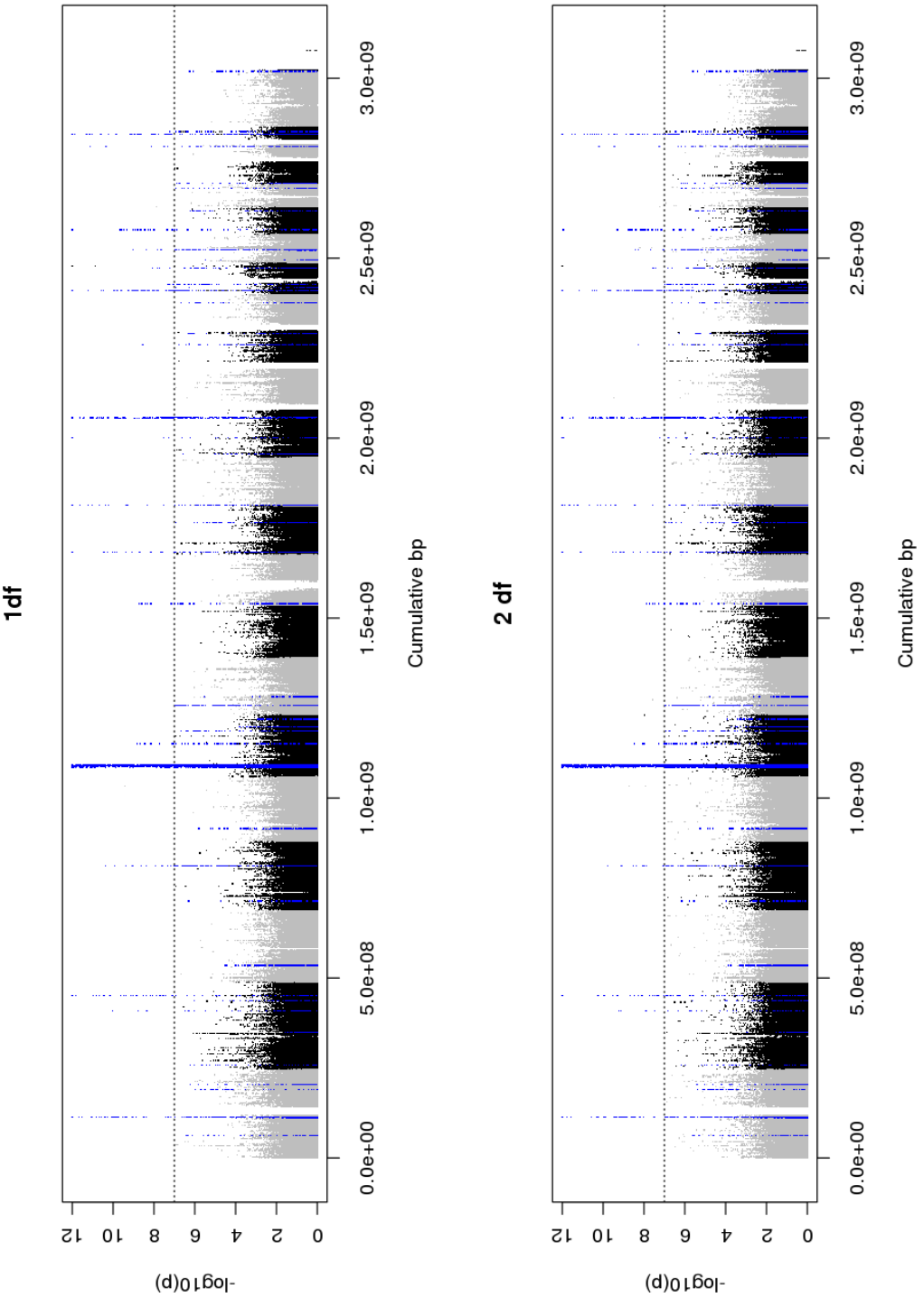
# The imprinted *DLK1-MEG3* gene region on chromosome 14q32.2 alters susceptibility to type 1 diabetes
## Supplementary Tables and Figures

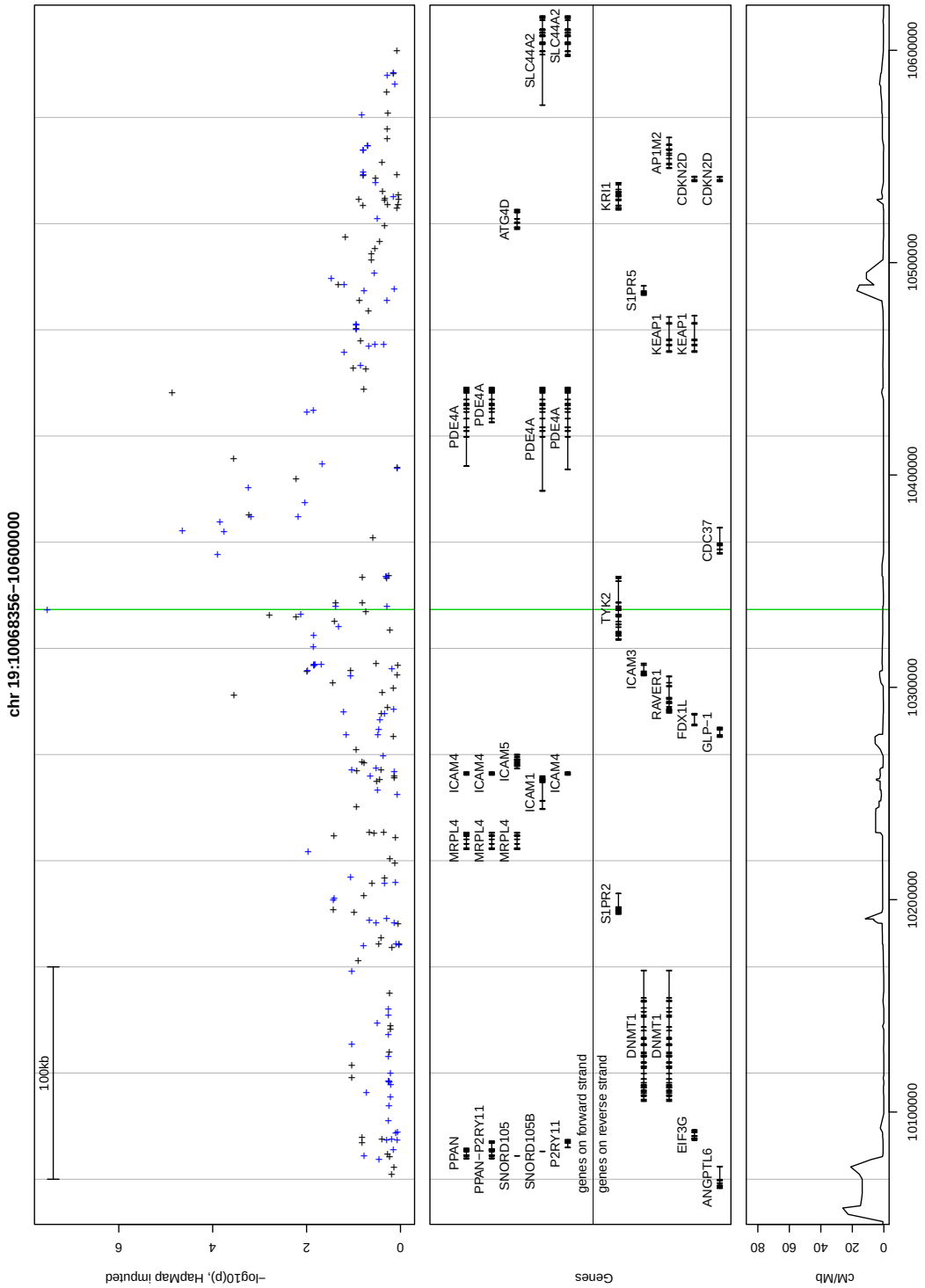
Chris Wallace, Deborah J Smyth, Meeta Maisuria-Armer, Neil Walker, John A Todd, and David G Clayton

Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge, UK.

**Supplementary Figure 1. Genomewide association with T1D.** The panels show -log10(p) for the 1 and 2 degree of freedom Cochran-Armitage test. SNPs within LD blocks surrounding known T1D loci (as defined by Barrett et al[4]) are shown in blue. Horizontal lines are drawn at $p = 1$ x $10^{-7}$. P values $< 1$ x $10^{-12}$ are drawn at 1 x $10^{-12}$



**Supplementary Figure 2. Association signals around rs2304256 on chromosome 19p13.2.** The top panel shows $-\log 10(p)$ from 1 degree of freedom tests of association with SNPs across the region. SNPs which were directly genotyped are in black, SNPs imputed from HapMap in blue. The second panel shows the location and orientation of genes in the region. The third panel shows recombination rates (cm/Mb) from HapMap. A solid green line shows the location of rs2304256 in all panels for reference. Positions are according to Hs_NCBI36.



# Supplementary Tables



**Supplementary Table 1. Case, control and family samples used in this analysis**

| Cohort | Genotyping Platform | Cases | Controls | Total | Families |
|---|---|---|---|---|---|
| *GWA case-control samples* | | | | | |
| T1DGC | Illumina 500K | 3983 (3978) | 3999 (3995) | 7982 (7973) | |
| GoKinD/NIMH | Affymetrix 500K | 1601 (0) | 1704 (0) | 3305 (0) | |
| WTCCC | Affymetrix 500K | 1930 (1929) | 3342 (1403) | 5272 (3332) | |
| Sub-total | | 7514 (5907) | 9045 (5398) | 16559 (11305) | |
| *Replication case-control samples* | | | | | |
| – | Taqman | 4840 | 2670 | 7510 | |
| *Total used for direct genotyping* | | | | | |
| Replication and GWA | Taqman | 10747 | 8068 | 18815 | |
| *Family samples* | | | | | |
| – | Taqman | | | | 4152 (5766) |

The numbers of GWA samples with DNA available for confirmation genotyping of imputed SNPs are shown in parentheses. The number of family samples is shown as number of families (number of triads), many of which come from affected sib-pair multiplex families.

**Supplementary Table 2. SNPs showing evidence for association in the imputed GWA analysis ($p < 10^{-7}$) in regions not previously associated with T1D**

| SNP | Chromosome | Position | Imputed $r^2$ | | MAF | $p$ values | |
|---|---|---|---|---|---|---|---|
| | | | Affymetrix | Illumina | | 1df | 2df |
| rs941576 | 14q32.2 | 100375798 | 0.76 | 0.82 | 0.46 | $1.23 \times 10^{-8}$ | $6.79 \times 10^{-8}$ |
| | | | | | | $1.42 \times 10^{-7}$ | $4.48 \times 10^{-7}$ |
| rs2304256 | 19p13.2 | 10336652 | 0.63 | 0.81 | 0.29 | $7.29 \times 10^{-8}$ | $2.48 \times 10^{-7}$ |
| | | | | | | $6.22 \times 10^{-6}$ | $1.35 \times 10^{-5}$ |
| rs229484 | 22q13.1 | 35884785 | 0.94 | 0.95 | 0.28 | $5.63 \times 10^{-8}$ | $3.95 \times 10^{-7}$ |
| | | | | | | $3.59 \times 10^{-6}$ | $1.43 \times 10^{-5}$ |

Position is according to Hs_NCBI36. $r^2$ is the estimated $r^2$ between the imputed genotypes and the underlying genotypes were they to be observed. MAF is the minor allele frequency in HapMap. $p$ values are given for the 1 df ("additive") and 2df ("genotype") models on two rows for each SNP: the top row shows the uncorrected $p$ values, and the second row the genomic control corrected values.

**Supplementary Table 3. Association testing of rs229484 G>C on chromosome 22q13.1 in case-control and family samples**

| Cohort | N | Fq (C) | Odds ratio (C:G) | (95% CI) | $p$ value |
|---|---|---|---|---|---|
| WTCCC | 1851/1397 | 0.353 | 1.14 | (1.27-1.03) | 0.013 |
| T1DGC | 3888/3938 | 0.363 | 1.10 | (1.17-1.02) | 0.008 |
| Additional | 2764/4895 | 0.377 | 1.06 | (1.14-0.99) | 0.087 |
| Families | 4030 | 0.376 | 1.02 | (0.96-1.09) | 0.508 |
| Case-control combined | 8503/10230 | 0.368 | 1.08 | (1.13-1.03) | $4.73 \times 10^{-4}$ |
| Families & case-control | (see above) | – | – | – | $1.11 \times 10^{-3}$ |

Association testing using observed (not imputed) genotypes in a subset of GWA samples, additional case control samples and family samples. SNP name followed by alleles, ordered as major>minor. N is number of cases/controls, or number of informative transmissions. Fq is the frequency of the minor allele in controls or parents.

**Supplementary Table 4. Analysis of imprinting and maternal genotype effects at chromosome 14q32.2 SNP rs941576**

| Model | -2 x Log-likelihood | N | Anova $p$ value | |
|---|---|---|---|---|
| | | | $M_i$ vs $M_3$ | $M_i$ vs $M_0$ |
| $M_3$: Imprinting + maternal genotype | 2486.941 | 3 | – | $1.0 \times 10^{-6}$ |
| $M_2$: Maternal genotype only | 2498.240 | 2 | $7.8 \times 10^{-4}$ | $6.5 \times 10^{-5}$ |
| $M_1$: Imprinting only | 2487.826 | 1 | 0.64 | $5.1 \times 10^{-8}$ |
| $M_0$: Neither effect | 2517.511 | 0 | $1.0 \times 10^{-6}$ | – |

Log-likelihood and number of parameters (N) for 3 models including imprinting and/or maternal genotype effects. Anova $p$ value relates to the $\chi^2$ likelihood ratio test of model $M_i$ with $M_3$ or $M_0$

**Supplementary Table 5. Testing for imprinting and maternal genotype effects in case-parent trios**

| Mating type | Genotype | | | Relative risk | Ratio (odds) |
|---|---|---|---|---|---|
| | $O$ | $M$ | $P$ | | |
| $1/2 + 2/2$ | $2/2$ | $2/2$ | $1/2$ | $\theta\phi_{2/2}\gamma_{2/2}$ | $\phi_{2/2}/\phi_{1/2}$ |
| | | $1/2$ | $2/2$ | $\theta\phi_{1/2}\gamma_{2/2}$ | |
| $1/2 + 2/2$ | $1/2$ | $2/2$ | $1/2$ | $\theta\phi_{2/2}\gamma_{1/2}$ | $\theta\phi_{2/2}/\phi_{1/2}$ |
| | | $1/2$ | $2/2$ | $\phi_{1/2}\gamma_{1/2}$ | |
| $1/1 + 2/2$ | $1/2$ | $2/2$ | $1/1$ | $\theta\phi_{2/2}\gamma_{1/2}$ | $\theta\phi_{2/2}$ |
| | | $1/1$ | $2/2$ | $\gamma_{1/2}$ | |
| $1/1 + 1/2$ | $1/2$ | $1/2$ | $1/1$ | $\theta\phi_{1/2}\gamma_{1/2}$ | $\theta\phi_{1/2}$ |
| | | $1/1$ | $1/2$ | $\gamma_{1/2}$ | |
| $1/1 + 1/2$ | $1/1$ | $1/2$ | $1/1$ | $\phi_{1/2}\gamma_{1/1}$ | $\phi_{1/2}$ |
| | | $1/1$ | $1/2$ | $\gamma_{1/1}$ | |

The table shows all configurations of parent ($M$=maternal and $P$=paternal) and offspring ($O$) genotype in which parental genotypes are discordant, divided into pairs by mating type and offspring genotype. In each pair, the configuration in which the mother carries more copies of allele "2" is listed first. The table also lists the prediction of the multiplicative model for relative risk of disease given offspring and parental genotype and the odds, within each mating type/offspring genotype combination, that the mother carries more copies of allele "2" than the father. The genotype relative risk for the offspring ($\gamma_{1/1}$, $\gamma_{1/2}$, and $\gamma_{2/2}$), are modified by multiplicative effects of the maternal genotype ($\phi_{1/2}$ and $\phi_{2/2}$, $\phi_{1/1}$ being taken as 1) and by a factor $\theta$ if a "2" allele was received from the mother rather than from the father

**Supplementary Table 6. Testing for imprinting and maternal genotype effects in affected sib pairs plus parents**

| Mating type | Genotype | | | Product of relative risks | Ratio (odds) |
|---|---|---|---|---|---|
| | $O_1, O_2$ | $M$ | $P$ | | |
| $1/2 + 2/2$ | 2/2, 2/2 | 2/2 | 1/2 | $\theta^2\phi^2_{2/2}\gamma^2_{2/2}$ | $\phi^2_{2/2}/\phi^2_{1/2}$ |
| | | 1/2 | 2/2 | $\theta^2\phi^2_{1/2}\gamma^2_{2/2}$ | |
| $1/2 + 2/2$ | 1/2, 2/2 | 2/2 | 1/2 | $\theta^2\phi^2_{2/2}\gamma_{1/2}\gamma_{2/2}$ | $\theta\phi^2_{2/2}/\phi^2_{1/2}$ |
| | | 1/2 | 2/2 | $\theta\phi^2_{1/2}\gamma_{1/2}\gamma_{2/2}$ | |
| $1/2 + 2/2$ | 1/2, 1/2 | 2/2 | 1/2 | $\theta^2\phi^2_{2/2}\gamma^2_{1/2}$ | $\theta^2\phi^2_{2/2}/\phi^2_{1/2}$ |
| | | 1/2 | 2/2 | $\phi^2_{1/2}\gamma^2_{1/2}$ | |
| $1/1 + 2/2$ | 1/2, 1/2 | 2/2 | 1/1 | $\theta^2\phi^2_{2/2}\gamma^2_{1/2}$ | $\theta^2\phi^2_{2/2}$ |
| | | 1/1 | 2/2 | $\gamma^2_{1/2}$ | |
| $1/1 + 1/2$ | 1/2, 1/2 | 1/2 | 1/1 | $\theta^2\phi^2_{1/2}\gamma^2_{1/2}$ | $\theta^2\phi^2_{1/2}$ |
| | | 1/1 | 1/2 | $\gamma^2_{1/2}$ | |
| $1/1 + 1/2$ | 1/1, 1/2 | 1/2 | 1/1 | $\theta\phi^2_{1/2}\gamma_{1/2}\gamma_{1/1}$ | $\theta\phi^2_{1/2}$ |
| | | 1/1 | 1/2 | $\gamma_{1/2}\gamma_{1/1}$ | |
| $1/1 + 1/2$ | 1/1, 1/1 | 1/2 | 1/1 | $\phi^2_{1/2}\gamma^2_{1/1}$ | $\phi^2_{1/2}$ |
| | | 1/1 | 1/2 | $\gamma^2_{1/1}$ | |

This table extends the calculations shown for case–parent trios in Supplementary Table 5 to quartets made up of an affected sib pair plus both parents. It is assumed that the SNP under observation is the sole causal variant or or has $r^2 = 1$ with a sole causal variant so that disease occurrences in offspring are conditionally independent given their genotypes ($O_1$, $O_2$) and their parents ($M$=maternal and $P$=paternal).