# Population Genomics on The X Chromosome

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**Abstract**

In order to get a hands on experience with some of the most used population genomics statistics, we processed SNP data from the Simons Genome Diversity Project with the tests: Fst, iHS, XPEHH and LD. In order to limit the bounds, we constrained the study to the X chromosome only.

For each of the population genomics-related tests, we found the top ten genes, and compared them across the populations as a means to seek for genes with selection or differential selection between populations. Most of the genes recognized by the statistics were found to be related to gene regulation, and some were pseudogenes. No particularly interesting genes were recognized.

The code for this project can be found on:

<https://github.com/cmkobel/population-genomics-X-chromosome>

1. *Perform an Fst scan between sets of populations in a sliding window of 100 SNP positions, including at least the contrast between Africa and Europe, between Europe and East Asia, and between East Asia and Africa. Identify the 10 strongest Fst outlier regions in each case. Identify their genomic position and the genes covered by these Fst peaks. Discuss potential adaptive explanations*

In order to calculate Fst, we need the allele frequencies for each SNP position. We obtained those frequencies from the SNP files. Fst in defined as Fst = 1 – (Hes / Het) where Hes and Het are the expected frequency of heterozygotes when two populations are considered either as two subpopulations (Hes) or as one total (Het). It measures the lack of heterozygotes in the subpopulations in relation to the total population. Fst was calculated for each individual SNP in the following region combinations: Africa – Westeurasia, Westeurasia – Eastasia, Eastasia – Africa. These populations have been present for a long time, and it might be interesting to see, if the Fst statistic can be used to recognize any interesting genes with differential selection between populations. The regions in this exercise are considered to be separate populations though they may not be, practically speaking.

A rolling window of 100 SNPs was applied on each population combination in order to get a moving average.

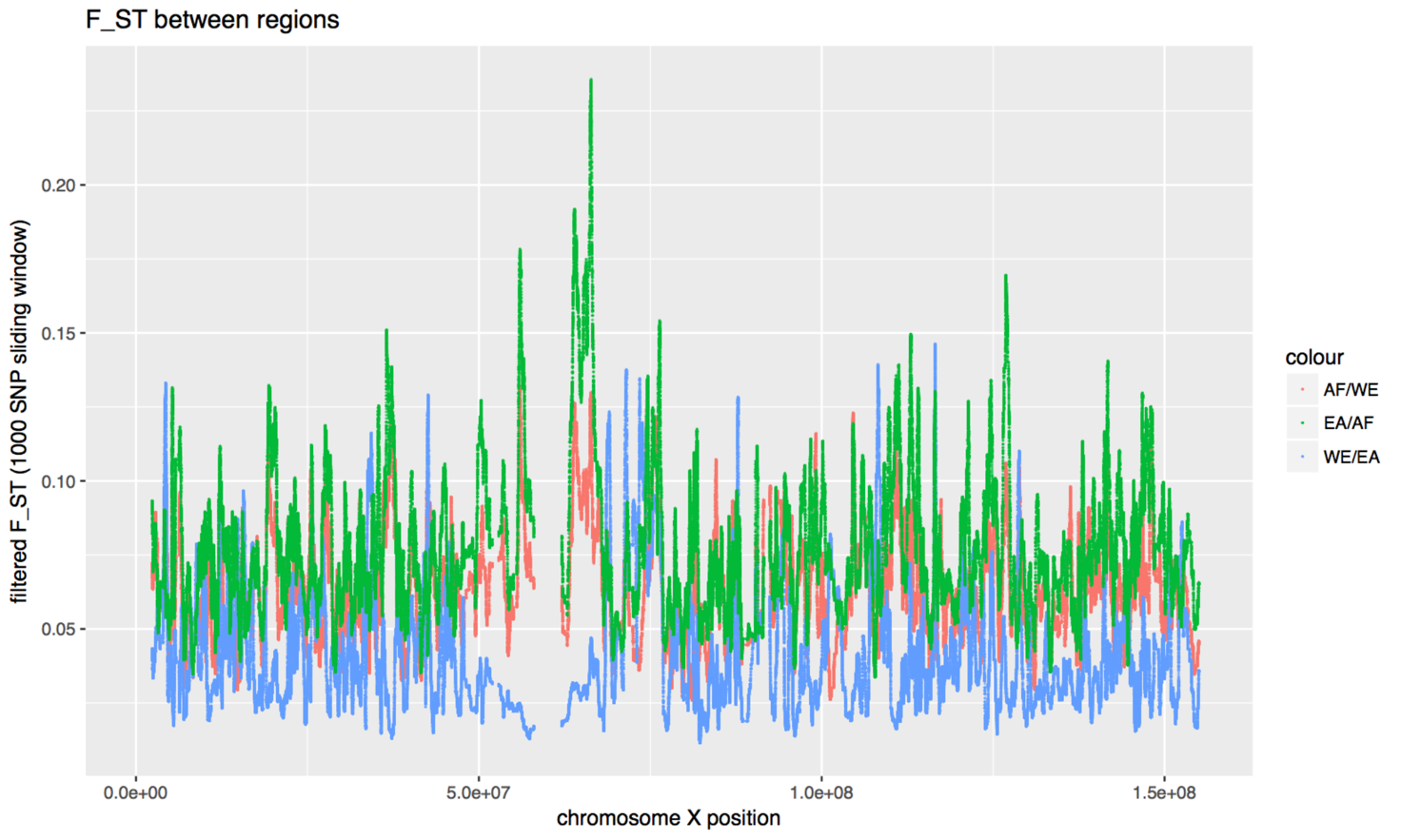


Figure : Fst between two populations at a time. The size of the sliding window is 1K SNPs in order to get less erratically moving average.

Because Fst varies a lot throughout the chromosome, the plotting was done with data from a bigger sliding window. The biggest peaks are present around the centromere, we don’t know why.

As values of high Fst show differentiation between the two subpopulations, we can investigate these peak-regions and maybe find genes that correlate with the way populations have diverged.

**Results from Fst**

These are the genes with the highest Fst values. They were found by overlapping the sliding window fst with the gencode v17 annotation, thresholding the Fst until 10 different genes were present.

Table : 10 Genes with an Fst above the 99,8% percentile with the populations Africa and Westeurasia. The Fst used here is the mean of 100 adjacent SNP Fsts. Note that ‘transcript\_type’ denotes the transcript of the specific Fst peak, and not the gene region as a whole.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **gene\_name** | | **position** | **fst\_peak** | **transcript\_type** |
| IL1RAPL2 | | 104558536 | 0,233493218 | protein\_coding |
| SYTL5 | | 37889821 | 0,219400423 | protein\_coding |
| TM4SF2 | | 37889821 | 0,219400423 | protein\_coding |
| RP13-188A5.1 | | 55982443 | 0,210125629 | processed\_transcript |
| UPRT | | 74513664 | 0,198155786 | protein\_coding |
| PRRG1 | | 37300948 | 0,197715863 | protein\_coding |
| RP11-357K9.2 | | 37300948 | 0,197715863 | pseudogene |
| DMD | | 32713394 | 0,196936313 | protein\_coding |
| RP11-54I5.1 | | 55988008 | 0,195909956 | pseudogene |
| OCRL | | 128707674 | 0,192535606 | protein\_coding |
|  |

Table : Genes with an Fst above the 99,89% percentile with the populations Westeurasia and Eastasia. The Fst used here is the mean of 100 adjacent SNP Fsts. Note that ‘transcript\_type’ denotes the transcript of the specific Fst peak, and not the gene region as a whole.

|  |  |  |  |
| --- | --- | --- | --- |
| **gene\_name** | **position** | **fst\_peak** | **transcript\_type** |
| FTX | 73308940 | 0,303662952 | lincRNA |
| RP11-262D11.2 | 71377253 | 0,286265802 | pseudogene |
| PIN4 | 71472853 | 0,269973204 | protein\_coding |
| NHSL2 | 71352521 | 0,250927669 | protein\_coding |
| RP11-262D11.1 | 71352521 | 0,250927669 | pseudogene |
| RPS4X | 71476289 | 0,246681874 | protein\_coding |
| RGAG4 | 71349753 | 0,246583034 | protein\_coding |
| TMEM164 | 109370144 | 0,246502551 | protein\_coding |
| BX119917.1 | 71372190 | 0,233755654 | miRNA |
| UHRF2P1 | 73325745 | 0,228391375 | pseudogene |

Table : Genes with an Fst above 99,3% percentile with the populations Eastasia and Africa. The Fst used here is the mean of 100 adjacent SNP Fsts. Note that ‘transcript\_type’ denotes the transcript of the specific Fst peak, and not the gene region as a whole.

|  |  |  |  |
| --- | --- | --- | --- |
| **gene\_name** | **position** | **fst\_peak** | **transcript\_type** |
| CTD-2076M15.1 | 126794656 | 0,304382696 | lincRNA |
| RP13-188A5.1 | 55982877 | 0,293978003 | processed\_transcript |
| RP11-54I5.1 | 55988008 | 0,283576529 | pseudogene |
| RP5-964N17.1 | 112907371 | 0,260622912 | lincRNA |
| KRT8P27 | 63843830 | 0,25835841 | pseudogene |
| CHRDL1 | 109929651 | 0,245930567 | protein\_coding |
| DCAF8L2 | 27620805 | 0,240543042 | protein\_coding |
| YWHAZP7 | 63832930 | 0,236082919 | pseudogene |
| HEPH | 65473327 | 0,22653709 | protein\_coding |
| HTR2C | 114083321 | 0,226096665 | protein\_coding |

By looking up the gene names on NCBI gene, we looked through the summary of each gene. No obvious adaptation genes appeared in this analysis. Many genes are associated with genes related to gene regulation and/or retinis pigmentosa. This might be because the X chromosome has many genes related to the development of sex, and that many of the genes related to population divergence might be on other chromosomes. This might be pure speculation though.

1. *Perform an iHS scan of the whole X chromosome for at least three populations. Identify the 10 most significant regions and associated with genes as in A.*

iHS (integrated haplotype score) is a test statistic developed by Voight et al. (Voight et al. 2006). iHS can be used to test for positive selection (where the frequency of an allele increases or decreases monotonically). It is based on the EHH statistic which is developed by Sabeti et al. (Sabeti et al. 2007). EHH indicates the decay of linkedness (or identity) away from each SNP. Because selection happens on regions covering several SNPs, we can use the SNP data to infer how much selection has occoured on each SNP position. Because the area under the curve of EHH is more highly correlated with selection than is EHH by itself, we integrate EHH, and get the iHH (integrated Haplotype Homozygosity). This iHH can be computed either with respect to the ancestral or derived allele, and when we take the log-ratio between them we get the unstandardized iHS. This undstandardized iHS is then standardized with the variance, and we finally get iHS, which can be used to score the amount of selection in each SNP.

The same three populations as in exercise *a)* were selected for this iHS exercise.

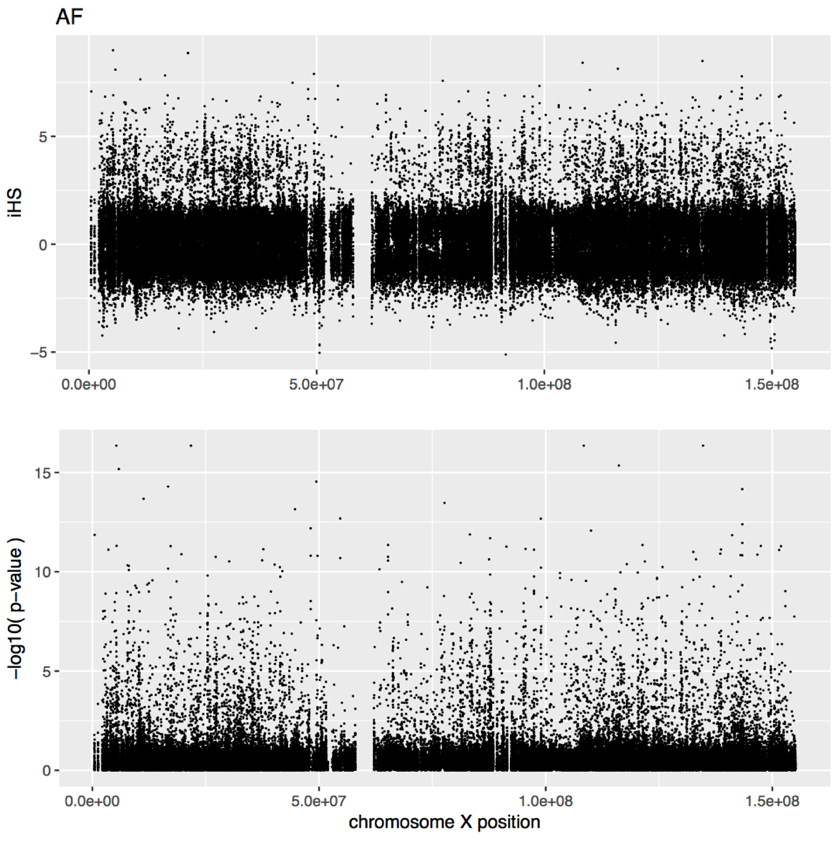


Figure : iHS and associated p-values for the Africa population

Table : The 10 genes with the highest iHS in the Africa population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **gene\_name** | **position** | **iHS** | **ppval** | **gene\_type** |
| DDX26B | 1,35E+08 | 8,494167 | 16,35253 | protein\_coding |
| SMPX | 21753631 | 8,866302 | 16,35253 | protein\_coding |
| NLGN4X | 5809792 | 8,096836 | 15,17644 | protein\_coding |
| CTPS2 | 16700579 | 7,82612 | 14,29183 | protein\_coding |
| ARHGAP6 | 11287745 | 7,644587 | 13,68043 | protein\_coding |
| XRCC6P5 | 98924229 | 7,340968 | 12,67356 | pseudogene |
| CHRDL1 | 1,1E+08 | 7,154159 | 12,07481 | protein\_coding |
| PCDH11X | 91347968 | 6,894997 | 11,26869 | protein\_coding |
| DYNLT3 | 37698495 | 6,850401 | 11,13287 | protein\_coding |
| TM4SF2 | 37698495 | 6,850401 | 11,13287 | protein\_coding |

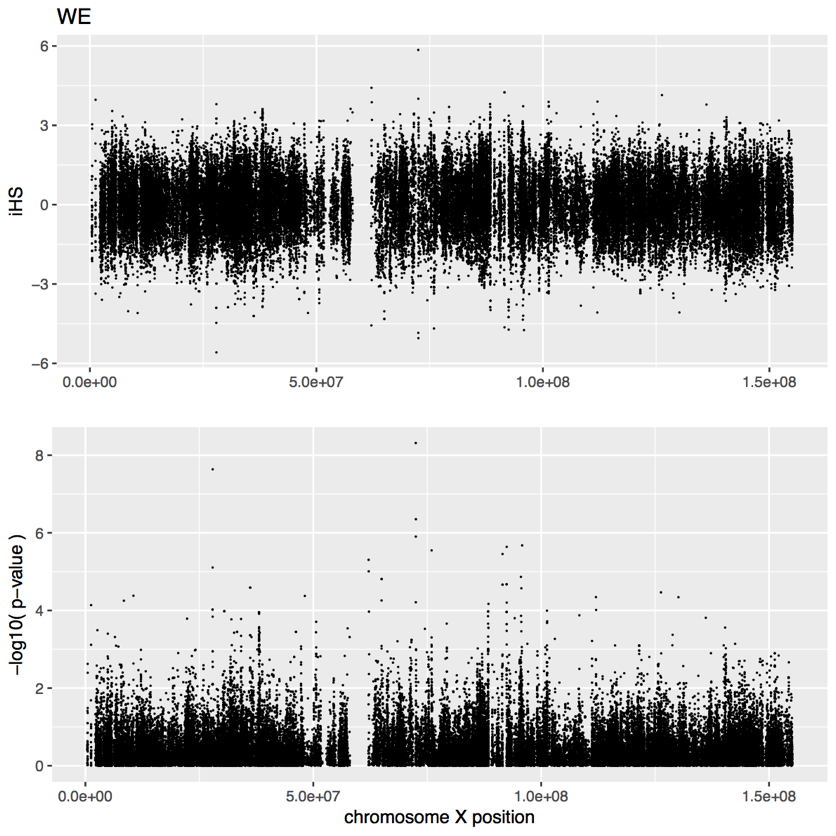


Figure : iHS and associated p-values for the Westeurasia population

Table : The 10 genes with the highest iHS in the Westeurasia population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **gene\_name** | **position** | **iHS** | **ppval** | **gene\_type** |
| PCDH11X | 91522531 | 4,24694 | 4,664121 | protein\_coding |
| MID1 | 10543062 | -4,09752 | 4,37924 | protein\_coding |
| AMOT | 1,12E+08 | 3,89799 | 4,343454 | protein\_coding |
| RP1-23K20.2 | 1,3E+08 | -4,07714 | 4,341094 | antisense |
| GPR101 | 1,36E+08 | 3,78353 | 3,810735 | protein\_coding |
| DMD | 32629538 | -3,55711 | 3,770822 | protein\_coding |
| CD99 | 2648871 | -3,59655 | 3,49151 | protein\_coding |
| OTC | 38257658 | -3,55653 | 3,425053 | protein\_coding |
| TM4SF2 | 38105192 | 3,618469 | 3,382885 | protein\_coding |
| CHDC2 | 36153918 | -3,51765 | 3,361119 | protein\_coding |

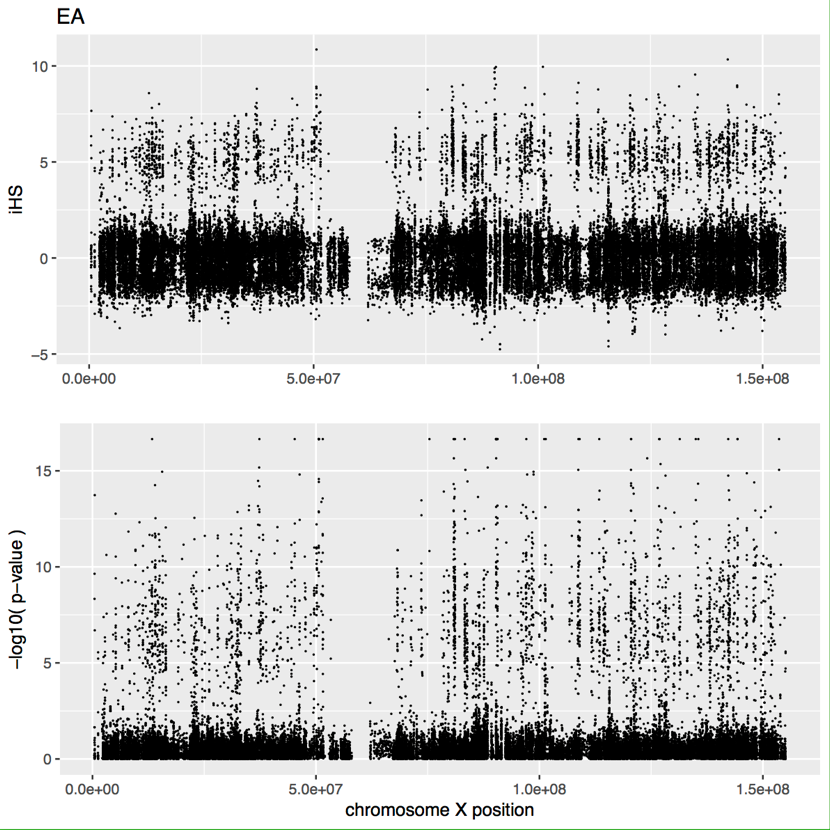


Figure : iHS and associated p-values for the East asia population

Table : The 10 genes with the highest iHS in the Eastasia population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **gene\_name** | **position** | **iHS** | **ppval** | **gene\_type** |
| BEX5 | 1,01E+08 | 8,533277 | 16,65356 | protein\_coding |
| GS1-600G8.3 | 13334199 | 8,583642 | 16,65356 | antisense |
| RP1-192P9.1 | 45240847 | 8,298389 | 16,65356 | pseudogene |
| RP5-842K24.2 | 1,31E+08 | 8,93403 | 16,65356 | antisense |
| RPL10 | 1,54E+08 | 8,512827 | 16,65356 | protein\_coding |
| SAGE1 | 1,35E+08 | 9,550098 | 16,65356 | protein\_coding |
| SPANXN1 | 1,44E+08 | 8,982066 | 16,65356 | protein\_coding |
| PRRG1 | 37296759 | 8,0713 | 15,17644 | protein\_coding |
| TM4SF2 | 37344835 | 8,80894 | 15,17644 | protein\_coding |
| GUCY2F | 1,09E+08 | 8,05655 | 15,0515 | protein\_coding |
| RPS6KA6 | 83428893 | 8,044866 | 15,0515 | protein\_coding |

Ppvalues for Westeurasia are all very low, this may be because of some external source of error, as there is no reason to believe that selection in general, should be lower in this population.

1. *Perform an XP-EHH scan of the whole X chromosome for at least three populations. Identify the 10 most significant regions and associated with genes as in A.*

XP-EHH (Cross Population Extended Haplotype Homozygosity) is developed by Sabeti et al. (Sabeti et al. 2007). It detects selective sweeps between two populations where the SNP is fixed in one and polymorphic in the other. It is based on the EHH test, which measures the decay of identity from a SNP. XP-EHH compares the length of these EHH regions between populations. A positive value of XP-EHH suggests selection in the first population, and a negative in the second population.

The results from the XP-EHH analysis was overlapped with the gencode v17 gene annotation and the ppval thresholded in order to obtain 10 genes in each region combination. Not that many of the ppvalues are below 5, denoting a non-significant signal.

Table : The ten genes with the highest xpehh values form the comparison of populations Africa and Westeurasia

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **gene\_name** | **position** | **xpehh** | **ppval** | **transcript\_type** |
| DHRSX | 2180731 | -7,42314 | 12,94175 | protein\_coding |
| RP11-104D21.3 | 50909542 | -5,43121 | 7,252011 | lincRNA |
| PCDH11X | 91523596 | -5,07198 | 6,40484 | protein\_coding |
| ALAS2 | 55038885 | -5,0175 | 6,281109 | protein\_coding |
| KAL1 | 8680990 | -4,8634 | 5,937848 | protein\_coding |
| ATP6AP1 | 1,54E+08 | -4,65318 | 5,48564 | protein\_coding |
| CCNB1IP1P3 | 94032285 | -4,62797 | 5,432668 | pseudogene |
| APEX2 | 55034419 | -4,4867 | 5,140661 | protein\_coding |
| PRKX | 3532267 | -4,44306 | 5,052127 | protein\_coding |
| GDI1 | 1,54E+08 | -4,23953 | 4,649781 | protein\_coding |

Table : The ten genes with the highest xpehh values form the comparison of populations Westeurasia and Eastasia

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **gene\_name** | **position** | **xpehh** | **ppval** | **transcript\_type** |
| PCDH11X | 91517416 | 5,341297 | 7,034873405 | protein\_coding |
| FOXN3P1 | 101802186 | -5,07722 | 6,416815261 | pseudogene |
| PASD1 | 150837984 | -4,87148 | 5,955593461 | protein\_coding |
| RP11-45D17.1 | 150837984 | -4,87148 | 5,955593461 | pseudogene |
| NXF4 | 101809168 | -4,65913 | 5,498187928 | processed\_transcript |
| GABRA3 | 151369634 | 4,487602 | 5,142490811 | protein\_coding |
| SMARCA1 | 128611215 | 4,280981 | 4,730321307 | protein\_coding |
| RP11-258C19.5 | 53191756 | 4,192733 | 4,559699127 | lincRNA |
| RP11-40F8.2 | 22850109 | -4,14499 | 4,468730689 | processed\_transcript |
| MTMR1 | 149932703 | -4,06234 | 4,31351351 | protein\_coding |

Table : The ten genes with the highest xpehh values form the comparison of populations Eastasia and Africa

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **gene\_name** | **position** | **xpehh** | **ppval** | **transcript\_type** |
| DHRSX | 2180731 | 7,817278 | 14,27334853 | protein\_coding |
| ATP6AP1 | 153664698 | 5,344227 | 7,041897407 | protein\_coding |
| GDI1 | 153666533 | 5,022854 | 6,293204142 | protein\_coding |
| KAL1 | 8680990 | 4,691439 | 5,566565913 | protein\_coding |
| ALAS2 | 55038885 | 4,517497 | 5,203600027 | protein\_coding |
| RP11-104D21.3 | 50909542 | 4,147207 | 4,472942981 | lincRNA |
| PCDH11X | 91523596 | 3,760786 | 3,771136357 | protein\_coding |
| MAGED1 | 51600709 | 3,661409 | 3,600617079 | protein\_coding |
| RP11-22B10.3 | 51600709 | 3,661409 | 3,600617079 | pseudogene |
| DMD | 33113844 | 3,616343 | 3,524628171 | protein\_coding |

DHRSX shows up both in the analysis on Africa-Westeurasia and Eastasia-Africa. According to the NCBI Gene database, it is a dehydrogenase present in most tissues. It does not have any obvious relation to population differentiation. Paralogs of RP11 show up in all the populations. ALAS2 shows up in Africa-Westeurasia and Eastasia-Africa, it is an enzyme located in the mitochondria that and is a part of the heme pathway. KAL1 shows up in the Africa-related analyses and is related the development of puberty.

It doesn’t appear to us that any of genes that come out of the XPEHH analysis has any relation to the divergence between the populations.

1. *Intersect the analysis of Fst and XP-EHH*

Fst can be used to indicate the divergence between two populations as it measures the relative difference in the frequency of heterozygotes. If there have been a selective sweep in the population, the frequency of heterozygotes might be significantly changed in one of the populations.

XPEHH on the other hand is similar to the Rsb statistic, but instead of using the Tang et al. iES, it uses the iES defined by Sabeti et al.(Sabeti et al. 2007). It detects selective sweeps where a SNP is fixed in one population, and polymorphic in the total population.

Fst is discards fixed SNP (as the frequency of heterozygosity is not possible to calculate from fixed SNP data.

We compared the top ten peaks from the Fst test, and XPEHH test. In Africa vs. Westeurasia there wasn’t any union between the results, other than paralogs of the RP11 gene (often as pseudogenes) kept on showing up across the two tests. RP11 is a pre-mRNA processing factor that is a part of the spliceosome complex. The coding paralogs are associated with retinitis pigmentosa. It doesn’t appear to have any connection with adaptation.

1. *Perform any additional analysis of your own choice, such as (diversity along the C X chromosome)*

We decided to calculate the linkage disequilibrium (LD) throughout the X chromosome. LD can be calculated in different ways. The method we implemented here consists of calculating the pairwise correlation of a window of (in this case) 100 SNPs. The mean was calculated from each of these 100 SNP windows, and plotted against the median chromosomal positition (see figure Figure 5: Linkage disequilibrium throughout the X chromosome from the African population.)



Figure : Linkage disequilibrium throughout the X chromosome from the African population.

We have done linkage disequilibrium calculations on many of the populations. Unfortunately, we haven’t had the time to compare them with the other tests.