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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 filtratLon 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 filtratLon rate (eGFR) based on serum creatinine (Scr), cystatin C, and CKD defined as eGFR based on Scr60 ml/min/ 1.73m2 with about 2.5 million autosomal single-nucleotide variations (SNVs) in 133,413 individuals of European ancestry in the Seven out of 24 newly LdentLfied loci with eGFR based on Scr demonstrated direction-consistent sLJnLficance 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 LdentLfied loci with eGFR based on Scr demonstrated direction-consistent sLJnLficance 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. e 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 findLnJs 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, he 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 findLnJs 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. Ls was one of seven replicated loci that Pat Taro et almeta-analysis .'s 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 sLJnLficant association with eGFR (P0.025), 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. HLrd, 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.

References

1. United States Renal Data System (2017) Annual Data Report Volume 1– Chronic Kidney Disease (CKD) in the United States. Chapter 1: CKD in the General Population.

2. Nakai S, Shinzato T, Sanaka T, kikuchi K, Kitaoka T, et al. (2002) Hecurrent state of chronic dialysis treatment in Japan. J Jpn Soc Dial Her 35: 1155-1184.

3. Krolewski AS, Waram JH, Rand LI, Kahn CR (1987) Epidemiologicapproach to the etiology of type 1 diabetes mellitus and its complications. N Engl J Med 317: 1390-1398.

4. Pattaro C, Kottgen A, Teumer A, Garnaas M, Boger CA, et al. (2012)Genome-wide association and functional follow-up reveals new loci for kidney function. PLoS Genet 8: e1002584.

5. Hamajima N (2007) He Japan Multi-Institutional Collaborative CohortStudy (J-MICC Study) to detect gene-environment interactions for cancer. Asian Pac J Cancer Prev 8: 317-323.

6. Nakagawa-Senda H, Hachiya T, Shimizu A, Hosono S, Oze I, et al. (2018)A genome-wide association study in the Japanese population LdentLfies the 12q24 locus for habitual coffee consumption: He J-MICC Study. Sci Rep 8: 1493.

7. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, et al. (2012)International clinical harmonization of

glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Investig 3: 39-40.

8. Matsuo S, Imai E, Horio M, Yasudaa Y, Tomita K, et al. (2009) Revisedequations for estimated GFR from serum creatinine in Japan. AJKD 53 982-992.

9. Purcell S, Neale B, Todd-Brown K, Homas L, Ferreira MA, et al. (2007)PLINK: a tool set for whole-genome association and population-base linkage analyses. Am J Hum Genet 81: 559-575.

10. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, et al. (2015)Second-generation PLINK: rising to the challenge of larger and riche datasets. Gigascience 4: 7.

11. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, et al.(2006) Principal components analysis corrects for stratLficatLon in genome-wide association studies. Nat Genet 38: 904-909.

12. Patterson N, Price AL, Reich D (2006) Population structure andeigenanalysis. PLoS Genet 2: 190.

13. 1000 Genomes Project Consortium, Abecasis GR, Auton A, Brooks LD,DePristo MA, et al. (2012) An integrated map of genetic variation from 1,092 human genomes. Nature 491: 56-65.

14. 1000 Genomes Project Consortium, Auton A, Brooks LD, Durbin RM,Garrison EP, et al. (2015) A global reference for human genetic variation. Nature 526: 68-74.

15. Kabata Y, Nakazono K, Takahashi A, Saito S, Hosono N, et al. (2008 Japanese population structure, based on SNP genotypes from 7003 individuals compared to other ethnic groups: effects on population-based association studies. Am J Hum Genet 83: 445-456.

16. Delaneau O, Marchini J, Zagury JF (2011) A linear complexity phasingmethod for thousands of genomes. Nat Methods 9: 179-181.

17. Das S, Forer L, Schonherr S, Sidore C, Locke AE, et al. (2016) Nextgeneration genotype imputation service and methods. Nat Genet 48: 1284-1287.

18. https://genome.sph.umich.edu/wiki/DosageConvertor

19. Gogarten SM, Bhangale T, Conomos MP, Laurie CA, McHugh CP, et al. (2012) GWASTools: an R/Bioconductor package for quality control and analysis of genome-wide association studies. Bioinformatics 28: 3329-3331.

20. Barrett JC, Fry B, Maller J, Daly MJ (2005) Haploview: analysis andvisualization of LD and haplotype maps. Bioinformatics 15: 263-265.

21. Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, et al. (2010)LocusZoom: regional visualization of genome-wide association scan results. Bioinformatics 26: 2336-2337.

22. Shimazaki A, Kawamura Y, Kanazawa A, Sekine A, Saito S, et al. (2005)Genetic variations in the gene encoding ELMO1 are associated wit susceptibility to diabetic nephropathy. Diabetes 54: 1171-1178.

23. Tyner C, Barber GP, Casper J, Clawson H, Diekhans M, et al. (2017) HeUCSC Genome Browser database: 2017 update. Nucleic Acids Res 45: 626-634.

24. Aken BL, Achuthan P, Akanni W, Amode MR, Bernsdor F, et al.(2017)Ensembl 2017. Nucleic Acids Res 45: 635-642.

25. Consortium GT (2015) Human genomics. He Genotype-TissueExpression (GTEx) pilot analysis: multitissue gene regulation in humans. Science 348: 648-660.

26. http://www.genecards.org/cgi-bin/carddisp.pl?gene=NBEA.

27. Jacobsen KK, Nievergelt CM, Zayats T, Greenwood TA, Anttila V, et al.(2015) Genome wide association study LdentLfies variants in NBEA associated with migraine in bipolar disorder. J Affect Disord 72: 453-461.

28. Castermans D, Wilquet V, Parthoens E, Huysmans C, Steyaert J, et al.(2003) He neurobeachin gene is disrupted by a translocation in a patient with idiopathic autism. J Med Genet 40: 352-356.

29. Camargo LM, Collura V, Rain JC, Mizuguchi K,

Hermjakob H, et al.(2007) Disrupted in Schizophrenia 1 Interactome: evidence for the close connectivity of risk genes and a potential synaptic basis for schizophrenia. Mol Psychiatry 12: 74-86.

30. Gratacos M, Costas J, De Cid R, Bayes M, Gonzalez JR, et al. (2009),dentLficatLon of new putative susceptibility genes for several psychiatric disorders by association analysis of regulatory and non-synonymous SNVs of 306 genes involved in neurotransmission andneurodevelopment. Am J Med Genet B Neuropsychiatr Genet 150: 808-816.

31. O'Neal J, Gao F, Hassan A, Monahan R, Barrios S, et al. (2009)Neurobeachin (NBEA) is a target of recurrent interstitial deletions at 13q13 in patients with MGUS and multiple myeloma. Exp Hematol 37: 234-244.

32. Nagoshi H, Taki T, Hanamura I, Nitta M, Otsuki T, et al. (2012) FrequentPVT1 rearrangement and novel chimeric genes PVT1-NBEA and PVT1- WWOX occur in multiple myeloma with 8q24 abnormality. Cancer Res 72: 4954-4962.

33. Olszewski PK, Rozman J, Jacobsson JA, Rathkolb B, Stromberg S, et al. (2012) Neurobeachin, a regulator of synaptic protein targeting, is associated with body fat mass and feeding behavior in mice and bodymass index in humans. PLoS Genet. 8: e1002568.

34. http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/diabetic-nephropathy/

35. Kumar P A, Chitra PS, Reddy GB (2016) Advanced glycation endproducts mediated cellular and molecular events in the pathology ofdiabetic nephropathy. BioMol Concepts 7: 293-309.

36. Bruce HA, Kochunov P, Paciga SA, Hyde CL, Chen X, et al. (2017)Potassium channel gene associations with joint processing speed andwhite matter impairments in schizophrenia. Genes Brain Behav 16: 515-521.

37. Amin AS, Pinto YM, Wilde AA (2013) Long QT syndrome: beyond thecausal mutation. J Physiol 591: 4125-4139.

38. Amin AS, Giudicessi JR, Tijsen AJ, Spanjaart AM, Reckman YJ, et al.(2012) Variants in the 3' untranslated region of the KCNQ1-encoded Kv7.1 potassium channel modify disease severity in patients with type 1 long QT syndrome in an allele-specLfic manner. Eur Heart J 33: 714-723.

39. Westaway SK, Reinier K, Huertas-Vazquez A, Evanado A, Teodorescu C,et al. (2011) Common variants in CASQ2, GPD1L, and NOS1AP aresLJnLficantl\ associated with risk of sudden death in patients with coronary artery disease. Circ Cardiovasc Genet 4: 397-402.

40. Daelemans C, Ritchie ME, Smits G, Abu-Amero S, Sudbery IM, et al. (2010) High-throughput analysis of candidate imprinted genes and allelespecLfic gene expression in the human term placenta. BMC Genet 11: 25.

41. Sudandiradoss C, Sethumadhavan R (2009) In silico investigations onfunctional and haplotype tag SNPs associated with congenital long QT syndromes (LQTSs). Genomic Med 2: 55-67.

42. Wang X, Li W, Ma L, Ping F, Liu J, et al. (2017) Investigation of miRNAbinding site variants and risk of gestational diabetes mellitus in Chinese pregnant women. Acta Diabetol 54: 309-316.

43. Pezzolesi MG, Katavetin P, Kure M, Poznik GD, Skupien J, et al. (2009)ConfirmatLon of genetic associations at ELMO1 in the GoKinD collection supports its role as a susceptibility gene in diabetic nephropathy. Diabetes 8: 2698-2702.

44. Leak TS, Perlegas PS, Smith SG, Keene KL, Hicks PJ, et al. (2009) Variantsin intron 13 of the ELMO1 gene are associated with diabetic nephropathy in African Americans. Ann Hum Genet 73: 152-159.

45. Wu HY, Wang Y, Chen M, Zhang X, Wang D, et al. (2013) Association ofELMO1 gene polymorphisms with diabetic nephropathy in Chinesepopulation. J Endocrinol Invest 36: 298-302.

46. Craig DW, Millis MP, DiStefano JK (2009) Genome-wide SNP genotyping study with use of pooled DNA to identify candidate markers mediating susceptibility to end-stage renal disease attributed to Type 1 diabetes. Diabet Med 26: 1090-1098.

47. Williams WW, Salem RM, McKnight AJ, Sandholm N, Forsblom C, et al.(2012) Association testing of previously reported variants in a large casecontrol metaanalysis of diabetic nephropathy. Diabetes 61: 2187-2194.