Supplementary Information for:

Genome-wide association study and meta-analysis indicates that over 40 loci affect risk of type 1 diabetes

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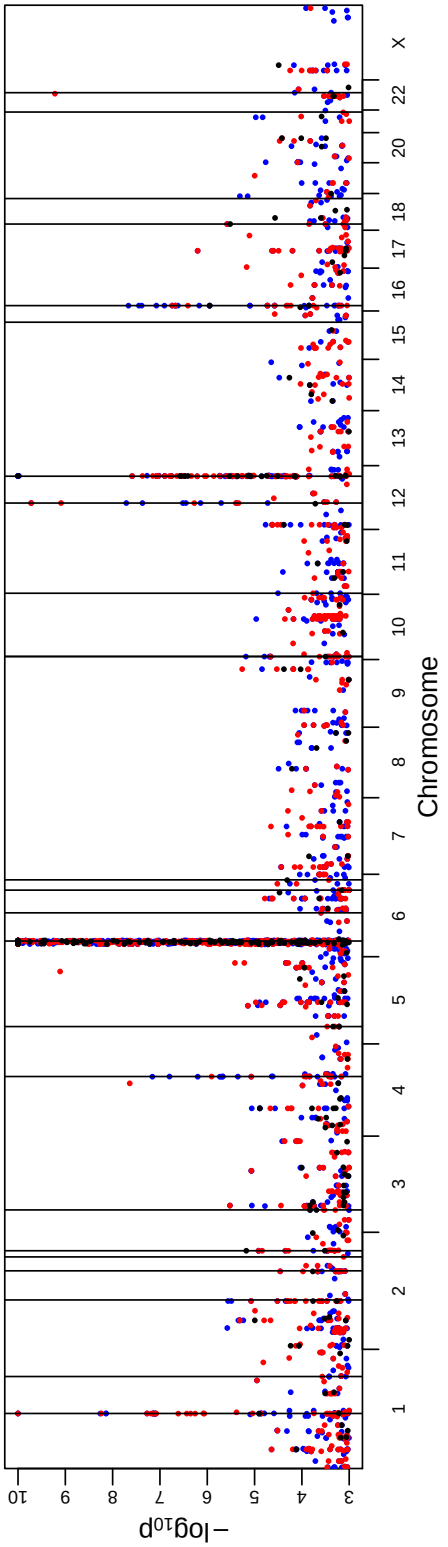
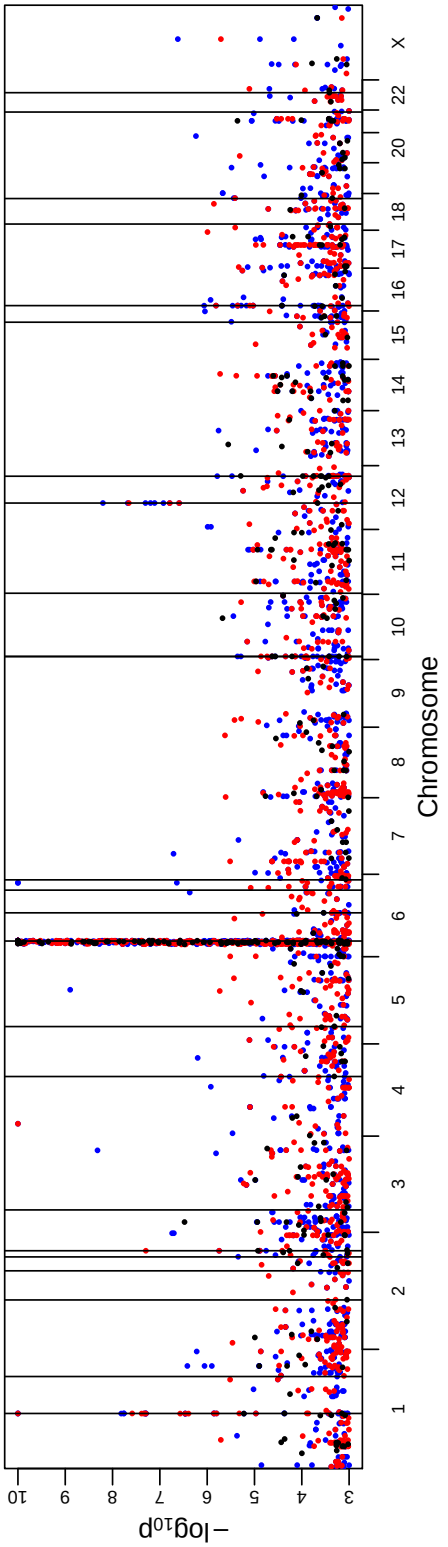


(a)



(b)

Supplementary Figure 1: (continued over-leaf)

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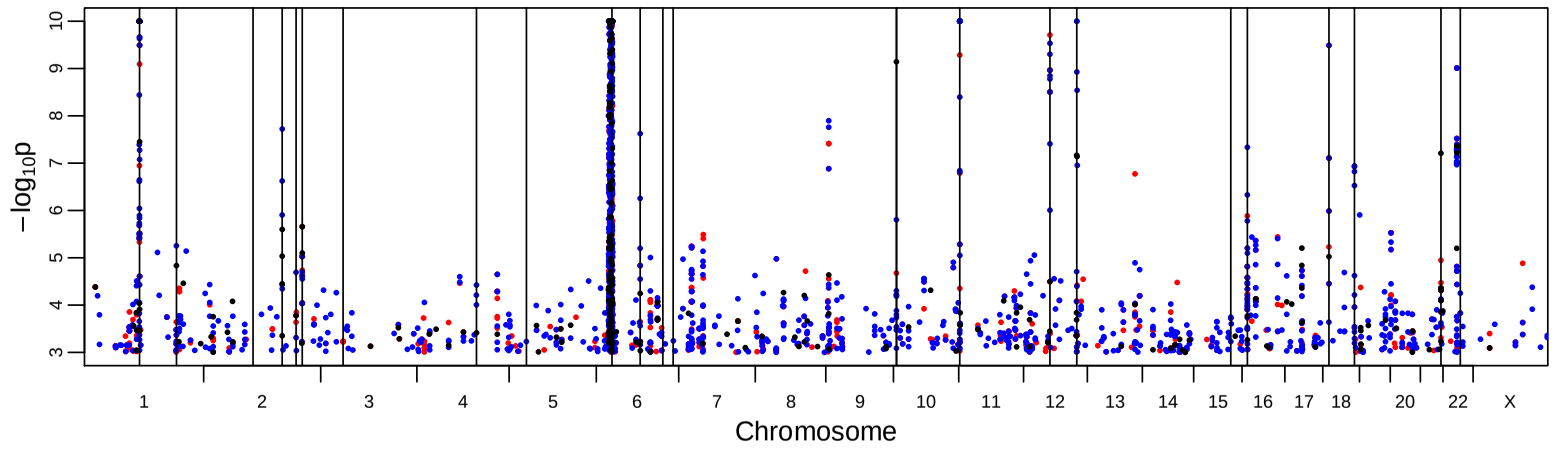
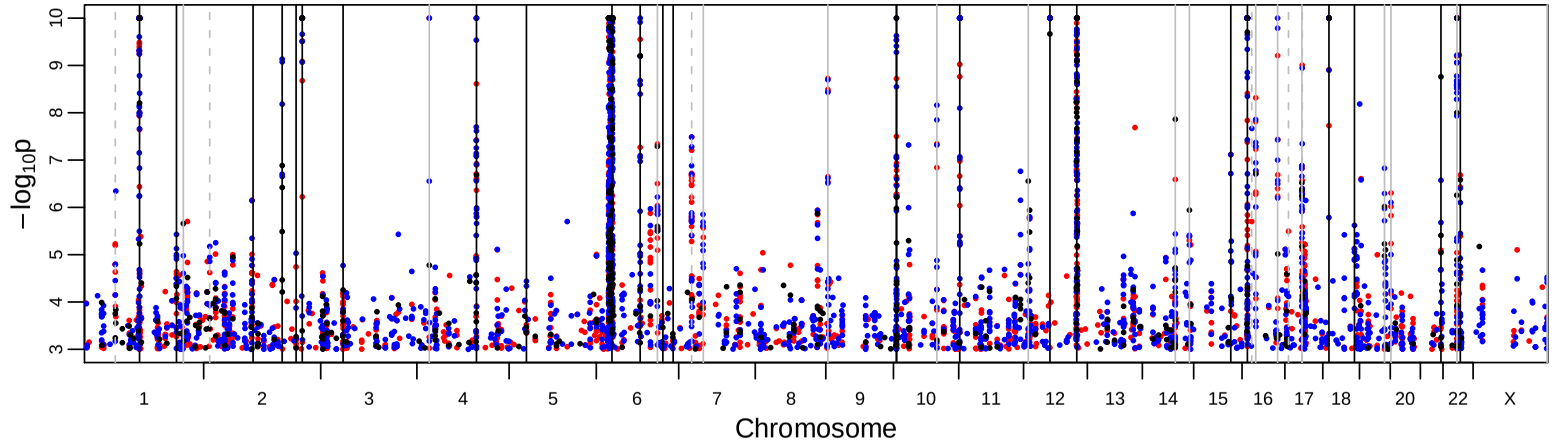
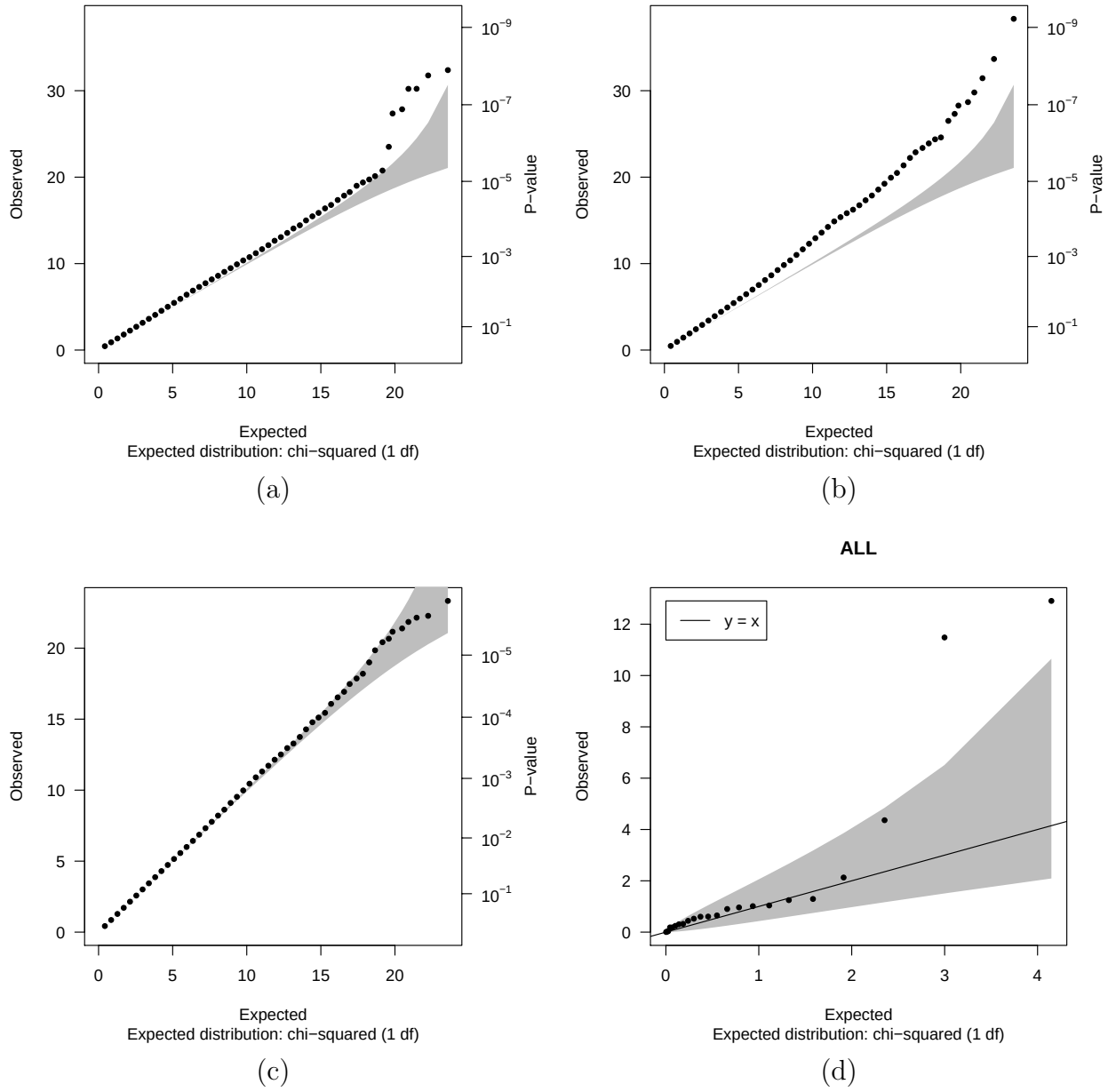


(c)



(d)

Supplementary Figure 1: Genome-wide plot of $-\log_{10} p$-values from stratified 1 df tests (a) in the WTCCC, (b) in the GoKinD/NIMH study, (c) in the T1DGC study, and (d) in the overall meta-analaysis. Values of $-\log_{10} p$ greater than 10 are plotted at 10 and values less than 3 are omitted. SNPs only present on the Illumina chip are shown in blue, those only present on the Affymetrix chip in red, and those present on both chips are shown in black. Points are plotted in the order blue, red, black in panels (a) and (b) and in the order red, blue, black in (c) and (d). Previously known disease susceptibility loci are marked by vertical black lines. In panel (d) new findings from the current analysis are marked by vertical grey lines (solid lines for convincingly replicated loci and dashed lines for nominally replicated results).



Supplementary Figure 2: Quantile-quantile plots for 1–df tests: (a) stratified tests in the T1DGC study alone, (b) stratified tests in the meta-analysis, (c) tests for interaction with MHC in the meta-analysis, and (d) tests for interaction with MHC for the most associated SNP in 44 regions associated with T1D in this or previous studies. The case-only approach has been used for interaction tests, which are stratified by geographical region (UK samples) or by PCA propensity score (US samples). In (a), (b) and (c), SNPs in regions surrounding putatively associated regions have been omitted and, for legibility, the lower 90% of the plot has been represented by only 50 points. In (d) the five nominally significant interactions were for rs1990760 (*IFIH1*, most significant), rs2476601 (*PTPN22*), rs16956936 (*DNAH2*), rs4900384 (gene desert), and rs3087243 (*CTLA4*, least significant). For rs4900384 interaction and main effect were in the same direction, indicating increased relative risk for this SNP with increased MHC risk, whilst the other four were consistent with reduced relative risk with increased MHC risk.

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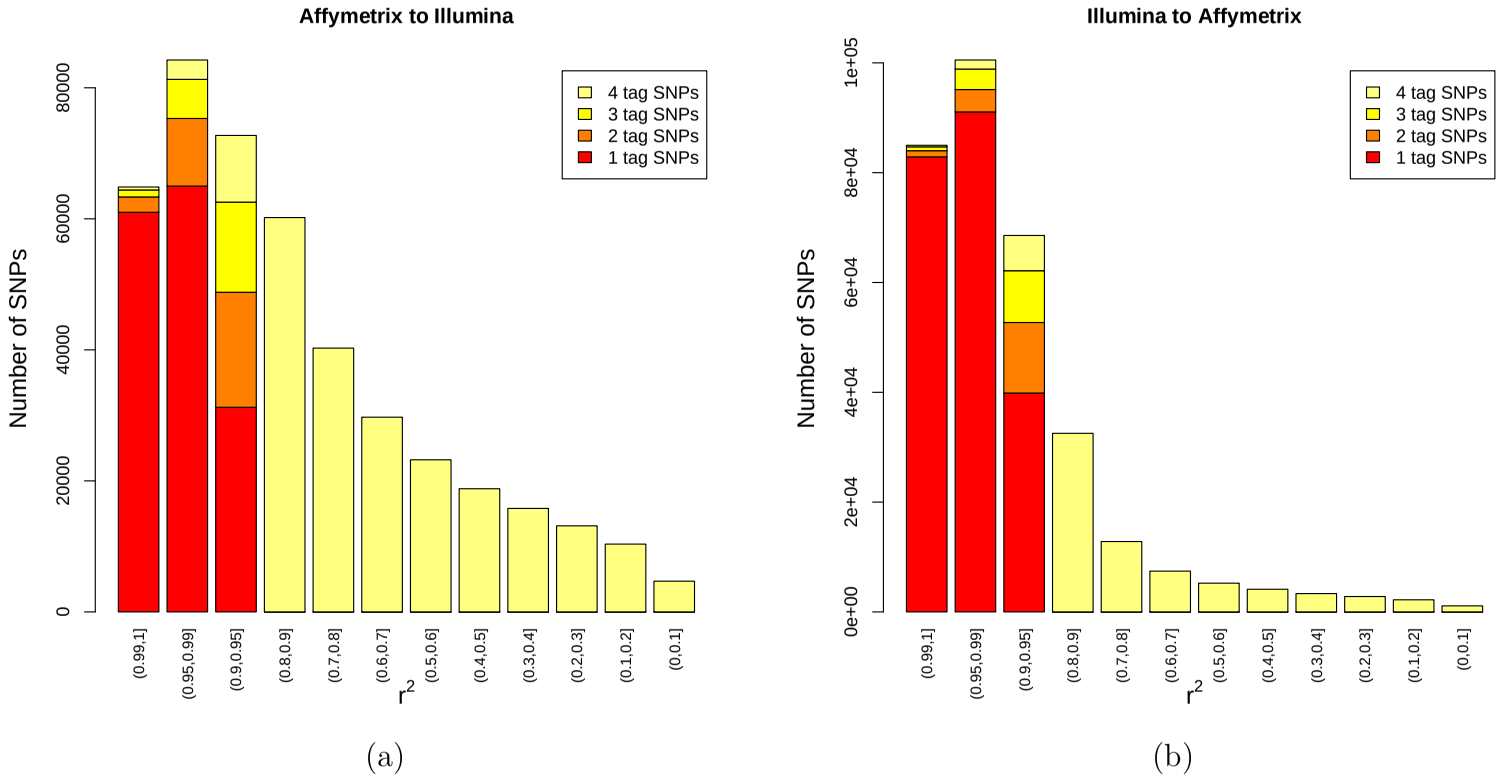
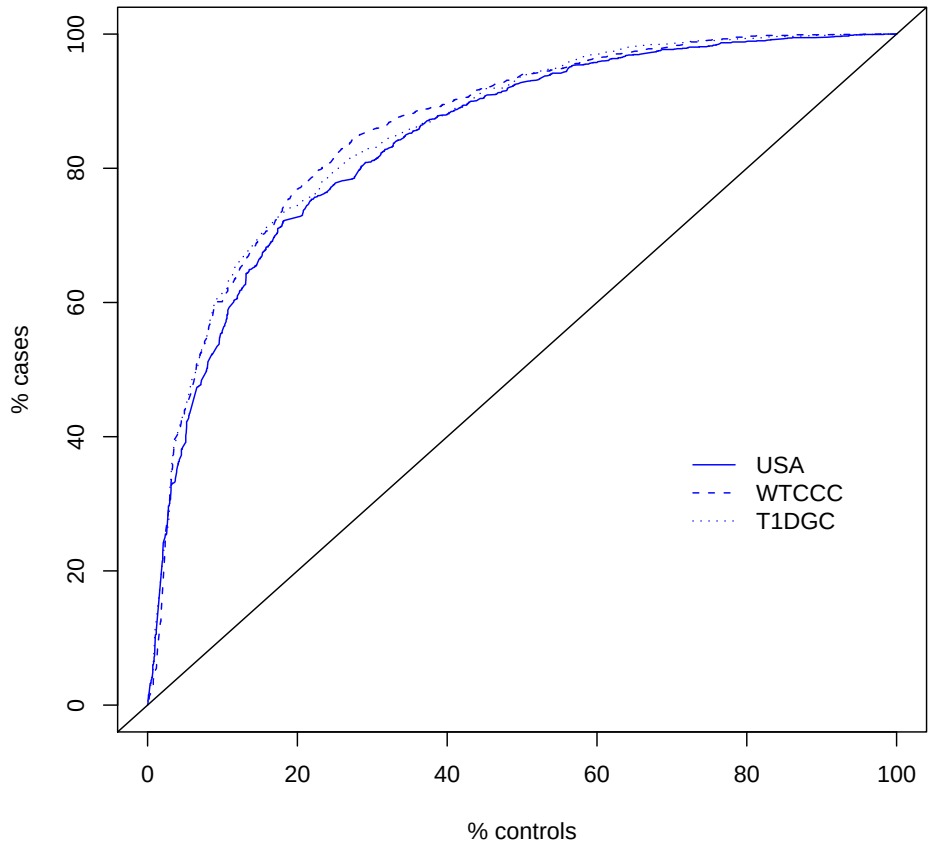


Supplementary Figure 3: Distribution of R^2 achieved in imputation, by linear regression, of (a) Illumina SNPs from the Affymetrix platform, and (b) Affymetrix SNPs from the Illumina platform. A step-wise regression approach was used, stopping either when an R^2 value of at least 0.9 was achieved or when four predictor SNPs had been used



Supplementary Figure 4: Receiver operating curve for prediction of risk of type 1 diabetes from SNPs in the MHC region in the WTCCC and GoKinD/NIMH studies using the Affymetrix 500K chip, and in the T1DGC study using the Illumina 550K chip

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			p-values (1 df tests)			p-values (2 df tests)	
SNP	Chromosome	Position	Simple	Stratified	GC–corrected	Simple	Stratified
rs2269241	1	63.881	3.6×10^{-7}	5.9×10^{-6}	1.9×10^{-5}	2.4×10^{-6}	3.4×10^{-5}
rs3024505	1	205.007	6.2×10^{-7}	2.2×10^{-6}	7.6×10^{-6}	2.1×10^{-11}	3.0×10^{-10}
rs946487	1	213.482	4.9×10^{-7}	2.0×10^{-6}	7.0×10^{-6}	7.3×10^{-7}	5.1×10^{-6}
rs1534422	2	12.558	7.9×10^{-7}	6.7×10^{-6}	2.1×10^{-5}	4.5×10^{-6}	3.6×10^{-5}
rs4851256	2	100.141	8.6×10^{-7}	2.5×10^{-5}	6.8×10^{-5}	4.4×10^{-6}	1.0×10^{-4}
rs10517086	4	25.695	4.9×10^{-7}	2.8×10^{-7}	1.2×10^{-6}	3.0×10^{-6}	1.7×10^{-6}
rs9388489	6	126.740	2.0×10^{-8}	5.1×10^{-8}	2.6×10^{-7}	8.2×10^{-13}	1.0×10^{-11}
rs7804356	7	26.858	7.4×10^{-9}	3.3×10^{-8}	1.7×10^{-7}	5.2×10^{-8}	2.2×10^{-7}
rs4948088	7	50.995	4.1×10^{-7}	2.7×10^{-6}	9.2×10^{-6}		
rs2608053	8	129.145	8.0×10^{-7}	1.4×10^{-6}	4.9×10^{-6}	3.6×10^{-6}	7.2×10^{-6}
rs7020673	9	4.282	3.5×10^{-11}	1.9×10^{-9}	1.4×10^{-8}	1.1×10^{-10}	5.0×10^{-9}
rs2793108	10	31.419	1.1×10^{-7}	4.8×10^{-8}	2.5×10^{-7}	7.2×10^{-7}	3.3×10^{-7}
rs10509540	10	90.013	6.3×10^{-9}	6.9×10^{-9}	4.3×10^{-8}	3.6×10^{-8}	3.8×10^{-8}
rs4763879	12	9.801	2.8×10^{-7}	2.8×10^{-7}	1.2×10^{-6}	1.8×10^{-6}	1.6×10^{-6}
rs1465788	14	68.333	2.8×10^{-9}	1.4×10^{-8}	8.0×10^{-8}	1.5×10^{-13}	3.1×10^{-12}
rs4900384	14	97.569	8.9×10^{-8}	1.1×10^{-6}	4.2×10^{-6}	5.3×10^{-7}	6.3×10^{-6}
rs12444268	16	20.250	3.9×10^{-6}	2.0×10^{-6}	7.0×10^{-6}	2.3×10^{-5}	1.2×10^{-5}
rs4788084	16	28.447	1.1×10^{-9}	5.2×10^{-8}	2.6×10^{-7}	1.6×10^{-9}	8.7×10^{-8}
rs7202877	16	73.805	1.7×10^{-10}	5.7×10^{-11}	5.9×10^{-10}		
rs16956936	17	7.574	6.5×10^{-7}	3.2×10^{-6}	1.1×10^{-5}	2.5×10^{-6}	1.2×10^{-5}
rs2290400	17	35.320	9.0×10^{-8}	1.3×10^{-7}	6.1×10^{-7}	6.1×10^{-7}	8.9×10^{-7}
rs7221109	17	36.024	6.0×10^{-10}	9.9×10^{-10}	7.6×10^{-9}	4.0×10^{-9}	7.3×10^{-9}
rs12982646	19	0.451	8.0×10^{-9}	6.5×10^{-9}	4.1×10^{-8}	3.5×10^{-8}	2.2×10^{-8}
rs425105	19	51.900	3.4×10^{-8}	1.5×10^{-7}	6.8×10^{-7}	2.4×10^{-7}	9.8×10^{-7}
rs2281808	20	1.559	1.9×10^{-7}	5.0×10^{-7}	2.0×10^{-6}	1.2×10^{-6}	3.2×10^{-6}
rs5753037	22	28.912	5.4×10^{-14}	1.8×10^{-14}	4.4×10^{-13}	1.1×10^{-13}	4.0×10^{-14}
rs2664170	X	153.599	1.3×10^{-6}	3.0×10^{-5}	8.0×10^{-5}	5.5×10^{-6}	1.1×10^{-4}

Supplementary Table 1: Simple and stratified association test results from the meta-analysis combining results of three GWA studies. Stratified test p–values are also shown after genomic control correction with $\lambda = 1.119$. The 2 df tests were only calculated if the minor allele frequency exceeded 10%

			p-value (1 df test)				
SNP	Chromosome	Position	WTCCC	GoKinD/NIMH	T1DGC	WTCCC+T1DGC	All studies
rs3024505	1	205.007	3.5×10^{-3}	6.1×10^{-1}	3.5×10^{-5}	4.2×10^{-7}	2.2×10^{-6}
rs10517086	4	25.695	3.4×10^{-4}	1.8×10^{-2}	2.7×10^{-3}	5.0×10^{-6}	2.8×10^{-7}
rs9388489	6	126.740	1.3×10^{-2}	3.6×10^{-3}	8.8×10^{-5}	3.7×10^{-6}	5.1×10^{-8}
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rs7020673	9	4.282	1.8×10^{-4}	6.2×10^{-3}	1.1×10^{-4}	8.8×10^{-8}	1.9×10^{-9}
rs10509540	10	90.013	1.4×10^{-3}	4.9×10^{-5}	3.3×10^{-3}	1.4×10^{-5}	6.9×10^{-9}
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rs425105	19	51.900	1.2×10^{-2}	1.5×10^{-3}	4.5×10^{-4}	1.6×10^{-5}	1.5×10^{-7}
rs2281808	20	1.559	4.6×10^{-2}	1.5×10^{-1}	3.0×10^{-6}	8.9×10^{-7}	5.0×10^{-7}
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rs2664170	X	153.599	1.0×10^{-1}	3.3×10^{-2}	1.2×10^{-3}	2.9×10^{-4}	3.0×10^{-5}
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rs12444268	16	20.250	3.0×10^{-2}	1.9×10^{-2}	2.2×10^{-4}	3.5×10^{-5}	2.0×10^{-6}
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rs7221109	17	36.024	6.3×10^{-7}	8.7×10^{-2}	2.2×10^{-4}	1.9×10^{-9}	9.9×10^{-10}
rs946487	1	213.482	4.1×10^{-2}	3.3×10^{-5}	1.6×10^{-2}	1.6×10^{-3}	2.0×10^{-6}
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rs2793108	10	31.419	8.9×10^{-3}	4.2×10^{-3}	1.1×10^{-4}	3.0×10^{-6}	4.8×10^{-8}
rs4851256	2	100.141	5.3×10^{-4}		8.4×10^{-3}	2.5×10^{-5}	2.5×10^{-5}
rs12982646	19	0.451	7.3×10^{-3}	5.9×10^{-2}	1.2×10^{-6}	3.8×10^{-8}	6.5×10^{-9}

Supplementary Table 2: SNPs in the follow-up study: results of stratified 1 df (Mantel extension) tests for each GWAS individually and in combination. Horizontal lines divide the SNPs into groups as strongly replicated, weakly replicated, not replicated, and failure

SNP	Coefficient
rs805294	0.021
rs2187668	0.660
rs9275313	0.346
rs9275388	0.300
rs9275425	0.129
rs9275614	0.276

(a)

SNP	Coefficient
rs3131631	0.043
rs377763	0.003
rs3135377	0.254
rs9273363	1.104
rs9275418	0.373
rs3916765	0.035

(b)

Supplementary Table 3: Coefficients for MHC SNPs used to predict disease risk: (a) for Illumina 550K platform, (b) for Affymetrix 500K platform

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Supplementary methods

Sample exclusions

The sample and SNP exclusion criteria we used were identical to those reported by the WTCCC (reference [7]), but we excluded a further 80 samples both because of a stricter cutoff for non-European ancestry and because several samples overlapped with the T1DGC, since they were drawn from the same pools. Of these, 48 subjects were excluded due to evidence of non-European ancestry, 16 were duplicated records (or unrecorded MZ twins), and 16 were closely related to other subjects. The composition of the GoKinD/NIMH case and control groups has been described elsewhere (reference [10]) and exclusions reported there were also applied in our analysis, These resulted in stringent cut-offs resulted in 124 exclusions, split 118:4:2 between the three exclusion categories described above. In the new T1DGC study, there were 82 exclusions, split 70:1:11 between non-European ancestry, duplicates, and close relatives.

SNP exclusions

In all studies, SNPs were excluded if the minor allele frequency (MAF) fell below 1% in cases or controls or if the 1 df chi-squared test for deviation from Hardy-Weinberg equilibrium exceeded 25 in controls ($p < 5.7 \times 10^{-7}$). Note that previously published results for the GoKinD/NIMH study reported results only for SNPs with MAF greater than 5%. For the WTCCC and T1DGC studies, individual genotype calls were only accepted if posterior probability of the best call exceeded a threshold (0.9 in the former case, 0.95 in the latter) and the SNP was excluded if the call rate fell below 95%. For the GoKinD/NIMH study, the best call was recorded in each case, but SNPs were discarded if a metric measuring separation of the genotype signal clouds indicated insufficient separation.

Follow-up studies

The most significantly associated SNP in each of the 26 regions with $p < 10^{-6}$ (unstratified Cochran–Armitage test), together with the most significantly associated SNP on the X chromosome were chosen for follow-up. For two SNPs, rs4851256 (at 100.14mb on chromosome 2) and rs12982646 (0.45mb on chromosome 19), reliable Taqman assays were not available. The (stratified) 1 df p-values for these two SNPs in the meta-analysis were, respectively, 2.5×10^{-5} and 6.5×10^{-9}. Three further SNPs, rs94648, rs2608053, and rs2793108 were followed up, but failed to provide any evidence of association ($p > 0.1$).

Statistical methods

In the current context, Mantel's extension to the Cochran–Armitage test (reference [24]) computes, in cases, an observed minus expected allele frequency score within each stratum together with its variance without assuming Hardy Weinberg equilibrium. The scores and their variances are then added over strata and the squared total score divided by the total variance to provide a chi-squared test statistic with 1 df. The corresponding 2 df test compare genotype frequencies between cases and controls and pool information over studies and strata in a similar manner; two observed-minus-expected scores must

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be computed for each stratum together with the corresponding 2×2 variance-covariance matrix; scores and variances are then summed over strata as in the 1 df test to yield an overall "score" vector, U of length 2, together with its 2×2 covariance matrix, V. The 2 df test is then obtained by computing $U^{\mathrm{T}} V^{-1} U$. Since, for loci on the X chromosome, males would be expected to show similar risk gradients to those between homozygous females, the method proposed by Clayton (reference [25]) scores male contributions to the test score for the 1 df test in the same way as homozygous females, with an appropriate adjustment to the variance estimate. The second degree of freedom in the 2 df test is derived entirely from data from females.

Imputation between the two platforms was carried out by simple linear regression, a method proposed some years ago. We chose this in preference to more recently proposed methods because these are based on the rather small sample of HapMap subjects, while the regression approach could make use of the 1,422 controls genotyped on both platforms. These were used to derive linear regression equations to predict those SNPs only genotyped on the Affymetrix platform using SNPs available on the Illumina platform, and vice-versa. For this purpose, all genotypes were coded numerically, as 0, 1 or 2, and the regression equations were used to obtain predictions for the missing genotypes in the remaining studies. The resulting predictions are real numbers so that observed numbers of genotypes in cases are no longer integers but, that apart, analysis proceeds in exactly the same way as for truly observed genotypes. Imputed SNPs also yield observed-minus-expected scores and associated variances and evidence was combined over studies in the same way as it is combined over strata within studies. Note that a natural consequence of poor prediction is shrinkage of the observed-minus-expected score so that the contribution of poorly imputed genotypes in the meta-analysis is naturally (and correctly) attenuated.

Follow-up case–control data were analyzed in the same way as the GWAS data, with Danish and UK studies treated as separate strata. The family study was analyzed by the transmission/disequilibrium test (TDT). The families were, for the most part, affected sib-pairs together with their parents so that each family contributed two caseparent trios. Since linkage (as reflected by distortion of the 0.25:0.5:0.25 IBD sharing probabilities between siblings) was imperceptible in these regions we were able to treat the two trios provided by each family as independent. For analysis of the family data for the SNP on the X chromosome, the TDT was modified following the same principles which prompted the modification to the case-control test; each transmission from a heterozygous mother to a male offspring was given twice the weight of a transmission to a female offspring. Since the TDT can also be formulated in terms of an observed-minus-expected allele count score in cases and its variance, pooling evidence from the family data and from case–control data follows identical principles to pooling of evidence across strata in case–control studies, *i.e.* scores and their variances are summed over studies before calculation of the final chi-squared test statistic.

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Supplementary Note

Membership list for the Type 1 Diabetes Genetics Consortium

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