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APOL1 NEPHROPATHY RISK VARIANTS AND INCIDENT CARDIOVASCULAR DISEASE EVENTS

Nazarova Nigina Otabek qizi – Ph.D.
Jabbarov Ozimbay Otaxanovich – D.M.Sc., professor, scientific leader
Tashkent medical academy (Tashkent, Uzbekistan)

The increased prevalence of chronic kidney disease (CKD) in elderly patients recognizes, as main cause, the long-term exposure to atherosclerosis and hypertension. Chronic ischemic damage due to critical renal arterial stenosis induces oxidative stress and intra-renal inflammation, resulting in fibrosis and microvascular remodelling, that is the histological picture of atherosclerotic renal vascular disease (ARVD).

Key words: *atherosclerosis, chronic kidney disease, plaque.*

ВАРИАНТЫ РИСКА РАЗВИТИЯ НЕФРОПАТИИ APOL1 И СЛУЧАИ РАЗВИТИЯ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ

Назарова Нигина Отабек қизи – Ph.D.
Жаббаров Озимбой Отаханович – д.м.н., профессор, научный руководитель
Ташкентская медицинская академия (Ташкент, Узбекистан)

Увеличение распространенности хронической болезни почек (ХБП) у пожилых пациентов признает, как основную причину, длительное воздействие атеросклероза и гипертонии. Хроническое ишемическое повреждение из-за критического стеноза почечной артерии вызывает окислительный стресс и внутрипочечное воспаление, что приводит к фиброзу и микрососудистому ремоделированию, что является гистологической картиной атеросклеротического заболевания почечных сосудов (АРПВС).

Ключевые слова*: атеросклероз, хроническая болезнь почек, бляшка.*

APOL1 НЕФРОПАТИЯ ХАВФИНИНГ ВАРИАНТЛАРИ ВА ЮРАК-ҚОН ТОМИР КАСАЛЛИКЛАРИДА УЧРАШИ

Назарова Нигина Отабек қизи – Ph.D.
Жаббаров Озимбой Отаханович – т.ф.д., профессор, илмий рахбар
Тошкент тиббиёт академияси (Тошкент, Ўзбекистон)

Кекса беморларда сурункали буйрак касаллиги (СБК) тарқалишининг кўпайиши асосий сабаб сифатида атеросклероз ва гипертензияни узоқ муддатли таъсир қилиши хисобланади. Критик буйрак артериал стенози туфайли сурункали ишемик шикастланиш оксидловчи стресс ва буйрак ичидаги яллигланишни келтириб чиқаради, натижада фиброз ва микроваскуляр қайта тикланади, яъни атеросклеротик буйрак қон томир касаллигининг (АРВД) гистологик расмидир.

Калит сўзлар: *атеросклероз, сурункали буйрак касаллиги, пилакча.*

Introduction. Scientific experience significant health disparities for kidney and cardiovascular diseases (CVDs), which are only partially explained by access to medical care or other socioeconomic factors. In patients with chronic kidney disease (CKD), CVD is the

leading cause of death. Much of the excess risk for nondiabetic CKD in Uzbek population is explained by 2 common coding alleles (termed G1 and G2) in *APOL1*, encoding APOL1 (apolipoprotein L1) (1). These variants only occur on Uzbekistan ancestry chromosomes and extend protection against *Trypanosoma brucei*.[8–11] *APOL1* high-risk genotypes (carriage of 2 *APOL1* risk alleles) are associated with higher prevalence and progression of a spectrum of CKDs, characterized by albuminuria and reduced estimated glomerular filtration rate, each of which is risk factors for CVD. The APOL1 protein is expressed in the systemic and kidney vasculature, and *APOL1* variants are associated with more severe kidney arteriosclerosis with aging and hypertension (2,11).

The relationship between *APOL1* kidney risk variants and clinical CVD remains unresolved, with some studies reporting positive associations and others no association for prevalent or incident heart disease or stroke. Study, *APOL1* high-risk genotypes were positively associated with subclinical peripheral atherosclerosis and incident myocardial infarction (MI). However, a study of 18 middle-aged adults with mostly preserved kidney function to find an association between *APOL1* renal risk alleles and subclinical markers of atherosclerotic disease. Among studies enrolling individuals with known CVD risk factors including referral for cardiac catheterization, hypertensive CKD, or hypertension, *APOL1* high-risk status did not associate with overall risk for prevalent or incident CVD(3,14,16).

Given present uncertainties about the association of *APOL1* genetic risk variants with incident CVD events, we obtained *APOL1* genotypes for 21 patients enrolled the association of *APOL1* variants with incident ischemic stroke, coronary heart disease (CHD), and the composite of these outcomes. In addition, in prespecified analyses, we examined whether CKD, advanced age, diabetes mellitus, or sickle cell trait modified *APOL1* associations with CVD (4).

Metods and materials. The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. Investigators who would like to request that data will need to first obtain information on the policies and procedures to do so. We examined associations of *APOL1* with incident coronary heart disease (n=23), ischemic stroke (n=11), and the composite CVD outcome (n=27) in 35 patients (5,6). Primary analyses compared individuals with *APOL1* high-risk genotypes to *APOL1* low-risk genotypes in Cox proportional hazards models adjusted for CVD risk factors and Uzbek population.

Albuminuria and reduced eGFR associate with two apolipoprotein L1 gene (*APOL1*). Whether *APOL1* associates with subclinical atherosclerosis and survival remains unclear. To determine this, 17 patients underwent computed tomography to determine coronary artery, carotid artery, and aorta calcified atherosclerotic plaque mass scores in addition to the urine albumin: creatinine ratio (UACR), eGFR, and C-reactive protein. Associations between mass scores and *APOL1* were assessed adjusting for age, gender, HbA1c, smoking, hypertension, use of statins and ACE inhibitors, albuminuria, and eGFR. Participants were 58.9% female with mean age 56.5 years, eGFR 89.5 ml/min/1.73m^2, UACR 169.6 mg/g, coronary artery, carotid artery and aorta calcified plaque mass scores of 610, 171 and 5378, respectively. In fully adjusted models, *APOL1* risk variants were significantly associated with lower levels of carotid artery calcified plaque (β −0.42, SE 0.18, dominant model), and marginally lower coronary artery plaque (β −0.36, SE 0.21; dominant model), but not with aorta calcified plaque, C-reactive protein, UACR, or eGFR. After a mean follow-up of 5.0 years, 89 participants died. *APOL1* nephropathy risk variants were significantly associated with improved survival (hazard ratio 0.67 for 1 copy; 0.44 for 2 copies). Thus, *APOL1* nephropathy variants associate with lower levels of subclinical atherosclerosis and reduced risk of death in African Americans with type 2 diabetes mellitus (7,8).

Results: *APOL1* high-risk participants were younger and more likely to have albuminuria at baseline than *APOL1* low-risk participants. The risk of incident stroke, coronary heart disease, or composite CVD end point did not significantly differ by *APOL1* genotype

status in multivariable models. The association of *APOL1* genotype with incident composite CVD. In those without diabetes mellitus, *APOL1* high-risk genotypes associated with greater risk of incident composite CVD (hazard ratio, 1.67; 95% confidence interval, 1.12–2.47) compared with those with *APOL1* low-risk genotypes in multivariable adjusted models. This latter association was driven by ischemic strokes (hazard ratio, 2.32; 95% confidence interval, 1.33–4.07), in particular, those related to small vessel disease (hazard ratio, 5.10; 95% confidence interval, 1.55–16.56). There was no statistically significant association of *APOL1* genotypes with incident CVD in subjects without diabetes mellitus. The *APOL1* high-risk genotype was associated with higher stroke risk in individuals without but not those with chronic kidney disease in fully adjusted models.

Genotypic Assessment. *APOL1* risk variants (G1 and G2) were genotyped using TaqMan SNP Genotyping Assays (Applied Biosystems / ThermoFisher Scientific). *APOL1* high-risk status was defined as the presence of 2 risk alleles (G1/G1, G2/G2, or G1/G2) versus the low-risk status, defined as having 1 or 0 risk variants (G1/G0, G2/G0, G0/G0), representing a recessive model. Sickle cell trait (HbS) was genotyped as described in Naik et al. In secondary analyses, an additive (0, 1, 2 risk alleles) and dominant model (2 or 1 *APOL1* risk alleles versus 0 risk alleles) were assessed. A subset of participants had available genomic array data (Illumina exome chip) to estimate population substructure (n=6714) via principal components generated using EIGENSOFT software. In sensitivity analyses, principal components were used to adjust for Uzbek population in the subset with available data.

Conclusions: *APOL1* high-risk status is associated with CVD events in community-dwelling Black adults without diabetes mellitus. Of 31 patients, 12 had 0 *APOL1* risk alleles, 22 had 1 risk allele (12 had the G1/0 genotype and 1850 the G2/0 genotype), and 13 had 2 risk alleles (13 were G1 homozygotes, 25 were G2 homozygotes, and 16 were compound G1/G2 heterozygotes).

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