Dissection of genetic variation in the neighbourhood of the SIGLEC5 gene underlying traits routinely evaluated in dairy cattle

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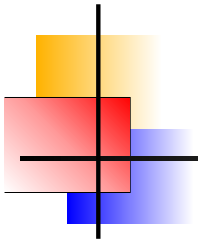


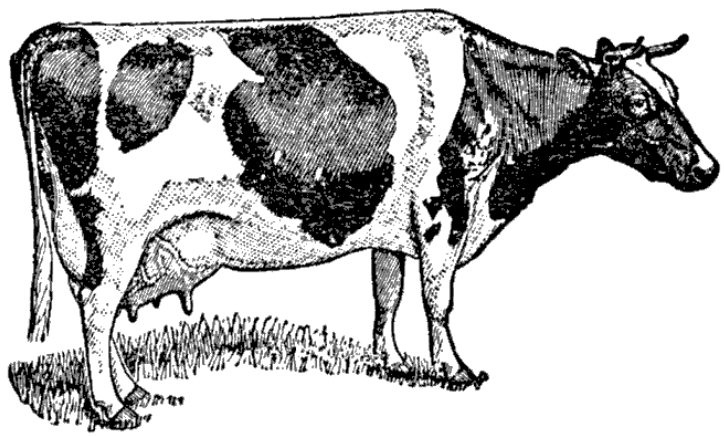
Motivation

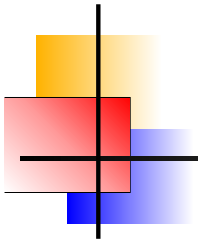
SIGLEC5 gene:

- Cole et at. JDS 2009
- fertility traits
- new missense mutation detected

Objectives

Testing influence of SIGLEC5 gene on 29 traits (type, production, fertility and somatic cell) in dairy cattle using three mixed models. Searching possible SNPs in high linkage disequilibrium with this gene, which affects the traits.

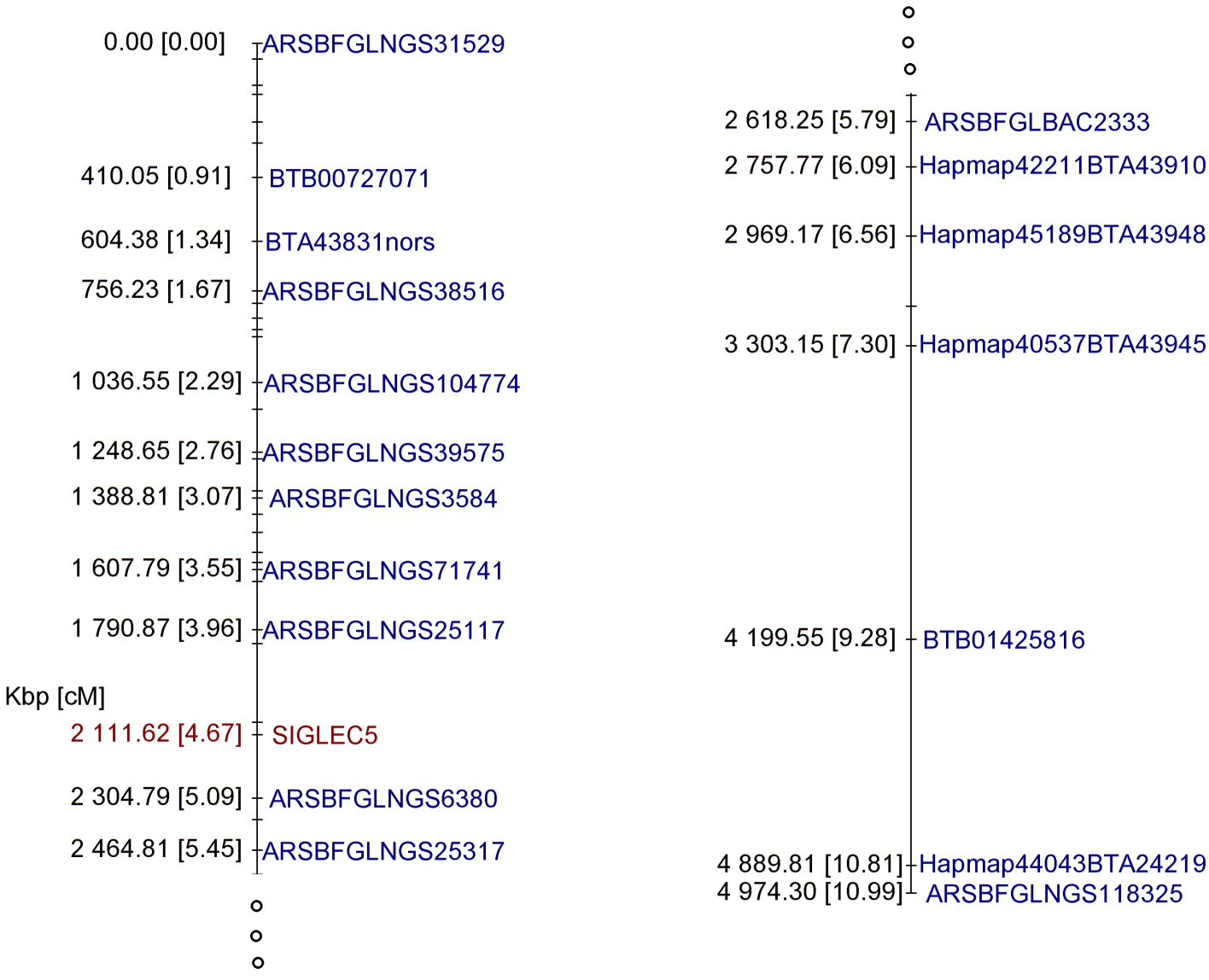


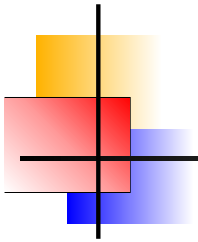


Material – animals

- 400 HF bulls
- EBV
- Traits:
  - 3 production traits
  - 21 type traits
  - 4 fertility traits
  - somatic cell score
- 41 SNP markers on BTA18
  - SIGLEC5 gene
  - 28 SNPs from the left side of SIGLEC5 gene
  - 12 SNPs from the right side of SIGLEC5 gene

Material – genetic map

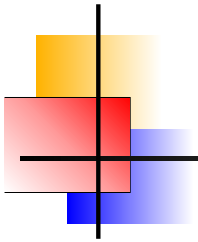




Methods – SNPs as a random term (M1)

$$\mathbf{y} = \boldsymbol{\mu} + \mathbf{Z}_\alpha \boldsymbol{\alpha} + \mathbf{Z}_q \mathbf{q} + \boldsymbol{\epsilon},$$

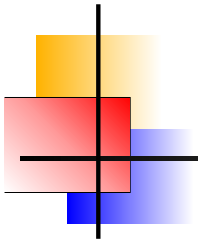
- $\mathbf{y}$ – EBV
- $\boldsymbol{\alpha}$ – random animal polygenic effect, $\boldsymbol{\alpha} \sim \mathcal{N}(\mathbf{0}, \mathbf{A}\sigma^2_\alpha)$
- $\mathbf{q}$ – random SNP effect, $\mathbf{q} \sim \mathcal{N}(\mathbf{0}, \mathbf{I}_K \sigma^2_q)$
- $\mathbf{Z}_\alpha = \mathbf{I}_N$ and $\mathbf{Z}_q \in \{-1, 0, 1\}$
- $\boldsymbol{\epsilon}$ – error term, $\boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \mathbf{I}_N \sigma^2_\epsilon)$



Methods – estimation of variance components

EM algorithm:

- $$\sigma_{\alpha}^{2[t+1]} = \frac{\widehat{\boldsymbol{\alpha}}'^{[t]}\mathbf{A}^{-1}\widehat{\boldsymbol{\alpha}}^{[t]} + tr\left(\mathbf{A}^{-1}\mathbf{C}^{\alpha[t]}\right)\sigma_{\epsilon}^{2[t]}}{N}$$
- $$\sigma_{q}^{2[t+1]} = \frac{\widehat{\mathbf{q}}'^{[t]}\widehat{\mathbf{q}}^{[t]} + tr\left(\mathbf{C}^{q[t]}\right)\sigma_{\epsilon}^{2[t]}}{K}$$
- $$\sigma_{\epsilon}^{2[t+1]} = \frac{\widehat{\boldsymbol{\epsilon}}'^{[t]}\widehat{\boldsymbol{\epsilon}}^{[t]} + tr\left([\mathbf{1}, \mathbf{Z}_{\alpha}, \mathbf{Z}_{q}]\mathbf{C}^{-1[t]}[\mathbf{1}, \mathbf{Z}_{\alpha}, \mathbf{Z}_{q}]'\right)\sigma_{\epsilon}^{2[t]}}{N}$$



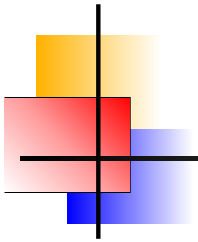
Methods – likelihood ratio test

- Tested hyphotesis

$$H_0 : \sigma_q^2 = 0 \quad \text{vs.} \quad H_1 : \sigma_q^2 \neq 0$$

- Test statistics

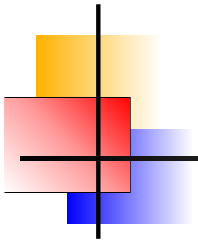
$$\Lambda = -2 \log \left(\frac{L\left(\widehat{\boldsymbol{\theta}}_0\right)}{L\left(\widehat{\boldsymbol{\theta}}\right)} \right) \sim \frac{1}{2}\chi_0^2 + \frac{1}{2}\chi_1^2$$



Methods – SNPs as a fixed term (M2)

$$\mathbf{y} = \boldsymbol{\mu} + \mathbf{X}_{\beta}\boldsymbol{\beta} + \mathbf{Z}_{\alpha}\boldsymbol{\alpha} + \boldsymbol{\epsilon}$$

- $\mathbf{y}$ – EBV;
- $\boldsymbol{\beta}$ – fixed SNP effects
- $\mathbf{X}_{\beta} \in \{0, 1, 2\}$
- $\boldsymbol{\alpha}$ – random animal polygenic effect, $\boldsymbol{\alpha} \sim \mathcal{N}(\mathbf{0}, \mathbf{A}\sigma^2_{\alpha})$
- $\boldsymbol{\epsilon}$ – error term, $\boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \mathbf{I}_N\sigma^2_{\epsilon})$



Methods – Wald test

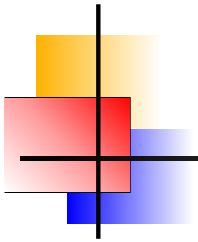
- Tested hyphotesis

$$H_0 : \beta_i = 0 \quad \text{vs.} \quad H_1 : \beta_i \neq 0$$

- Test statistics

$$W = \frac{\widehat{\beta}_i}{S\left(\widehat{\beta}_i\right)} \sim \mathcal{N}(0,1)$$

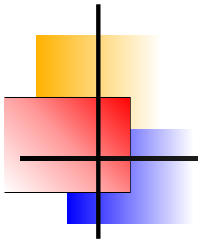
$$S\left(\widehat{\beta}_i\right) = \left(\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}\right)^{-1}[i,i]$$



Methods – interval QTL mapping (every 0.5 cM) (M3)

$$\mathbf{y} = \boldsymbol{\mu} + \mathbf{Z}_{\alpha}\boldsymbol{\alpha} + \mathbf{Z}_{\eta}\boldsymbol{\eta}_{\boldsymbol{x}} + \boldsymbol{\epsilon}$$

- $\mathbf{y}$ – EBV;
- $\boldsymbol{\alpha}$ – random animal polygenic effect, $\boldsymbol{\alpha} \sim \mathcal{N}(\mathbf{0}, \mathbf{A}\sigma^2_{\alpha})$
- $\boldsymbol{\eta}_{\boldsymbol{x}}$ – random QTL effect at xth position, $\boldsymbol{\eta}_{\boldsymbol{x}} \sim \mathcal{N}(\mathbf{0}, \mathbf{IBD}\sigma^2_{\eta_x})$
- $\boldsymbol{\epsilon}$ – error term, $\boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \mathbf{I}_N\sigma^2_{\epsilon})$



Methods – likelihood ratio test

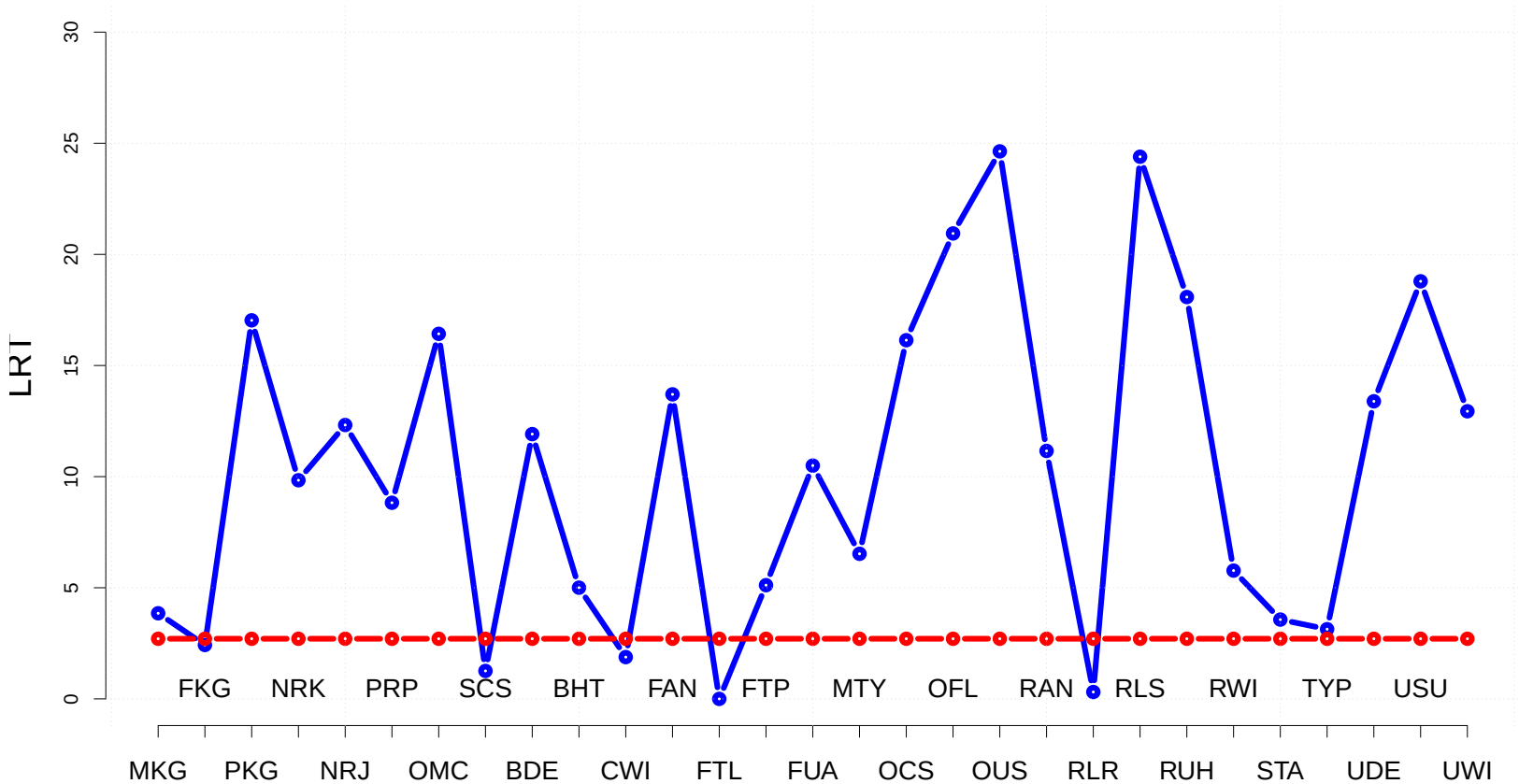
- Tested hyphotesis

$$H_0 : \sigma^2_{\eta_x} = 0 \quad \text{vs.} \quad H_1 : \sigma^2_{\eta_x} \neq 0$$

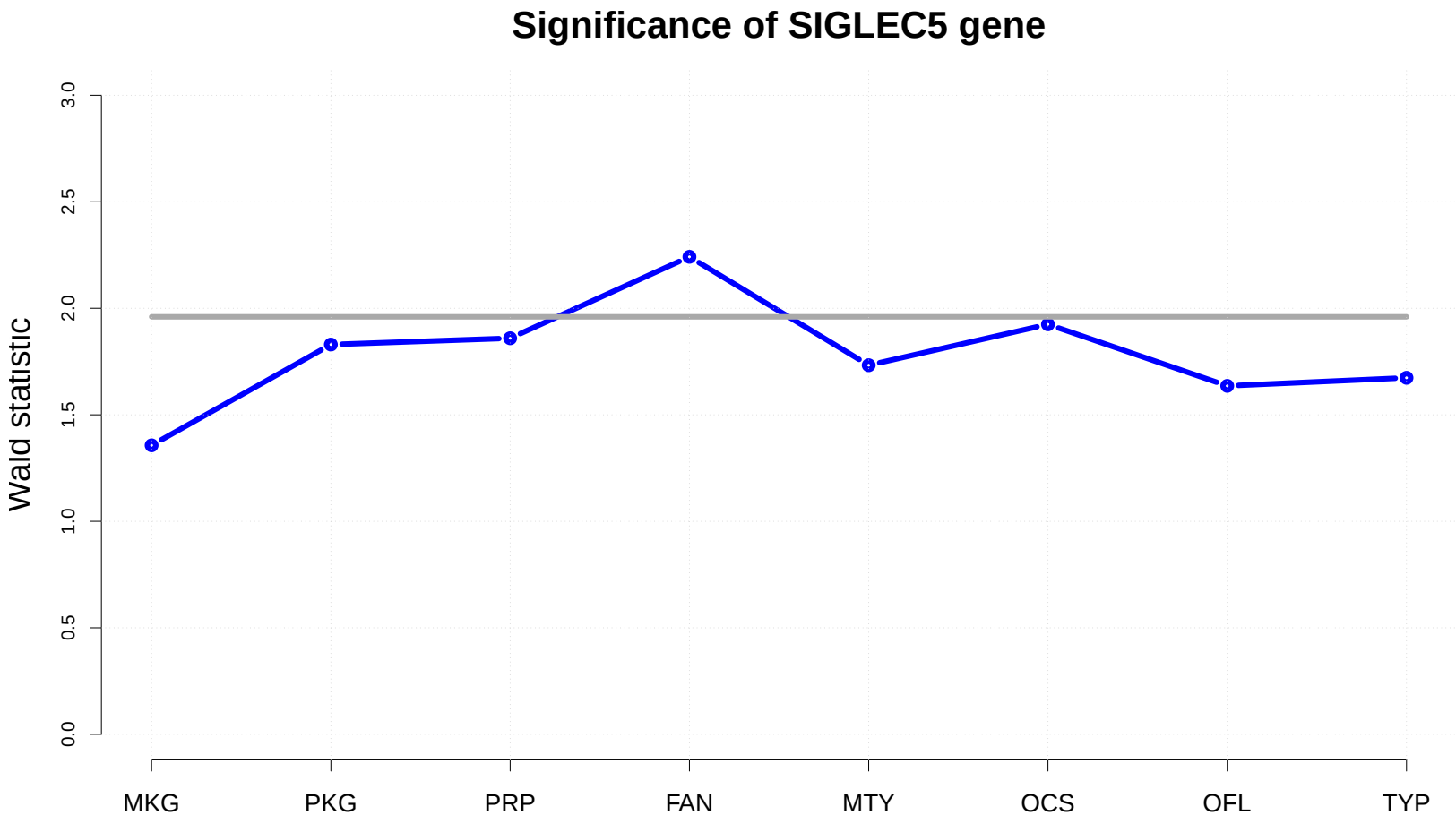
- Test statistics

$$\Lambda = -2 \log \left(\frac{L\left(\widehat{\boldsymbol{\theta}}_0\right)}{L\left(\widehat{\boldsymbol{\theta}}\right)} \right) \sim \frac{1}{2}\chi^2_0 + \frac{1}{2}\chi^2_1$$

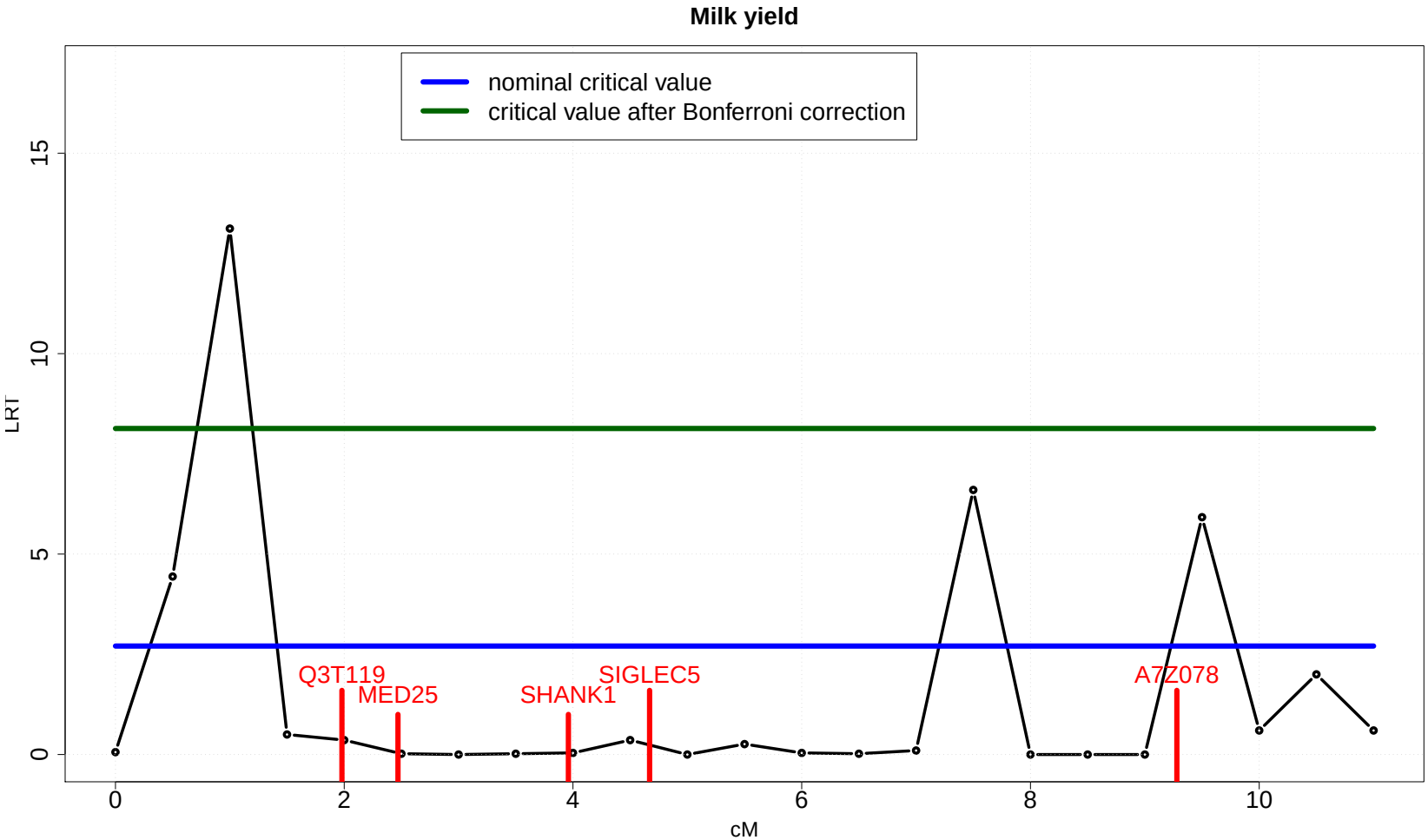
Results – M1


LRT
0
5
10
15
20
25
30
FKG
NRK
PRP
SCS
BHT
FAN
FTP
MTY
OFL
RAN
RLS
RWI
TYP
USU
MKG
PKG
NRJ
OMC
BDE
CWI
FTL
FUA
OCS
OUS
RLR
RUH
STA
UDE
UWI

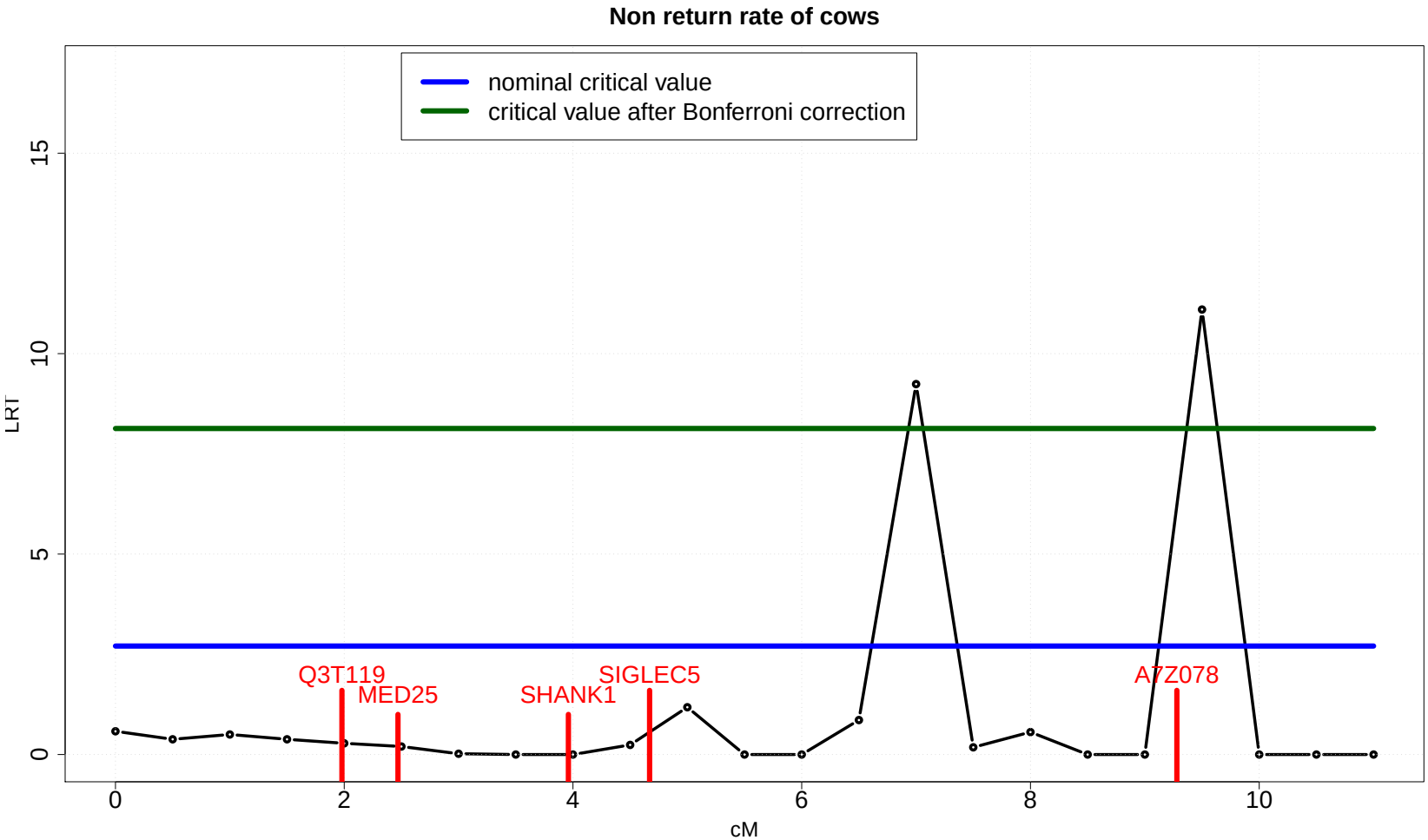
Results – M2


Significance of SIGLEC5 gene
Wald statistic
0.0
0.5
1.0
1.5
2.0
2.5
3.0
MKG
PKG
PRP
FAN
MTY
OCS
OFL
TYP

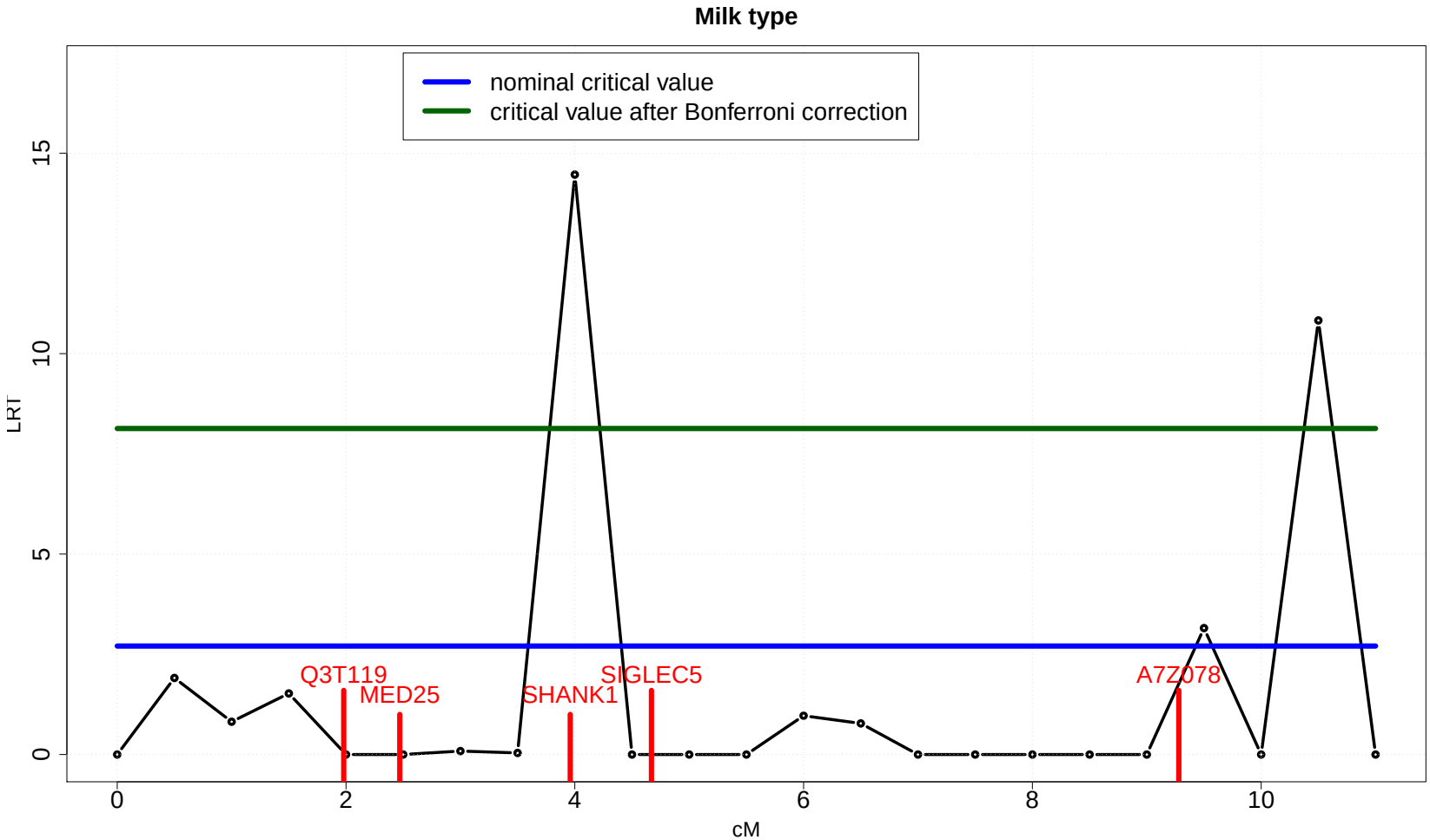
Results – M3


Milk yield
nominal critical value
critical value after Bonferroni correction
LRT
0
5
10
15
0
2
4
6
8
10
cM
Q3T119
MED25
SHANK1
SIGLEC5
A7Z078

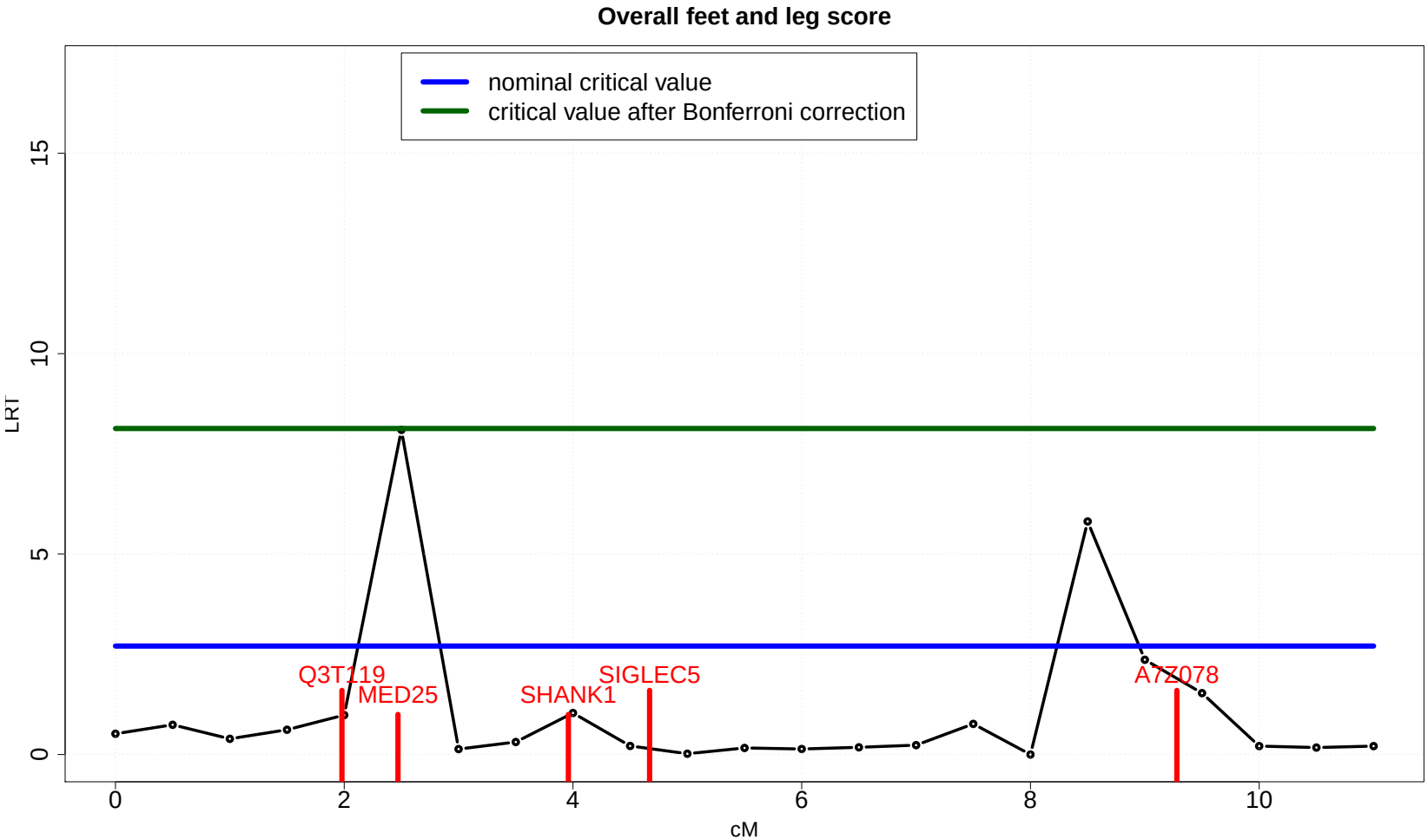
Results – M3


Non return rate of cows
nominal critical value
critical value after Bonferroni correction
LRT
0
5
10
15
0
2
4
6
8
10
cM
Q3T119
MED25
SHANK1
SIGLEC5
A7Z078

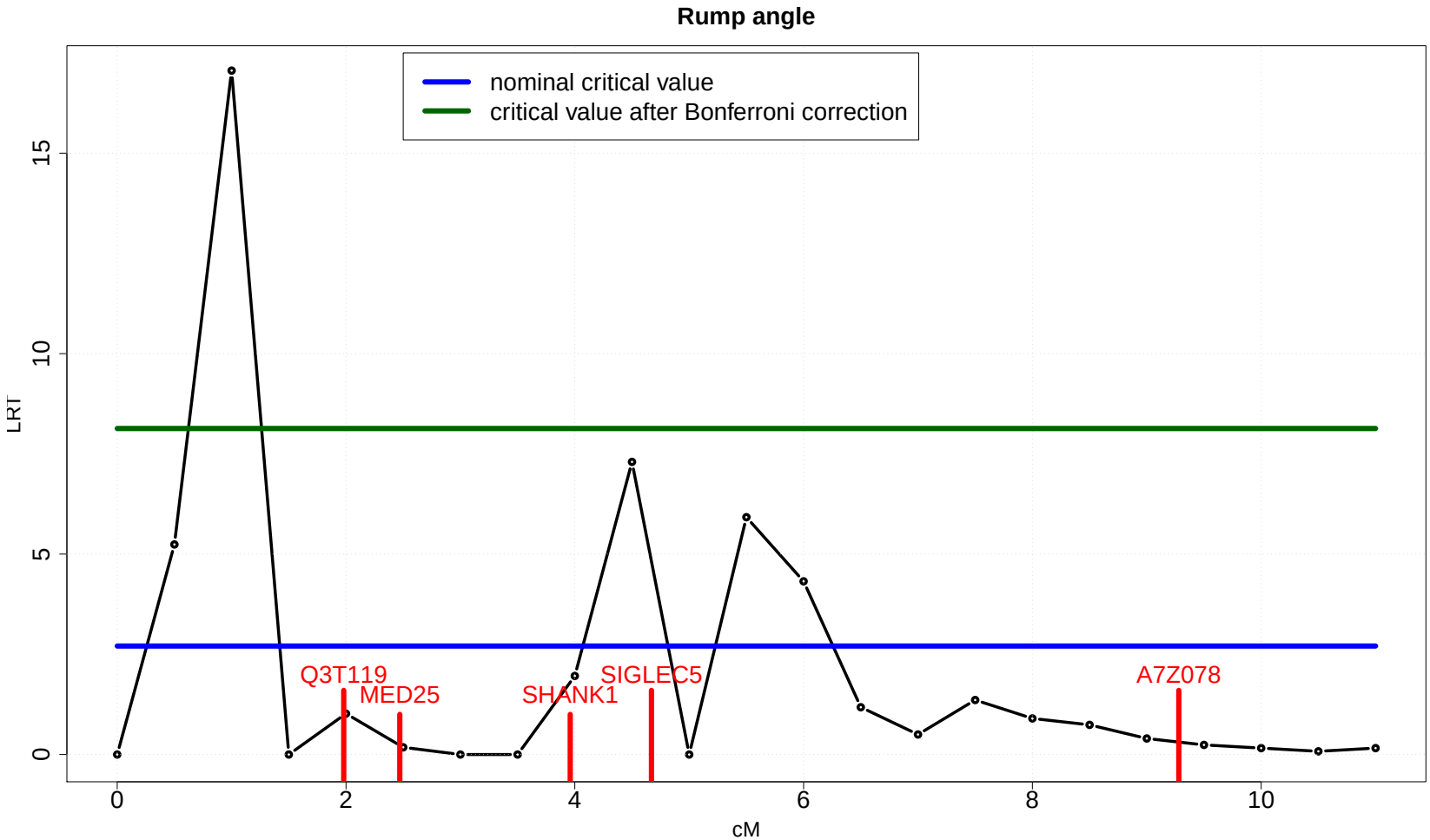
Results – M3


Milk type
nominal critical value
critical value after Bonferroni correction
LRT
0
5
10
15
0
2
4
6
8
10
cM
Q3T119
MED25
SHANK1
SIGLEC5
A7Z078

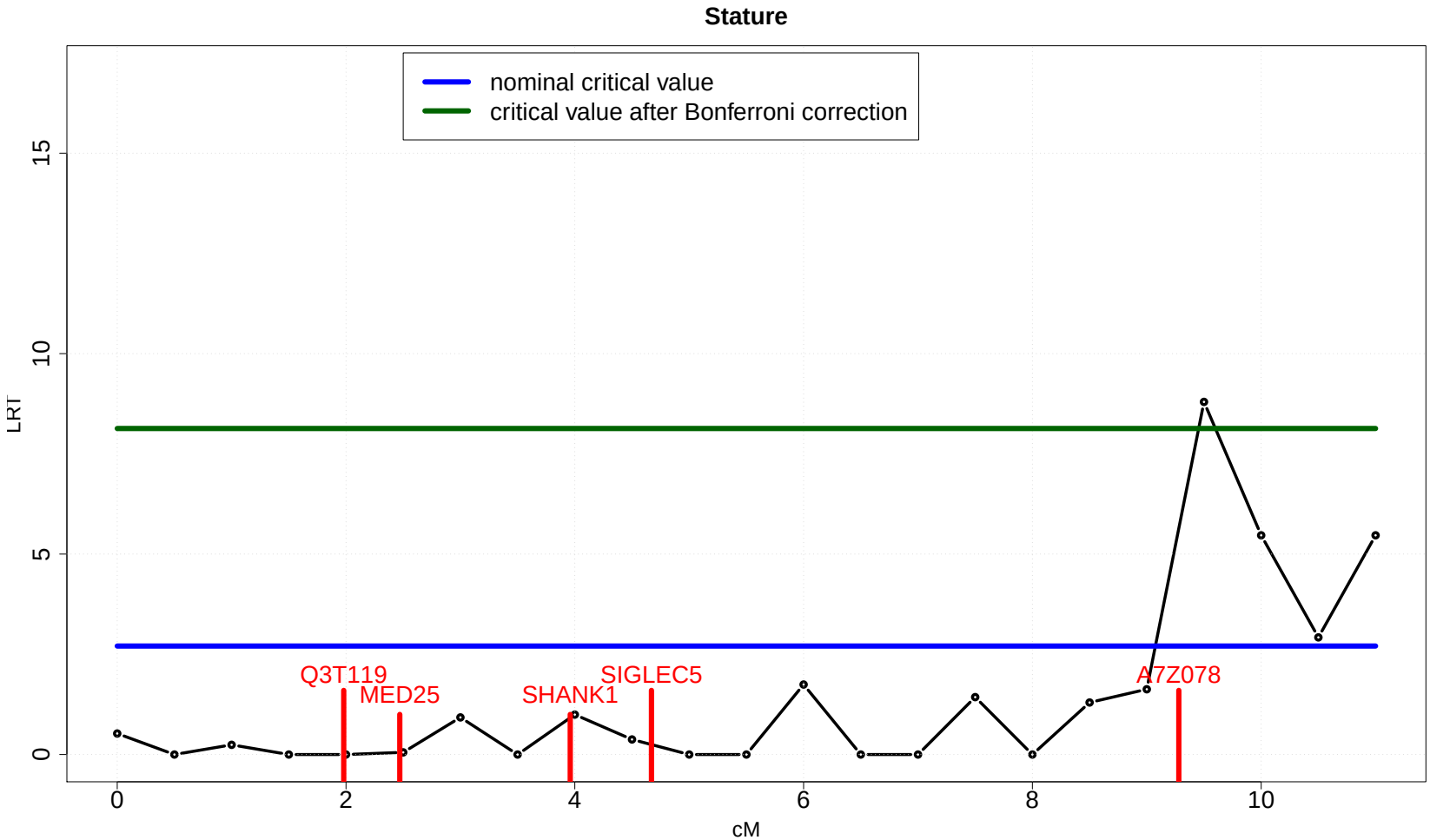
Results – M3


Overall feet and leg score
nominal critical value
critical value after Bonferroni correction
LRT
0
5
10
15
0
2
4
6
8
10
cM
Q3T119
MED25
SHANK1
SIGLEC5
A7Z078

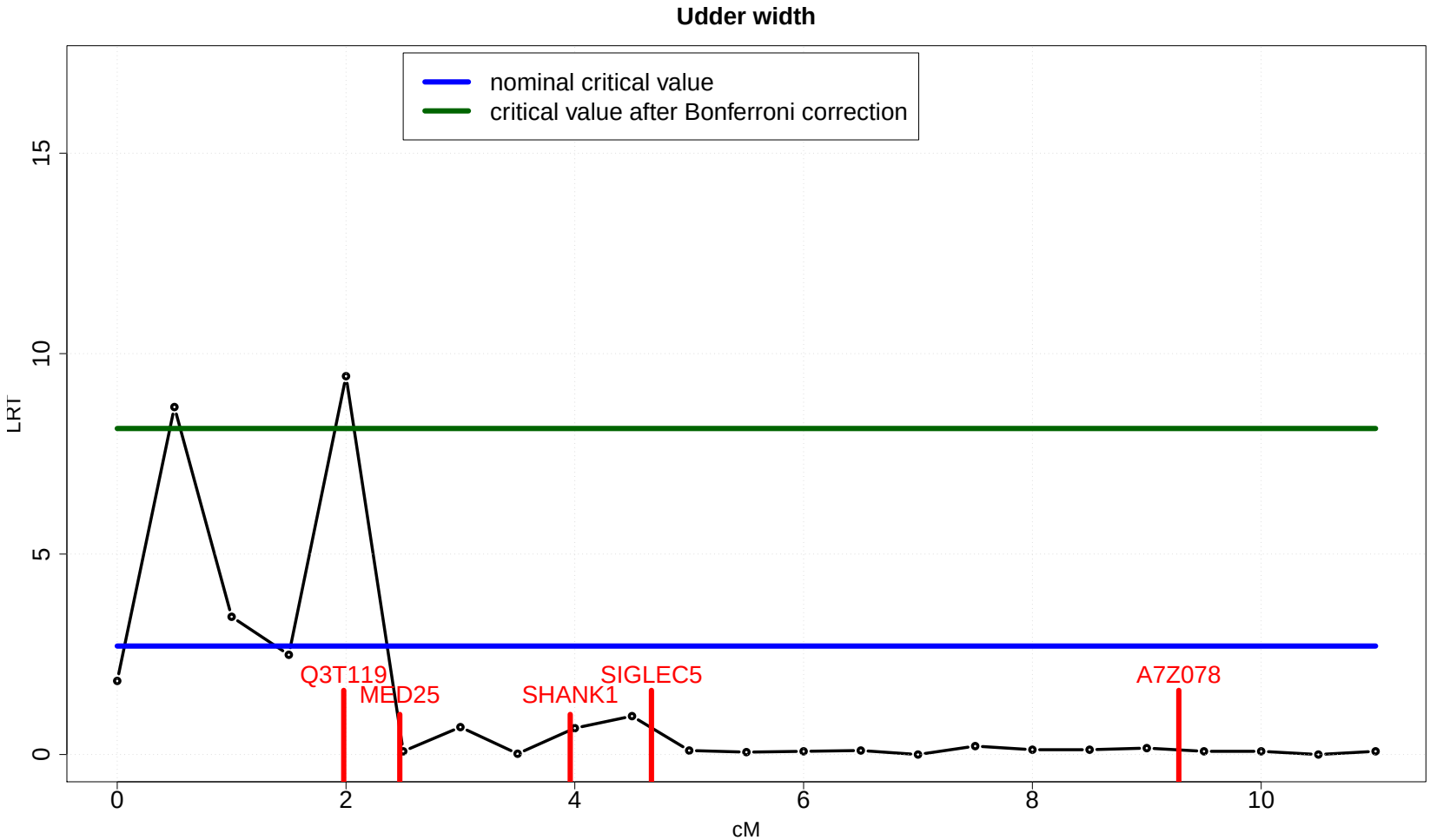
Results – M3

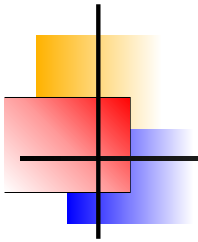

Rump angle
nominal critical value
critical value after Bonferroni correction
LRT
0
5
10
15
0
2
4
6
8
10
cM
Q3T119
MED25
SHANK1
SIGLEC5
A7Z078

Results – M3


Stature
nominal critical value
critical value after Bonferroni correction
LRT
0
5
10
15
0
2
4
6
8
10
cM
Q3T119
MED25
SHANK1
SIGLEC5
A7Z078

Results – M3


Udder width
nominal critical value
critical value after Bonferroni correction
LRT
0
5
10
15
0
2
4
6
8
10
cM
Q3T119
MED25
SHANK1
SIGLEC5
A7Z078



Conclusions

- Siglec5 gene
  - milk type (0.9 cM)
  - non return rate of cows (2.5 cM)
- Other genes near concidered SNPs positions
  - SHANK1 for milk type
  - A7Z078 for nonreturn rate of cows and stature
  - MED25 for overall feet and leg score
  - Q3T119 for milk yield, rump angle and udder width

Thank You!