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## Multifaceted role of apolipoprotein L1 risk variants and nephropathy

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#### Implication for health policy/practice/research/medical education:

APOL1 protein is encoded by the *APOL1* gene in humans and plays a role in innate immunity. The spectrum of APOL1-related nephropathies consists of HIV-associated nephropathy (HIVAN), segmental glomerulosclerosis (FSGS), membranous nephropathy (MGN), sickle-cell nephropathy, hypertensive nephropathy, arterionephrosclerosis, lupus nephritis, microalbuminuria, chronic kidney disease and end-stage renal disease. Moreover, APOL1 nephropathy risk variants are associated with shorter survival of deceased kidney allografts, lower renal function, interstitial and fibrosis glomerulosclerosis.

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### Dear Editor,

The discovery of apolipoprotein L-1 (APOL1) risk variants has highlighted the possible role of genetic factors as a key player in the development of chronic kidney disease (CKD). In humans, APOL1 protein is encoded by the *APOL1* gene and plays a role in innate immunity (1). In persons with African ancestry, the carriers of APOL1 G1 and/or G2 alleles offer protection from trypanosomiasis. However, the carriers of G1 and/or G2 alleles have shown an susceptibility to developing CKD in these populations (2,3). APOL1 related nephropathy includes HIV-associated nephropathy (HIVAN), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MGN), sickle-cell nephropathy, hypertensive nephropathy, arterionephrosclerosis, lupus nephritis, microalbuminuria, non-diabetic kidney diseases, CKD and end-stage renal disease (ESRD) (4,5). Further, APOL1 nephropathy risk variants are associated with shorter survival of deceased kidney allografts (6), lower renal function, interstitial and fibrosis glomerulosclerosis (7) and also age-related alterations in the volume and number of glomeruli over the lifespan (8). However, not all carriers of the risk variants developing the renal disease,

indicating the potential interaction of APOL1 genotype with the environmental factors in CKD pathogenesis and progression. In normal human kidney, the APOL1 protein localizes to the proximal tubules, podocytes and extra-glomerular arterioles and small arteries of endothelium (7). Although the exact pathogenic mechanism by which APOL1 variants make patients susceptible to CKD is not known, diminished APOL1 expression is reported in the podocytes of HIVAN and FSGS kidney biopsies compared to normal kidneys (2, 4). The other potential mechanisms include activation of inflammation, impairment of kidney microcirculation, vascular endothelial dysfunction, cation pore formation and activation of protein kinase R (9). The APOL1 variants can be cytotoxic to proximal tubular cells and leading to podocytic apoptosis (10-12). Further, APOL1 variants form cation K(+) pores in the plasma membrane that facilitate the reduction in intracellular K+ and subsequent activation of stress kinases pathways that exert nephrotoxicity (13). It is also reported that the APOL1 risk variants are associated with collapsing glomerulopathy (14). Furthermore, elevated CKD risk associated with APOL1 risk variants is modulated by other genetic, environmental and factors (15).

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Another mechanism for CKD is that the soluble urokinase plasminogen activator receptor (suPAR) and APOL1 variants synergize to activate  $\alpha v\beta 3$  integrin on podocytes. Activation of podocyte integrin leads to deregulation of the actin cytoskeleton and consequently results in podocyte effacement and loss (16). Inflammation is the additional factor that involved in the renal injury. The signaling pathways of interferon- $\gamma$ , tumor necrosis factor- $\alpha$  and p53 induce expression the APOL1 (17). A recent study examined the molecular behavior of APOL1 in mitochondrial dysfunction in vitro. This study demonstrated that the APOL1 risk variants could translocate into mitochondria and bind to the permeability transition pore components, leading to cell death (18). APOL1 risk variants also diminish mitochondrial superoxide dismutase 2 and catalase and make the cell susceptible to oxidative stress, leading to mitochondrial dysfunction (19). In conclusion, the understanding of non-diabetic nephropathy has been enhanced by the discovery of the association of APOL1 with a spectrum of nephropathies. Outlining the renal injury pathways and uncovering the relationships between APOL1 and renal diseases brings hopeful horizons for effective therapy of these diseases. However, our knowledge on role of APOL1 in CKD is still in its toddling stage, further research is needed for better understanding the pathogenesis of renal injury in patients with the high-risk genotype.

#### Authors' contribution

MAS prepared the primary draft. BN edited the paper. All authors read and approved the final paper.

#### Conflicts of interest

The authors declared no competing interests.

#### Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

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