Exploring Resistance to Nematodes in 3SR Sheep and Goat Populations

Steve Bishop

+ V. Riggio, G. Salle, N. Mandonnet, M.G. Usai, S. Casu, O. Keane, M. Poli, A. Carta & C.R. Moreno

3SR: 3.5-year project aimed at:

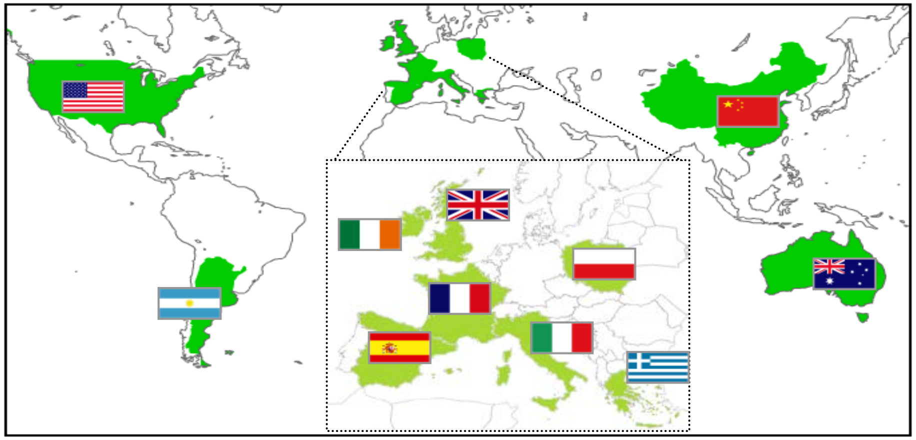
- **Developing & verifying selectable markers for:**
  - ***Mastitis susceptibility (sheep and goats)***
  - ***Resistance to Nematodes (sheep and goats)***
  - ***Ovulation (sheep)***
- **Developing tools and genomic resources (sheep and goats)**

3SR: 3.5-year project aimed at:

- **Developing & verifying selectable markers for:**
  - *Mastitis susceptibility (sheep and goats)*
  - *Resistance to Nematodes (sheep and goats)*
  - *Ovulation (sheep)*
- **Developing tools and genomic resources (sheep and goats)**

Through the efforts of 14 Partners in 11 countries

www.3srbreeding.eu



3SR Research Activities

- **GWAS (sheep and goats) for nematode & mastitis resistance**

Breed	Population	N. genotyped/ phenotype
Blackface	Half sib families in complex pedigree	750
Sarda x Lacaune	BC design (10 F1+G1+G2)	2375
Blackbelly x Romaine	BC design	1000

3SR Research Activities

- **GWAS (sheep and goats) for nematode & mastitis resistance**

Breed	Population	N. genotyped/ phenotyped
Churra	Daughter design (16 families)	1630
Sarda*Lacaune	BC design (10 F1+ G1+G2)	2375
Lacaune	GD design (33 families)	1010
Lacaune	Divergent lines	330

3SR Research Activities

- **GWAS (sheep and goats) for nematode & mastitis resistance**
  - ***SNP validation studies***
  - ***Genomic prediction***

3SR Research Activities

- GWAS (sheep and goats) for nematode & mastitis resistance
  - *SNP validation studies*
  - *Genomic prediction*
- **Mapping ovulation rate mutations**

Breed	N. geno+pheno	Target phenotype
Olkuska	**64**	**High vs. low LS for ≥ 4 lambings**
Grivette	**40**	**High vs. low LS for ≥ 4 lambings**
Cambridge	**21**	**Unexplained sterility**

+ targeted sequencing

3SR Research Activities

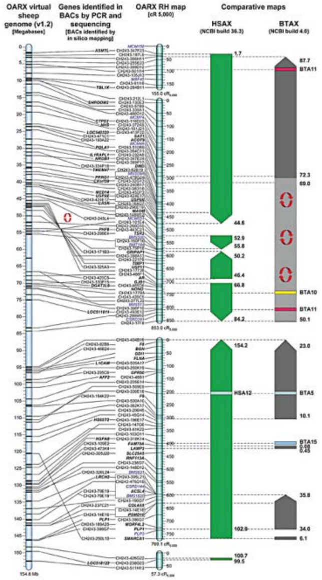
- GWAS (sheep and goats) for nematode & mastitis resistance
  - *SNP validation studies*
  - *Genomic prediction*
- Mapping ovulation rate mutations
- **Functional (RNA) studies of phenotypes**

SEVENTH FRAMEWORK PROGRAMME

3SR Research Activities

- GWAS (sheep and goats) for nematode & mastitis resistance
    - *SNP validation studies*
    - *Genomic prediction*
- Mapping ovulation rate mutations
- Functional (RNA) studies of phenotypes
- **Improving Genomic Resources**

Improving Genome Resources: Caprine

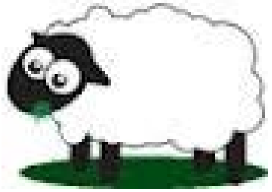


- Radiation Hybrid map

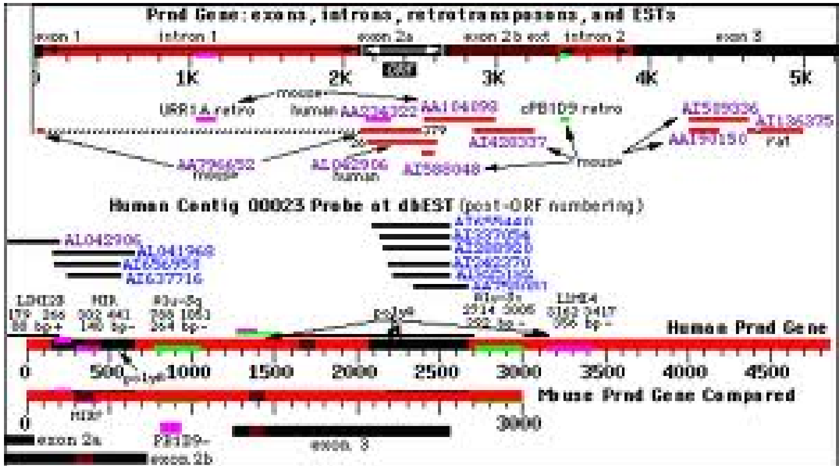
- 50k SNP chip

- Genome Sequence:
  - Nature Biotechnology Volume (2013): 31, 135–141

Improving Genome Resources: Ovine



- Improvement of sheep genome assemblies
  - Deep sequencing of Texel male
  - Sequencing of BAC clones to help close known gaps
- RNA-seq (& DNA-seq) to enable annotation
  - Texel trios: the <u>major</u> data source for sheep genome annotation
    - 1.17 x 10^9 nucleotides of RNA sequence (i.e. >1 TB data)
- CNV detection



3SR Research Activities

- GWAS (sheep and goats) for nematode & mastitis resistance
  - *SNP validation studies*
  - *Genomic prediction*
- Mapping ovulation rate mutations
- Functional (RNA) studies of phenotypes
- Improving Genomic Resources
- **Developing Bioinformatic tools**
  - *GBrowse-based synteny browser: Ovis aries* v3.1 – *Capra hircus* v1.0

http://genome.itb.cnr.it/gb2/gbrowse_syn/sheep3.1-goat/

CHAIN NET alignments for Sheep and Goat

Instructions

Select a Region to Browse and a Reference species:

Examples: sheep Chr1:1..200000.

Search

Landmark:

Search Reset

Genome to Search:

Data Source :

CHAIN NET alignments for Sheep and Goat

Display settings

Image widths : ○640 ○768 ●800 ○1024 ○1280

Update Image

Image options :

Chain alignments ○on ●off Flip minus strand panels ●on ○off Grid lines ●on ○off Edges ●on ○off Shading ●on ○off

SEVENTH FRAMEWORK PROGRAMME

Exploring Nematode Resistance

- **Starting point GWAS for nematode resistance**

Breed	Population	N. genotyped/ phenotype
Blackface	Half sib families in complex pedigree	750
Sarda x Lacaune	BC design (10 F1+G1+G2)	2375
Blackbelly x Romaine	BC design	1000

Exploring Nematode Resistance

- Starting point GWAS for nematode resistance

Breed	Population	N. genotyped/ phenotype
Blackface	Half sib families in complex pedigree	750
Sarda x Lacaune	BC design (10 F1+G1+G2)	2375
Blackbelly x Romaine	BC design	1000

- Faecal Egg Count (FEC) = common phenotype
  - FEC always heritable
  - QTL always found: several and diverse

Exploring Nematode Resistance

- Key Question: is genetic resistance common across breeds?
  - If so, at what level?

1. Individual SNP level

2. Genomic region level

3. Whole genome level

Exploring Nematode Resistance

- Key Question: is genetic resistance common across breeds?
  - If so, at what level?

1. Individual SNP level
   - Lack of concordance across studies

   => Could we ever expect it?
2. Genomic region level

3. Whole genome level

Exploring Nematode Resistance

- Key Question: is genetic resistance common across breeds?
  - If so, at what level?

1. Individual SNP level
   - Lack of concordance across studies

2. Genomic region level
   - Joint analysis by regional heritability mapping (Riggio et al. today)
   - Validation studies
3. Whole genome level

3SR

SEVENTH FRAMEWORK PROGRAMME

Exploring Nematode Resistance

- Key Question: is genetic resistance common across breeds?
  - If so, at what level?

1. Individual SNP level
   - Lack of concordance across studies

2. Genomic region level
   - Joint analysis by regional heritability mapping (Riggio et al. today)
   - Validation studies

Blackface
Sarda x Lacaune
Blackbelly x Romaine

Region-specific
1k SNP chips →

Suffolk, Texel
Blackface, Manech,
Corriedale, Pampinta

Exploring Nematode Resistance

- **Key Question: is genetic resistance common across breeds?**
  - **If so, at what level?**

1. **Individual SNP level**
   - **Lack of concordance across studies**

2. **Genomic region level**
   - **Joint analysis by regional heritability mapping (Riggio et al. today)**
   - **Validation studies**
3. **Whole genome level**
   - **Genomic prediction**

3SR

SEVENTH FRAMEWORK
PROGRAMME

Genomic Prediction for Nematode Resistance

- **Datasets:**

Blackface	750	(sheep with 50k genotypes)
Sarda x Lacaune	2375	
Blackbelly x Romaine	1000	
Texel	80	

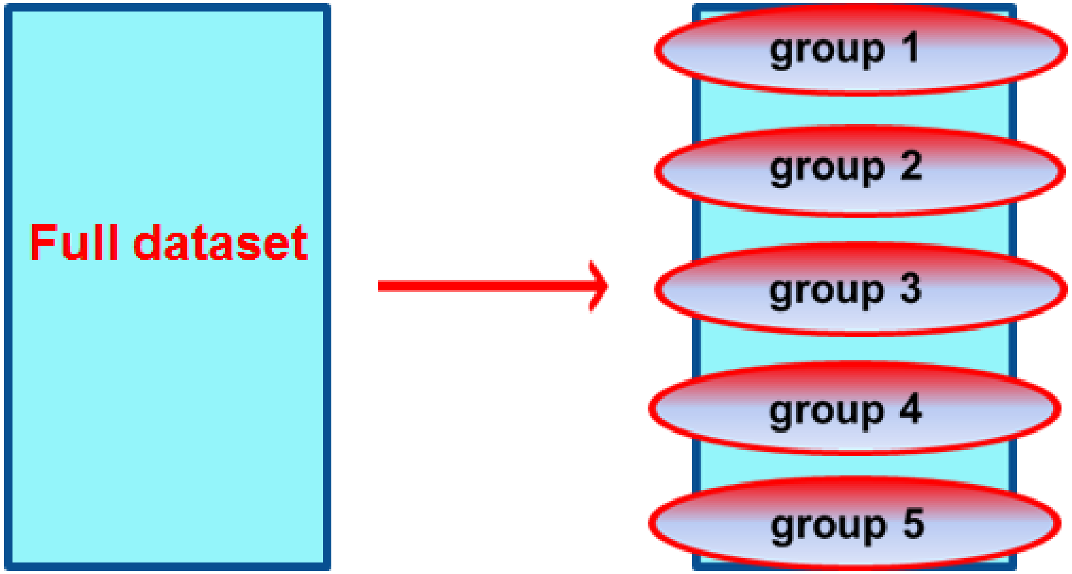
- **Approach**
  - Within-breed (Blackface) cross validation (5-fold)
  - Across-breed prediction

3SR

SEVENTH FRAMEWORK
PROGRAMME

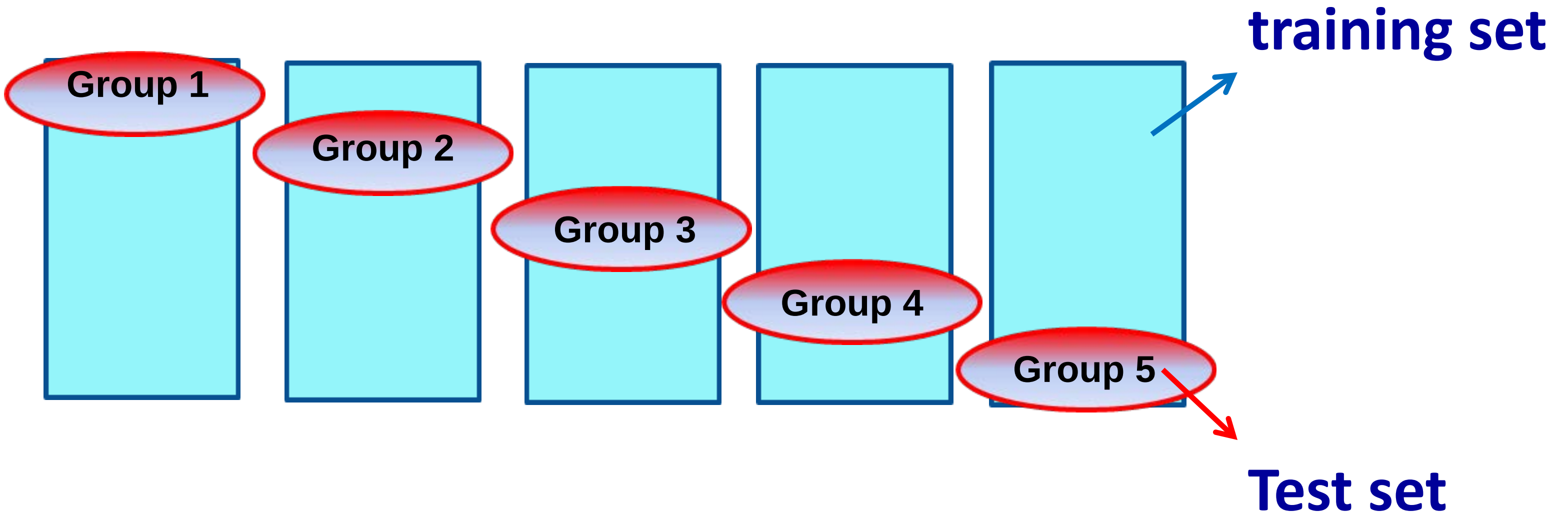
Genomic Prediction for Nematode Resistance

- **Assessing Genomic Prediction by cross validation**



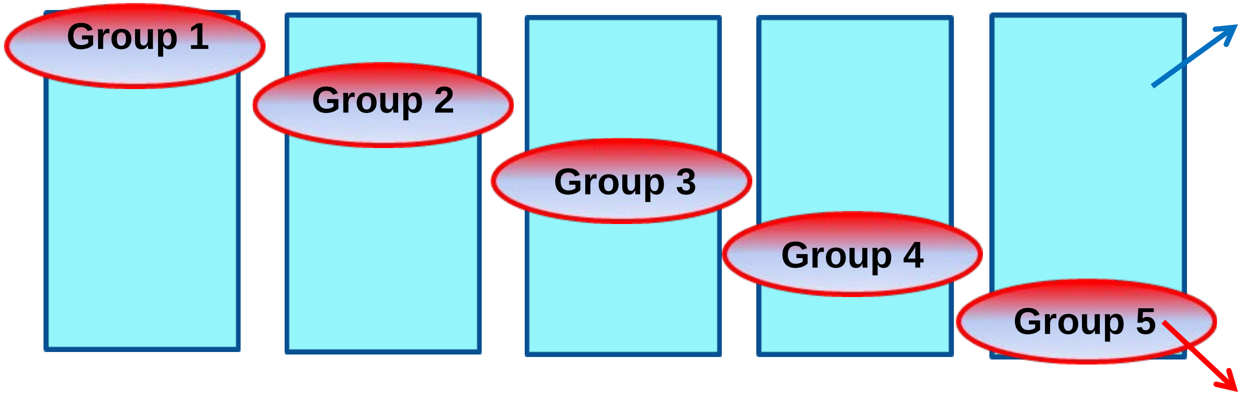
Genomic Prediction for Nematode Resistance

- **Assessing Genomic Prediction by cross validation**



Genomic Prediction for Nematode Resistance

- **Assessing Genomic Prediction by cross validation**



training set

Group 1

Group 2

Group 3

Group 4

Group 5

Test set

  - **Estimate correlation[Predicted GEBV (•), Phenotype (y)]**
  - **Accuracy: $r_{g\bullet} = r_{\bullet y}/h$**

Genomic Prediction for Nematode Resistance

- **Genomic Prediction: within-breed accuracy**

Trait	Accuracy
FEC (Strongyles)	0.54
FEC (Nematodirus)	0.48
IgA	0.53
Weight	0.52

Genomic Prediction for Nematode Resistance

- **Genomic Prediction: within-breed accuracy**

Trait	Accuracy
FEC (Strongyles)	0.54
FEC (Nematodirus)	0.48
IgA	0.53
Weight	0.52

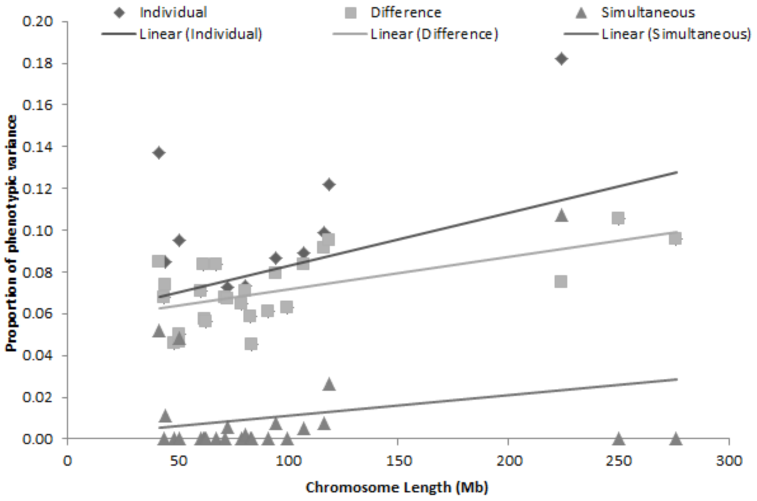
- **Genomic Prediction: across-breed accuracy**

Trait	Accuracy
FEC (Strongyles)	~zero

SEVENTH FRAMEWORK PROGRAMME

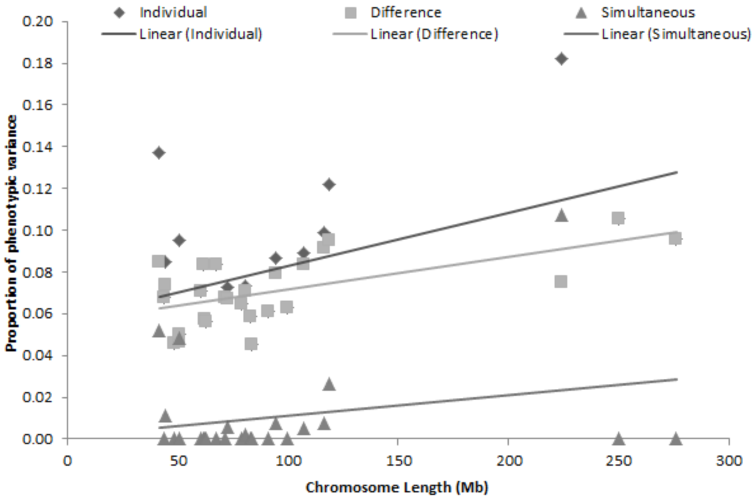
Genomic Prediction Interpretation

- **Within-breed**
  - **Accuracy from SNPs describing relatedness of animals**
    - **~85%**
  - **LD (SNP, causative mutation) minor contribution**



Genomic Prediction Interpretation

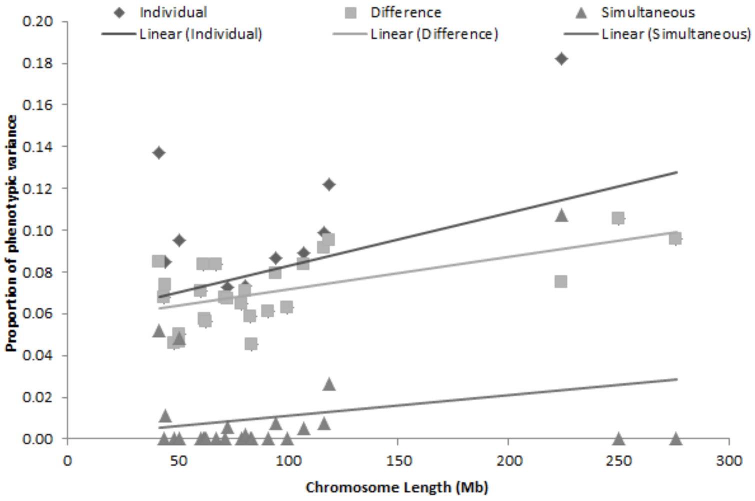
- **Within-breed**
  - **Accuracy from SNPs describing relatedness of animals**
    - **~85%**
  - **LD (SNP, causative mutation) minor contribution**



- **Across-breed**
  - **IBS relationships uninformative**
  - **Linkage phase (marker, causative) differs**
  - **Too few SNPs for LD**

Genomic Prediction Interpretation

- **Within-breed**
  - **Accuracy from SNPs describing relatedness of animals**
    - **~85%**
  - **LD (SNP, causative mutation) minor contribution**



- **Across-breed**
  - **IBS relationships uninformative**
  - **Linkage phase (marker, causative) differs**
  - **Too few SNPs for LD**
  - **Common regions of importance are still possible**

Exploring Nematode Resistance

- **Key Question: is genetic resistance common across breeds?**

1. **Individual SNP level**
    - Unlikely
2. **Genomic region level**
    - Under investigation, promising so far
3. **Whole genome level**
    - Difficult to demonstrate

- **Key Question: what are the mechanisms underlying variation in resistance?**
    - Under investigation …

3SR

SEVENTH FRAMEWORK PROGRAMME

Conclusions

3SR has been flexible: adapted to & contributed to advances in small ruminant genomic resources

- **Major contribution to:**
  - **Quality of ovine & caprine reference sequences**
  - **Annotation of sequences**
  - **Tools and resources for future projects**

- **Several QTL identified for nematode resistance**
  - **Proportion of variation accounted for is modest**
  - **Genomic prediction – works within-breed**
  - **Across-breed validation is underway**
  - **Functional studies underway**

SEVENTH FRAMEWORK PROGRAMME

Acknowledgements

Key People:

- Coordinator: Huw Jones (Biosciences KTN)
- Manager: Kezia Williamson (Biosciences KTN)
- WP Leaders: Noelle Cockett, Rachel Rupp, Loys Bodin, Alessandra Stella, Georgios Banos
- Key Researchers: Carole Moreno, Gwenola Tosser–Klopp
- 3SR consortium (www.3SRbreeding.eu)

Funding

SEVENTH FRAMEWORK PROGRAMME

Agreement no. 245140

Collaborators

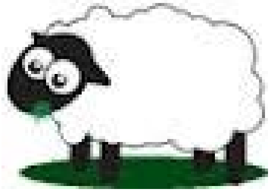
ISGC

IGGC

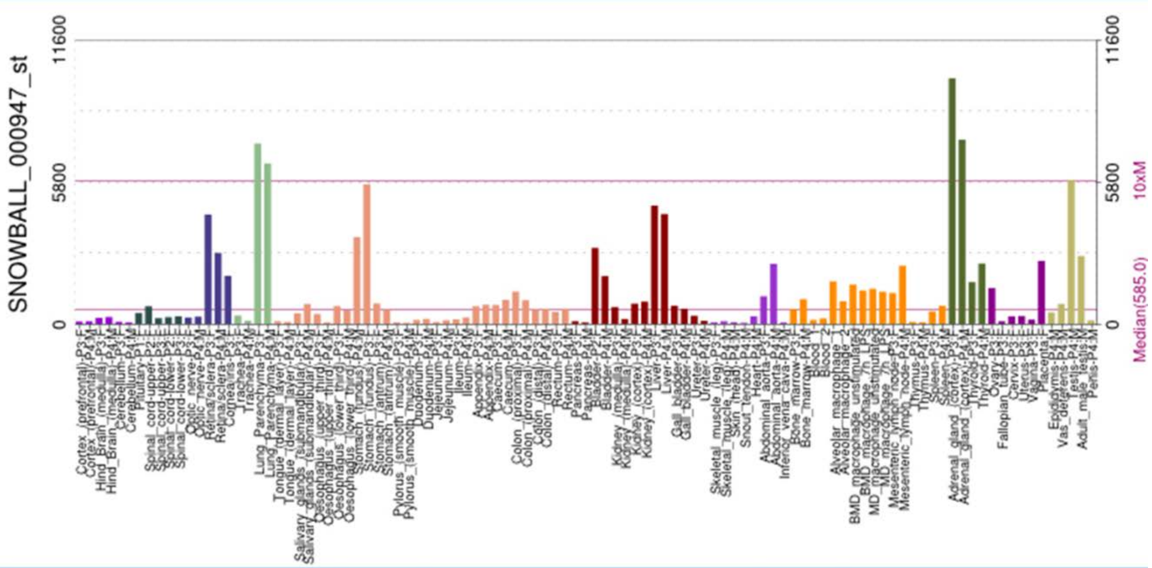
ROSLIN FOUNDATION

Thank you for your attention

Improving Genome Resources: Ovine



- **RNA-seq to enable annotation**
  - **Texel (ram, ewe, ewe lamb, 16d embryo)**
  - **30+ tissues per animal, whole embryo**
  - **1.17 x 10^9 nucleotides of RNA sequence (i.e. 1.1TB)**
  - **2 x 150 bp paired-end reads, stranded**
  - **~ 100 x 10^6 read pairs per sample**



SEVENTH FRAMEWORK PROGRAMME