

**Supplementary Methods:**

**MAGIC (Meta-Analyses of Glucose and Insulin-related traits Consortium): HbA1c meta-analysis methods – see Supplementary Table 9 for list of investigators.**

We obtained summary statistics for HbA1c associations from a meta-analysis of HbA1c levels carried out by MAGIC (unpublished data). Briefly, the meta-analysis included 23 cohorts with available HbA1c measurements and GWAS genotypes, for a total of 27,589 to 36,585 individuals depending on the SNPs analyzed. Cohorts included: B58C-WTCCC (N=1,428), BLSA (N=490), DGI (N=480), EPIC cancer cases (N=957), EPIC cohort (N=1,911), Fenland (N=1,378), FHS (N=1,996), KORA F3 (N=1,644), Lolipop (N=770), SardiNIA (N=3,346), 1958BC-T1DGC (N=2,501), ARIC (N=6,777), Croatia (N=659), deCODE (N=342), DESIR (N=731), GenomeEUtwin (N=568), HEALTH2000 (N=1,205), KORA\_S4 (N=1,814), NTRNESDA (N=1,452), ORCADES (N=651), PROCARDIS (N=831), SHIP (N=3,538) and Sorbs (N=630), see (26) for details.

All participants were adults of white ancestry from Europe or the United States, and free of diabetes (define as either receiving diabetes treatment or having a fasting glucose  $\geq 7$  mmol/L). Local research ethic committees approved all studies and all participants gave informed consent. In each study glycated hemoglobin (HbA1c, in %) was measured from whole blood (fasting or non-fasting), with NGSP-certified methods. SNPs were either directly genotyped or imputed from the HapMap CEU phase 2 reference panel using the software MACH or IMPUTE. QC metrics were applied to genotyped (Hardy-Weinberg equilibrium  $P < 10^{-4}$  or  $10^{-6}$  and call-rate  $< 0.90$  or  $0.95$ ) and imputed (observed-by-expected variance ratio (r2.hat)  $< 0.3$  (if MACH was used for imputation), proper-info  $< 0.4$  (if IMPUTE was used)) SNPs. In each cohort, a linear regression model was fitted using untransformed HbA1c as the dependent variable to evaluate the additive effect of genotyped and imputed SNPs, adjusting for age, sex, study-site (when applicable) and/or family structure. Regression estimates for each SNP were combined across studies in a meta-analysis using a fixed effect inverse-variance approach, as implemented in METAL software.

**Supplementary Table 1.** Association results for mean HbA1c in DCCT, separately by treatment group and combined, for SNPs that have previously been associated with HbA1c in non-diabetic individuals (see introduction for details and references).

| chr | snp        | position    | Gene region  | alleles | freq1 | rsqr | Conventional Group p value | Intensive Group p value | Combined Groups p value |
|-----|------------|-------------|--------------|---------|-------|------|----------------------------|-------------------------|-------------------------|
| 2   | rs1260326  | 27,584,444  | GCKR         | C,T     | 0.59  | 1    | 0.34                       | 0.15                    | 0.76                    |
| 2   | rs780094   | 27,594,741  | GCKR         | C,T     | 0.6   | 1    | 0.33                       | 0.15                    | 0.77                    |
| 2   | rs1402837  | 169,465,600 | G6PC2/ABCB11 | C,T     | 0.78  | 1    | 0.93                       | 0.36                    | 0.49                    |
| 2   | rs560887   | 169,471,394 | G6PC2/ABCB11 | C,T     | 0.71  | 1    | 0.86                       | 0.6                     | 0.79                    |
| 2   | rs563694   | 169,482,317 | G6PC2/ABCB11 | A,C     | 0.66  | 1    | 0.87                       | 0.99                    | 0.96                    |
| 2   | rs552976   | 169,499,684 | G6PC2/ABCB11 | A,G     | 0.35  | 1    | 0.68                       | 0.90                    | 1.00                    |
| 2   | rs6709087  | 169,507,256 | G6PC2/ABCB11 | A,G     | 0.77  | 1    | 0.54                       | 0.34                    | 0.87                    |
| 7   | rs10244051 | 15,030,358  | -            | G,T     | 0.54  | 1    | 0.23                       | 0.34                    | 0.13                    |
| 7   | rs2191348  | 15,030,780  | -            | G,T     | 0.46  | 1    | 0.23                       | 0.35                    | 0.14                    |
| 7   | rs1799884  | 44,195,593  | GCK          | C,T     | 0.82  | 1    | 0.33                       | 0.25                    | 0.1                     |
| 7   | rs730497   | 44,263,224  | GCK          | A,G     | 0.18  | 1    | 0.32                       | 0.25                    | 0.10                    |
| 7   | rs4607517  | 44,275,173  | GCK          | A,G     | 0.18  | 1    | 0.36                       | 0.24                    | 0.10                    |
| 8   | rs2722425  | 40,603,396  | ZMAT4        | C,T     | 0.89  | 1    | 0.9                        | 0.19                    | 0.49                    |
| 8   | rs13266634 | 118,253,694 | SLC30A8      | C,T     | 0.69  | 1    | <b>0.03</b>                | <b>0.08</b>             | 0.73                    |
| 9   | rs4240702  | 136,735,680 | -            | C,T     | 0.54  | 1    | 0.84                       | 0.65                    | 0.58                    |
| 10  | rs906216   | 70,768,201  | HK1          | G,T     | 0.55  | 1    | 0.61                       | 0.87                    | 0.62                    |
| 10  | rs7072268  | 70,769,919  | HK1          | C,T     | 0.52  | 1    | 0.69                       | 0.81                    | 0.76                    |
| 10  | rs2305198  | 70,798,881  | HK1          | C,T     | 0.39  | 1    | 0.35                       | 0.16                    | 0.17                    |
| 10  | rs7901695  | 114,744,078 | TCF7L2       | C,T     | 0.32  | 1    | 0.36                       | 0.23                    | 0.80                    |
| 11  | rs1387153  | 92,313,476  | MTNR1B       | C,T     | 0.71  | 1    | 0.37                       | 0.51                    | 0.75                    |
| 11  | rs10765573 | 92,322,980  | MTNR1B       | A,T     | 0.34  | 0.99 | 0.12                       | 0.44                    | 0.51                    |
| 11  | rs7936247  | 92,329,680  | MTNR1B       | G,T     | 0.66  | 0.99 | 0.12                       | 0.45                    | 0.51                    |
| 11  | rs11020124 | 92,330,309  | MTNR1B       | C,T     | 0.29  | 0.97 | 0.37                       | 0.55                    | 0.74                    |
| 11  | rs10830963 | 92,348,358  | MTNR1B       | C,G     | 0.7   | 0.88 | 0.18                       | 0.3                     | 0.65                    |
| 11  | rs1447352  | 92,362,409  | MTNR1B       | A,G     | 0.52  | 1    | 0.15                       | 0.24                    | 0.68                    |

**Supplementary Table 2. Definitions of complications outcomes, statistical models, covariates included and the prevalence of outcomes separately by treatment group**

| System                                | Specific outcome  | Time period        | Model                                      | Covariates  | Outcome Frequency (number with event /number censored) etc.        | Conventional  | Intensive   |
|---------------------------------------|---|--------------------|--|---|--|---|---|
| <b>Retinal</b> <sup>29, 43</sup>      |   |                    |  |   |  |   |   |
|                                       | <b>Mild Retinopathy:</b> Time from DCCT baseline to mild non-proliferative diabetic retinopathy (EDTRS step 4, patient level 35/<35) *  | DCCT and EDIC yr10 | Cox Proportional Hazards                   | Stratified by DCCT year of entry, cohort as covariate | 75% (807 vs 264), 1071   | 85% (453 vs 82), 535                                      | 66% (354 vs 182), 536                                     |
|                                       | <b>Severe retinopathy:</b> Time from DCCT baseline to severe non-proliferative retinopathy (ETDRS step 10, patient level at least 53/<53) or scatter laser                                  | “                  | “  | “   | 19% (246 vs 1057) = 1304   | 27% (178 vs 488), 666                                     | 11% (68 vs 569), 637                                      |
|                                       | <b>Clinically Significant Macular Edema:</b> Time from DCCT baseline to macular edema or focal laser  | “                  | “  | “   | 18% (240 vs 1064) =1303  | 24% (162 vs 505), 667                                     | 12% (78 vs 559), 637                                      |
| <b>Renal</b> <sup>11, 29</sup>        |   |                    |  |   |  |   |   |
|                                       | <b>Persistent Microalbuminuria:</b> Time from DCCT baseline to the first of two consecutive visits with Albumin Excretion Rate >30 mg/day   | DCCT and EDIC yr12 | ”  | “   | 22% (268 vs 976)   | 28% (177 vs 462), 639                                     | 15% (91 vs 514), 605                                      |
|                                       | <b>Severe nephropathy:</b> Time from DCCT entry to either Albumin Excretion Rate >300 mg/day or dialysis or transplant (plus two consecutive visits with Albumin Excretion Rate >30 mg/day) | “                  | “  | “   | 10% (132 vs 1172)  | 15% (101 vs 566), 667                                     | 5% (32 vs 605), 637                                       |
| <b>Cardiac</b> <sup>10</sup>          |   |                    |  |   |  |   |   |
|                                       | <b>Coronary Calcium</b>   | EDIC yr 7-9        | Tobit regression with log coronary calcium | 4 models with difference covariates                   | 759 (69%) with zero values, 1102                                   | 382 with zero values, median in 176 >0 is 74              | 377 with zero values, median in 167 with >0 is 51         |
| <b>Neuropathy</b> <sup>1</sup>        |   |                    |  |   |  |   |   |
|                                       | <b>Confirmed Clinical Neuropathy</b>  | EDIC yr 13/14      | Logistic regression                        | none  | 30%, 303 case, 723 control, 1026 total                             | 34%, 171 case, 334 control, 505 total                     | 25%, 132 case, 389 control, 521 total                     |
| <b>System</b>                         | <b>Specific outcome</b>   | <b>Time period</b> | <b>Model</b>                               | <b>Covariates</b>                                     | <b>Outcome Frequency (number with event /number censored) etc.</b> | <b>Conventional</b>                                       | <b>Intensive</b>  |
| <b>Hypoglycemia</b> <sup>44, 45</sup> |   |                    |  |   |  |   |   |
|                                       | <b>Requiring medical assistance (DEF2)</b>  | During DCCT        | Ordinal regression                         | none  | 656 with no events, 198 with one event, 450 with >1 event          | 429 with no events, 100 with one event, 138 with >1 event | 227 with no events, 98 with one event, 312 with >1 event  |
|                                       | <b>Resulting in coma/seizure (DEF1)</b>   | “                  | “  | none  | 938 with no events, 187 with one event, 179 with >1 event          | 540 with no events, 82 with one event, 45 with >1 event   | 398 with no events, 105 with one event, 134 with >1 event |

\*Approximately 20% of the secondary intervention cohort had Mild Retinopathy at baseline thus the smaller sample size for time-to-event.

**Supplementary Table 3.** Association results of top 13 SNPs for HbA1c in DCCT with renal complications in DCCT/EDIC.

| nearest gene | chr | pos         | snp        | trx          | mild renal   |             |             |                    |                      | severe renal |             |             |                    |                      |
|--------------|-----|-------------|------------|--------------|--------------|-------------|-------------|--------------------|----------------------|--------------|-------------|-------------|--------------------|----------------------|
|              |     |             |            |              | hazard ratio | HR lower CI | HR upper CI | univariate p value | multivariate p value | hazard ratio | HR lower CI | HR upper CI | univariate p value | multivariate p value |
| BNC2         | 9   | 16,791,850  | rs2254193  | intensive    | 0.7726       | 0.4215      | 1.4159      | 3.88E-1            | 3.97E-1              | 9E-08        | 0           | 3.3248      | 8.95E-4            | 2.29E-3              |
| BNC2         | 9   | 16,791,850  | rs2254193  | conventional | 1.9806       | 1.3865      | 2.8292      | 5.32E-4            | 1.38E-3              | 2.1222       | 1.3545      | 3.3248      | 2.51E-3            | 1.29E-2              |
| BNC2         | 9   | 16,791,850  | rs2254193  | combined     | 1.3411       | 0.9847      | 1.8266      | 7.28E-2            | 6.69E-2              | 1.2638       | 0.8192      | 1.9497      | 3.05E-1            | 2.13E-1              |
| BNC2         | 9   | 16,779,878  | rs4961760  | intensive    | 0.8045       | 0.4595      | 1.4086      | 4.34E-1            | 4.41E-1              | 0.3193       | 0.0777      | 1.3125      | 5.68E-2            | 8.42E-2              |
| BNC2         | 9   | 16,779,878  | rs4961760  | conventional | 1.8005       | 1.2806      | 2.5315      | 1.57E-3            | 2.95E-3              | 1.8125       | 1.1659      | 2.8176      | 1.33E-2            | 3.85E-2              |
| BNC2         | 9   | 16,779,878  | rs4961760  | combined     | 1.2938       | 0.9666      | 1.7318      | 9.35E-2            | 7.61E-2              | 1.2338       | 0.8191      | 1.8584      | 3.28E-1            | 3.03E-1              |
| BNC2         | 9   | 16,779,436  | rs6475082  | intensive    | 0.8045       | 0.4595      | 1.4086      | 4.34E-1            | 4.41E-1              | 0.3193       | 0.0777      | 1.3125      | 5.68E-2            | 8.42E-2              |
| BNC2         | 9   | 16,779,436  | rs6475082  | conventional | 1.8171       | 1.2923      | 2.555       | 1.35E-3            | 2.72E-3              | 1.826        | 1.1745      | 2.8387      | 1.23E-2            | 3.80E-2              |
| BNC2         | 9   | 16,779,436  | rs6475082  | combined     | 1.2974       | 0.9693      | 1.7365      | 9.01E-2            | 7.39E-2              | 1.2369       | 0.8212      | 1.8629      | 3.22E-1            | 3.01E-1              |
| BNC2         | 9   | 16,779,024  | rs10810632 | intensive    | 0.8045       | 0.4595      | 1.4086      | 4.34E-1            | 4.41E-1              | 0.3193       | 0.0777      | 1.3125      | 5.68E-2            | 8.42E-2              |
| BNC2         | 9   | 16,779,024  | rs10810632 | conventional | 1.8455       | 1.3128      | 2.5943      | 1.02E-3            | 2.01E-3              | 1.8498       | 1.1899      | 2.8755      | 1.07E-2            | 3.41E-2              |
| BNC2         | 9   | 16,779,024  | rs10810632 | combined     | 1.3085       | 0.9777      | 1.7511      | 8.03E-2            | 6.74E-2              | 1.2438       | 0.826       | 1.8729      | 3.10E-1            | 2.94E-1              |
| SORCS1       | 10  | 108,113,589 | rs1358030  | intensive    | 1.2493       | 0.9347      | 1.6697      | 1.36E-1            | 6.01E-2              | 1.0033       | 0.6138      | 1.6399      | 9.90E-1            | 9.18E-1              |
| SORCS1       | 10  | 108,113,589 | rs1358030  | conventional | 1.2564       | 1.0087      | 1.565       | 4.29E-2            | 4.22E-2              | 1.3942       | 1.0413      | 1.8667      | 2.66E-2            | 6.03E-2              |
| SORCS1       | 10  | 108,113,589 | rs1358030  | combined     | 1.2617       | 1.0628      | 1.4979      | 8.47E-3            | 1.11E-2              | 1.2355       | 0.9708      | 1.5723      | 8.81E-2            | 1.52E-1              |
| GSC          | 14  | 94,407,241  | rs8007115  | intensive    | 0.8798       | 0.6209      | 1.2468      | 4.66E-1            | 5.27E-1              | 0.77         | 0.4186      | 1.4162      | 3.88E-1            | 5.65E-1              |
| GSC          | 14  | 94,407,241  | rs8007115  | conventional | 1.0938       | 0.8498      | 1.4078      | 4.89E-1            | 8.11E-1              | 1.0123       | 0.7223      | 1.4187      | 9.44E-1            | 5.17E-1              |
| GSC          | 14  | 94,407,241  | rs8007115  | combined     | 0.9888       | 0.8084      | 1.2095      | 9.13E-1            | 7.98E-1              | 0.9275       | 0.6931      | 1.2411      | 6.10E-1            | 6.79E-1              |
| GSC          | 14  | 94,405,244  | rs11160219 | intensive    | 0.9024       | 0.6387      | 1.275       | 5.57E-1            | 6.25E-1              | 0.8332       | 0.4601      | 1.5087      | 5.40E-1            | 6.67E-1              |
| GSC          | 14  | 94,405,244  | rs11160219 | conventional | 1.0684       | 0.8315      | 1.3729      | 6.07E-1            | 9.20E-1              | 0.9866       | 0.7039      | 1.3829      | 9.37E-1            | 4.58E-1              |
| GSC          | 14  | 94,405,244  | rs11160219 | combined     | 0.9836       | 0.8048      | 1.2022      | 8.72E-1            | 8.18E-1              | 0.9219       | 0.6895      | 1.2327      | 5.81E-1            | 6.98E-1              |
| GSC          | 14  | 94,375,765  | rs11624318 | intensive    | 1.0109       | 0.7093      | 1.4408      | 9.52E-1            | 6.29E-1              | 0.7649       | 0.4017      | 1.4565      | 4.00E-1            | 6.05E-1              |
| GSC          | 14  | 94,375,765  | rs11624318 | conventional | 0.9463       | 0.7272      | 1.2314      | 6.80E-1            | 2.98E-1              | 1.0186       | 0.7271      | 1.4269      | 9.15E-1            | 6.52E-1              |
| GSC          | 14  | 94,375,765  | rs11624318 | combined     | 0.9722       | 0.7877      | 1.1999      | 7.92E-1            | 6.80E-1              | 0.9602       | 0.7128      | 1.2935      | 7.89E-1            | 8.31E-1              |
| WDR72        | 15  | 51,296,486  | rs482541   | intensive    | 1.3587       | 0.8851      | 2.0858      | 1.76E-1            | 3.65E-2              | 1.0248       | 0.469       | 2.2389      | 9.51E-1            | 5.98E-1              |
| WDR72        | 15  | 51,296,486  | rs482541   | conventional | 0.9481       | 0.6674      | 1.3468      | 7.64E-1            | 8.60E-1              | 0.7382       | 0.4407      | 1.2367      | 2.30E-1            | 3.45E-1              |
| WDR72        | 15  | 51,296,486  | rs482541   | combined     | 1.0915       | 0.8338      | 1.4288      | 5.28E-1            | 1.57E-1              | 0.8038       | 0.524       | 1.2329      | 3.02E-1            | 9.20E-1              |
| WDR72        | 15  | 51,295,884  | rs566369   | intensive    | 1.3587       | 0.8851      | 2.0858      | 1.76E-1            | 3.65E-2              | 1.0248       | 0.469       | 2.2389      | 9.51E-1            | 5.98E-1              |
| WDR72        | 15  | 51,295,884  | rs566369   | conventional | 0.9481       | 0.6674      | 1.3468      | 7.64E-1            | 8.60E-1              | 0.7382       | 0.4407      | 1.2367      | 2.30E-1            | 3.45E-1              |
| WDR72        | 15  | 51,295,884  | rs566369   | combined     | 1.0915       | 0.8338      | 1.4288      | 5.28E-1            | 1.57E-1              | 0.8038       | 0.524       | 1.2329      | 3.02E-1            | 9.20E-1              |
| WDR72        | 15  | 51,291,964  | rs690271   | intensive    | 1.3587       | 0.8851      | 2.0858      | 1.76E-1            | 3.65E-2              | 1.0248       | 0.469       | 2.2389      | 9.51E-1            | 5.98E-1              |
| WDR72        | 15  | 51,291,964  | rs690271   | conventional | 0.95         | 0.6688      | 1.3494      | 7.73E-1            | 8.66E-1              | 0.7396       | 0.4416      | 1.2388      | 2.32E-1            | 3.45E-1              |
| WDR72        | 15  | 51,291,964  | rs690271   | combined     | 1.0922       | 0.8343      | 1.4297      | 5.26E-1            | 1.56E-1              | 0.8042       | 0.5243      | 1.2336      | 3.03E-1            | 9.21E-1              |
| WDR72        | 15  | 51,291,924  | rs572221   | intensive    | 1.3659       | 0.89        | 2.0962      | 1.69E-1            | 3.57E-2              | 1.0263       | 0.4699      | 2.2415      | 9.48E-1            | 5.99E-1              |
| WDR72        | 15  | 51,291,924  | rs572221   | conventional | 0.95         | 0.6688      | 1.3494      | 7.73E-1            | 8.66E-1              | 0.7396       | 0.4416      | 1.2388      | 2.32E-1            | 3.45E-1              |
| WDR72        | 15  | 51,291,924  | rs572221   | combined     | 1.0947       | 0.8363      | 1.4328      | 5.15E-1            | 1.55E-1              | 0.8052       | 0.525       | 1.235       | 3.06E-1            | 9.16E-1              |
| WDR72        | 15  | 51,277,554  | rs493218   | intensive    | 1.3587       | 0.8851      | 2.0858      | 1.76E-1            | 3.65E-2              | 1.0412       | 0.4767      | 2.2737      | 9.20E-1            | 5.70E-1              |
| WDR72        | 15  | 51,277,554  | rs493218   | conventional | 0.9247       | 0.6483      | 1.319       | 6.63E-1            | 7.82E-1              | 0.6959       | 0.4093      | 1.1831      | 1.59E-1            | 2.96E-1              |
| WDR72        | 15  | 51,277,554  | rs493218   | combined     | 1.0748       | 0.8196      | 1.4095      | 6.05E-1            | 1.88E-1              | 0.7759       | 0.5016      | 1.2002      | 2.37E-1            | 8.24E-1              |

**Supplementary Table 4.** Association results of top 13 SNPs for HbA1c in DCCT with coronary calcium measured during EDIC.

| nearest gene | CHR | pos         | snp        | GROUP        | M1 p value | M2 p value | M3 p value | M4 p value | M1 parameter estimate | M1 SE | M2 parameter estimate | M2 SE | M3 parameter estimate | M3 SE | M4 parameter estimate | M4 SE |
|--------------|-----|-------------|------------|--------------|------------|------------|------------|------------|-----------------------|-------|-----------------------|-------|-----------------------|-------|-----------------------|-------|
| BNC2         | 9   | 16,779,024  | rs10810632 | conventional | 0.24424    | 0.23373    | 0.37679    | 0.30206    | 0.89                  | 0.76  | 0.81                  | 0.68  | 0.56                  | 0.63  | 0.64                  | 0.62  |
| BNC2         | 9   | 16,779,024  | rs10810632 | intensive    | 0.13643    | 0.0379     | 0.01862    | 0.0186     | 0.99                  | 0.66  | 1.25                  | 0.6   | 1.34                  | 0.57  | 1.34                  | 0.57  |
| BNC2         | 9   | 16,779,024  | rs10810632 | COMBINED     | 0.06475    | 0.04556    | 0.07268    | 0.04541    | 0.93                  | 0.5   | 0.9                   | 0.45  | 0.76                  | 0.42  | 0.84                  | 0.42  |
| BNC2         | 9   | 16,779,436  | rs6475082  | conventional | 0.2776     | 0.26097    | 0.39401    | 0.31815    | 0.83                  | 0.76  | 0.76                  | 0.67  | 0.54                  | 0.63  | 0.62                  | 0.62  |
| BNC2         | 9   | 16,779,436  | rs6475082  | intensive    | 0.13643    | 0.0379     | 0.01862    | 0.0186     | 0.99                  | 0.66  | 1.25                  | 0.6   | 1.34                  | 0.57  | 1.34                  | 0.57  |
| BNC2         | 9   | 16,779,436  | rs6475082  | COMBINED     | 0.07264    | 0.05217    | 0.07922    | 0.05034    | 0.9                   | 0.5   | 0.87                  | 0.45  | 0.74                  | 0.42  | 0.82                  | 0.42  |
| BNC2         | 9   | 16,779,878  | rs4961760  | conventional | 0.30866    | 0.30326    | 0.42986    | 0.35022    | 0.78                  | 0.76  | 0.7                   | 0.67  | 0.5                   | 0.63  | 0.58                  | 0.61  |
| BNC2         | 9   | 16,779,878  | rs4961760  | intensive    | 0.13643    | 0.0379     | 0.01862    | 0.0186     | 0.99                  | 0.66  | 1.25                  | 0.6   | 1.34                  | 0.57  | 1.34                  | 0.57  |
| BNC2         | 9   | 16,779,878  | rs4961760  | COMBINED     | 0.07986    | 0.05846    | 0.0845     | 0.05391    | 0.88                  | 0.5   | 0.85                  | 0.45  | 0.73                  | 0.42  | 0.81                  | 0.42  |
| BNC2         | 9   | 16,791,850  | rs2254193  | conventional | 0.2438     | 0.25557    | 0.37916    | 0.30716    | 0.95                  | 0.81  | 0.82                  | 0.72  | 0.59                  | 0.67  | 0.68                  | 0.66  |
| BNC2         | 9   | 16,791,850  | rs2254193  | intensive    | 0.31739    | 0.09241    | 0.05748    | 0.05338    | 0.7                   | 0.7   | 1.07                  | 0.64  | 1.15                  | 0.6   | 1.17                  | 0.6   |
| BNC2         | 9   | 16,791,850  | rs2254193  | COMBINED     | 0.13581    | 0.08898    | 0.15687    | 0.10153    | 0.8                   | 0.53  | 0.81                  | 0.48  | 0.64                  | 0.45  | 0.73                  | 0.45  |
| SORCS1       | 10  | 108,113,589 | rs1358030  | conventional | 0.1864     | 0.1295     | 0.0276     | 0.0198     | 0.56                  | 0.43  | 0.58                  | 0.38  | 0.8                   | 0.36  | 0.83                  | 0.36  |
| SORCS1       | 10  | 108,113,589 | rs1358030  | intensive    | 0.1877     | 0.107      | 0.0761     | 0.0502     | 0.53                  | 0.4   | 0.59                  | 0.37  | 0.62                  | 0.35  | 0.68                  | 0.35  |
| SORCS1       | 10  | 108,113,589 | rs1358030  | COMBINED     | 0.0608     | 0.0282     | 0.0095     | 0.0043     | 0.55                  | 0.29  | 0.58                  | 0.26  | 0.65                  | 0.25  | 0.71                  | 0.25  |
| GSC          | 14  | 94,375,765  | rs11624318 | conventional | 0.0338     | 0.06319    | 0.01727    | 0.01987    | 1.04                  | 0.49  | 0.81                  | 0.44  | 0.95                  | 0.4   | 0.93                  | 0.4   |
| GSC          | 14  | 94,375,765  | rs11624318 | intensive    | 0.56384    | 0.24589    | 0.29317    | 0.21918    | -0.28                 | 0.48  | -0.52                 | 0.45  | -0.45                 | 0.42  | -0.52                 | 0.42  |
| GSC          | 14  | 94,375,765  | rs11624318 | COMBINED     | 0.25733    | 0.49085    | 0.21342    | 0.26365    | 0.39                  | 0.34  | 0.21                  | 0.31  | 0.36                  | 0.29  | 0.33                  | 0.29  |
| GSC          | 14  | 94,405,244  | rs11160219 | conventional | 0.39221    | 0.3388     | 0.16105    | 0.21132    | 0.41                  | 0.48  | 0.42                  | 0.44  | 0.59                  | 0.42  | 0.52                  | 0.41  |
| GSC          | 14  | 94,405,244  | rs11160219 | intensive    | 0.83883    | 0.71476    | 0.48678    | 0.43876    | -0.09                 | 0.46  | -0.15                 | 0.42  | -0.28                 | 0.4   | -0.31                 | 0.4   |
| GSC          | 14  | 94,405,244  | rs11160219 | COMBINED     | 0.64742    | 0.76645    | 0.50959    | 0.63954    | 0.15                  | 0.33  | 0.09                  | 0.3   | 0.19                  | 0.29  | 0.13                  | 0.29  |
| GSC          | 14  | 94,407,241  | rs8007115  | conventional | 0.39029    | 0.34282    | 0.15165    | 0.19768    | 0.42                  | 0.48  | 0.42                  | 0.45  | 0.6                   | 0.42  | 0.54                  | 0.42  |
| GSC          | 14  | 94,407,241  | rs8007115  | intensive    | 0.82192    | 0.69159    | 0.51525    | 0.44594    | -0.1                  | 0.46  | -0.17                 | 0.42  | -0.26                 | 0.4   | -0.3                  | 0.4   |
| GSC          | 14  | 94,407,241  | rs8007115  | COMBINED     | 0.65577    | 0.78948    | 0.4696     | 0.59935    | 0.15                  | 0.33  | 0.08                  | 0.31  | 0.21                  | 0.29  | 0.15                  | 0.29  |
| WDR72        | 15  | 51,277,554  | rs493218   | conventional | 0.61858    | 0.70967    | 0.52761    | 0.52509    | -0.33                 | 0.67  | -0.22                 | 0.6   | 0.35                  | 0.56  | 0.36                  | 0.56  |
| WDR72        | 15  | 51,277,554  | rs493218   | intensive    | 0.14821    | 0.15828    | 0.03032    | 0.09229    | 0.87                  | 0.6   | 0.78                  | 0.55  | 1.15                  | 0.53  | 0.88                  | 0.52  |
| WDR72        | 15  | 51,277,554  | rs493218   | COMBINED     | 0.49992    | 0.60516    | 0.114      | 0.16924    | 0.3                   | 0.45  | 0.21                  | 0.41  | 0.61                  | 0.39  | 0.53                  | 0.38  |
| WDR72        | 15  | 51,291,924  | rs572221   | conventional | 0.72723    | 0.77537    | 0.54209    | 0.54754    | -0.23                 | 0.66  | -0.17                 | 0.6   | 0.34                  | 0.56  | 0.34                  | 0.56  |
| WDR72        | 15  | 51,291,924  | rs572221   | intensive    | 0.15599    | 0.15476    | 0.02977    | 0.09129    | 0.86                  | 0.6   | 0.79                  | 0.55  | 1.16                  | 0.53  | 0.88                  | 0.52  |
| WDR72        | 15  | 51,291,924  | rs572221   | COMBINED     | 0.44957    | 0.56355    | 0.11907    | 0.17809    | 0.34                  | 0.45  | 0.24                  | 0.41  | 0.6                   | 0.38  | 0.52                  | 0.38  |
| WDR72        | 15  | 51,291,964  | rs690271   | conventional | 0.72723    | 0.77537    | 0.54209    | 0.54754    | -0.23                 | 0.66  | -0.17                 | 0.6   | 0.34                  | 0.56  | 0.34                  | 0.56  |
| WDR72        | 15  | 51,291,964  | rs690271   | intensive    | 0.16647    | 0.16637    | 0.0326     | 0.09809    | 0.83                  | 0.6   | 0.77                  | 0.55  | 1.14                  | 0.53  | 0.86                  | 0.52  |
| WDR72        | 15  | 51,291,964  | rs690271   | COMBINED     | 0.46457    | 0.5825     | 0.12452    | 0.18581    | 0.33                  | 0.45  | 0.22                  | 0.41  | 0.59                  | 0.38  | 0.51                  | 0.38  |
| WDR72        | 15  | 51,295,884  | rs566369   | conventional | 0.71659    | 0.74533    | 0.56241    | 0.56688    | -0.24                 | 0.66  | -0.19                 | 0.6   | 0.32                  | 0.56  | 0.32                  | 0.56  |
| WDR72        | 15  | 51,295,884  | rs566369   | intensive    | 0.16647    | 0.16637    | 0.0326     | 0.09809    | 0.83                  | 0.6   | 0.77                  | 0.55  | 1.14                  | 0.53  | 0.86                  | 0.52  |
| WDR72        | 15  | 51,295,884  | rs566369   | COMBINED     | 0.4706     | 0.59601    | 0.1278     | 0.19031    | 0.32                  | 0.45  | 0.22                  | 0.41  | 0.59                  | 0.38  | 0.5                   | 0.38  |
| WDR72        | 15  | 51,296,486  | rs482541   | conventional | 0.71659    | 0.74533    | 0.56241    | 0.56688    | -0.24                 | 0.66  | -0.19                 | 0.6   | 0.32                  | 0.56  | 0.32                  | 0.56  |
| WDR72        | 15  | 51,296,486  | rs482541   | intensive    | 0.16647    | 0.16637    | 0.0326     | 0.09809    | 0.83                  | 0.6   | 0.77                  | 0.55  | 1.14                  | 0.53  | 0.86                  | 0.52  |
| WDR72        | 15  | 51,296,486  | rs482541   | COMBINED     | 0.4706     | 0.59601    | 0.1278     | 0.19031    | 0.32                  | 0.45  | 0.22                  | 0.41  | 0.59                  | 0.38  | 0.5                   | 0.38  |

**Supplementary Table 5.** Association results of top 13 SNPs for HbA1c in DCCT with hypoglycemia during DCCT.

| nearest gene | chr | pos         | snp        | GROUP        | ordinal uv def1=coma/seizure |            |          |          | ordinal a1c def1 |            |          |          | ordinal uv def2=requiring assistance |            |          |          | ORDINAL DEF2 WITH A1c |            |          |          |
|--------------|-----|-------------|------------|--------------|------------------------------|------------|----------|----------|------------------|------------|----------|----------|--------------------------------------|------------|----------|----------|-----------------------|------------|----------|----------|
|              |     |             |            |              | ProbChisq                    | Odds Ratio | Lower CL | Upper CL | ProbChisq        | Odds Ratio | Lower CL | Upper CL | ProbChisq                            | Odds Ratio | Lower CL | Upper CL | ProbChisq             | Odds Ratio | Lower CL | Upper CL |
| BNC2         | 9   | 16,779,024  | rs10810632 | INTENSIVE    | 5.8E-01                      | 0.89       | 0.60     | 1.33     | 6.1E-01          | 0.90       | 0.60     | 1.35     | 9.4E-01                              | 1.02       | 0.70     | 1.47     | 9.4E-01               | 1.01       | 0.70     | 1.47     |
| BNC2         | 9   | 16,779,024  | rs10810632 | CONVENTIONAL | 9.9E-02                      | 0.59       | 0.32     | 1.10     | 4.9E-01          | 0.80       | 0.42     | 1.51     | 4.4E-03                              | 0.49       | 0.30     | 0.80     | 1.0E-01               | 0.66       | 0.39     | 1.09     |
| BNC2         | 9   | 16,779,024  | rs10810632 | COMBINED     | 2.5E-01                      | 0.83       | 0.60     | 1.14     | 3.6E-01          | 0.86       | 0.61     | 1.19     | 2.7E-01                              | 0.86       | 0.65     | 1.13     | 4.2E-01               | 0.89       | 0.67     | 1.18     |
| BNC2         | 9   | 16,779,436  | rs6475082  | INTENSIVE    | 5.8E-01                      | 0.89       | 0.60     | 1.33     | 6.1E-01          | 0.90       | 0.60     | 1.35     | 9.4E-01                              | 1.02       | 0.70     | 1.47     | 9.4E-01               | 1.01       | 0.70     | 1.47     |
| BNC2         | 9   | 16,779,436  | rs6475082  | CONVENTIONAL | 1.5E-01                      | 0.64       | 0.35     | 1.17     | 6.2E-01          | 0.85       | 0.46     | 1.58     | 7.3E-03                              | 0.51       | 0.32     | 0.84     | 1.4E-01               | 0.69       | 0.42     | 1.14     |
| BNC2         | 9   | 16,779,436  | rs6475082  | COMBINED     | 2.9E-01                      | 0.84       | 0.61     | 1.16     | 4.1E-01          | 0.87       | 0.63     | 1.21     | 3.1E-01                              | 0.87       | 0.66     | 1.14     | 4.7E-01               | 0.90       | 0.68     | 1.20     |
| BNC2         | 9   | 16,779,878  | rs4961760  | INTENSIVE    | 5.8E-01                      | 0.89       | 0.60     | 1.33     | 6.1E-01          | 0.90       | 0.60     | 1.35     | 9.4E-01                              | 1.02       | 0.70     | 1.47     | 9.4E-01               | 1.01       | 0.70     | 1.47     |
| BNC2         | 9   | 16,779,878  | rs4961760  | CONVENTIONAL | 1.4E-01                      | 0.64       | 0.35     | 1.15     | 5.9E-01          | 0.84       | 0.46     | 1.56     | 1.1E-02                              | 0.54       | 0.34     | 0.87     | 2.0E-01               | 0.73       | 0.44     | 1.18     |
| BNC2         | 9   | 16,779,878  | rs4961760  | COMBINED     | 2.7E-01                      | 0.84       | 0.60     | 1.15     | 3.9E-01          | 0.87       | 0.62     | 1.20     | 3.5E-01                              | 0.88       | 0.67     | 1.15     | 5.3E-01               | 0.91       | 0.69     | 1.21     |
| BNC2         | 9   | 16,791,850  | rs2254193  | INTENSIVE    | 5.4E-01                      | 0.88       | 0.58     | 1.34     | 5.5E-01          | 0.88       | 0.58     | 1.34     | 5.5E-01                              | 0.89       | 0.60     | 1.31     | 5.5E-01               | 0.89       | 0.60     | 1.31     |
| BNC2         | 9   | 16,791,850  | rs2254193  | CONVENTIONAL | 1.1E-01                      | 0.58       | 0.30     | 1.14     | 5.2E-01          | 0.80       | 0.40     | 1.59     | 4.7E-03                              | 0.46       | 0.26     | 0.79     | 9.8E-02               | 0.63       | 0.36     | 1.09     |
| BNC2         | 9   | 16,791,850  | rs2254193  | COMBINED     | 2.8E-01                      | 0.83       | 0.58     | 1.17     | 3.9E-01          | 0.86       | 0.60     | 1.22     | 1.3E-01                              | 0.80       | 0.60     | 1.07     | 2.2E-01               | 0.82       | 0.61     | 1.12     |
| SORCS1       | 10  | 108,113,589 | rs1358030  | INTENSIVE    | 6.4E-01                      | 1.05       | 0.85     | 1.31     | 8.6E-01          | 1.02       | 0.82     | 1.27     | 2.8E-01                              | 0.89       | 0.72     | 1.10     | 3.0E-01               | 0.89       | 0.72     | 1.10     |
| SORCS1       | 10  | 108,113,589 | rs1358030  | CONVENTIONAL | 9.7E-04                      | 0.60       | 0.44     | 0.81     | 3.3E-02          | 0.71       | 0.52     | 0.97     | 1.4E-04                              | 0.63       | 0.50     | 0.80     | 1.8E-02               | 0.75       | 0.58     | 0.95     |
| SORCS1       | 10  | 108,113,589 | rs1358030  | COMBINED     | 7.2E-02                      | 0.85       | 0.72     | 1.01     | 3.9E-01          | 0.93       | 0.78     | 1.10     | 5.5E-04                              | 0.77       | 0.66     | 0.89     | 7.0E-02               | 0.87       | 0.74     | 1.01     |
| GSC          | 14  | 94,375,765  | rs11624318 | INTENSIVE    | 5.1E-01                      | 0.91       | 0.70     | 1.19     | 6.0E-01          | 0.93       | 0.71     | 1.22     | 5.2E-01                              | 0.92       | 0.72     | 1.18     | 5.1E-01               | 0.92       | 0.71     | 1.18     |
| GSC          | 14  | 94,375,765  | rs11624318 | CONVENTIONAL | 7.3E-01                      | 0.94       | 0.67     | 1.32     | 5.2E-01          | 0.89       | 0.64     | 1.26     | 5.9E-01                              | 0.93       | 0.71     | 1.22     | 3.8E-01               | 0.88       | 0.67     | 1.16     |
| GSC          | 14  | 94,375,765  | rs11624318 | COMBINED     | 4.3E-01                      | 0.92       | 0.75     | 1.13     | 2.7E-01          | 0.89       | 0.72     | 1.10     | 3.9E-01                              | 0.93       | 0.77     | 1.10     | 1.6E-01               | 0.88       | 0.73     | 1.05     |
| GSC          | 14  | 94,405,244  | rs11160219 | INTENSIVE    | 9.6E-01                      | 0.99       | 0.77     | 1.28     | 9.2E-01          | 1.01       | 0.79     | 1.31     | 6.5E-01                              | 1.06       | 0.83     | 1.34     | 6.0E-01               | 1.07       | 0.84     | 1.36     |
| GSC          | 14  | 94,405,244  | rs11160219 | CONVENTIONAL | 7.7E-01                      | 1.05       | 0.76     | 1.44     | 7.4E-01          | 0.95       | 0.68     | 1.31     | 8.8E-01                              | 1.02       | 0.79     | 1.32     | 5.7E-01               | 0.93       | 0.71     | 1.21     |
| GSC          | 14  | 94,405,244  | rs11160219 | COMBINED     | 7.7E-01                      | 1.03       | 0.85     | 1.25     | 8.3E-01          | 0.98       | 0.80     | 1.19     | 4.1E-01                              | 1.07       | 0.91     | 1.27     | 9.9E-01               | 1.00       | 0.84     | 1.19     |
| GSC          | 14  | 94,407,241  | rs8007115  | INTENSIVE    | 9.6E-01                      | 1.01       | 0.78     | 1.30     | 8.3E-01          | 1.03       | 0.80     | 1.33     | 5.7E-01                              | 1.07       | 0.84     | 1.37     | 5.2E-01               | 1.08       | 0.85     | 1.38     |
| GSC          | 14  | 94,407,241  | rs8007115  | CONVENTIONAL | 8.9E-01                      | 1.02       | 0.74     | 1.41     | 6.4E-01          | 0.92       | 0.67     | 1.28     | 8.4E-01                              | 1.03       | 0.79     | 1.33     | 6.3E-01               | 0.94       | 0.72     | 1.22     |
| GSC          | 14  | 94,407,241  | rs8007115  | COMBINED     | 8.1E-01                      | 1.02       | 0.84     | 1.25     | 7.9E-01          | 0.97       | 0.80     | 1.19     | 3.7E-01                              | 1.08       | 0.91     | 1.28     | 9.3E-01               | 1.01       | 0.84     | 1.20     |
| WDR72        | 15  | 51,277,554  | rs493218   | INTENSIVE    | 7.7E-01                      | 0.95       | 0.67     | 1.34     | 8.6E-01          | 1.03       | 0.73     | 1.47     | 8.7E-01                              | 1.03       | 0.74     | 1.42     | 9.5E-01               | 1.01       | 0.73     | 1.41     |
| WDR72        | 15  | 51,277,554  | rs493218   | CONVENTIONAL | 5.5E-01                      | 0.87       | 0.55     | 1.37     | 6.6E-01          | 0.90       | 0.57     | 1.43     | 6.6E-01                              | 1.08       | 0.76     | 1.53     | 4.5E-01               | 1.15       | 0.80     | 1.63     |
| WDR72        | 15  | 51,277,554  | rs493218   | COMBINED     | 6.4E-01                      | 0.94       | 0.72     | 1.23     | 3.4E-01          | 0.87       | 0.66     | 1.15     | 6.2E-01                              | 1.06       | 0.84     | 1.33     | 8.2E-01               | 0.97       | 0.77     | 1.24     |
| WDR72        | 15  | 51,291,924  | rs572221   | INTENSIVE    | 7.4E-01                      | 0.94       | 0.67     | 1.33     | 8.8E-01          | 1.03       | 0.72     | 1.46     | 8.8E-01                              | 1.03       | 0.74     | 1.42     | 9.6E-01               | 1.01       | 0.73     | 1.40     |
| WDR72        | 15  | 51,291,924  | rs572221   | CONVENTIONAL | 5.0E-01                      | 0.86       | 0.54     | 1.35     | 5.9E-01          | 0.88       | 0.56     | 1.40     | 7.6E-01                              | 1.06       | 0.75     | 1.49     | 5.5E-01               | 1.11       | 0.78     | 1.59     |
| WDR72        | 15  | 51,291,924  | rs572221   | COMBINED     | 5.9E-01                      | 0.93       | 0.71     | 1.22     | 3.0E-01          | 0.87       | 0.66     | 1.14     | 6.8E-01                              | 1.05       | 0.83     | 1.32     | 7.6E-01               | 0.96       | 0.76     | 1.22     |
| WDR72        | 15  | 51,291,964  | rs690271   | INTENSIVE    | 7.2E-01                      | 0.94       | 0.66     | 1.32     | 9.1E-01          | 1.02       | 0.72     | 1.45     | 8.9E-01                              | 1.02       | 0.74     | 1.41     | 9.7E-01               | 1.01       | 0.72     | 1.40     |
| WDR72        | 15  | 51,291,964  | rs690271   | CONVENTIONAL | 5.0E-01                      | 0.86       | 0.54     | 1.35     | 5.9E-01          | 0.88       | 0.56     | 1.40     | 7.6E-01                              | 1.06       | 0.75     | 1.49     | 5.5E-01               | 1.11       | 0.78     | 1.59     |
| WDR72        | 15  | 51,291,964  | rs690271   | COMBINED     | 5.8E-01                      | 0.93       | 0.71     | 1.21     | 2.9E-01          | 0.86       | 0.66     | 1.13     | 6.7E-01                              | 1.05       | 0.84     | 1.32     | 7.4E-01               | 0.96       | 0.76     | 1.22     |
| WDR72        | 15  | 51,295,884  | rs566369   | INTENSIVE    | 7.2E-01                      | 0.94       | 0.66     | 1.32     | 9.1E-01          | 1.02       | 0.72     | 1.45     | 8.9E-01                              | 1.02       | 0.74     | 1.41     | 9.7E-01               | 1.01       | 0.72     | 1.40     |
| WDR72        | 15  | 51,295,884  | rs566369   | CONVENTIONAL | 5.0E-01                      | 0.85       | 0.54     | 1.34     | 5.9E-01          | 0.88       | 0.55     | 1.40     | 7.3E-01                              | 1.06       | 0.75     | 1.50     | 5.3E-01               | 1.12       | 0.79     | 1.60     |
| WDR72        | 15  | 51,295,884  | rs566369   | COMBINED     | 5.7E-01                      | 0.93       | 0.71     | 1.21     | 2.9E-01          | 0.86       | 0.66     | 1.13     | 6.6E-01                              | 1.05       | 0.84     | 1.32     | 7.5E-01               | 0.96       | 0.76     | 1.22     |
| WDR72        | 15  | 51,296,486  | rs482541   | INTENSIVE    | 7.2E-01                      | 0.94       | 0.66     | 1.32     | 9.1E-01          | 1.02       | 0.72     | 1.45     | 8.9E-01                              | 1.02       | 0.74     | 1.41     | 9.7E-01               | 1.01       | 0.72     | 1.40     |
| WDR72        | 15  | 51,296,486  | rs482541   | CONVENTIONAL | 5.0E-01                      | 0.85       | 0.54     | 1.34     | 5.9E-01          | 0.88       | 0.55     | 1.40     | 7.3E-01                              | 1.06       | 0.75     | 1.50     | 5.3E-01               | 1.12       | 0.79     | 1.60     |
| WDR72        | 15  | 51,296,486  | rs482541   | COMBINED     | 5.7E-01                      | 0.93       | 0.71     | 1.21     | 2.9E-01          | 0.86       | 0.66     | 1.13     | 6.6E-01                              | 1.05       | 0.84     | 1.32     | 7.5E-01               | 0.96       | 0.76     | 1.22     |

**Supplementary Table 6.** Association results of top 13 SNPs for HbA1c in DCCT with retinal complications in DCCT/EDIC.

| nearest gene | chr | pos         | snp        | trx          | mild retinal |           |           |                 |                 | csme |           |           |          |          | severe retinal |           |           |            |            |
|--------------|-----|-------------|------------|--------------|--------------|-----------|-----------|-----------------|-----------------|------|-----------|-----------|----------|----------|----------------|-----------|-----------|------------|------------|
|              |     |             |            |              | hr0          | hr_lowci0 | hr_uppci0 | mild retinal_uv | mild retinal_mv | hr1  | hr_lowci1 | hr_uppci1 | csme_uv  | csme_mv  | hr2            | hr_lowci2 | hr_uppci2 | sev ret_uv | sev ret_mv |
| BNC2         | 9   | 16,779,024  | rs10810632 | intensive    | 1.02         | 0.77      | 1.35      | 9.01E-01        | 8.05E-01        | 0.97 | 0.56      | 1.69      | 9.19E-01 | 9.82E-01 | 0.61           | 0.3       | 1.25      | 1.49E-01   | 1.89E-01   |
| BNC2         | 9   | 16,779,024  | rs10810632 | conventional | 1.73         | 1.31      | 2.27      | 1.99E-04        | 6.79E-06        | 1.87 | 1.31      | 2.67      | 1.36E-03 | 1.54E-03 | 1.83           | 1.28      | 2.62      | 1.69E-03   | 2.04E-03   |
| BNC2         | 9   | 16,779,024  | rs10810632 | combined     | 1.15         | 0.95      | 1.4       | 1.52E-01        | 2.83E-01        | 1.36 | 1.01      | 1.83      | 4.81E-02 | 3.93E-02 | 1.19           | 0.88      | 1.62      | 2.72E-01   | 1.99E-01   |
| BNC2         | 9   | 16,779,436  | rs6475082  | combined     | 1.15         | 0.95      | 1.39      | 1.63E-01        | 2.71E-01        | 1.35 | 1.01      | 1.82      | 5.36E-02 | 4.11E-02 | 1.18           | 0.87      | 1.61      | 2.99E-01   | 2.08E-01   |
| BNC2         | 9   | 16,779,436  | rs6475082  | conventional | 1.68         | 1.28      | 2.2       | 3.82E-04        | 8.28E-06        | 1.83 | 1.28      | 2.62      | 1.89E-03 | 1.95E-03 | 1.79           | 1.25      | 2.56      | 2.51E-03   | 2.67E-03   |
| BNC2         | 9   | 16,779,436  | rs6475082  | intensive    | 1.02         | 0.77      | 1.35      | 9.01E-01        | 8.05E-01        | 0.97 | 0.56      | 1.69      | 9.19E-01 | 9.82E-01 | 0.61           | 0.3       | 1.25      | 1.49E-01   | 1.89E-01   |
| BNC2         | 9   | 16,779,878  | rs4961760  | intensive    | 1.02         | 0.77      | 1.35      | 9.01E-01        | 8.05E-01        | 0.97 | 0.56      | 1.69      | 9.19E-01 | 9.82E-01 | 0.61           | 0.3       | 1.25      | 1.49E-01   | 1.89E-01   |
| BNC2         | 9   | 16,779,878  | rs4961760  | conventional | 1.63         | 1.24      | 2.14      | 7.45E-04        | 2.23E-05        | 1.81 | 1.27      | 2.59      | 2.22E-03 | 2.35E-03 | 1.78           | 1.25      | 2.54      | 2.72E-03   | 2.84E-03   |
| BNC2         | 9   | 16,779,878  | rs4961760  | combined     | 1.14         | 0.94      | 1.38      | 1.82E-01        | 3.02E-01        | 1.35 | 1         | 1.82      | 5.59E-02 | 4.29E-02 | 1.18           | 0.87      | 1.61      | 3.03E-01   | 2.10E-01   |
| BNC2         | 9   | 16,791,850  | rs2254193  | intensive    | 1.06         | 0.79      | 1.42      | 7.03E-01        | 9.70E-01        | 1.02 | 0.57      | 1.82      | 9.41E-01 | 9.15E-01 | 0.8            | 0.4       | 1.58      | 5.04E-01   | 5.35E-01   |
| BNC2         | 9   | 16,791,850  | rs2254193  | conventional | 1.54         | 1.15      | 2.06      | 5.93E-03        | 2.26E-04        | 1.85 | 1.26      | 2.72      | 3.59E-03 | 6.53E-03 | 1.89           | 1.29      | 2.75      | 2.01E-03   | 2.84E-03   |
| BNC2         | 9   | 16,791,850  | rs2254193  | combined     | 1.13         | 0.92      | 1.39      | 2.41E-01        | 4.04E-01        | 1.35 | 0.99      | 1.86      | 7.14E-02 | 7.53E-02 | 1.28           | 0.93      | 1.76      | 1.44E-01   | 1.27E-01   |
| SORCS1       | 10  | 108,113,589 | rs1358030  | combined     | 1.14         | 1.02      | 1.27      | 1.66E-02        | 2.29E-02        | 1.12 | 0.93      | 1.34      | 2.43E-01 | 3.67E-01 | 1.22           | 1.02      | 1.46      | 3.02E-02   | 3.83E-02   |
| SORCS1       | 10  | 108,113,589 | rs1358030  | conventional | 1.15         | 0.99      | 1.34      | 7.49E-02        | 1.11E-01        | 1.16 | 0.92      | 1.46      | 2.23E-01 | 2.20E-01 | 1.3            | 1.04      | 1.63      | 2.19E-02   | 2.81E-02   |
| SORCS1       | 10  | 108,113,589 | rs1358030  | intensive    | 1.16         | 0.99      | 1.35      | 7.34E-02        | 3.32E-02        | 1.1  | 0.8       | 1.5       | 5.68E-01 | 4.49E-01 | 1.27           | 0.92      | 1.77      | 1.53E-01   | 8.40E-02   |
| GSC          | 14  | 94,375,765  | rs11624318 | intensive    | 1.09         | 0.9       | 1.32      | 3.88E-01        | 1.95E-01        | 0.9  | 0.6       | 1.33      | 5.79E-01 | 9.26E-01 | 0.69           | 0.44      | 1.1       | 1.04E-01   | 2.88E-01   |
| GSC          | 14  | 94,375,765  | rs11624318 | combined     | 0.98         | 0.86      | 1.11      | 7.19E-01        | 5.32E-01        | 1.02 | 0.82      | 1.26      | 8.92E-01 | 9.57E-01 | 0.93           | 0.74      | 1.16      | 5.07E-01   | 5.66E-01   |
| GSC          | 14  | 94,375,765  | rs11624318 | conventional | 0.87         | 0.73      | 1.04      | 1.21E-01        | 7.86E-02        | 1.11 | 0.85      | 1.45      | 4.54E-01 | 4.26E-01 | 1.08           | 0.83      | 1.4       | 5.62E-01   | 6.00E-01   |
| GSC          | 14  | 94,405,244  | rs11160219 | combined     | 0.96         | 0.86      | 1.09      | 5.55E-01        | 6.31E-01        | 0.88 | 0.71      | 1.09      | 2.42E-01 | 1.72E-01 | 1.01           | 0.82      | 1.25      | 9.26E-01   | 9.09E-01   |
| GSC          | 14  | 94,405,244  | rs11160219 | intensive    | 1.13         | 0.94      | 1.35      | 1.91E-01        | 8.70E-02        | 1.12 | 0.78      | 1.59      | 5.46E-01 | 3.80E-01 | 1.01           | 0.69      | 1.49      | 9.56E-01   | 5.66E-01   |
| GSC          | 14  | 94,405,244  | rs11160219 | conventional | 0.81         | 0.68      | 0.96      | 1.14E-02        | 4.77E-03        | 0.8  | 0.6       | 1.06      | 1.11E-01 | 6.05E-02 | 1.1            | 0.85      | 1.42      | 4.61E-01   | 7.60E-01   |
| GSC          | 14  | 94,407,241  | rs8007115  | combined     | 0.96         | 0.85      | 1.09      | 5.29E-01        | 5.46E-01        | 0.87 | 0.7       | 1.08      | 2.10E-01 | 1.24E-01 | 1.01           | 0.82      | 1.25      | 9.13E-01   | 9.36E-01   |
| GSC          | 14  | 94,407,241  | rs8007115  | conventional | 0.82         | 0.69      | 0.97      | 1.86E-02        | 6.88E-03        | 0.79 | 0.59      | 1.05      | 9.16E-02 | 4.78E-02 | 1.1            | 0.86      | 1.42      | 4.50E-01   | 7.46E-01   |
| GSC          | 14  | 94,407,241  | rs8007115  | intensive    | 1.12         | 0.94      | 1.34      | 2.21E-01        | 8.54E-02        | 1.09 | 0.76      | 1.56      | 6.36E-01 | 4.28E-01 | 0.98           | 0.66      | 1.45      | 9.30E-01   | 6.54E-01   |
| WDR72        | 15  | 51,277,554  | rs493218   | intensive    | 0.75         | 0.57      | 0.97      | 2.47E-02        | 1.09E-02        | 0.62 | 0.35      | 1.12      | 9.18E-02 | 7.88E-02 | 0.36           | 0.16      | 0.82      | 4.30E-03   | 5.70E-03   |
| WDR72        | 15  | 51,277,554  | rs493218   | combined     | 0.92         | 0.78      | 1.09      | 3.52E-01        | 2.96E-01        | 0.76 | 0.55      | 1.04      | 7.67E-02 | 1.20E-01 | 0.71           | 0.51      | 0.99      | 3.38E-02   | 7.30E-02   |
| WDR72        | 15  | 51,277,554  | rs493218   | conventional | 1.19         | 0.95      | 1.5       | 1.41E-01        | 1.11E-01        | 0.83 | 0.57      | 1.23      | 3.47E-01 | 4.62E-01 | 0.9            | 0.62      | 1.31      | 5.70E-01   | 8.59E-01   |
| WDR72        | 15  | 51,291,924  | rs572221   | intensive    | 0.76         | 0.58      | 0.98      | 3.14E-02        | 1.27E-02        | 0.62 | 0.34      | 1.11      | 8.53E-02 | 6.85E-02 | 0.36           | 0.16      | 0.81      | 3.80E-03   | 4.58E-03   |
| WDR72        | 15  | 51,291,924  | rs572221   | conventional | 1.2          | 0.96      | 1.51      | 1.18E-01        | 9.01E-02        | 0.83 | 0.56      | 1.22      | 3.24E-01 | 4.39E-01 | 0.87           | 0.6       | 1.27      | 4.56E-01   | 7.54E-01   |
| WDR72        | 15  | 51,291,924  | rs572221   | combined     | 0.94         | 0.79      | 1.11      | 4.35E-01        | 3.49E-01        | 0.75 | 0.54      | 1.03      | 6.55E-02 | 1.04E-01 | 0.69           | 0.5       | 0.97      | 2.38E-02   | 5.70E-02   |
| WDR72        | 15  | 51,291,964  | rs690271   | combined     | 0.93         | 0.78      | 1.1       | 3.87E-01        | 3.26E-01        | 0.75 | 0.54      | 1.03      | 6.38E-02 | 1.03E-01 | 0.69           | 0.5       | 0.97      | 2.33E-02   | 5.69E-02   |
| WDR72        | 15  | 51,291,964  | rs690271   | conventional | 1.2          | 0.96      | 1.51      | 1.18E-01        | 9.01E-02        | 0.83 | 0.56      | 1.22      | 3.24E-01 | 4.39E-01 | 0.87           | 0.6       | 1.27      | 4.56E-01   | 7.54E-01   |
| WDR72        | 15  | 51,291,964  | rs690271   | intensive    | 0.75         | 0.57      | 0.97      | 2.47E-02        | 1.09E-02        | 0.62 | 0.34      | 1.11      | 8.42E-02 | 6.81E-02 | 0.36           | 0.16      | 0.81      | 3.72E-03   | 4.54E-03   |
| WDR72        | 15  | 51,295,884  | rs566369   | combined     | 0.93         | 0.78      | 1.1       | 3.79E-01        | 3.19E-01        | 0.75 | 0.54      | 1.03      | 6.31E-02 | 1.02E-01 | 0.69           | 0.5       | 0.97      | 2.32E-02   | 5.67E-02   |
| WDR72        | 15  | 51,295,884  | rs566369   | conventional | 1.2          | 0.95      | 1.5       | 1.28E-01        | 1.00E-01        | 0.82 | 0.56      | 1.22      | 3.18E-01 | 4.31E-01 | 0.87           | 0.6       | 1.26      | 4.53E-01   | 7.51E-01   |
| WDR72        | 15  | 51,295,884  | rs566369   | intensive    | 0.75         | 0.57      | 0.97      | 2.47E-02        | 1.09E-02        | 0.62 | 0.34      | 1.11      | 8.42E-02 | 6.81E-02 | 0.36           | 0.16      | 0.81      | 3.72E-03   | 4.54E-03   |
| WDR72        | 15  | 51,296,486  | rs482541   | combined     | 0.93         | 0.78      | 1.1       | 3.79E-01        | 3.19E-01        | 0.75 | 0.54      | 1.03      | 6.31E-02 | 1.02E-01 | 0.69           | 0.5       | 0.97      | 2.32E-02   | 5.67E-02   |
| WDR72        | 15  | 51,296,486  | rs482541   | intensive    | 0.75         | 0.57      | 0.97      | 2.47E-02        | 1.09E-02        | 0.62 | 0.34      | 1.11      | 8.42E-02 | 6.81E-02 | 0.36           | 0.16      | 0.81      | 3.72E-03   | 4.54E-03   |
| WDR72        | 15  | 51,296,486  | rs482541   | conventional | 1.2          | 0.95      | 1.5       | 1.28E-01        | 1.00E-01        | 0.82 | 0.56      | 1.22      | 3.18E-01 | 4.31E-01 | 0.87           | 0.6       | 1.26      | 4.53E-01   | 7.51E-01   |

**Supplementary Table 7.** Association of top 13 SNPs for HbA1c identified in DCCT, tested for association with HbA1c in GoKinD, cases and controls separately.

| TRAIT        | group           | chr       | pos                | nearest gene  | MARKER           | ALLELES    | FREQ1        | RSQR          | EFFECT1_add  | STDERR_add   | CHISQ_add    | PVALUE_add     |
|--------------|-----------------|-----------|--------------------|---------------|------------------|------------|--------------|---------------|--------------|--------------|--------------|----------------|
| hba1c        | cases           | 9         | 16,779,024         | BNC2          | rs10810632       | T,C        | 0.9296       | 0.9388        | 0.164        | 0.127        | 1.6612       | <b>0.1974</b>  |
| hba1c        | controls        | 9         | 16,779,024         | BNC2          | rs10810632       | T,C        | 0.9296       | 0.9388        | 0.082        | 0.097        | 0.7044       | <b>0.4013</b>  |
| hba1c        | cases           | 9         | 16,779,436         | BNC2          | rs6475082        | A,G        | 0.9278       | 0.9962        | 0.153        | 0.123        | 1.5495       | <b>0.2132</b>  |
| hba1c        | controls        | 9         | 16,779,436         | BNC2          | rs6475082        | A,G        | 0.9278       | 0.9962        | 0.068        | 0.093        | 0.5317       | <b>0.4659</b>  |
| hba1c        | cases           | 9         | 16,779,878         | BNC2          | rs4961760        | T,C        | 0.9278       | 0.9977        | 0.153        | 0.123        | 1.5473       | <b>0.2135</b>  |
| hba1c        | controls        | 9         | 16,779,878         | BNC2          | rs4961760        | T,C        | 0.9278       | 0.9977        | 0.068        | 0.093        | 0.5281       | <b>0.4674</b>  |
| hba1c        | cases           | 9         | 16,791,850         | BNC2          | rs2254193        | A,C        | 0.931        | 0.9998        | 0.141        | 0.12         | 1.3778       | <b>0.2405</b>  |
| hba1c        | controls        | 9         | 16,791,850         | BNC2          | rs2254193        | A,C        | 0.931        | 0.9998        | 0.082        | 0.098        | 0.7089       | <b>0.3998</b>  |
| hba1c        | cases           | 10        | 108,113,589        | SORCS1        | rs1358030        | G,A        | 0.3561       | 0.8017        | -0.019       | 0.074        | 0.0626       | <b>0.8024</b>  |
| <b>hba1c</b> | <b>controls</b> | <b>10</b> | <b>108,113,589</b> | <b>SORCS1</b> | <b>rs1358030</b> | <b>G,A</b> | <b>0.356</b> | <b>0.8017</b> | <b>0.146</b> | <b>0.057</b> | <b>6.635</b> | <b>0.01</b>    |
| hba1c        | cases           | 14        | 94,375,765         | GSC           | rs11624318       | C,A        | 0.8051       | 0.8483        | -0.078       | 0.086        | 0.8315       | <b>0.3618</b>  |
| hba1c        | controls        | 14        | 94,375,765         | GSC           | rs11624318       | C,A        | 0.8051       | 0.8483        | -0.045       | 0.067        | 0.4401       | <b>0.5071</b>  |
| hba1c        | cases           | 14        | 94,405,244         | GSC           | rs11160219       | G,A        | 0.7613       | 0.4048        | -0.209       | 0.114        | 3.3627       | <b>0.06669</b> |
| hba1c        | controls        | 14        | 94,405,244         | GSC           | rs11160219       | G,A        | 0.7613       | 0.4048        | 0            | 0.09         | 0            | <b>0.9992</b>  |
| hba1c        | cases           | 14        | 94,407,241         | GSC           | rs8007115        | C,T        | 0.7721       | 0.3254        | -0.178       | 0.128        | 1.9201       | <b>0.1658</b>  |
| hba1c        | controls        | 14        | 94,407,241         | GSC           | rs8007115        | C,T        | 0.7721       | 0.3254        | -0.016       | 0.101        | 0.0251       | <b>0.8742</b>  |
| hba1c        | cases           | 15        | 51,277,554         | WDR72         | rs493218         | T,C        | 0.9016       | 0.989         | 0.087        | 0.115        | 0.5628       | <b>0.4531</b>  |
| hba1c        | controls        | 15        | 51,277,554         | WDR72         | rs493218         | T,C        | 0.9016       | 0.989         | 0.058        | 0.08         | 0.5174       | <b>0.472</b>   |
| hba1c        | cases           | 15        | 51,291,924         | WDR72         | rs572221         | G,A        | 0.9025       | 1             | 0.083        | 0.115        | 0.5207       | <b>0.4705</b>  |
| hba1c        | controls        | 15        | 51,291,924         | WDR72         | rs572221         | G,A        | 0.9025       | 1             | 0.059        | 0.08         | 0.5446       | <b>0.4605</b>  |
| hba1c        | cases           | 15        | 51,291,964         | WDR72         | rs690271         | G,A        | 0.9025       | 1             | 0.083        | 0.115        | 0.5207       | <b>0.4705</b>  |
| hba1c        | controls        | 15        | 51,291,964         | WDR72         | rs690271         | G,A        | 0.9025       | 1             | 0.059        | 0.08         | 0.5446       | <b>0.4605</b>  |
| hba1c        | cases           | 15        | 51,295,884         | WDR72         | rs566369         | G,A        | 0.9025       | 1             | 0.083        | 0.115        | 0.5207       | <b>0.4705</b>  |
| hba1c        | controls        | 15        | 51,295,884         | WDR72         | rs566369         | G,A        | 0.9025       | 1             | 0.059        | 0.08         | 0.5446       | <b>0.4605</b>  |
| hba1c        | cases           | 15        | 51,296,486         | WDR72         | rs482541         | G,A        | 0.9024       | 0.999         | 0.083        | 0.115        | 0.5199       | <b>0.4709</b>  |
| hba1c        | controls        | 15        | 51,296,486         | WDR72         | rs482541         | G,A        | 0.9024       | 0.999         | 0.059        | 0.08         | 0.5473       | <b>0.4594</b>  |



**Supplementary Table 8.** Association of top 13 SNPs for HbA1c identified in DCCT, tested for association with renal disease case-control status in GoKinD.

| CHR | SNP        | BP          | nearest gene | A1 | F_A     | F_U     | A2 | CHISQ   | P       | OR     |
|-----|------------|-------------|--------------|----|---------|---------|----|---------|---------|--------|
| 9   | rs10810632 | 16,779,024  | BNC2         | C  | 0.0717  | 0.07301 | T  | 0.02126 | 0.8841  | 0.9806 |
| 9   | rs6475082  | 16,779,436  | BNC2         | G  | 0.0717  | 0.07301 | A  | 0.02126 | 0.8841  | 0.9806 |
| 9   | rs4961760  | 16,779,878  | BNC2         | C  | 0.0717  | 0.07301 | T  | 0.02126 | 0.8841  | 0.9806 |
| 9   | rs2254193  | 16,791,850  | BNC2         | C  | 0.0717  | 0.06659 | A  | 0.3348  | 0.5629  | 1.083  |
| 9   | rs2254468  | 16,794,197  | BNC2         | G  | 0.06981 | 0.06484 | A  | 0.3253  | 0.5684  | 1.082  |
| 10  | rs1358030  | 108,113,589 | SORCS1       | G  | 0.3314  | 0.3405  | A  | 0.3053  | 0.5806  | 0.9601 |
| 14  | rs11624318 | 94,375,765  | GSC          | A  | 0.1943  | 0.1846  | C  | 0.5118  | 0.4744  | 1.066  |
| 14  | rs11160219 | 94,405,244  | GSC          | A  | 0.2019  | 0.212   | G  | 0.5167  | 0.4723  | 0.94   |
| 14  | rs8007115  | 94,407,241  | GSC          | T  | 0.1761  | 0.1904  | C  | 1.128   | 0.2882  | 0.9087 |
| 15  | rs493218   | 51,277,554  | WDR72        | C  | 0.08868 | 0.1057  | T  | 2.721   | 0.09901 | 0.8231 |
| 15  | rs572221   | 51,291,924  | WDR72        | A  | 0.08868 | 0.1057  | G  | 2.721   | 0.09901 | 0.8231 |
| 15  | rs690271   | 51,291,964  | WDR72        | A  | 0.08868 | 0.1057  | G  | 2.721   | 0.09901 | 0.8231 |
| 15  | rs566369   | 51,295,884  | WDR72        | A  | 0.08868 | 0.1057  | G  | 2.721   | 0.09901 | 0.8231 |
| 15  | rs482541   | 51,296,486  | WDR72        | A  | 0.08868 | 0.1057  | G  | 2.721   | 0.09901 | 0.8231 |

**Supplementary Table 9.** Effect on SNP association with mean HbA1c in DCCT when either no covariates, mean BMI, or mean insulin dose during DCCT were used as covariates.

| chr | SNP        | Treatment group | Covariate    | SNP effect                         |                      |
|-----|------------|-----------------|--------------|------------------------------------|----------------------|
|     |            |                 |              | $\beta$ (SE)                       | P value              |
| 10  | rs1358030  | CONVENTIONAL    | none         | 0.329 (0.055)                      | 3.5 E-9              |
| 10  | rs1358030  | CONVENTIONAL    | BMI          | 0.328 (0.055)                      | 3.6 E-9              |
| 10  | rs1358030  | CONVENTIONAL    | Insulin dose | 0.334 (0.055)                      | 2.0E-9               |
| 9   | rs10810632 | CONVENTIONAL    | none         | 0.568 (0.102)                      | 3.7E-8               |
| 9   | rs10810632 | CONVENTIONAL    | BMI          | 0.578 (0.102)                      | 3.8E-8               |
| 9   | rs10810632 | CONVENTIONAL    | Insulin dose | 0.562 (0.102)                      | 4.8E-8               |
| 14  | rs11624318 | CONVENTIONAL    | none         | 0.554 (0.193)*<br>0.560 (0.198)†   | 4.2E-3*<br>4.9E-3†   |
| 14  | rs11624318 | CONVENTIONAL    | BMI          | 0.550 (0.193)*<br>0.556 (0.198)†   | 4.5E-3*<br>5.3 E-3†  |
| 14  | rs11624318 | CONVENTIONAL    | Insulin dose | 0.560 (0.192)*<br>0.564 (0.198)†   | 3.8 E-3*<br>4.5 E-3† |
| 14  | rs11624318 | INTENSIVE       | none         | 0.600 (0.192) *<br>0.521 (0.200) † | 1.9 E-3*<br>9.2 E-3† |
| 14  | rs11624318 | INTENSIVE       | BMI          | 0.564 (0.190) *<br>0.481 (0.197) † | 3.1 E-3*<br>1.5 E-2† |
| 14  | rs11624318 | INTENSIVE       | Insulin dose | 0.592 (0.182) *<br>0.524 (0.189) † | 1.2 E-3*<br>5.8 E-3† |
| 15  | rs482541   | INTENSIVE       | none         | -0.434 (0.084)                     | 3.5 E-7              |
| 15  | rs482541   | INTENSIVE       | BMI          | -0.419 (0.083)                     | 6.1 E-7              |
| 15  | rs482541   | INTENSIVE       | Insulin dose | -0.413 (0.080)                     | 3.7 E-7              |

Results for all SNPs, apart from rs11624318, are from an additive coding of genotypes. For rs11624318, since there is evidence for deviation from an additive model (Table 2), we used a 2df test, and report genotype specific parameter estimates and p values, with the following coded: \* = common homozygote compared to rare homozygote, † = heterozygote compared to rare homozygote.

From file: hba1c\_covar\_bmi\_ins\_all; dated: 24jul09

Supplementary Table 10. List of MAGIC investigators.

AUTHORSHIP FOR MAGIC HbA1C  
DATA

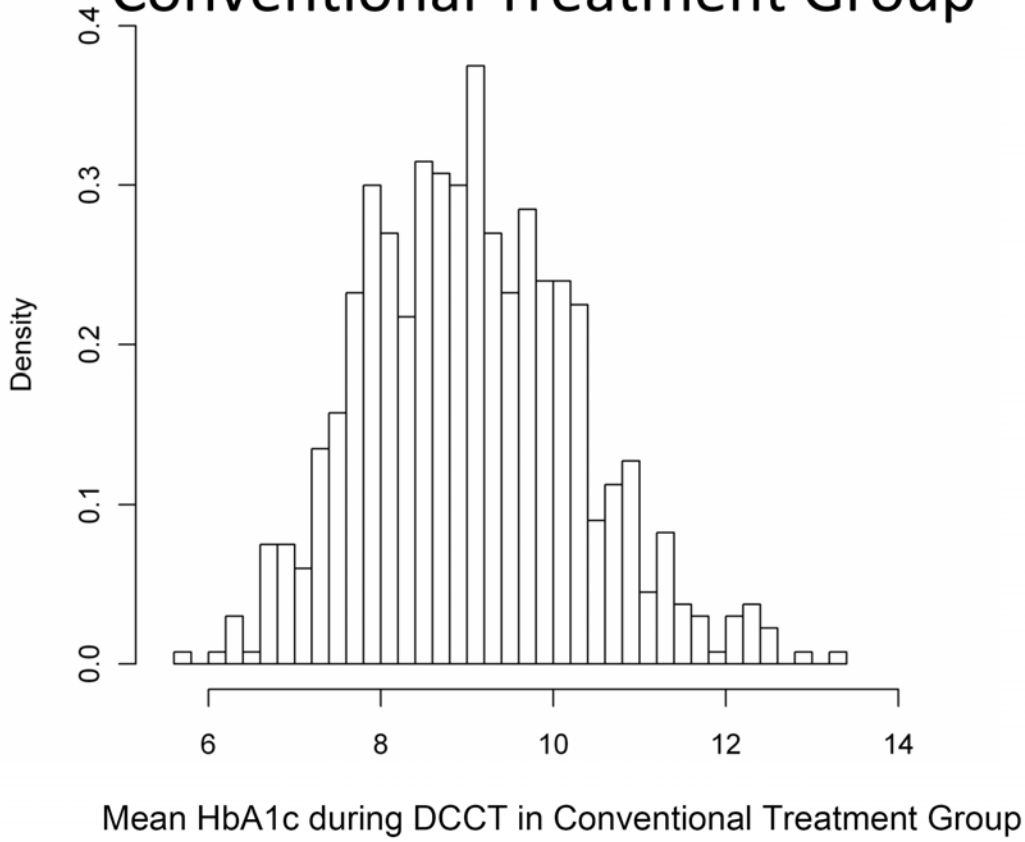
| Cohort             | First       | Middle | Last           | Dept   | Univ/Corp   | Street  | City       | Postal Code                  | Country     |
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|                                 |                  |              |                   |   |   |  |                    |                     |         |  |
|---------------------------------|------------------|--------------|-------------------|---|---|--|--------------------|---------------------|---------|--|
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| deCODE                   | Valgerdur |    | Steinthorsdottir     | Population Genomics   | deCODE genetics   | Sturlugata 8   | Reykjavik       | 101      | Iceland     |
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| Lolipop                  | Dawn      | M  | Waterworth           | Genetics, Drug Discovery                                    | GlaxoSmithKline   | 709 Swedeland Road                                       | King of Prussia | PA       | USA         |
|                          |           |    | Watkins on behalf of |   |   |  |                 |          |             |
| Procardis                | Hugh      |    | Procardis Consortium | Department of Cardiovascular Medicine                       | University of Oxford  |  | Oxford          | OX3 9DU  | UK          |
| WTSI                     | Eleanor   |    | Wheeler              | Human Genetics  | Wellcome Trust Sanger Institute   | Genome Campus  | Hinxton         | CB10 1SA | UK          |
|                          |           |    |                      |   | Helmholtz Zentrum München, German Research<br>Center for Environmental Health | Ingolstaedter Landstr. 1                                 | Neuherberg      | 85764    | Germany     |
| KORA F3/S4               | H-Erich   |    | Wichmann             | Institute of Epidemiology                                   | University of Edinburgh   | Teviot Place   | Edinburgh       | EH8 9AG  | Scotland    |
| ORCADES                  | Sarah H   |    | Wild                 | Centre for Population Health Sciences                       | VU University   | Van der Boechorststraat 1                                | Amsterdam       | 1081 BT  | Netherlands |
| NTR                      | Gonneke   |    | Willemsen            | Biological Psychology                                       | VU University   | Van der Boechorststraat 1                                | Amsterdam       | 1081 BT  | Netherlands |
| genomeEUtwin/Dutch       | Gonneke   |    | Willemsen            | Biological Psychology                                       | University of Edinburgh   | Teviot Place   | Edinburgh       | EH8 9AG  | Scotland    |
| ORCADES                  | James F   |    | Wilson               | Centre for Population Health Sciences                       | Medical Research Council  | Crewe Road   | Edinburgh       | EH4 2XU  | UK          |
| CROATIA                  | Alan      | F. | Wright               | Human Genetics Unit   | Institute of Metabolic Science  | Box 285 Addenbrooke's Hospital                           | Cambridge       | CB2 2QQ  | UK          |
| Fenland and EPIC-Norfolk | Jing Hua  |    | Zhao                 | MRC Epidemiology Unit                                       |   |  |                 |          |             |

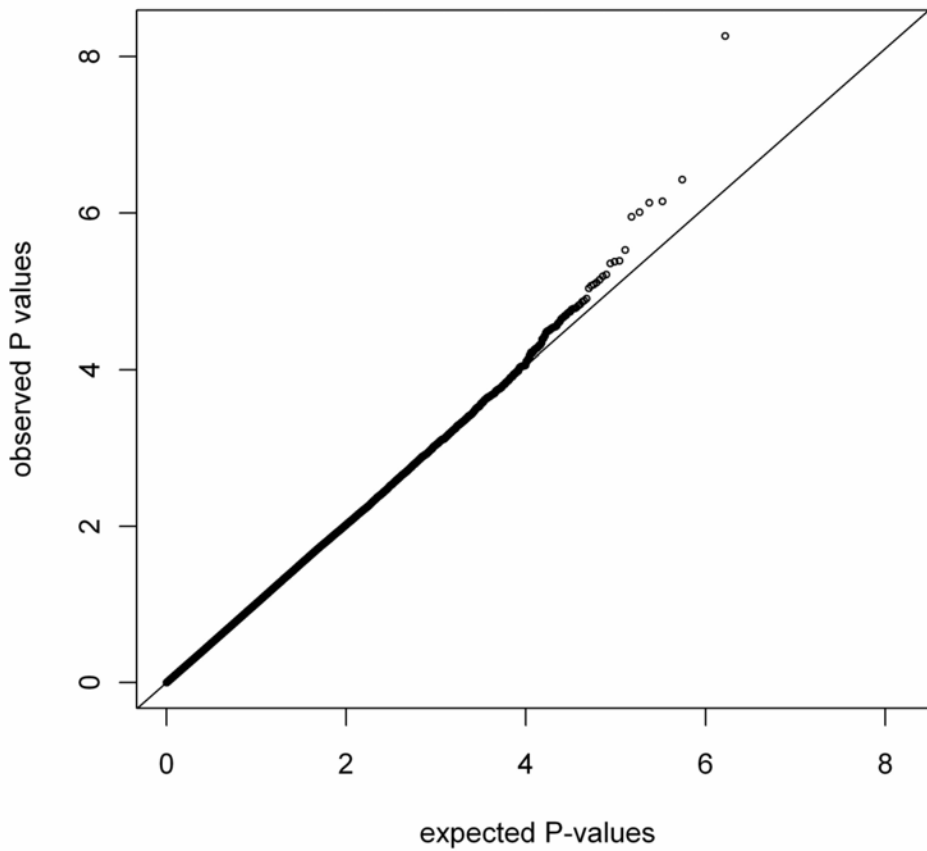
**Supplementary Figure 1.** Histogram of Mean HbA1c during DCCT in the conventional treatment group.

## Supplementary Figure 1: mean HbA1c in Conventional Treatment Group



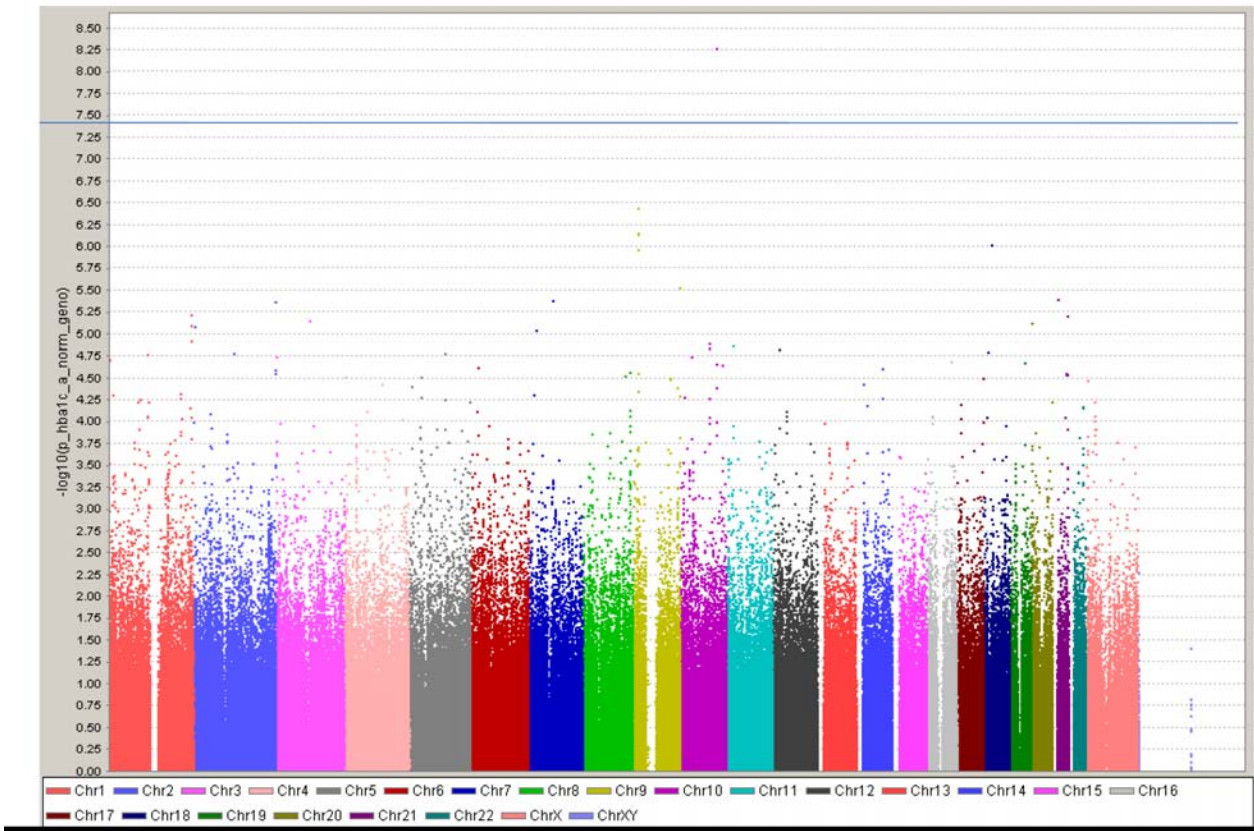
**Supplementary Figure 2.** Q-Q plot of the observed and expected distribution of  $-\log_{10}(p \text{ values})$  from the normal score 2df genotype test comparing the 841K SNPs for Stage 1 (association with mean HbA1c during DCCT in the conventional treatment group).

## Supplementary Figure 2: Q-Q plot for mean HbA1c in Conventional



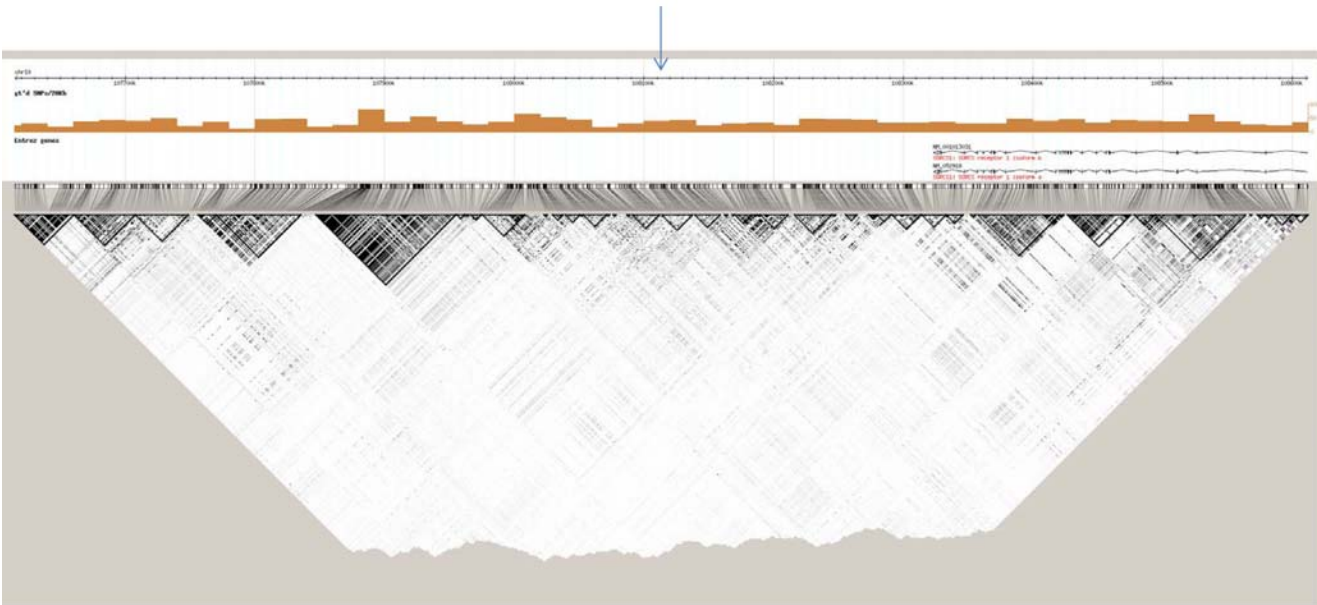
**Supplementary Figure 3.** Genome-wide association analysis of mean Hba1c in the Conventional group (Stage 1). The X axis is the genome (chromosomes 1-22 and X and Y chromosomes in different colors) and SNPs ordered along chromosomes by nucleotide position. The gaps in the middle of some chromosomes are due to the low SNP density around the centromeres. The Y axis is the  $-\log_{10}(P \text{ value})$ , so a value of 8 denotes a p value of  $10^{-8}$ . The blue horizontal line at 7.3 is the criterion for genome-wide significance ( $p=5 \times 10^{-8}$ ).

## Supplementary Figure 3: GWAS of mean Hba1c in the Conventional



**Supplementary Figure 4.** Linkage disequilibrium between SNPs in a 1Mb region centered around rs1358030 in the *SORCS1* genomic region from chromosome 10 in CEU HapMap phase II data (release 23a). Linkage disequilibrium between SNPs is indicated by pairwise  $r^2$  value. The grey scale indicates the relative strength of linkage disequilibrium (darker, higher  $r^2$  value). *SORCS1* gene is annotated. The blue arrow indicates the location of rs1358030.

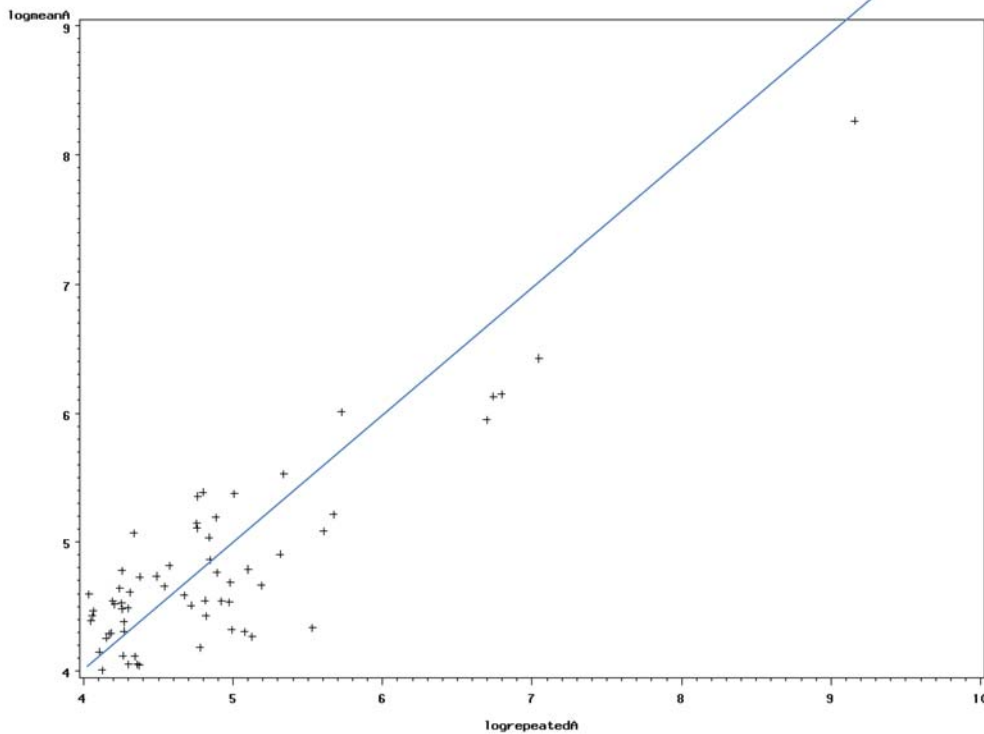
## Supplementary Figure 4: Linkage disequilibrium in a 1Mb region centered around rs1358030 in the *SORCS1*





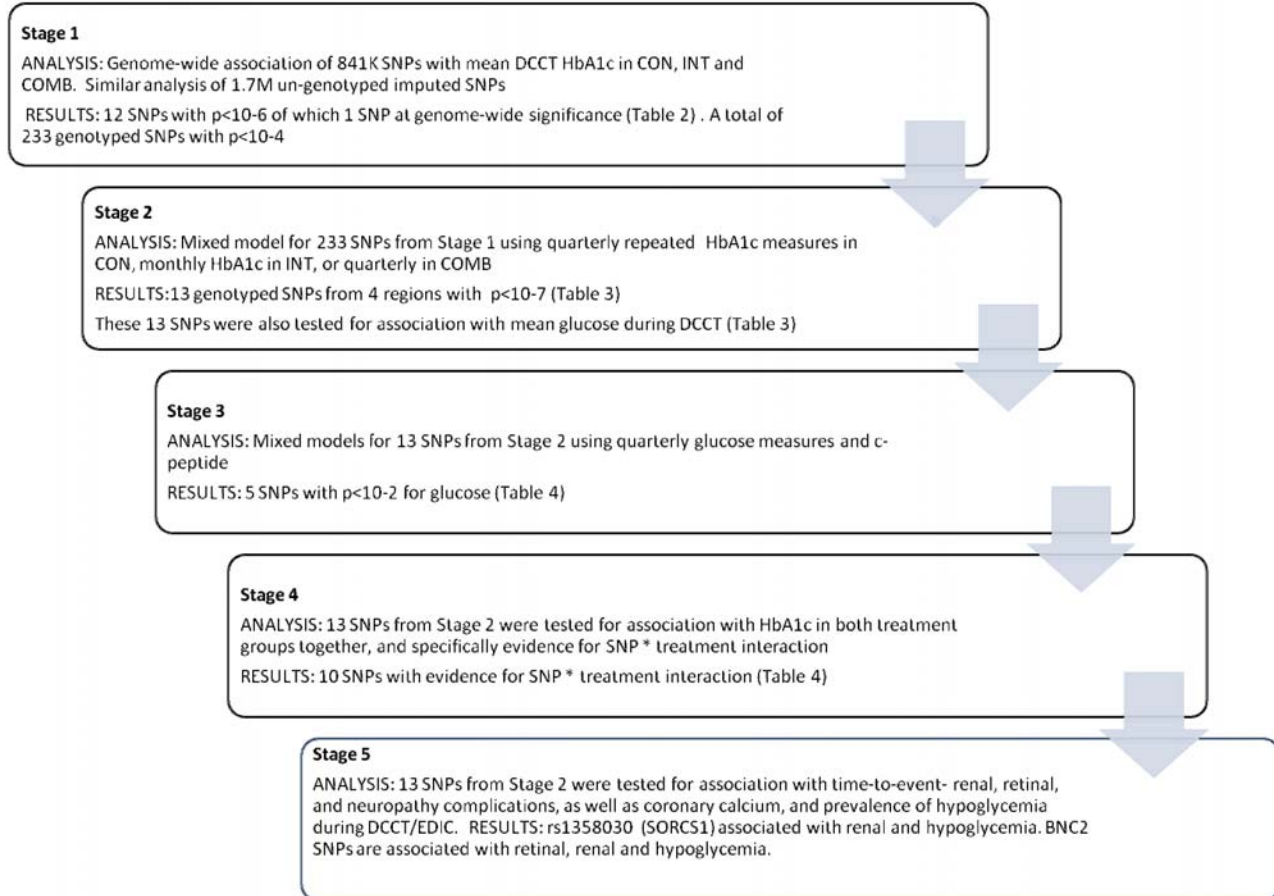
**Supplementary Figure 5.** Comparison of p values from the conventional treatment group for the top 62 SNPs with  $p < 10^{-4}$  from Stage 1 using mean HbA1c to the results from the mixed models using longitudinal repeated measures from Stage 2. For each SNP, the mean DCCT HbA1c  $-\log_{10}(p \text{ value})$  is plotted on the Y axis, while the repeated measures  $-\log_{10}(p \text{ value})$  is on the X axis, with a line indicating unity plotted. As can be seen, the evidence for association as assessed by the p value was smaller (i.e. more significant) using the longitudinal mixed model compared to the analysis of the mean, especially for the SNPs with the smallest p values from the mean results.

**Supplementary Figure 5:**  
**p values from conventional for the top 62 SNPs with**  
 **$p < 10^{-4}$  from mean (Y axis) and repeated (X axis)**



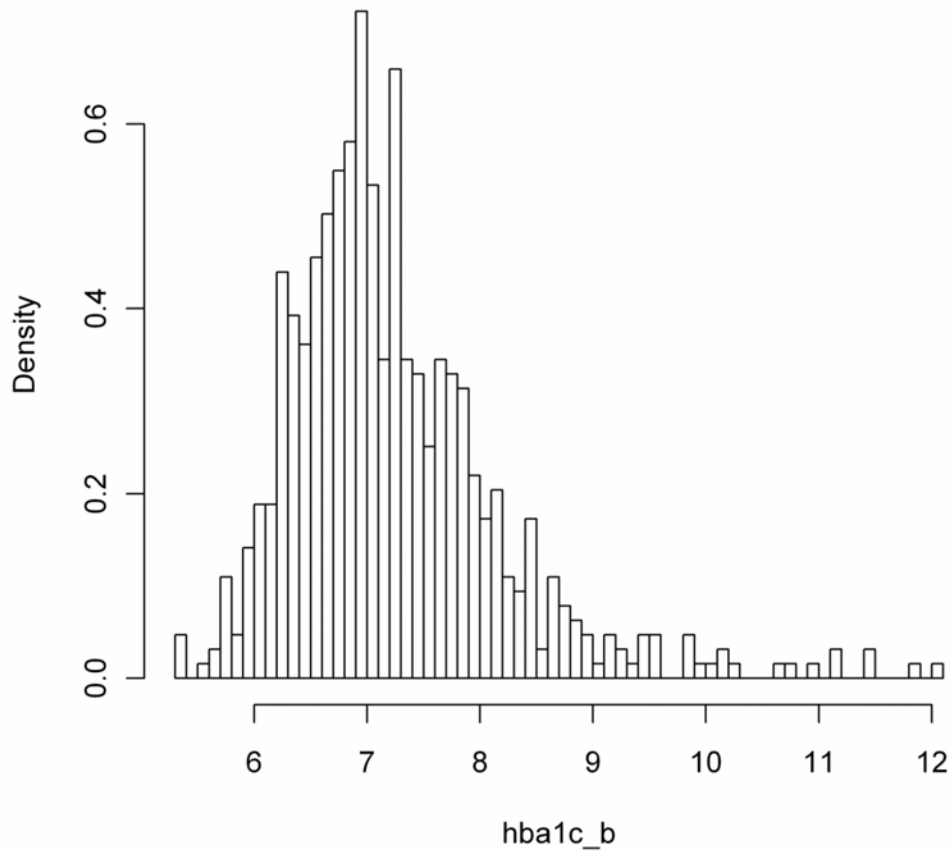
**Supplementary Figure 6.** Flow-chart describing the multi-stage analysis of the DCCT data. CON=Conventional Treatment Group, INT=Intensive Treatment Group.

## Supplementary Figure 6: Flowchart of DCCT analysis plan



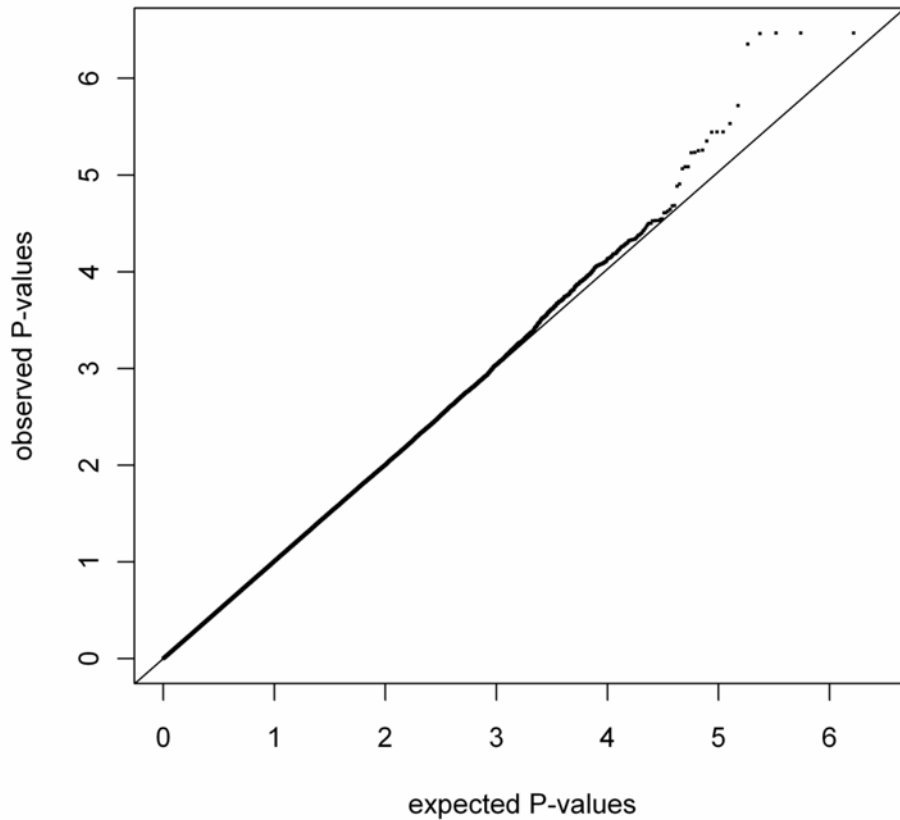
Supplementary Figure 7. Histogram of Mean HbA1c during DCCT in the intensive treatment group.

## Supplementary Figure 7: Mean HbA1c in Intensive treatment group



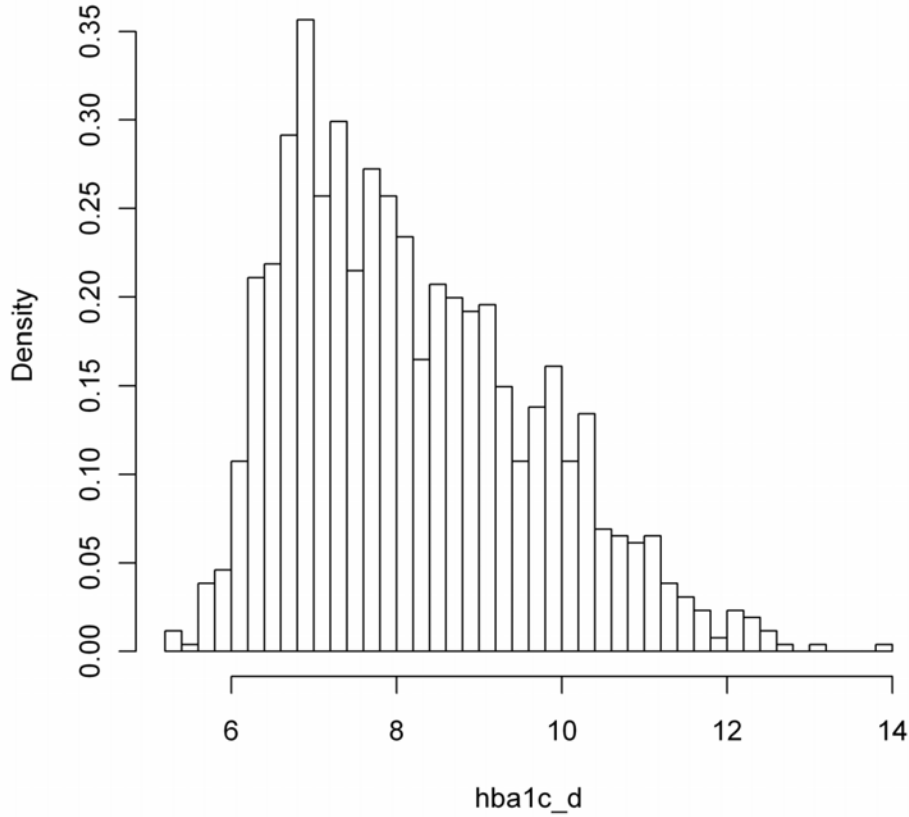
**Supplementary Figure 8.** QQ plot of SNP p value test statistics for INT group.

## Supplementary Figure 8: INT mean HbA1c qq plot



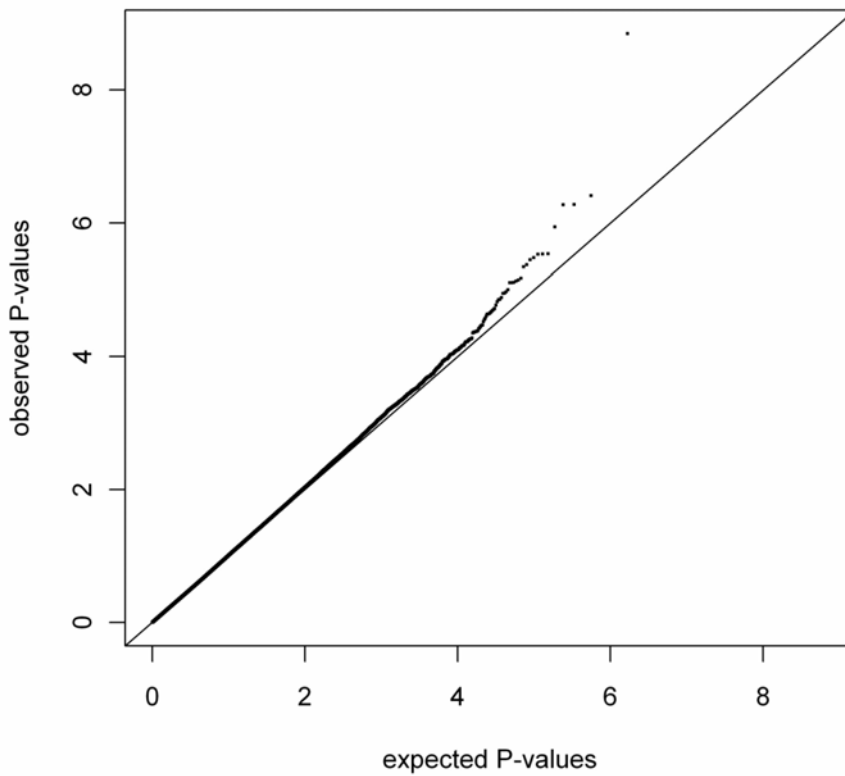
Supplementary Figure 9. Histogram of Mean HbA1c during DCCT in the combined treatment groups.

## Supplementary Figure 9: Mean HbA1c in both treatment groups



**Supplementary Figure 10.** QQ plot of SNP p value test statistics for the combined treatment groups.

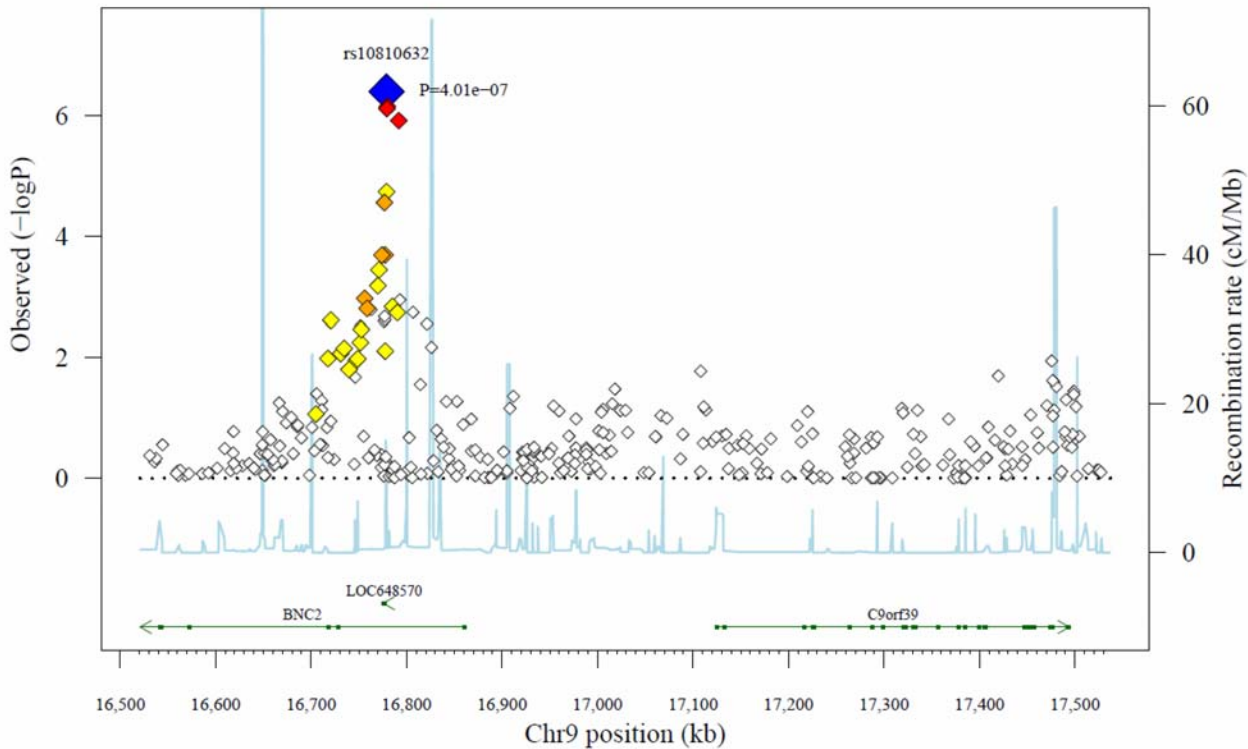
## Supplementary Figure 10: QQ plot for Mean HbA1c in both treatment groups



**Supplementary Figure 11.** Association results for mean HbA1c levels in the conventional treatment group at a region of 500kb surrounding the BNC2 locus (chromosome 9). On the left Y axis is the  $-\log_{10}(P)$  value for each SNP genotyped. On the right Y axis and plotted in the blue line is the recombination rate estimated from our data. The annotated genes in the region are indicated along the bottom of the figure. SNPs are colored based on their linkage disequilibrium with the most significant SNP, i.e. rs10810632, where blue indicates the index SNP, red  $r^2 \geq 0.8$ , orange  $0.8 > r^2 > 0.5$ , yellow  $0.5 > r^2 > 0.2$ , and white  $r^2 < 0.2$ .

### Supplementary Figure 11: Region plot for Conventional BNC2

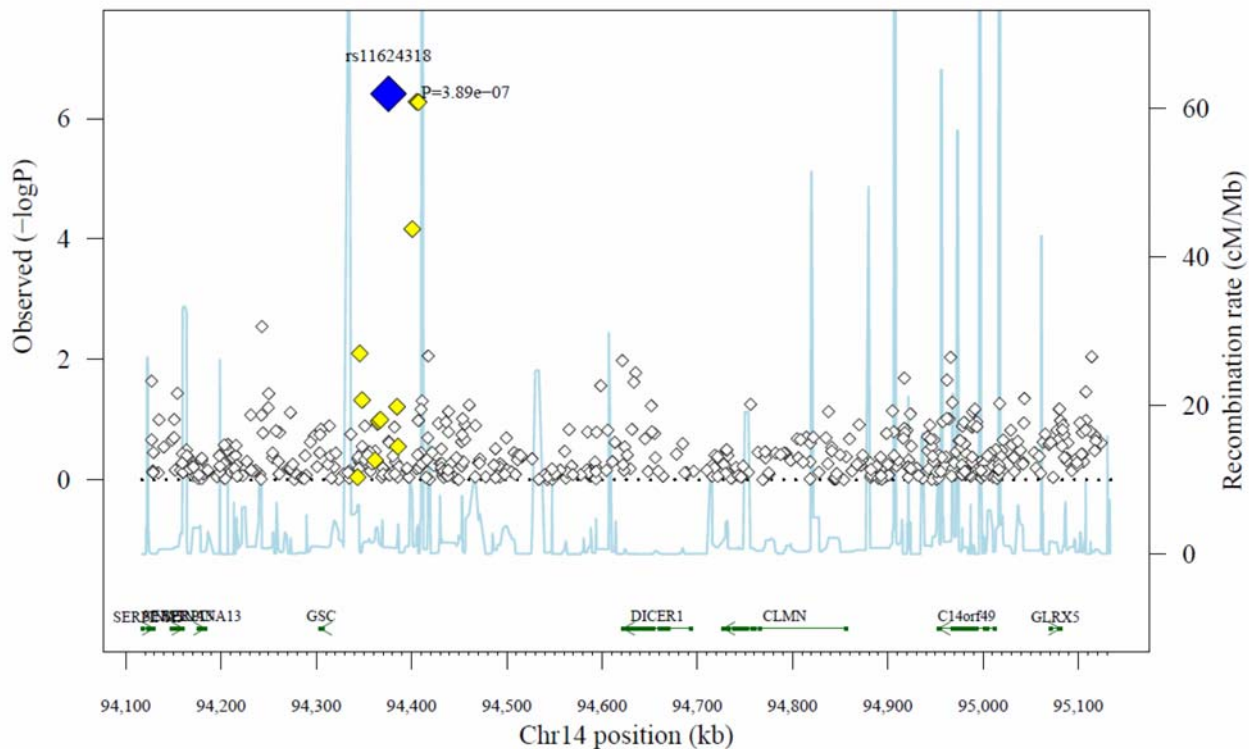
1M pval\_hba1c\_a\_norm\_gen0 : rs10810632



**Supplementary Figure 12.** Association results for mean HbA1c levels at a region of 500kb surrounding the WDR72 locus (chromosome 14) in the combined treatment groups. On the left Y axis is the  $-\log_{10}(P)$  value for each SNP genotyped. On the right Y axis and plotted in the blue line is the recombination rate estimated from our data. The annotated genes in the region are indicated along the bottom of the figure. SNPs are colored based on their linkage disequilibrium with the most significant SNP, i.e. rs11624318, where blue indicates the index SNP, red  $r^2 \geq 0.8$ , orange  $0.8 > r^2 > 0.5$ , yellow  $0.5 > r^2 > 0.2$ , and white  $r^2 < 0.2$ .

Supplementary Figure 12: Region plot for Combined chr 14 (WDR72)

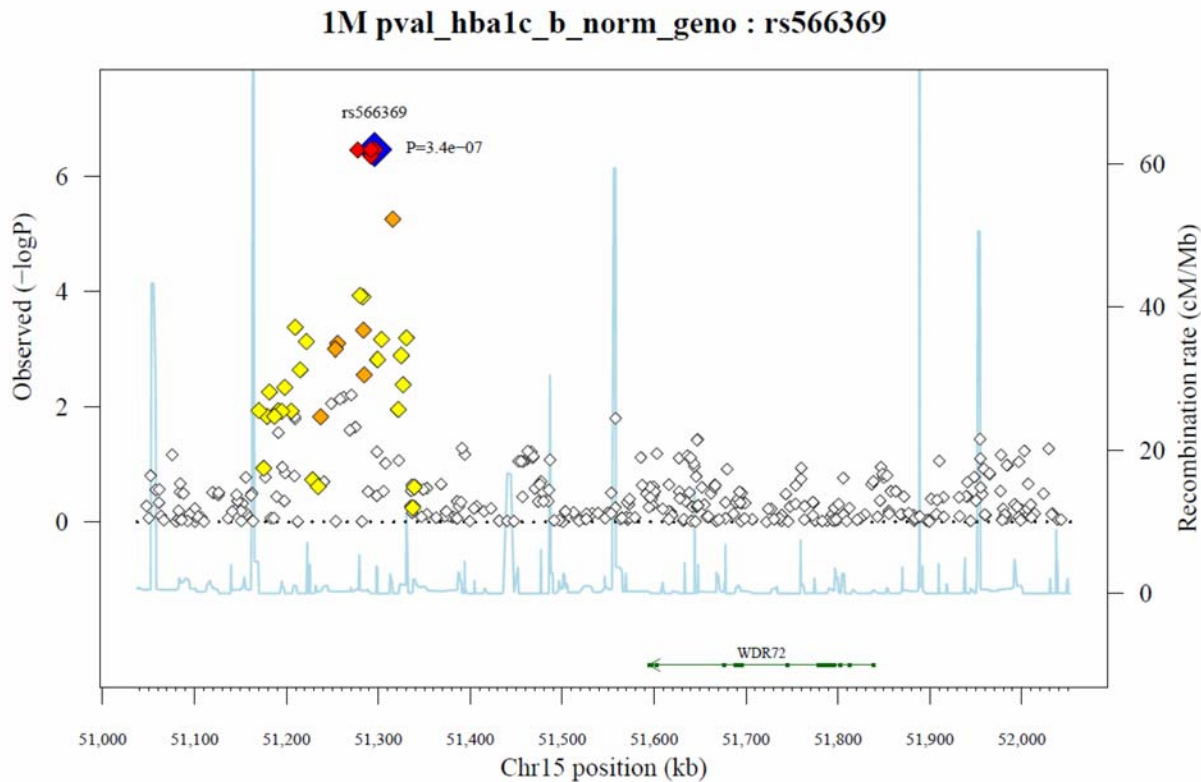
1M pval\_hba1c\_d\_norm\_gen0 : rs11624318





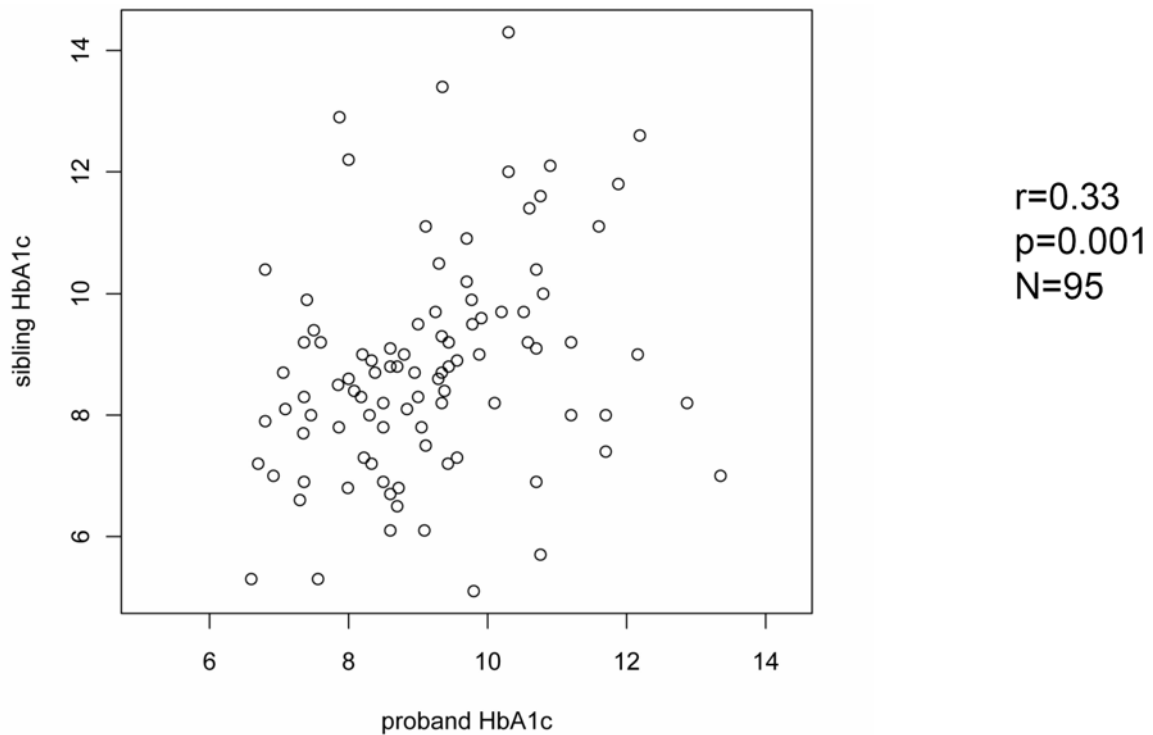
**Supplementary Figure 13.** Association results for mean HbA1c levels at a region of 500kb surrounding the GSC locus (chromosome 15) in the intensive treatment group. On the left Y axis is the  $-\log_{10}(P)$  value for each SNP genotyped. On the right Y axis and plotted in the blue line is the recombination rate estimated from our data. The annotated genes in the region are indicated along the bottom of the figure. SNPs are colored based on their linkage disequilibrium with the most significant SNP, i.e. rs566369, where blue indicates the index SNP, red  $r^2 \geq 0.8$ , orange  $0.8 > r^2 > 0.5$ , yellow  $0.5 > r^2 > 0.2$ , and white  $r^2 < 0.2$ .

Supplementary Figure 13: Region plot for Intensive chr 15 (GSC)



**Supplementary Figure 14.** Correlation of HbA1c measured at eligibility for DCCT probands and HbA1c measured either during the DCCT family study, or the EDIC genetics study in their sibling with type 1 diabetes.

## Supplementary Figure 14: Correlation of DCCT proband's eligibility HbA1c with type 1 diabetic sibs HbA1c



**Supplementary Figure 15.** Cluster-plot of called genotypes by theta and R for rs1358030 from the Illumina 1M data, plotted using polar co-ordinates. This shows that there is good separation of the 3 genotype groups at this SNP, consistent with high quality genotype data. Red are called TT, purple are called TC, and blue are called CC. No calls are in black.

# Supplementary Figure 15: Cluster-plot for rs1358030

