

The Japan Multi-Institutional Collaborative Cohort Study Identifies the 13q35.43-35.46 Locus as Associated with Estimated Glomerular Filtration Rate in Diabetic Patients.

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Abstract

Objective:to carry out a genome-wide association study (GWAS) in Japan to identify genetic variants that impacted renal function.

Research design and methods : In a Japanese sample of 14,091 adults suitable for GWAS from the Japan Multi-Institutional Collaborative Cohort (JMICC) study, 955 patients with type 2 diabetes mellitus (T2D) were identified. A HumanOmniExpressExome-8 v1.2 BeadChip array was used for genotyping at a central lab. Utilizing SHAPEIT and Minimac3 software (with the 1000 Genomes phase 3 as the reference panel), genotype imputation was carried out. According to Matsuo et al., we evaluated the glomerular filtration rate (eGFR) for each patient. By using linear regression analysis with adjustments for age and sex, the association between the imputed variants and eGFR was determined.

Results : With P values of 5×10^{-8} , we discovered 77 SNVs upstream of the NBEA gene that were substantially linked with eGFR in T2D individuals. This gene was reported to be involved in a number of metabolic processes and to be linked to a number of medical disorders. However, no prior research suggested a connection between the gene and diabetic nephropathy.

Keywords: Genome-wide association study; Diabetes mellitus; Estimated glomerular filtration rate; Chronic kidney disease

Introduction

In developed nations, diabetic nephropathy is the most

typical cause of chronic kidney disease (CKD) [1]. The development of nephropathy in diabetic patients is not entirely predicted by the clinical features. Genetic background is thought to play a significant influence in the development of this kidney illness, according to epidemiological findings [2,3]. Numerous genome-wide association studies have been conducted (GWAS).

In a recent meta-analysis by Pattaro et al. on associations of estimated glomerular filtration rate (eGFR) based on serum creatinine (Scr), cystatin C, and CKD defined as eGFR based on $\text{Scr} \geq 60 \text{ ml/min/1.73m}^2$ with about 2.5 million autosomal single-nucleotide variations (SNVs) in 133,413 individuals of European ancestry in the Seven out of 24 newly identified loci with eGFR based on Scr demonstrated direction-consistent significance in their trans-ethnic analysis in 42,296 Asian subjects. Some other SNVs might have been discovered if the GWAS discovery analysis had been conducted on an Asian population. Here, we discovered 77 SNVs that affected renal function in a Japanese population with type 2 diabetes mellitus upstream of the NBEA gene (T2D). 7 out of 24 newly identified loci with eGFR based on Scr demonstrated direction-consistent significance in 42,296 Asian people. Some other SNVs might have been discovered if the GWAS discovery analysis had been conducted on an Asian population. Here, we discovered 77 SNVs that affected renal function in a Japanese population with type 2 diabetes mellitus upstream of the NBEA gene (T2D).

Discussion and Conclusion

We discovered 77 unique SNVs upstream of the NBEA gene in the current GWAS of patients with T2D in a Japanese population that were connected to eGFR. A member of the vast, varied class of A-kinase anchor proteins, which are encoded by the NBEA gene, directs the activity of protein kinase A to particular subcellular sites by binding to its type II regulatory subunits. Blood cells, the brain, internal organs like the kidneys and intestines, and secretory organs like the pancreas and adrenal glands all express NBEA [26]. Numerous illnesses, such as bipolar disorder-related migraine [27], idiopathic autism [28], schizophrenia [29], major depression [30], substance misuse [30], and multiple myeloma [31,32], are linked to NBEA. Olszewski et al. discovered a significant relationship between BMI as a continuous quality and trends for weight among the overweight adult men and two upstream SNVs in

NBEA, rs17775456 and rs7990537. We also discovered that early adulthood body weight is slightly higher in Nbea⁺/2 mice. This phenotype is associated with elevated insulin concentrations [33]. Despite these, there are no findings linking this gene to renal function generally or in diabetes. Our findings support the observed connection between SNVs at the NBEA gene locus and eGFR in T2D and call for replication studies and more functional research. Two upstream SNVs in NBEA, rs17775456 and rs7990536, have a significant connection with BMI as a continuous quality and trends for weight among overweight adult men. Additionally, we discovered that early adulthood body weight is moderately raised in Nbea⁺/2 mice. This phenotype is associated with elevated insulin concentrations [33]. Despite these, there are no findings linking this gene to renal function generally or in diabetes. Our findings support the observed connection between SNVs at the NBEA gene locus and eGFR in T2D and call for replication studies and more functional research.

Proteinuria is a sign of diabetic nephropathy. Increased glomerular permeability results in plasma protein leakage into the urine. These proteins can cause interstitial scarring and an inflammatory response when absorbed by proximal tubular cells, leading to the development of fibrosis [34]. Recent studies have revealed that advanced glycation end products play a significant role in the aetiology of proteinuria and kidney degeneration [35]. The inclusion of urine protein in the model did not reduce the relationships between recently discovered SNVs upstream of the NBEA gene and eGFR in one of our confounding factor adjustment analyses. The results showed that the gene influences eGFR without regard to urine protein.

Other confounding factor adjustment analyses, such as those that took PCA scores, BMI, smoking, and alcohol consumption into account, did not change the relationship between the gene and eGFR. Despite the fact that there were fewer participants, the results from the age- and sex-adjusted analysis of the results from 519 T2D patients with urine protein data were more significant and significant P values were bigger than the results from all 955 T2D patients. The cause of this discovery is obscure. It's likely that T2D data with protein urine data had higher data quality than T2D data without protein urine data.

Our replication of previously reported SNVs in the Asian population involved the KCNQ1 gene significantly. It was one of seven replicated loci that Pat Taro et al. meta-analysis study found to be related to eGFR in Asian subjects. The voltage-gated potassium channel associated with the KCNQ1 gene is necessary for the cardiac action potential's repolarization phase. Long QT Syndrome [36–41] and gestational diabetes mellitus [42] are two illnesses linked to KCNQ1. We discovered 8 SNVs at the ELMO1 gene in the current study that showed significant association with eGFR (P=0.025), despite the fact that we were unable to replicate the nine SNVs at the ELMO1 gene

that Shimazaki et al. previously reported to be associated with nephropathy in diabetes in a Japanese population [22]. Replication investigations of ELMO1 in non-Japanese populations were successful, according to reports [43–47].

The limitations of this study should be stated. We did not do a replication research in a different population, to start. Additionally, there isn't a because J-MICC is not a trial specifically for T2D, there are a lot of people who have the disease. However, only a portion of the patients had semi-quantitative urine protein data, and we were missing crucial information like the length of T2D. As a result, we have found that T2D patients in the Japanese population who carry the 13q35.43-35.46 locus had lower eGFR. Future research is required to look at the biochemical process between the locus and renal function in T2D.

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