Objective: This research was conducted to identify blood-derived DNA methylation in individuals with type 1 diabetes (T1D) who progressed to diabetic kidney disease (T1DKD, n=651) compared to persons with T1D and no evidence of kidney disease (n=651). The study included participants with at least 10-year duration of T1D from the United Kingdom (UK), Republic of Ireland (ROI) and Finland.Design: Case-control analysis of differentially methylated CpG sites (dmCpGs) was undertaken. The Infinium HD Methylation Assay, MethylationEPIC BeadChips (Illumina) were used to evaluate the methylation status of 862,927 CpG sites. The distribution of single-site methylation levels between individuals with T1DKD and those with T1D was assessed adjusting for covariates including age, sex, white cell counts (WCCs) and smoking using RnBeads and Bioconductor R packages. Individuals from the UK-ROI and Finnish populations were analysed separately before results were compared. Quality control included the removal of cross-reactive probes, those located near common SNPs, or on sex chromosomes. Raw intensities were normalised using the bmiq method. Setting: Wet-lab work was completed in research laboratories within the Belfast HSC Trust regional genetics diagnostic centre. Harmonised data analysis was conducted using RnBeads and Bioconductor R packages for each population. Patients: DNA was extracted from peripheral blood from individuals with T1D and known renal status recruited to the UK-ROI (n=502) and Finnish Diabetic Nephropathy (FinnDiane, n=800) studies. Case individuals had T1DKD defined as persistent macroalbuminuria (≥500 mg/24hr), eGFR <60 mL/min/m2, hypertension (≥135/85 mmHg) and diabetic retinopathy. Control individuals had T1D and no evidence of kidney disease on repeat testing.Main Outcome Measurements: For all CpG sites, β values were generated, M values derived, and p values computed. Comparisons of dmCpGs between cases and controls were performed. Results: When comparing independent outcomes from UK-ROI and FinnDiane, adjusting for the minimal model of age, sex and WCCs, comparisons of dmCpGs identified 11 dmCpGs common to both cohorts (FDRadjp≤x10-5). Of these, cg17944885, located close to ZNF44 and cg25544931 were more significant in both populations (FDRadjp≤x10-8). Both were located on chr19 within CpG shelves and shores. Further adjustment for smoking status reduced the number of common dmCpGs to two in both populations; cg17944885 (FDRadjp<x10-8) and cg05710777 located within LOC101927438 (FDRadjp≤x10-5).Conclusions: Investigation of additional potential confounding factors such as duration of diabetes, BMI, HbA1c and lipid measures are ongoing. These analyses provided the opportunity to assess previously unexplored regions of the methylome for T1DKD using two independent populations with harmonised inclusion criteria. Blood-derived methylation signatures may have utility as minimally invasive biomarkers for DKD attributed to T1D. Objective: This research was conducted to identify blood-derived DNA methylation in individuals with type 1 diabetes (T1D) who progressed to diabetic kidney disease (T1DKD, n=651) compared to persons with T1D and no evidence of kidney disease (n=651). The study included participants with at least 10-year duration of T1D from the United Kingdom (UK), Republic of Ireland (ROI) and Finland.Design: Case-control analysis of differentially methylated CpG sites (dmCpGs) was undertaken. The Infinium HD Methylation Assay, MethylationEPIC BeadChips (Illumina) were used to evaluate the methylation status of 862,927 CpG sites. The distribution of single-site methylation levels between individuals with T1DKD and those with T1D was assessed adjusting for covariates including age, sex, white cell counts (WCCs) and smoking using RnBeads and Bioconductor R packages. Individuals from the UK-ROI and Finnish populations were analysed separately before results were compared. Quality control included the removal of cross-reactive probes, those located near common SNPs, or on sex chromosomes. Raw intensities were normalised using the bmiq method. Setting: Wet-lab work was completed in research laboratories within the Belfast HSC Trust regional genetics diagnostic centre. Harmonised data analysis was conducted using RnBeads and Bioconductor R packages for each population. Patients: DNA was extracted from peripheral blood from individuals with T1D and known

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