A Putative Recessive Gene Responsible For A Leg Defect Syndrome In A Genetic Sire Line Nucleus Population Of Pigs

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Introduction

Leg weakness, measured as a continuous trait in adult pigs, has been reported to cause heavy economic losses (Hill 1990). It has been reported to result in substantial costs with 20 to 50% of eligible boars being culled as breeding animals (Webb et al. 1993). Among the reported causes are bone and joint diseases, microbial infections, nutritional imbalances and modern rearing systems (Rothschild & Christian, 1988). Leg weakness also impinges on animal welfare (Nakano & Aherne 1993). Estimated heritabilities range from low to intermediate (Bereskin, 1979; Jorgensen and Andersen, 2000; Rothschild & Christian, 1988). More recently there have been studies performed to identify QTL responsible for the classical leg weakness condition (Guo et al. 2009, Uemoto et al. 2009).

However, in a recently developed Large White sire line population, piglets have been born with a severe leg deformity that significantly impacted on their chances of survival. The appearance in 2007 of this condition coincided with legislation affecting dietary and mineral supplements. Normally, leg soundness is evaluated with leg and gait scores (Draper et al 1992). However, in the current study, the condition was so severe that the normal leg scoring was redundant and piglets were diagnosed as either having or not having this condition, with affected animals normally failing to reach weaning age (circa. 28 days). The main aim of the study is to evaluate and determine the genetic architecture underlying this condition and to propose methods limiting its spread.

Material and methods

Animals and measurement. Data were from piglets born in a recently developed line reared on a genetic nucleus unit using standard commercial conditions albeit with additional data recording to facilitate the nucleus function. The available data comprised 15577 piglets phenotyped since the seriousness of the condition was first realised, in 2007. The available pedigree comprised 23481 animals over six generations with 242 sires mated to 1414 dams. Summaries of the pedigree and observed data are presented in Table 1 and 2. Sow farrowing was recorded over seven parturitions. The recorded parameters included numbers born alive, dead or mummified, parity, year of birth and leg disorder as a binary trait. The leg defect affects the tendons around the knuckle, mostly on front legs, resulting in the piglet not able

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to straighten the legs to stand; hence, they are slow to suckle. This usually results in death either from starvation or being crushed by the sow.

Table 1. Summary statistics on pedigree data structure

Description	Numbers of animals
Total Pedigree	23481
Sires	242
Sire of sire	113
Dam of sire	152
Dams	1414
Sires of Dam	164
Dams of Dam	618

Table 2 Summary statistics on observation data

Description	Number affected*	Total records	Percent affected
Sires	72	90	80.0
Dams	280	716	39.1
Litters	387	1543	25.1
Piglets	946	15577	6.1

* Shown are the numbers of litters with one or more affected piglets, or the number of dams or sires with one or more affected progeny, or the actual number of affected piglets.

Statistical analyses. Initially the data were analysed either as continuous trait or as binary (0/1) fitting a logit link function using ASREML software (Gilmour et al. 2006). Models explored random effects due to the animal, sire, dam and their combinations. Other non genetic random effects fitted were the permanent environmental effects due to the sow and litter effects. Environmental effects fitted included of month and year of birth, and sow parity as fixed effects, with numbers born alive or dead included as covariates. Likelihood ratio tests were used to choose the most appropriate random effects model.

Inspection of the data suggested that the syndrome may be due to a major recessive gene, and this hypothesis was tested using chi square tests and segregation analyses. We assumed a genetic model where the defect is due to a single recessive gene with *A* being the healthy allele and *a* being disease allele. The genotype expectation was that *AA* and *Aa* were healthy and healthy carriers respectively and *aa* were affected (with no observations in sires or dams). The approximate genotype frequencies in the parents were calculated using simplified assumptions that parents who have any progeny with the defect are heterozygous and otherwise homozygous, ignoring dams mated to apparently non-carrier sires. Data were also explored using complex segregation analyses (Walling et al. 2002), implemented using a Gibbs sampler to formally investigate the major gene hypothesis

Results and discussion

The most appropriate random model was where sire and dam were fitted together with non

genetic random effects of litter and permanent environment due to the sow. Estimates of heritability were moderate to high for both the sire and sire plus dam models fitted (Table 3) and their standard errors were small (data not shown). Estimates were slightly higher for the generalised linear models fitting a Logit link function, than for linear models transformed to the underlying liability scale. These values were similar to those reported in literature for leg weakness score as a continuous trait (Bereskin, 1979; Jorgensen and Andersen, 2000; Rothschild & Christian, 1988), despite the fact that the trait in the current study used a binary scale and performed the measurements on newly born piglets.

The overall prevalence of leg weakness was 6.1% (Table 2). A summary of affected sires, dams and litters is given in Table 2. The percentage of affected litter out of total litters in the data was 25.1%. Under the assumption of a single recessive gene, within affected litters we expected 25% of the piglets to be affected. In our data, the mean proportion of affected piglets, summing across all piglets born to affected litters, was 23% ± 0.7, and the average within-litter proportion of affected piglets was 24% ± 0.8. (N.B. this is not the same as the 25.1% affected litters out of total litters shown in Table 2). Comparing differences expected with observed using a chi square test, the value of 23.2% is significantly different from 25% (χ^2=8.1, 1 df, p<0.01), however the average within-litter prevalence of 24% is not (p>0.05). Therefore, the within-litter prevalence is consistent with expectation, and it is difficult to reject the hypothesis of a recessive major gene. Further, we hypothesised that the accuracy of diagnosing the condition improved over time and we hence tested the recessive major gene hypothesis on the subset of the animals born in 2009 which had 348 animals affected out 1359 piglets; there was no significant difference between observed and expected in this subset (χ^2=0.27,1 df, p>0.50).

We computed the allele frequencies in the parents by letting p be the frequency of the A healthy allele transmitted, and q be the frequency of the diseased a. Then, counting the alleles transmitted we find that in sires p=0.60, q=0.40, and in dams p=0.79 and q=0.21. The approximate expected proportion of affected piglets calculated using these frequencies was 8% which is similar to, although significantly (p<0.01) greater than the observed prevalence in the data of 6%.

Given the inheritance pattern observed across families, a complex Bayesian segregation analysis was carried out where a polygenic component as well as the effect of a single major gene with large effect was included into the model. Allowing for dominance, almost all the variation was explained by a single gene with almost no polygenic or environmental variation. Results from the Bayesian segregation analysis gave a mean estimate of the additive effect of 0.50 ±0.001 and mean dominance effect of -0.50 ± 0.001, which is in precise agreement with the recessive gene model hypothesis.

Conclusion

Although there are no previously published results on this condition, the high estimates of heritability together with results of observed vs. expected number of affected piglets with affected litters, and segregation analysis results lead us to postulate that this leg defect condition may be due to a single recessive gene segregating in the population. To test this hypothesis, we are genotyping cases and controls using the 50k SNP chip and we will use

homozygosity mapping to map this putative gene. A genetic test would help in the identification of carriers and the eradication of this condition in the population under study with minimal impact on selection on other traits.

Table 3. Estimates of variance and heritability for leg weakness using generalised linear models with a logit link function and linear models

	Models			
Description	Logit link function		Linear	
	1	2	3	4
σ^2_{Pe}	1.091	0.655	0.003	0.002
σ^2_{litter}	0.711	0.722	0.006	0.006
σ^2_{sire}	0.792	0.815	0.001	0.001
σ^2_{dam}		0.492		0.001
$\sigma^2_{residual}$	3.300	3.300	0.046	0.046
$\sigma^2_{Phenotypic}$	5.894	5.974	0.057	0.057
s.e.	0.291	0.304	0.001	0.001
$h^2_{additive}$	0.537	0.437	0.097	0.095
s.e.	0.150	0.105	0.033	0.028
$\sigma^2_{Pe}/\sigma^2_{Phenotypic}$	0.185	0.108	0.059	0.038
s.e.	0.028	0.042	0.009	0.012
$\sigma^2_{litter}/\sigma^2_{Phenotypic}$	0.121	0.121	0.110	0.110
se	0.025	0.025	0.009	0.009
$h^2_{underlying\ additive}$			0.377	0.370

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