Selection, validation, and utilization of mitogenome SNP array information in cattle breeding

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Rotterdam, 2022-07-07, 11am

S46 - Bovine Dairy

The aim of this study

To increase the use of **mitogenome** information in **animal breeding and genetics:**

- **NGS mitogenome** sequence study → **GGP mitogenome** SNPs study
  - **To select and verify of 331** mitochondrial SNPs for the **new NEOGEN GGP Bovine 100K SNP Chip**
    - To develop **a pipeline** for practical analysis
      - New version of **MaGeILAn v2.0** software

NEOGEN® Europe Ltd

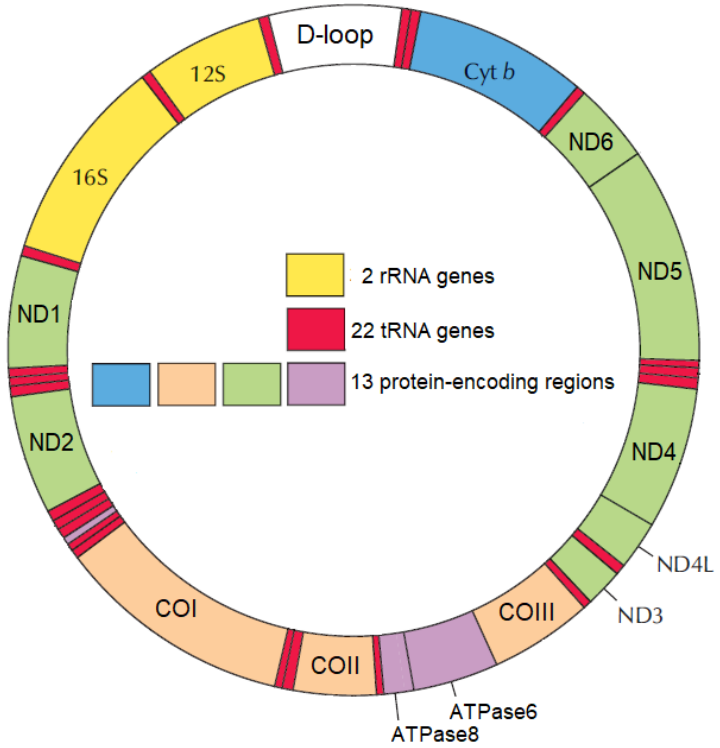
Background

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

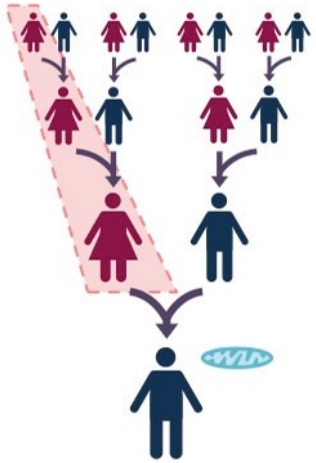
MitoTAUROmics 1.7.2014. – 31.10.2018

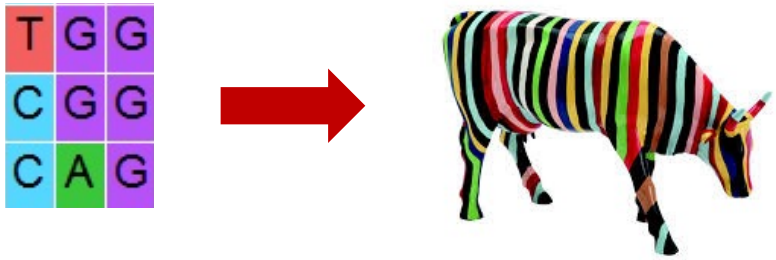
- Diversity & Domestication
- Pedigree verification & imputation – Magellan 1.0
- Impact on the milk production
- Identification of detrimental mutations
- Presence of selection

Background



Mitogenome





- maternal transmission ♀ → **maternal lineage = mitogenome**
- coding of 37 genes (13 of ~ 85 OXPHOS components → **cell energy** ⚡)
- small circular molecule (**mtDNA≈16.472 bp** : **nDNA≈3*10^9 bp**)

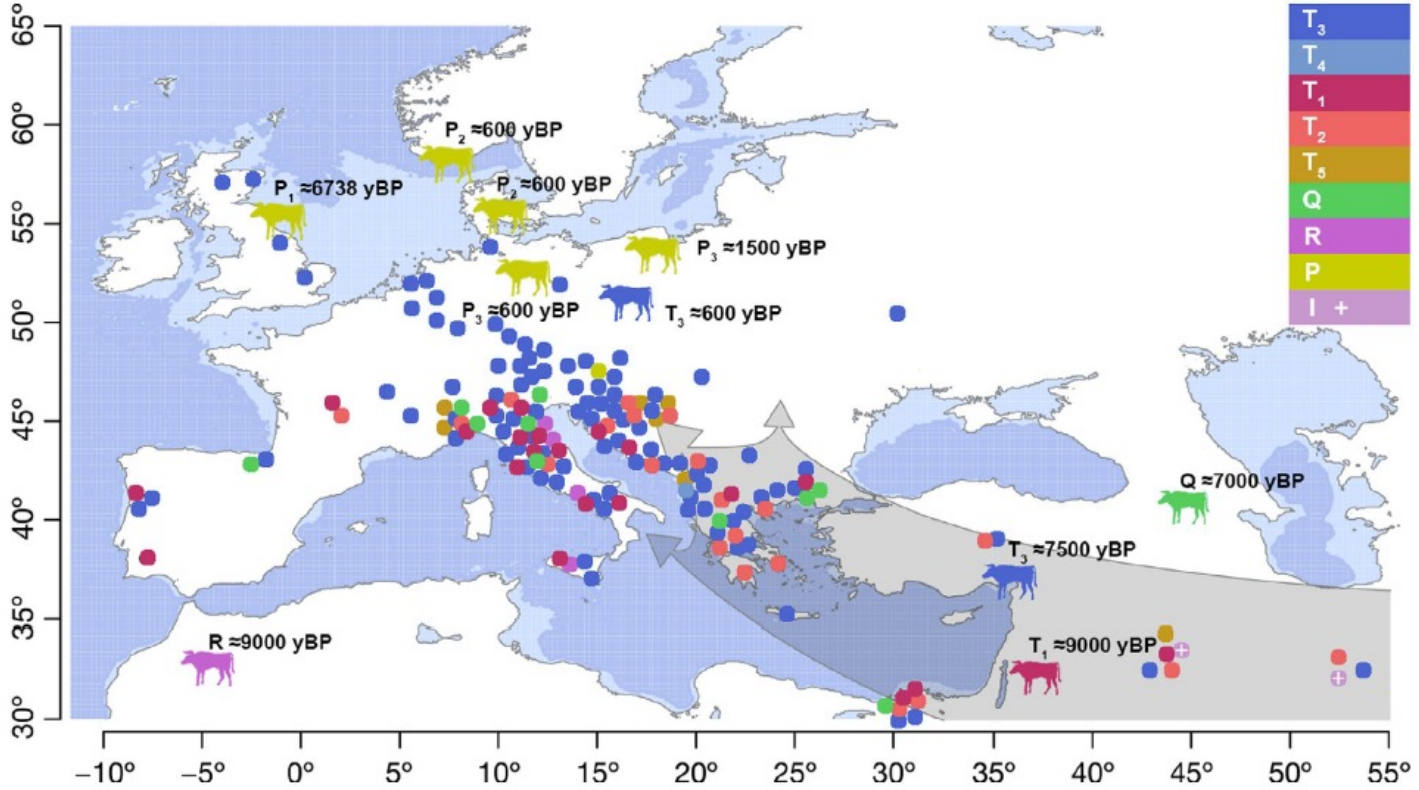
Background

Large-scale mitogenome sequencing reveals consecutive expansions of domestic taurine cattle and supports sporadic aurochs introgression

Evolutionary Applications Open Access

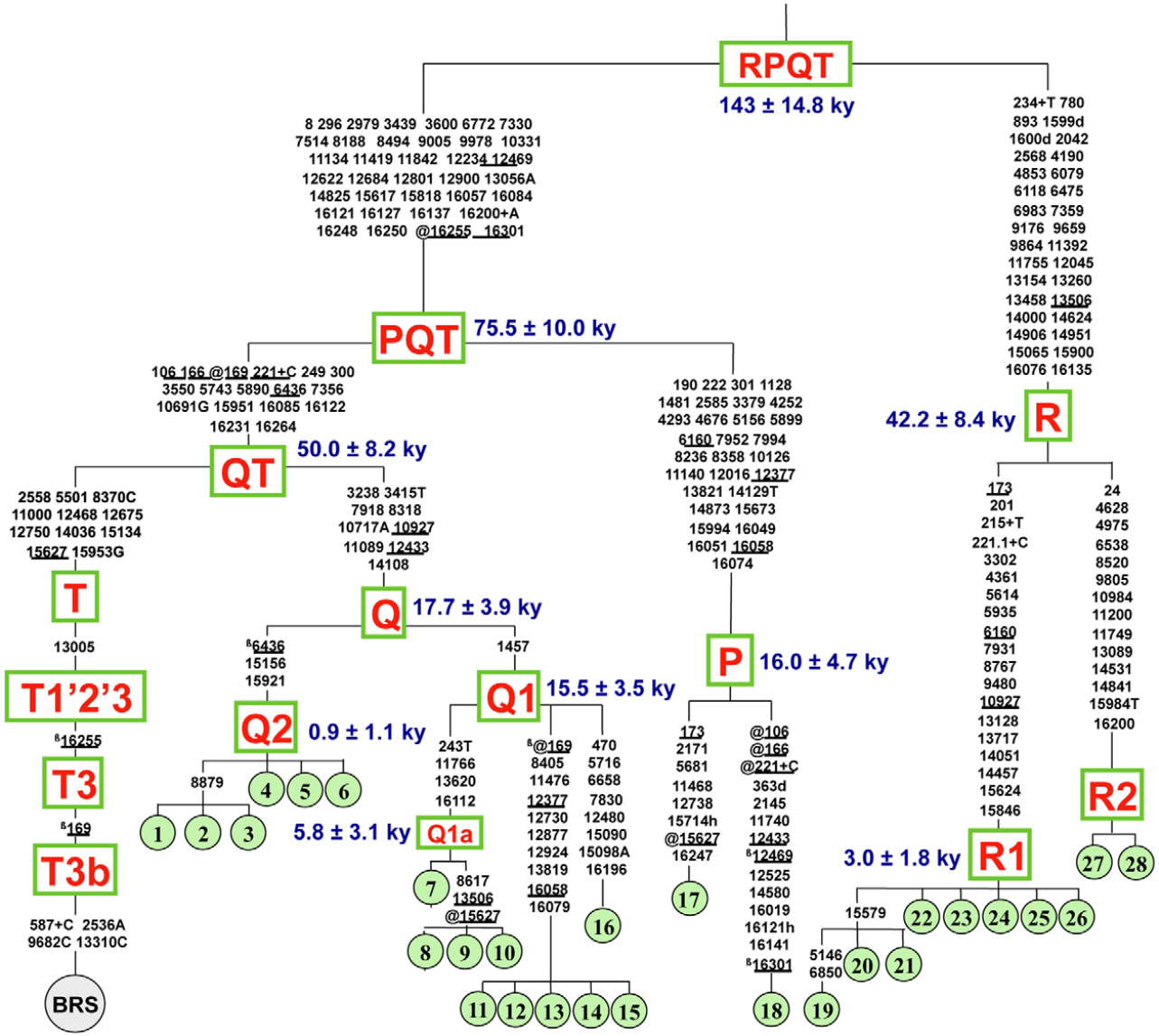
Vlatka Cubric-Curik, Dinko Novosel, Vladimir Brajkovic, Omar Rota Stabelli, Stefan Krebs, Johann Sölkner, Dragica Šalamon, Strahil Ristov, Beate Berger ... See all authors

First published: 08 November 2021 | https://doi.org/10.1111/eva.13315 | Citations: 2



1068 (741) mitogenome sequences, > 150 (92) breeds

SNP preselection material and methods



Bonfiglio et al. 2012 *PLoS ONE*

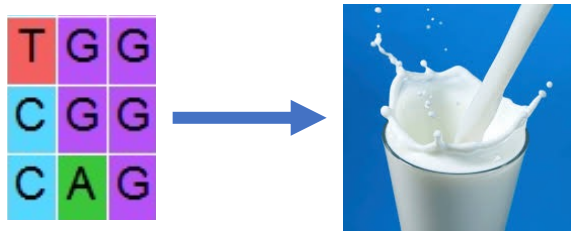
- **mitogenome SNPs -** pairwise SNP $F_{ST} = 1$

	P	Q	R	T1	T2	T3	T5	I1	I2
P	-								
Q	29	-							
R	77	65	-						
T1	21	7	39	-					
T2	33	11	67	4	-				
T3	13	2	22	2	1	-			
T5	45	13	83	1	6	1	-		
I1	117	102	107	55	95	32	118	-	
I2	186	172	174	100	166	62	199	7	-

SNP selection n=331

- SNP selection included **331 SNPs:**
  - i) **289 SNPs** for haplogroup classification (T_1, T_2, T_3, T_4, T_5, P, Q, R, I)
  - ii) **10 SNPs** for LHON[1] disease
  - iii) **32 SNPs** for MELAS[2] disease

More detailed haplogroup classification within the T3 haplogroup

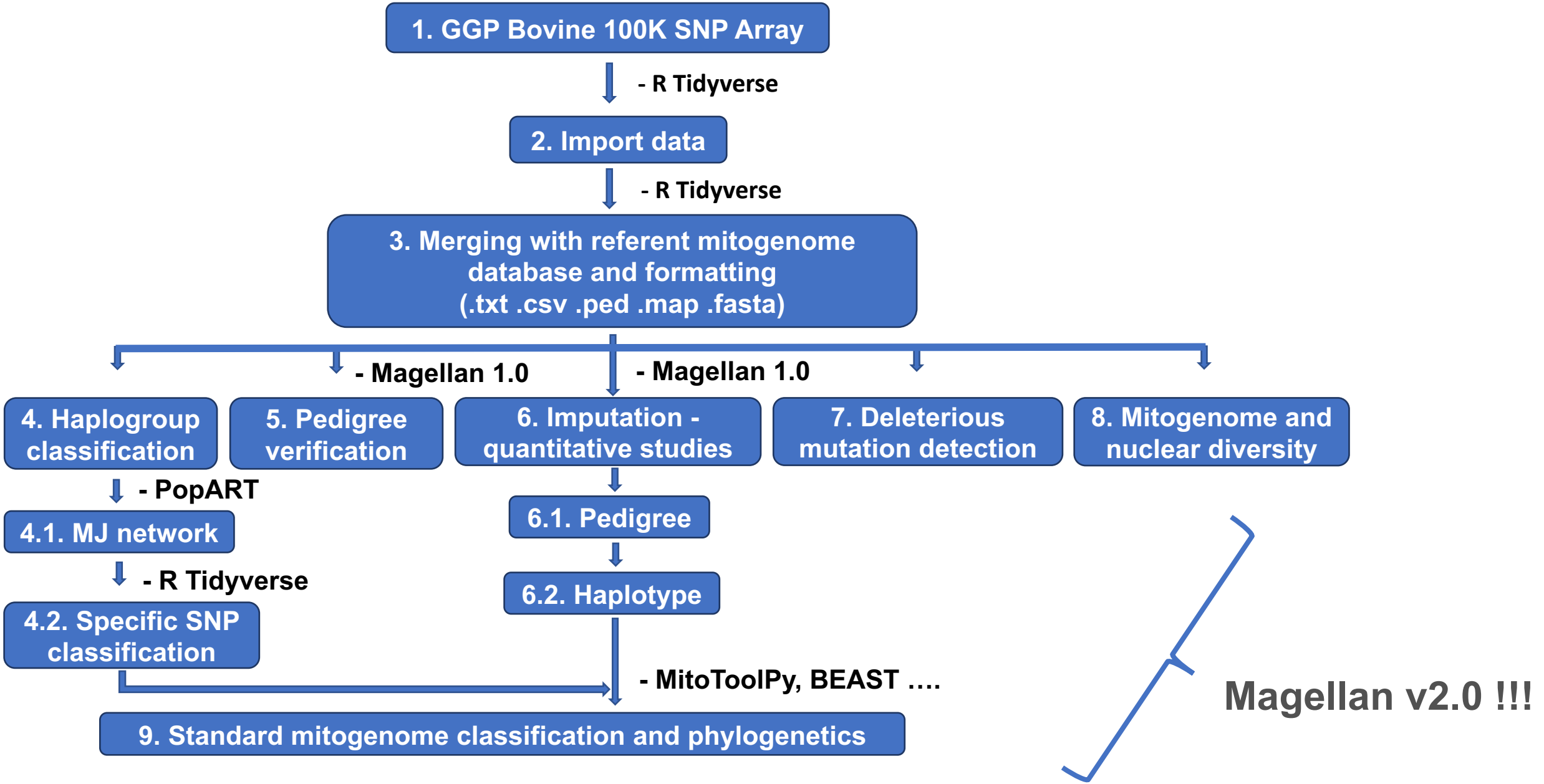


Quantitative trait variation

[1]Leber Hereditary Optic Neuropathy

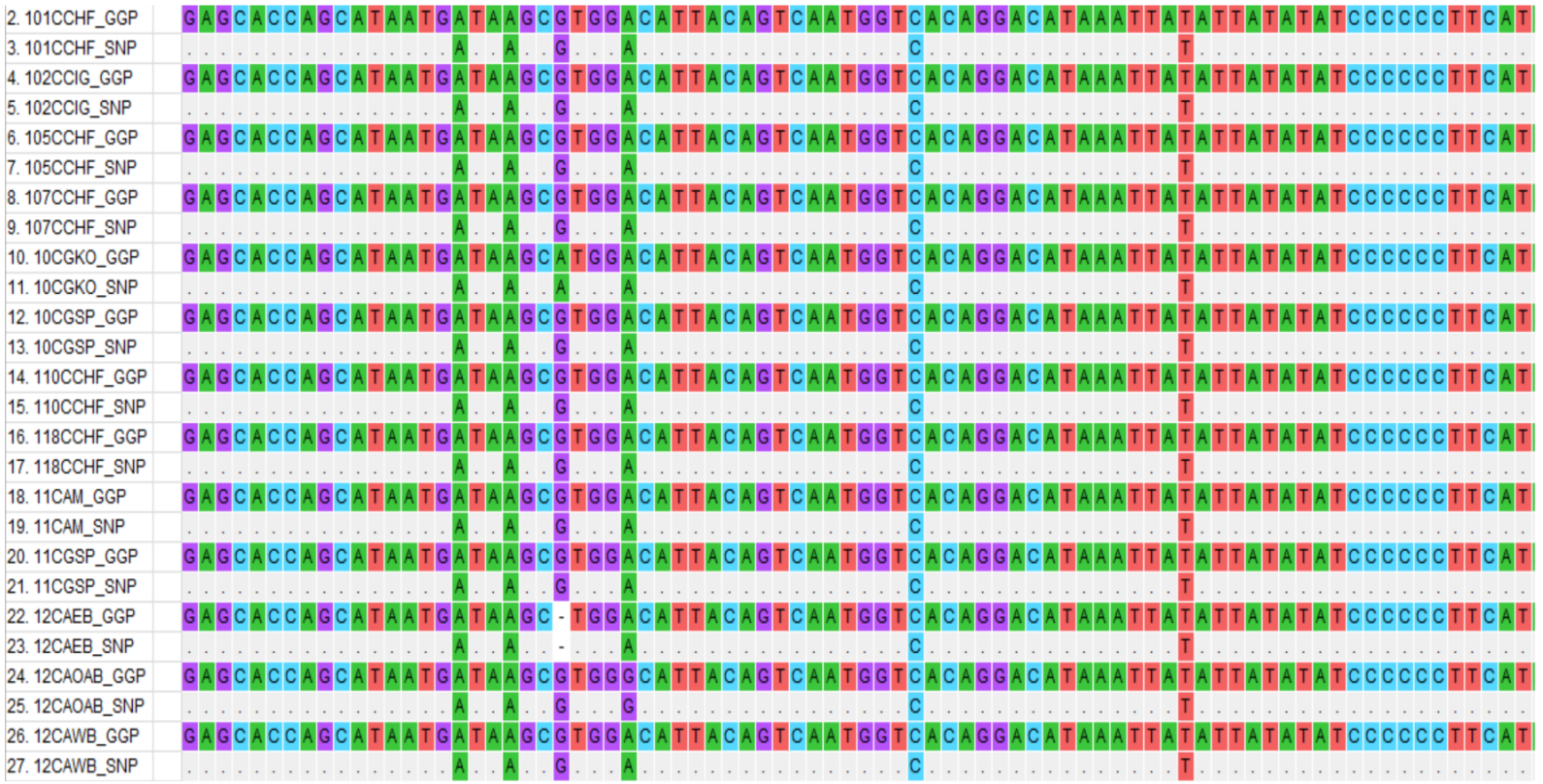
[2]Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes

Workflow


1. GGP Bovine 100K SNP Array
- R Tidyverse
2. Import data
- R Tidyverse
3. Merging with referent mitogenome database and formatting (.txt .csv .ped .map .fasta)
- Magellan 1.0
- Magellan 1.0
4. Haplogroup classification
5. Pedigree verification
6. Imputation - quantitative studies
7. Deleterious mutation detection
8. Mitogenome and nuclear diversity
- PopART
4.1. MJ network
- R Tidyverse
4.2. Specific SNP classification
6.1. Pedigree
6.2. Haplotype
- MitoToolPy, BEAST ….
9. Standard mitogenome classification and phylogenetics
Magellan v2.0 !!!

3. Merging with the referent mitogenome database

- Checking SNP consistency



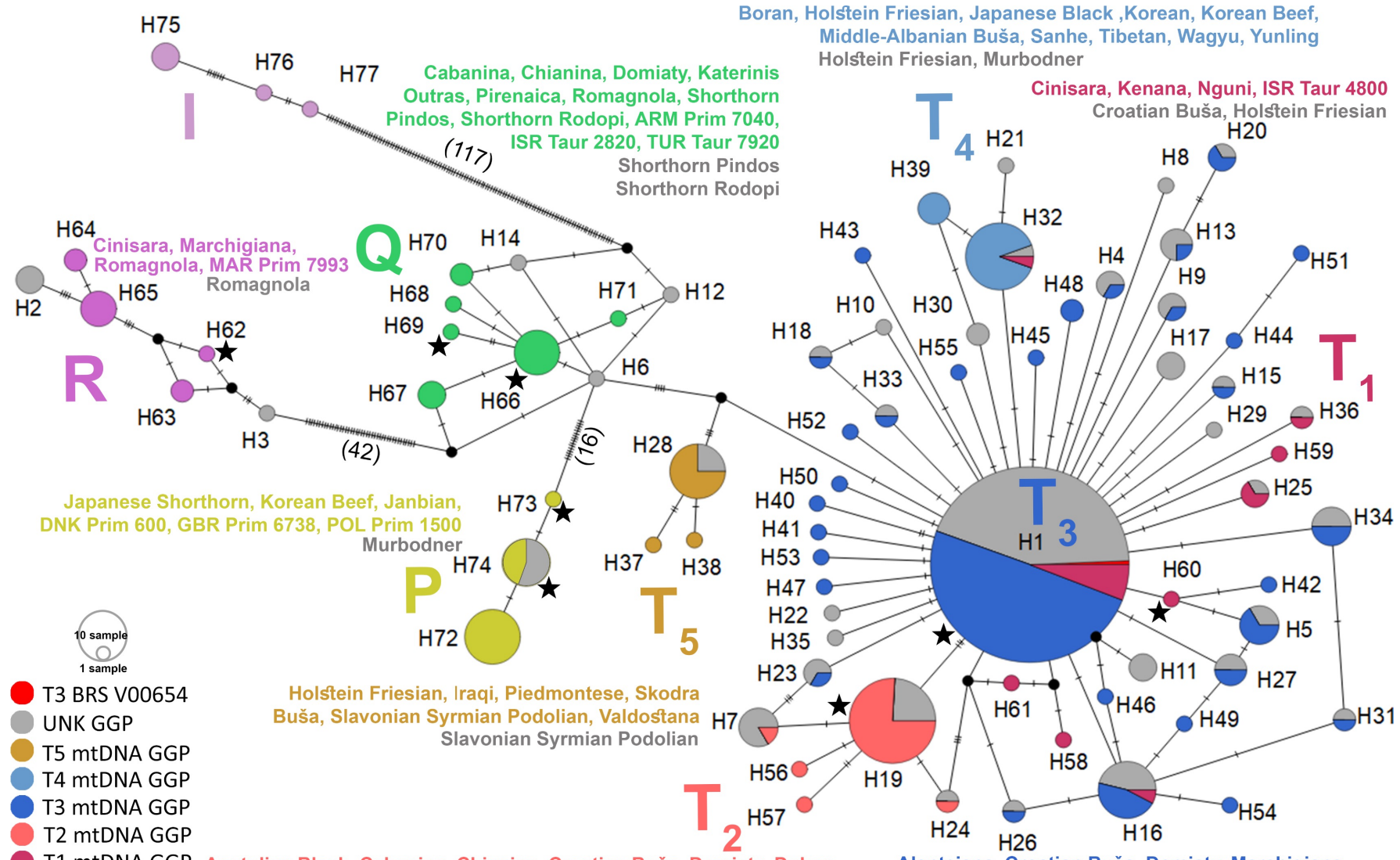
NGS SNP string (.fasta)

GGP SNP string (.fasta)

A A G A C T

NGS Sequences ⟺ **NEOGEN GGP Bovine 100K SNP Chip**

4. Haplogroup classification - validation



5.-6. Pedigree analysis and imputation

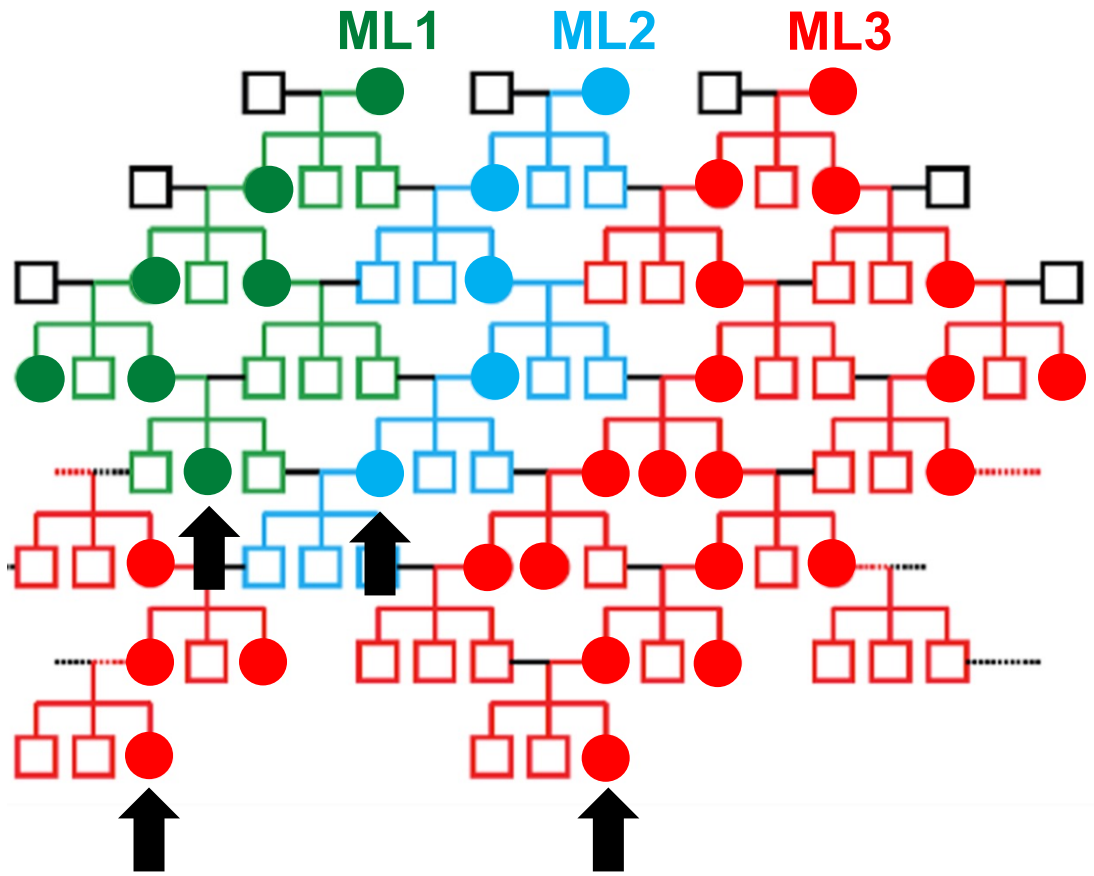
Maternal lineages

↓

founders = 109

individuals = 2373

individuals = 109



Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/livsci

Short communication

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,*]

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

GSE Genetics Selection Evolution

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

Strahil Ristov[1*], Vladimir Brajkovic[2], Vlatka Cubric-Curik[2], Ivan Michieli[1] and Ino Curik[2]

”Maternal inheritance without recombination”

MaGelLAn (Maternal Genealogy Lineage Analyser)

- mag_verif.py
- mag_stat.py
- mag_sampl.py
- mag_calc.py

Pedigree

↕

“Molecular pedigree”

↕

Imputation

6.1-2. Mitogenome impact on the milk production

Variance components ratios (± SE) for milk yield

Lactation	Model	Heritability	"Mito-effect"	HYS	ΔAICc
1.	CITO	0.39±0.04	**0.07±0.02**	0.15±0.02	26.9
	HAPLO	0.40±0.04	**0.07±0.02**	0.15±0.02	**0.0**
	AMINO	0.42±0.04	**0.09±0.03**	0.15±0.02	35.1
	EVOL	0.51±0.04	0.00±0.01	0.16±0.02	54.2
2.	CITO	0.28±0.04	**0.07±0.02**	0.19±0.03	0.2
	HAPLO	0.29±0.04	**0.07±0.02**	0.19±0.03	**0.0**
	AMINO	0.31±0.04	**0.09±0.03**	0.18±0.03	1.4
	EVOL	0.40±0.04	0.01±0.01	0.21±0.03	24.1
3.	CITO	0.31±0.06	**0.07±0.02**	0.26±0.04	2.4
	HAPLO	0.31±0.05	**0.07±0.02**	0.26±0.04	**0.0**
	AMINO	0.32±0.05	**0.10±0.04**	0.25±0.04	0.2
	EVOL	0.40±0.05	0.02±0.02	0.27±0.04	11.0

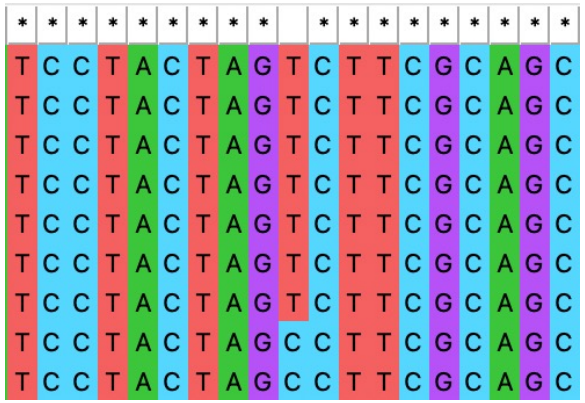
MTDFREML

sas

R - INLA

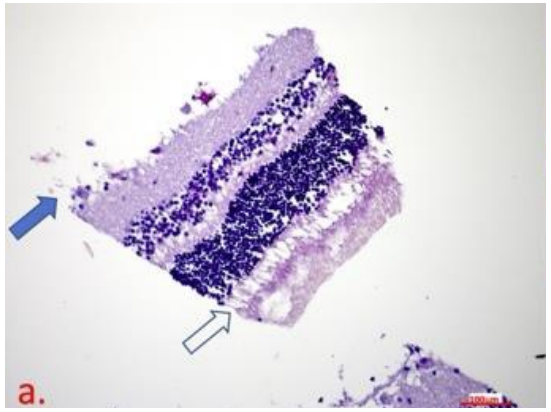
Brajkovic et al., submitted soon!

7. Deleterious mutation detection

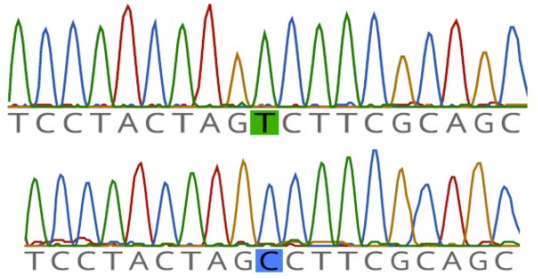


Multifasta file

Exophthalmos
Gavtraža



Histopathological examination and IHC detection of caspase-3 – apoptosis and oedema in the eye bulb and brain



Homoplasmic mutation

› Int J Mol Sci. 2022 Jun 6;23(11):6335. doi: 10.3390/ijms23116335.

The Consequences of Mitochondrial T10432C Mutation in Cika Cattle: A "Potential" Model for Leber's Hereditary Optic Neuropathy

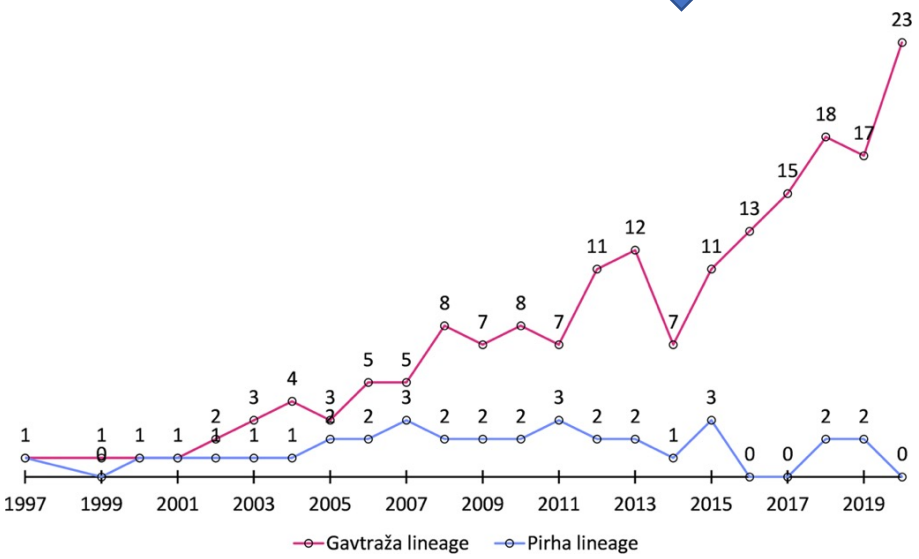
Dinko Novosel [1 2], Vladimir Brajković [2], Mojca Simčič [3], Minja Zorc [3], Tanja Svara [4], Karmen Branovic Cakanic [1], Andreja Jungić [5], Betka Logar [6], Vlatka Cubric-Curik [2], Peter Dovc [3], Ino Curik [2]

Affiliations + expand

PMID: 35683014 PMCID: PMC9181260 DOI: 10.3390/ijms23116335

First detrimental mitogenome mutation in cattle

Model for better understanding of the pathogenesis of LHON

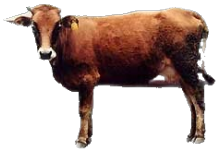


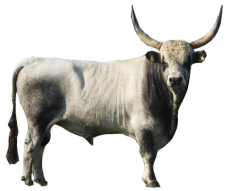
Maternal lineage analysis

8. Mitogenome and nuclear diversity

- F_{ST} values: **mitogenome SNPs (317)** vs **autosomal SNPs (70242)**









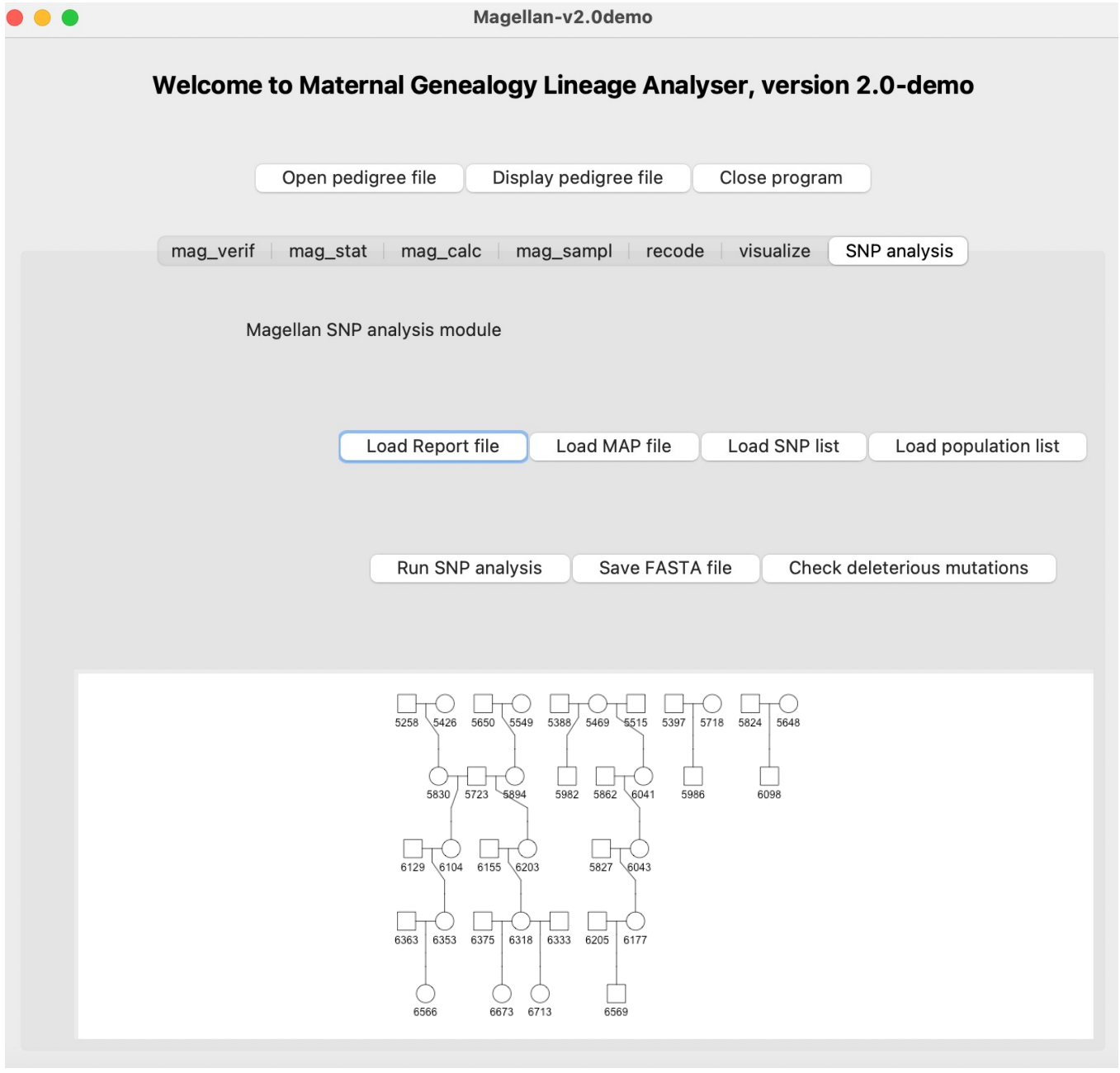
	(10) Katerini O.		(12) Short. Pin.		(13) Short. Rod.		(10) Katerini T.		(24) Sla.Syr.Pod.		(25) Busa		(24) Murbodner		(30) Boskarin		(85) Holstein	
Short. Pin.	0.04	0.05																
Short. Rod.	-0.02	0.09	0.03	0.11														
Katerini T.	0.31	0.16	0.35	0.18	0.34	0.22												
Sla.Syr.Pod.	0.08	0.11	0.21	0.13	0.09	0.17	0.44	0.23										
Busa	0.06	0.03	0.16	0.05	0.10	0.08	0.20	0.15	0.14	0.10								
Murbodner	0.05	0.07	0.07	0.09	0.06	0.12	0.19	0.19	0.14	0.13	0.13	0.05						
Boskarin	0.10	0.08	0.24	0.10	0.10	0.14	0.47	0.20	0.14	0.14	0.15	0.07	0.15	0.10				
Holstein	0.07	0.09	0.21	0.11	0.10	0.14	0.45	0.20	0.11	0.15	0.14	0.08	0.24	0.10	0.09	0.13	-	

Genetic differentiation levels

<0.05 little	0.05 – 0.15 moderate	0.15 – 0.25 great	> 0.25 very great

Hart and Clark 1997

*New version of Magellan 2.0 !!!



Dalibor Hršak

Institut Ruđer Bošković

Croatia

- **New version – testing!!!**
  - GUI
  - Pedigree drawing
  - Paternal inheritance
  - Haplogroup classification
  - Imputation of GGP SNPs
  - Potential disease identification
  - **Import** NEOGEN GGP final report and **export**:

SNP string (.fasta)

.lgen .fam .map

(.ped, .map; .bim, .bam, .fam)

Conclusion

- **317**/331 mitogenome SNPs have been successfully validated

- Contribution as **additional information** to autosomal markers in Neogene GGP Bovine 100K :
    - biodiversity
    - population genomic analyses
    - cattle breeding
    - detrimental mutation detection

- Analyses in progress:

    updating of **MaGeILAn 1.0 to a New GUI MaGeILAn 2.0**

Acknowledgments

NEOGEN's Scottish laboratory in Ayr

ANAGRAMS: IP-2018-01-8708 "Application of **N**GS in the **A**ssessment of **G**enomic va**R**i**A**bility in ru**M**inant**S**"

HrZZ Croatian Science Foundation

ALGSEQ18: IP-2018-01-7317 "Advanced deterministic and hybrid algorithms on strings. sequences and trees with applications in technical and life sciences"

HrZZ Croatian Science Foundation

Sir je IN: K.K.01.1.1.04.0058

EUROPSKI STRUKTURNI I INVESTICIJSKI FONDOVI

Europska unija
Zajedno do fondova EU

See you at:

The 30th International Symposium Animal Science Days 2022, Zadar, Croatia

https://asd2022.agr.hr/

Thank you for your attention!