

File S1. The DCCT Genetic Study

Characterization of direct and/or indirect genetic associations for multiple traits in longitudinal studies of disease progression

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The Diabetes Control and Complications Trial (DCCT) data

The DCCT data was a randomized-controlled trial that demonstrated that intensive insulin therapy could prevent and/or delay progression of long-term T1DC (The Diabetes Control and Complications Trial Research Group 1993). A total of 1,441 T1D patients were recruited between 1983 and 1993 in two cohorts: a primary prevention cohort (726 patients with a short duration of diabetes (1-5 years), exhibiting normal albuminuria (Albumin Excretion Rate (AER) <40 mg/day) and without evidence of retinopathy); a secondary intervention cohort (715 patients with diabetes duration of 1-15 years, with AER<200 mg/day and non-proliferative retinopathy). Members of each cohort were randomly assigned to receive either conventional or intensive insulin treatment and were followed over scheduled visits for the development of complications. Due to significant outcome differences between intensive and conventional treatment groups, the DCCT trial was stopped early. At the closeout visit, patients were administratively censored and had a mean follow-up time of 6.5 years (range 3 to 9), 99% had completed the study, and more than 95% of all scheduled examinations were completed (The Diabetes Control and Complications Trial Research Group 1993). DCCT participants continued to be followed for disease progression after the trial in a long-term epidemiologic cohort study and were genotyped for GWAS in the DCCT Genetics Study.

Genome-wide genotyping in DCCT subjects was performed subsequently using Illumina 1M and HumanCoreExome Bead Arrays (Illumina, San Diego, CA, USA) and standard quality controls procedures were applied to individuals and genetic markers (Paterson et al. 2010; Roshandel et al. 2018). In this study, we use individuals genotyped with the HumanCoreExome Bead Array and ungenotyped autosomal SNPs imputed using 1000 Genomes (The 1000 Genomes Project Consortium 2015) data phase 3 (v5) and minimac3 [(Das et al. 2016), v.1.0.13], as previously described (Roshandel et al. 2018).

Because the goal of intensive therapy was to reduce HbA1c into the non-diabetic range, which produced treatment differences in HbA1c values, we focus on $N=667$ unrelated individuals of European descent ancestry from the Conventional treatment group. Longitudinal measurements for HbA1c and SBP were collected at up to 39 quarterly visits during DCCT, while DR and DN events were diagnosed at annual and semi-annual visits respectively. HbA1c and SBP were

recorded irrespective of the occurrence of any complication event(s). Although the DCCT implemented robust quality assurance procedures to minimize potential sources of error during and after data collection (Steffes et al. 2005; Lorenzi et al. 2015), HbA1c and SBP are subject to large within-subject variability.

List of the participants of the DCCT/EDIC Research Group (as of January 1, 2021)

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