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Version of Record: https://www.sciencedirect.com/science/article/pii/S176972551930046X
Manuscript_e7d7ea057bf9638e648c5fc71fd9e714

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Balancing the genetic risk of *APOL1* kidney disease variants

Variations génétiques d'APOL1 et pathologies rénales associées

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Conflict of interests

None to declare.

1. Introduction

The 2012 Kidney Disease Outcomes Quality Initiative (KDOQI) defined chronic kidney disease as the persistence for more than 3 months of kidney damage (including albuminuria, imaging or histology-detected abnormalities) or kidney function impairment (characterized by a glomerular filtration rate below 60 ml/min/1.73m²) (1). Chronic kidney disease severity is classified into five stages (from G1 to G5) based on glomerular filtration rates and albuminuria range (1,2). Progression to stage G5 is known as end-stage kidney disease and is defined as kidney failure requiring renal replacement therapy (dialysis or kidney transplantation).

Chronic kidney disease represents a major and growing public health burden worldwide with 2 million deaths and 51 million disability-adjusted life-years (DALY) attributed to the disease in 2015 (3). Chronic kidney disease prevalence is estimated around 10 to 15% globally, and varies across populations with 3.3 to 17.3% reported in Europe, 14.8% in the United States of America (USA), 10.8% in China, and 5-17% in sub-Saharan Africa (4-9). In France, approximately 6 million people (10%) live with chronic kidney disease and 83,000 patients were treated for end-stage kidney disease in 2015 (10). The incidence rate for end-stage kidney disease increases every year by 2% and was of 166 per million inhabitants in France in 2015, which represents one of the highest values in Europe (mean incidence=119pmp) (10). Managing chronic kidney disease and its related complications has a considerable economic impact, with 3.4 billion euros spent in 2017 and more than 5 billion euros of projected costs for 2025 by the French national health insurance (CNAMTS) for end-stage kidney disease management alone (10,11).

The USA are even more affected by chronic and end-stage kidney disease, with an incidence of the latter of 378pmp and up to 7.2% of Medicare costs dedicated to its management (12). The total health insurance expenditure for chronic and end-stage kidney disease management exceeded $98 billion in 2015 only (13). These high numbers notably conceal a major health disparity in kidney diseases with an increased risk for the African-American population, even after controlling for social economic status, life-style and other confounding factors (14,15). African-Americans are overall 3.5 times more likely to develop end-stage kidney disease than their counterparts of European ancestry. When discriminating by aetiology, African-Americans are more at risk for developing end-stage kidney disease for every major cause: diabetes, hypertension and glomerulopathies (12). These observations and the clustering of chronic and end-stage kidney disease among families supported the existence of genetic risk factors causing kidney diseases in African Americans (16,17).

Most of the increased risk for chronic kidney disease in African-Americans has been attributed to two genetic variants in the *APOL1* gene, named G1 and G2. This review summarizes the discovery

of *APOL1* renal risk alleles, the evolutionary arms race with trypanosomes, and the clinical applications for kidney transplantation.

2. Discovery of *APOL1* renal risk variants

Considering the overt disparity for chronic kidney disease in African-Americans, two groups implemented a mapping by admixture linkage disequilibrium strategy to identify the genetic determinants for this racial disparity in the recently admixed African-American population (18,19). The first group focused on non-diabetic end-stage kidney disease, when the second investigated two glomerulopathies, focal segmental glomerulosclerosis and human immunodeficiency virus (HIV)-associated nephropathy (or collapsing focal segmental glomerulosclerosis). Indeed, African-Americans are four to five times more likely to develop focal segmental glomerulosclerosis and have more than 18 times higher risk for developing HIV-associated nephropathy than European Americans (20,21). Using ancestry-informative markers spread across the genome, mapping by admixture linkage disequilibrium can differentiate chromosome portions originating from European or African ancestry in African-American individuals. By scrutinizing the genomes of an African-American population affected with kidney disease, mapping by admixture linkage disequilibrium can therefore map the genetic loci with increased African ancestry, that are likely associated with kidney disease. Both groups identified a strong association on chromosome 22 in a locus encompassing more than 30 different genes and centred on the *MYH9* gene.

The culprit gene was discovered two years later with the advent of the 1000 Genomes Project in the vicinity of *MYH9*. Two common coding genetic variants in the *APOL1* gene (G1 and G2) exhibited even stronger associations with focal segmental glomerulosclerosis and non-diabetic end-stage kidney disease than previously described (22,23). G1 corresponds to the rs73885319 nonsynonymous coding variant (p.S342G, NM_003661.3, 23% in the African-American population), and G2 is the rs71785313 two amino acid deletion (p.delN388/Y389, NM_003661.3, 13% in the African-American population). These two alleles appeared independently on opposing chromosomes and have never undergone genetic recombination, hence no haplotype carries simultaneously G1 and G2. The association with renal pathologies follows a recessive inheritance model (24): only African-Americans carrying two renal risk alleles (G1/G1 homozygous, G2/G2 homozygous and G1/G2 compound heterozygous, also known as the high-risk genotypes) have an increased risk for chronic kidney disease (**Figure 1a**). Approximately 14% of the African-American population carries two *APOL1* risk variants.

APOL1 associations with focal segmental glomerulosclerosis (OR 17) and HIV-associated nephropathy (OR 29) represent the strongest associations ever reported for common variants with a complex disease (25). Beyond focal segmental glomerulosclerosis/HIV-associated nephropathy, *APOL1* high-risk was further associated with numerous non-diabetic kidney phenotypes: hypertension-attributed end-stage kidney disease , sickle-cell nephropathy, lupus nephritis,

microalbuminuria and faster kidney function decline (22, 26-29). Finally, although no association was reported with the onset of the diabetic nephropathy, *APOL1* high-risk was associated with a more rapid kidney function decline in African Americans with diabetes (29).

3. Geographic distribution of *APOL1* variants and recent selective pressure

APOL1 renal risk variants have only been reported on African-derived chromosomes from the Americas (USA African-Americans, Afro-Caribbeans, Central Americans, Brazilians from Salvador) and Africa (24,30). G1 and G2 alleles are widely spread across sub-Saharan Africa, and reach very high frequencies in West Africa (over 40% for G1 and over 20% for G2) (24,30).

APOL1 G1 and G2 deleterious variants reached such high frequencies in West Africa due to recent positive selection events (22,31). It is believed that a coevolutionary arms race occurred between *APOL1* and African trypanosomes. *Trypanosoma brucei* are parasites transmitted by the tsetse fly that cause African sleeping sickness or trypanosomiasis. The *T.b. rhodesiense* subspecies is responsible for the acute form of the disease and restricted to Eastern and Southern Africa, whereas the *T.b. gambiense* subspecies is responsible for the chronic form of the disease in Western and Central Africa (32). APOL1 is known as the human trypanolytic factor that can kill *T.b. brucei*, but *T.b. rhodesiense* and *T.b. gambiense* have evolved resistance mechanisms against APOL1 lysis (33,34). Both G1 and G2 can restore in vitro APOL1 trypanolytic activity against *T.b. rhodesiense* (**Figure 1b**) but have no impact on *T.b. gambiense* lysis (22,31). Interestingly, G2 was recently associated with a five times decreased risk of *T.b. rhodesiense* infection in a Uganda population (n=184 *T.b.r* infected vs. 180 controls) and G1 was associated with a protection against *T.b. gambiense* severity (OR 3) in Guineans (n=167 *T.b.g* clinical stage vs. 60 *T.b.g* asymptomatic carriers) (35). These reports clearly establish a role for *APOL1* G1 and G2 variants in the fight against African trypanosomiasis, and illustrate a perfect example of balancing selection between chronic kidney disease risk and trypanosomiasis protection (**Figure 1**).

However, the evolution story of *APOL1* variants seems to be more complex than described above. There is indeed a geographic paradox between G2 high frequency in West Africa and *T.b. rhodesiense* distribution in Eastern and Southern Africa (24,35,36). One hypothesis is that *T.b. rhodesiense* was the driving positive selection force for G2, and that its endemicity would have shifted toward East due to the rising G2 frequency or due to an environmental pressure. However, there is very little epidemiological data supporting this theory to date. In addition, G2 was found to confer an increased risk to *T.b. gambiense* severity (OR 3) in Guineans (35), which might seem in contradiction with the current West Africa endemicity of *T.b. gambiense*. An alternate hypothesis to explain this puzzle is that another pathogen would have driven G2 selection in West Africa. This model is supported by several piece of evidence indicating that APOL1 might play a broader innate immunity role against infections (37–39).

4. APOL1 cellular function

The mechanisms leading to APOL1 resistance against *T. brucei* infections have been largely studied. Briefly, APOL1 circulates in the bloodstream as a component of high density lipoproteins. Upon receptor-mediated endocytosis, the progressive acidification of the endolysosomal compartment triggers a conformational change that drives APOL1 to the lysosomal membrane where it forms a pore provoking the parasite lysis (40,41). To counteract APOL1 trypanolytic activity, both *T.b.* subspecies have evolved independent mechanisms to prevent APOL1 lethal membrane insertion: *T.b. rhodesiense* acquired a SRA glycoprotein that directly interacts with APOL1 C-terminal region, whereas *T.b. gambiense*-specific glycoprotein (TgsGP) stiffens the endolysosomal parasitic membrane (33,34).

Beyond its trypanolytic activity, APOL1 plays a broader protective role in innate immunity. It is upregulated by proinflammatory cytokines including interferon γ and tumour necrosis factor α, protects against Leishmania parasitic infection, and restricts HIV in vitro replication (37-39,42,43).

The investigation of APOL1 cellular function has been hampered by its high level of associated cytotoxicity (44,42,45), and the lack of proper animal models. APOL1 is a member of the APOL family (APOL1-6) that arose by gene duplications in primates only. *APOL* homologs are found throughout the animal kingdom, but only humans, gorillas and baboons retained a functional *APOL1* gene, which suggest that the fitness cost is greater than the innate immunity benefit, and that APOL1 is not necessary for kidney development or normal function (46–48).

Most reports investigating APOL1 renal function are therefore based on cell models, but recently some transgenic mouse models were successfully established (36). Numerous mechanisms have been proposed to explain APOL1-induced kidney injury, and the identification of the clinically relevant pathway(s) is yet to be confirmed. First, APOL1 renal risk variants were shown to impair mitochondrial function in cell models (49,50). Second, autophagy and an alteration of vesicle trafficking were proven as major actors of APOL1-mediated cell death mechanism, both in cell and animal models (51–54). Interestingly, the mouse model developed by Beckerman et al. successfully recapitulates proteinuria, podocyte effacement, and the molecular signature of human APOL1-related kidney disease (54). Third, the soluble urokinase plasminogen activator receptor (suPAR) was reported to form a complex with APOL1 and $\alpha_v\beta3$ integrin on mouse podocytes causing proteinuria in a suPAR-dependent manner (55). Similarly, suPAR levels were shown to modulate APOL1-related renal risk in two independent cohorts, but the implication of suPAR in chronic kidney disease remains controversial (55,56). Finally, a surprising role for *APOL1* RNA was recently associated with podocyte damage through the activation of protein kinase R (PKR) in cells and transgenic mice (57).

Further studies will be necessary to discriminate the pathway(s) relevant for drug targeting. Ultimately, any molecular mechanism proposed for APOL1-driven kidney injury will have to (i) reconcile with the strong recessive pattern of inheritance observed in every epidemiological study, and

(ii) account for the fact that the majority of African-Americans carrying APOL1 high-risk (14% of African-Americans) do not develop chronic kidney disease, suggesting the intervention of a second factor (58).

5. APOL1 and clinical translation – the kidney transplantation case

Shortly after the discovery of *APOL1* renal risk variants, several groups became interested in their potential impact on kidney allograft survival. If allograft survival is not affected by the recipient *APOL1* genotype, the donor *APOL1* high-risk genotype was significantly associated with shorter survival in three independent studies involving deceased donors (HR ~2) (59–62) (**Figure 2**). In addition, *APOL1* high-risk was associated with an increased risk for postnephrectomy end-stage kidney disease in living kidney donors (63,64).

These observations raise the question of systematic *APOL1* genotyping in potential African-American kidney donors (deceased or living). *APOL1* genotyping could contribute to upgrade donor-recipient matching to extend allograft survival and limit adverse kidney transplantation outcomes. *APOL1* genotyping could also be beneficial for potential living kidney donors with African ancestry by assessing their future risk for end-stage kidney disease.

A recent study rose hope in potential positive impact of *APOL1* genotyping for kidney transplantation outcomes (65). Before the identification of *APOL1* renal risk variants, racial disparities had been observed in kidney transplantation outcomes: allografts from African-American donors exhibit a shorter survival compared to organs donated by European Americans. Race was therefore one of the ten donor characteristics (along with age, body mass index, history of diabetes or hypertension, etc.) included in the kidney donor risk index that quantifies risk for allograft failure and enhances graft allocation from deceased donors (66). The kidney donor risk index assigns the same negative weight to all African-American donors, whether they carry the *APOL1* high-risk genotype or not. Very interestingly, one group demonstrated that replacing donor race with *APOL1* genotype was improving the predictive power of the kidney donor risk index and graft allocation, while increasing the pool of potential functioning organs (65).

Beyond this study, very few data support a clinical benefit for *APOL1* genotyping. The National Institutes of Health (NIH) initiated the APOL1 long-term kidney transplantation outcomes (APOLLO) network to provide prospective, objective and critical information on potential benefits and ethical considerations for genotyping African-American donors (67). This project has the potential to (i) provide revised policies on donor-recipient matching, with positive consequences on prolonged allograft survival and reduced organ discard, and (ii) provide critical safety data for potential living kidney donors regarding postdonation end-stage kidney disease risk.

6. Conclusion

The identification of *APOL1* renal risk variants has been a major discovery for the nephrology community in understanding most of the excess risk for non-diabetic chronic kidney disease in African-Americans. In less than 10 years, data have immensely mounted up on the *APOL1* gene and cellular function. APOL1 is a perfect example of balancing selection between the chronic kidney disease susceptibility of high-risk carriers and the positive selection for resistance against trypanosome infections, even if the evolutive story might be more complex than anticipated. Investigating further cellular and animal models will be necessary to decipher the precise molecular mechanisms of APOL1-induced kidney injury and will be an essential step toward developing new therapeutic strategies. Finally, the community has hope to soon leverage *APOL1* genotyping for improving the management of kidney transplantation and living donation, as a promise of personalized medicine approach.

Author contribution

NFK and SL have compiled the literature and cowritten this review. SL realized the figures.

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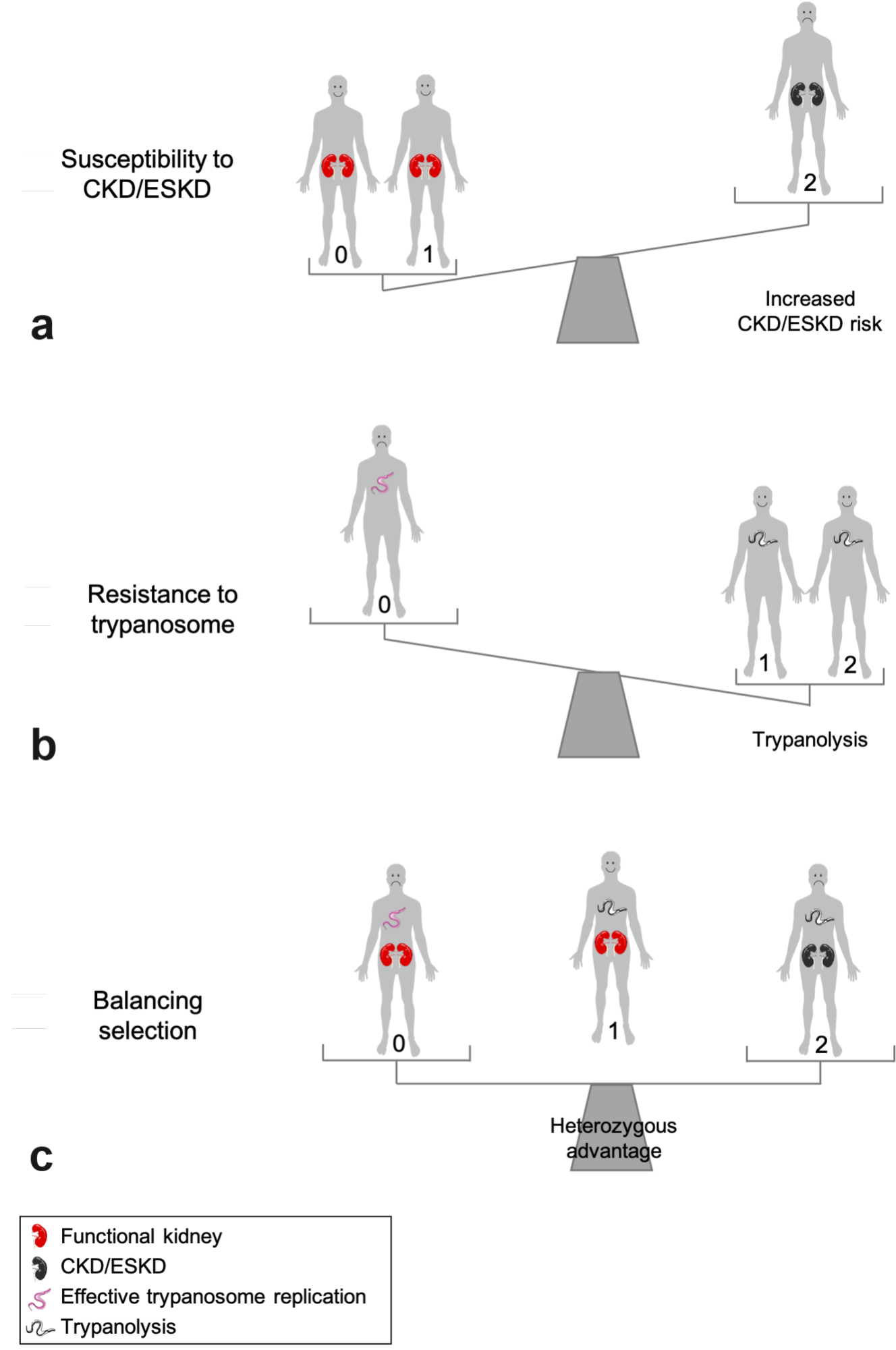
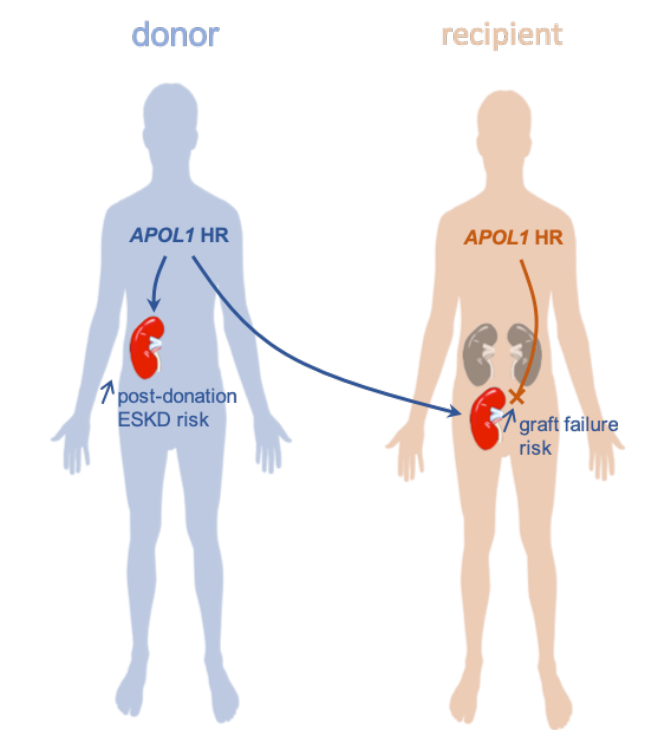
Figure legends

Figure 1. APOL1, an example of balancing selection. a: African-Americans carrying two *APOL1* risk variants (recessive model) are at increased risk for non-diabetic chronic and end-stage kidney diseases (22,23,25-28); **b**: *APOL1* renal risk variants showed a signature of recent positive selection in West Africa by African trypanosomes, especially *T.b. rhodesiense* (22,31). Carriage of one *APOL1* allele is sufficient for protecting against trypanosome infection. However, the evolutive story might be more complex (see main text); **c**: Overall, *APOL1* alleles are a perfect example of balancing selection between chronic/end-stage kidney disease risk and trypanosomiasis protection. Individuals carrying only one *APOL1* allele present a fitness advantage compared to individuals carrying 0 or 2 risk alleles, as they are simultaneously protected from trypanosome infections and not at increased risk for chronic/end-stage kidney disease. The number of *APOL1* risk alleles is indicated under each individual. Zero risk allele: G0/G0 (or WT/WT); one risk allele: G0/G1 or G0/G2; two risk alleles: renal high-risk genotypes, G1/G1, G1/G2 or G2/G2. CKD, chronic kidney disease; ESKD, end-stage kidney disease.

Figure 2. APOL1-associated outcomes in kidney transplantation. Donor *APOL1* high-risk genotypes (and not recipient) were associated with a faster allograft failure (59-62) and with higher rates of post-donation end-stage kidney disease in living kidney donors (63,64). *APOL1* HR: *APOL1* high-risk genotypes; ESKD: end-stage kidney disease.


Susceptibility to CKD/ESKD
0
1
2
Increased CKD/ESKD risk
a
Resistance to trypanosome
0
1
2
Trypanolysis
b
Balancing selection
0
1
2
Heterozygous advantage
c
Functional kidney
CKD/ESKD
Effective trypanosome replication
Trypanolysis


donor
recipient
APOL1 HR
APOL1 HR
post-donation
ESKD risk
graft failure
risk