SUPPLEMENTARY DATA

Haptoglobin Genotype and the Rate of Renal Function Decline in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

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Principal components of ancestry analysis

We performed genome-wide genotyping in subjects from the DCCT/EDIC [1, 2]. Genotype data were generated using the Illumina 1M beadchip assay (www.illumina.com, San Diego, CA) of which ~ 841K SNPs with a minor allele frequency >1% were subjected to subsequent statistical analysis. We limited the analysis to individuals who self-identified as white, and also excluded individuals who were determined to be admixed between Caucasian and other ethnic groups by population genetic approaches, using the software Eigenstrat [3], seeding with genotype data from the 3 major populations genotyped in HapMap phase II [4]. We selected SNPs for this latter analysis by first removing SNPs from regions known to be in strong linkage disequilibrium with each other (MHC, the polymorphic chromosome 8 inversion). Then we selected independent SNPs by requiring them to have $r^2<0.2$ over a shifting window of 500kb. This resulted in ~ 98K SNPs being used for analysis. We then conducted a principal components analysis based on these 98K SNPs. The first three principal components which captured the largest proportion of the total variation between subjects were included in the regression models to adjust for the population of ancestry, or “population stratification”.

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Supplementary Table 1. Effects of HP Type on Risk of Impaired GFR (Sustained eGFR<60mL/min/1.73m^2) in 1303 Caucasian DCCT/EDIC Participants with Principal Components of Ancestry Cox Proportional Hazard Model*

	DCCT Intensive Therapy (INT)					DCCT Conventional Therapy (CON)					DCCT Treatment Effect by HP Type *
HP Type *	**N**	**N with Events**	**Patient Years**	**Event Rate Per 1000 Patient Years**	**Hazard Ratio (95%CI)**	**N**	**N with Events**	**Patient Years**	**Event Rate Per 1000 Patient Years**	**Hazard Ratio (95%CI)**	**Risk Reduction by INT (%, 95 CI)**
1-1	76	1	1621	0.6	1	93	5	1953	2.6	1	76% (-97%, 106%) P=0.19
2-1	323	9	7071	1.3	2.1 (0.3, 16.2)	295	15	6299	2.4	0.9 (0.3, 2.6)	48% (-20%, 77%) P=0.12
2-2	237	10	5235	1.9	3.1 (0.4, 24.2)	279	24	5793	4.1	1.7 (0.6, 4.4)	**56% (8%, 79%) P=0.031**
Trend in risk of GFR across HP Type**	**Trend in risk of GFR across 0, 1, 2 Risk Allele 2:** P=0.65					**Trend Test Z Value**		**Trend P value**			**Interaction between HP Type & DCCT Therapy** (df=2) P=0.80
						2.81		**0.005**			

*Effect of HP type and DCCT treatment group on risk of impaired GFR defined as sustained eGFR<60 was assessed by a Cox proportional hazards model after adjustment for DCCT baseline estimated GFR, an interaction term of HP type and DCCT treatment group, and three principal components of ancestry.

** Trend test is based on a Wald Chi-square test from a Cox proportional hazards model assessing the effect of number of HP 2 allele (0, 1, 2) on risk of impaired GFR after adjustment for DCCT baseline estimated GFR, an interaction term of number of HP 2 allele and DCCT treatment group, and three principal components of ancestry.

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Supplementary Table 2. Effects of HP Type on Rate of Change in estimated GFR in 1303 Caucasian DCCT/EDIC Participants with Principal Components of Ancestry General Linear Mixed Model (GLMM)

Haptoglobin Type *	**Rate of Change in eGFR in DCCT and EDIC (mL per minute per 1.73 m^2 per year)**		**DCCT Treatment Effect by HP Type ***
	DCCT Intensive Therapy	**DCCT Conventional Therapy**	**Rate of Decline Reduction by Intensive Therapy (95 CI)**
1-1	**-1.25(-1.46, -1.03) P<.0001^**	**-1.43 (-1.63, -1.23) P<.0001^**	0.19 (0.09, 0.46) P=0.18
2-1	**-1.25(-1.36, -1.15) P<.0001^**	**-1.50(-1.61, -1.39) P<.0001^**	**0.25 (0.10, 0.40) P=0.001**
2-2	**-1.28(-1.40, -1.16) P<.0001^**	**1.65(-1.77, -1.53) P<.0001^**	**0.37 (0.21, 0.53) P<.0001**
Trend in GFR Slope Across Haptoglobin Types**	**Change in GFR Slope Per One Additional HP Allele 2:** P=0.74	**Slope Difference Per One Additional HP Allele 2 -0.12 (-0.22, -0.01) X2= 4.82, P=0.028**	**Interaction between HP Type & DCCT Therapy in GFR Slope** (df=2) P=0.38

*Effect of HP type and DCCT treatment group on rate of change in estimated GFR in each treatment group was assessed by a General Linear Mixed Model by allowing for random intercept and random slope, after adjustment for DCCT baseline estimated GFR, DCCT treatment group, HP type, a three-way interaction term of DCCT treatment group, HP type, and time, and three principal components of ancestry.

** Trend test is based on a variation of the Cochran-Armitage trend test.

^ P values indicate whether the respective slope or rate of change in eGFR is significantly different from 0, i.e., a flat slope.

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