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Syreeni, A., Dahlström, E. H., Smyth, L. J., Gupta, Y., Forsblom, C., Kilner, J., McKay, G. J., Maxwell, A., McKnight, A., Groop, P.-H., & Sandholm, N. (2022). DNA methylation is a risk factor for kidney failure in individuals with type 1 diabetes. *Diabetologia*, 65(Supplement 1), S21. Article 38.

Published in:
Diabetologia

Document Version:
Publisher's PDF, also known as Version of record

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Control/Tracking Number: A-22-374-EASD

Activity: Abstract

Current Date/Time: 4/1/2022 2:26:59 AM

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 ($> 200 \mu\text{g}/\text{min}$ or $> 300 \text{mg}/24\text{h}$) 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 $p < 6.6 \times 10^{-8}$ - 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], $p = 1.4 \times 10^{-21}$). Seven significant CpGs were located in or near genes; cg23597162 in *JAZF1*, cg12272104 in *DAZAP1*, cg21871803 in *AHCYL2*, cg12065228 in *PQLC2*, cg26236214 in *ARHGFEF7*, 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 ($p < 10^{-9}$). Additionally, cg17944885 was strongly associated with DKD in our cross-sectional meta-analysis of the FinnDiane and Belfast cohorts (tot $n = 1,304$, $p = 2.0 \times 10^{-44}$).

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 ($3.7 \times 10^{-13} \leq p \leq 0.05$). 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 ($p < 1.1 \times 10^{-7}$; 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.

Author Disclosure Information:

A. Syreeni: None.

Keyword (Complete): 56 Nephropathy

Study information (Complete):

***Human studies:** Yes

***Animal Studies:** No

Grant Acknowledgement (Complete):

Please select Yes or No: Yes

Support : NIH (1R01DK105154-01A1) GENIE II

Clinical Trial Registration Number (Complete):

: No

: N/A

Status: Complete

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