Identifying footprints of selection in genome-wide SNP data from haplotype structure REHH

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REHH Overview

Comparisons of local haplotype diversity

- iHS : Within–Population ("outliers")
- rSB and rSB : Between populations (pairwise)
- Empirical (model–free) approach : calibration of the statistics is based on the observed distribution

Haplotype Data

- Need a prior phasing of the data (with e.g., FastPHASE, BEAGLE, SHAPE–IT) and optionnally ((but recommended) imputation (with e.g., FastPHASE, IMPUTE)
  $\Rightarrow$ 3 data format allowed in REHH
- Map information (genetic $>$ physical distances)
- For iHS only : ancestral/derived allele status of SNPs

General principles

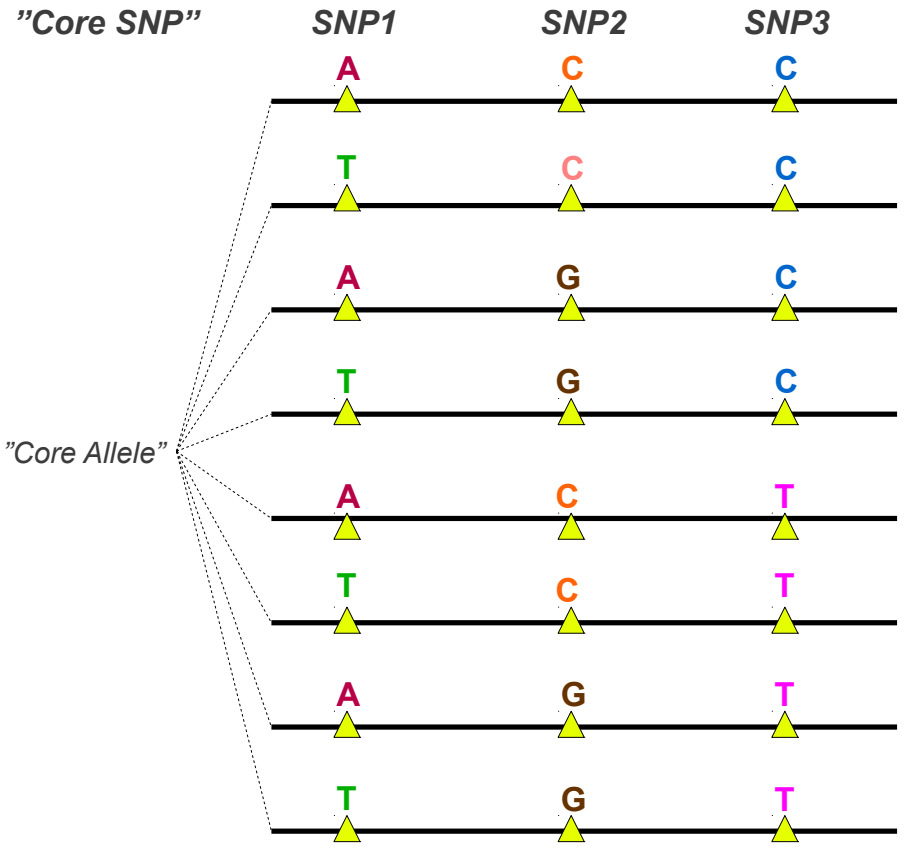
- Selection (when recent) tends to reduce haplotype diversity

  ($\Leftrightarrow$) increase Linkage Disequilibrium

- *Extended Haplotype Homozygosity* (Sabeti *et al.*, 2002)
  - EHH : An estimator of Haplotype Variability
  - Probability that two randomly chosen chromosomes carrying the core allele of interest are IBD for the entire interval from the core region to a distance x (assuming SNP homozygosity=IBS $\Rightarrow$ IBD)
  - EHH detects the transmission of an extended haplotype without recombination

- $EHH_i(x) = \frac{\sum_{k=1}^{h_i} \binom{n_k^{h_i}}{2}}{\binom{n_i}{2}} = \sum_{k=1}^{h_i} \frac{n_k^{h_i}(n_k^{h_i}-1)}{n_i(n_i-1)} \quad \left(\simeq \sum_{k=1}^{h_i} \left(\frac{n_k^{h_i}}{n_i} \right)^2 = \sum_{k=1}^{h_i} (f_k^{h_i})^2 \right)$
  - h_i : Nb. of unique haplotypes carrying the core allele
  - $n_k^{h_i}$: Nb. of each unique haplotypes ($f_i^{h_i}$=observed freq)
  - $n_i = \sum_{k=1}^{h_i} n_k^{h_i}$: Nb. of haplotypes carrying the core allele

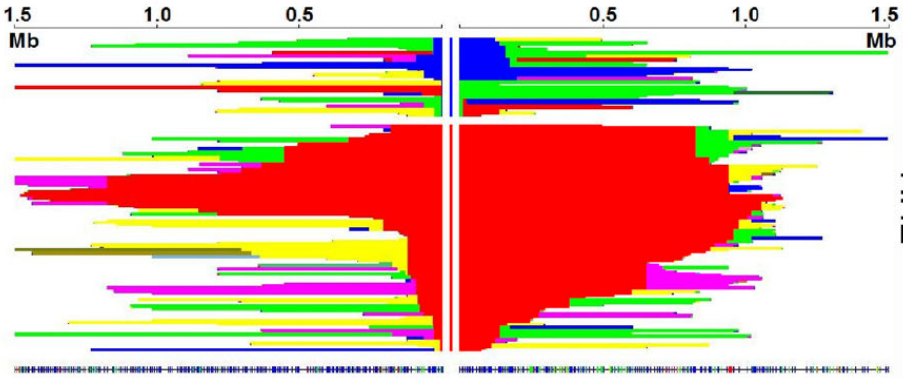
A Simple Example

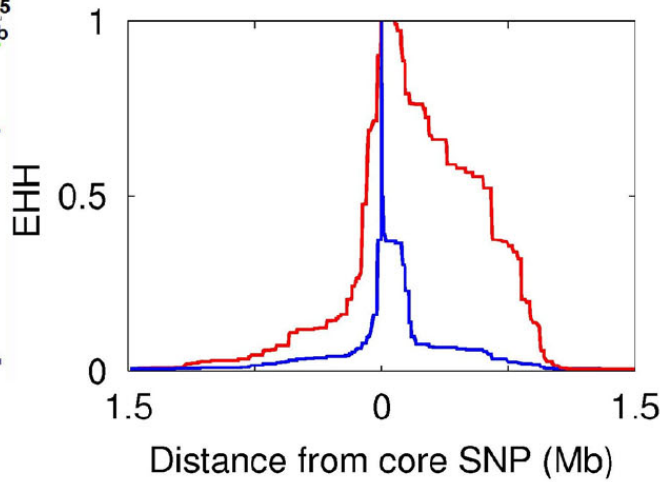


	n_k^{hi}	n_k^{hi}	n_k^{hi}
	10	8	77
	10	7	0
	10	17	0
	10	11	0
	10	3	2
	10	21	0
	10	1	1
	10	12	0
EHH =	**0.116**	**0.164**	**0.926**
EHH_{appr}=	*0.125*	*0.175*	*0.927*

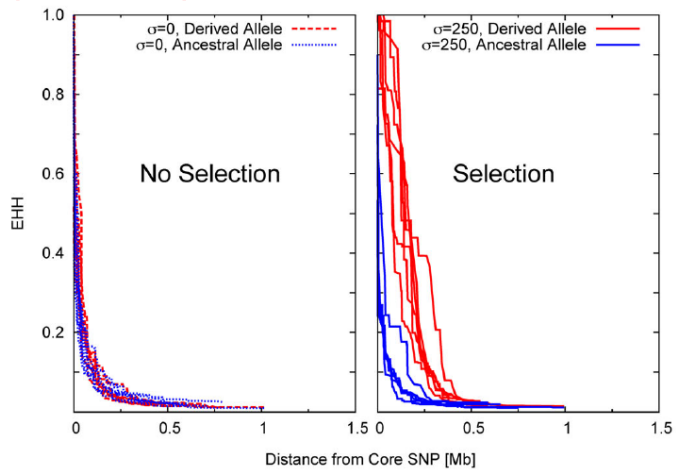
EHH as a function of the distance to core allele

By construction EHH at a core allele decreases with distance





(Recent) selection decays the decrease



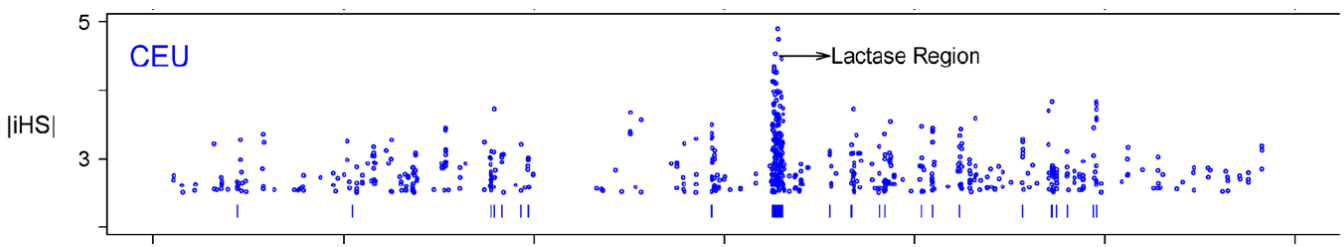
Genome wide scan

Limitations of EHH

At the genome scale, decrease depends on recombination rate ("cold spot" might mimic selection) $\Rightarrow$ Difficult to compare across positions

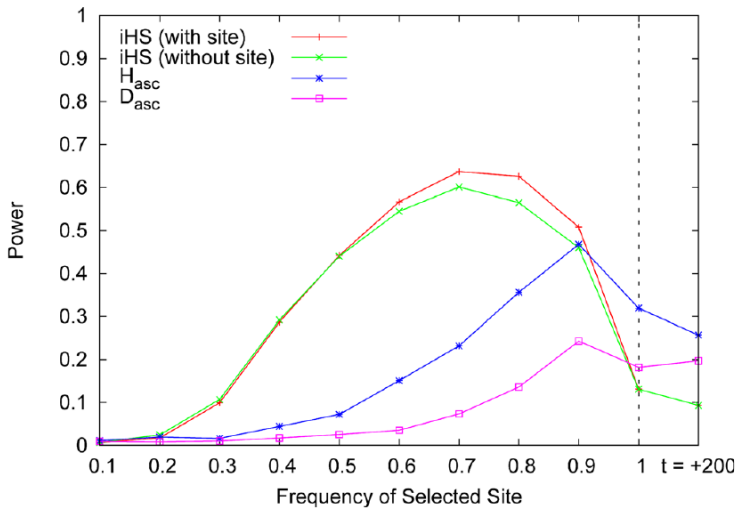
A new measure *iHS* (Voight *et al.*, 2006)

- iHH_A et iHH_D area under EHH curves for the Ancestral and Derived core allele
- $iHH = \frac{iHH_A}{iHH_D}$ and $\widetilde{iHH} = ln(iHH)$ ($\Rightarrow$ correct for recombination)
- Standardization : $iHS = \frac{(\widetilde{iHH}_i - \mu_{\widetilde{iHH}})^2}{\sigma_{\widetilde{iHH}}}$ ($\Rightarrow$ per-class of ancestral allele freq. $\simeq$ age)
- Ex. : $|iHS| > 2.58 \Rightarrow$ outier at the 0.1% (nominal) threshold



Comparisons across populations (Tang *et al.*, 2007)

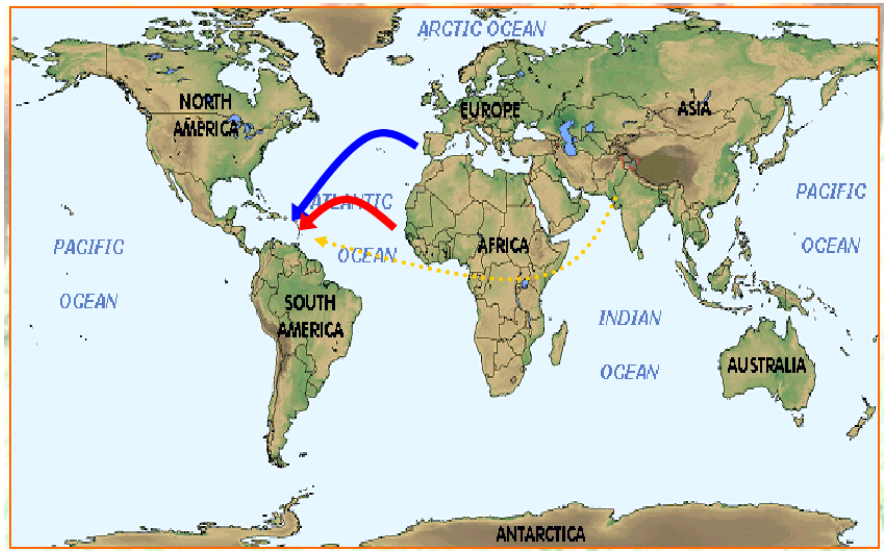
iHS-based test lacks power when the variant is close to fixation



Comparisons across populations : R_{SB} (Tang et al., 2007) or XP–EHH (Sabeti et al., 2007)

- within population : $EHHS \simeq \frac{p_A^2 EHH_A + p_D^2 EHH_D}{p_A^2 + p_D^2} \Rightarrow iES$ (area under the EHHS curve)
- across population : $\widetilde{R_{SB}} = \log\left(\frac{iES_1}{iES_2}\right) \Rightarrow$ standardization : $R_{SB} = \frac{\left(\widetilde{R_{SB}}_i - med_{\widetilde{R_{SB}}}\right)^2}{\sigma_{\widetilde{R_{SB}}}}$
- Same definition for XP–EHH (except iES is not computed the same way)

The Creole cattle from Guadeloupe : *3 origins ?*



- European Taurine (Iberia) with the first spanish colonizer (1493) et more recently (French breeds)
- African Taurines similar routes than the slave trade ones between the 16^th and 18^th centuries
- Zebus From India, introduced in America (South and US) during the 19^th century

The study (Gautier and Naves, 2011)

Design

- 140 CGU individuals combined with data on pop. from European (275 ind. from 11 breeds), African (6 breeds) and Zebu (n=3 breeds) ancestry
- Genome Scan (29 autosomes) with a 50K assay (44,507 SNPs after QC) :
    - Phasing done with FastPHASE
    - Allele polarization for iHS according to ADMIXTURE cluster freq. weighted by average CGU ancestry prop. (anc. allele=the one with the highest weighted allele frequencies)

Example of whole genome scan

- iHS scan within CGU (n=280 haplotypes)
- CGU vs. EUT (n=530 combined haplos.) comparisons using rSB and XP–EHH

The data

Haplotype Files (default format)

- Example with file `EHH_10_CGU.hap.bz2`
- 240 CGU haplos for Chromosome 10 (BTA10) with 1,877 SNPs

```
1 2 2 1 2 2 2 1 2 2 1 2 2 2 1 2 1 2 1 2 2 2 1 2 2 2 2 1 1 1 2 2 2 2 2 1 ... [1,877 col.]
2 1 2 1 2 2 1 1 2 2 1 2 1 1 1 1 1 2 2 1 2 1 2 2 2 1 1 2 1 1 2 1 1 1 1 1 ... [1,877 col.]
3 2 1 1 2 1 2 2 2 1 1 2 1 1 1 1 1 2 2 1 2 2 2 2 2 1 1 2 2 2 2 1 1 1 1 1 ... [1,877 col.]
4 2 1 1 2 2 1 1 2 2 1 2 1 1 1 1 1 2 2 2 2 2 2 2 2 2 1 1 1 2 1 2 1 1 1 ... [1,877 col.]
5 1 2 2 2 1 1 2 2 2 1 2 2 2 1 1 2 2 2 1 2 1 2 2 2 1 1 2 2 2 2 1 1 1 1 1 ... [1,877 col.]
..............................
[280 rows in total]
```

Map File

- 44,507 SNPs from 29 chromosomes (file `map.all.inp`)

```
F0100190 1 113642 1 2
F0100220 1 244699 1 2
F0100250 1 369419 1 2
F0100270 1 447278 1 2
..............................
[44,045 rows in total]
```

Loading the data and Computing iHH's (and iES's) on CGU

```
cnt=0
for(i in 10:15){#Example for Five chromosomes only
 cnt=cnt+1
 #File Name
 tmp.hapfile=bzfile(paste0("EHH_",code.chr[i],"_CGU.hap.bz2"))
 #Read data
 tmp.hap=data2haplohh(hap_file=tmp.hapfile,
                      map_file="map.all.inp",
                      chr.name=i)
 #Compute stats
 tmp.scan=scan_hh(tmp.hap,threads=4)
 if(cnt==1){
  wgscan.cgu=tmp.scan
  }else{
  wgscan.cgu=rbind(wgscan.cgu,tmp.scan)
  }
}
 head(wgscan.cgu)
```

Computing and plotting iHS

```
ihs.cgu=ihh2ihs(wgscan.cgu,minmaf=0.05,freqbin=0.025)

head(ihs.cgu$iHS,25)
ihs.cgu$frequency.class
distribplot(ihs.cgu$iHS$iHS)

ihsplot(ihs.cgu)
```

Comparing CGU vs. EUT with rSB and XP-EHH

Computing iES for European Taurines

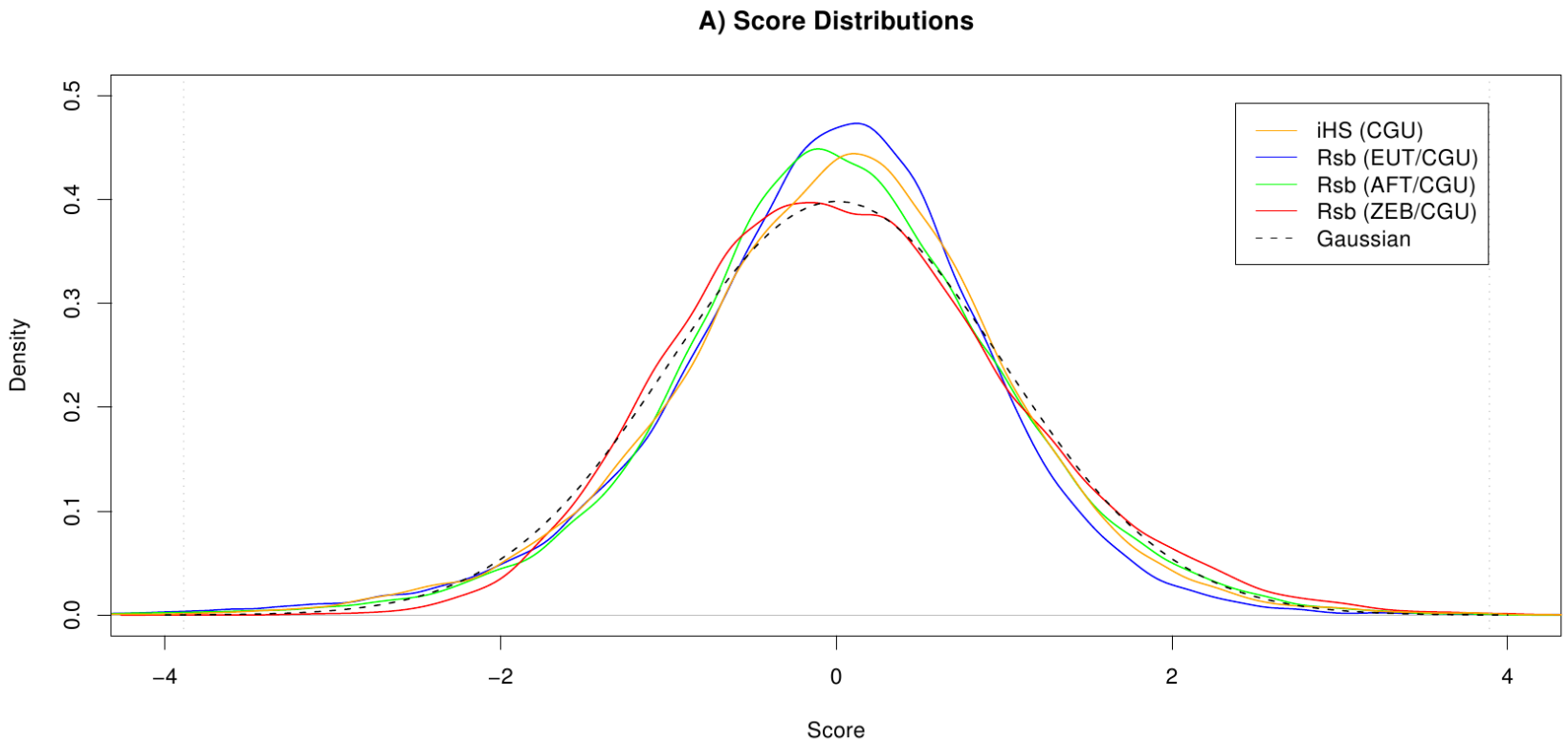
```
cnt=0
for(i in 10:15){
 cnt=cnt+1
 tmp.hap=data2haplohh(hap_file=bzfile(paste0("EHH_",code.chr[i],"_EUT.hap.bz2")),
                      map_file="map.all.inp",chr.name=i)
 tmp.scan=scan_hh(tmp.hap,threads=4)
 if(cnt==1){wgscan.eut=tmp.scan}else{wgscan.eut=rbind(wgscan.eut,tmp.scan)}
}
```

Computing Rsb and XpEHH (CGU vs. EUT)

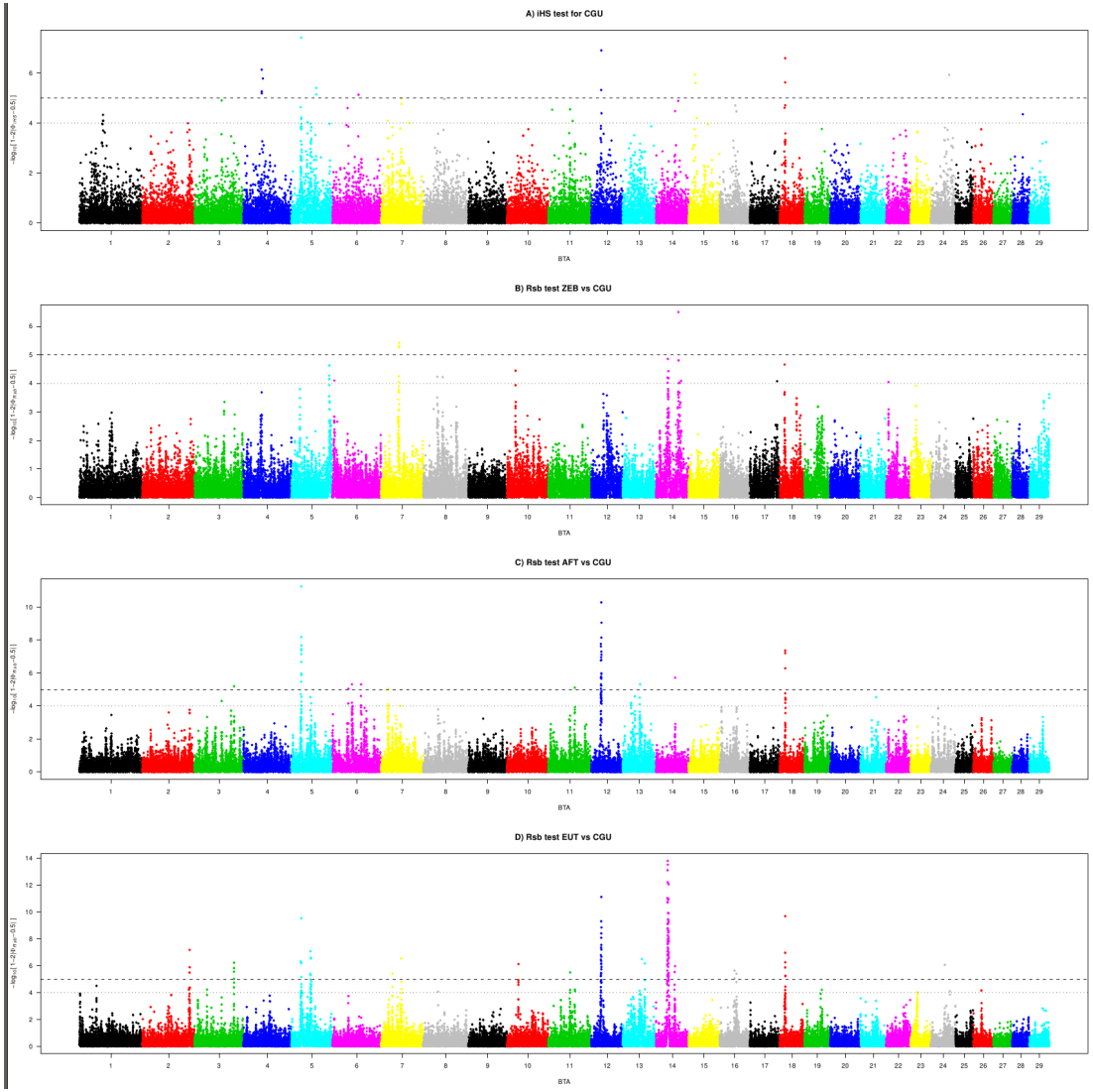
```
rsb=ies2rsb(wgscan.cgu,wgscan.eut)
xpehh=ies2xpehh(wgscan.cgu,wgscan.eut)

rsbplot(rsb)
xpehhplot(xpehh)
```

Computing *iHS* within CGU and R_{SB} CGU versus each of the 3 ancestries



Footprints of Selection



Footprints of selection

Variant origin

- Most signals are common to several tests (including admixture based tests)
- 14/15 significant regions with an excess of ZEB ancestry (better adaptation ?)

Candidate genes and biological functions

- Reproduction : RXFP2, PMEPA1, IGFBP3 et SLCA5
- Metabolism : CYP46A1, PDE1B
- Disease resistance : CENTD3

Vizualising haplotype structure around RXFP2 SNP

```
i=12
tmp.hap=data2haplohh(
          hap_file=bzfile(paste0("EHH_",code.chr[i],"_CGU.hap.bz2")),
          map_file="map.all.inp",chr.name=i)
layout(matrix(1:2,2,1))

bifurcation.diagram(tmp.hap,mrk_foc=456,all_foc=1,nmrk_l=20,nmrk_r=20,
            main="Bifurcation diagram (RXFP2 SNP on BTA12): Ancestral Allele")

bifurcation.diagram(tmp.hap,mrk_foc=456,all_foc=2,nmrk_l=20,nmrk_r=20,
            main="Bifurcation diagram (RXFP2 SNP on BTA12): Derived Allele")
```

Key features of REHH

- Identify footprints of selection using haplotype structure (LD information)
  - Within population (iHS) [ancestral allele information needed in theory]
  - Across pairs of population (rSB or XP-EHH) (polarization of the signal)
  - If npop>2, combining signals ?
- Computationnally efficient (e.g., parallel computing)
- Indirect approach (Need complementary approaches to understand/validate the origin of the signal)
- For more details, see the REHH vignette
  `https://cran.r-project.org/web/packages/rehh/vignettes/rehh.pdf`