# A Closer Look: Scrapie Resistant Genetics within the U.S. Sheep Flock

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U.S. DEPARTMENT OF AGRICULTURE

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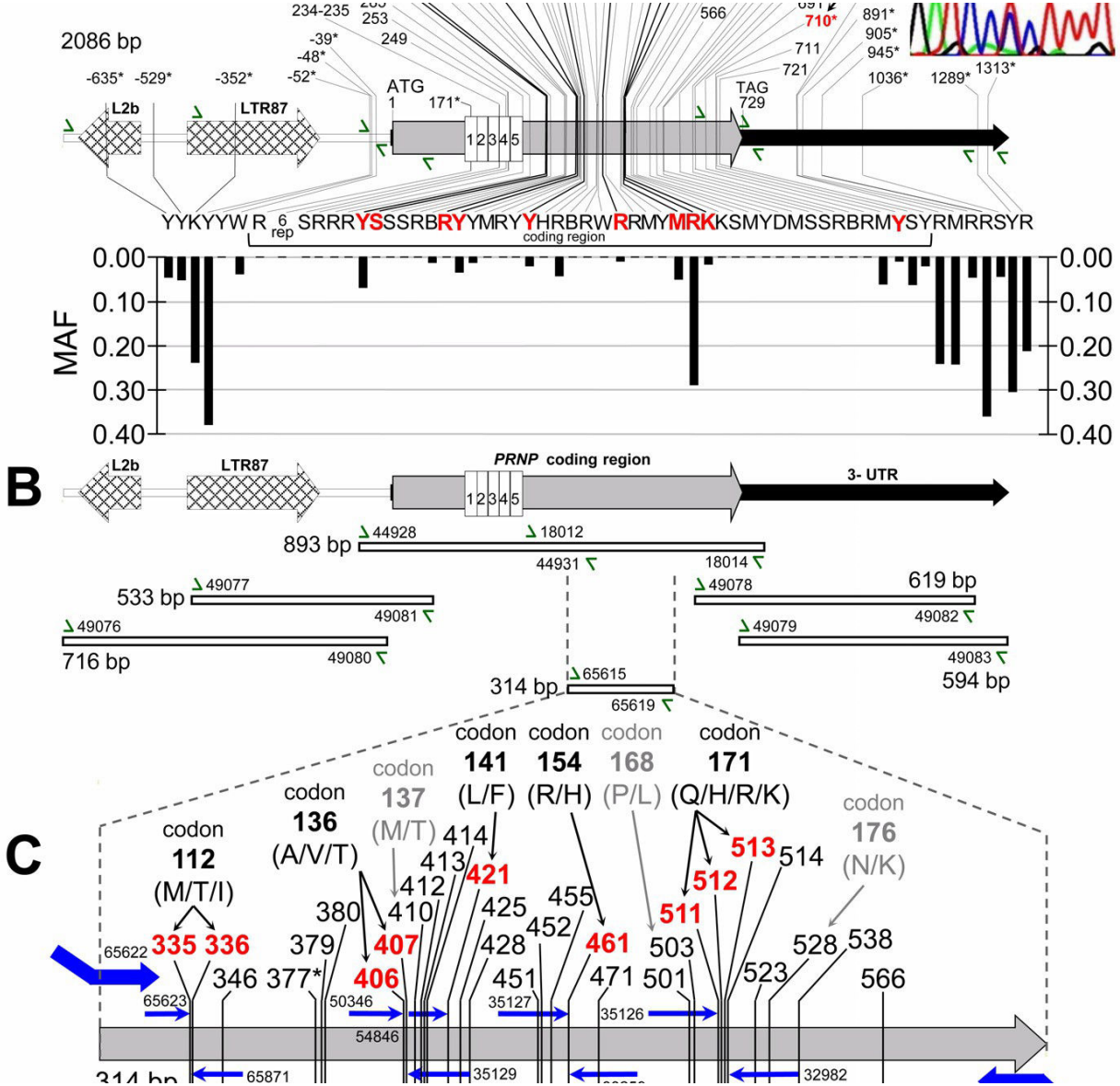
# Outline for today

- PRNP structure and variation
- Estimation of relevant allele freq. in Sheep GEMS populations (Rambouillet, Katahdin, Polypay, Suffolk)
- Relationships to NSIP trait EBVs
- An example of how to use genotype information to change a flock over time.




Lots !!
Of variation at PRNP locus (Heaton et al.,2010)

Multiple alleles not inherited independently

# Scrapie (classical) Susceptibility

- Nucleotide variants affecting codons 136, 154, and 171 of the *PRNP* gene are the most often studied polymorphisms associated with variation in susceptibility to scrapie
  - Considering only the 136 and 171 codons :
  - Resistant (AA136, RR171)
  - Rarely susceptible (AA136, QR 171)
  - Somewhat susceptible (AV136, QR 171)
  - Highly susceptible (VV136, QQ 171)

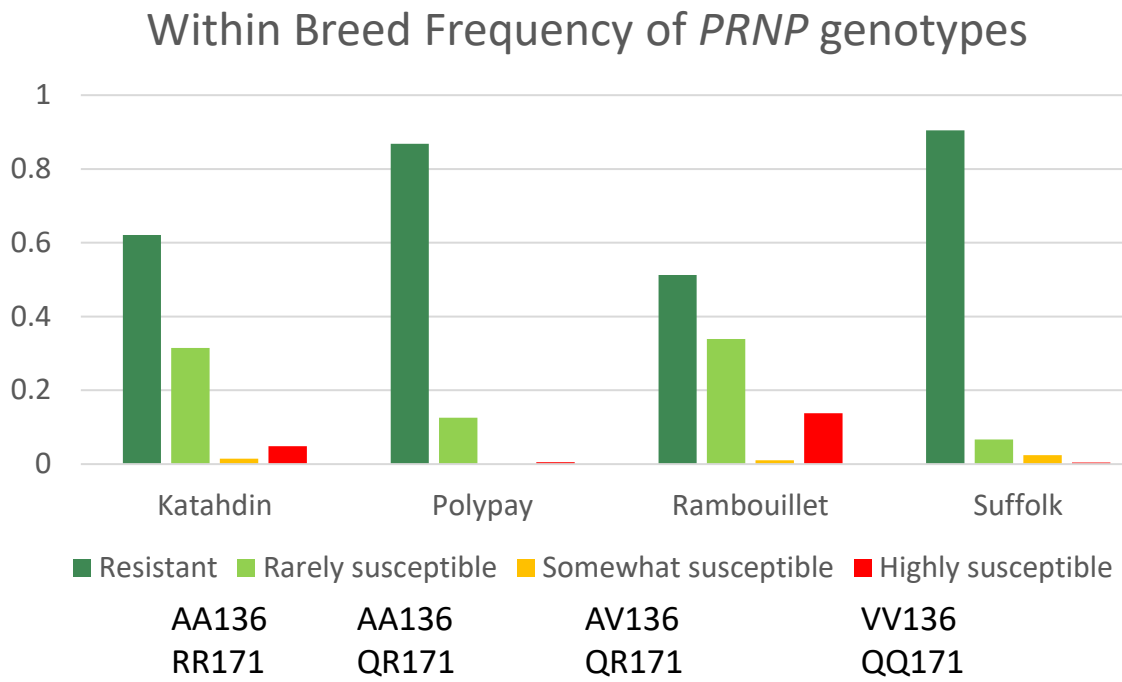
https://scrapiecanada.ca/about-scrapie/

# Genetic Conditions Validated

- Genetic Conditions from 50K chip
  - Scrapie susceptibility determined by multiple **variants** in *PRNP*
    - 23 unique probes for PRNP variation exists on the 50K chip
    - Blind submission of control samples had 100% concordance
    - Reports provided to NSIP producers for codons 136, 171

Lewis et al, 2023

# Scrapie Susceptibility




| Animals Genotyped | |
|---|---|
| **Katahdin** | **14,775** |
| **Polypay** | **2,522** |
| **Rambouillet** | **2,757** |
| **Suffolk** | **2,163** |
| **Total** | **22,217** |

Lewis et al, 2025

# Example of Associations reported

**Table 4.** Significant contrasts for traits associated with *PRNP* haplotype in the Romanov breed of origin[1]

| Trait | Estimate | *P*-value |
|---|---|---|
| Rump width, cm | −0.35 ± 0.14 | 0.013 |
| Carcass length, cm | 0.84 ± 0.40 | 0.038 |
| Longissimus marbling[2] | −48.4 ± 21.0 | 0.022 |

[1]Contrast between scrapie resistant (ARR) and the average of ARQ and VRQ *PRNP* haplotypes.
[2]Subjective marbling score in which 300 equals slight and 400 equals small.

Selection for ARR

(-)
(+)
(-)

**Isler et al, 2006**

**Dorset x Romanov**

# Example of Associations reported

Table 4
Estimated differences, standard error and significance of *t*-test compared to homozygote ARQ*/ARQ* genotype (model 2)

| Genotype | $EBV_{littersize}$ | | | $EBV_{135\ days\ weight}$ | | |
|---|---|---|---|---|---|---|
| | Estimate | S.E. | Significance[a] | Estimate | S.E. | Significance[a] |
| ARQ*/ARR | 0.605 | 0.108 | b | 0.098 | 0.132 | |
| ARQ*/VRQ | 2.182 | 0.311 | b | 2.360 | 0.382 | b |
| ARQ*/AHQ | 0.600 | 0.448 | | 0.556 | 0.538 | |
| ARR/ARR | 1.103 | 0.147 | b | − 0.203 | 0.179 | |
| ARR/VRQ | 1.977 | 0.364 | b | 1.889 | 0.445 | b |

[a] $t < -1.96$ or $> 1.96 =$ [b] = significant.

Selection for ARR

Small (+) for litter size

Small (-) For d135 wt

**Brandsma et al, 2003**

**Dutch Texel**

# Example of Associations reported

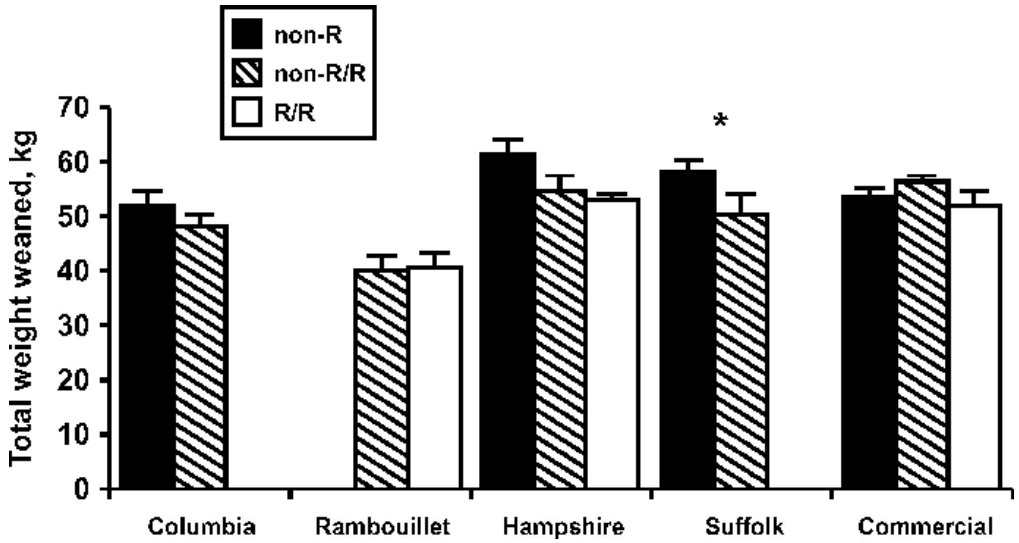



Figure 2. Total weight of lamb weaned (kg) from ewes with genotypes *non-R/non-R, non- R/R,* and *R/R* at codon 171 within breed. *Quantity of lamb weaned differed between genotypes in the Suffolk breed, $P \leq 0.03$.

Selection for ARR

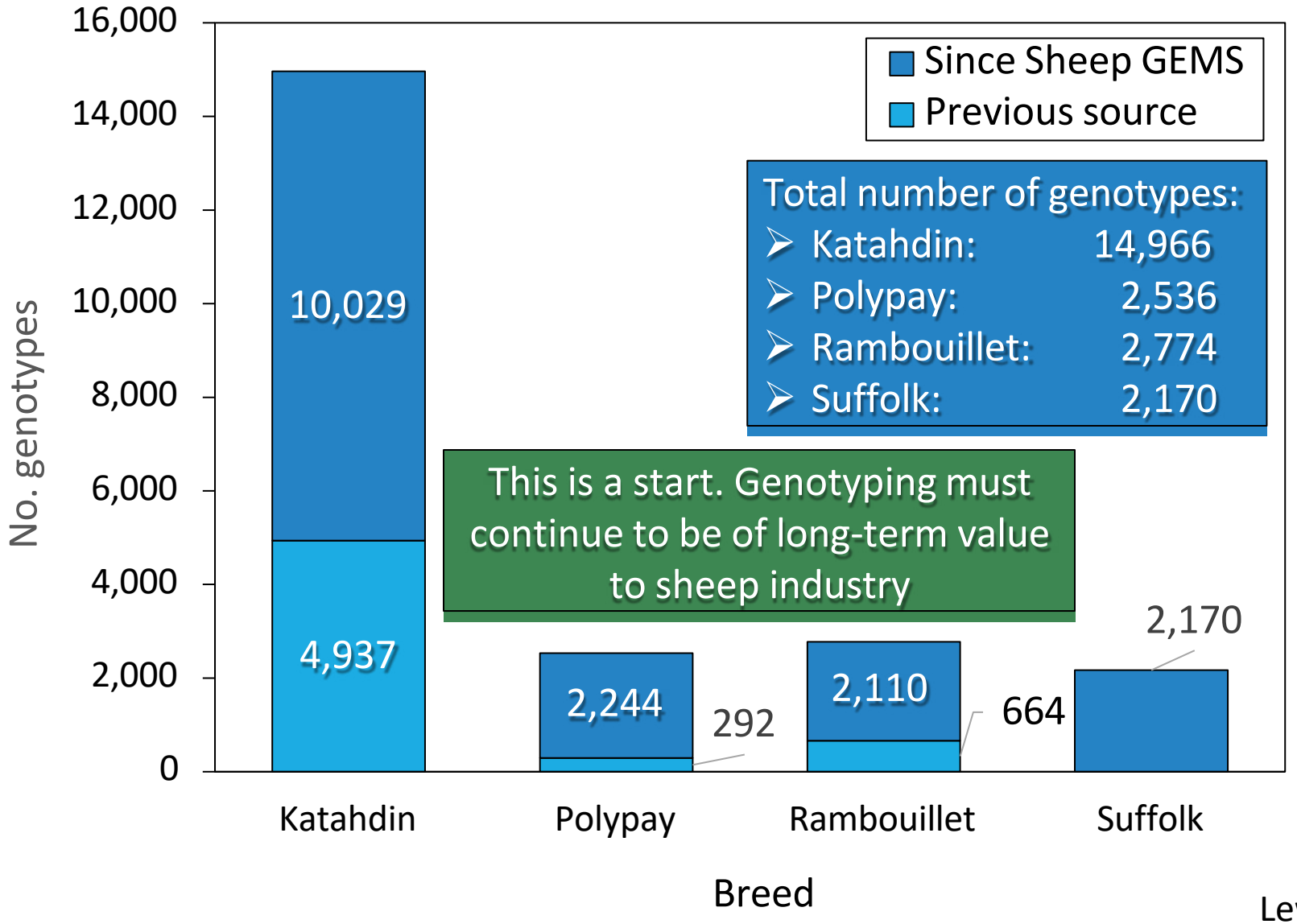
Ewe Productivity

Small (-) For Suffolk

**Alexander et al, 2005**

**Five Breeds Wyoming and USSES**

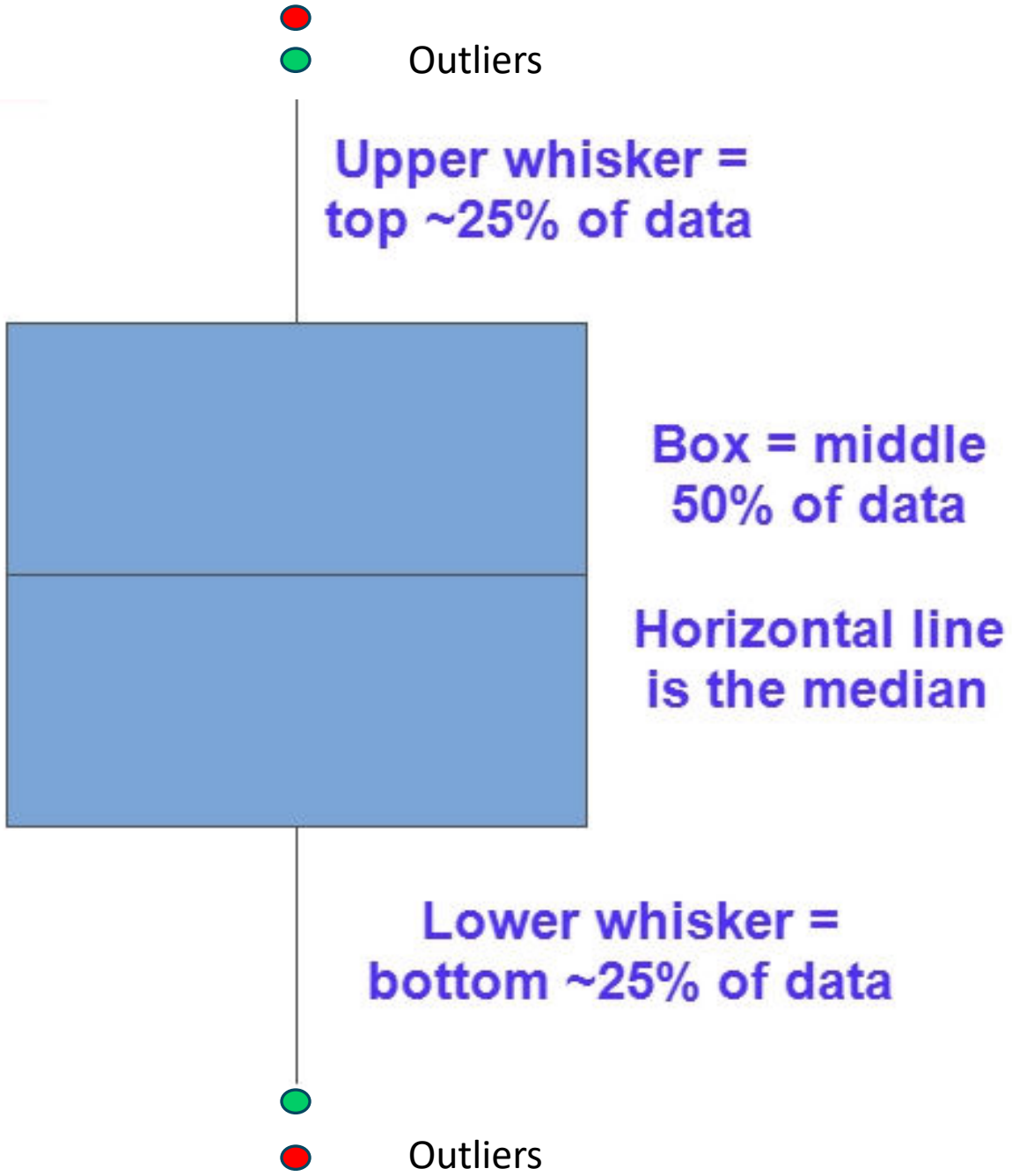
# GEMS data contribution to association testing




Lewis et al, unpublished

# What would cause a significant association ?

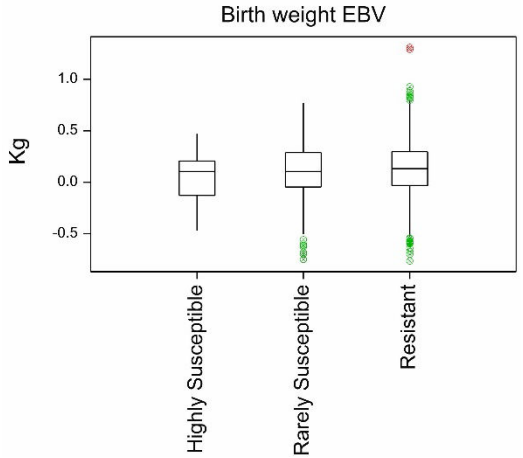
- Genes in linkage disequilibrium with PRNP on Chr 13
- Genetic bias among selected individuals
  - Different breeding value thresholds for QQ vs QR or RR rams ?
- Explain how to interpret box plots



# Polypay

# Impact of PRNP class on EBVs for NSIP recorded traits

- NSIP breeding values within PRNP genotype groups
  - Highly Susceptible (VV QQ) (18)
  - Rarely Susceptible (AA QR) (448)
  - Resistant (AA RR) (2301)
  - Somewhat Susceptible (AV QR) (-)

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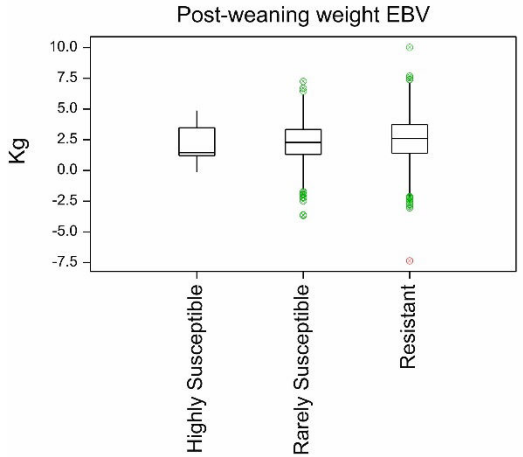
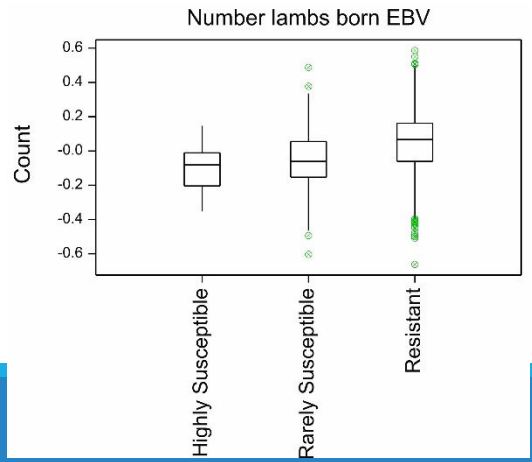



Small (+)

Small (+)

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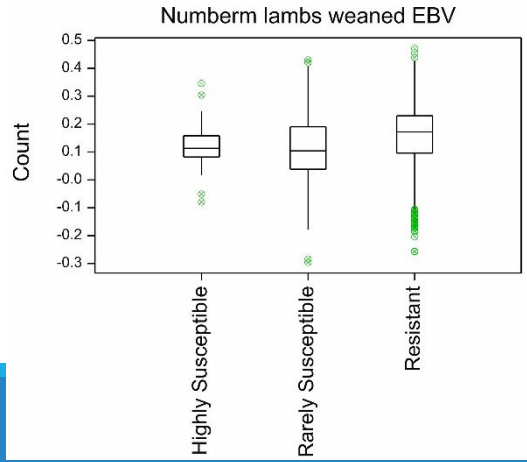


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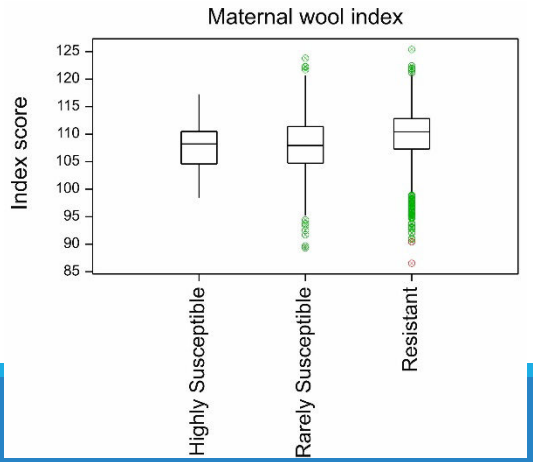
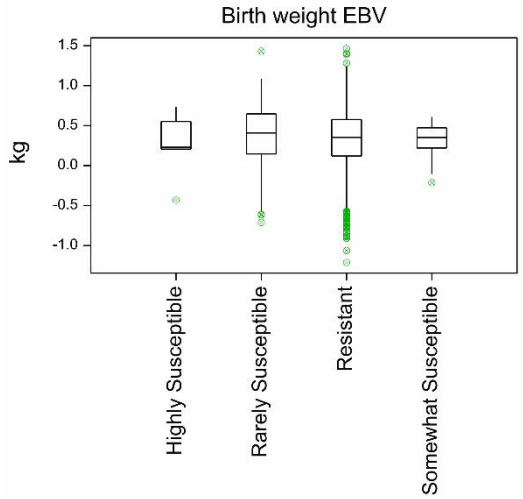



Lewis et al, unpublished

# Suffolk

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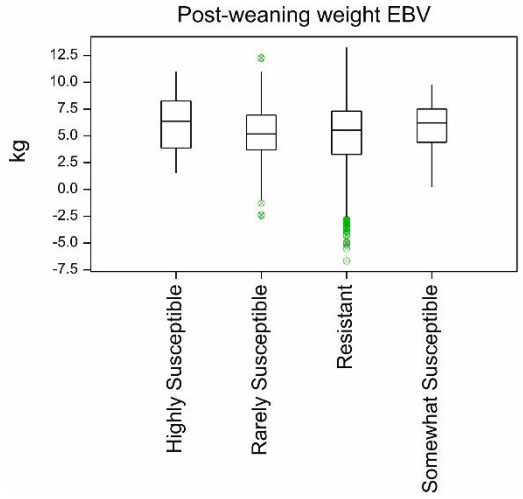


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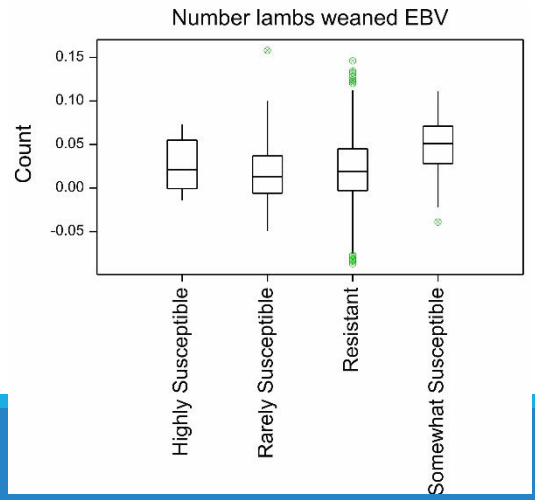
Lewis et al, unpublished

# Impact of PRNP class on EBVs for NSIP recorded traits

- NSIP breeding values within PRNP genotype groups

| | | |
|---|---|---|
| Highly Susceptible | (VV QQ) | (7) |
| Rarely Susceptible | (AA QR) | (148) |
| Resistant | (AA RR) | (1793) |
| Somewhat Susceptible | (AV QR) | (50) |

Small (+)

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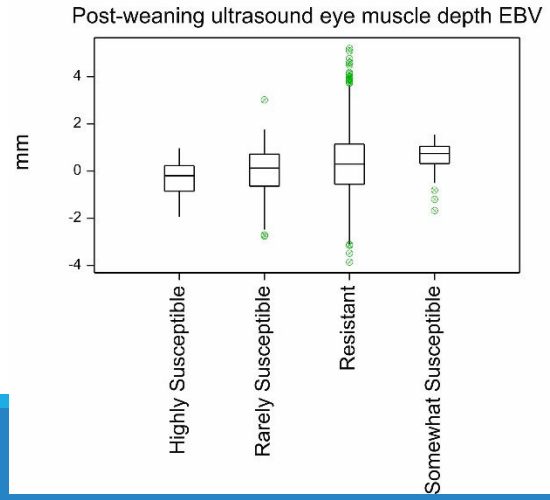


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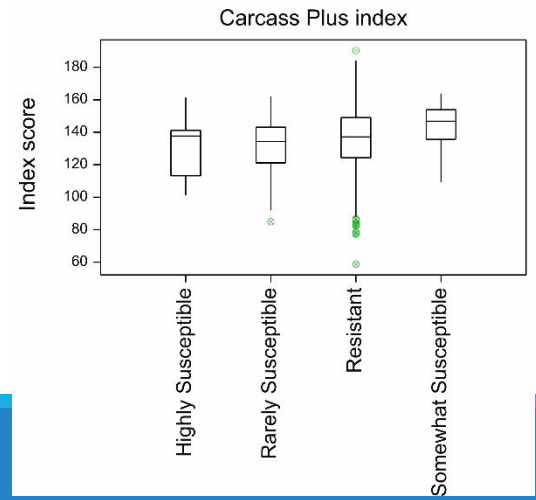
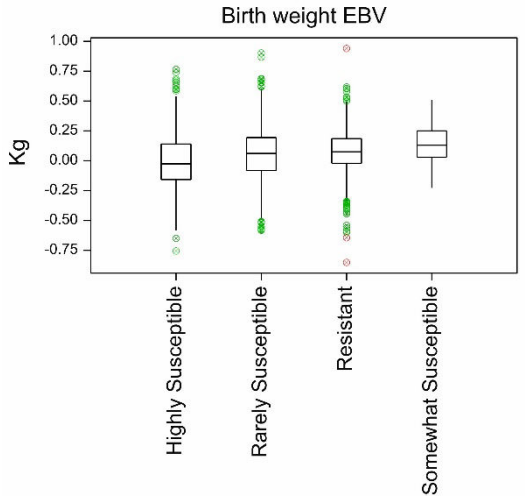


# Rambouillet

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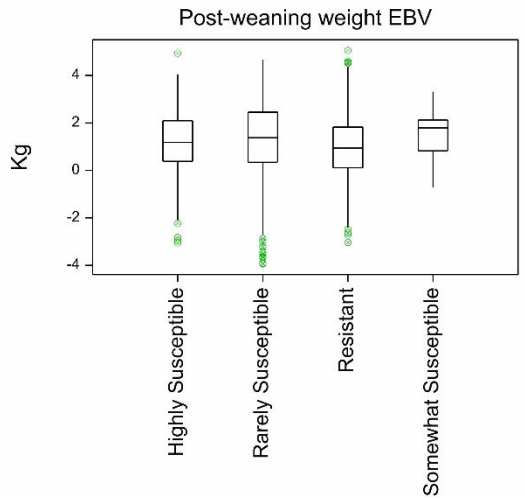


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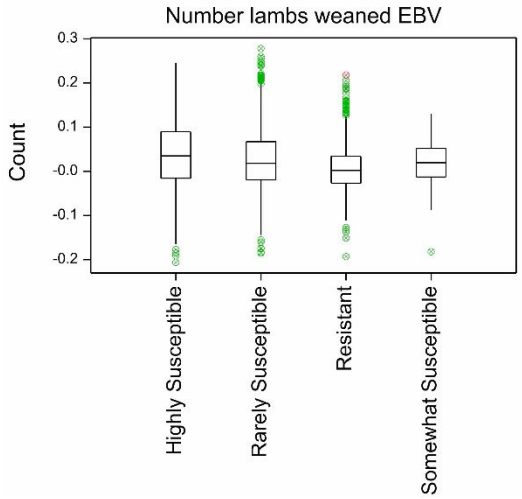
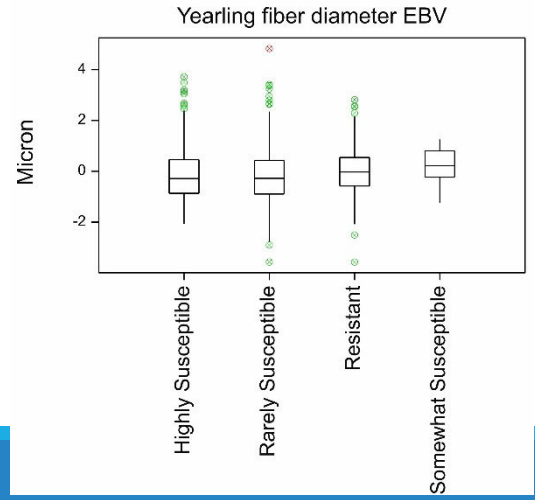



Small (-)

# Impact of PRNP class on EBVs for NSIP recorded traits

- NSIP breeding values within PRNP genotype groups
  - Highly Susceptible (VV QQ) (338)
  - Rarely Susceptible (AA QR) (782)
  - Resistant (AA RR) (1085)
  - Somewhat Susceptible (AV QR) (18)

Small (-)

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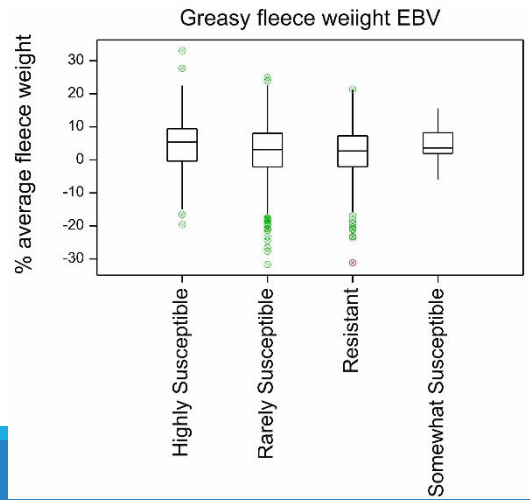


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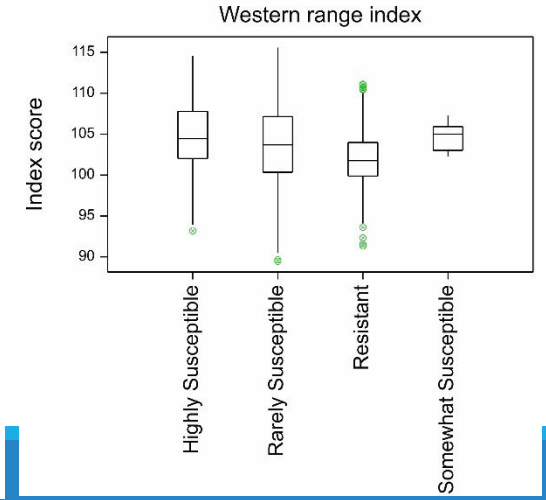
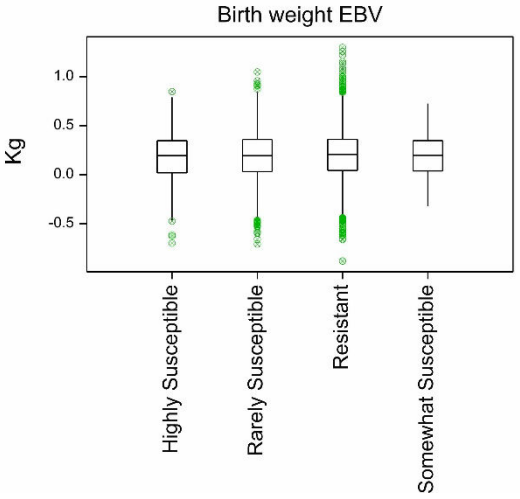



Lewis et al, unpublished

# Impact of PRNP class on EBVs for NSIP recorded traits

- NSIP breeding values within PRNP genotype groups
  - Highly Susceptible (VV QQ) (593)
  - Rarely Susceptible (AA QR) (4054)
  - Resistant (AA RR) (8124)
  - Somewhat Susceptible (AV QR) (199)

## Katahdin

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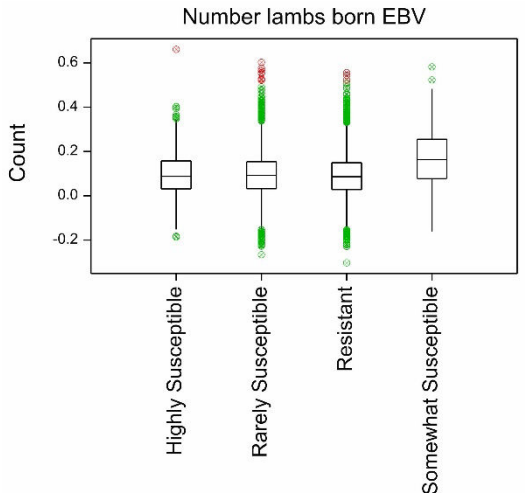
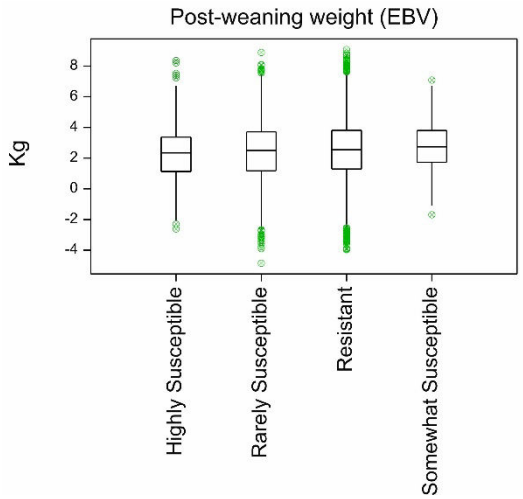



Net 0 to Small +

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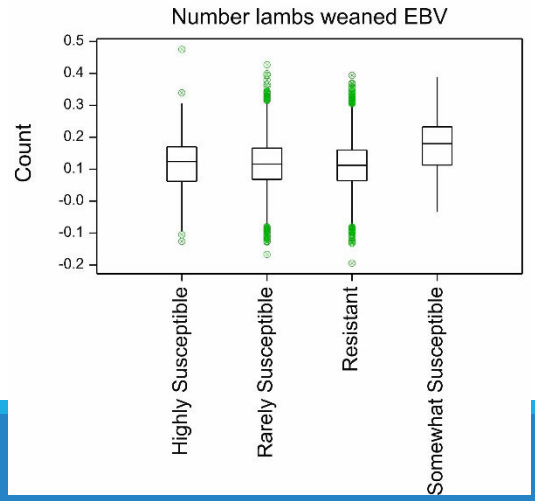


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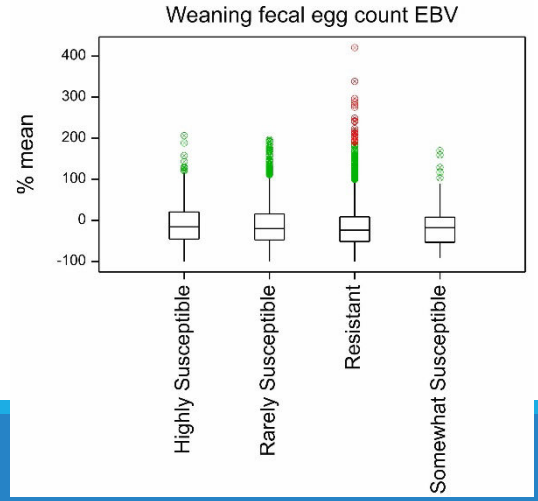


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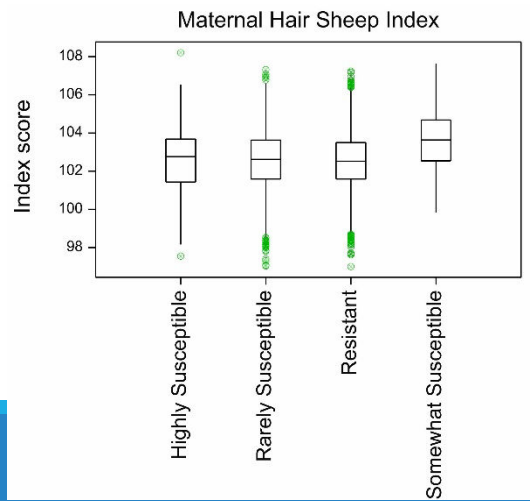



Lewis et al, unpublished

# Example of within flock selection for PRNP

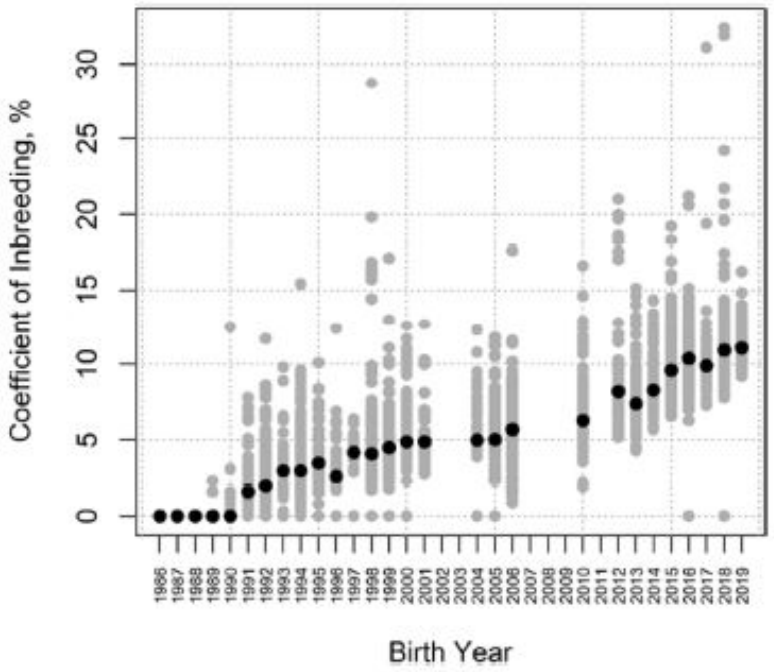
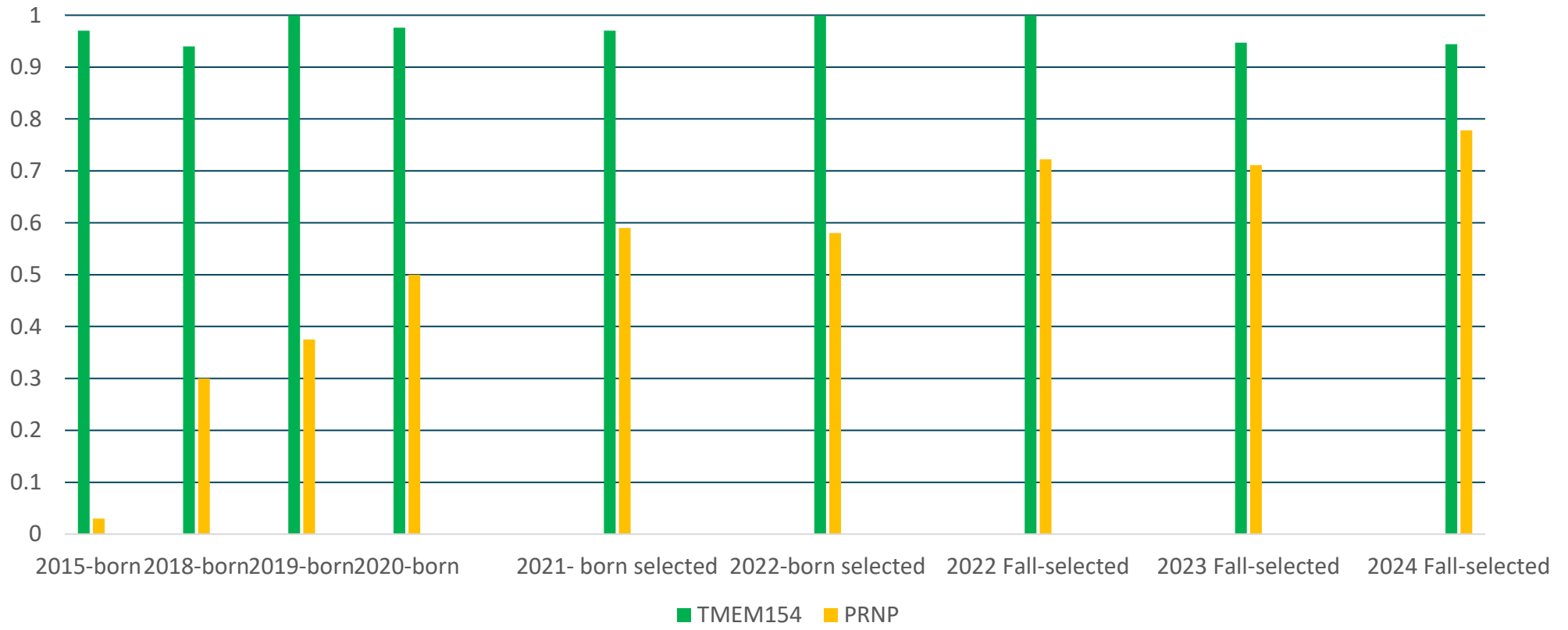



**Figure 1.** Individual (gray circles) and median (black circles) inbreeding coefficients by birth year for Romanov lambs born at the U.S. Meat Animal Research Center.

**Murphy et al, 2020**

- USMARC Romanov flock (~ 300 ewes lambing annually)
  - Goal : Increase Freq of PRNP ARR and TMEM154 “1” without dramatically reducing genetic diversity of the flock.
  - Approach : Genotype candidate ram sons each year and select sons with more favorable genotype each year with all other selection objectives being equal. Only replace sire with a son if the genotype is as good or better than the sire.
  - Matings were assigned to minimize flock inbreeding, each ram (n=10-12 hd) exposed to equal number of ewes.

# Favorable allele frequency present in Romanov breeding status selected rams




Freking et al, unpublished

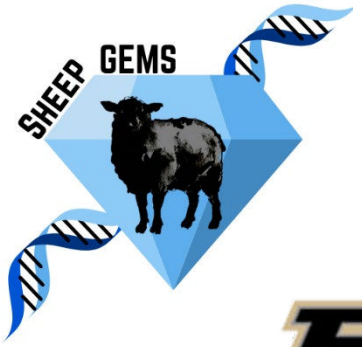
# Fixation of alleles without additional genotyping?

- Once allele frequency is reasonably higher, you can use male genotypes generated each year to identify dams in the flock that are either carriers or homozygous for the unfavorable allele

| Sires | Dams | Sons |
| --- | --- | --- |
| RR | ?? | QR |

# Summary for PRNP status in U.S. sheep

- Breeds differ in current frequency of favorable haplotypes
  - Value is in insurance/protection for future exposure !
  - Options for breeds without favorable haplotypes include introgression and gene editing (regulatory approval?)
- Associated genetic changes due to PRNP selection are mostly small some favorable, some unfavorable
- Selection should be applied within the context of existing breeding objectives

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For any additional questions please feel free to contact:

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