Supplementary Online Material

Common genetic variation near melatonin receptor *MTNR1B* contributes to raised plasma glucose and increased risk of type-2 diabetes amongst Indian Asians and European whites.

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Table S1. Pairwise r^2 between SNPs in the *MTNR1B* locus, amongst Indian Asians and the HapMap CEU sample (HapMap PhaseIII/Rel#1 Sept 2008, NCBI B36 assembly, dbSNP b126)

	Indian Asians			**HapMap CEU**		
	rs2166706	rs3847554	rs1387153	rs2166706	rs3847554	rs1387153
rs3847554	0.80			0.79		
rs1387153	0.71	0.57		0.60	0.56	
rs10830963†	-	-	-	0.45	0.45	0.65

†rs10830963 – previously reported to be associated with glucose levels in Europeans

Table S2. SNPs associated with glucose levels amongst Indian Asians at P<5x10-8, in combined analysis of the Hap610 and Hap300 samples. G=genotyped, I=imputed.

SNP	**Chr**	**Position**	**Locus**	**Hap610**	**Hap300**	**P=**
rs10830963	11	92348358	*MTNR1B*	I	I	$8x10^{-12}$
rs10830962	11	92338075	*MTNR1B*	I	I	$3x10^{-10}$
rs11523890	11	92319426	*MTNR1B*	I	I	$6x10^{-10}$
rs10765573	11	92322980	*MTNR1B*	I	I	$6x10^{-10}$
rs7936247	11	92329680	*MTNR1B*	I	I	$7x10^{-10}$
rs10830961	11	92334405	*MTNR1B*	I	I	$9x10^{-10}$
rs10830956	11	92320661	*MTNR1B*	I	I	$2x10^{-9}$
rs2166706	11	92331180	*MTNR1B*	G	G	$2x10^{-9}$
rs12792753	11	92308623	*MTNR1B*	I	I	$2x10^{-9}$
rs7933855	11	92323970	*MTNR1B*	I	I	$2x10^{-9}$
rs11020124	11	92330309	*MTNR1B*	I	I	$3x10^{-9}$
rs3781638	11	92353155	*MTNR1B*	I	I	$3x10^{-9}$
rs1387153	11	92313476	*MTNR1B*	G	G	$4x10^{-9}$
rs4753072	11	92357053	*MTNR1B*	I	I	$6x10^{-9}$
rs1447350	11	92357775	*MTNR1B*	I	I	$6x10^{-9}$
rs4753426	11	92341244	*MTNR1B*	I	I	$7x10^{-9}$
rs4753073	11	92357123	*MTNR1B*	I	I	$8x10^{-9}$
rs7951037	11	92345823	*MTNR1B*	I	I	$9x10^{-9}$
rs7112766	11	92311669	*MTNR1B*	I	-	$9x10^{-9}$
rs11020107	11	92307378	*MTNR1B*	I	I	$1x10^{-8}$
rs3847554	11	92308474	*MTNR1B*	G	G	$1x10^{-8}$
rs1402837	2	169465600	*G6PC2*	G	I	$2x10^{-8}$
rs730497	7	44190246	*GCK*	G	I	$2x10^{-8}$
rs2908289	7	44190467	*GCK*	G	I	$2x10^{-8}$
rs1799884	7	44195593	*GCK*	G	I	$3x10^{-8}$
rs6975024	7	44198411	*GCK*	I	I	$4x10^{-8}$
rs2908282	7	44215353	*GCK*	I	I	$4x10^{-8}$
rs4607517	7	44202193	*GCK*	G	G	$5x10^{-8}$
rs917793	7	44212378	*GCK*	I	I	$5x10^{-8}$

Table S3. Risk allele frequencies and association test results amongst Indian Asians and European whites, for SNPs at the *GCKR*, *GCK* and *G6PC2* reported to be associated with glucose levels (1-3). Effect sizes are shown as change in fasting glucose (95% confidence interval) per copy of risk allele.

			Risk allele frequency (%)			Effect (mmol/L)				
SNP	**Gene**	**Risk Allele**	**Indian Asians**	**European whites**	**P=**	**Indian Asians**	**P=**	**European whites**	**P=**	**Interaction P=**
rs1260326	*GCKR*	G	73	65	7.9×10^{-32}	0.039 (0.011 to 0.066)	0.006	0.016 (-0.003 to 0.034)	0.10	0.09
rs560887	*G6PC2*	G	85	69	1.4×10^{-146}	0.068 (0.034 to 0.102)	9.0×10^{-5}	0.059 (0.040 to 0.078)	2.0×10^{-9}	0.53
rs4607517[†]	*GCK*	A	12	12	0.56	0.068 (0.031 to 0.106)	3.8×10^{-4}	0.043 (0.016 to 0.070)	0.002	0.57

[†] rs4607517 is a perfect proxy (r^2=1.0) for rs730497

Figure S1. QQ plot of the association test results with glucose levels in the Hap610 sample (Figure S1a), the Hap300 sample (Figure S1b), and in meta-analysis (Figure S1c). The red line shows the expected distribution under the null hypothesis of no association at any locus, and the green line the 95% confidence limits of the null hypothesis distribution.

Figure S1a

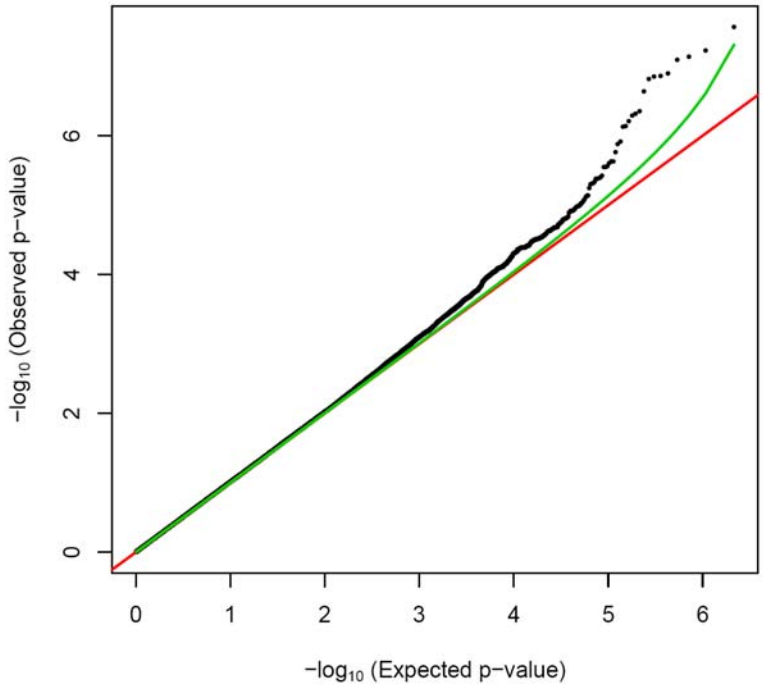

Figure S1b

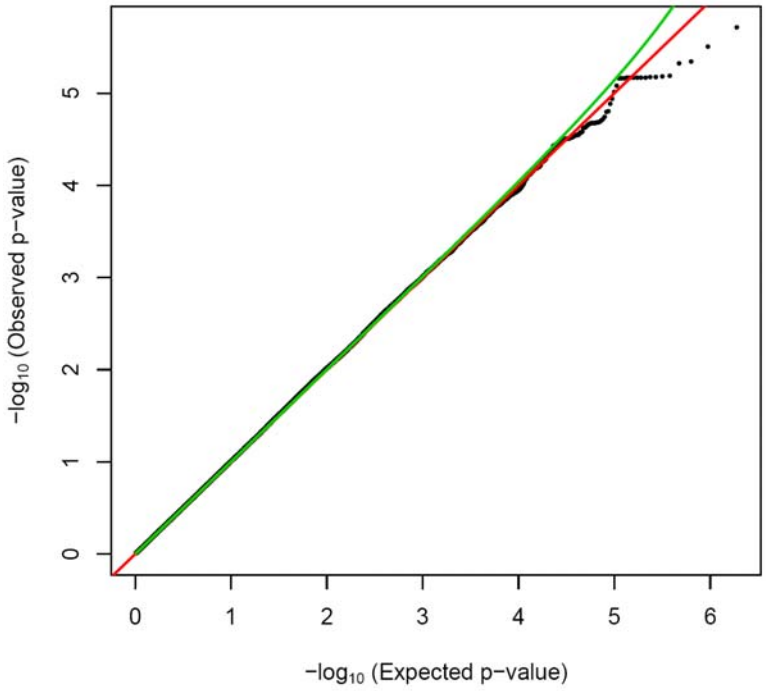

Figure S1c

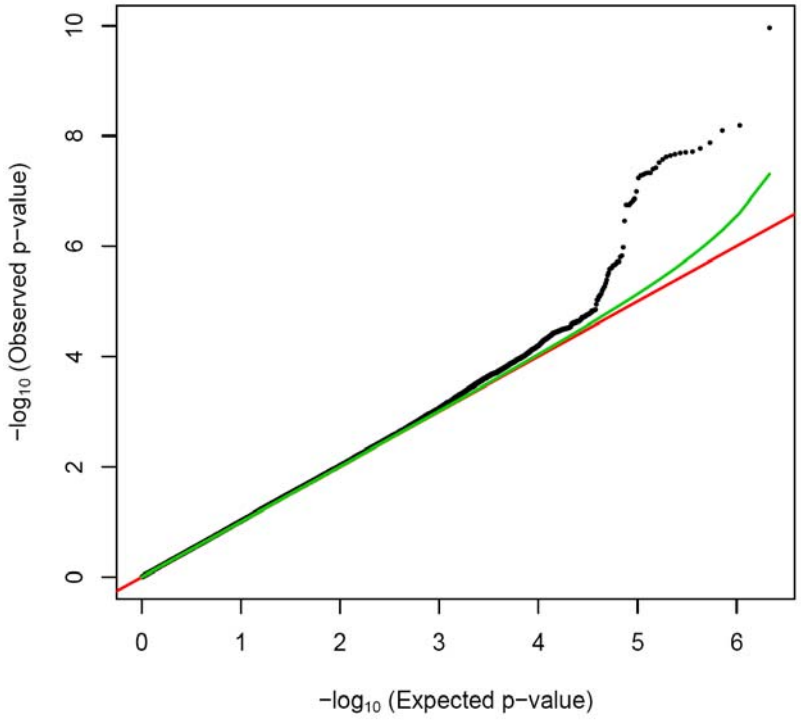

Figure S2. Signal-Intensity (Manhattan) plot showing the association of SNPs with glucose levels in the Hap610 sample (Figure S2a), the Hap300 sample (Figure S2b), and in meta-analysis (Figure S2c).

Figure S2a

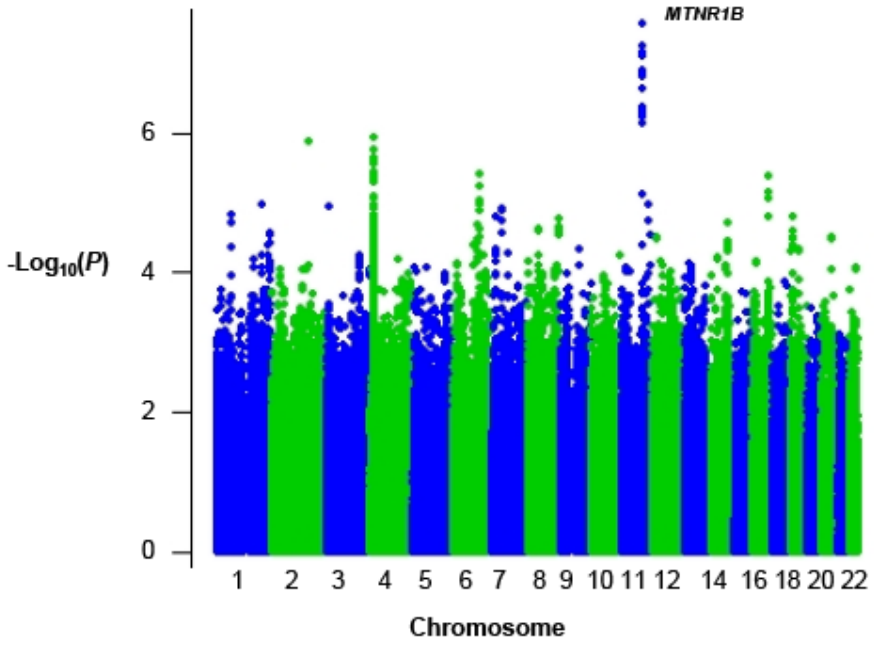

Figure S2b

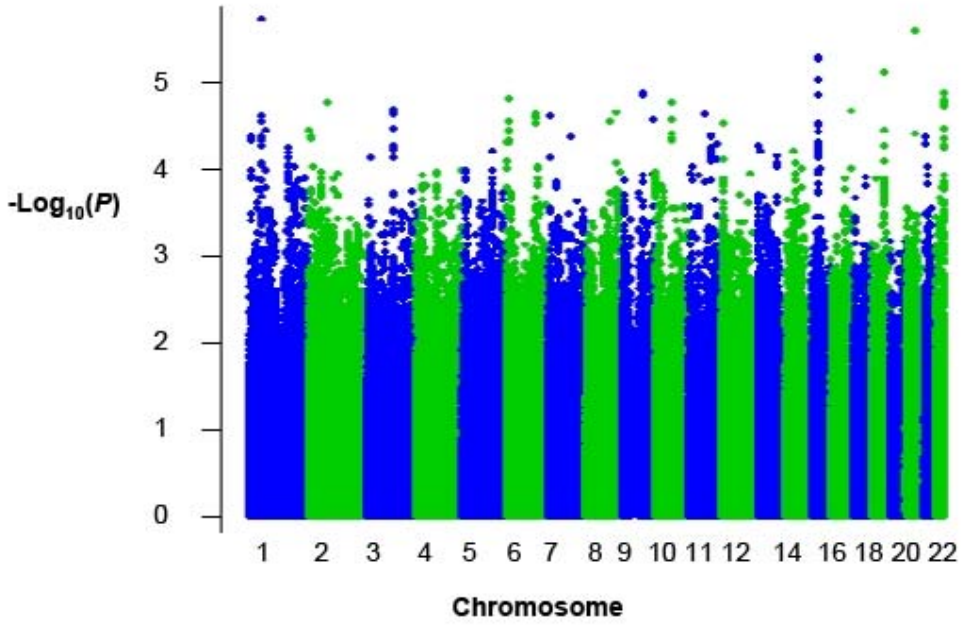

Figure S2c

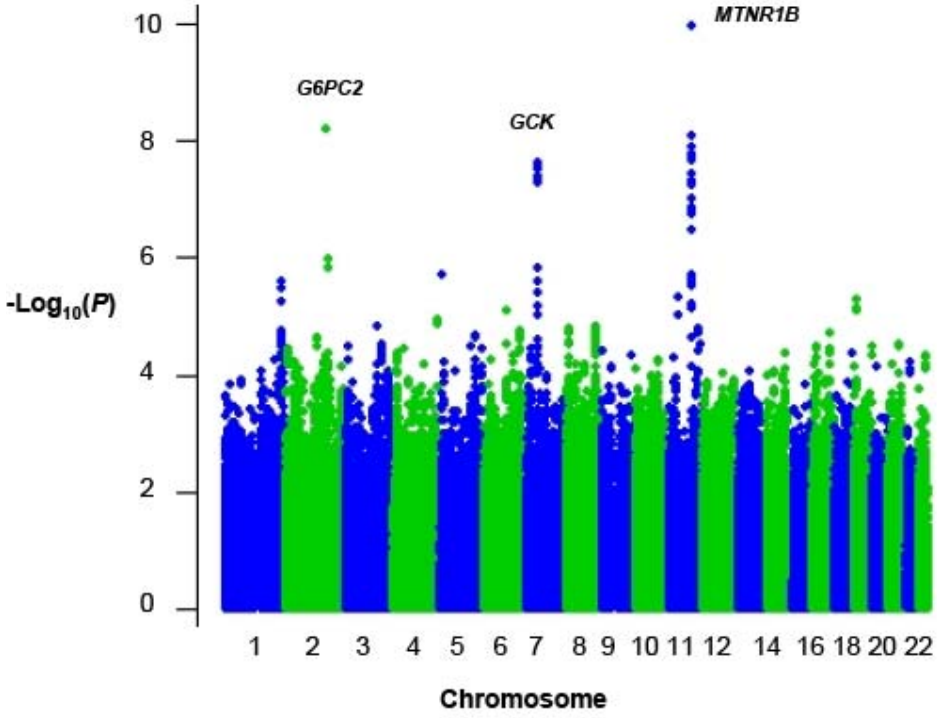

Figure S3. Genomic context of *GCK* region (chromosome 7) showing pairwise linkage disequilibrium between SNPs with MAF ≥ 0.05 directly genotyped amongst Indian Asians (Figure S3a) and European whites (Figure S3b), using Haploview's standard color scheme.

Figure S3a: Indian Asians.

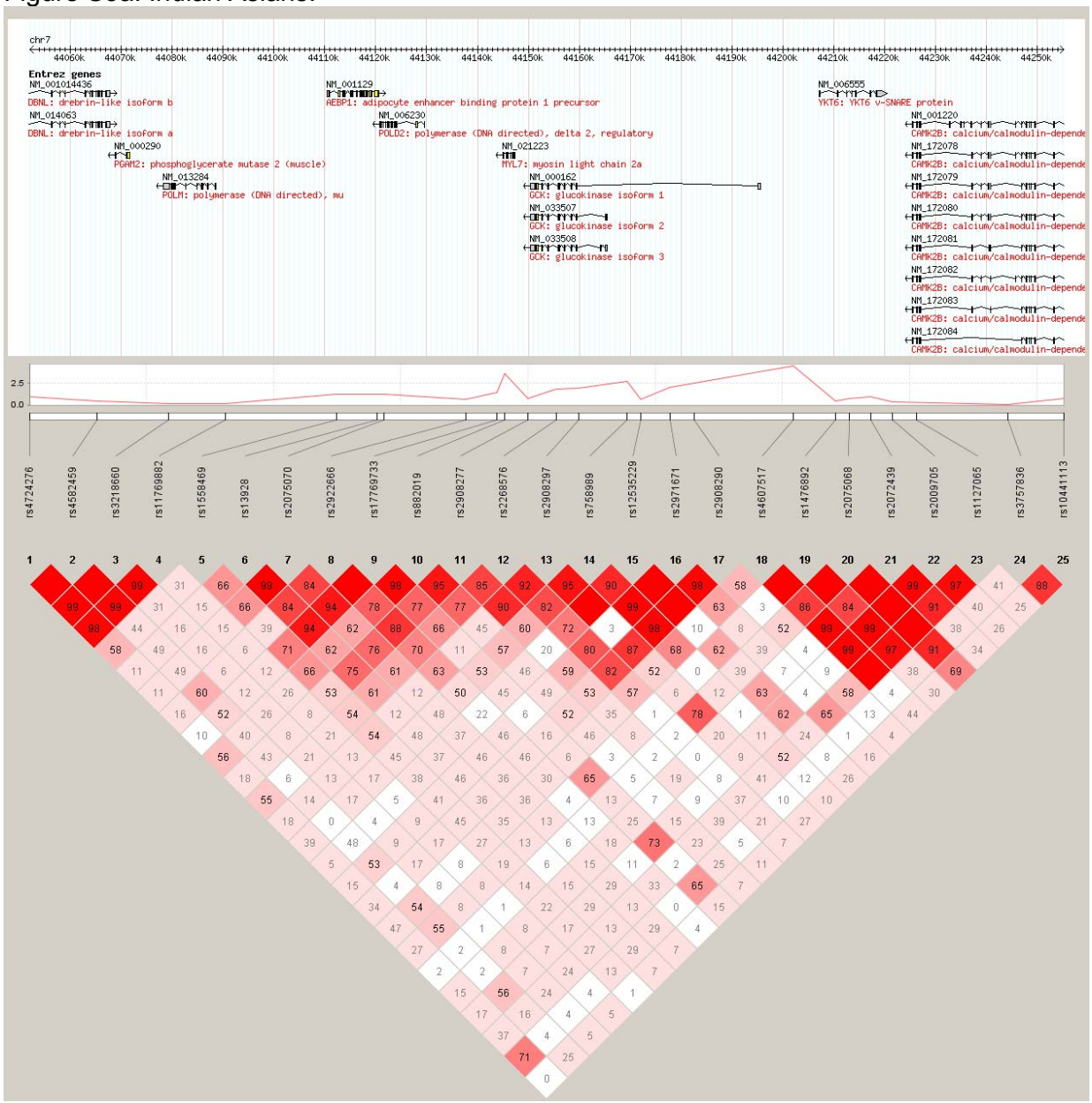

Figure S3b: European whites.

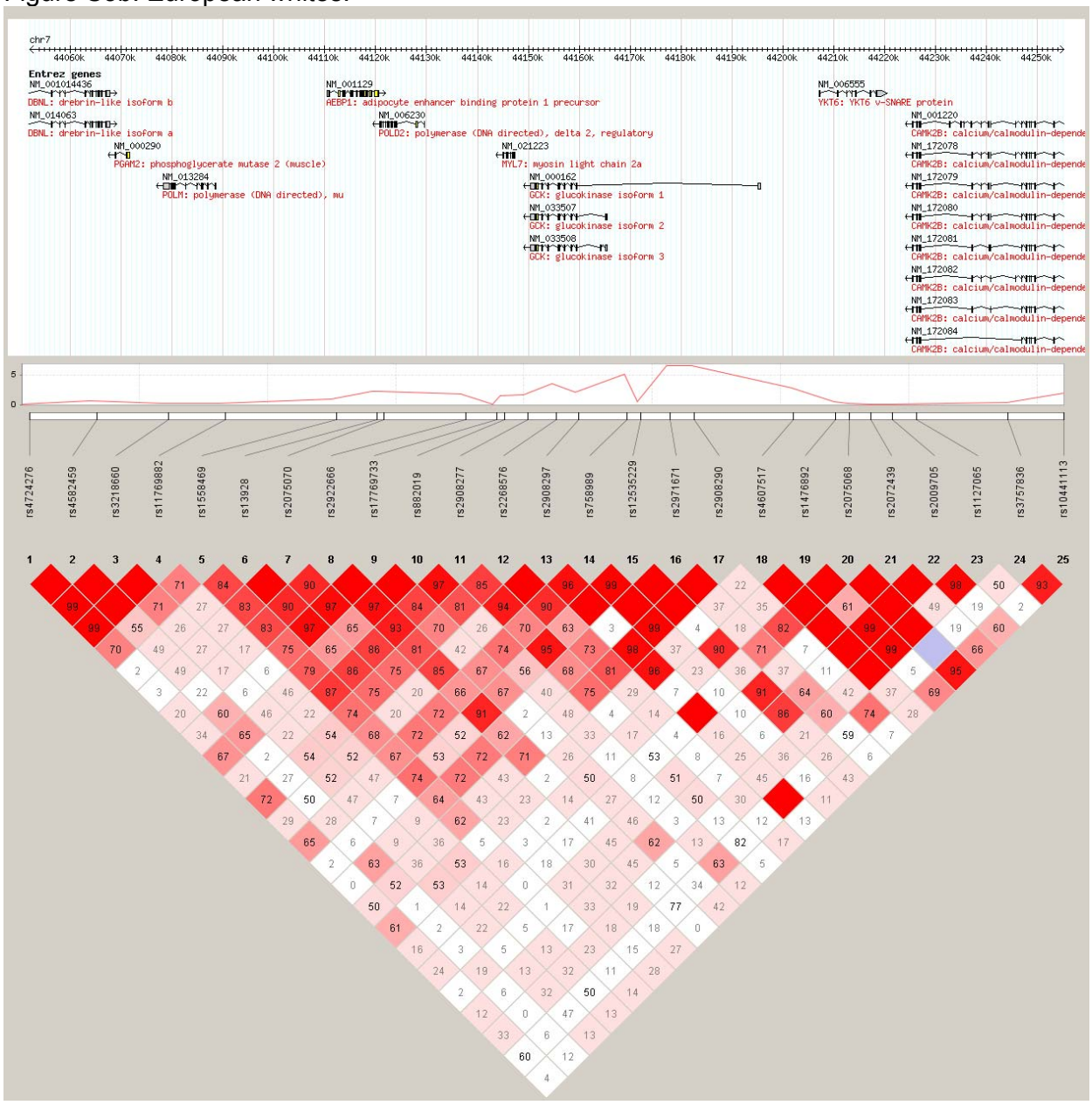

Figure S4. Genomic context of *G6PC2* (chromosome 2) showing pairwise linkage disequilibrium between SNPs with MAF ≥ 0.05 directly genotyped amongst Indian Asians (Figure S4a) and the European whites (Figure S4b), using Haploview's standard color scheme.

Figure S4a: Indian Asians.

Figure S4b: European whites.

Supplementary references

1. Bouatia-Naji,N, Rocheleau,G, Van,LL, Lemaire,K, Schuit,F, Cavalcanti-Proenca,C, Marchand,M, Hartikainen,AL, Sovio,U, De,GF, Rung,J, Vaxillaire,M, Tichet,J, Marre,M, Balkau,B, Weill,J, Elliott,P, Jarvelin,MR, Meyre,D, Polychronakos,C, Dina,C, Sladek,R, Froguel,P: A polymorphism within the G6PC2 gene is associated with fasting plasma glucose levels. *Science* 320:1085-1088, 2008
2. Vaxillaire,M, Cavalcanti-Proenca,C, Dechaume,A, Tichet,J, Marre,M, Balkau,B, Froguel,P: The common P446L polymorphism in GCKR inversely modulates fasting glucose and triglyceride levels and reduces type 2 diabetes risk in the DESIR prospective general French population. *Diabetes* 57:2253-2257, 2008
3. Sabatti,C, Service,SK, Hartikainen,AL, Pouta,A, Ripatti,S, Brodsky,J, Jones,CG, Zaitlen,NA, Varilo,T, Kaakinen,M, Sovio,U, Ruokonen,A, Laitinen,J, Jakkula,E, Coin,L, Hoggart,C, Collins,A, Turunen,H, Gabriel,S, Elliot,P, McCarthy,MI, Daly,MJ, Jarvelin,MR, Freimer,NB, Peltonen,L: Genome-wide association analysis of metabolic traits in a birth cohort from a founder population. *Nat Genet* 41:35-46, 2009