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Association of genetic variants with pre-diabetes and type 2 diabetes using illness-death model in Korean adults

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Diabetes is a chronic disease influenced by various factors such as lifestyle, dietary habits, and genetic factors. We aim to investigate the effects of genetic markers on the progression of type 2 diabetes (T2D) stages in Korean adults using a multi-state illness-death model with data from the Korea Association REsource (KARE) cohort. We used a multi-state illness-death model to estimate the hazard transition of single nucleotide polymorphism (SNP) in three T2D transition models based on the T2D state progression: Normal glucose tolerance (NGT)→Pre-diabetes (PD), NGT→T2D, PD→T2D. Hazard ratios with 95% confidence intervals were calculated using multivariate Cox proportional hazards regression to estimate the SNP effect on each transition model. The *p*-value for each SNP was adjusted for multiple testing using the false discovery rate (FDR). We identified 2 significant SNPs (rs4607517, and rs758982) in the NGT→PD model and 8 significant SNPs (rs59813747, rs147467153, rs35566993, rs145386384, rs4784964, rs59595912, rs11698919, and rs7575023) in the NGT→T2D model. However, no significant SNPs were identified in the PD→T2D model. rs4607517 in the *GCK* gene, identified in NGT→PD model, had combined annotation-dependent depletion (CADD) scores > 12.37 and deleterious annotation of genetic variants using neural networks (DANN) scores > 0.8. rs59595912 in the *PTOV1* gene, identified in NGT→T2D model, had CADD scores > 12.37 and DANN scores > 0.9. We found significant SNPs that influence the incidence and progression of PD and T2D. The analysis conducted using the multi-state illness-death model provides a comprehensive understanding of the genetic factors impacting T2D progression.