosclerosis, collapsing glomerulopathy, albuminuria, chronic kidney disease, and accelerated progression to end-stage kidney disease. However, most carriers of APOL1 variants do not develop kidney disease, suggesting that additional factors are required for the clinical manifestations to appear. Observational studies reveal a relationship between insulin resistance and the clinical expression of the APOL1 genotype. Bearers of APOL1 variants may be more susceptible to developing insulin resistance due to the absence of APOL1 at the lipid droplet, which leads to defective formation of these organelles and consequent insulin resistance. Accordingly, subjects with APOL1 high-risk genotype experience clinical features of insulin resistance, such as obesity, essential hypertension, arterionephrosclerosis, focal segmental glomerulosclerosis (in the setting of insulin resistance-associated glomerular hyperfiltration), and glomerulomegaly, more frequently than individuals with low-risk genotypes, indicating

that carriers of APOL1 variants may experience more severe insulin resistance. In addition, subjects with increased plasma APOL1 level show more pronounced insulin resistance and higher incidence of type 2 diabetes than individuals with lower circulating APOL1. Furthermore, APOL1 may be involved in the implementation of protein synthesis reduction associated with insulin resistance by inhibiting the kinase target of rapamycin complex-1 and promoting phosphorylation of the α subunit of eukaryotic initiation factor-2, leading to global translational cessation. Further human research may help to establish the extent to which insulin resistance may modulate the clinical phenotype associated with the carriage of APOL1 variants, its role in the pathogenic mechanisms underlying the clinical manifestations of the APOL1 high-risk genotype, and the molecular processes that may lead to this metabolic alteration in carriers of mutated APOL1.

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Declarations

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