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SHORT REPORT

Missense mutations in the *APOL1* gene are highly associated with end stage kidney disease risk previously attributed to the *MYH9* gene

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Abstract *MYH9* has been proposed as a major genetic risk locus for a spectrum of nondiabetic end stage kidney disease (ESKD). We use recently released sequences from the 1000 Genomes Project to identify two western African-specific missense mutations (S342G and I384M) in the neighboring *APOL1* gene, and demonstrate that these are more strongly associated with ESKD than previously reported *MYH9* variants. The *APOL1* gene product, apolipoprotein L-1, has been studied for its roles in trypanosomal lysis, autophagic cell death, lipid metabolism, as well as vascular and other biological activities. We also show that the distribution of these newly identified *APOL1* risk variants in African populations is consistent with the pattern of African ancestry ESKD risk previously attributed to *MYH9*.

Mapping by admixture linkage disequilibrium (MALD) localized an interval on chromosome 22, in a region that includes the *MYH9* gene, which was shown to contain African ancestry risk variants associated with certain forms of ESKD (Kao et al. 2008; Kopp et al. 2008). *MYH9* encodes nonmuscle myosin heavy chain IIa, a major cytoskeletal nanomotor protein expressed in many cell types, including podocyte cells of the renal glomerulus. Moreover, 39 different coding region mutations in *MYH9* have been identified in patients with a group of rare syndromes, collectively termed the Giant Platelet Syndromes, with clear autosomal dominant inheritance, and various clinical manifestations, sometimes also including glomerular pathology and chronic kidney disease (Kopp 2010; Sekine et al. 2010). Accordingly, *MYH9* was further explored in

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these studies as the leading candidate gene responsible for the MALD signal. Dense mapping of *MYH9* identified individual single nucleotide polymorphisms (SNPs) and sets of such SNPs grouped as haplotypes that were found to be highly associated with a large and important group of ESKD risk phenotypes, which as a consequence were designated as *MYH9*-associated nephropathies (Bostrom and Freedman 2010). These included HIV-associated nephropathy (HIVAN), primary nonmonogenic forms of focal segmental glomerulosclerosis, and hypertension affiliated chronic kidney disease not attributed to other etiologies (Bostrom and Freedman 2010). The *MYH9* SNP and haplotype associations observed with these forms of ESKD yielded the largest odds ratios (OR) reported to date for the association of common variants with common disease risk (Winkler et al. 2010). Two specific *MYH9* variants (rs5750250 of S-haplotype and rs11912763 of F-haplotype) were designated as most strongly predictive on the basis of Receiver Operating Characteristic analysis (Nelson et al. 2010). These *MYH9* association studies were then also extended to earlier stage and related kidney disease phenotypes and to population groups with varying degrees of recent African ancestry admixture (Behar et al. 2010; Freedman et al. 2009a, b; Nelson et al. 2010), and led to the expectation of finding a functional African ancestry causative variant within *MYH9*. However, despite intensive efforts including re-sequencing of the *MYH9* gene no suggested functional mutation has been identified (Nelson et al. 2010; Winkler et al. 2010). This led us to re-examine the interval surrounding *MYH9* and to the detection of novel missense mutations with predicted functional effects in the neighboring *APOL1* gene, which are significantly more associated with ESKD than all previously reported SNPs in *MYH9*.

SNPs and haplotypes for analysis in previous studies were taken from the HapMap databases available at the time of study (http://www.hapmap.org). These antedated the release and availability of more extensive and detailed DNA diversity information from complete genomic sequences currently available through the 1000 Genomes Project (http://www.1000genomes.org), which in particular provide an enriched sampling of SNPs that are rare in Europe compared to the reported HapMap SNPs, and therefore especially useful for our purposes. Therefore, upon availability of the March 2010 release of the 1000 Genomes Project, we analyzed 119 whole genome sequences of which 60 are of European origin (CEU), and 59 are of West-African origin (YRI), yielding a total of 7,479 SNPs in the 1.55 Mbp chromosome 22 interval surrounding *MYH9* and spanning nucleotide positions 34,000,000–35,550,000 (NCBI36). We then applied filtering criteria to identify candidates for further consideration and analysis based on (1) low allele frequency in CEU but not in YRI and (2) linkage disequilibrium (LD) patterns with the previously identified leading *MYH9* risk variants (see supplementary material). Of the 250 variants that met these criteria, four are coding region nonsynonymous mutations (Table 1), none of which were reported in HapMap. The first two SNPs (rs73885319 and rs60910145) are missense mutations in the last exon of the *APOL1* gene (S342G and I384M) which is the neighboring gene, located 14 kbp 3′ downstream from *MYH9*. A third SNP (rs11089781) is a nonsense mutation (Q58X) in the *APOL3* gene located 110 kbp further 3′ downstream. The fourth SNP (rs56767103) is a missense mutation (R71C) in the gene *FOXRED2* located 100 kbp upstream to the 5′ side of *MYH9* (Supplementary Fig. 1). Of note, the two variants located 128 bp apart in *APOL1* are in almost perfect LD (237 out of 238 chromosomes from the 1000 Genomes Project).

These four variants were genotyped in a previously reported composite sample set of 955 subjects taken from two different populations, namely African American and Hispanic American cases and controls (Behar et al. 2010) (supplementary material). In this composite sample set, subjects with ESKD etiologies designated as *MYH9*-associated nephropathies as defined above, and notably excluding diabetic nephropathy, which was not previously found to be associated with *MYH9* (Behar et al. 2010; Kao et al. 2008; Kopp et al. 2008), were designated as cases ($n = 430$). Subjects without known kidney disease and a creatinine concentration below 1.7 at age 55 or greater were designated as controls ($n = 525$). Associations of the candidate mutations with these ESKD phenotypes, previously attributed to *MYH9*, was determined using logistic regression, with correction for global and local ancestry, and considering three modes of inheritance as previously reported (Behar et al. 2010). It should be noted that the four variants were genotyped for the two population sources using two different techniques each conducted in a separate laboratory, and with sequence validation of the genotyping method (Supplementary Fig. 6). We chose to use two different population sources, African American and Hispanic American, with markedly differing degrees of global African ancestry admixture (Bedoya et al. 2006; Behar et al. 2010), rather than two different collections from the same population, in order to test whether associations were robust to differing global background genomic composition.

Table 1 shows the association results for the combined dataset of the African American and Hispanic American cohorts. For comparison, we include the results from the two previously reported leading *MYH9* risk variants as noted above (S-1 rs5750250, F-1 rs11912763) (Nelson et al. 2010). We found that the *APOL1* missense variants (rs73885319 and rs60910145) are more strongly associated with ESKD risk than the leading *MYH9* risk variants, both in terms of OR and p values (Table 1). In contrast, the

Table 1 Association with nondiabetic ESKD of nonsynonymous SNPs in *APOL1*, *APOL3*, and *FOXRED2* in the MALD peak and comparison with leading *MYH9* SNPs

rs number	Gene	Type	Chr22 location[a]	Alleles[b]	YRI risk frequency[c] (%)	CEU risk frequency (%)	Mode[d]	OR	*p* value
rs73885319[e]	*APOL1*	exon 5 S342G missense	34,991,852	A/**G**	46	0	Recessive	6.7	2.71E−06
							Additive	2.22	2.38E−08
							Dominant	2.23	8.11E−06
rs60910145	*APOL1*	exon 5 I384M missense	34,991,980	T/**G**	45	0	Recessive	6.74	9.89E−06
							Additive	2.28	3.00E−08
							Dominant	2.32	4.75E−06
rs11089781	*APOL3*	exon 1 Q58X nonsense	34,886,714	G/**A**	31	0	Recessive	6.62	2.82E−03
							Additive	2.18	3.79E−06
							Dominant	2.22	3.23E−05
rs56767103	*FOXRED2*	exon 1 R71C missense	35,232,205	G/**A**	18	0	Recessive	1.33	6.83E−01
							Additive	1.52	5.19E−02
							Dominant	1.66	3.64E−02
rs11912763	*MYH9*	intron 33 F-1 designation	35,014,668	G/**A**	48	0	Recessive	2.38	2.86E−02
							Additive	1.96	4.05E−05
							Dominant	2.28	4.20E−05
rs5750250	*MYH9*	intron13 S-1 designation	35,038,429	A/**G**	66	6	Recessive	2.48	4.29E−05
							Additive	1.78	6.68E−05
							Dominant	1.55	4.97E−02

[a] Location on Chromosome 22 in NCBI36 assembly

[b] African ESKD "risk" state in bold

[c] Frequencies according to available 1000 Genomes data

[d] Association results were derived using logistic regression, correcting for global and local African ancestry, and combining the Hispanic and African American cohorts. See supplementary text for details

[e] See Supplementary Fig. 5 for allele frequency pie-charts in cases versus controls

lower allele frequency and OR, with a higher *p* value for the *APOL3* nonsense variant, and the weak association for the *FOXRED2* missense mutation, render these variants to be very unlikely candidates to explain the risk attributed to this genomic region. For the highly associated *APOL1* missense mutations, the risk allele frequency in the African American control cohort is 21% in contrast to 37% in the cases (corresponding values for Hispanic Americans are 6 and 23%, respectively). The most striking difference is in the frequency of the homozygote risk state, with only 3% in controls compared to 18% in cases for African Americans (corresponding values for Hispanic Americans are 0.5 and 11%, respectively) (see also Supplementary Fig. 5). We also show that the results for combined and meta-analysis of the two separate cohort-based results are congruent (Supplementary Table 1). As also evident from Table 1 and Supplementary Table 1, the modes of inheritance for which the associations of the disease risk phenotype with the *APOL1* missense mutations are significant is consistent with an additive effect, wherein carrying the missense mutations on a single parental allele is sufficient to confer significantly increased risk, but with a still greater jump in risk conferred by carrying the missense mutations on both parental alleles. As noted above, the two missense mutations are in nearly perfect LD, and therefore, on a population genetics basis alone they can be considered as designating a "missense risk haplotype". Examination of the predicted effect on protein structure and functional studies with artificial constructs which separate the two missense mutations will determine whether disease risk relates to either or both together as a functional missense haplotype. Therefore, for further analysis in the current study, we go on to use *APOL1* SNP rs73885319 as tagging the "missense risk haplotype". Analysis of deviance of the combined logistic regression indicates that LD with *APOL1* SNP rs73885319 accounted for most of the statistical association previously attributed to the leading *MYH9* variants with ESKD (supplementary material). In this regard, we also examined two noncoding variants in the *APOL1* region which are in high LD with the *APOL1* missense mutations, and as expected, both showed significant disease risk association (Supplementary Fig. 2; Supplementary Table 1).

HIVAN has been considered as the most prominent of the nondiabetic forms of kidney disease within what has been termed the *MYH9*-associated nephropathies (Kopp et al. 2008; Winkler et al. 2010). We have reported absence of HIVAN in HIV infected Ethiopians, and attributed this to host genomic factors (Behar et al. 2006). Therefore, we examined the allele frequencies of the *APOL1* missense mutations in a sample set of 676 individuals from 12 African populations, including 304 individuals from four Ethiopian populations (Supplementary Table 2). We coupled this with the corresponding distributions for the African ancestry leading *MYH9* S-1 and F-1 risk alleles. A pattern of reduced frequency of the *APOL1* missense mutations and also of the *MYH9* risk variants was noted in northeastern African in contrast to most central, western, and southern African populations examined (Supplementary Fig. 3). Especially striking was the complete absence of the *APOL1* missense mutations in Ethiopia. This combination of the reported lack of HIVAN and observed absence of the *APOL1* missense mutations is consistent with *APOL1* being the functionally relevant gene for HIVAN risk and likely the other forms of kidney disease previously associated with *MYH9*.

The *APOL1* gene encodes apolipoprotein L-1, whose known activities include powerful trypanosome lysis (Vanhamme et al. 2003), autophagic cell death (Wan et al. 2008), lipid metabolism, cellular senescence, as well as vascular and other biological activities (Monajemi et al. 2002; Vanhollebeke and Pays 2006). Of note, in humans, *APOL1* is one of six closely spaced and related *APOL* genes, respectively, encoding six gene products apolipoproteins L-1 through L-6 (Duchateau et al. 1997, 2001). While *APOL3* is thought to have arisen first in genomic evolution of the region, with the others having arisen as a result of duplication events (Monajemi et al. 2002), only apolipoprotein L-1 has a signal peptide which enables it to be both a circulating and intracellular protein (Vanhollebeke and Pays 2006). This latter capacity is of crucial importance to the protective and lytic activity of human serum to many species of trypanosoma. *Trypanosoma brucei rhodesiense* transmitted by tsetse flies causes human African trypanosomiasis as a result of the expression of serum resistance associated protein (SRA), which interacts with the C-terminal domain of apolipoprotein L-1 and inactivates its lytic function (Lecordier et al. 2009). Apolipoprotein L-1 protein structure is divided into three distinctive structural and functional domains: (1) an anionic pore-forming domain which is thought to be involved in organellar permeation and cell death, (2) a membrane addressing-domain consisting of a pH-sensitive hairpin bridging two alpha helices which facilitates association with the circulating HDL particle at neutral pH and intracellular organellar localization at acidic pH, and 3) a C-terminus amphipathic alpha helix with a leucine zipper for protein–protein interaction (Vanhollebeke and Pays 2006). It should be noted that the *APOL1* S342G variant, powerfully associated with kidney disease risk in the current study, is predicted to modify the binding site of the C-terminus domain of the *APOL1* gene product (Supplementary Fig. 4).

With respect to kidney disease risk, apolipoprotein L-1 is also prominently involved in autophagic pathways (Zhaorigetu et al. 2008), and a recent study has provided compelling evidence for the role of well-preserved autophagy in the integrity of renal glomerular podocytes (Hartleben et al. 2010). It is thus possible that variation in the C-terminus domain of endogenously expressed or endocytosed apolipoprotein L-1 modifies interaction with an as yet unidentified renal intracellular protein, which regulates the availability of apolipoprotein L-1 in its pore-forming or other functions. Given the numerous known functions of apolipoprotein L-1 noted above, a number of other mechanisms for kidney disease risk are possible, including those related to lipid metabolism or vascular integrity (Monajemi et al. 2002). The involvement of other classes of apolipoproteins in nephropathy has been well documented (Takemura et al. 1993). Moreover, apolipoproteins have also been identified as circulating inhibitors of glomerular proteinuria (Candiano et al. 2001). Remarkably, in this latter study, the amino acid sequence of the apolipoprotein L fraction isolated and studied corresponds exactly to what we now know to be apolipoprotein L-1.

Functional assays of the effect of the *APOL1* missense variants described herein in appropriate experimental model systems will be needed to link the strong and biologically plausible association to a functional pathogenic pathway in kidney disease and to the possible selective factors which contributed to the observed African allele frequency distribution.

It is noteworthy that this entire region of the genome shows a high degree of LD and evidence of strong evolutionary selection, which may well explain why *MYH9* yielded such a strong association signal in prior studies due to a hitchhiking effect of *MYH9* with variants in the *APOL* gene family that have conferred adaptive advantage (Grossman et al. 2010; Smith and Malik 2009; Stephan et al. 2006). It should also be noted that the expression of apolipoproteins L in vascular and immune cells is greatly increased by viral infections, interferons, and inflammatory mediators (Vanhollebeke and Pays 2006), any or all of which might constitute the basis for a second "trigger" needed to induce the actual clinical manifestation of nephropathy in a genotypically "at risk" individual. Moreover, given the close evolutionary relationship of the six members of the human apolipoprotein L family and their manifold and overlapping functions, it is conceivable that additional rare or common variants might also interact and be involved in kidney disease risk (Supplementary Table 3).

The current findings strongly suggest that the intensive efforts (http://www3.niddk.nih.gov/fund/other/MYH9KidneyDisease/) currently underway to identify the ESKD disease phenotype risk causative variant in the chromosome 22 MALD peak should certainly be extended beyond the *MYH9* locus. In particular, a strong emphasis should also be placed on *APOL1* mutations with strong association and functional plausibility.

Methods and supplementary information and any associated references are available on the *Human Genetics* website: http://www.springer.com/biomed/human+genetics/journal/439.

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