**APOL1** variants and kidney disease. There is no such thing as a free lunch*

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**Abstract**

A recent study by Genovese *et al.* unraveled the findings of the intensively discussed gene region around *MYH9* and its association with non-diabetic chronic kidney disease in African-Americans. First, it is not the genetic variation in *MYH9* but in the neighbouring *APOL1* that causes the strong association with disease in African-Americans and second, the study showed strong evidence for a positive selection against vulnerability for *Trypanosoma brucei rhodesiense* infection but at the price of a higher susceptibility of non-diabetic chronic kidney disease. This overview reviews the findings and the possible impact of the study mentioned above as well as of related studies.

**Summary of the key findings**

There is an ongoing discussion about the reasons for the markedly higher frequency of chronic kidney disease (CKD) in African-Americans compared to Caucasian populations. The study by Genovese *et al.* [1] might have identified a major contributor to these ethnic differences. They described a pronounced association of two independent genetic variants within the *APOL1* gene with focal segmental glomerulosclerosis (FSGS) and hypertension-attributed end-stage renal disease (ESRD). These variants increased the risk for the two disease entities 10.5 and 7.3 times, respectively, which is spectacular considering that both diseases are thought to be complex diseases to which several genes and environmental factors contribute. The described variants are very common in African-Americans, but obviously absent in chromosomes of European origin. Since the protein apolipoprotein L1 (apoL1) lyases trypanosomes, it was highly interesting from the African perspective that *in vitro*, only the disease-associated apoL1 variants lysed the sleeping disease-causing *Trypanosoma brucei rhodesiense*. The authors speculated that the evolution of this *APOL1* variant might be a critical survival factor in certain parts of the African continent, which on the other hand may have contributed to the high incidence and prevalence of CKD in African-Americans.

**Brief review of the field**

African-Americans have a 3- to 4-fold increased risk for ESRD compared to European Americans, and it was calculated that the cumulative lifetime risk is 7.5 versus 2.1%, respectively [2]. The search for underlying factors for these differences included socio-economic and lifestyle factors but recently also genetic factors. In the search for genes to help explain the differences in prevalence of CKD, two studies in 2008 [3,4] used a ‘mapping by admixture linkage disequilibrium’ approach, which is based on the fact that genomes of African-Americans contain, in most cases, a mixture of African and European ancestry [5]. If a disease shows a pronounced ethnic difference, genetic regions involved in the disease should contain a higher percentage of African ancestry compared to noninvolved gene regions. Both studies used this approach. Kopp *et al.* [4] identified *MYH9* (nonmuscle myosin heavy chain 9) as a gene associated with idiopathic and HIV-associated FSGS and extended these findings to hypertensive ESRD but not to type 2 diabetic ESRD. Kao *et al.* [3] independently found similar results in ESRD patients and described odds ratios for FSGS between 3 and 7 and for hypertensive glomerulosclerosis between 2 and 3, respectively. The latter study calculated that, theoretically, the prevalence of nondiabetic ESRD in African-Americans would decrease to 30% if all African-Americans would have inherited the European gene variants at the *MYH9* locus [3]. These odds ratios of 2–7 for *MYH9* in African-Americans are very much higher than the odds ratios observed in genome-wide association studies in Caucasian populations, which aimed to identify genes influencing kidney function. In those studies, the risk for CKD was changed by 20% at best [6,7].

Several reports followed with extended association studies and fine mapping of the *MYH9* region with virtually the
same results—a strong association of the MYH9 locus with FSGS and hypertension-attributed ESRD [8–10]. In contrast to the first publications, a study in type 2 diabetes mellitus-associated ESRD revealed only a weak association with MYH9 alleles, which was interpreted to be caused by a small fraction of patients with coincident FSGS or global glomerulosclerosis [11]. Similarly, an investigation in hypertensive sibling pairs and their offspring in the HyperGEN study who were not primarily recruited because of CKD revealed that albuminuria was associated with several SNPs at the MYH9 locus in African-Americans. Since the strength of the association was weaker than that in FSGS and hypertensive ESRD, it was suggested that the MYH9 risk variants appear to be associated with primary FSGS with secondary hypertension or that high blood pressure directly caused albuminuria in a subset of genetically predisposed individuals [12]. All these studies had in common that the association was observed in African-Americans but not in European Americans or other ethnicities.

Although the findings of risk variants within the MYH9 region were quite impressive and consistent, data that have recently become available from the ‘1000 Genomes Project’ represent a further milestone in the study of this highly interesting gene region. Genovese et al. [1] identified from this new sequence source polymorphisms within and around this extended gene region with large frequency differences between Africans and Europeans which were then tested in African-Americans with biopsy-proven FSGS but no family history of FSGS and controls of the same ethnicity and in a second sample of hypertension-attributed ESRD and controls. The strongest association signals no longer clustered in the MYH9 region but in the neighbouring APOL1 region with a statistical significance 35 orders of magnitude stronger (P = 10$^{-63}$). After controlling for the APOL1 region, MYH9 was no longer significant. This was surprising since MYH9 was indeed a highly interesting candidate gene whose gene product localized to the podocyte foot process and is responsible for moving actin filaments in the cells. Therefore, it was suggested that mutations in this podocyte protein could have an influence on the cytoskeleton with disruption of the filtration barrier [9]. However, the associations with APOL1 are strong and were independently confirmed by another group [13]. The reason why MYH9 was able to fool researchers was that it had not only the reasonable candidate gene characteristics of MYH9 but also the strong linkage disequilibrium of variants within MYH9 and APOL1. This signifies a strong correlation of variants of the two gene loci which transformed variants of MYH9 to a ‘deputy without authority’ which simply mirrored the variants in the APOL1 gene.

Nevertheless, APOL1 turned out to be an even more interesting candidate gene for two reasons: first (and this is less from a nephrological standpoint), the two nonsynonymous variants most strongly associated with nondiabetic CKD were in HapMap populations observed in 40% of the Yoruba population from Nigeria in West Africa but not in European, Japanese or Chinese populations. An extended statistical

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**Fig. 1.** Schematic illustration describing the association between variants in the APOL1 gene and trypanolytic ability of apolipoprotein L1 (apoL1) on the one hand and increased risk for nondiabetic kidney disease. In the case of wild type alleles of the APOL1 gene, the apoL1 protein as part of an HDL particle interacts with the SAF expressed by the parasites. This inactivates apoL1 and no longer lysed the parasites which results in sleeping sickness. In the case of the mutations at position 342/384, the SAF protein is no longer able to bind to apoL1, which allows apoL1 to lyse the parasite through ionic pore formation in endosomal membranes of the parasite. This might have resulted in a positive selection of these variants in African-Americans since carriers of these variants had a major survival advantage since they were resistant against Trypanosoma brucei rhodesiense and therefore against sleeping sickness. These variants, however, are associated with an increased risk for nondiabetic CKD for which the pathogenetic mechanisms are not yet elucidated. The originally described associations between variants within the MYH9 gene had to be revised since the association finding was simply caused by the high linkage disequilibrium (LD) between the variants in the MYH9 and the APOL1 gene.
analysis revealed that these variants might be the result of positive selection in Africa which could be related to the fact that apoL1 is a trypanolytic factor in human serum \cite{14,15} that confers resistance to \textit{T. brucei rhodesiense} which is transmitted by the tsetse flies causing sleeping sickness. Usually, apoL1 lyses these parasites through ionic pore formation in endosomal membranes of the parasite. This parasite can only infect humans by an interaction of a so-called serum resistance-associated protein (SAF) with apoL1 \cite{15}. The \textit{T. brucei rhodesiense} and \textit{gambiense} resist this apoL1-lytic activity. Most interestingly, the nonsynonymous variants found to be associated with non-diabetic CKD are located exactly at the site where the SAF protein binds to apoL1 (Figure 1). Genovese et al. demonstrated that human plasma samples were able to lyse \textit{T. brucei rhodesiense} clones when the plasma originated from persons who carry the nonsynonymous variants that are associated with non-diabetic CKD \cite{1}. A second reason makes apoL1 highly interesting from a more nephrological perspective: apoL1 is involved in autophagic pathways \cite{16} and Hartleben et al. \cite{17} recently postulated that autophagy is a major protective mechanism against podocyte aging and glomerular injury. Whether the described genetic variants in \textit{APOL1} have an influence on disturbances in the cellular homeostasis of the glomerular system remains to be investigated.

**How could this affect clinical work?**

At this stage, the described findings do not impact the clinical practice of the nephrologist. Although \textasciitilde{}10 to 12\% of African-Americans carry two copies of the risk allele, it is considered to be too early to recommend genetic testing to identify those at increased risk for non-diabetic CKD. It was calculated that \textasciitilde{}12\% of the HIV-negative and \textasciitilde{}50\% of the HIV-positive African-American homozygote carriers of the \textit{APOL1} allele carriers may be susceptible to kidney disease \cite{18}. However, another aspect could influence clinical work in the future, at least in geographic regions where infections with \textit{T. brucei rhodesiense} play an important role. It was demonstrated in \textit{vitro} that even 10000-fold dilutions of plasma containing the described mutations are active against this parasite. Genovese et al. \cite{1} raised the hope that transfusion of small amounts of plasma or apoL1-containing HDL particles, or even recombinant apoL1 protein, might be an effective treatment for infections caused by this parasite. This finding was paralleled by successful experimental work, demonstrating that influencing the apoL1-domain that interacts with the SAF protein might be a highly targeted approach to break the resistance to trypanolysis \cite{19,20}.

**Take-home message**

Particular genetic variants within the \textit{APOL1} gene are associated with a 7- to 10-fold increased risk for non-diabetic CKD. This pronounced association was only observed in African-American populations but not in European Americans and which might contribute to the markedly higher incidence of CKD in African-Americans. These variants possibly have been derived through positive selection in Africa, which might protect against infection with the parasite \textit{T. brucei rhodesiense} but at the price of an increased susceptibility to nondiabetic CKD.

**Conflict of interest statement.** None declared.

**References**

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