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Dna methylation is a risk factor for kidney failure in individuals with type 1 diabetes

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Abstract:

Background and aims: We previously identified DNA methylation differences at multiple CpG loci in a cross-sectional study of individuals with or without diabetic kidney disease (DKD). Here, we aimed to study DNA methylation as a risk factor for the development of kidney failure in individuals with type 1 diabetes and DKD.

Materials and methods: The study included 397 individuals with type 1 diabetes and macroalbuminuria at baseline from the Finnish Diabetic Nephropathy (FinnDiane) Study. At baseline, the mean (SD) age was 43 (±10.8) years, and 38% were women. Macroalbuminuria (>200 µg/min or >300 mg/24h) was determined from two of three overnight or 24 h urine collections. The study participants were followed up until either kidney failure developed or December 31, 2017. Data on kidney failure requiring dialysis and/or a transplant was collected from the Finnish Care Register for Health Care, study visits, or medical files.

Genome-wide blood-derived DNA methylation data was generated for the Infinium HD Methylation EPIC BeadChips (Illumina) in Belfast. After quality control, we extracted M-values ($M = \log_2(\beta / (1-\beta))$ for 763,064 CpG sites using RnBeads v.2.6.0. M-values for each CpG site were analysed separately with the Cox proportional-hazards model with sex, baseline age, and six estimated white blood cell counts as covariates.

Results: During a median of 7.2 (interquartile range: 2.9-14.0) years of follow-up, 196 individuals developed kidney failure. Eleven CpGs were associated with developing kidney failure with $p < 6.6\times10^{-8}$ - a p-value threshold corrected for the number of studied CpGs. The top CpG cg17944885 is located on chromosome 19 between genes *ZNF788P* and *ZNF625-ZNF20*. Higher methylation at this locus was a risk factor for kidney failure (HR [95%CI] = 2.32 [1.95, 2.76], $p = 1.4\times10^{-21}$). Seven significant CpGs were located in or near genes; cg23597162 in *JAZF1*, cg12272104 in *DAZAP1*, cg21871803 in *AHCYL2*, cg12065228 in *PQLC2*, cg26236214 in *ARHGEF7*, cg19942083 in the promoter of *PTPN6*, and cg03262246 <1500 bp from the transcription start site of *CDKN2AIPNL*. In an independent cohort look-up from Belfast of kidney failure vs controls with no evidence of kidney disease (n = 519), 10 of these CpGs were significantly associated ($p < 10^{-8}$). Additionally, cg17944885 was strongly associated with DKD in our cross-sectional meta-analysis of the FinnDiane and Belfast cohorts (tot n = 1,304, $p = 2.0\times10^{-44}$).

In a cohort of 473 individuals with diabetes from the Chronic Renal Insufficiency cohort, six of eleven significant CpGs were associated with eGFR in the whole blood DNA methylation analysis ($3.7\times10^{-13} \le p \le 0.05$). Furthermore, all six of our eleven top CpGs that were available in the epigenome-wide meta-analysis for eGFR in 33,605 individuals from the Chronic Kidney Disease Genetics Consortium were significantly ($p < 1.1\times10^{-7}$; cg17944885 and CpGs in *JAZF1* and *PQLC2*) or nominally ($p < 0.05$; CpGs in or near *DAZAP1*, *AHCYL2*, and *PTPN6*) associated with eGFR in their study.

Conclusion: DNA methylation at several CpGs show consistent associations with kidney function and the risk of developing kidney failure.

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