

## **Supplementary Information**

**Supplementary Table 1. List of polypeptide cell surface receptor and their cognate ligand genes.**

**Supplementary Table 2. List of coding SNPs with high  $F_{ST}$  ( $> 0.5$ ) in human GPCR and their cognate ligand genes.**

**Supplementary Table 3. List of coding SNPs with high  $F_{ST}$  ( $> 0.5$ ) in human nonGPCR receptor and ligand genes.**

**Supplementary Table 4. List of genotyped SNPs from 44246961 to 44542055 on chromosome 17.** The HapMap II dataset was analyzed using HaploView. The 101 SNPs included in LD plots of Supplementary Fig. 3 (A-C) are highlighted by a grey background. The 37 SNPs used in the haplotype analysis of Fig. 2C are indicated by red letters. SNPs that are linked with rs2291725 are indicated by bold red letters.

**Supplementary Table 5. Allele frequency of rs2291725 in the HGDP-CEPH populations.**

Frequencies of  $GIP^{103T}$  and  $GIP^{103C}$  alleles in each of the 52 populations from the seven geographical regions and the number of chromosomes analyzed for each population.

**Supplementary Table 6. EC<sub>50</sub> values for GIP receptor activation at four different time points after incubation with pooled human serum or pooled complement-preserved human serum (N=4).**

**Supplementary Table 7. EC<sub>50</sub> values for GIP receptor activation at three different time points after incubation with a recombinant DPP IV enzyme (N=4).**

**Supplementary Fig. 1. Cumulative distribution function (CDF) plots for the  $F_{ST}$  of coding SNPs in human GPCRs and their cognate ligand genes (blue) and all other human genes (magenta).** The  $F_{ST}$  was computed between three HapMap II populations (CEU, YRI, and ASN), and coding SNPs have been split into synonymous and nonsynonymous groups. The CDF for synonymous and nonsynonymous SNPs were plotted separately because the CDF of the  $F_{ST}$  for nonsynonymous SNPs has been shown to shift toward the right as compared to that of synonymous SNPs (Barreiro et al. 2008), perhaps due to a global increase of population differentiation at nonsynonymous sites.

**Supplementary Fig. 2. CDF plots for the  $F_{ST}$  of coding SNPs in human GPCR and ligand genes (blue) and nonGPCR receptor and ligand genes (green).**  $F_{ST}$  was computed between three HapMap II populations (CEU, YRI, and ASN) and coding SNPs have been split into synonymous and nonsynonymous SNPs.

**Supplementary Fig. 3. Plots of linkage disequilibrium (LD) between each pair of genotyped SNPs in a 200-kb region surrounding rs2291725 (Ch. 17, 44325258-44495998) in CEU (A), ASN (B), and YRI (C).** The International HapMap II dataset was analyzed using HaploView (Barrett et al. 2005). Putative LD block structures (defined by D) are indicated by black triangles. In

CEU and ASN, rs2291725 is positioned within a ~90-kb block with high LD whereas the link between rs2291725 and neighboring SNPs is negligible in YRI. Red squares represent regions with a high degree of LD and a high likelihood of odds (LOD;  $D' = 1$ ,  $LOD > 2$ ). Blue squares represent regions of high LD but low LOD ( $D' = 1$ ,  $LOD < 2$ ). Blue horizontal bars above LD plots represent gene regions of *CALCOCO2*, *ATP5G1*, *UBE2Z*, *SNF8*, *GIP*, and *IGF2BP1*. D) Alignments of 13 haploblock sequences (A-M) found in a 70-kb genomic region neighboring rs2291725 (Ch. 17, 44325258-44394253). Among the 37 SNPs in this region, 22 are linked with rs2291725 and are indicated by asterisks above the alignment. Sequences with an identical nucleotide are highlighted by a select color. The positions of individual SNPs are shown on the top, and SNPs that flank the region (rs1962412 and rs2291726) are indicated by arrows. The position of rs2291725 is indicated by a red box. The putative ancestral haplotype from chimpanzees is also shown at the bottom of the alignment.

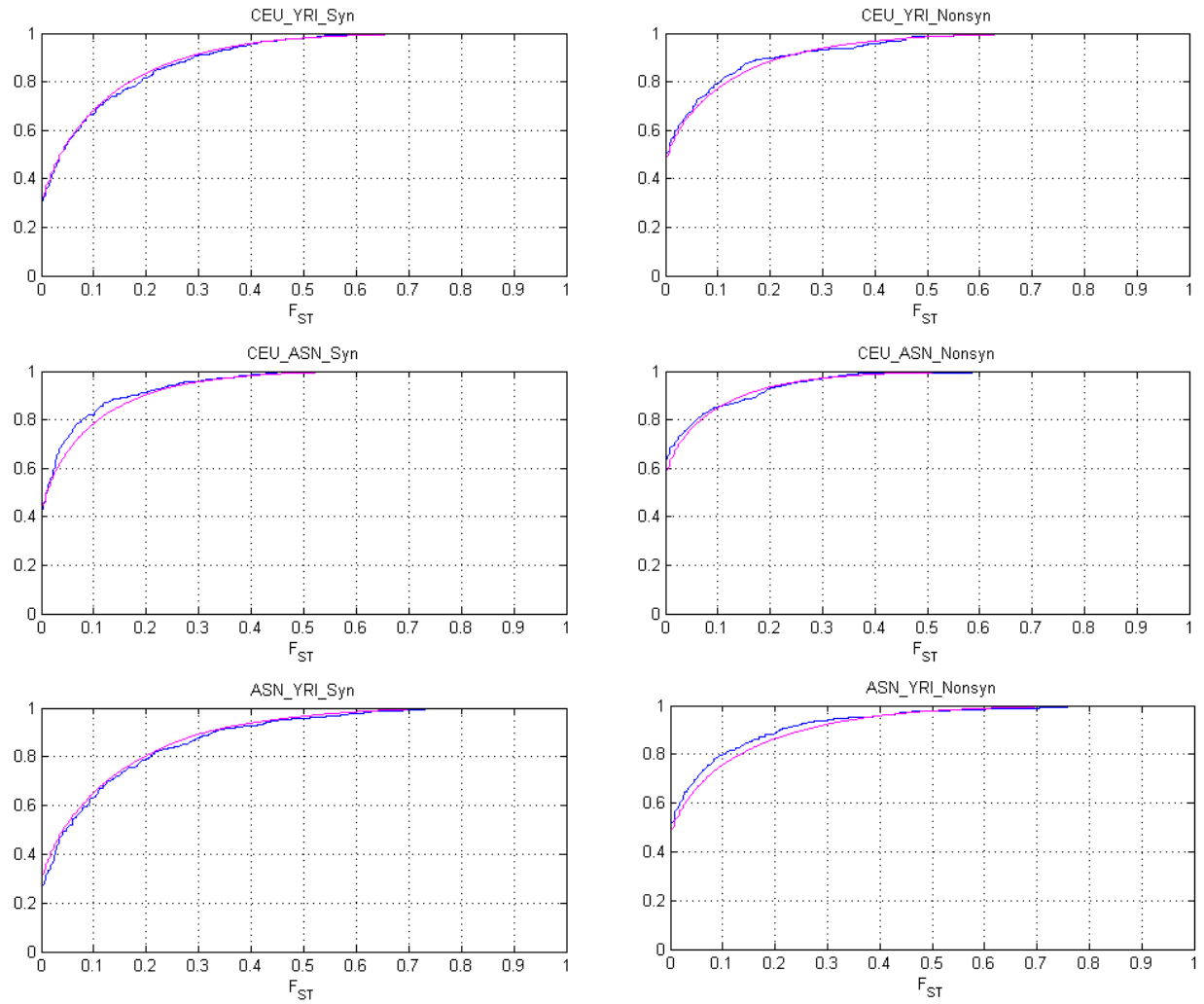
**Supplementary Fig. 4. Observed iHS for rs2291725 and the distribution of iHS under neutral evolution.** **A)** The distribution of simulated iHS under three scenarios: hotspot, neutral, and bottleneck. The distribution of iHS is constructed using coalescent simulations. Observed iHS for rs2291725 in the HapMap ASN population is indicated with a red vertical line. The means of simulated iHS under the hotspot, neutral, and bottleneck scenarios are 0.1977, 0.2746, and 0.3694, respectively. Under all three scenarios, the result rejected the hypothesis that the observed iHS of rs2291725 is larger than the simulated result. The p-values for the hotspot, neutral, and bottleneck models are  $8.0 \times 10^{-4}$ , 0, and 0, respectively. **B)** The hypothetical demographic history used to condition the effect of bottleneck on population expansion. We assumed that ASN population is one panmictic population that underwent a size reduction, followed by a period of constant size

(bottleneck), and then proceeded with population expansion (Gutenkunst et al. 2009). The population had an ancestral population size of  $N_1$  which at time  $T_2$  instantaneously shrank to size  $N_2$ . It remained constant at size  $N_2$  until time  $T_1$ , at which point it began expanding exponentially until the present time. The population size at present time is  $N_3$ .

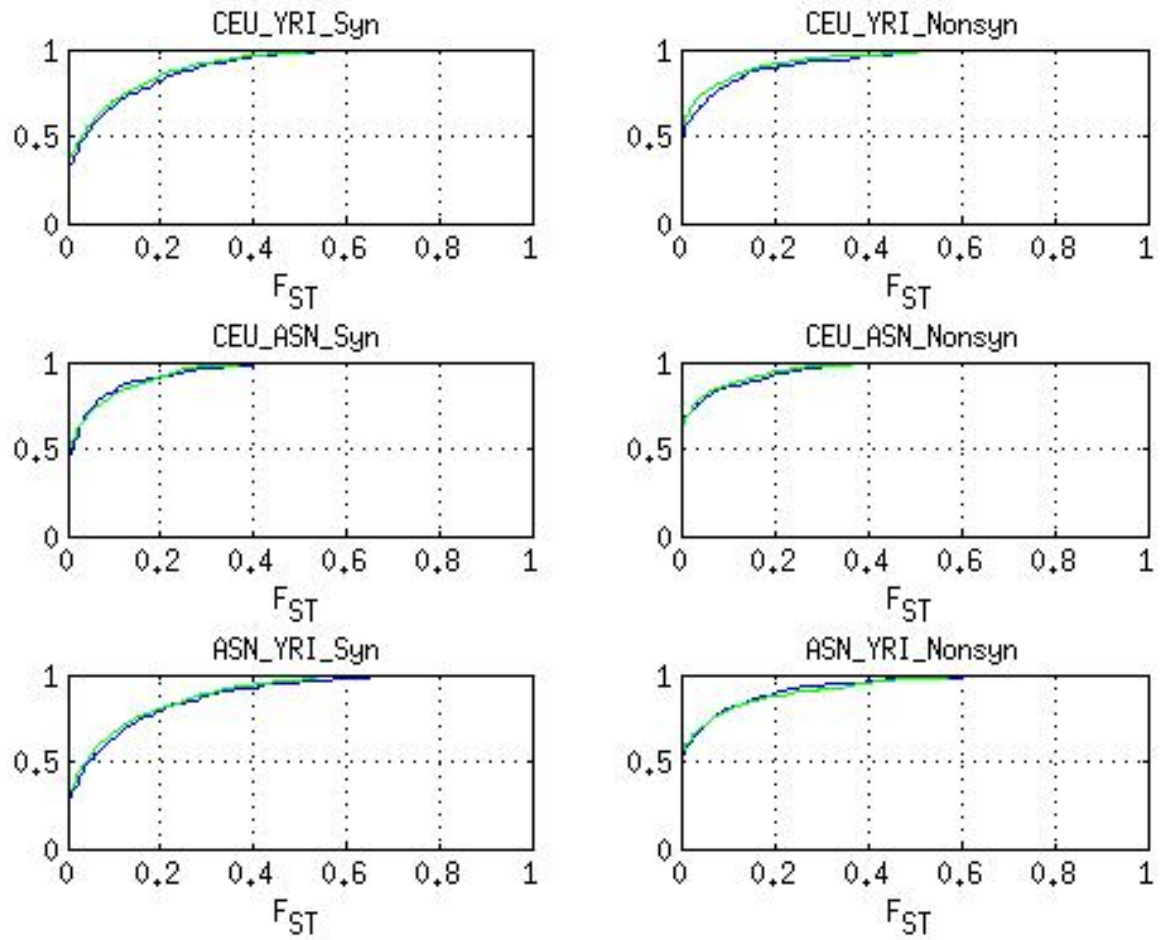
**Supplementary Fig. 5. GIP55G is resistant to degradation by pooled complement-preserved human serum.** Receptor-activation activities of GIP, GIP55G, or GIP55S following incubation with pooled complement-preserved human serum for 3, 6, and 12 hr were analyzed in HEK293T cells expressing a recombinant human GIP receptor. Error bars represent SEM of triplicate samples. Significant differences in cAMP production between GIP and GIP55G treatments at a given peptide concentration are indicated by asterisks ( $p < 0.01$ ).

**Supplementary Fig. 6. Haplotypes within the LD block at the *GIP* locus in ASN and CEU.** We defined LD blocks in a 250-kb region around the *GIP* locus using HaploView with default parameters. LD blocks in CEU and ASN are approx 91 and 97 kb, respectively. The triangle indicates the position of rs2291752. Haplotype frequencies are given on the right. The block with *GIP*<sup>103C</sup> allele is in blue for ASN and in red for CEU. The ASN block contains eight haplotypes. Four out of the eight haplotypes are linked with the derived *GIP*<sup>103C</sup> allele, and these haplotypes have been referred to as “*GIP*<sup>103C</sup> haplotypes.”

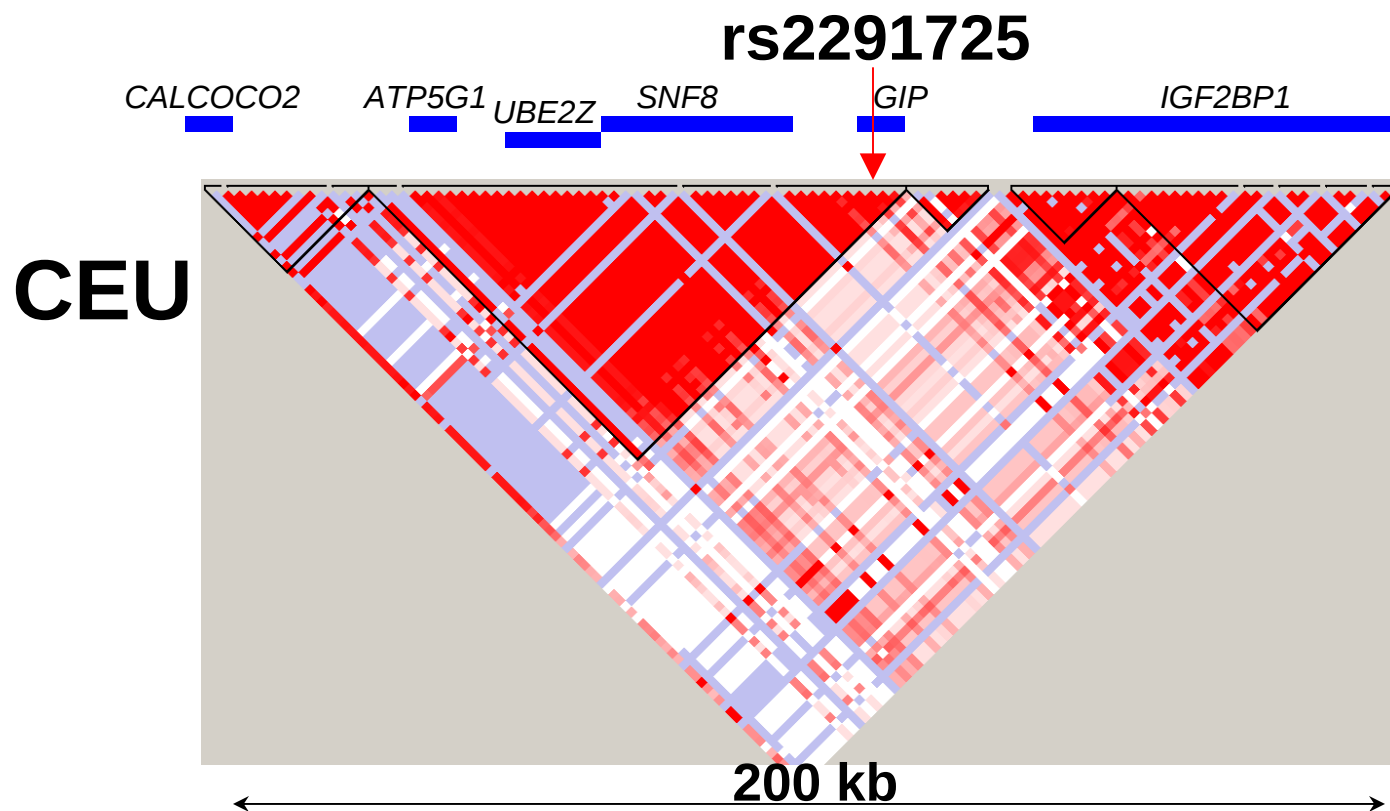
**Supplementary Fig. 1.** Cumulative distribution function (CDF) plots for  $F_{ST}$  of coding SNPs in human GPCRs and their cognate ligand genes (blue) and the rest of human genes (magenta).  $F_{ST}$  is computed between three HapMap II populations (CEU, YRI, and ASN) and coding SNPs are split into synonymous and nonsynonymous SNPs.



**Supplementary Fig. 2.** Cumulative distribution function (CDF) plots for  $F_{ST}$  of coding SNPs in human GPCR and ligand genes (blue) and nonGPCR receptor and ligand genes (green).  $F_{ST}$  is computed between three HapMap II populations (CEU, YRI, and ASN) and coding SNPs are split into synonymous and nonsynonymous SNPs.

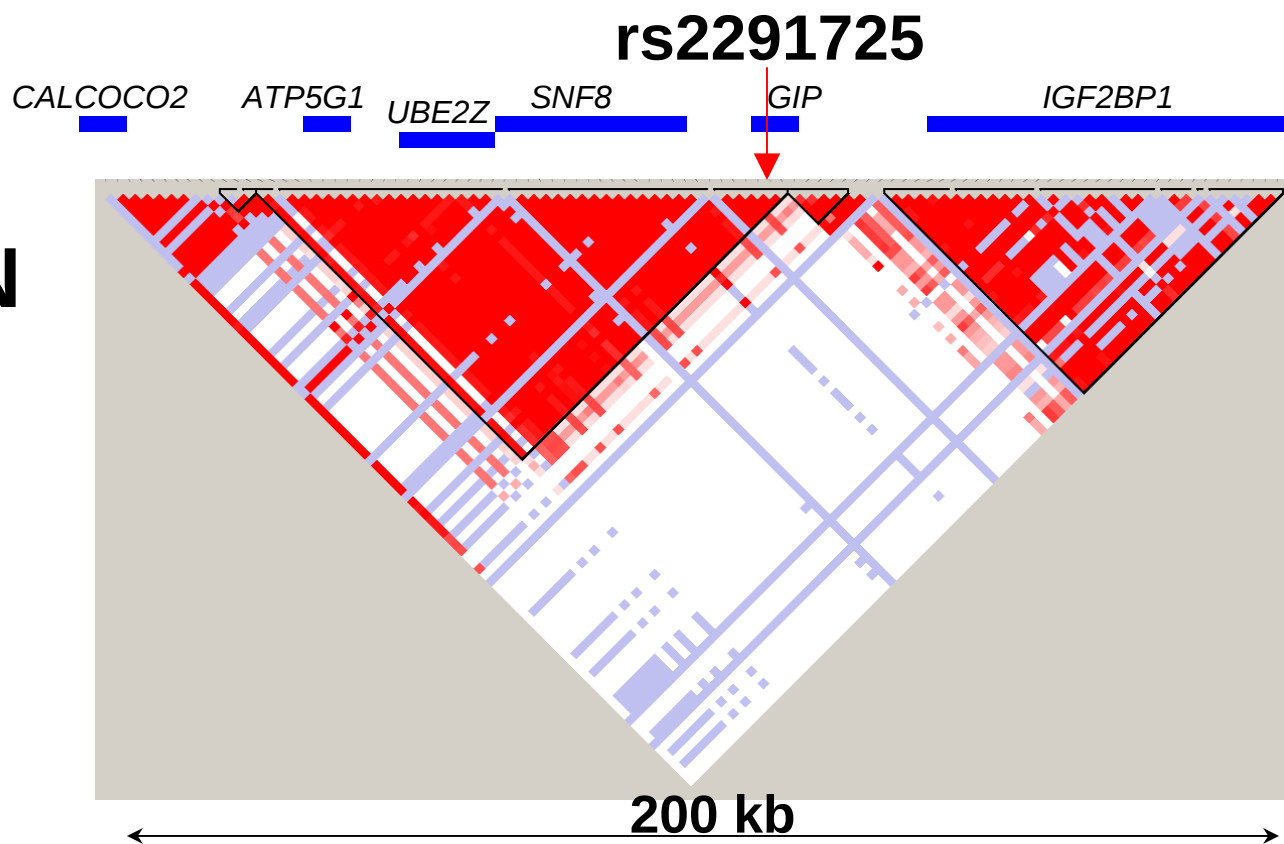


**A**

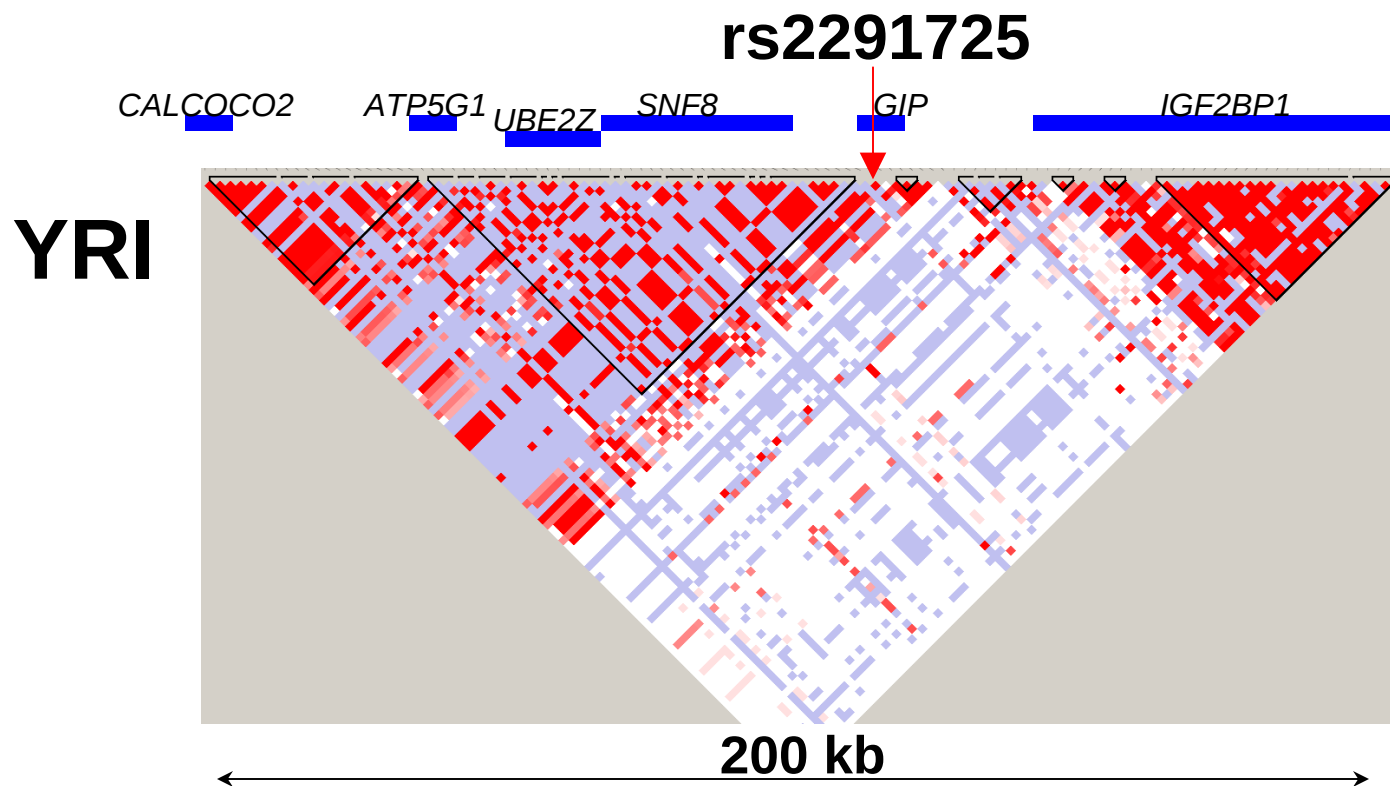


**B**

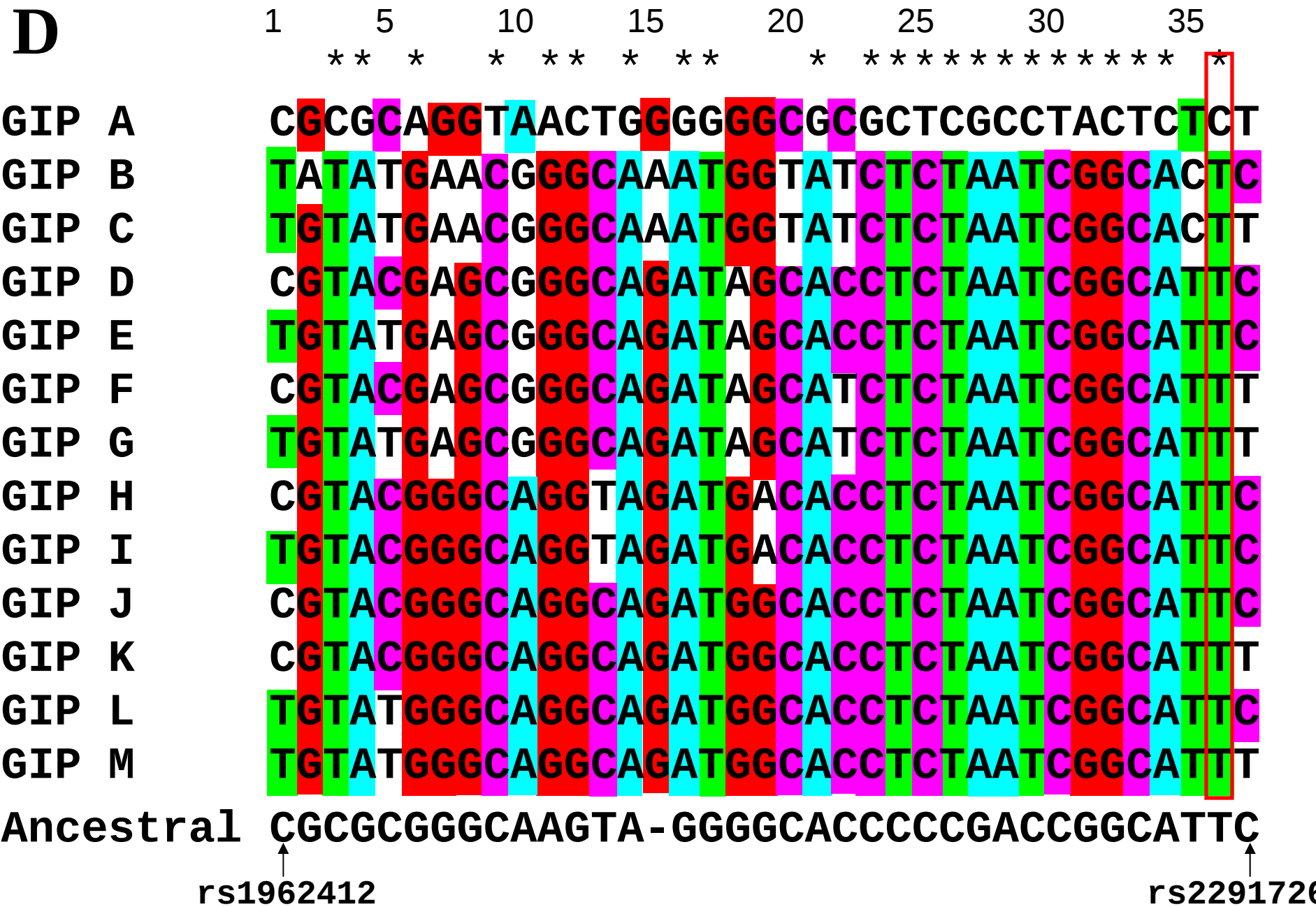
**ASN**

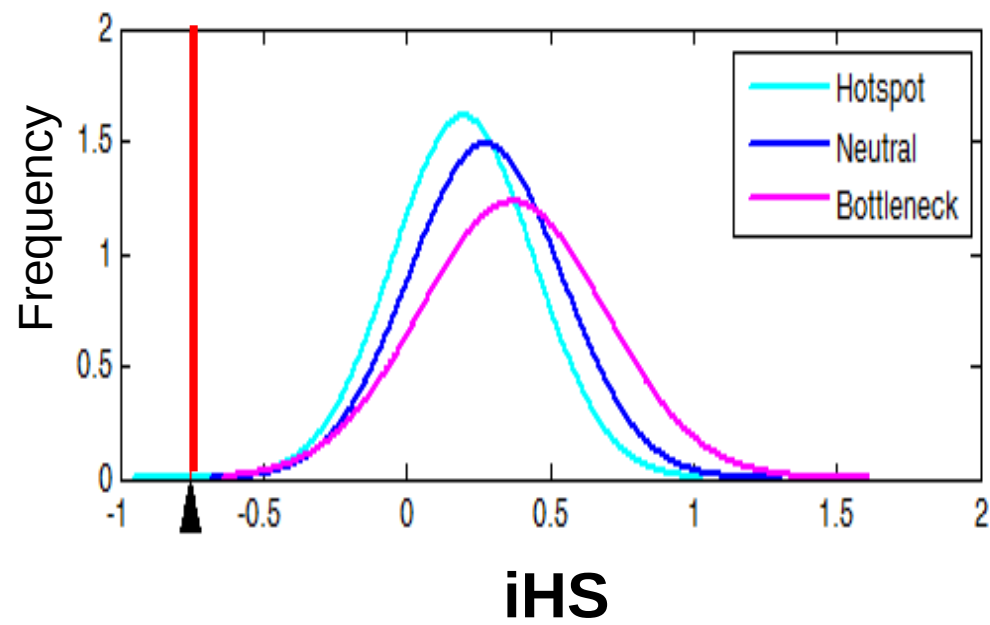
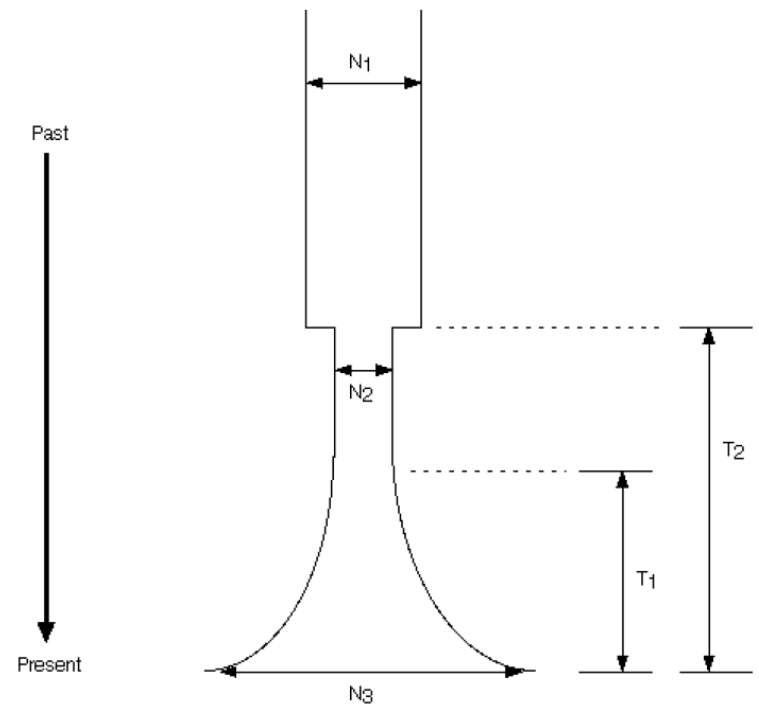


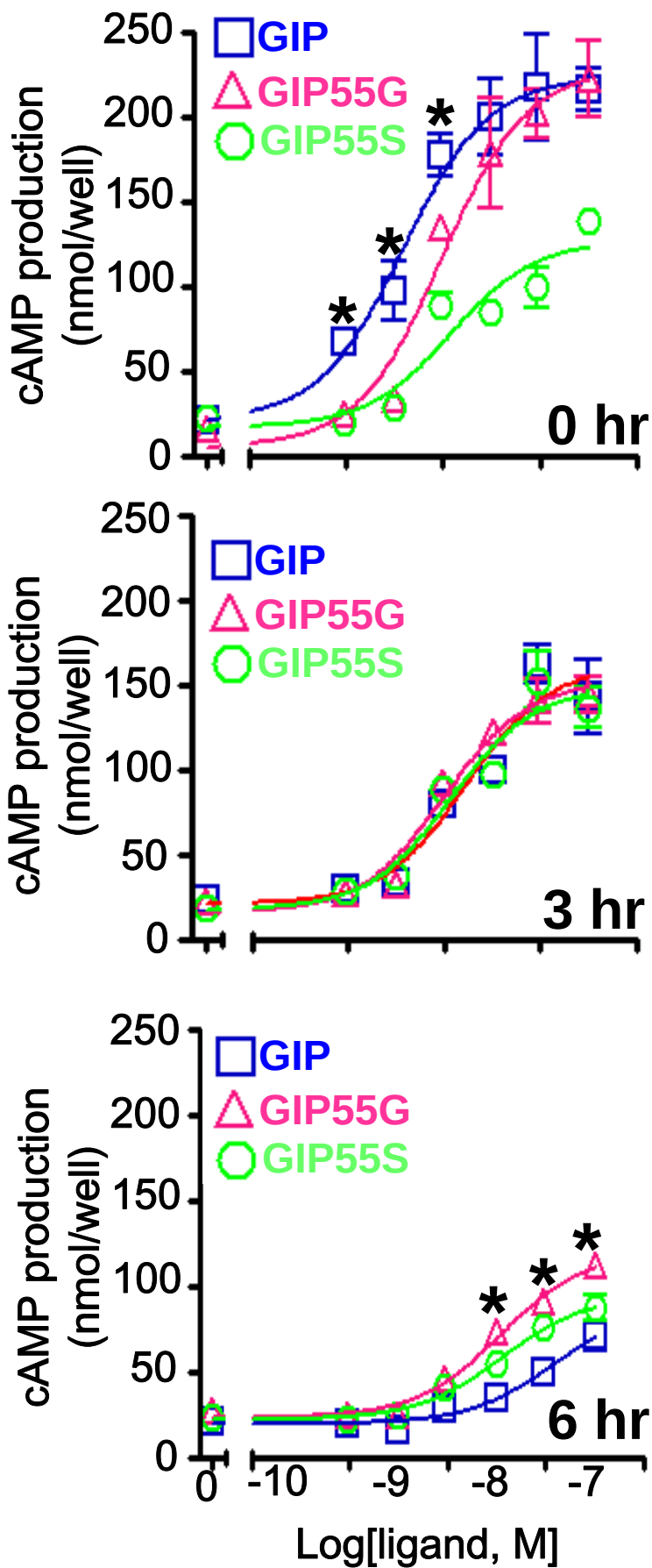
C



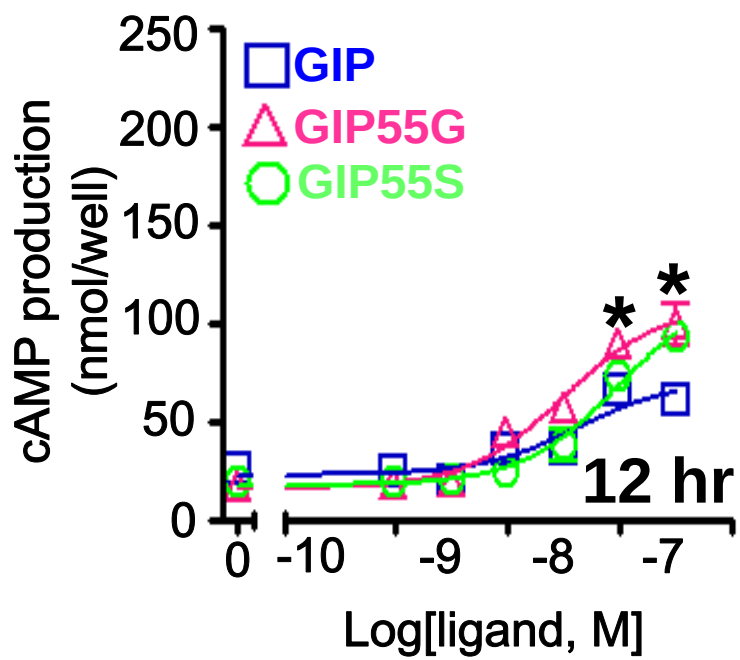
D



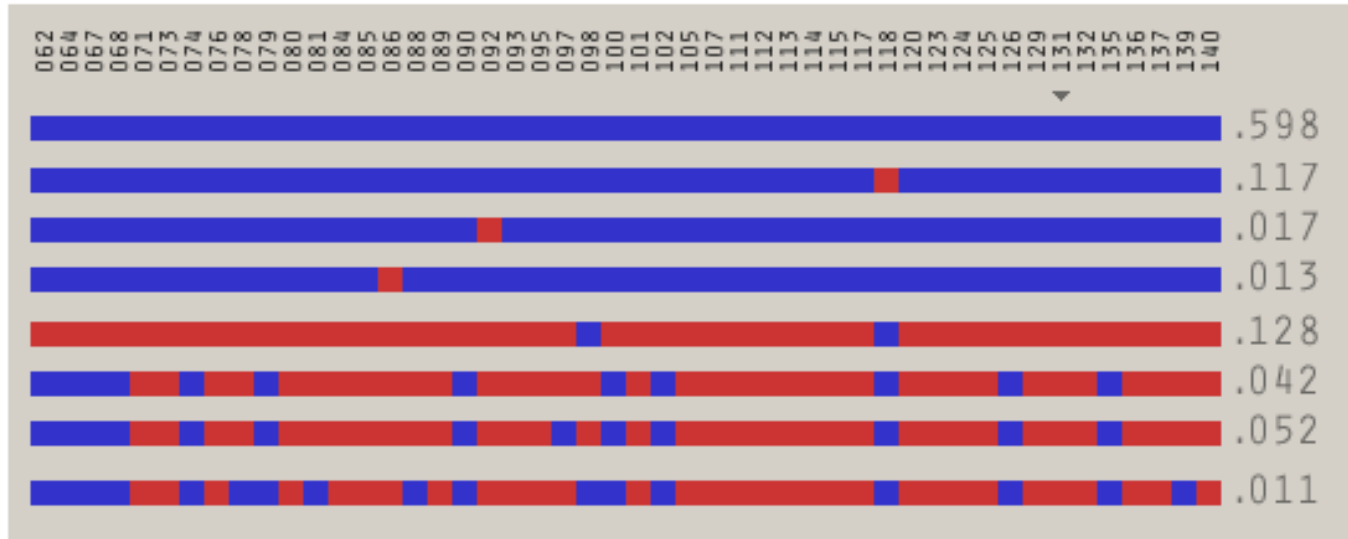
**A****B**



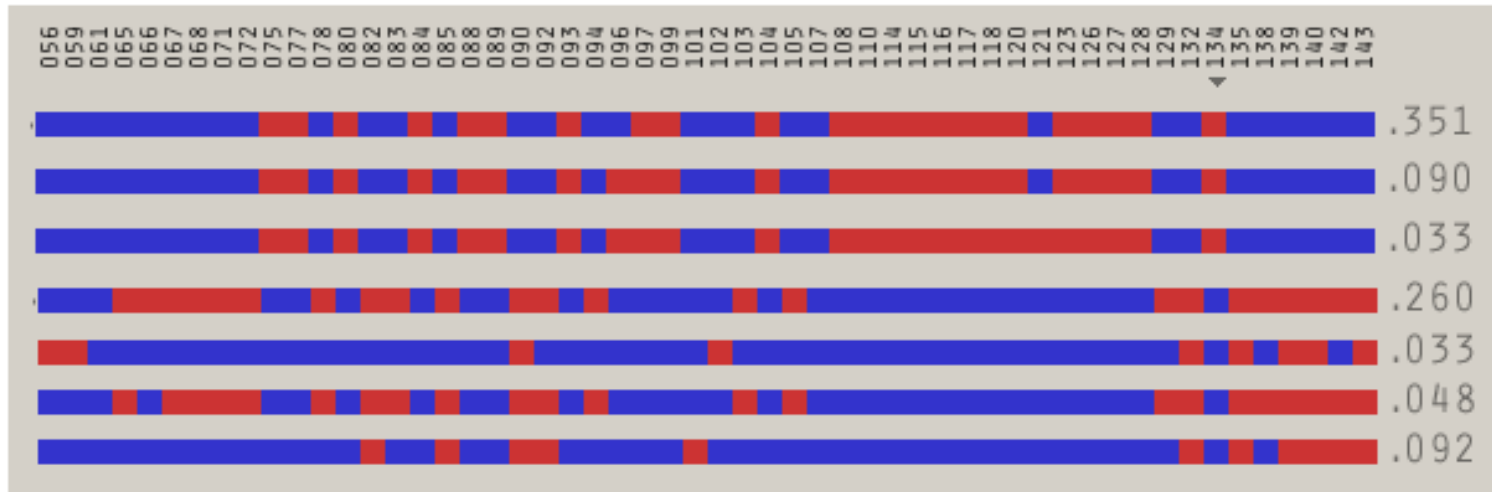
Sup. Fig. 5



## ASN LD block (91 kb)



## CEU LD block (97 kb)



**Supplementary Table 1. List of polypeptide cell surface receptors and their cognate ligand genes that were analyzed.**

| <b>Gene category</b> | <b>Gene Name</b> | <b>Gene category</b> | <b>Gene Name</b> |
|----------------------|------------------|----------------------|------------------|
| GPCR                 | ADCYAP1R1        | nonGPCR              | ACVR1            |
| GPCR                 | ADORA1           | nonGPCR              | ACVR1B           |
| GPCR                 | ADORA2A          | nonGPCR              | ACVR1C           |
| GPCR                 | ADORA2B          | nonGPCR              | ACVR2A           |
| GPCR                 | ADORA3           | nonGPCR              | ACVR2B           |
| GPCR                 | ADRA1A           | nonGPCR              | ACVRL1           |
| GPCR                 | ADRA1B           | nonGPCR              | ALK              |
| GPCR                 | ADRA1D           | nonGPCR              | AMH              |
| GPCR                 | ADRA2A           | nonGPCR              | AMHR2            |
| GPCR                 | ADRA2B           | nonGPCR              | ANGPT1           |
| GPCR                 | ADRA2C           | nonGPCR              | ANGPT2           |
| GPCR                 | ADRB1            | nonGPCR              | ANGPTL4          |
| GPCR                 | ADRB2            | nonGPCR              | AREG             |
| GPCR                 | ADRB3            | nonGPCR              | ARTN             |
| GPCR                 | AGTR1            | nonGPCR              | AXL              |
| GPCR                 | AGTR2            | nonGPCR              | BAMBI            |
| GPCR                 | APLNR            | nonGPCR              | BMP10            |
| GPCR                 | AVPR1A           | nonGPCR              | BMP15            |
| GPCR                 | AVPR1B           | nonGPCR              | BMP2             |
| GPCR                 | AVPR2            | nonGPCR              | BMP4             |
| GPCR                 | BAI1             | nonGPCR              | BMP6             |
| GPCR                 | BAI2             | nonGPCR              | BMP7             |
| GPCR                 | BAI3             | nonGPCR              | BMPR1A           |
| GPCR                 | BDKRB1           | nonGPCR              | BMPR1B           |
| GPCR                 | BDKRB2           | nonGPCR              | BMPR2            |
| GPCR                 | BRS3             | nonGPCR              | BOC              |
| GPCR                 | C3AR1            | nonGPCR              | BTC              |
| GPCR                 | C5AR1            | nonGPCR              | CD40             |
| GPCR                 | CALCR            | nonGPCR              | CD40LG           |
| GPCR                 | CALCRL           | nonGPCR              | CDON             |
| GPCR                 | CASR             | nonGPCR              | CER1             |
| GPCR                 | CCBP2            | nonGPCR              | CNTFR            |
| GPCR                 | CCKAR            | nonGPCR              | CRLF1            |
| GPCR                 | CCKBR            | nonGPCR              | CSF1R            |
| GPCR                 | CCR1             | nonGPCR              | CSF2RA           |
| GPCR                 | CCR10            | nonGPCR              | CSF2RB           |
| GPCR                 | CCR2             | nonGPCR              | CSF3R            |
| GPCR                 | CCR3             | nonGPCR              | DCC              |
| GPCR                 | CCR4             | nonGPCR              | DDR2             |
| GPCR                 | CCR5             | nonGPCR              | DHH              |
| GPCR                 | CCR6             | nonGPCR              | DLL1             |
| GPCR                 | CCR7             | nonGPCR              | DLL3             |
| GPCR                 | CCR8             | nonGPCR              | DLL4             |
| GPCR                 | CCR9             | nonGPCR              | EDA              |
| GPCR                 | CCRL1            | nonGPCR              | EDA2R            |
| GPCR                 | CCRL2            | nonGPCR              | EDAR             |
| GPCR                 | CD97             | nonGPCR              | EFNA1            |

|      |         |         |       |
|------|---------|---------|-------|
| GPCR | CELSR1  | nonGPCR | EFNA2 |
| GPCR | CELSR2  | nonGPCR | EFNA3 |
| GPCR | CELSR3  | nonGPCR | EFNA4 |
| GPCR | CHRM1   | nonGPCR | EFNA5 |
| GPCR | CHRM2   | nonGPCR | EFNB1 |
| GPCR | CHRM3   | nonGPCR | EFNB2 |
| GPCR | CHRM5   | nonGPCR | EFNB3 |
| GPCR | CMKLR1  | nonGPCR | EGF   |
| GPCR | CNR1    | nonGPCR | EGFR  |
| GPCR | CNR2    | nonGPCR | EPHA1 |
| GPCR | CRHR1   | nonGPCR | EPHA2 |
| GPCR | CRHR2   | nonGPCR | EPHA3 |
| GPCR | CX3CR1  | nonGPCR | EPHA4 |
| GPCR | CXCR1   | nonGPCR | EPHA5 |
| GPCR | CXCR2   | nonGPCR | EPHA6 |
| GPCR | CXCR3   | nonGPCR | EPHA7 |
| GPCR | CXCR4   | nonGPCR | EPHA8 |
| GPCR | CXCR5   | nonGPCR | EPHB1 |
| GPCR | CXCR6   | nonGPCR | EPHB2 |
| GPCR | CXCR7   | nonGPCR | EPHB3 |
| GPCR | CYSLTR1 | nonGPCR | EPHB4 |
| GPCR | CYSLTR2 | nonGPCR | EPHB6 |
| GPCR | DARC    | nonGPCR | EPOR  |
| GPCR | DRD1    | nonGPCR | ERBB2 |
| GPCR | DRD2    | nonGPCR | ERBB3 |
| GPCR | DRD3    | nonGPCR | ERBB4 |
| GPCR | DRD4    | nonGPCR | EREG  |
| GPCR | DRD5    | nonGPCR | FAS   |
| GPCR | EDNRA   | nonGPCR | FASLG |
| GPCR | EDNRB   | nonGPCR | FGF1  |
| GPCR | ELTD1   | nonGPCR | FGF10 |
| GPCR | EMR1    | nonGPCR | FGF11 |
| GPCR | EMR2    | nonGPCR | FGF12 |
| GPCR | EMR3    | nonGPCR | FGF13 |
| GPCR | EMR4P   | nonGPCR | FGF14 |
| GPCR | F2R     | nonGPCR | FGF16 |
| GPCR | F2RL1   | nonGPCR | FGF17 |
| GPCR | F2RL2   | nonGPCR | FGF18 |
| GPCR | F2RL3   | nonGPCR | FGF19 |
| GPCR | FFAR1   | nonGPCR | FGF2  |
| GPCR | FFAR2   | nonGPCR | FGF20 |
| GPCR | FFAR3   | nonGPCR | FGF21 |
| GPCR | FPR1    | nonGPCR | FGF22 |
| GPCR | FPR2    | nonGPCR | FGF23 |
| GPCR | FPR3    | nonGPCR | FGF3  |
| GPCR | FSHR    | nonGPCR | FGF4  |
| GPCR | FZD1    | nonGPCR | FGF5  |
| GPCR | FZD10   | nonGPCR | FGF6  |
| GPCR | FZD2    | nonGPCR | FGF7  |
| GPCR | FZD3    | nonGPCR | FGF8  |
| GPCR | FZD4    | nonGPCR | FGF9  |

|      |         |         |         |
|------|---------|---------|---------|
| GPCR | FZD5    | nonGPCR | FGFR1   |
| GPCR | FZD6    | nonGPCR | FGFR2   |
| GPCR | FZD7    | nonGPCR | FGFR3   |
| GPCR | FZD8    | nonGPCR | FGFR4   |
| GPCR | FZD9    | nonGPCR | FGFRL1  |
| GPCR | GABBR1  | nonGPCR | FIGF    |
| GPCR | GALR1   | nonGPCR | FLT1    |
| GPCR | GALR2   | nonGPCR | FLT3    |
| GPCR | GALR3   | nonGPCR | FLT4    |
| GPCR | GHRHR   | nonGPCR | GDF1    |
| GPCR | GHSR    | nonGPCR | GDF10   |
| GPCR | GIPR    | nonGPCR | GDF11   |
| GPCR | GLP1R   | nonGPCR | GDF15   |
| GPCR | GLP2R   | nonGPCR | GDF2    |
| GPCR | GNRHR   | nonGPCR | GDF3    |
| GPCR | GNRHR2  | nonGPCR | GDF5    |
| GPCR | GPER    | nonGPCR | GDF6    |
| GPCR | GPR1    | nonGPCR | GDF7    |
| GPCR | GPR101  | nonGPCR | GDF9    |
| GPCR | GPR109A | nonGPCR | GDNF    |
| GPCR | GPR109B | nonGPCR | GHR     |
| GPCR | GPR110  | nonGPCR | GREM1   |
| GPCR | GPR111  | nonGPCR | GREM2   |
| GPCR | GPR112  | nonGPCR | GUCA2A  |
| GPCR | GPR113  | nonGPCR | GUCA2B  |
| GPCR | GPR114  | nonGPCR | GUCY2C  |
| GPCR | GPR115  | nonGPCR | GUCY2D  |
| GPCR | GPR116  | nonGPCR | GUCY2F  |
| GPCR | GPR119  | nonGPCR | HBEGF   |
| GPCR | GPR12   | nonGPCR | IFNA1   |
| GPCR | GPR120  | nonGPCR | IFNAR1  |
| GPCR | GPR123  | nonGPCR | IFNAR2  |
| GPCR | GPR124  | nonGPCR | IFNB1   |
| GPCR | GPR125  | nonGPCR | IFNG    |
| GPCR | GPR126  | nonGPCR | IFNGR1  |
| GPCR | GPR128  | nonGPCR | IFNGR2  |
| GPCR | GPR132  | nonGPCR | IFNW1   |
| GPCR | GPR133  | nonGPCR | IGF1    |
| GPCR | GPR135  | nonGPCR | IGF1R   |
| GPCR | GPR139  | nonGPCR | IGF2    |
| GPCR | GPR141  | nonGPCR | IHH     |
| GPCR | GPR142  | nonGPCR | IL10    |
| GPCR | GPR144  | nonGPCR | IL10RA  |
| GPCR | GPR146  | nonGPCR | IL10RB  |
| GPCR | GPR15   | nonGPCR | IL11    |
| GPCR | GPR150  | nonGPCR | IL11RA  |
| GPCR | GPR151  | nonGPCR | IL12A   |
| GPCR | GPR152  | nonGPCR | IL12B   |
| GPCR | GPR160  | nonGPCR | IL12RB1 |
| GPCR | GPR161  | nonGPCR | IL12RB2 |
| GPCR | GPR17   | nonGPCR | IL13    |

|      |         |         |          |
|------|---------|---------|----------|
| GPCR | GPR171  | nonGPCR | IL13RA1  |
| GPCR | GPR173  | nonGPCR | IL13RA2  |
| GPCR | GPR174  | nonGPCR | IL15     |
| GPCR | GPR176  | nonGPCR | IL15RA   |
| GPCR | GPR18   | nonGPCR | IL17A    |
| GPCR | GPR182  | nonGPCR | IL17B    |
| GPCR | GPR183  | nonGPCR | IL17RA   |
| GPCR | GPR19   | nonGPCR | IL17RB   |
| GPCR | GPR20   | nonGPCR | IL17RC   |
| GPCR | GPR21   | nonGPCR | IL18     |
| GPCR | GPR22   | nonGPCR | IL18R1   |
| GPCR | GPR25   | nonGPCR | IL18RAP  |
| GPCR | GPR26   | nonGPCR | IL19     |
| GPCR | GPR27   | nonGPCR | IL1A     |
| GPCR | GPR3    | nonGPCR | IL1B     |
| GPCR | GPR31   | nonGPCR | IL1R1    |
| GPCR | GPR32   | nonGPCR | IL1R2    |
| GPCR | GPR34   | nonGPCR | IL1RAP   |
| GPCR | GPR35   | nonGPCR | IL1RAPL1 |
| GPCR | GPR37   | nonGPCR | IL1RL1   |
| GPCR | GPR37L1 | nonGPCR | IL2      |
| GPCR | GPR39   | nonGPCR | IL20     |
| GPCR | GPR4    | nonGPCR | IL20RA   |
| GPCR | GPR42   | nonGPCR | IL20RB   |
| GPCR | GPR44   | nonGPCR | IL21     |
| GPCR | GPR45   | nonGPCR | IL21R    |
| GPCR | GPR50   | nonGPCR | IL22     |
| GPCR | GPR51   | nonGPCR | IL22RA1  |
| GPCR | GPR52   | nonGPCR | IL22RA2  |
| GPCR | GPR55   | nonGPCR | IL23A    |
| GPCR | GPR56   | nonGPCR | IL23R    |
| GPCR | GPR6    | nonGPCR | IL24     |
| GPCR | GPR61   | nonGPCR | IL25     |
| GPCR | GPR62   | nonGPCR | IL28A    |
| GPCR | GPR63   | nonGPCR | IL28B    |
| GPCR | GPR64   | nonGPCR | IL28RA   |
| GPCR | GPR65   | nonGPCR | IL29     |
| GPCR | GPR68   | nonGPCR | IL2RA    |
| GPCR | GPR73   | nonGPCR | IL2RB    |
| GPCR | GPR75   | nonGPCR | IL2RG    |
| GPCR | GPR77   | nonGPCR | IL3      |
| GPCR | GPR78   | nonGPCR | IL31     |
| GPCR | GPR81   | nonGPCR | IL31RA   |
| GPCR | GPR82   | nonGPCR | IL3RA    |
| GPCR | GPR83   | nonGPCR | IL4      |
| GPCR | GPR84   | nonGPCR | IL4R     |
| GPCR | GPR85   | nonGPCR | IL5      |
| GPCR | GPR87   | nonGPCR | IL5RA    |
| GPCR | GPR88   | nonGPCR | IL6      |
| GPCR | GPR97   | nonGPCR | IL6R     |
| GPCR | GPR98   | nonGPCR | IL6ST    |

|      |        |         |        |
|------|--------|---------|--------|
| GPCR | GPRC5A | nonGPCR | IL7    |
| GPCR | GPRC5B | nonGPCR | IL7R   |
| GPCR | GPRC5C | nonGPCR | IL9    |
| GPCR | GPRC5D | nonGPCR | IL9R   |
| GPCR | GPRC6A | nonGPCR | INHA   |
| GPCR | GRM1   | nonGPCR | INHBA  |
| GPCR | GRM2   | nonGPCR | INHBB  |
| GPCR | GRM3   | nonGPCR | INHBC  |
| GPCR | GRM4   | nonGPCR | INS    |
| GPCR | GRM5   | nonGPCR | INSR   |
| GPCR | GRM6   | nonGPCR | INSRR  |
| GPCR | GRM7   | nonGPCR | JAG1   |
| GPCR | GRM8   | nonGPCR | JAG2   |
| GPCR | GRPR   | nonGPCR | KDR    |
| GPCR | HCRTR1 | nonGPCR | KIT    |
| GPCR | HCRTR2 | nonGPCR | KITLG  |
| GPCR | HRH1   | nonGPCR | LDLR   |
| GPCR | HRH2   | nonGPCR | LEPR   |
| GPCR | HRH3   | nonGPCR | LIFR   |
| GPCR | HRH4   | nonGPCR | LRP1   |
| GPCR | HTR1A  | nonGPCR | LRP10  |
| GPCR | HTR1B  | nonGPCR | LRP11  |
| GPCR | HTR1D  | nonGPCR | LRP12  |
| GPCR | HTR1E  | nonGPCR | LRP2   |
| GPCR | HTR1F  | nonGPCR | LRP3   |
| GPCR | HTR2A  | nonGPCR | LRP5   |
| GPCR | HTR2B  | nonGPCR | LRP6   |
| GPCR | HTR2C  | nonGPCR | LRP8   |
| GPCR | HTR4   | nonGPCR | LTBR   |
| GPCR | HTR5A  | nonGPCR | LTK    |
| GPCR | HTR6   | nonGPCR | MERTK  |
| GPCR | HTR7   | nonGPCR | MET    |
| GPCR | KISS1R | nonGPCR | MPL    |
| GPCR | LGR4   | nonGPCR | MST1R  |
| GPCR | LGR5   | nonGPCR | MUSK   |
| GPCR | LGR6   | nonGPCR | NBL1   |
| GPCR | LHCGR  | nonGPCR | NDP    |
| GPCR | LPAR1  | nonGPCR | NEO1   |
| GPCR | LPAR2  | nonGPCR | NGFR   |
| GPCR | LPAR3  | nonGPCR | NLGN1  |
| GPCR | LPAR4  | nonGPCR | NLGN2  |
| GPCR | LPAR5  | nonGPCR | NLGN3  |
| GPCR | LPAR6  | nonGPCR | NLGN4X |
| GPCR | LPHN1  | nonGPCR | NODAL  |
| GPCR | LPHN2  | nonGPCR | NOTCH1 |
| GPCR | LPHN3  | nonGPCR | NOTCH2 |
| GPCR | LTB4R  | nonGPCR | NOTCH3 |
| GPCR | LTB4R2 | nonGPCR | NPPA   |
| GPCR | MAS1   | nonGPCR | NPPB   |
| GPCR | MC1R   | nonGPCR | NPPC   |
| GPCR | MC2R   | nonGPCR | NPR1   |

|      |         |         |        |
|------|---------|---------|--------|
| GPCR | MC3R    | nonGPCR | NPR2   |
| GPCR | MC4R    | nonGPCR | NPR3   |
| GPCR | MC5R    | nonGPCR | NRG1   |
| GPCR | MCHR1   | nonGPCR | NRG2   |
| GPCR | MCHR2   | nonGPCR | NRG3   |
| GPCR | MLNR    | nonGPCR | NRTN   |
| GPCR | MRGPRD  | nonGPCR | NTN1   |
| GPCR | MRGPRE  | nonGPCR | NTN4   |
| GPCR | MRGPRF  | nonGPCR | NTNG1  |
| GPCR | MRGPRG  | nonGPCR | NTNG2  |
| GPCR | MRGPRX1 | nonGPCR | NTRK1  |
| GPCR | MRGPRX2 | nonGPCR | NTRK2  |
| GPCR | MRGPRX3 | nonGPCR | NTRK3  |
| GPCR | MRGPRX4 | nonGPCR | NXPH1  |
| GPCR | MTNR1A  | nonGPCR | NXPH2  |
| GPCR | MTNR1B  | nonGPCR | NXPH3  |
| GPCR | NMBR    | nonGPCR | NXPH4  |
| GPCR | NMUR1   | nonGPCR | OSMR   |
| GPCR | NMUR2   | nonGPCR | PDGFA  |
| GPCR | NPBWR1  | nonGPCR | PDGFB  |
| GPCR | NPBWR2  | nonGPCR | PDGFC  |
| GPCR | NPFFR1  | nonGPCR | PDGFD  |
| GPCR | NPFFR2  | nonGPCR | PDGFRA |
| GPCR | NPSR1   | nonGPCR | PDGFRB |
| GPCR | NPY1R   | nonGPCR | PGF    |
| GPCR | NPY2R   | nonGPCR | PRLR   |
| GPCR | NPY5R   | nonGPCR | PSPN   |
| GPCR | NTSR1   | nonGPCR | PTCH2  |
| GPCR | NTSR2   | nonGPCR | PTK7   |
| GPCR | OPN1LW  | nonGPCR | PTPRA  |
| GPCR | OPN1MW  | nonGPCR | PTPRD  |
| GPCR | OPN1SW  | nonGPCR | PTPRE  |
| GPCR | OPN3    | nonGPCR | PTPRF  |
| GPCR | OPN4    | nonGPCR | PTPRG  |
| GPCR | OPN5    | nonGPCR | PTPRH  |
| GPCR | OPRD1   | nonGPCR | PTPRJ  |
| GPCR | OPRK1   | nonGPCR | PTPRK  |
| GPCR | OPRL1   | nonGPCR | PTPRM  |
| GPCR | OPRM1   | nonGPCR | PTPRN  |
| GPCR | OXER1   | nonGPCR | PTPRN2 |
| GPCR | OXGR1   | nonGPCR | PTPRO  |
| GPCR | OXTR    | nonGPCR | PTPRS  |
| GPCR | P2RY1   | nonGPCR | PTPRT  |
| GPCR | P2RY10  | nonGPCR | PTPRU  |
| GPCR | P2RY12  | nonGPCR | PTPRZ1 |
| GPCR | P2RY13  | nonGPCR | RASSF8 |
| GPCR | P2RY14  | nonGPCR | RET    |
| GPCR | P2RY2   | nonGPCR | ROBO1  |
| GPCR | P2RY4   | nonGPCR | ROBO2  |
| GPCR | P2RY6   | nonGPCR | ROBO3  |
| GPCR | P2RY8   | nonGPCR | ROBO4  |

|             |         |         |           |
|-------------|---------|---------|-----------|
| GPCR        | PPYR1   | nonGPCR | ROR1      |
| GPCR        | PRLHR   | nonGPCR | ROR2      |
| GPCR        | PROKR2  | nonGPCR | ROS1      |
| GPCR        | PTAFR   | nonGPCR | RYK       |
| GPCR        | PTGDR   | nonGPCR | SHH       |
| GPCR        | PTGER1  | nonGPCR | SLIT1     |
| GPCR        | PTGER2  | nonGPCR | SLIT2     |
| GPCR        | PTGER3  | nonGPCR | SLIT3     |
| GPCR        | PTGER4  | nonGPCR | SORL1     |
| GPCR        | PTGFR   | nonGPCR | SOST      |
| GPCR        | PTGIR   | nonGPCR | SOSTDC1   |
| GPCR        | PTH1R   | nonGPCR | TDGF1     |
| GPCR        | PTH2R   | nonGPCR | TEK       |
| GPCR        | QRFPR   | nonGPCR | TFG       |
| GPCR        | RGR     | nonGPCR | TGFA      |
| GPCR        | RHO     | nonGPCR | TGFB1     |
| GPCR        | RRH     | nonGPCR | TGFB2     |
| GPCR        | RXFP1   | nonGPCR | TGFB3     |
| GPCR        | RXFP2   | nonGPCR | TGFBR1    |
| GPCR        | RXFP3   | nonGPCR | TGFBR2    |
| GPCR        | RXFP4   | nonGPCR | TIE1      |
| GPCR        | S1PR1   | nonGPCR | TLR1      |
| GPCR        | S1PR2   | nonGPCR | TLR10     |
| GPCR        | S1PR3   | nonGPCR | TLR2      |
| GPCR        | S1PR4   | nonGPCR | TLR3      |
| GPCR        | S1PR5   | nonGPCR | TLR4      |
| GPCR        | SCTR    | nonGPCR | TLR5      |
| GPCR        | SMO     | nonGPCR | TLR6      |
| GPCR        | SSTR1   | nonGPCR | TLR7      |
| GPCR        | SSTR2   | nonGPCR | TLR8      |
| GPCR        | SSTR3   | nonGPCR | TLR9      |
| GPCR        | SSTR4   | nonGPCR | TNFRSF10A |
| GPCR        | SSTR5   | nonGPCR | TNFRSF10B |
| GPCR        | SUCNR1  | nonGPCR | TNFRSF10C |
| GPCR        | TAAAR1  | nonGPCR | TNFRSF10D |
| GPCR        | TAAAR2  | nonGPCR | TNFRSF11A |
| GPCR        | TAAAR5  | nonGPCR | TNFRSF11B |
| GPCR        | TAAAR6  | nonGPCR | TNFRSF12A |
| GPCR        | TAAAR8  | nonGPCR | TNFRSF13B |
| GPCR        | TACR1   | nonGPCR | TNFRSF13C |
| GPCR        | TACR2   | nonGPCR | TNFRSF14  |
| GPCR        | TACR3   | nonGPCR | TNFRSF17  |
| GPCR        | TBXA2R  | nonGPCR | TNFRSF18  |
| GPCR        | TRHR    | nonGPCR | TNFRSF19  |
| GPCR        | TSHR    | nonGPCR | TNFRSF1A  |
| GPCR        | UTS2R   | nonGPCR | TNFRSF1B  |
| GPCR        | VIPR1   | nonGPCR | TNFRSF21  |
| GPCR        | VIPR2   | nonGPCR | TNFRSF25  |
| GPCR        | XCR1    | nonGPCR | TNFRSF4   |
| GPCR ligand | ADCYAP1 | nonGPCR | TNFRSF6B  |
| GPCR ligand | ADM     | nonGPCR | TNFRSF8   |

|             |        |         |          |
|-------------|--------|---------|----------|
| GPCR ligand | ADM2   | nonGPCR | TNFRSF9  |
| GPCR ligand | AGT    | nonGPCR | TNFSF10  |
| GPCR ligand | APLN   | nonGPCR | TNFSF11  |
| GPCR ligand | AVP    | nonGPCR | TNFSF12  |
| GPCR ligand | CALCA  | nonGPCR | TNFSF13  |
| GPCR ligand | CCK    | nonGPCR | TNFSF13B |
| GPCR ligand | CCL1   | nonGPCR | TNFSF14  |
| GPCR ligand | CCL11  | nonGPCR | TNFSF15  |
| GPCR ligand | CCL13  | nonGPCR | TNFSF18  |
| GPCR ligand | CCL14  | nonGPCR | TNFSF4   |
| GPCR ligand | CCL15  | nonGPCR | TNFSF8   |
| GPCR ligand | CCL16  | nonGPCR | TNFSF9   |
| GPCR ligand | CCL17  | nonGPCR | TRAF2    |
| GPCR ligand | CCL18  | nonGPCR | TRAF3    |
| GPCR ligand | CCL19  | nonGPCR | TRAF5    |
| GPCR ligand | CCL2   | nonGPCR | TYRO3    |
| GPCR ligand | CCL20  | nonGPCR | UNC5A    |
| GPCR ligand | CCL21  | nonGPCR | UNC5B    |
| GPCR ligand | CCL22  | nonGPCR | UNC5C    |
| GPCR ligand | CCL23  | nonGPCR | UNC5D    |
| GPCR ligand | CCL24  | nonGPCR | VEGFC    |
| GPCR ligand | CCL26  | nonGPCR | VLDLR    |
| GPCR ligand | CCL27  | nonGPCR | WNT1     |
| GPCR ligand | CCL3   | nonGPCR | WNT11    |
| GPCR ligand | CCL4   | nonGPCR | WNT3     |
| GPCR ligand | CCL5   | nonGPCR | WNT4     |
| GPCR ligand | CCL7   | nonGPCR | WNT5A    |
| GPCR ligand | CCL8   | nonGPCR | WNT7A    |
| GPCR ligand | CGA    | nonGPCR | WNT7B    |
| GPCR ligand | CRH    |         |          |
| GPCR ligand | CXCL1  |         |          |
| GPCR ligand | CXCL12 |         |          |
| GPCR ligand | CXCL13 |         |          |
| GPCR ligand | CXCL14 |         |          |
| GPCR ligand | CXCL16 |         |          |
| GPCR ligand | CXCL2  |         |          |
| GPCR ligand | CXCL3  |         |          |
| GPCR ligand | CXCL5  |         |          |
| GPCR ligand | CXCL6  |         |          |
| GPCR ligand | CXCL9  |         |          |
| GPCR ligand | EDN1   |         |          |
| GPCR ligand | EDN2   |         |          |
| GPCR ligand | EDN3   |         |          |
| GPCR ligand | FSHB   |         |          |
| GPCR ligand | GAL    |         |          |
| GPCR ligand | GALP   |         |          |
| GPCR ligand | GAST   |         |          |
| GPCR ligand | GCG    |         |          |
| GPCR ligand | GHRH   |         |          |
| GPCR ligand | GHRL   |         |          |
| GPCR ligand | GIP    |         |          |

|             |       |
|-------------|-------|
| GPCR ligand | GNRH1 |
| GPCR ligand | GNRH2 |
| GPCR ligand | GPHB5 |
| GPCR ligand | GRP   |
| GPCR ligand | HCRT  |
| GPCR ligand | IAPP  |
| GPCR ligand | IL8   |
| GPCR ligand | INSL5 |
| GPCR ligand | KISS1 |
| GPCR ligand | KNG1  |
| GPCR ligand | LHB   |
| GPCR ligand | MLN   |
| GPCR ligand | NMB   |
| GPCR ligand | NMS   |
| GPCR ligand | NMU   |
| GPCR ligand | NPB   |
| GPCR ligand | NPFF  |
| GPCR ligand | NPS   |
| GPCR ligand | NPVF  |
| GPCR ligand | NPW   |
| GPCR ligand | NPY   |
| GPCR ligand | NTS   |
| GPCR ligand | OXT   |
| GPCR ligand | PDYN  |
| GPCR ligand | PENK  |
| GPCR ligand | PF4V1 |
| GPCR ligand | PMCH  |
| GPCR ligand | PNOC  |
| GPCR ligand | POMC  |
| GPCR ligand | PPBP  |
| GPCR ligand | PRLH  |
| GPCR ligand | PROK1 |
| GPCR ligand | PROK2 |
| GPCR ligand | PTH   |
| GPCR ligand | PTH2  |
| GPCR ligand | PTHLH |
| GPCR ligand | PYY   |
| GPCR ligand | QRFP  |
| GPCR ligand | RLN2  |
| GPCR ligand | RLN3  |
| GPCR ligand | SCT   |
| GPCR ligand | SST   |
| GPCR ligand | TAC1  |
| GPCR ligand | TAC3  |
| GPCR ligand | TAC4  |
| GPCR ligand | TRH   |
| GPCR ligand | TSHB  |
| GPCR ligand | UCN   |
| GPCR ligand | UCN2  |
| GPCR ligand | UCN3  |
| GPCR ligand | UTS2  |

GPCR ligand  
GPCR ligand

UTS2D  
VIP

**Supplementary Table 2.** List of coding SNPs with high  $F_{ST}$  ( $> 0.5$ ) in human GPCRs and their cognate ligand genes.

| <b>F<sub>st</sub></b> | <b>chr</b> | <b>position</b> | <b>rsid</b>      | <b>gene</b> | <b>group</b>       |
|-----------------------|------------|-----------------|------------------|-------------|--------------------|
| <b>0.992</b>          | 4          | 9393463         | rs2227852        | DRD5        | ceu_asn_nsy        |
| <b>0.992</b>          | 4          | 9393463         | rs2227852        | DRD5        | ceu_yri_nsy        |
| <b>0.908</b>          | 1          | 157441978       | rs12075          | DARC        | asn_yri_nsy        |
| <b>0.834</b>          | 22         | 45140161        | rs12165943       | CELSR1      | asn_yri_nsy        |
| <b>0.776</b>          | 12         | 12952561        | rs2075288        | GPRC5A      | asn_yri_syn        |
| <b>0.759</b>          | 17         | 31364397        | rs1003645        | CCL23       | ceu_yri_nsy        |
| <b>0.758</b>          | 22         | 45166358        | rs6008794        | CELSR1      | asn_yri_nsy        |
| <b>0.749</b>          | 22         | 45164979        | rs4044210        | CELSR1      | asn_yri_nsy        |
| <b>0.735</b>          | 2          | 237154643       | rs1045879        | CXCR7       | asn_yri_syn        |
| <b>0.731</b>          | 7          | 124174610       | rs724356         | GPR37       | asn_yri_syn        |
| <b>0.720</b>          | <b>17</b>  | <b>44394131</b> | <b>rs2291725</b> | <b>GIP</b>  | <b>asn_yri_nsy</b> |
| <b>0.704</b>          | 16         | 88513655        | rs885479         | MC1R        | asn_yri_nsy        |
| <b>0.697</b>          | 22         | 45142335        | rs7285515        | CELSR1      | asn_yri_syn        |
| <b>0.689</b>          | 10         | 86002693        | rs1042454        | RGR         | asn_yri_syn        |
| <b>0.676</b>          | 22         | 45159185        | rs6007897        | CELSR1      | asn_yri_nsy        |
| <b>0.649</b>          | 9          | 132758990       | rs3847193        | QRFP        | asn_yri_syn        |
| <b>0.645</b>          | 10         | 85994853        | rs2279227        | RGR         | ceu_yri_syn        |
| <b>0.631</b>          | 19         | 6877378         | rs4807916        | EMR1        | asn_yri_nsy        |
| <b>0.628</b>          | 9          | 100380122       | rs2808536        | GPR51       | asn_yri_syn        |
| <b>0.628</b>          | 10         | 85994853        | rs2279227        | RGR         | asn_yri_syn        |
| <b>0.613</b>          | 8          | 54304710        | rs702764         | OPRK1       | asn_yri_syn        |
| <b>0.612</b>          | 6          | 146534159       | rs9485052        | GRM1        | ceu_yri_nsy        |
| <b>0.603</b>          | 2          | 48774879        | rs2293275        | LHCGR       | asn_yri_nsy        |
| <b>0.600</b>          | 19         | 6848464         | rs330880         | EMR1        | ceu_yri_nsy        |
| <b>0.596</b>          | 10         | 86002693        | rs1042454        | RGR         | ceu_yri_syn        |
| <b>0.593</b>          | 2          | 48769375        | rs11125179       | LHCGR       | asn_yri_syn        |
| <b>0.592</b>          | 19         | 3546794         | rs4523           | TBXA2R      | asn_yri_syn        |
| <b>0.589</b>          | 16         | 88513655        | rs885479         | MC1R        | ceu_asn_nsy        |
| <b>0.586</b>          | 7          | 92893689        | rs1801197        | CALCR       | ceu_asn_nsy        |
| <b>0.576</b>          | 12         | 107210138       | rs1057401        | CMKLR1      | asn_yri_syn        |
| <b>0.570</b>          | 6          | 70127894        | rs913543         | BAI3        | asn_yri_syn        |
| <b>0.562</b>          | 22         | 45140161        | rs12165943       | CELSR1      | ceu_yri_nsy        |
| <b>0.557</b>          | 12         | 130188688       | rs7302341        | GPR133      | asn_yri_syn        |
| <b>0.555</b>          | 3          | 45962984        | rs2234355        | CXCR6       | asn_yri_nsy        |
| <b>0.549</b>          | 2          | 132891234       | rs2241764        | GPR39       | ceu_yri_nsy        |
| <b>0.548</b>          | 8          | 54304710        | rs702764         | OPRK1       | ceu_yri_syn        |
| <b>0.543</b>          | 2          | 231483541       | rs1992186        | GPR55       | asn_yri_syn        |

|              |    |           |            |         |             |
|--------------|----|-----------|------------|---------|-------------|
| <b>0.543</b> | 6  | 146534159 | rs9485052  | GRM1    | asn_yri_nsy |
| <b>0.539</b> | 6  | 46940772  | rs614826   | GPR116  | ceu_yri_syn |
| <b>0.539</b> | 3  | 45962984  | rs2234355  | CXCR6   | ceu_yri_nsy |
| <b>0.537</b> | 3  | 115373505 | rs6280     | DRD3    | asn_yri_nsy |
| <b>0.535</b> | 17 | 31364397  | rs1003645  | CCL23   | asn_yri_nsy |
| <b>0.532</b> | 11 | 66975485  | rs949252   | GPR152  | asn_yri_syn |
| <b>0.529</b> | 22 | 45142335  | rs7285515  | CELSR1  | ceu_yri_syn |
| <b>0.528</b> | 11 | 66975485  | rs949252   | GPR152  | ceu_yri_syn |
| <b>0.520</b> | 11 | 18115569  | rs12291017 | MRGPRX3 | asn_yri_nsy |
| <b>0.518</b> | 11 | 66976751  | rs1638560  | GPR152  | ceu_yri_syn |
| <b>0.513</b> | 7  | 158543995 | rs2098349  | VIPR2   | asn_yri_syn |
| <b>0.513</b> | 2  | 100463392 | rs1519654  | NMS     | ceu_asn_syn |

**Supplementary Table 3.** List of coding SNPs with high  $F_{ST}$  ( $> 0.5$ ) in human nonGPCR receptor and ligand genes.

| <b>F<sub>st</sub></b> | <b>chr</b> | <b>position</b> | <b>rsid</b> | <b>gene</b> | <b>group</b> |
|-----------------------|------------|-----------------|-------------|-------------|--------------|
| <b>0.874</b>          | 2          | 108880033       | rs3827760   | EDAR        | ceu_asn_nsy  |
| <b>0.874</b>          | 2          | 108880033       | rs3827760   | EDAR        | asn_yri_nsy  |
| <b>0.841</b>          | 9          | 14712477        | rs3747532   | CER1        | asn_yri_nsy  |
| <b>0.769</b>          | 16         | 27281901        | rs1801275   | IL4R        | asn_yri_nsy  |
| <b>0.769</b>          | 19         | 6326831         | rs2304198   | PSPN        | ceu_yri_syn  |
| <b>0.749</b>          | 8          | 32572900        | rs3924999   | NRG1        | asn_yri_nsy  |
| <b>0.748</b>          | 19         | 60571684        | rs1126757   | IL11        | asn_yri_syn  |
| <b>0.738</b>          | 4          | 96475639        | rs4699423   | UNC5C       | asn_yri_syn  |
| <b>0.731</b>          | 8          | 23115269        | rs4871857   | TNFRSF10A   | asn_yri_nsy  |
| <b>0.723</b>          | 8          | 23116201        | rs6557634   | TNFRSF10A   | asn_yri_nsy  |
| <b>0.706</b>          | 17         | 35137563        | rs1058808   | ERBB2       | ceu_yri_nsy  |
| <b>0.692</b>          | 13         | 27781061        | rs7993418   | FLT1        | asn_yri_syn  |
| <b>0.686</b>          | 14         | 102411802       | rs1131877   | TRAF3       | ceu_yri_nsy  |
| <b>0.683</b>          | 16         | 27281473        | rs2234900   | IL4R        | asn_yri_syn  |
| <b>0.676</b>          | 1          | 155115619       | rs6337      | NTRK1       | ceu_asn_syn  |
| <b>0.661</b>          | 19         | 44480955        | rs30461     | IL29        | asn_yri_nsy  |
| <b>0.661</b>          | 12         | 14685329        | rs10772800  | GUCY2C      | asn_yri_syn  |
| <b>0.659</b>          | 12         | 14685329        | rs10772800  | GUCY2C      | ceu_yri_syn  |
| <b>0.657</b>          | 1          | 65809029        | rs1137100   | LEPR        | asn_yri_nsy  |
| <b>0.630</b>          | 16         | 27281901        | rs1801275   | IL4R        | ceu_yri_nsy  |
| <b>0.625</b>          | 2          | 29794033        | rs2246745   | ALK         | asn_yri_syn  |
| <b>0.618</b>          | 16         | 27281473        | rs2234900   | IL4R        | ceu_yri_syn  |
| <b>0.606</b>          | 2          | 169711678       | rs4667591   | LRP2        | ceu_yri_nsy  |
| <b>0.606</b>          | 3          | 53858762        | rs1025689   | IL17RB      | ceu_yri_syn  |
| <b>0.605</b>          | 1          | 53565239        | rs3820198   | LRP8        | ceu_yri_nsy  |
| <b>0.576</b>          | 19         | 44480955        | rs30461     | IL29        | ceu_yri_nsy  |
| <b>0.574</b>          | 3          | 38499746        | rs1046048   | ACVR2B      | ceu_yri_syn  |
| <b>0.571</b>          | 6          | 137367540       | rs1555498   | IL20RA      | asn_yri_nsy  |
| <b>0.569</b>          | 2          | 102334507       | rs4988957   | IL1RL1      | asn_yri_syn  |
| <b>0.569</b>          | 2          | 102334717       | rs4988958   | IL1RL1      | asn_yri_syn  |
| <b>0.569</b>          | 2          | 102334788       | rs10192157  | IL1RL1      | asn_yri_nsy  |
| <b>0.569</b>          | 2          | 102334794       | rs10206753  | IL1RL1      | asn_yri_nsy  |
| <b>0.569</b>          | 2          | 102334439       | rs4988956   | IL1RL1      | asn_yri_nsy  |
| <b>0.559</b>          | 4          | 96325345        | rs2289043   | UNC5C       | ceu_yri_nsy  |
| <b>0.558</b>          | 8          | 23115269        | rs4871857   | TNFRSF10A   | ceu_asn_nsy  |
| <b>0.558</b>          | 8          | 23116201        | rs6557634   | TNFRSF10A   | ceu_asn_nsy  |
| <b>0.557</b>          | 2          | 102334644       | rs10204137  | IL1RL1      | asn_yri_nsy  |

|              |    |           |            |          |             |
|--------------|----|-----------|------------|----------|-------------|
| <b>0.555</b> | 1  | 53565239  | rs3820198  | LRP8     | asn_yri_nsy |
| <b>0.555</b> | 16 | 27281373  | rs1805011  | IL4R     | asn_yri_nsy |
| <b>0.554</b> | 9  | 138517528 | rs10521    | NOTCH1   | ceu_asn_syn |
| <b>0.547</b> | 1  | 155115619 | rs6337     | NTRK1    | ceu_yri_syn |
| <b>0.541</b> | 20 | 10568386  | rs1051419  | JAG1     | asn_yri_syn |
| <b>0.541</b> | 6  | 137367540 | rs1555498  | IL20RA   | ceu_yri_nsy |
| <b>0.539</b> | 8  | 35703234  | rs6983275  | UNC5D    | ceu_yri_syn |
| <b>0.537</b> | 20 | 61796554  | rs3208008  | TNFRSF6B | asn_yri_nsy |
| <b>0.537</b> | 3  | 136153214 | rs7644369  | EPHB1    | asn_yri_syn |
| <b>0.535</b> | 8  | 35703357  | rs6996645  | UNC5D    | ceu_yri_syn |
| <b>0.530</b> | 11 | 48122843  | rs4752904  | PTPRJ    | ceu_yri_nsy |
| <b>0.529</b> | 1  | 29503042  | rs2295061  | PTPRU    | ceu_asn_syn |
| <b>0.527</b> | 16 | 27281416  | rs2234898  | IL4R     | asn_yri_syn |
| <b>0.523</b> | 7  | 116223258 | rs2023748  | MET      | asn_yri_syn |
| <b>0.523</b> | 7  | 116223004 | rs41736    | MET      | asn_yri_syn |
| <b>0.523</b> | 7  | 116223333 | rs41737    | MET      | asn_yri_syn |
| <b>0.523</b> | 2  | 108880086 | rs12623957 | EDAR     | asn_yri_syn |
| <b>0.520</b> | 3  | 13871285  | rs12639607 | WNT7A    | asn_yri_syn |
| <b>0.514</b> | 2  | 29794033  | rs2246745  | ALK      | ceu_yri_syn |
| <b>0.514</b> | 17 | 7259120   | rs2241233  | NLGN2    | asn_yri_syn |
| <b>0.508</b> | 14 | 102411802 | rs1131877  | TRAF3    | asn_yri_nsy |
| <b>0.507</b> | 20 | 2893759   | rs1178027  | PTPRA    | ceu_yri_nsy |

# Supplementary Table 4.

List of genotyped single nucleotide polymorphisms (SNPs) from 44246961 to 44542055 on chromosome 17.

| #  | Name       | Position | ObsHET | PredHET | HWPval | %Geno | FamTrio | MendErr | MAF   | Alleles |
|----|------------|----------|--------|---------|--------|-------|---------|---------|-------|---------|
| 1  | rs674310   | 44246961 | 0.483  | 0.5     | 0.9497 | 100.0 | 0       | 0       | 0.492 | C:G     |
| 2  | rs674755   | 44247046 | 0.483  | 0.5     | 0.9497 | 100.0 | 0       | 0       | 0.492 | A:T     |
| 3  | rs7208074  | 44249072 | 0.467  | 0.473   | 1.0    | 100.0 | 0       | 0       | 0.383 | G:A     |
| 4  | rs532154   | 44251363 | 0.467  | 0.499   | 0.752  | 100.0 | 0       | 0       | 0.483 | A:G     |
| 5  | rs639679   | 44254253 | 0.267  | 0.278   | 1.0    | 100.0 | 0       | 0       | 0.167 | A:G     |
| 6  | rs606911   | 44263227 | 0.267  | 0.278   | 1.0    | 100.0 | 0       | 0       | 0.167 | G:A     |
| 7  | rs8076178  | 44263279 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:C     |
| 8  | rs12450440 | 44266352 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | A:T     |
| 9  | rs8080446  | 44267435 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | A:G     |
| 10 | rs8078984  | 44267550 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:A     |
| 11 | rs8078992  | 44267572 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:T     |
| 12 | rs7207087  | 44272952 | 0.35   | 0.45    | 0.1338 | 100.0 | 0       | 0       | 0.342 | C:G     |
| 13 | rs612720   | 44273203 | 0.45   | 0.5     | 0.561  | 100.0 | 0       | 0       | 0.492 | G:A     |
| 14 | rs497270   | 44273773 | 0.267  | 0.278   | 1.0    | 100.0 | 0       | 0       | 0.167 | A:G     |
| 15 | rs12945070 | 44277734 | 0.367  | 0.455   | 0.1974 | 100.0 | 0       | 0       | 0.35  | G:C     |
| 16 | rs533842   | 44278383 | 0.267  | 0.278   | 1.0    | 100.0 | 0       | 0       | 0.167 | G:A     |
| 17 | rs12948015 | 44279979 | 0.483  | 0.493   | 1.0    | 100.0 | 0       | 0       | 0.442 | G:T     |
| 18 | rs3744604  | 44280858 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:A     |
| 19 | rs2303015  | 44284907 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | T:C     |
| 20 | rs8074034  | 44287297 | 0.483  | 0.493   | 1.0    | 100.0 | 0       | 0       | 0.442 | A:G     |
| 21 | rs1422645  | 44294657 | 0.35   | 0.45    | 0.1338 | 100.0 | 0       | 0       | 0.342 | C:G     |
| 22 | rs11434    | 44296244 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:A     |
| 23 | rs7222365  | 44296816 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | C:T     |
| 24 | rs11654595 | 44297999 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | A:G     |
| 25 | rs12450692 | 44300502 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | C:T     |
| 26 | rs12450563 | 44300565 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:C     |
| 27 | rs12453671 | 44300832 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | A:T     |
| 28 | rs882150   | 44301645 | 0.483  | 0.493   | 1.0    | 100.0 | 0       | 0       | 0.442 | A:G     |
| 29 | rs12449856 | 44301996 | 0.133  | 0.124   | 1.0    | 100.0 | 0       | 0       | 0.067 | C:T     |
| 30 | rs8078826  | 44302434 | 0.483  | 0.493   | 1.0    | 100.0 | 0       | 0       | 0.442 | A:G     |
| 31 | rs2411377  | 44303217 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:A     |
| 32 | rs318102   | 44305495 | 0.45   | 0.5     | 0.561  | 100.0 | 0       | 0       | 0.492 | G:C     |
| 33 | rs178467   | 44305868 | 0.267  | 0.278   | 1.0    | 100.0 | 0       | 0       | 0.167 | A:G     |
| 34 | rs8079874  | 44305974 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | C:T     |
| 35 | rs1990936  | 44307486 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:A     |
| 36 | rs9904761  | 44311829 | 0.367  | 0.455   | 0.1974 | 100.0 | 0       | 0       | 0.35  | C:G     |
| 37 | rs4793990  | 44315759 | 0.367  | 0.455   | 0.1974 | 100.0 | 0       | 0       | 0.35  | A:G     |

| #  | Name       | Position | ObsHET | PredHET | HWpval | %Geno | FamTrio | MendErr | MAF   | Alleles |
|----|------------|----------|--------|---------|--------|-------|---------|---------|-------|---------|
| 38 | rs1962412  | 44325258 | 0.4    | 0.455   | 0.4682 | 100.0 | 0       | 0       | 0.35  | C:T     |
| 39 | rs1800632  | 44325508 | 0.4    | 0.444   | 0.5758 | 100.0 | 0       | 0       | 0.333 | G:A     |
| 40 | rs318095   | 44329733 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | T:C     |
| 41 | rs962272   | 44333282 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | A:G     |
| 42 | rs962273   | 44333352 | 0.4    | 0.455   | 0.4682 | 100.0 | 0       | 0       | 0.35  | C:T     |
| 43 | rs4294857  | 44338390 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | G:A     |
| 44 | rs999474   | 44342664 | 0.467  | 0.498   | 0.771  | 100.0 | 0       | 0       | 0.467 | G:A     |
| 45 | rs999475   | 44343043 | 0.4    | 0.455   | 0.4682 | 100.0 | 0       | 0       | 0.35  | G:A     |
| 46 | rs46522    | 44343596 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | C:T     |
| 47 | rs9894220  | 44344153 | 0.467  | 0.498   | 0.771  | 100.0 | 0       | 0       | 0.467 | A:G     |
| 48 | rs318090   | 44346751 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | G:A     |
| 49 | rs12453374 | 44349845 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | G:C     |
| 50 | rs1058018  | 44355250 | 0.467  | 0.498   | 0.771  | 100.0 | 0       | 0       | 0.467 | T:C     |
| 51 | rs4793991  | 44356800 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | A:G     |
| 52 | rs11079842 | 44357761 | 0.4    | 0.455   | 0.4682 | 100.0 | 0       | 0       | 0.35  | G:A     |
| 53 | rs15563    | 44360192 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | A:G     |
| 54 | rs1057897  | 44360508 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | T:G     |
| 55 | rs12941604 | 44362012 | 0.217  | 0.193   | 0.9665 | 100.0 | 0       | 0       | 0.108 | G:A     |
| 56 | rs16944762 | 44362496 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | G:A     |
| 57 | rs2270576  | 44362962 | 0.4    | 0.455   | 0.4682 | 100.0 | 0       | 0       | 0.35  | C:T     |
| 58 | rs4793992  | 44363206 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | A:G     |
| 59 | rs4793993  | 44363545 | 0.4    | 0.455   | 0.4682 | 100.0 | 0       | 0       | 0.35  | C:T     |
| 60 | rs17708633 | 44366619 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | C:G     |
| 61 | rs1994970  | 44369126 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | T:C     |
| 62 | rs9747646  | 44371881 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | C:T     |
| 63 | rs12601858 | 44372476 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | T:C     |
| 64 | rs8182364  | 44373024 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | A:G     |
| 65 | rs4793995  | 44374398 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | A:C     |
| 66 | rs4793996  | 44374596 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | T:C     |
| 67 | rs4793998  | 44374898 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | C:T     |
| 68 | rs11079844 | 44383333 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | G:A     |
| 69 | rs12602933 | 44384279 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | G:C     |
| 70 | rs4794003  | 44384903 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | C:T     |
| 71 | rs12602746 | 44386740 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | A:C     |
| 72 | rs9904288  | 44386972 | 0.4    | 0.455   | 0.4682 | 100.0 | 0       | 0       | 0.35  | T:C     |
| 73 | rs2291725  | 44394131 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | T:C     |
| 74 | rs2291726  | 44394253 | 0.5    | 0.5     | 1.0    | 100.0 | 0       | 0       | 0.5   | C:C     |
| 75 | rs8078510  | 44400861 | 0.383  | 0.439   | 0.448  | 100.0 | 0       | 0       | 0.325 | G:A     |
| 76 | rs937301   | 44401275 | 0.483  | 0.5     | 0.9497 | 100.0 | 0       | 0       | 0.492 | A:G     |
| 77 | rs3848460  | 44402113 | 0.483  | 0.5     | 0.9497 | 100.0 | 0       | 0       | 0.492 | A:G     |
| 78 | rs3809770  | 44402595 | 0.45   | 0.493   | 0.6283 | 100.0 | 0       | 0       | 0.442 | A:G     |

| #   | Name       | Position | ObsHET | PredHET | HWPval | %Geno | FamTrio | MendErr | MAF   | Alleles |
|-----|------------|----------|--------|---------|--------|-------|---------|---------|-------|---------|
| 79  | rs3895874  | 44402867 | 0.5    | 0.499   | 1.0    | 100.0 | 0       | 0       | 0.483 | A:G     |
| 80  | rs9899404  | 44408827 | 0.367  | 0.473   | 0.1246 | 100.0 | 0       | 0       | 0.383 | C:T     |
| 81  | rs9894411  | 44417476 | 0.1    | 0.095   | 1.0    | 100.0 | 0       | 0       | 0.05  | T:C     |
| 82  | rs4794012  | 44420090 | 0.367  | 0.464   | 0.1551 | 100.0 | 0       | 0       | 0.367 | T:G     |
| 83  | rs4794015  | 44422825 | 0.517  | 0.5     | 1.0    | 100.0 | 0       | 0       | 0.492 | A:G     |
| 84  | rs2411759  | 44426073 | 0.533  | 0.499   | 0.8395 | 100.0 | 0       | 0       | 0.483 | T:C     |
| 85  | rs1390154  | 44426482 | 0.383  | 0.469   | 0.2278 | 100.0 | 0       | 0       | 0.375 | G:A     |
| 86  | rs11650936 | 44427260 | 0.55   | 0.5     | 0.6492 | 100.0 | 0       | 0       | 0.492 | G:C     |
| 87  | rs7223256  | 44430989 | 0.017  | 0.017   | 1.0    | 100.0 | 0       | 0       | 0.008 | C:T     |
| 88  | rs1495274  | 44432647 | 0.117  | 0.139   | 0.5523 | 100.0 | 0       | 0       | 0.075 | G:A     |
| 89  | rs1994969  | 44435430 | 0.4    | 0.491   | 0.2132 | 100.0 | 0       | 0       | 0.433 | T:G     |
| 90  | rs9674544  | 44439710 | 0.417  | 0.493   | 0.3127 | 100.0 | 0       | 0       | 0.442 | A:G     |
| 91  | rs12939375 | 44444716 | 0.4    | 0.491   | 0.2132 | 100.0 | 0       | 0       | 0.433 | G:C     |
| 92  | rs6504592  | 44445297 | 0.133  | 0.124   | 1.0    | 100.0 | 0       | 0       | 0.067 | C:G     |
| 93  | rs11079849 | 44445784 | 0.483  | 0.489   | 1.0    | 100.0 | 0       | 0       | 0.425 | C:T     |
| 94  | rs9906710  | 44446282 | 0.483  | 0.493   | 1.0    | 100.0 | 0       | 0       | 0.442 | C:A     |
| 95  | rs9906944  | 44446419 | 0.45   | 0.483   | 0.7385 | 100.0 | 0       | 0       | 0.408 | C:T     |
| 96  | rs10853104 | 44447075 | 0.433  | 0.498   | 0.417  | 100.0 | 0       | 0       | 0.467 | T:C     |
| 97  | rs11079851 | 44447309 | 0.4    | 0.491   | 0.2132 | 100.0 | 0       | 0       | 0.433 | C:G     |
| 98  | rs4794018  | 44448397 | 0.483  | 0.493   | 1.0    | 100.0 | 0       | 0       | 0.442 | T:C     |
| 99  | rs8076012  | 44456988 | 0.417  | 0.5     | 0.271  | 100.0 | 0       | 0       | 0.492 | A:G     |
| 100 | rs17708997 | 44457037 | 0.15   | 0.139   | 1.0    | 100.0 | 0       | 0       | 0.075 | A:G     |
| 101 | rs9912906  | 44459431 | 0.417  | 0.477   | 0.44   | 100.0 | 0       | 0       | 0.392 | A:T     |
| 102 | rs9899580  | 44461877 | 0.417  | 0.477   | 0.44   | 100.0 | 0       | 0       | 0.392 | T:G     |
| 103 | rs4794019  | 44462289 | 0.417  | 0.477   | 0.44   | 100.0 | 0       | 0       | 0.392 | G:T     |
| 104 | rs8079385  | 44464426 | 0.25   | 0.219   | 0.7369 | 100.0 | 0       | 0       | 0.125 | C:G     |
| 105 | rs4794020  | 44466398 | 0.417  | 0.477   | 0.44   | 100.0 | 0       | 0       | 0.392 | C:T     |
| 106 | rs11870560 | 44469032 | 0.433  | 0.498   | 0.417  | 100.0 | 0       | 0       | 0.467 | C:T     |
| 107 | rs12942084 | 44469391 | 0.417  | 0.477   | 0.44   | 100.0 | 0       | 0       | 0.392 | A:G     |
| 108 | rs16945851 | 44469481 | 0.067  | 0.064   | 1.0    | 100.0 | 0       | 0       | 0.033 | C:T     |
| 109 | rs8073244  | 44470037 | 0.233  | 0.206   | 0.8491 | 100.0 | 0       | 0       | 0.117 | C:T     |
| 110 | rs1463761  | 44473087 | 0.233  | 0.206   | 0.8491 | 100.0 | 0       | 0       | 0.117 | A:G     |
| 111 | rs11872073 | 44474134 | 0.017  | 0.017   | 1.0    | 100.0 | 0       | 0       | 0.008 | G:A     |
| 112 | rs3816272  | 44475466 | 0.417  | 0.477   | 0.44   | 100.0 | 0       | 0       | 0.392 | A:G     |
| 113 | rs8068981  | 44477524 | 0.417  | 0.477   | 0.44   | 100.0 | 0       | 0       | 0.392 | T:C     |
| 114 | rs4643373  | 44478422 | 0.417  | 0.469   | 0.5116 | 100.0 | 0       | 0       | 0.375 | T:C     |
| 115 | rs9896443  | 44480981 | 0.383  | 0.5     | 0.1046 | 100.0 | 0       | 0       | 0.492 | T:C     |
| 116 | rs2969     | 44483246 | 0.317  | 0.349   | 0.6576 | 100.0 | 0       | 0       | 0.225 | C:T     |
| 117 | rs11655950 | 44484120 | 0.417  | 0.477   | 0.44   | 100.0 | 0       | 0       | 0.392 | G:A     |
| 118 | rs2241932  | 44485229 | 0.067  | 0.064   | 1.0    | 100.0 | 0       | 0       | 0.033 | G:C     |
| 119 | rs3744085  | 44486900 | 0.4    | 0.499   | 0.1751 | 100.0 | 0       | 0       | 0.483 | G:A     |

| #   | Name       | Position | ObsHET | PredHET | HWpval | %Geno | FamTrio | MendErr | MAF   | Alleles |
|-----|------------|----------|--------|---------|--------|-------|---------|---------|-------|---------|
| 120 | rs6504593  | 44487818 | 0.4    | 0.499   | 0.1751 | 100.0 | 0       | 0       | 0.483 | C:T     |
| 121 | rs8069452  | 44495998 | 0.433  | 0.5     | 0.3994 | 100.0 | 0       | 0       | 0.5   | A:A     |
| 122 | rs1523136  | 44499531 | 0.433  | 0.48    | 0.5797 | 100.0 | 0       | 0       | 0.4   | T:C     |
| 123 | rs12939237 | 44499563 | 0.183  | 0.167   | 1.0    | 100.0 | 0       | 0       | 0.092 | G:A     |
| 124 | rs940088   | 44500847 | 0.433  | 0.48    | 0.5797 | 100.0 | 0       | 0       | 0.4   | T:C     |
| 125 | rs11656072 | 44502360 | 0.167  | 0.18    | 0.9127 | 100.0 | 0       | 0       | 0.1   | T:C     |
| 126 | rs11656250 | 44512427 | 0.3    | 0.278   | 0.9897 | 100.0 | 0       | 0       | 0.167 | G:A     |
| 127 | rs11657661 | 44520235 | 0.283  | 0.289   | 1.0    | 100.0 | 0       | 0       | 0.175 | C:T     |
| 128 | rs4319818  | 44520997 | 0.517  | 0.489   | 0.9112 | 100.0 | 0       | 0       | 0.425 | C:G     |
| 129 | rs9972911  | 44532746 | 0.483  | 0.477   | 1.0    | 100.0 | 0       | 0       | 0.392 | C:T     |
| 130 | rs9303547  | 44532912 | 0.267  | 0.231   | 0.6317 | 100.0 | 0       | 0       | 0.133 | A:T     |
| 131 | rs9910632  | 44537708 | 0.433  | 0.464   | 0.7541 | 100.0 | 0       | 0       | 0.367 | C:T     |
| 132 | rs1523135  | 44538319 | 0.433  | 0.464   | 0.7541 | 100.0 | 0       | 0       | 0.367 | G:C     |
| 133 | rs6504595  | 44542055 | 0.3    | 0.339   | 0.5365 | 100.0 | 0       | 0       | 0.217 | G:T     |

**Supplementary Table 5.**  
**Allele frequency of rs2291725 in the HGDP-CEPH populations.**

|                                 | Allele Frequency (%) |         | Chromosome No. |
|---------------------------------|----------------------|---------|----------------|
|                                 | GIP103T              | GIP103C |                |
| AFRICA (Sub-Sahara)             |                      |         |                |
| C. African Republic-Biaka Pygmy | 100.0                | 0.0     | 44             |
| D. R. of Congo-Mbuti Pygmy      | 92.2                 | 3.8     | 26             |
| Kenya-Bantu                     | 100.0                | 0.0     | 22             |
| Namidia-San                     | 100.0                | 0.0     | 10             |
| Nigeria-Yoruba                  | 90.5                 | 9.5     | 42             |
| Senegal-Mandenka                | 93.2                 | 6.8     | 44             |
| South Africa-Bantu              | 93.7                 | 6.3     | 16             |
| subtotal                        |                      |         | 102            |
| AMERICA                         |                      |         |                |
| Brazil-Karitiana                | 75.0                 | 25.0    | 28             |
| Brazil-Surui                    | 75.0                 | 25.0    | 16             |
| Colombia-Piapoco and Curripaco  | 78.6                 | 21.4    | 14             |
| Mexico-Maya                     | 71.4                 | 28.6    | 42             |
| Mexico-Pima                     | 57.1                 | 42.9    | 28             |
| subtotal                        |                      |         | 64             |
| EUROPE                          |                      |         |                |
| France-Basque                   | 58.3                 | 41.7    | 48             |
| France-French                   | 48.2                 | 51.8    | 56             |
| Italy-Sardinian                 | 39.3                 | 60.7    | 56             |
| Italy-Tuscan                    | 50.0                 | 50.0    | 16             |
| Italy-Bergamo                   | 53.8                 | 46.2    | 26             |
| Orkney Islands-Orcadian         | 43.3                 | 56.7    | 30             |
| Russia Caucasus-Adygei          | 33.0                 | 67.0    | 34             |
| Russia-Russian                  | 52.0                 | 48.0    | 50             |
| subtotal                        |                      |         | 158            |
| MIDDLE EAST                     |                      |         |                |
| Algeria (Mzab)-Mozabite         | 79.3                 | 20.7    | 58             |
| Israel (Carmel)-Druze           | 45.2                 | 54.8    | 84             |
| Israel (central)-Palestinian    | 56.5                 | 43.5    | 92             |
| Israel (Negev)-Bedouin          | 45.7                 | 54.3    | 92             |
| subtotal                        |                      |         | 163            |
| CENTRAL-SOUTH ASIA              |                      |         |                |
| China-Uygur                     | 55.0                 | 45.0    | 20             |
| Pakistan-Balochi                | 47.9                 | 52.1    | 48             |
| Pakistan-Brahui                 | 44.0                 | 56.0    | 50             |
| Pakistan-Burusho                | 52.0                 | 48.0    | 50             |
| Pakistan-Hazara                 | 38.6                 | 61.4    | 44             |

|                             |      |      |            |
|-----------------------------|------|------|------------|
| Pakistan-Kalash             | 56.5 | 43.5 | 46         |
| Pakistan-Makrani            | 48.0 | 52.0 | 50         |
| Pakistan-Pathan             | 45.5 | 54.5 | 44         |
| Pakistan-Sindhi             | 64.6 | 35.4 | 48         |
| <b>subtotal</b>             |      |      | <b>200</b> |
| <b>OCEANIA</b>              |      |      |            |
| Bougainville-NAN Melanesian | 27.3 | 72.7 | 22         |
| New Guinea-Papuan           | 58.8 | 41.2 | 34         |
| <b>subtotal</b>             |      |      | <b>28</b>  |
| <b>EAST ASIA</b>            |      |      |            |
| Cambodia-Cambodian          | 40.0 | 60.0 | 20         |
| China-Dai                   | 45.0 | 55.0 | 20         |
| China-Daur                  | 38.9 | 61.1 | 18         |
| China-Han                   | 28.4 | 71.6 | 88         |
| China-Hezhen                | 27.8 | 72.2 | 18         |
| China-Lahu                  | 31.2 | 68.8 | 16         |
| China-Miao                  | 40.0 | 60.0 | 20         |
| China-Mongola               | 30.0 | 70.0 | 20         |
| China-Naxi                  | 62.5 | 37.5 | 16         |
| China-Oroquen               | 22.2 | 77.8 | 18         |
| China-She                   | 30.0 | 70.0 | 20         |
| China-Tu                    | 35.0 | 65.0 | 20         |
| China-Tujia                 | 35.0 | 65.0 | 20         |
| China-Xibo                  | 5.6  | 94.4 | 18         |
| China-Yizu                  | 35.0 | 65.0 | 20         |
| Japan-Japanese              | 21.4 | 78.6 | 56         |
| Siberia-Yakut               | 24.0 | 76.0 | 50         |
| <b>subtotal</b>             |      |      | <b>229</b> |
| <b>Total</b>                |      |      | <b>944</b> |

**Supplementary Table 6.**

**EC50 values (-Log EC50, mean  $\pm$  SEM) for GIP, GIP55G, and GIP55S.**

**With pooled human serum**

| <b><i>Hours of incubation</i></b> | <b><i>GIP</i></b> | <b><i>GIP55G</i></b> | <b><i>GIP55S</i></b> |
|-----------------------------------|-------------------|----------------------|----------------------|
| 0                                 | 9.02 $\pm$ 0.15   | 8.47 $\pm$ 0.14      | 8.56 $\pm$ 0.19      |
| 3                                 | 8.21 $\pm$ 0.13   | 8.32 $\pm$ 0.19      | 8.34 $\pm$ 0.14      |
| 6                                 | 8.21 $\pm$ 0.15   | 8.02 $\pm$ 0.10      | 7.74 $\pm$ 0.14      |
| 12                                | 7.52 $\pm$ 0.19   | 7.93 $\pm$ 0.09      | 7.38 $\pm$ 0.16      |

**With pooled complement preserved human serum**

| <b><i>Hours of incubation</i></b> | <b><i>GIP</i></b> | <b><i>GIP55G</i></b> | <b><i>GIP55S</i></b> |
|-----------------------------------|-------------------|----------------------|----------------------|
| 0                                 | 8.91 $\pm$ 0.15   | 8.51 $\pm$ 0.14      | 8.43 $\pm$ 0.18      |
| 3                                 | 8.53 $\pm$ 0.16   | 8.22 $\pm$ 0.15      | 8.49 $\pm$ 0.13      |
| 6                                 | 8.18 $\pm$ 0.12   | 7.88 $\pm$ 0.09      | 7.79 $\pm$ 0.13      |
| 12                                | 7.53 $\pm$ 0.17   | 7.86 $\pm$ 0.14      | 7.12 $\pm$ 0.22      |

**Supplementary Table 7.**

**EC50 values (-Log EC50, mean  $\pm$  SEM) for GIP, GIP55G, and GIP55S  
after pre-incubation with a recombinant dipeptidyl peptidase IV enzyme (1mIU/ml)**

| <b><i>Hours of incubation</i></b> | <b><i>GIP</i></b> | <b><i>GIP55G</i></b> | <b><i>GIP55S</i></b> |
|-----------------------------------|-------------------|----------------------|----------------------|
| 0                                 | 8.91 $\pm$ 0.15   | 8.51 $\pm$ 0.14      | 8.43 $\pm$ 0.18      |
| 3                                 | 7.92 $\pm$ 0.14   | 7.70 $\pm$ 0.09      | 7.79 $\pm$ 0.14      |
| 6                                 | 7.32 $\pm$ 0.12   | 7.25 $\pm$ 0.09      | 7.10 $\pm$ 0.08      |

## Supplementary Methods

### Coalescent simulations of the integrated haplotype score (iHS)

To determine the distribution of iHS under neutral evolution, we conducted coalescent simulation using *ms* (Hudson 2002). We adopted parameters that were estimated based on the genomic region of *GIP* in the ASN population: sample size = 180,  $\theta = 388$ , recombination rate =  $9.7 \times 10^{-7}$  cM/bp,  $N_0 = 10,000$ , and the length of the region = 750 kb. We generated 10,000 samples, in which every sample has the same number of segregating sites regardless of the size of the genealogy generated. This was performed using the -s option on the command line:

**ms 180 10000 -s 388 -r 292 750000**

In this case,  $r = 292$  because the cross-over probability between the two ends of the locus is  $(750000-1) * 9.7 \times 10^{-7} * 0.01 = 0.0073$ , and thus  $r = 4 * 10000 * 0.0073 = 292$ .

To take into account the potential effects of demography, we conducted the coalescent simulations under the model of population bottleneck. The demographic history is shown in Supplementary Fig. 4B. We assumed that ASN is a panmictic population that underwent a size reduction, followed by a period of constant size (bottleneck), and proceeded with an exponential expansion. We assumed that the population sizes are  $N_0 = N_1 = 10,000$ ;  $N_2 = 5,000$ ; and  $N_3 = 20,000$ . We used the model for human demography with parameters that have been previously inferred (Gutenkunst et al. 2009). We also assumed that  $T_1$  is 480 generations, or  $480 / (4 * 10,000) = 0.012$  in units of  $4N_0$  generations, and  $T_2$  is 920 generations or 0.023 in units of  $4N_0$  generations. To specify the exponential growth on the command line, we calculated the growth parameter  $\alpha$  by

solving the equation,  $5,000 = 20,000 \cdot \exp(-\alpha 0.012)$ , which is  $\alpha = -(1/0.012) \cdot \log(5,000/20,000) = 115.52$ . Thus, the command line to generate 10,000 samples of size 180 is:

```
ms 180 10000 -s 388 -r 292 750000 -G 115.52 -eG 0.012 0.0 -eN 0.023 1
```

We also attempted to take into account the effect of the presence of recombination hotspot on the distribution of iHS. We used *msHOT* (Hellenthal and Stephens 2007), a modified *ms* simulator that has incorporated crossover and gene conversion hotspots, to conduct the simulation. In this simulation, we introduced a hotspot with intensity of 10 between the 350- and 400-kb region. The command line of *msHOT* is:

```
msHOT 180 10000 -s 388 -r 292 750000 -v 1 350000 400000 10
```