# Supplementary materials for

# Functional annotation of HOT regions in the human genome: implications for human disease and cancer

Hao Li[1], Hebing Chen[1], Feng Liu[1], Chao Ren[1], Shengqi Wang[1], Xiaochen Bo[1*], Wenjie Shu[1*]

[1]Department of Biotechnology, Beijing Institute of Radiation Medicine, Beijing 100850, China

[*]Corresponding author. To whom correspondence should be addressed. Tel & Fax: +86 10 68210077 66932211; Email: shuwj@bmi.ac.cn. Correspondence may also be addressed to: boxc@bmi.ac.cn.

# Supplementary figures

## Supplementary Figure S1. Catalogue of SNPs linked to phenotypic traits and diseases in GWASs, related to Figure 1

(A) Proportions of noncoding GWAS SNPs localised within HOT regions (blue), in strong LD ($r^2 > 0.8$) with a SNP in a HOT region (red), or neither (green). Note that 84% of the GWAS SNPs are either within HOT regions or in strong LD with HOT regions. (B) Pie chart that shows the percentages of SNPs associated with the highlighted classes of traits and diseases. (C) The SNP enrichment values of noncoding SNPs linked to the highlighted traits and diseases in the union of HOT regions and LOT regions in 57 human cell and tissue samples.

## Supplementary Figure S2. GWAS SNPs in disease- and trait-specific HOT regions, related to Figure 4

(A) (Upper) Bar plots that show the density (SNP/MB sequence) of trait-associated noncoding SNPs linked to ventricular conduction in the HOT and LOT region domains identified in 16 human cell and tissue types. (Middle) List of genes associated with ventricular conduction SNP-containing HOT regions in heart cells. (Bottom) DNase-seq profiles at the *SCN10A* locus in HCM cell. The positions of the ventricular conduction SNPs are highlighted with red lines, the HOT regions are highlighted with red bars, and the LOT regions are highlighted with blue bars above the binding profile. (B) (Upper) Bar plots that show the density (SNP/MB sequence) of trait-associated noncoding SNPs linked to rheumatoid arthritis in the HOT and LOT region domains identified in 16 human cell and tissue types. (Middle) List of genes associated with rheumatoid arthritis SNP-containing HOT regions in lymphoid cells. (Bottom) DNase-seq profile surrounding rheumatoid arthritis SNP rs657075 (red line). The HOT regions are highlighted with red bars, and the LOT regions are highlighted with blue bars above the binding profile. (C) (Upper) Bar plots that show the density (SNP/MB sequence) of trait-associated noncoding SNPs linked to celiac disease in the HOT and LOT region domains identified in 16 human cell and tissue types. (Middle) List of genes associated with celiac disease SNP-containing HOT regions in Th cells. (Bottom) DNase-seq profile in Th cells. The positions of celiac disease SNPs are highlighted with red lines, the HOT regions are highlighted with red bars, and the LOT regions are highlighted with blue bars above the binding profile.

**Supplementary Figure S3. HOT regions in cancers, related to Figure 7**

(A) Enrichment of 522 oncogenes associated with HOT regions and LOT regions in 25 cancer cell lines. (B) DNase-seq profiles are shown surrounding the oncogene in selected cancers and their healthy counterparts. Cancer-specific HOT regions are found surrounding the TSS of oncogenes. (C) Percentage of cancer and normal HOT and LOT regions in breakpoint clusters.

# Supplementary tables

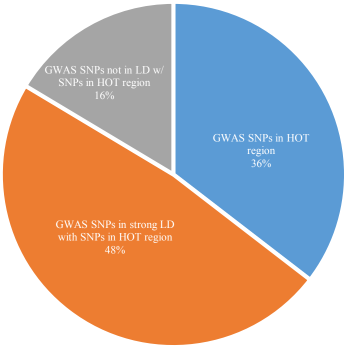
## Table S1. 154 Cell lines used in this study

154 Cell lines used in this study.

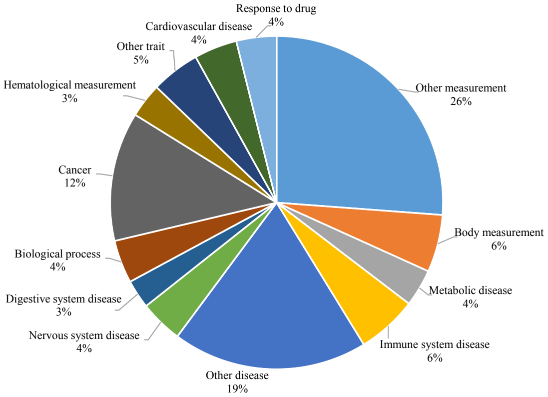
## Table S2. SNPs in HOT, LOT and TFBS-clustered regions, related to Figure 1

Summary of trait-associated SNPs in the union of the HOT and LOT regions in 154 human cell lines. The percentage of the 4,985 trait-associated noncoding SNPs located in these regions is displayed. The percentage of the genome (3.4 billion bases) covered by the union of these regions in the 154 human cell and tissue types is also displayed. The SNP enrichment is defined as the percentage of SNPs contained in the percentage of the genome covered by these regions.

S1A



S1B

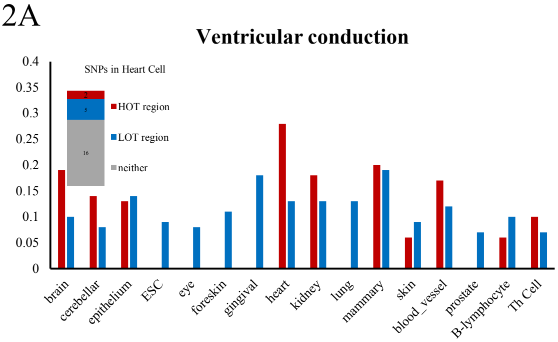


S1C

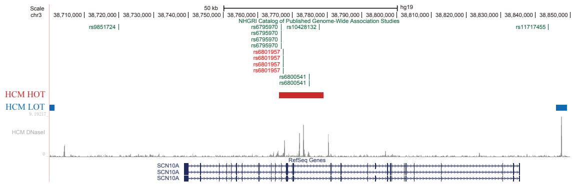
**Trait enrichment**

| Trait | HOT region | LOT region |
|---|---|---|
| Multiple sclerosis | 4.21 | 1.60 |
| Systemic sclerosis | 4.21 | 1.60 |
| Chronic lymphocytic leukemia | 4.14 | 1.59 |
| Type 1 diabetes | 3.75 | 1.55 |
| Celiac disease | 3.70 | 1.61 |
| Rheumatoid arthritis | 3.23 | 1.51 |
| Inflammatory bowel disease | 3.16 | 1.55 |
| Colorectal cancer | 3.11 | 1.61 |
| Crohn’s disease | 3.09 | 1.55 |
| Systemic lupus erythematosus | 3.05 | 1.56 |

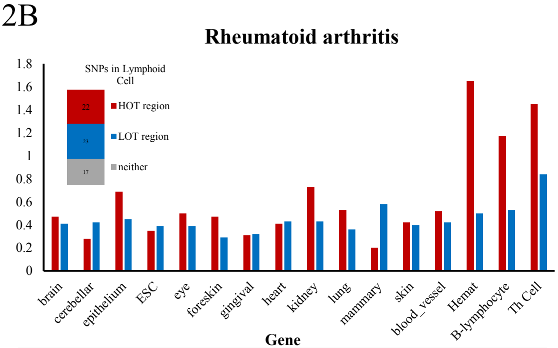
S2A



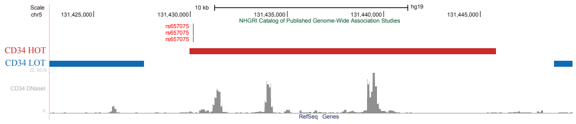
| Gene | | | | |
|---|---|---|---|---|
| KLF12 | PRKCA | SETBP1 | CRIM1 | SCN10A |
| TKT | | | | |



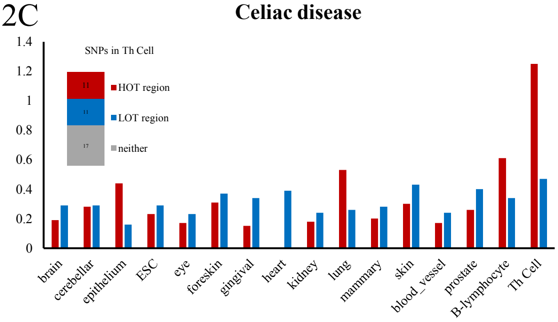
S2B



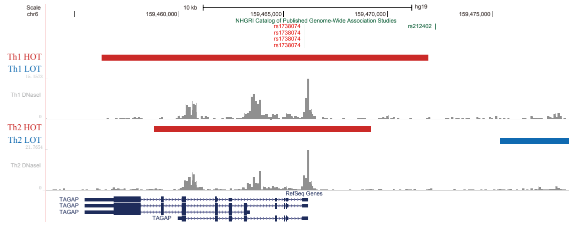
| Gene | | | | |
|---|---|---|---|---|
| MMEL1 | CD247 | IL2RA | ARID5B | PDE2A |
| KIF5A | GCH1 | PLD4 | PRKCB | REL |
| SPRED2 | STAT4 | CTLA4 | CD40 | UBASH3A |
| ARHGEF3 | KIAA1109 | C5orf30 | APOM | CCR6 |
| CDK6 | TNPO3 | BLK | TRAF1 | |



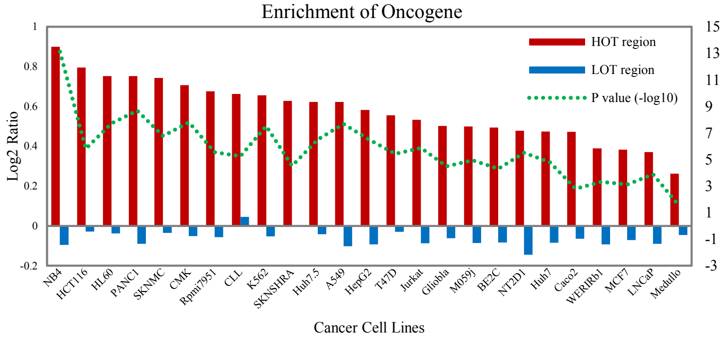
S2C



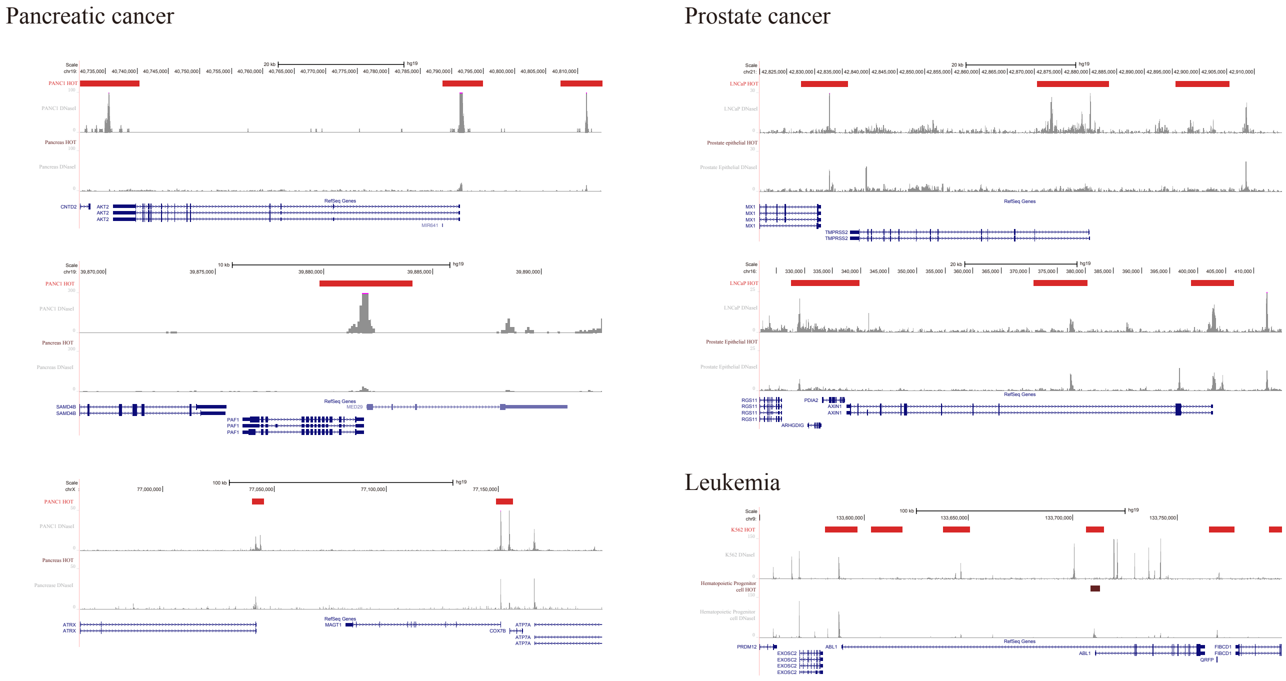
| Gene | | | | |
|---|---|---|---|---|
| CD247 | ZMIZ1 | ICOS | ICOSLG | ARHGAP31 |
| LPP | KIAA1109 | HLA-DQA1 | BACH2 | TAGAP |
| ELMO1 | | | | |



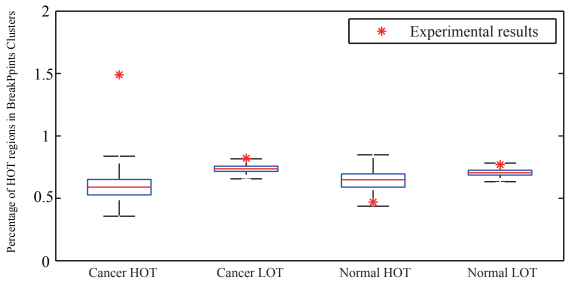
S3A


Enrichment of Oncogene
HOT region
LOT region
P value (-log10)
Log2 Ratio
1
0.8
0.6
0.4
0.2
0
-0.2
15
13
11
9
7
5
3
1
-1
-3
NB4
HCT116
HL60
PANC1
SKNMC
CMK
Rpmi7951
CLL
K562
SKNSHRA
Huh7.5
A549
HepG2
T47D
Jurkat
Gliobla
M059j
BE2C
NT2D1
Huh7
Caco2
WERIRb1
MCF7
LNCaP
Medullo
Cancer Cell Lines

S3B


Pancreatic cancer
Prostate cancer
Leukemia
PANC1 HOT
PANC1 DNaseI
Pancreas HOT
Pancreas DNaseI
RefSeq Genes
CNTD2
AKT2
MIR641
SAMD4B
PAF1
MED29
ATRX
MAGT1
COX7B
ATP7A
LNCaP HOT
LNCaP DNaseI
Prostate epithelial HOT
Prostate Epithelial DNaseI
MX1
TMPRSS2
RGS11
PDIA2
AXIN1
ARHGDIG
K562 HOT
K562 DNaseI
Hematopoetic Progenitor cell HOT
Hematopoetic Progenitor cell DNaseI
PRDM12
EXOSC2
ABL1
FIBCD1
QRFP
hg19

S3C


Experimental results
Percentage of HOT regions in BreakPpints Clusters
2
1.5
1
0.5
0
Cancer HOT
Cancer LOT
Normal HOT
Normal LOT

# Table S1. 154 Cell Lines Used in this Study

| Use as Cancer Cell | Use as Normal Cell | | Others | |
|---|---|---|---|---|
| Duke_CLL | Duke_GM12891 | Uw_HCF | Cd4naivewb11970640_UW | Lhcnm2_UW |
| Duke_Gliobla | Duke_GM12892 | Uw_HCM | Cd4naivewb78495824_UW | Msc_UW |
| Duke_Huh7 | Duke_GM18507 | Uw_HConF | Duke_8988T | Nhbera_UW |
| Duke_Huh7.5 | Duke_GM19238 | Uw_HEEpiC | Duke_AoSMC | Th17_UW |
| Duke_Medullo | Duke_GM19239 | Uw_HFF | Duke_Chorion | Tregwb83319432_UW |
| Duke_T47D | Duke_GM19240 | Uw_HGF | Duke_Fibrobl | Uw_AG04450 |
| M059j_UW | Duke_H9ES | Uw_HMF | Duke_Fibrobl.overlap | Uw_CD20 |
| Rpmi7951_UW | Duke_HPDE6E6E7 | Uw_HMVECdAd | Duke_FibroP | Uw_GM06990 |
| Uw_BE2C | Duke_RWPE1 | Uw_HMVECdBlAd | Duke_HeLaS3IFNa4h | Uw_GM12864 |
| Uw_Caco2 | Hbvp_UW | Uw_HMVECdBlNeo | Duke_Hepatocytes | Uw_HAEpiC |
| Uw_CMK | Hbvsmc_UW | Uw_HMVECdLyAd | Duke_HSMMemb | Uw_HAsp |
| Uw_HCT116 | Th1_UW | Uw_HMVECdLyNeo | Duke_HTR8svn | Uw_HBMEC |
| Uw_HL60 | Th1wb33676984_UW | Uw_HMVECdNeo | Duke_iPS | Uw_HCFaa |
| Uw_Jurkat | Th1wb54553204_UW | Uw_HMVECLBl | Duke_IshikawaEstradiol | Uw_HCPEpiC |
| Uw_NB4 | Th2_UW | Uw_HMVECLLy | Duke_IshikawaTamoxifen | Uw_HFFMyc |
| Uw_NT2D1 | Th2wb33676984_UW | Uw_HPAEC | Duke_LNCaPAndrogen | Uw_HIPEpiC |
| Uw_PANC1 | Th2wb54553204_UW | Uw_HPAF | Duke_MCF7Hypoxia | Uw_HNPCEpiC |
| Uw_SKNMC | Tregwb78495824_UW | Uw_HPdLF | Duke_Melano | Uw_HRCEpiC |
| Uw_SKNSHRA | Uw_AG04449 | Uw_HPF | Duke_Myometr | Uw_HRE |
| Uw_WERIRb1 | Uw_AG09309 | Uw_HRGEC | Duke_Osteobl | Uw_HVMF |
| UWDuke_A549 | Uw_AG09319 | Uw_HRPEpiC | Duke_PanIsletD | Uw_MonocytesCD14RO01746 |
| UWDuke_HepG2 | Uw_AG10803 | Uw_NHA | Duke_PanIslets | Uw_NHLF |
| UWDuke_K562 | Uw_AoAF | Uw_NHDFAd | Duke_pHTE | Uw_RPTEC |
| UWDuke_LNCaP | Uw_BJ | Uw_NHDFneo | Duke_ProgFib | Uw_SKMC |
| UWDuke_MCF7 | Uw_CD34Mobilized | Uw_PrEC | Duke_Stellate | Uw_Th2 |
| | Uw_GM12865 | Uw_SAEC | Duke_Th0 | Uw_WI38 |
| | Uw_H7hESC | UWDuke_GM12878 | Duke_Urothelia | Uw_WI38TamoxifenTamoxifen |
| | Uw_HAc | UWDuke_H1hESC | Duke_UrotheliaUT189 | UWDuke_HeLaS3 |
| | Uw_HAh | | Gm04503_UW | UWDuke_HMEC |
| | | | Gm04504_UW | UWDuke_HSMM |
| | | | H7es_UW | UWDuke_HSMMtube |
| | | | H7esDiffa14d_UW | UWDuke_HUVEC |
| | | | H7esDiffa2d_UW | UWDuke_NHEK |
| | | | H7esDiffa5d_UW | UWDuke_Th1 |
| | | | H7esDiffa9d_UW | Hs27a_UW |
| | | | Hmec_UW | Hs5_UW |

**Table S2. SNPs in HOT, LOT and TFBS-clustered regions, related to figure 1B**

| | HOT region | LOT region | TFBS-clusters |
|---|---|---|---|
| Trait-associated SNPs | 35.45% | 85.18% | 86.48% |
| % genome contrained | 15.27% | 58.08% | 58.60% |
| SNP enrichment | 2.32 | 1.47 | 1.48 |