Analysis of the Spring Leg Defect in the Canadian Dorset Sheep Breed

J. Cameron[1], M. Jafarikia[2,3], L. Maignel[2], R. Morel[1]

[1] *Centre d'expertise en production ovine du Québec, La Pocatière, Québec, Canada,*

[2] *Canadian Centre for Swine Improvement, Ottawa, Ontario, Canada,*

[3] *Centre for Genetic Improvement of Livestock, University of Guelph, Guelph, Ontario, Canada*

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Abstract

Since the early 2000s, purebred sheep breeders have noticed the emergence of a new defect in their herds. Sick animals present with a hyperflexion of one or both hind limbs when moving at a slow pace. Planned matings were carried out to produce 150 Dorset lambs and validate the hypothesis of a genetic determinism for the spring leg defect in sheep. Two groups of lambs were produced through planned matings; one at risk of developing spring leg and one at low risk of developing the defect. In the high risk group, 23.1% of the lambs developed the defect, versus 3.4% in the low risk group. A total of 192 sick and normal animals were genotyped with the ovine 600K SNP panel, and association studies were carried out between SNP genotypes and the expression of the defect. Three promising SNPs were detected on chromosome 24, with polymorphisms being significantly associated with the spring leg defect.

Objectives

- **Objective 1**: Confirm the genetic determinism of the spring-leg defect through the validation of hypotheses raised in a preliminary project
- **Objective 2**: Identify early detection methods of spring leg on live animals

Methods

- Two groups of lambs were produced following planned matings at the *Centre d'expertise en production ovine du Québec* (CEPOQ) experimental farm.
- Planned matings produced a total of 150 lambs (72 males and 78 females) assigned to two experimental groups: AT RISK and at LOW RISK of developing the condition, based on the degree of relatedness with suspect ancestors identified as part of a previous project
- Necropsies performed on 6 normal and 6 sick animals to find potential related abnormalities in the central nervous system
- Genotyping of 192 animals (including all rams and a subset of normal and sick ewes and lambs) with the ovine 600K SNP panel.
- Genome wide association studies performed using the single-locus mixed model of the Golden Helix SNP and Variation (SVS) software.

CCSI CCAP Canadian Centre for Swine Improvement inc. / Centre Canadien pour l'Amélioration des Porcs inc.

CEPOQ Centre d'expertise en production ovine du Québec

centre for genetic improvement of livestock CGIL

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Results

- **Results of mating plans**

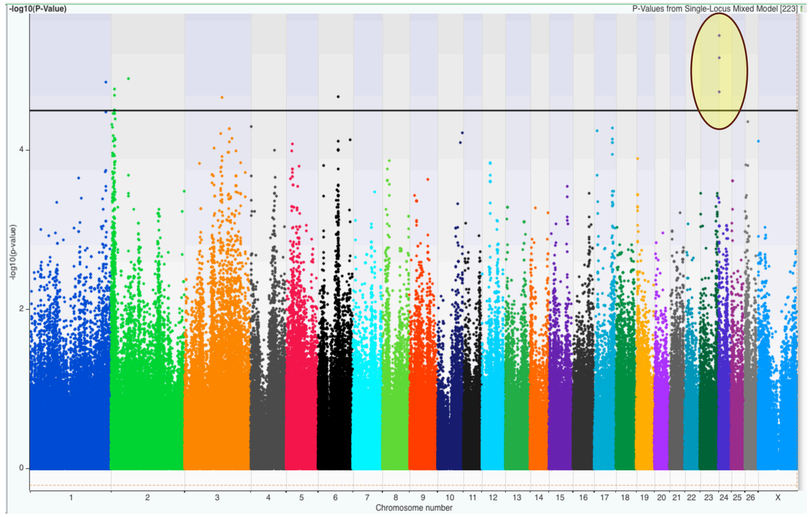
STATUS	HIGH RISK		LOW RISK	
	# lambs	Freq	# lambs	Freq
SICK	21	23.1 %	2	3.4 %
SUSPECT	20	33.0 %	9	18.6 %
NORMAL	40	43.9 %	46	78.0 %

As expected, the spring-leg defect is significantly more frequent in families related to a specific group of ancestors.

- **SNP genotyping and GWAS**

There are 606,006 SNPs on the ovine high-density SNP panel. SNPs were distributed at an average distance of 4.6 kb from each other. Excluding 30,744 SNPs with a call rate of zero, the average MAF across the remaining 575,262 SNPs was 0.21 for genotyped animals. A total number of 162,624 SNPs with MAF less than 0.10 and 30,744 SNPs with call frequencies inferior to 0.95 were excluded from analyses. The 412,638 remaining SNPs were included in association analyses.
Only 3 significant SNPs were detected on chromosome 24 (FDR<0.05) after adjusting p-values for multiple tests. The three significant SNPs were oar3_OAR24_1341130, oar3_OAR24_1343567 and oar3_OAR24_1358660 located approximately 18 kb far apart. in the same haplotype block at a very high LD (r2>0.86).

- **Association of SNPs on the ovine 600K SNP panel with the spring leg defect**



- **Spring-leg status and haplotype frequencies for SNPs oar3_OAR24_1341130, oar3_OAR24_1343567, oar3_OAR24_1358660**

Haplotype	AGG / AGG		GAA/AGG		GAA/GAA	
	#	%	#	%	#	%
SICK	3	9%	13	15%	25	44%
SUSPECT	7	21%	13	15%	15	26%
NORMAL	23	70%	60	70%	17	30%
TOTAL	33		86		57	

To further explore the region with significant SNPs, an area of about 250 kb on each side of the three significant SNPs on chromosome 24 (from base pair 1,042,158 to 1,574,441) was mapped according to the sheep genome (Oar_v3.1, Ensembl 74), and a total of 34 genes were identified, including the NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10, 22kDa (NDUFB10) which is involved in different pathways that cause diseases such as Parkinson's Alzheimer's and Huntington's.

Conclusions

- This study confirmed the existence of a genetic component in the spring leg defect.
- Genomic analyses showed some promising SNPs on chromosome 24 that could be used in selecting against spring leg, but it is necessary to continue genotyping more animals to estimate marker effects in a larger population and perform validation tests.
- A simple validation could consist of looking at the frequency of the three significant SNPs on an independent dataset of normal animals.
- It is also recommended to further explore the regions of the genome that contain significant SNPs as a means of understanding the process involved in causing the spring leg defect and to identify one or more causative mutations leading to the defect. In the medium term, if validation tests confirm these findings, a simple, affordable DNA test based on the three significant SNPs could be developed.

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