Abstract Type : Oral Presentation
Abstract Submission No. : F-007003

Unveiling Shared Genetic Risks of Type 2 and Post-transplant Diabetes Mellitus in East Asians Through Polygenic Risk Scores

Seokwoo Park[1], Hye-Mi Jang[2], Jaeseok Yang[3], Bong-Jo Kim[2], Myoung Soo Kim[4], Hyun-Young Park[5], Young Jin Kim[2], Jong Cheol Jeong[1]

[1]Department of Nephrology, Seoul National University Bundang Hospital, Republic of Korea
[2]Department of Precision Medicine, National Institute of Health, Republic of Korea
[3]Department of Nephrology, Severance Hospital, Yonsei University, Republic of Korea
[4]Department of Surgery, Severance Hospital, Yonsei University, Republic of Korea
[5]Department of President, National Institute of Health, Republic of Korea

Introduction: Post-transplant diabetes mellitus (PTDM) contributes to adverse cardiovascular outcomes in kidney transplant recipients (KTRs). We examined whether polygenic risk scores (PRSs) for type 2 diabetes mellitus (T2D) can predict PTDM in an East Asian Cohort. Further, partitioned T2D PRSs representing distinct clusters of cardiometabolic traits were utilized to investigate whether PTDM exhibits unique associations.

Methods: We constructed T2D PRSs with genome-wide association study (GWAS) data from BioBank Japan (PRS_{BBJ}) and from the East Asian ($PRS_{EastAsian}$) and Trans-ethnic (PRS_{Trans}) components of the Diabetes Meta-Analysis of Trans-Ethnic association studies. The performances of the T2D PRSs were validated in the general population (T2D, n=12,983; control, n=101,267) from the Korean Genome Epidemiology Study (KoGES). We devised a PTDM PRS (PRS_{PTDM}) with the previous PTDM GWAS by McCaughan *et al.* The associations of the PRSs and PTDM development were explored in 1,524 KTRs including 190 PTDM cases from the Korean Organ Transplantation Registry. We further acquired another set of T2D PRSs based on eight mechanistic clusters from the largest T2D multi-ancestry GWAS meta-analysis to date by Suzuki *et al.* 2023. We compared the associations of the mechanism-specific PRSs with T2D and PTDM to understand possible genetic discrepancy. Genotyping was performed using the Korea Biobank Array.

Results: PRS_{BBJ}, $PRS_{EastAsian}$, and PRS_{Trans} were externally validated to predict T2D using logistic regressions, with Nagelkerke pseudo-R^2 values of 0.088, 0.083, and 0.087, respectively. Cox regressions demonstrated that PRS_{BBJ} (hazard ratio [HR] 1.60, $P=1.08 \times 10^{-10}$), $PRS_{EastAsian}$ (HR 1.58, $P=2.29 \times 10^{-10}$), and PRS_{Trans} (HR 1.56, $P=7.04 \times 10^{-10}$) were significantly associated with the PTDM development. PRS_{PTDM} (HR 1.00, $P=0.954$) failed to predict PTDM, possibly due to the limited number of variants. Incident T2D from the KoGES and PTDM showed similar associations with mechanism-specific PRSs (Table).

Conclusion: T2D PRS can stratify PTDM risks. Thorough PRS analyses suggest shared genetic mechanisms between T2D and PTDM.