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**Post-weaning multisystemic wasting syndrome (PMWS) clinical expression under
field conditions is modulated by the pig genetic background**

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ABSTRACT

Post-weaning multisystemic wasting syndrome (PMWS) is a worldwide distributed disease of multifactorial origin and porcine circovirus type 2 (PCV2) has been identified as its essential infectious aetiology. Pig genetic background has been pointed to influence disease expression. In the present study, three different boar lines, namely A (100% Pietrain), B (50% Large White x 50% Pietrain) and C (25% Large White x 75% Duroc), were used to inseminate sows from the same genetic line (37.5% Large White x 37.5% Duroc x 25% Landrace) located on two PMWS-affected farms (farm-1 and farm-2). The PMWS clinical expression of their offspring was studied from weaning to slaughter, evaluating three parameters: total post-weaning mortality (PWM), PWM associated to PMWS (PMWS-PWM) and body weight (BW) evolution. The effect of other variables potentially related with PMWS, including sow and piglet PCV2 exposure, sow parity, piglet gender and piglet BW at weaning, were also considered in the study design. Overall, a total of 6.5% PWM and 4.3% PMWS-PWM occurred in the monitored farms. Pigs from boar line C showed the highest PWM (16.3%) and PMWS-PWM (12.4%), and the lowest BW; pigs from boar line A showed the lowest PWM (1.8%) and the highest BW. Furthermore, PWM was also higher in piglets from farm-2 and from multiparous sows. In farm-2, PMWS-PWM was higher in piglets from multiparous sows. Finally, BW was influenced by interactions between genetics and both farm and pig age, and was lower in piglets from farm-2. This study represents a consistent observation of the genetic background effect on PMWS clinical expression under field conditions.

Key Words: Genetics, Pig, Porcine circovirus type 2, Post-weaning multisystemic wasting syndrome.

1. Introduction

Porcine circovirus type 2 (PCV2) is found worldwide in pigs and has been linked to several pathological conditions collectively named porcine circovirus diseases (PCVD) (Segalés et al., 2005). The most economically important PCVD is post-weaning multisystemic wasting syndrome (PMWS), which results in losses of €900 million per year in the European Union (Armstrong and Bishop, 2004).

Infection of pigs with PCV2 and other infectious/non-infectious triggers are required for PMWS to occur (Segalés et al., 2005). Evaluation of the role of these other triggers is essential in order to understand the pathogenesis of PMWS. Several studies have linked PMWS expression to management measures, presence of concurrent viral infections, stimulation of the immune system, PCV2 viraemia and low serological titres to PCV2 of the sow at farrowing, nutrition, male castration and lower piglet weight at weaning (Segalés et al., 2005).

Farmers and veterinarians in the field have suggested that different pig breeds or genetic lines have different susceptibilities to PMWS. Similar effects have been previously demonstrated for other diseases, including bacterial (Michaels et al., 1994; Wigley, 2004), parasitic (Reiner et al., 2002a) and viral (Depner et al., 1997; Reiner et al., 2002b; Vincent et al., 2006) diseases. Preliminary experimental studies have suggested a higher susceptibility to PCV2-associated lesions and even on PMWS

development of Landrace pigs compared to Duroc, Large White and Pietrain pigs (Opriessnig et al., 2006, 2009). Experiences in the field have reported a significantly less often occurrence of clinical signs resembling PMWS in pure bred conventional Hampshire boars than in pure bred conventional Yorkshire or Landrace boars (Wallgren et al., 2009). However, the introduction of a terminal Pietrain boar onto affected farms showed no effect on PMWS expression (Rose et al., 2005). Besides these preliminary studies minimal scientific work has so far been focused on the relationship between genetics and PMWS development. The objective of the present study was to compare the effect of 3 different genetic boar lines on the expression of PMWS in their offspring.

2. Materials and methods

Animal care and use conformed to the European Union guidelines and Good Clinical Practice.

The study was carried out in 2 almost identical 5000-sow farms (farm-1 and farm-2) separated by 300 m. Farm-1 and farm-2 belonged to the same producer company, which had a multi-site production system that used the same sow genetic line (37.5% Large White x 37.5% Duroc x 25% Landrace) across all sites. Farms were seronegative to porcine reproductive and respiratory syndrome (PRRSV) and Aujeszky's disease virus (ADV), and no evidence of porcine parvovirus (PPV) circulation was found in a subsample of 90 piglets from the studied batches (data not shown). Post-weaning mortality in the year before study start ranged from 4 to 8% in both farms and was mainly attributed to PMWS, according to previous diagnostic analyses performed in the farms.

Boars from three genetic lines, A (100% Pietrain), B (50% Large White x 50% Pietrain) and C (25% Large White x 75% Duroc), were used for artificial insemination. Fifteen A, eight B, and four C boars were used. Sow insemination with each boar line was assigned randomly. Each sow was not always inseminated with semen from the same boar in repeated inseminations, but the boars were always from the same genetic line. A total of 63 pregnant sows was obtained on farm-1 (24 pregnant from A boars, 20 from B boars and 19 from C boars) On farm-2 the figures were 67 pregnant sows (29 A, 23 B and 15 C). Sows were randomly placed in the farrowing facilities in both farms taking into account that approximately one third of sows inseminated with each boar line had to be present in each room (there were three rooms per farm). No cross-fostering was allowed.

Semen (diluted for insemination and non-diluted from direct extraction) and serum samples were collected from boars at the moment of the semen extraction. Serum samples from sows were collected 1 week before farrowing.

A total of 1062 piglets (517 from farm-1 and 545 from farm-2) were obtained and ear-tagged before entering the nursery period (3 weeks of age) and monitored until the end of the fattening period (21 weeks of age). Piglet distribution by farm, genetic background, gender and sow parity is shown in Table 1. Sow parity was categorized as 1 or >1 farrowings (Calsamiglia et al., 2007). Nursery pigs (3 to 10 weeks of age) from farm-1 and farm-2 were placed in the same nursery building but in separate rooms (two rooms per group). Fattening pigs (from 10 weeks of age to slaughter) from farm-1 were placed in pens located in front of those of farm-2 from the same room and farm. All

pens in both the nursery and fattening units contained pigs from all three genetic backgrounds.

Mortality was monitored during the post-weaning period, from 3 to 21 weeks of age; all dead pigs during this period were necropsied and tissue samples (mesenteric lymph node and lung) collected. A subpopulation of 207 piglets was randomly selected, blocked by genetic background, farm, sow of origin and sex (33 to 36 pigs for each genetic background and farm); these pigs were bled at 3 weeks of age and weighed at 3, 9, 15 and 21 weeks of age.

2.1 Laboratory Analyses

A standard polymerase chain reaction (PCR) method to detect PCV2 (Quintana et al., 2002) was performed on serum samples from sows and piglets and serum, diluted and non-diluted semen from boars. An immunoperoxidase monolayer assay (IPMA) was used to detect PCV2 antibodies (Rodríguez-Arrioja et al., 2000) in sera from boars, sows and piglets. Antibody titres were classified as negative or low titre ($<1:320$) or medium to high titre ($\geq 1:320$) (Rodríguez-Arrioja et al., 2000). Mesenteric lymph node and lung samples collected from necropsied pigs were fixed by immersion in 10% buffered neutral formalin and routinely processed for histopathology. The presence of PCV2 in these tissues was detected using an *in situ* hybridization technique (Rosell et al., 1999). A pig was considered as suffering from PMWS when moderate to severe lymphocyte depletion and histiocytic infiltration were found in lymphoid tissues associated with moderate to high amount of PCV2 (Segalés, 2002).

2.2 Statistical Analysis

PMWS expression was evaluated using 3 parameters: body weight (BW) at 3, 9, 15 and 21 weeks of age, total post-weaning mortality (PWM), and PWM due to PMWS (PMWS-PWM). Total PWM, which includes non-PMWS-related mortality, was considered as a relevant production parameter because of the reported synergism between PMWS and other causes of mortality (Segalés et al., 2005).

Two logistic regression models (Hosmer and Lemeshow, 2000) were established to evaluate both PWM and PMWS-PWM, including the sow as a random effect. A longitudinal linear mixed model with repeated measures (Verbeke and Molenberghs, 1997) was performed to analyze BW. Covariates included in all models were genetic background, farm, sow presence of PCV2 viraemia and antibody titre at farrowing, sow parity, piglet's sex and BW, PCV2 infectious status and PCV2 antibodies at 3 weeks of age. Interactions with farm were also included. The sow was included as a random effect.

All results were obtained using GLIMMIX and MIXED procedures of the SAS System V.9.1 (SAS Institute Inc.). Significance level was fixed at 5%.

3. Results

PCV2 was not detected in any boar and sow serum sample, or any semen sample. The proportion of sows with medium to high PCV2 antibody titres as well as the proportion of piglets that came from them is shown in Table 1.

PMWS-PWM occurred on farm-1 from 10 to 15 weeks of age (except for one pig at 20 weeks), and from 9 to 15 weeks of age on farm-2. Further information on PWM and PMWS-PWM expression by farm and genetic background is shown in Table 1. The antibody titres and BW changes of the 207 monitored piglets are also shown in Table 1.

Logistic regression models showed a significant effect of genetic background ($P < 0.001$), farm ($P = 0.001$) and parity ($P = 0.038$) on total PWM. Specifically, PWM was more likely in piglets from C boars than both A (OR=11.95, CI_{OR} = 5.10 to 28.02) and B (OR=4.42, CI_{OR} = 2.29 to 8.55). Also, PWM was more likely for B than for A (OR=2.70, CI_{OR} = 1.08 to 6.77) backgrounds. In addition, PWM was more likely in piglets from farm-2 than farm-1 (OR=2.88, CI_{OR} = 1.56 to 5.33). Finally, PWM was more likely in piglets from multiparous than primiparous sows (OR= 2.18, CI_{OR} = 1.04 to 4.54).

A significant effect of genetic background ($P < 0.001$) and a farm and parity interaction ($P = 0.048$) on PMWS-PWM was obtained. PMWS-PWM was more likely for piglets from C boars than both A (OR=15.55, CI_{OR}= 4.92 to 43.06) and B (OR=8.26, CI_{OR} = 3.19 to 21.39). An effect of sow parity was only observed on farm-2, where PMWS-PWM was more likely in piglets from multiparous than primiparous sows (OR=6.86, CI_{OR} = 1.35 to 34.94).

Significant covariates for BW in the longitudinal mixed models were genetic background ($P < 0.001$), farm ($P = 0.003$), age ($P < 0.001$), genetics and farm interaction

($P = 0.044$) and genetics and age interaction ($P = 0.004$). Piglets from farm-2 showed lower weights than those from farm-1. Detailed results from the longitudinal mixed model are shown in Table 2.

4. Discussion

Most evidence of the effect of genetic background on PMWS susceptibility has come from the experimental side (Opriessnig et al., 2006, 2009). These studies included a limited number of pigs and used pure-bred animals, which is unusual under field conditions. Furthermore, few studies have been performed in the field in regards genetics and PMWS occurrence, where no apparent relationship between boar genetic background and disease expression was observed in the offspring (Rose et al., 2005) or minimal information was available when genetic background susceptibility was observed (Wallgren et al., 2009).

This study aimed to assess whether clinical expression of PMWS was influenced by genetic background. Three different boar lines that swine producers had suggested as having different PMWS outcome severity in their offspring were used. Using BW, PMWS-PWM and total PWM as measures of PMWS expression, this study confirmed those suggestions. It also confirmed that other factors, such as farm of origin, sow parity and piglet age, were associated with the effects of PMWS.

Several measures to diminish potential biases that may occur under field conditions were adopted for this study. Two sow farms which were located together, with the same farm management and characteristics and sow genetic background were used. Piglets were reared on the same nursery and fattening farms, so were kept under

the most similar environmental conditions. Furthermore, any potential biases due to concurrent diseases are unlikely in this study as PPV, PRRSV and ADV, three viruses reported to be related to clinical expression of PMWS (Ellis et al., 2004), did not circulate in the studied batches. In addition, total PWM was mainly associated to PMWS based on pathological findings. Finally, other factors, i.e. sow and pig PCV2 infectious status and antibody titre, sow parity, piglet gender and weaning BW, that could influence PMWS expression were also studied.

PCV2 infectious status of sows, boars and weaned piglets was assessed as PCV2 status has a significant effect on litter mortality in PMWS-affected farms (Calsamiglia et al., 2007), and the earlier the pig is infected with PCV2, the higher the risk of suffering from PMWS (Rose et al., 2003; López-Soria et al., 2005). The fact that no sample demonstrated PCV2 infection reinforces the role of the genetic background as a risk factor for PMWS, and suggests that it was probably the most significant one on the farms in this study.

Significant differences between genetic backgrounds were observed in the present study. Piglets from C boars were the most affected, showing lower BW and higher rates of PWM and PMWS-PWM than those from A and B boars. Piglets from A boars had higher BW at slaughter age and lower PWM compared to those from the other two studied boar lines. These findings are in agreement with the experimental study by Opriessnig et al., (2009) who reported that Landrace piglets developed more severe PMWS-like lesions than Pietrain. However they contradict a previous French field study which did not find any difference when the usual terminal boar breed was replaced by Pietrain (Rose et al., 2005). These results may seem contradictory; however,

differences in study design may be the cause of these inconsistencies. Moreover, such differences could be attributed to the fact that different Pietrain genetic lines were used in different studies, and it is possible that PMWS genetic susceptibility/resistance might be related to particular genetic lines rather than breeds or potential allele variants within lines.

The critical period for BW differences between lines was between 15 and 21 weeks of age, just after the PMWS outbreak. The significantly higher weights found in piglets from A boars at 21 weeks of age was noteworthy because Duroc and Large White breeds are expected to show better growth rates than Pietrain (Whittemore, 1998). This result thus supports the idea of a significant impact of PMWS on average daily gain, and is consistent with the improvement of growth rate in pigs vaccinated against PCV2 (Fachinger, et al., 2008; Horlen et al., 2008; Kixmüller et al., 2008).

The link reported here (farm-2) between sow parity and PMWS-associated mortality, and also reported in another study (Armstrong and Bishop, 2004), seems to be a controversial point since others did not find it (Madec et al., 2000; Calsamiglia et al., 2007). In fact, piglets from multiparous sows showed higher total PWM on both farms, but it was only higher for PMWS-PWM on farm-2. There are no apparent consistent explanations for these discrepancies and they may be attributable to the multifactorial nature of PMWS, in which unknown triggering factors may account for specific farm differences.

Several studies have shown that humoral immunity plays a major role on PMWS development. PCV2 maternally derived antibodies seem to protect against piglet

mortality based on field (Allan et al., 2002; Calsamiglia et al., 2007; Grau-Roma et al., 2009) and experimental (Allan et al., 2002; McKeown et al., 2005; Ostanello et al., 2005) data. However, no effect of sow IPMA antibody titre at farrowing or piglet titre at 3 weeks of age in PMWS-PWM were observed in the present study, probably because of the very high percentage of piglets coming from sows with medium to high PCV2 antibody titres. Curiously, piglets from A boars experienced lower total PWM and PMWS-PWM despite showing the lowest proportion of piglets with medium to high PCV2 antibody titres in farm-1 and the highest in farm-2. Again, PCV2 antibody titres in sows and piglets should be considered as elements that modulate PMWS expression within the context of a multifactorial disease. Therefore, not all the risk factors so far identified for PMWS have an equal on different farms with different production scenarios.

PMWS-PWM records in the present study were very similar between females and males, being 4.3 and 4.4%, respectively. Previous studies have found that castrated males had higher PMWS-associated mortality than females (Corrége et al., 2001; Rodríguez-Arriola et al., 2002). In the present study males were not castrated, suggesting that physiological and behavioural changes or surgical complications due to male castration (Prunier et al., 2006) may be a risk factor for PMWS occurrence.

Susceptibility of lighter weanling pigs to clinically compatible PMWS has been reported (Corrége et al., 2001). This association between BW and PMWS has not been observed in the present study, although disease has been measured with different parameters in both studies.

5. Conclusion

This study represents a consistent observation of the genetic background effect on PMWS clinical expression under field conditions. However, such study cannot be used to determine if the observed effect was an effect of breed (such as a protective effect for Pietrain or susceptibility in Duroc), particular boar lines or individuals (only 4 boars from genetic line C were used in the study, so the effect of each individual was higher than in the other genetic lines). Furthermore, it cannot be concluded that this effect would appear if a different sow genetic line was used. Further studies are needed to elucidate the exact role by which porcine genetics affect susceptibility/resistance to PMWS.

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Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Table 1. Descriptive statistics on explanatory and response variables from piglets included in the study.

Variable	Farm-1			Farm-2		
	A	B	C	A	B	C
No. of boars	13	7	4	10	6	4
No. of sows	24	20	19	29	23	15
No. of piglets	196	169	152	243	203	99
Piglets' male : female ratio	50 : 50	54 : 46	55 : 45	51 : 49	46 : 54	63 : 37
Piglets from first parity sows, %	20	22	26	33	37	27
Sows with medium to high PCV2 IPMA antibody titres, %	79	85	89	100	100	100
Piglets from sows with medium to high PCV2 IPMA antibody titres, %	82	75	87	100	100	100
PWM, % (n)	1.5 (3)	4.7 (8)	9.9 (15)	2.1 (5)	5.9 (12)	26.3 (26)
PMWS-PWM, % (n)	1.5 (3)	2.4 (4)	6.6 (10)	0.8 (2)	3.0 (6)	21.2 (21)
PMWS-PWM in piglets from primiparous sows – multiparous sows, %	2.6 – 1.3	0 – 3.1	7.7 – 6.2	0 – 1.2	1.3 – 3.9	3.7 – 27.8
PMWS-PWM (Males – Females), %	1.0 – 2.0	3.3 – 1.3	7.2 – 5.8	0.8 – 0.8	2.1 – 3.7	18.0 – 26.3
Piglets with medium to high PCV2 IPMA antibody titres at 3 weeks of age, % ^a	9	70	26	47	37	23
BW at 3 weeks of age ($\mu \pm SD$), Kg ^a	7.0 $\pm$ 1.5	6.8 $\pm$ 1.4	5.9 $\pm$ 1.3	6.9 $\pm$ 1.4	6.0 $\pm$ 1.2	6.2 $\pm$ 1.7
BW at 9 weeks of age ($\mu \pm SD$), Kg ^a	24.7 $\pm$ 3.7	22.8 $\pm$ 3.3	21.7 $\pm$ 3.2	22.6 $\pm$ 4.0	20.6 $\pm$ 2.9	21.9 $\pm$ 3.6
BW at 15 weeks of age ($\mu \pm SD$), Kg ^a	55.7 $\pm$ 7.7	53.2 $\pm$ 8.3	50.0 $\pm$ 9.6	53.1 $\pm$ 6.7	50.3 $\pm$ 5.8	48.1 $\pm$ 7.2
BW at 21 weeks of age ($\mu \pm SD$), Kg ^a	88.2 $\pm$ 10.4	82.9 $\pm$ 12.8	78.4 $\pm$ 15.2	85.2 $\pm$ 10.5	80.2 $\pm$ 10	80.2 $\pm$ 5.6

PCV2: Porcine circovirus type 2; IPMA: immunoperoxidase monolayer assay; PWM: post-weaning mortality; PMWS-PWM: post-weaning mortality associated to post-weaning multisystemic wasting syndrome.

^aStatistics were obtained using the subpopulation of 207 pigs.

Table 2. Longitudinal mixed model estimates for BW evolution.

Covariate/s	Estimate	Confidence Interval ^a		<i>P</i> ^a
		Lower	Upper	
<i>Genetic background</i>				
A vs B	2.300	0.893	3.708	< 0.001
A vs C	4.009	2.563	5.455	< 0.001
C vs B	-1.708	-3.159	-0.258	0.016
<i>Genetic background and farm interaction</i>				
Farm-1: A vs C	5.168	2.665	7.670	< 0.001
C vs B	-3.185	-5.685	-0.686	0.004
Farm-2: A vs B	2.618	0.257	4.979	0.020
A vs C	2.850	0.373	5.326	0.014
B farm-1 vs B farm-2	2.711	0.280	5.142	0.019
<i>Genetic background and age interaction</i>				
15 weeks of age ^b : A vs C	5.601	1.489	9.713	< 0.001
21 weeks of age ^c : A vs B	4.479	0.499	8.460	0.013
A vs C	7.493	3.271	11.715	< 0.001

^aConfidence intervals and *P*-values adjusted with the Tukey correction.^bMean weight±standard deviation for piglets with A and C background were 54.6±7.2Kg and 49.1±8.6Kg, respectively.^cMean weight±standard deviation for piglets with A, B and C background were 86.6±10.5Kg, 81.5±11.4Kg and 79.1±12.1Kg, respectively.