Abstract Type : Oral
Abstract Submission No. : 1341

Genome-wide association study and fine-mapping based on Korean biobank study to discover glomerular filtration rate associated variants

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Objectives: Chronic kidney disease is a burden for global health with continuous increases. For a decade, several genome-wide association studies (GWAS) were published to reveal associated single nucleotide polymorphisms (SNP); however, most of the effects were focused on European ancestry.

Methods: The sample and clinical data collected in the Korean Genome and Epidemiology Study (KoGES) were used. The genotyping was done using Genome-Wide Human SNP Array 5.0 and Korean Chip. Imputation was performed using Beagle. METAL was used for fixed-effect meta-GWAS analysis. The creatinine-based estimated glomerular filtration rate (eGFRcr) calculated using the CKD-EPI equation was used for a quantitative trait. GWAS on other traits including blood urea nitrogen (BUN) and eGFR based on cystatin C (eGFRcys) were used for validation of the result. A web-based tool FUMA was used for clumping and fine-mapping of causal variants. MAGMA gene analysis was used to aggregate of effects of several SNPs on a single gene. DisGeNet, a database of gene-disease associations, was used for over-representation analysis of significant genes.

Results: More than five million SNPs from 58406 participants were analyzed. After meta-GWAS, there were 1360 loci associated with eGFR with a genome-wide significant level (P = 5e-8, Figure 1, manhattan plot). Among them, 399 loci were validated with at least one other biomarker (BUN or eGFRcys) and 149 loci were validated using both markers. Followed fine-mapping and integrative analysis discovered several variants and relevant genes (Figure 2).

Conclusions: In this study, we performed GWAS in more than 50000 Korean populations and discovered several variants associated with renal function traits, including eGFR, BUN, and eGFRcysc. Also, we investigated the function of relevant genes with integrative methods.

Figure 1