Comparative analyses of inbreeding on the X-chromosome in Croatian sheep breeds

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Estimation of inbreeding - increase in homozygosity (autozygosity)

- ✓ Higher frequency of detrimental genetic disorders
    - ✓ Inbreeding depression
    - ✓ Redistribution of genetic variances
- – central point of population genetics/genomics –

X-chromosome at non-PAR

- ❖ Higher genetic drift & smaller Ne (3/4), $Ne_X = (9\ N_m\ N_f) / (4\ N_m + 2\ N_f)$
- ❖ Reduced genetic diversity (48-80%)
- ❖ Mutations occur less frequently (lower in females vs. males in mammals)
- ❖ Lower recombination rate & higher linkage disequilibrium (2/3)
- ❖ Specific selection pressure (detrimental mutations)
- ❖ Sex-biased admixture

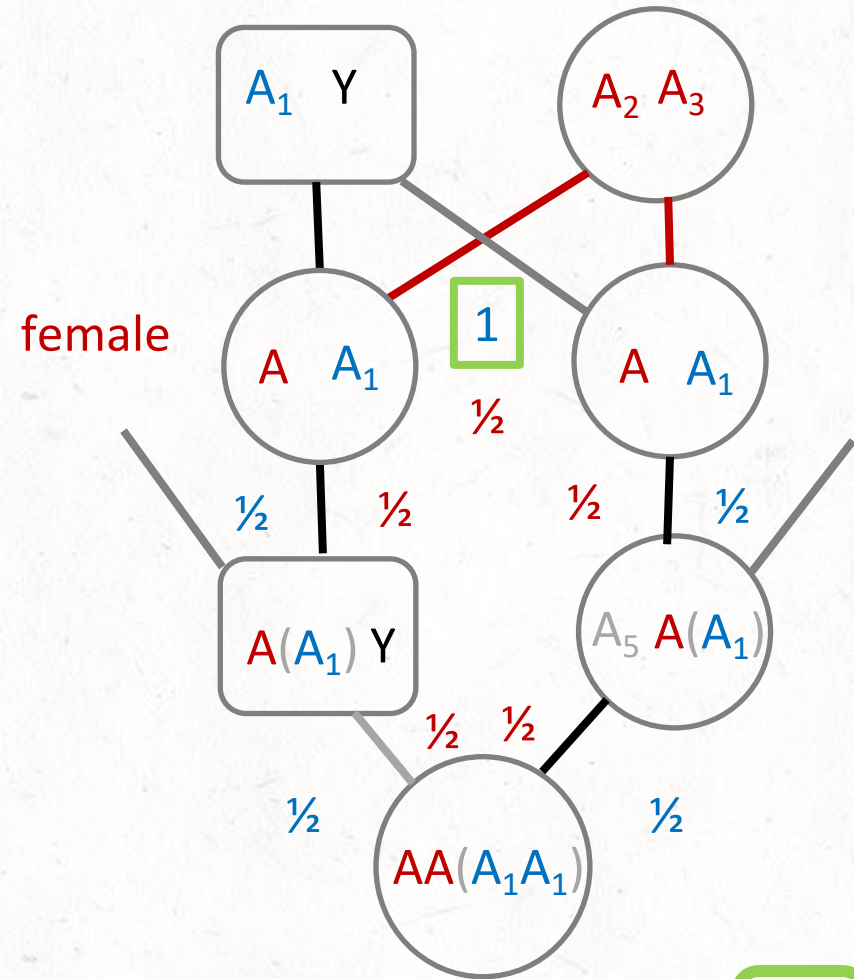## Inbreeding & X chromosome - limited information available

Pedigree sex (X-chromosome) inbreeding coefficient

male

A₁ Y
A₂ A₃
A Y ½
A₁ A
½
A₄ Y
A₅ A
½
A₄ A
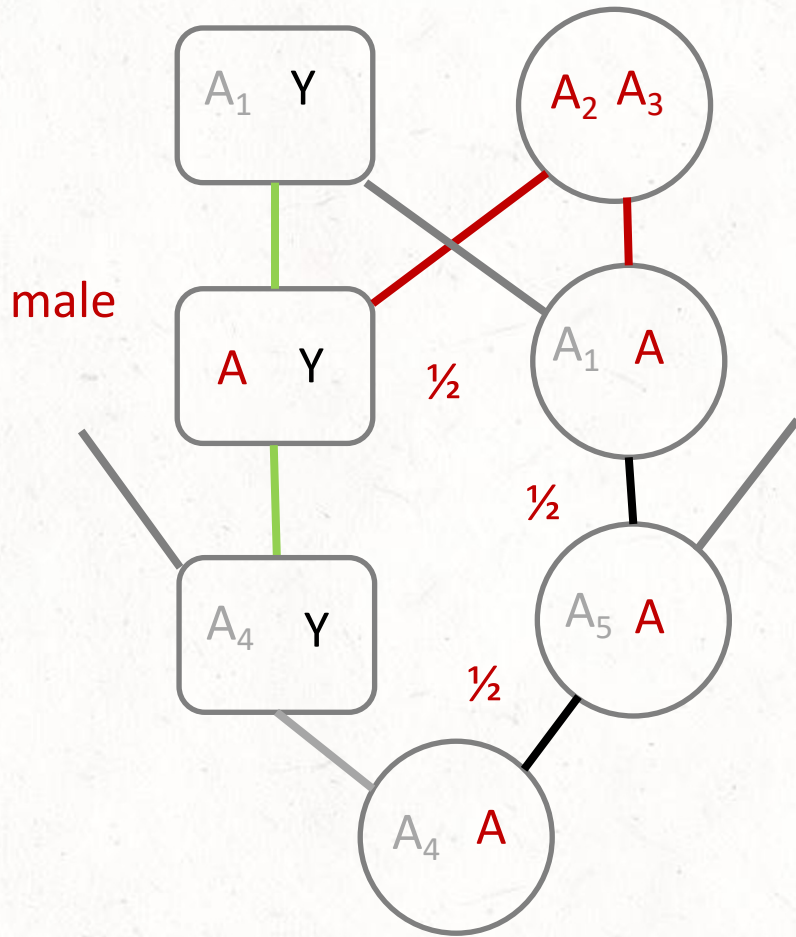
$Pr(A_2A_2 \text{ or } A_3A_3) = 0$

No possibility of A_2A_2 or A_3A_3 female !

$F_{sex} = 0$ versus $F = 0.0625$

female

A₁ Y
A₂ A₃
A A₁ 1
½
A A₁
½ ½ ½ ½
A(A₁) Y
A₅ A(A₁)
½ ½
½ ½
AA(A₁A₁)

$Pr(A_2A_2 \text{ or } A_3A_3) = \tfrac{1}{2} * \tfrac{1}{2} * \tfrac{1}{2} * \tfrac{1}{2} * \tfrac{1}{2} = (\tfrac{1}{2})^5$

$Pr(A_1A_1) = 1 * \tfrac{1}{2} * \tfrac{1}{2} * \tfrac{1}{2} * \tfrac{1}{2} * \tfrac{1}{2} = (\tfrac{1}{2})^4$

$F_{sex} = (\tfrac{1}{2})^5 + (\tfrac{1}{2})^4 = \mathbf{0.09375}$ versus $F = \mathbf{0.0625}$

1. Estimation of **genomic inbreeding** coefficients on the **X chromosome** in Croatian **sheep** breeds

2. **Comparison** of **different** estimated **genomic coefficients** & **X** versus **autosomal chromosomes**

3. **Segmental variation** of inbreeding on **X chromosome**

Genomic inbreeding coefficients

a) Identity-by-state (IBS)

- LH_1 (Li & Horvitz 1953, AJHG)

- VR_1 (VanRaden 2008, JDS)

- Ya_2 (Yang et al., 2010, NG)

b) Identity-by-descent (IBD)

- ROH (McQuillan et al., 2008, AJHG)

- HBD (Druet & Gautier, 2017, ME)

7 East Adriatic sheep breeds – 98 female individuals

Krk Island Sheep (13), Pag Island Sheep (13), Cres Island Sheep (14), Rab Island Sheep (12), Istrian sheep (13), Dalmatian Pramenka (13) & Dubrovnik Ruda (20)

Ovine Infinium® HD SNP BeadChip 600K

GenTrain score <0.4

GenCall score <=0.8

Genotype call rate <0.9

HWE 10^{-7}

Duplicates

Individual call rate <0.95

27 questionable SNPs

X chromosome: 18 983 SNPs   **Autosomes:** 391 755 SNPs

IBS

Genomic inbreeding coefficients, F_{LH1} & F_{LH1X} : Li & Horvitz, 1953
  - PLINK as F_{HOM}

Genomic inbreeding coefficients, F_{VR1} & F_{VR1X} : VanRaden 2008

  - GCTA as F_{HOM} with the option --make-grm-alg 1

Genomic inbreeding coefficients, F_{Ya2} & F_{Ya2X} : Yang et al., 2010
  - GCTA as F_{HAT3}

Genomic inbreeding coefficients without Hi-IBD segment (40 – 75.8 Mb)
  - F_{LH1Xr}, F_{VR1Xr} & F_{Ya2Xr}

IBD

ROH inbreeding coefficients, F_{ROH} & F_{ROHX} : Ferenčaković et al., 2013
  - SVS, ROH sizes related to 1, 4 & 8 Mb
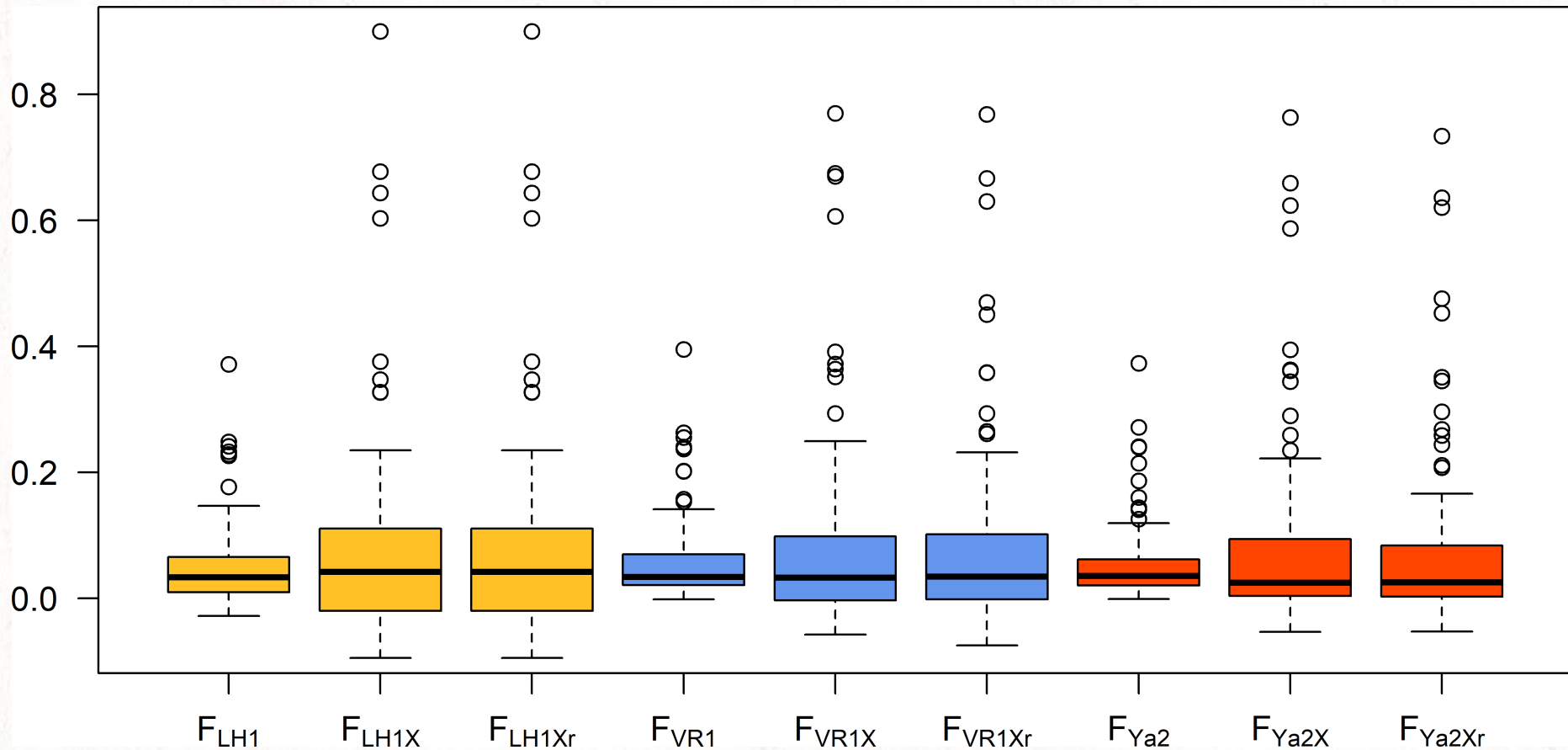 - sliding window of 7.03 Mb (by 0.2) along X chromosome

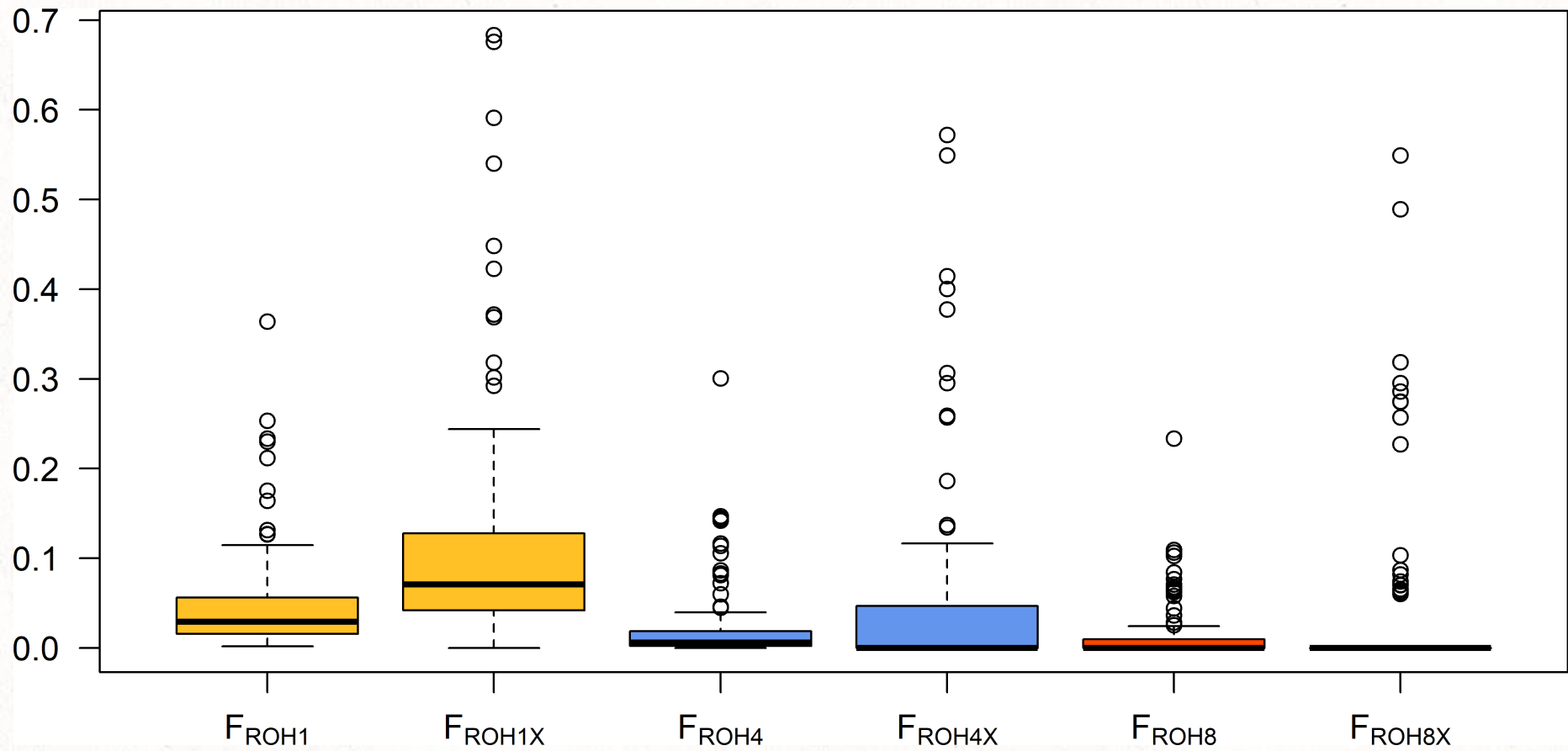Homozygosity by Descent coefficients, F_{HBD} : Druet & Gautier, 2017
  - Mixkr model with predefined rates, base_rate of 2 & with 8
  classes (2, 4, …, 128 & non-HBD) going 64 generations back
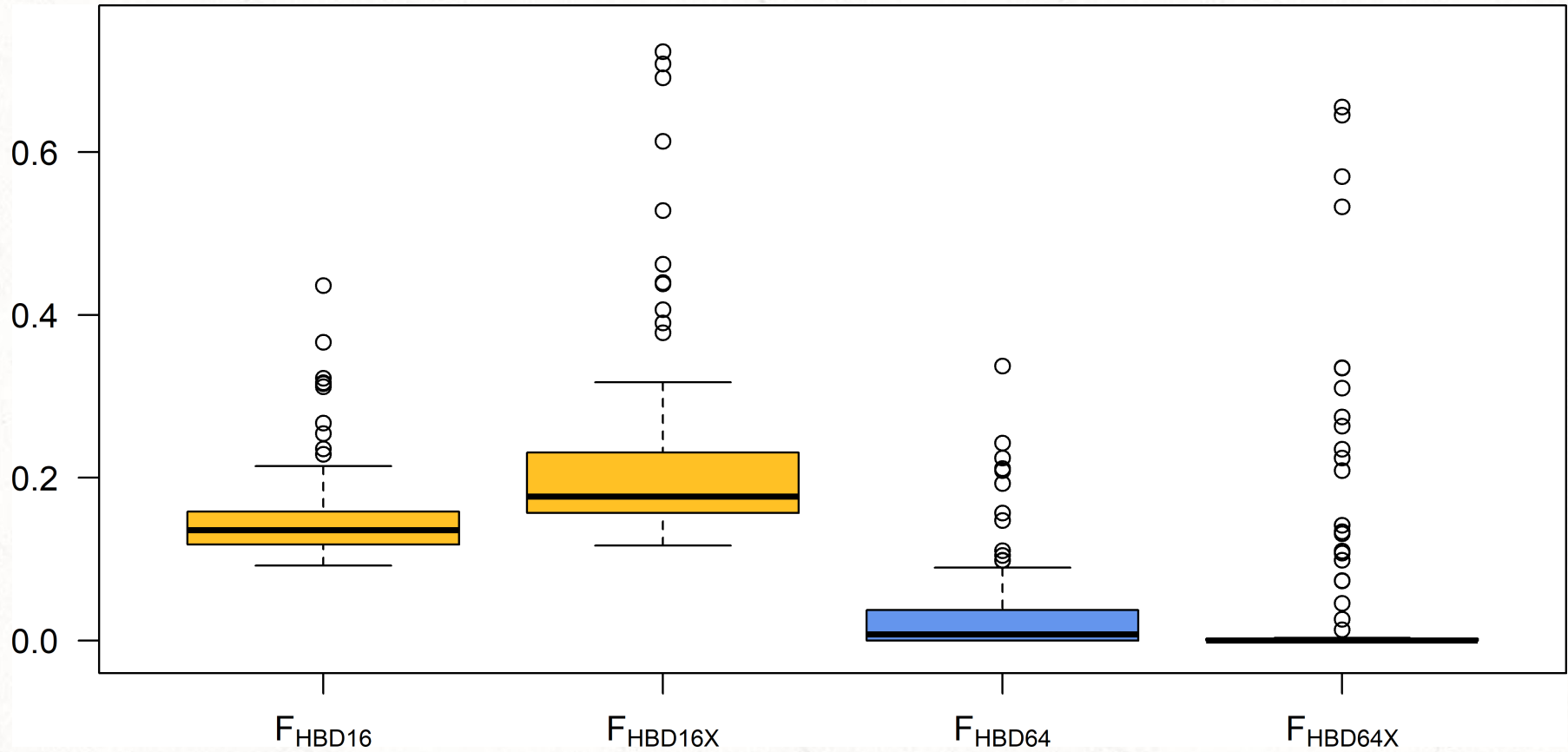
Genomic Inbreeding coefficients; F_{LH1}, F_{VR1} & F_{Ya2}

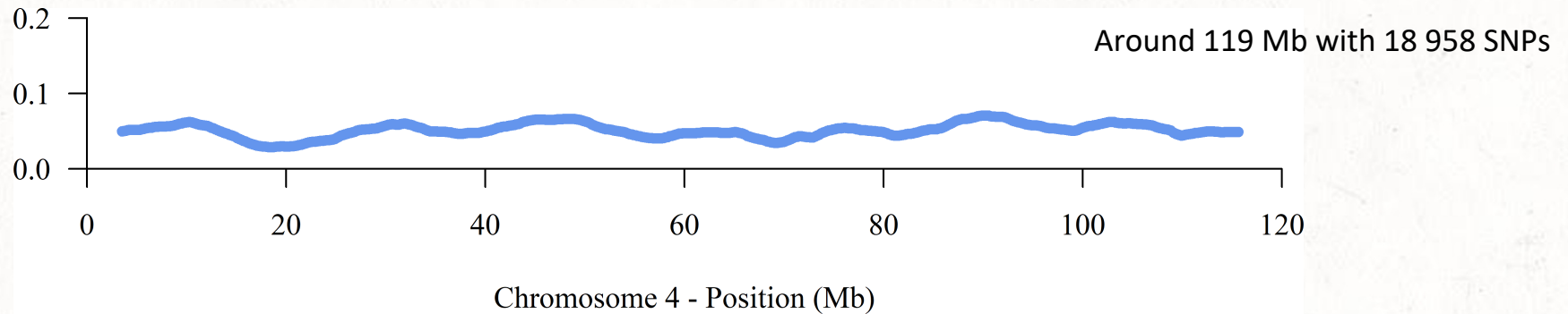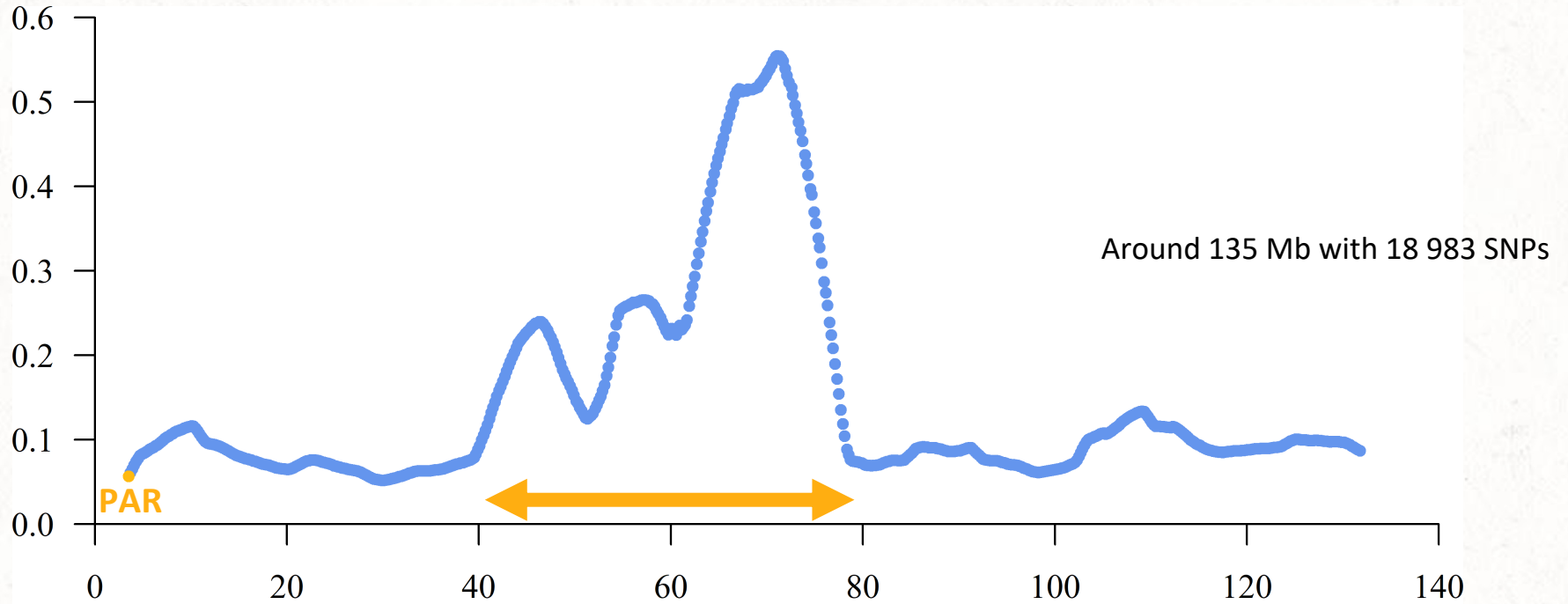ROH Inbreeding coefficients; F_{ROH1}, F_{ROH4} & F_{ROH8} (>1, >4 & >8 Mb)

HBD Inbreeding coefficients; F_{HBD64} & F_{HBD16}

Regional variation for the X chromosome inbreeding (F_{ROH1X})

Around 135 Mb with 18 983 SNPs

PAR

X chromosome - Position (Mb)

Around 119 Mb with 18 958 SNPs
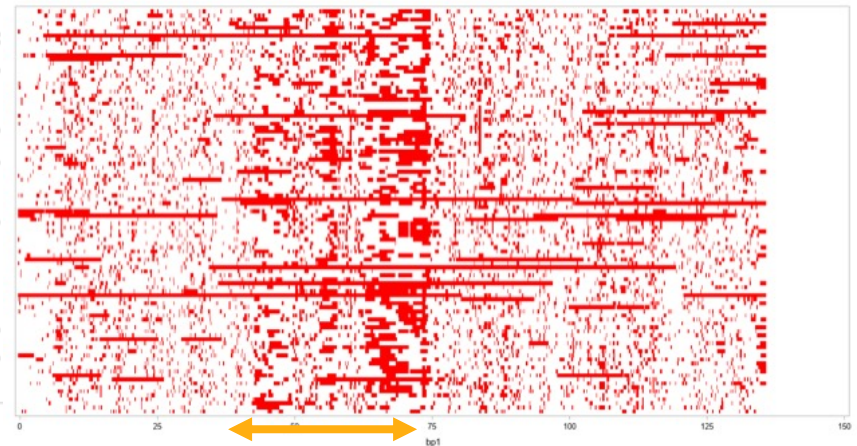
Chromosome 4 - Position (Mb)

► sliding window of 7.03 Mb (by 0.2)

Comparative illustration of the estimation of IBD genomic inbreeding

ROH1X
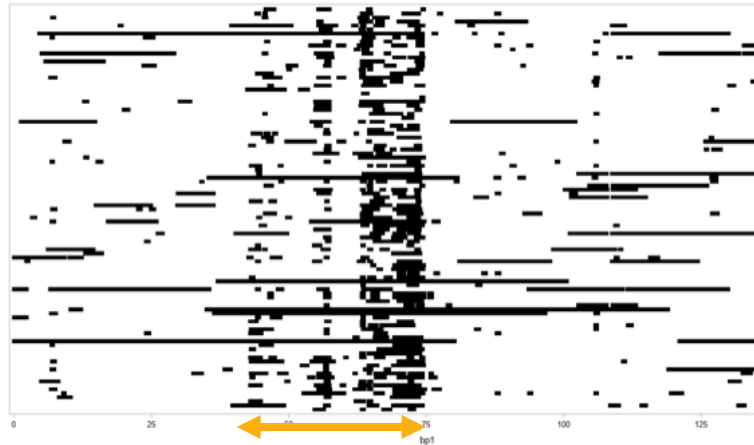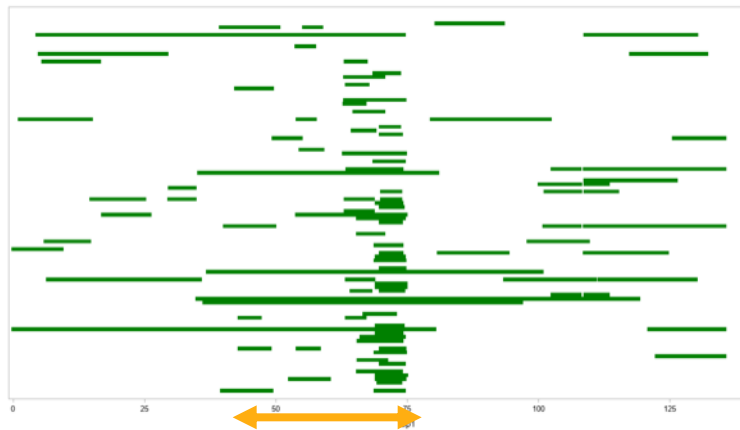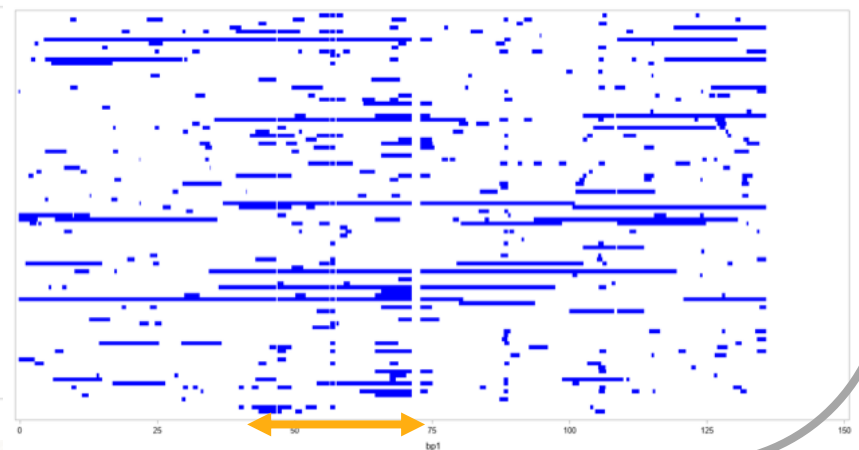
HBD64X

ROH4X

HBD64X-50K

High IBD appearance - recombination and/or selection ?

Correlations – inbreeding coefficients for the X chromosome

	F_{LH1X}	F_{VR1X}	F_{Ya2X}	F_{ROH1X}	F_{ROH4X}	F_{ROH8X}	F_{HBD64X}	F_{HBD16X}
F_{LH1X}	1.00	0.98	**0.97**	0.92	0.89	0.85	0.93	0.95
F_{VR1X}		1.00	**0.99**	0.96	0.92	0.86	0.98	0.97
F_{Ya2X}			**1.00**	**0.97**	**0.93**	**0.87**	**0.99**	**0.97**
F_{ROH1X}				1.00	0.96	0.92	0.97	0.96
F_{ROH4X}					1.00	0.97	0.91	0.94
F_{ROH8X}						1.00	0.85	0.89
F_{HBD64X}							1.00	0.98
F_{HBD16X}								1.00

Correlations – autosomes versus X chromosome : 0.65 – 0.70

Inbreeding coefficient - IBS	Partial correlations
F_{LH1}, F_{LH1X}	0.65
F_{VR1}, F_{VR1X}	0.68
F_{Ya2}, F_{Ya2X}	0.67
F_{LH1}, F_{LH1Xr}	**0.65**
F_{VR1}, F_{VR1Xr}	**0.68**
F_{Ya2}, F_{Ya2Xr}	**0.68**

Inbreeding coefficient - IBD	Partial correlations
F_{ROH1}, F_{ROH1X}	0.66
F_{ROH4}, F_{ROH4X}	0.67
F_{ROH8}, F_{ROH8X}	0.66
F_{HBD64}, F_{HBD64X}	0.69
F_{HBD16}, F_{HBD16X}	0.70

Genomic inbreeding coefficients for the X chromosome

❖ **IBS** genomic **inbreeding** coefficients, **X chromosome** versus **autosomes,** were **not different by magnitude**

❖ **IBD** genomic **inbreeding** coefficients were **higher in X chromosome**, particularly for remote estimates. Region with **dense IBD segments detected**

❖ Almost all **X chromosome inbreeding** coefficients had **larger variation** in comparison to autosome estimates

❖ For all (IBS & IBD) genomic inbreeding coefficients **correlations** between **X chromosome** and **autosomes** were similar ranging from **0.65 to 0.70**

Part of the PhD thesis - Mario Shihabi

Future work and challenges:

- to include more species

- to support evidence by computer simulations

- to evaluate impact of recombination

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any
questions
?

glad to answer

Thanks for your attention!