

Impact and utilisation of the mitogenome in livestock breeding & genetics

Information beyond nuclear inheritance

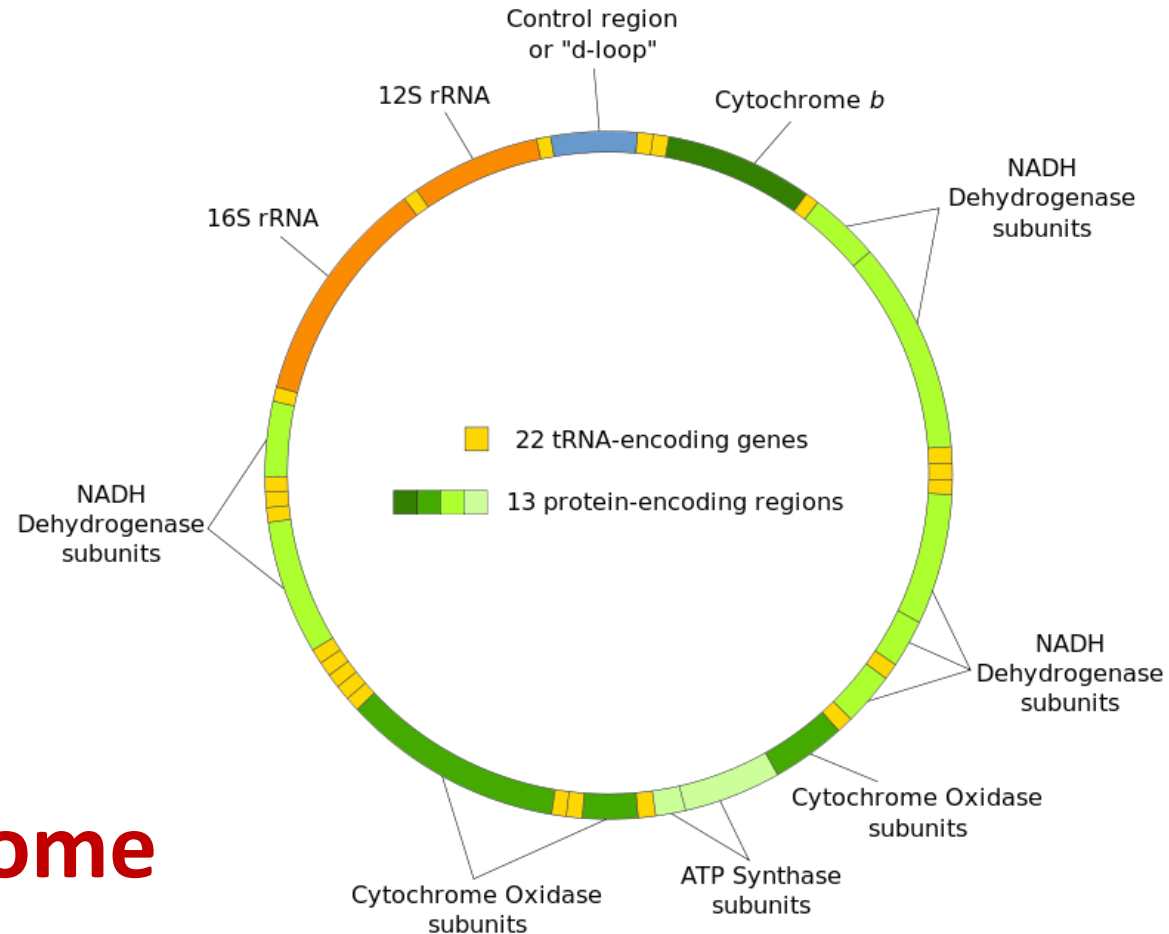
Curik Ino, Vladimir Brajković, Dinko Novosel, Strahil Ristov, Marija Špehar, Mato Čačić, Maja Ferenčaković, Dragica Šalamon, Nikola Raguž, Vlatka Čubrić Čurik



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2. Mitogenome determination
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1. Biology and role of the mitogenome



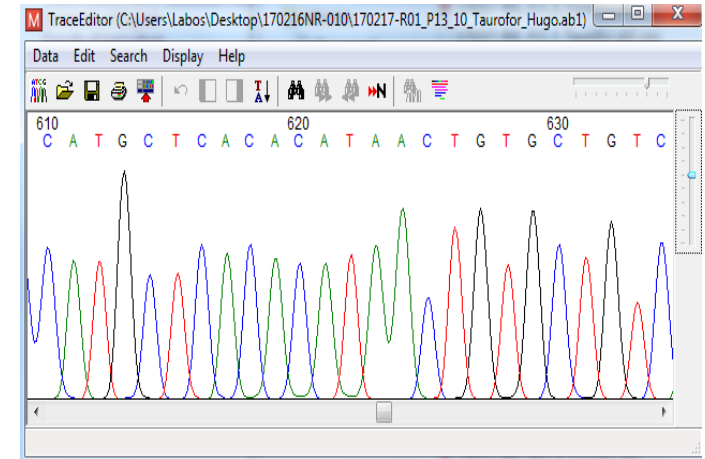
Mitogenome

- small circular molecule (mtDNA $\approx 16,472$ bp : nDNA $\approx 3 \cdot 10^9$ bp)
- coding of 37 genes (13 of 87 OXPHOS components \rightarrow cell energy)

2. Mitogenome determination

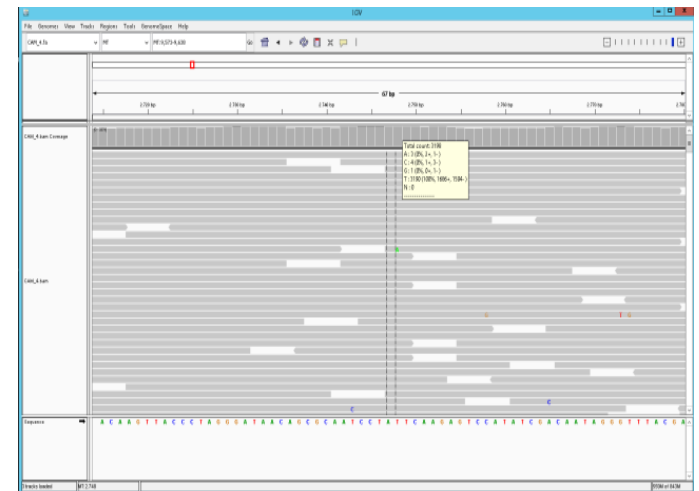
Sanger sequencing

- Approximately >20 sequences



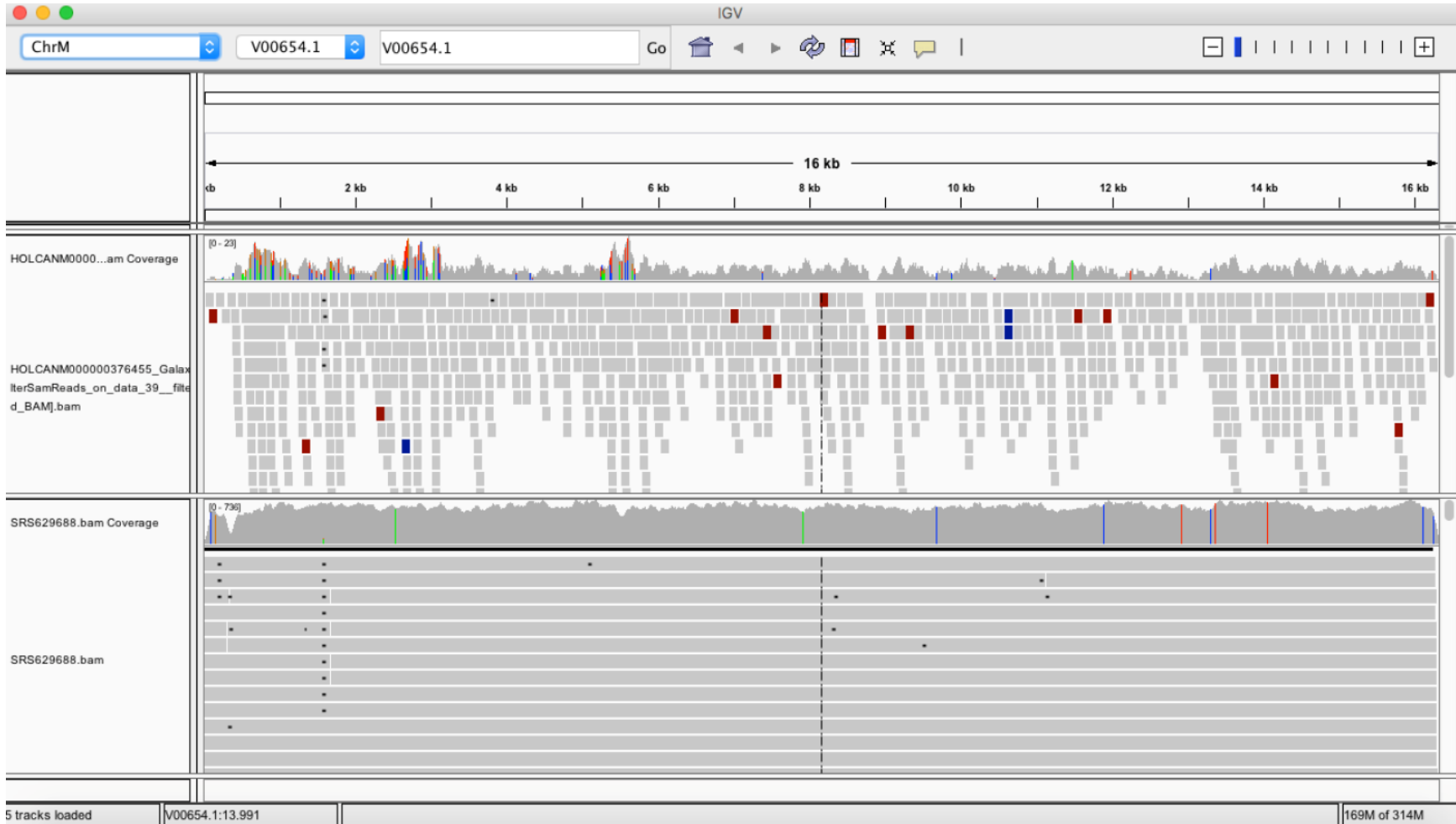
NGS sequencing

- Sequencing after long range PCRs
- Retrieval from WGS



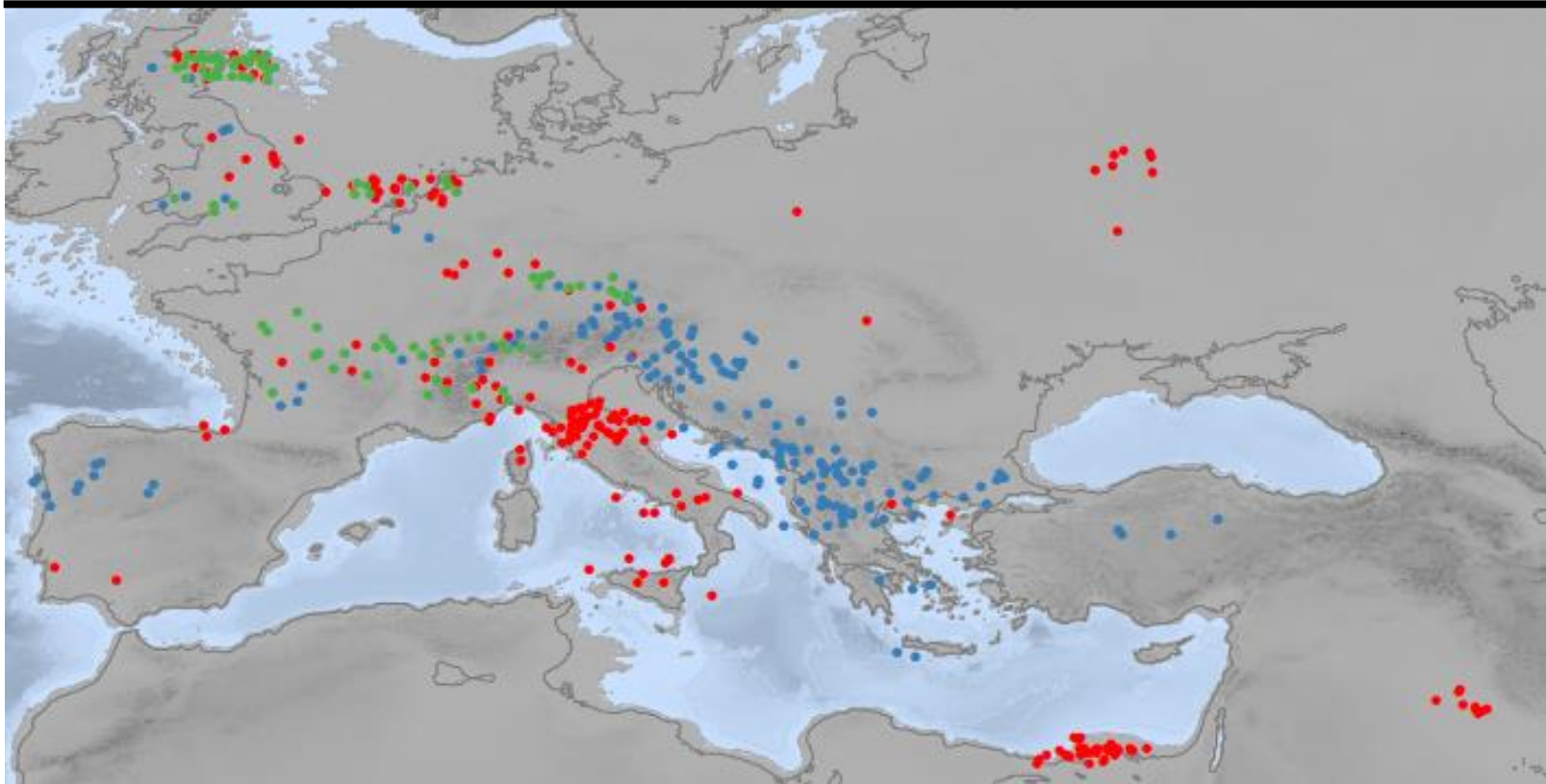
NGS → IGV

Bed sequence



Good sequence

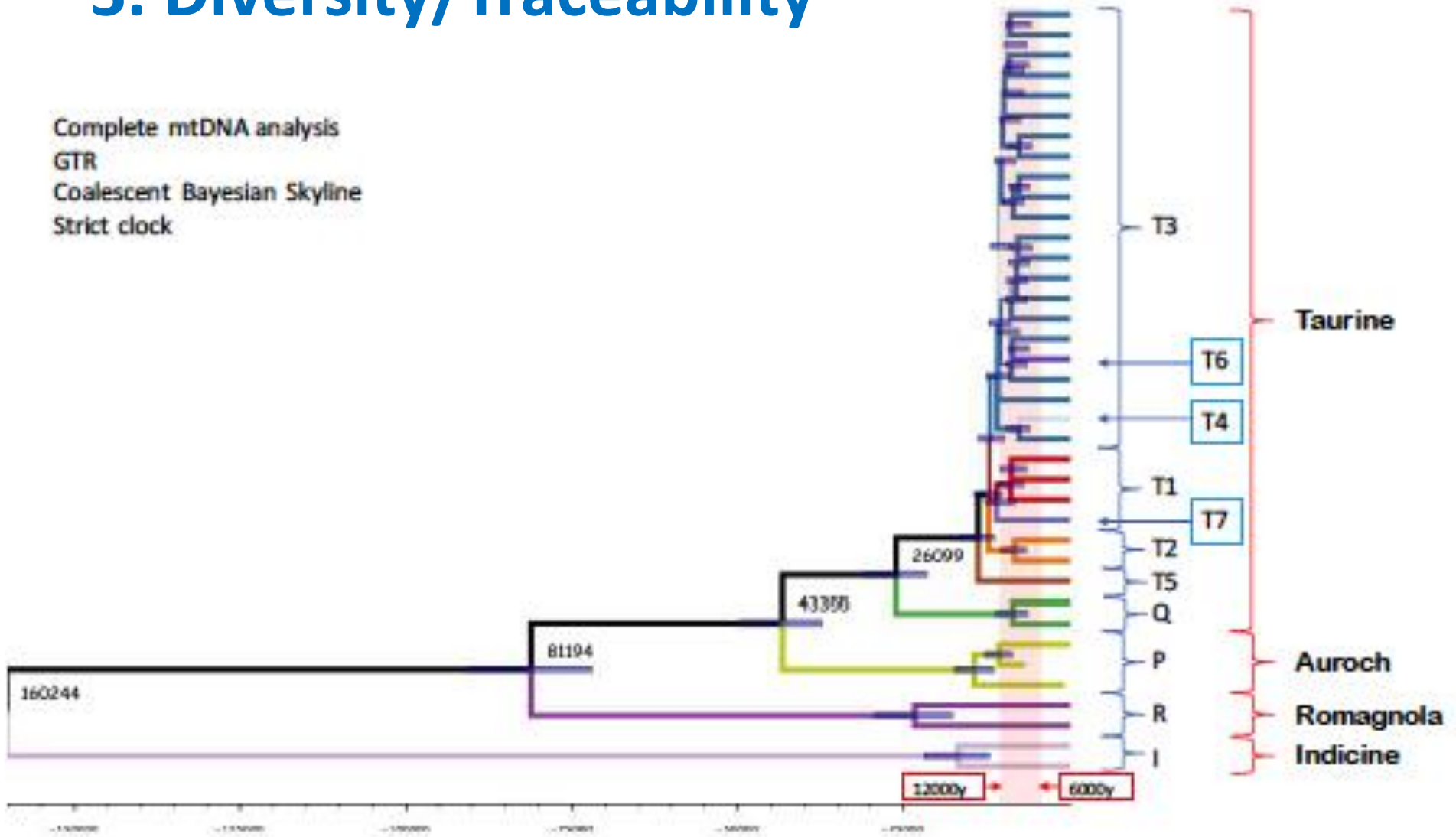
| | NCBI | NGS | WGSr | Δ (%) |
|---------|-------------|------------|-------------|--------------|
| Animals | 298 | 190 | 115 | 102 |
| Breeds | 52 | 44 | 10 | 104 |



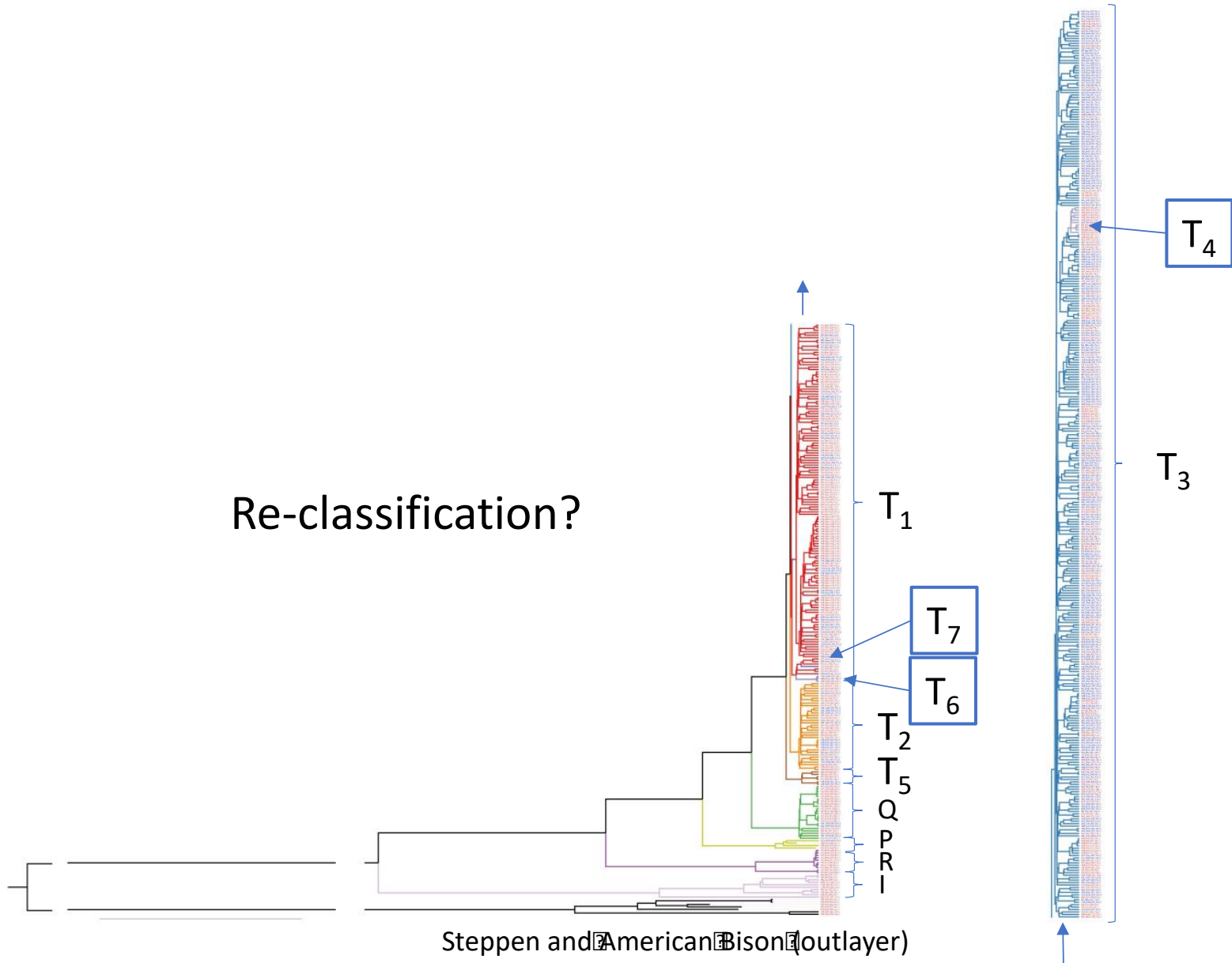
Origin of the analysed samples with emphasis on Europe (origin of all samples not presented): **NCBI sequences in red**, **Illumina NGS obtained sequences in blue** & **Sequences retrieved from the whole-genome sequences in green**.

3. Diversity/Traceability

Complete mtDNA analysis
GTR
Coalescent Bayesian Skyline
Strict clock



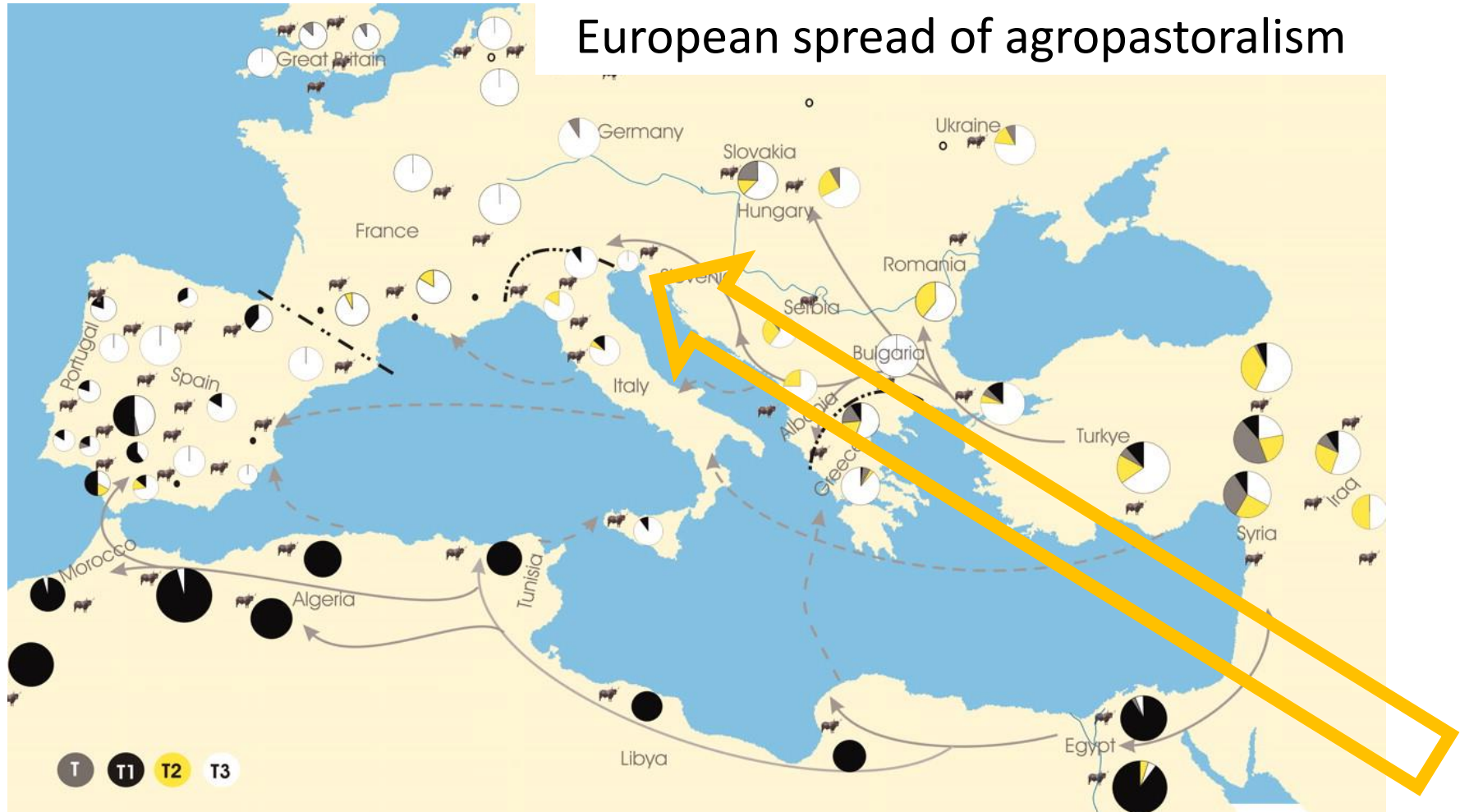
Re-classification?



Steppen and American Bison (outlayer)

3. Domestication/Archaeogenetics

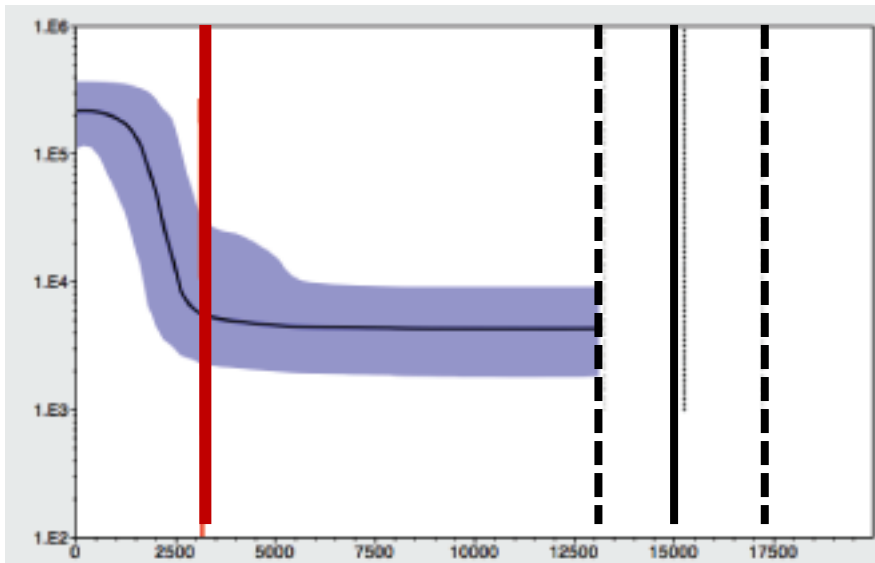
European spread of agropastoralism



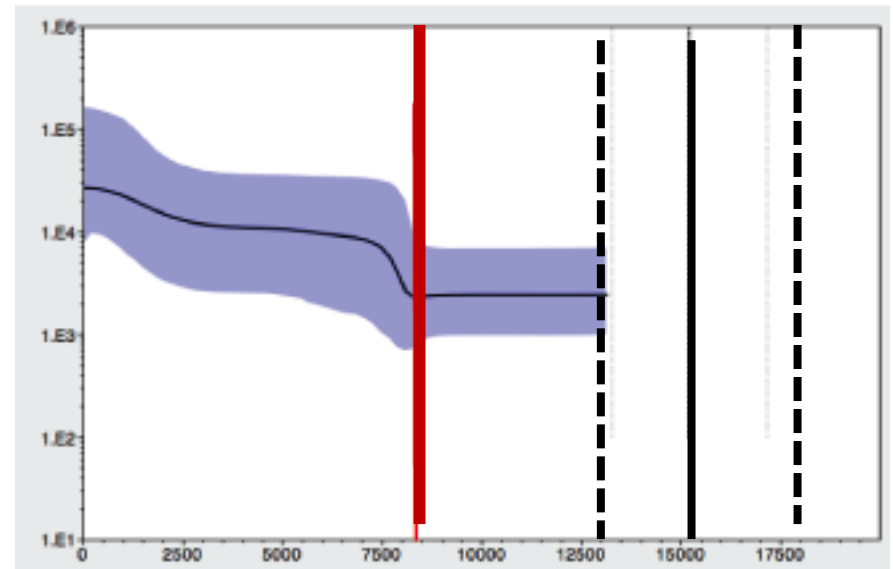
Demographic models – Bayesian skyline analysis

1. “African” haplotype (T_1) – around **3 kya** demographic explosion – beginning of domestication in Africa?

3 kya T_1 haplotype



8 kya



Q haplotype

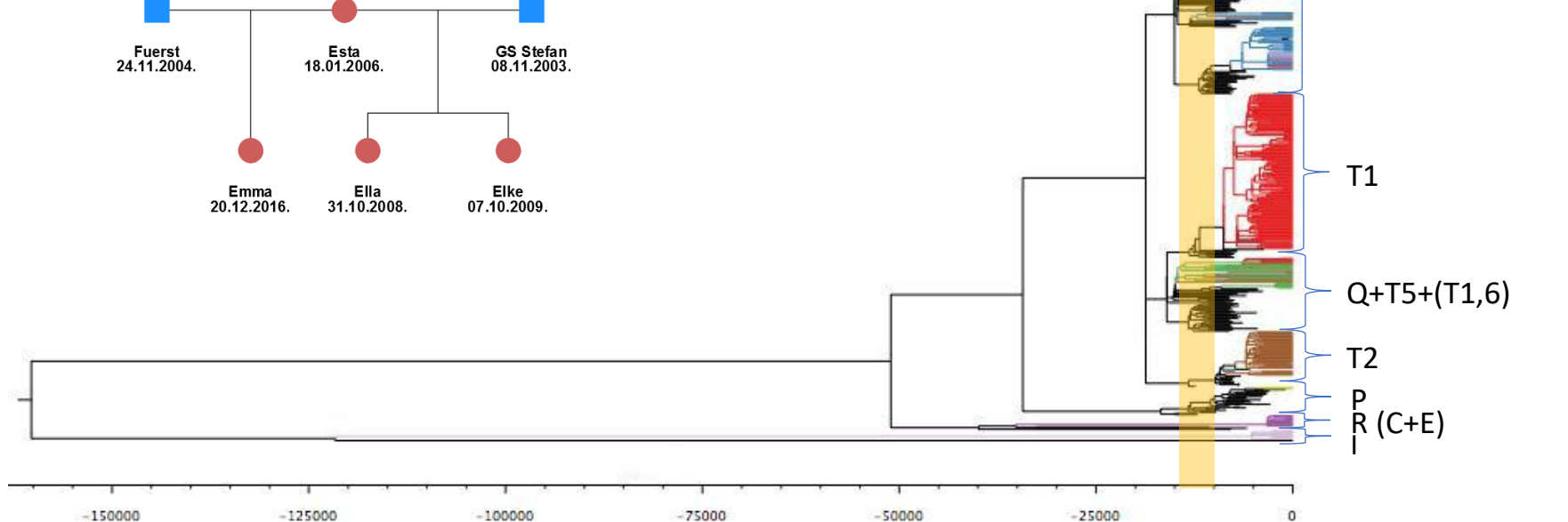
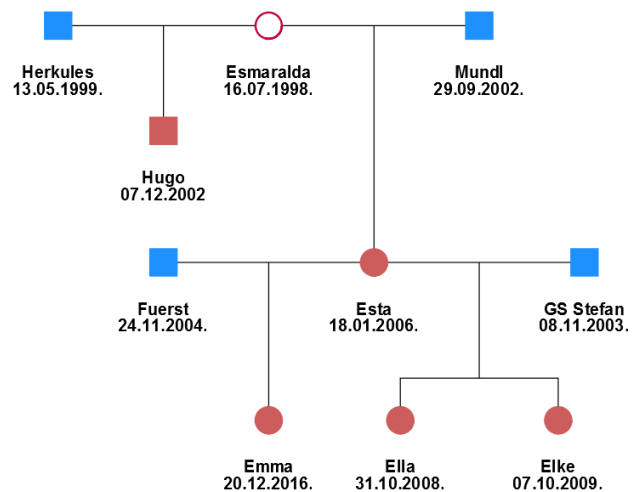
2. “Fertile Crescent” haplotype (Q) – around **8 kya** demographics explosion – earliest sign of domestication?

Partial D-loop sequence analysis, GTR, Coalescent Bayesian Skyline, Strict clock

12000 BP

6000 BP

Haplogroup P Murbodner Lineage



4. Pedigree analysis and imputation

Ristov et al. *Genet Sel Evol* (2016) 48:65
DOI 10.1186/s12711-016-0242-9




SOFTWARE

Open Access

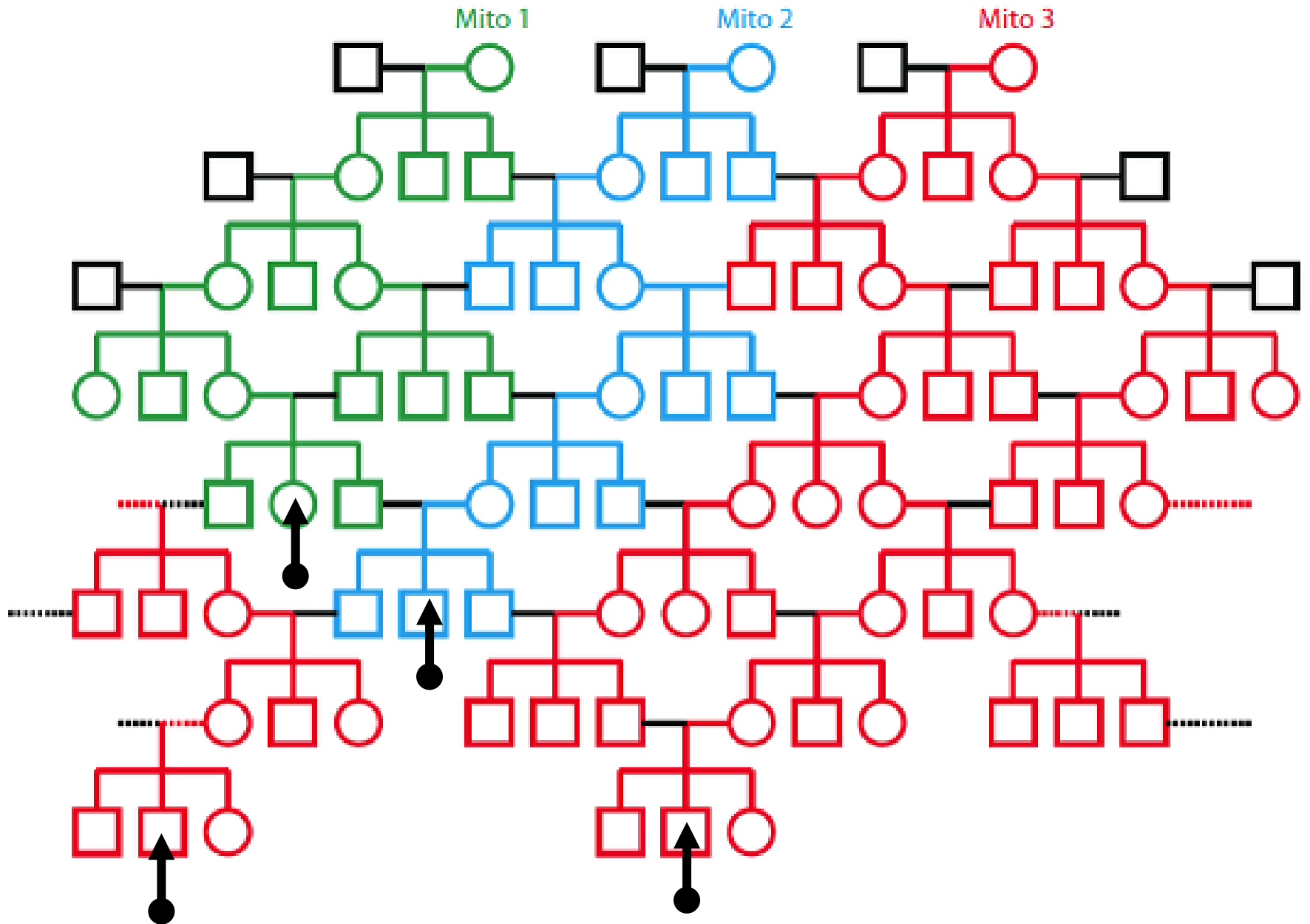


MaGelLAn 1.0: a software to facilitate quantitative and population genetic analysis of maternal inheritance by combination of molecular and pedigree information

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MaGelLAn (Maternal Genealogy Lineage Analyser)

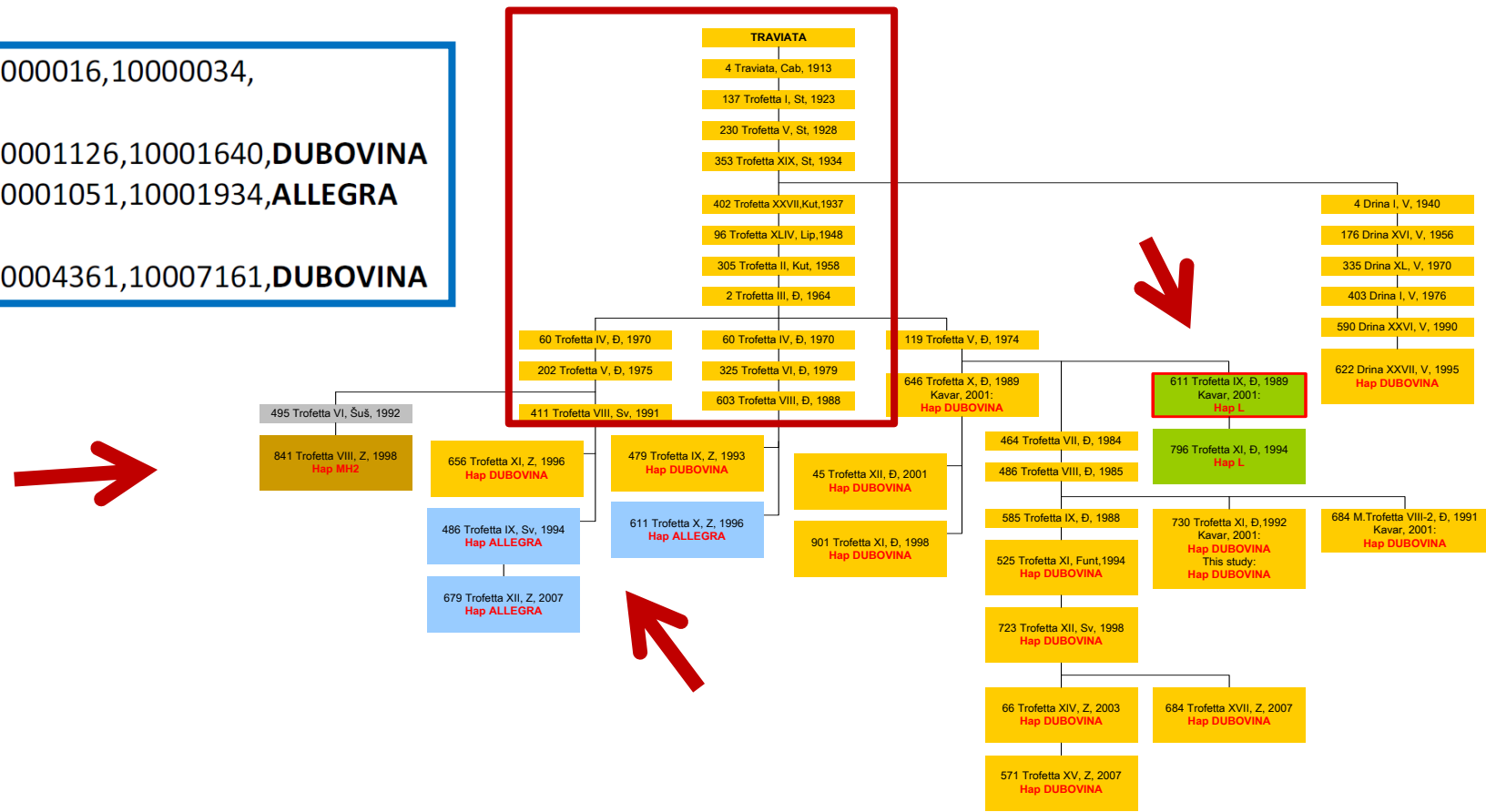
- maternal inheritance without recombination



Computational approach to utilisation of mitochondrial DNA in the verification of complex pedigree errors

Mato Čačić^a, Vlatka Cubric-Curik^b, Strahil Ristov^{c,*}, Ino Curik^{b,*}

1,10000033,10000016,10000034,
 ...
 22,10001911,10001126,10001640,**DUBOVINA**
 23,10001933,10001051,10001934,**ALLEGRA**
 ...
 42,10007252,10004361,10007161,**DUBOVINA**



5. Mitogenome impact on the phenotypic variability

**Analyses with cytoplasmic models (D-loop mtDNA) and rarely with the complete mitogenome analyses:
⇒ 0 to 4-5% phenotypic variability**

Milk production traits – cattle

Kennedy, 1986 (JDS);

Boettcher et al., 1996 (JDS); ML, Mitogenome

Boettcher and Gibson, 1997 (JDS); ML

Albuquerque et al., 1998 (JDS); ML

Špehar et al., 2017 (ASD); ML ⇒ Wednesday - talk

Growth traits – cattle

Pun et al., 2012 (LS); ML

Male fertility traits – cattle

Garmyn et al., 2011 (JAS); ML

Sutarno et al., 2002 (Theriogenology); D-loop, ND5

Ferenčaković et al., 2017 (ASD); ML ⇒ Thursday - poster

Production traits – pig

Fernandez et al., 2008 (JAS); ML

Fertility traits – pig

Yen et al., 2007 (RDA); ML, mtDNA

6. Identification of detrimental mutations

MITOMAP (Ruiz-Persini *et al.* 2007;

<http://www.mitomap.org/MITOMAP>),

ZARAMIT (Blanco *et al.* 2011;

<http://webdiis.unizar.es/~robertob/zaramit/>)

Mito Tool (Fan and Yao, 2011, Fan and Yao, 2013;).

Potential detrimental mutations – access to individuals

Table 2 | **Clinical disorders that are caused by mutations in mitochondrial DNA**

| Mitochondrial DNA disorder | Clinical phenotype | mtDNA genotype | Gene | Status | Inheritance | Reference |
|----------------------------|--|---|--------------------|------------------------|-------------|-----------|
| MELAS | Myopathy, encephalopathy lactic acidosis, stroke-like episodes | 3243A>G; 3271T>C Individual mutations | <i>TRNL1</i> | Heteroplasmic | Maternal | 159 |
| | | | <i>ND1 and ND5</i> | Heteroplasmic | Maternal | 160, 161 |
| MERRF | Myoclonic epilepsy, myopathy | 8344A>G; 8356T>C | <i>TRNK</i> | Heteroplasmic | Maternal | 162 |
| NARP | Neuropathy, ataxia, retinitis pigmentosa | 8993T>G | <i>ATP6</i> | Heteroplasmic | Maternal | 163 |
| MILS | Progressive brain-stem disorder | 8993T>C | <i>ATP6</i> | Heteroplasmic | Maternal | 67 |
| MIDD | Diabetes, deafness | 3243A>G | <i>TRNL1</i> | Heteroplasmic | Maternal | 164 |
| LHON | Optic neuropathy | 3460G>A 11778G>A 14484T>C | <i>ND1</i> | Hetero- or homoplasmic | Maternal | 165 |
| | | | <i>ND4</i> | Hetero- or homoplasmic | Maternal | 62 |
| | | | <i>ND6</i> | Hetero- or homoplasmic | Maternal | 166 |
| Myopathy and diabetes | Myopathy, weakness, diabetes | 14709T>C | <i>TRNE</i> | Hetero- or homoplasmic | Maternal | 167,168 |
| Sensorineural hearing loss | Deafness | 1555A>G Individual mutations | <i>RNR1</i> | Homoplasmic | Maternal | 55 |
| | | | <i>TRNS1</i> | Hetero- or homoplasmic | Maternal | 169,170 |

Taylor et al. 2005. Nature review genetics

7. Future challenges

Mitogenome nuclear disequilibrium

≈600 loci that are functionally interacting with mitogenome in providing mitochondrial functions

- Population genomics
- Mito-nuclear GWAS

The impact of heteroplasmy on phenotypic variation

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MitoTAUROmics

1.7.2014. – 30.6.2018.

"Utilisation of the **whole mitogenome** in cattle **breeding** and **conservation** genetics"



IP-11-2013-9070

<http://mitotauromics.agr.hr/>

Thank you for your attention!

