

BERND BUSKE, INA STERNSTEIN, MONIKA REIBMANN, PETER REINECKE and
GUDRUN BROCKMANN

Analysis of association of GPX5, FUT1 and ESR2 genotypes with litter size in a commercial pig cross population

Dedicated to Professor Dr. Gerhard Seeland on the occasion of his 65th birthday

Abstract

The aim of this study was to investigate, if special genotypes of the genes glutathione peroxidase 5 (GPX5), fucosyltransferase 1 (FUT1) and estrogen receptor 2 (ESR2) are associated with litter size in a commercial pig cross population. For this purpose, a total of 123 F₂ sows were divided into two extreme performance groups, one with a high litter size (n = 61, ≥ 14.3 piglets per litter) and one with a low litter size (n = 62, ≤ 11.3 piglets per litter) and genotyped using PCR-RFLP methods. The Chi-square test was used in order to investigate, if a special genotype occurs significantly more often in one of the two performance groups (p < 0.05). Whereas no association was found between different ESR2 or GPX5 genotypes with one of the two performance groups, the number of sows with AB genotypes at the FUT1 gene was significantly increased in the high performance group in comparison to the low performance group.

Key Words: candidate gene, ESR2, FUT1, GPX5, litter size, pigs, reproductive trait, two-tail analysis

Zusammenfassung

Titel der Arbeit: Untersuchung der GPX5, FUT1 und ESR2 Genotypen auf Assoziation zu Wurfgröße bei einer kommerziellen Zuchtsauen-Population

Ziel dieser Untersuchung war es, die Gene Glutathion-Peroxidase 5 (GPX5), Fucosyltransferase 1 (FUT1) und Östrogenrezeptor 2 (ESR2) auf Assoziation zu Wurfgröße bei einer kommerziellen Zuchtsauen-Population zu untersuchen. 123 F₂ Sauen wurden in zwei extreme Leistungsgruppen aufgeteilt, eine mit hoher Wurfgröße (n = 61, ≥ 14.3 Ferkel pro Wurf) und eine mit niedriger Wurfgröße (n = 62, ≤ 11.3 Ferkel pro Wurf) und mittels PCR-RFLP Methode genotypisiert. Unter Verwendung des Chi-Quadrat-Tests wurde geprüft, ob ein bestimmter Genotyp signifikant (p < 0.05) mit einer der beiden Leistungsgruppen assoziiert ist. Während die beobachtete Genotypenverteilung der Gene ESR2 und GPX5 in den beiden Leistungsgruppen zu keinen signifikanten Unterschieden führte, waren Sauen des Genotyps AB des Gens FUT1 überwiegend in der Hochleistungsgruppe anzutreffen.

Schlüsselwörter: Kandidatengen, ESR2, FUT1, GPX5, Schweine, Reproduktionsmerkmal, „two-tail“ Analyse, Wurfgröße

Introduction

The genetical improvement of litter size in swine is of expanding interest for pig producers mainly because ameliorations due to feeding regime and housing systems are limited. It has been observed, that up to the middle of the nineties in the past century, improvements were first of all made concerning meat quality. This led to a stagnancy, and even in some cases to a decrease of litter size especially in swine production (KISNER et al., 1995). Therefore, an improvement of fecundity in swine is desirable. Selection programmes, however, are almost only based on phenotypical

traits, which are laborious, expensive and especially in pig production time consuming. Since a few years, marker assisted selection (MAS), employed in conjunction with traditional selection methods has been in progress to increase litter size in swine. One marker, which is used in commercial pig production, is the estrogen receptor gene 1 (ESR1), and ROTHSCCHILD et al. (1996) were the first who observed an association between ESR1 genotypes and litter size in swine. However, so far, there are a lot of inconsistent studies with regard to influence on the ESR1 gene on fecundity parameters in swine (SHORT et al., 1997; DEPUYDT et al., 1999; DRÖGEMÜLLER et al., 1999; KMIEĆ et al., 2002; GIBSON et al., 2002; VAN RENS and VAN DER LENDE, 2002; MATOUŠEK et al., 2003; GOLIÁŠOVÁ and WOLF, 2004; HORÁK et al., 2005; HOROGH et al., 2005; WANG et al., 2006). Therefore, additional candidate genes with potential influence on litter size are studied.

The glutathione peroxidase 5 gene (GPX5) on SSC7 is located in a chromosomal region in which several quantitative trait loci (QTL) for reproductive traits in swine, such as uterine capacity, ovulation rate and litter size have been detected. Linkage analyses of GPX5 showed that this gene is closely linked to the major histocompatibility complex (MHC), which has been suggested to have an effect on reproductive traits in swine (VAIMAN et al., 1998; BUSKE et al., 2005).

The fucosyltransferase 1 gene (FUT1) on SSC6 is also located in a chromosomal region which is associated with litter size in swine. Actually, the FUT1 gene has been determined as a candidate gene for the *Escherichia coli* F18 receptor locus (MEIJERINK et al., 1997) and an association with oedema disease, diarrhea, and thus an association with animal health was severalfold observed. Because animal health is strongly attended with fecundity, FUT1 could also serve as a candidate gene for litter size in swine (HORÁK et al., 2005).

Concerning estrogen receptors, there are at least two different classes, and MUÑOZ et al. (2004) mapped the estrogen receptor 2 (ESR2) gene at the telomeric end on the q arm of SSC1 in contrast to the ESR1 gene, which is located at the telomeric end on the p arm of SSC1. The polymorphism in the coding region of exon 5 in the ESR2 gene leads to an amino acid substitution (MET→VAL) in the hormone binding domain, which is critical for its role as transcription factor. Moreover, the ESR2 gene has been characterized in the rat, mouse and human, and several studies suggest that this receptor displays a high binding affinity to estrogens and therefore might be involved in ovarian follicular growth and development at periimplantation (KOWALSKI et al., 2002). Hence, ESR2 could also serve as a candidate gene for litter size in swine.

Therefore, the aim of this study was to investigate, whether the candidate genes GPX5, FUT1 and ESR2 are associated with litter size in swine in a commercial population. In most cases, association studies were conducted by using a variable number of sows of a resource population. In contrast, we used sows of two extreme performance groups with high and low litter size (two-tail analysis) which were kept in a commercial sow farm.

Material and Methods

Animals

Investigations were performed with a commercial pig population from a German sow farm (Polkenberg, Sachsen, Germany). 447 F₂-sows of a cross between (Large White x Landrace) sows x Leicoma boars that had four litters at minimum represented the basic

population. Average litter size of these sows was 13.1 piglets per litter according to the number of total newborn (TNB) piglets from the second to the fourth litter. From this basic population, two extreme performance groups were formed comprising 14 % best and 14 % worst sows, according to the number of TNB piglets. The high performance group consisted of 61 sows with at least averaged 14.3 piglets per litter from the second to the fourth litter whereas the low performance group consisted of 62 sows with less than averaged 11.3 piglets per litter from the second to the fourth litter (Table 1). The first litter was ignored, because in general, first litters are more uneven than the following litters. About 20 % of the 123 selected sows were full-sibs. It was ensured, that there was no significant accumulation of these sows in one of the two performance groups. The rest of the sows were half-sibs or unrelated. All sows were mated with Piétrain boars by artificial insemination with a constant amount of fresh sperm. The age of first insemination of the sows, as well as feeding and housing regime were kept constant. A total of 76 boars were distributed randomly to the sows of both performance groups in order to prevent significant paternal influence on litter size. Directly after farrowing, TNB and the number of born alive (NBA) piglets were recorded. DNA of sows was obtained from ear chondral tissue and was isolated according to standard methods.

Table 1

Litter size parameters of selected and genotyped sows of two performance groups (Wurfgröße der ausgewählten und genotypisierten Sauen der beiden Leistungsgruppen)

Performance group	Number of F ₂ -sows	Litter size (2 nd – 4 th litter)					
		TNB			NBA		
		Mean	SD	Range	Mean	SD	Range
High	61	15.73	2.24	12-24	14.10	2.13	9-19
Low	62	10.39	2.44	3-14	9.83	2.31	3-14

TNB = Total number born; NBA = Number born alive

Genotyping

The gene variants were amplified and distinguished according to standard PCR-RFLP methods with small modifications in reference to the original literature (Table 2).

Table 2

Different PCR-RFLP parameters for the genes GPX5, FUT1 and ESR2 (Unterschiedliche PCR-RFLP Parameter für die Gene GPX5, FUT1 und ESR2)

Gene Access. no.	Primer sequence (forward and reverse) 5' to 3'	MgCl ₂ (mM)	Annealing temp. (°C)	Restriction enzyme (U)
GPX5 ¹ AF124818	TTC ATG TAG AAC TTA TTT CTG TGA CTT ACC CAT TCT TCA G	2.0	51	HinfI 10
FUT1 ² U70883	CTG CCT GAA CGT CTA TCA AGA TC CTT CAG CCA GGG CTC CTT TAA G	2.5	56	HhaI 2
ESR2 ³ AF164957	AAA ATA CTG ATA CCC ACC CCA CAT CGC CAC ATC AGC CCC ACC AT	2.0	61	Hsp92II 5

1,2,3: Original methods in (1) BERTANI et al. (1999); (2) KLUKOWSKA et al. (1999); (3) MUÑOZ et al. (2004); GPX5 = Glutathione peroxidase 5; FUT1 = Fucosyltransferase 1; ESR2 = Estrogen receptor 2

For the PCR, all genes were amplified separately in a total reaction volume of 25 µl containing approximately 75 to 150 ng of genomic DNA, 1 x Taq reaction buffer

without MgCl₂, 0.2 mM dNTPs, 0.2 µM of each primer, appropriate amount of MgCl₂ (Table 2), and 1 U Taq DNA polymerase (Genaxxon, Germany). After denaturation at 94°C for 2 min, 35 amplification cycles comprising denaturation at 94°C for 1 min, annealing at appropriate temperature (Table 2) for 30 s, and extension at 72°C for 40 s were performed followed by a final 5-min extension step at 72°C.

After the amplification of the genes, PCR products were incubated with the appropriate restriction enzyme (Table 2) at 37°C for 4h in order to show the gene variants. DNA-fragments were separated on 2 % agarose-gels. Table 3 shows the expected fragment length of the different genotypes for the investigated genes.

Table 3

Fragment length in basepairs of the genotypes for the GPX5, FUT1 and ESR2 genes (Fragmentlängen in Basenpaaren der Genotypen für die Gene GPX5, FUT1 und ESR2)

Gene	PCR-product (bp)	Fragment length of genotypes (bp)			Remarks
		AA	AB	BB	
GPX5	501	<u>298</u> , 94, 53, 33, 23	<u>298</u> , <u>234</u> , 94, 64, 53, 33, 23	<u>234</u> , 94, 64, 53, 33, 23	23, 33, 53 and 64 are not visible
FUT1	421	<u>328</u> , 93	<u>328</u> , <u>241</u> , 93, 87	<u>241</u> , 93, 87	87 and 93 are inseparable
ESR2	218	<u>202</u> , 16	<u>202</u> , <u>142</u> , 60, 16	<u>142</u> , 60, 16	16 and 60 are not visible

Underlined fragments: main fragments in order to distinguish genotypes

Statistical analyses

Firstly, the correlation between TNB and the number of NBA piglets for each performance group was calculated by using the Pearson's Correlation Coefficient (r). Afterwards, it was investigated, if a special genotype occurs significantly more often in one of the two performance groups ($p < 0.05$). For this purpose, the Chi-square test with the extension of the Fisher's Exact test was used. The latter one was carried out in order to determine the exact p -values for the expected frequencies of the genotyped sows, when the expected frequencies were smaller than 5 in at least one class. The statistical analyses were performed with the SPSS programme (version 12.0).

Results

Development of the TNB and the number of NBA piglets in the two performance groups

The Figure shows the development of litter size in the two extreme performance groups of the sows from litter number 1 up to litter number 4. Whereas there is no remarkable difference between the two extreme performance groups for the first litter, both performance groups differed considerably amount in the following litters for TNB and the number of NBA piglets, respectively.

Correlation between the TNB and the number of NBA piglets in the two performance groups

Table 4 shows the mean values for litter size and the coefficients of correlation (r) between TNB and NBA piglets for the two extreme performance groups for the litters 1 to 4 and for all 4 litters.

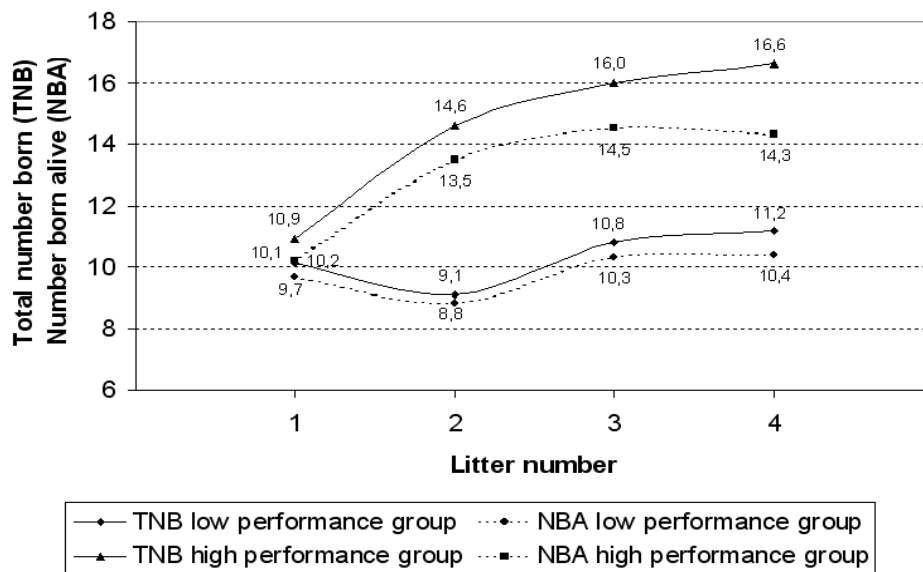


Figure: Development of litter size in dependency of the litter number in the two performance groups (Entwicklung der Wurfgröße in Abhängigkeit von der Wurfnummer in den beiden Leistungsgruppen)

Table 4

Mean values for TNB and NBA piglets and coefficients of correlation (r) between TNB and NBA piglets for the litters 1 to 4 for sows in the two performance groups (Mittelwerte der Wurfleistung sowie Korrelationskoeffizienten (r) zwischen insgesamt und lebend geborenen Ferkel der Würfe 1 bis 4 der Sauen in den beiden Leistungsgruppen)

Litter no.	F ₂ -sows (N=123)									
	Low performance group (N=62)					High performance group (N=61)				
	TNB	NBA		r	TNB	NBA		r		
Mean	SD	Mean	SD		Mean	SD	Mean		SD	
1	10.1	3.13	9.7	3.10	0.972	10.9	3.02	10.2	2.91	0.924
2	9.1	2.79	8.8	2.68	0.971	14.6	2.16	13.5	1.87	0.720
3	10.8	2.06	10.3	1.86	0.929	16.0	2.06	14.5	2.26	0.662
4	11.2	1.91	10.4	1.95	0.860	16.6	2.26	14.3	2.17	0.577
1-4	10.3	2.63	9.8	2.53	0.950	14.5	3.23	13.1	2.89	0.845
2-4	10.4	2.44	9.8	2.31	0.938	15.7	2.24	14.1	2.13	0.652

The level of significance for r is always $p < 0.01$

TNB = Total number born; NBA = Number born alive

Genotype and allele frequencies and genotype distribution

The genotype and allele frequencies for the GPX5, FUT1 and ESR2 genes over all genotyped sows are presented in Table 5.

Table 5

Genotype and allele frequencies over all genotyped sows (Genotypen und Allelfrequenzen aller genotypisierten Sauen)

Gene	N	Genotype frequency			Allele frequency	
		AA	AB	BB	A	B
GPX5	123	0.057	0.333	0.610	0.22	0.78
FUT1	120	0.025	0.292	0.683	0.17	0.83
ESR2	123	0.130	0.870	0.000	0.57	0.43

For the genes GPX5 and FUT1, expected genotype frequencies corresponded well to the observed genotype frequencies according to Hardy-Weinberg equilibrium, however, this was not the case for the ESR2 gene. According to the nearly balanced allele frequencies, one could expect, that there should be about 25 % animals with the homozygous BB genotype, but no animal with this genotype was observed. Table 6 shows the distribution of the different genotypes for the GPX5, FUT1 and ESR2 genes in the two performance groups of the commercial F₂-sows. Only for the FUT1 gene, the genotype distribution between the low and the high performance group was significantly different. Sows with the heterozygous AB genotype occurred significantly more often in the high performance group, whereas sows with the BB genotype occurred significantly more often in the low performance group.

Table 6

Genotype distribution of the GPX5, FUT1 and ESR2 genes in the two performance groups (Genotypenverteilung der Gene GPX5, FUT1 und ESR2 in den beiden Leistungsgruppen)

Genotype	GPX5		Gene FUT1		ESR2	
	Performance group		Performance group		Performance group	
	low	high	low	high	low	high
AA	4	3	2	1	8	8
AB	24	17	11*	24*	54	53
BB	34	41	48*	34*	0	0
N / Performance group	62	61	61	59	62	61
N (Total)	123		120**		123	

* significantly different ($p < 0.05$), Chi-square-test

**3 sows could not be genotyped for the FUT1 gene

Discussion

In the Figure we present the development of litter size in the two extreme performance groups. Because the selection of the sows for the two performance groups based only on the litters 2 to 4, it is interesting to note that for the first litter, litter performance was almost equal for both, the low and the high performance group. A reason for this unexpected result is probably - provided that the age of first insemination was kept constant - that the development of sows has not been finished at the age of first insemination. Therefore, genetical effects on phenotypical fecundity parameters cannot be seen entirely until the sows are not completely full-grown. This observation is important for further investigations, particularly, when gilts are investigated for reproductive traits such as uterine capacity or ovulation rate. For example, ISLER et al. (2002) observed an increased ovulation rate in sows from 17.22 corpora lutea for the first litter up to 19.92 for the third litter. The conclusion of non-genetical effects for a phenotypical trait, which does not differ at an early stage of development could be false because of confusion with immaturity of the organism and the general physiological status of the animal, which hides a potential genetic predisposition.

Because the selection of sows based only on TNB piglets, it was interesting to evaluate the correlation between TNB and the number of NBA piglets in the two performance groups of high and low litter size (Table 4). The expectation was, that in general, the correlation between both traits was high, and, that the correlation in the high performance group should be less than in the low performance group. These

expectations were fulfilled. However, there was a strong trend for lower correlations between TNB and the number of NBA piglets in higher litter numbers particularly for the high performance group without any exception. An explanation for these results is probably, that sows with a high potential of farrowing piglets are more susceptible to losses during farrowing or directly before, also due to non-genetical effects.

GPX5 has been mapped on SSC7 at 7(1/2)p12-p11 (BERTANI et al., 1999) and was mainly chosen as a candidate gene because many QTL for fecundity parameters such as litter size (DE KONING et al., 2001), ovulation rate (WILKIE et al., 1999) and age of puberty (CASSADY et al., 2001) were observed in this chromosomal region. Both, VAIMAN et al. (1998) and BUSKE et al. (2005) speculated of a physiological influence of this chromosomal region on fecundity parameters by the MHC class III region, however, in our population, no association between litter size and a special genotype of GPX5 was observed. From a physiological point of view, GPX5 is mainly involved in sperm quality. Therefore, GPX5 is rather involved in paternal, than in maternal fertility.

A chromosomal region for association with litter size in swine is located at the centromeric region on the q-arm of porcine chromosome 6 (YASUE et al., 1999). FUT1 has been mapped on SSC6 at 6q11 (VÖGELI et al., 1996) and is located in this region. At first, however, the FUT1 gene has been determined as a candidate gene for *Escherichia coli* F18 receptor locus (MEIJERINK et al., 1997). The single nucleotide polymorphism (SNP) at position 307 in exon 2 is strongly associated with oedema disease and diarrhea in swine, and therefore, with animal health. Because animal health is generally required for high fecundity, the hypothesis was, that FUT1 might also be associated with reproductive traits, such as litter size in pigs. Recently, HORÁK et al. (2005) investigated this SNP of the FUT1 gene with regard to litter size at 104 sows of the local autochthonous Czech breed. They investigated up to 6 litters for each sow and observed, that the heterozygous AB and the homozygous BB genotypes were the favorable ones for the traits TNB and the number of NBA piglets. Their hypothesis was, however, that the AA genotype should be beneficial on fecundity parameters due to the resistance to *Escherichia coli* F18 infection of this genotype. Because we also found that the AB genotype was favorable on litter size parameters, a pleiotropic effect of the FUT1 gene cannot be excluded. However, it is more likely, that not the FUT1 gene itself but rather another closely linked gene could be responsible for the observed results. According to VÖGELI et al. (1996), a distorted linkage disequilibrium between those genes can lead to such results, when just the beneficial genotype for resistance to *Escherichia coli* F18 infection is linked with another adjacent gene with unfavorable genotypes for litter size parameters.

For the ESR2 gene, Hardy-Weinberg equilibrium was not fulfilled because of the lack of any homozygous BB genotype (Table 5). One explanation could be that genotyped animals were selected F₂-sows. In selected populations, deviations of genotype frequencies from the Hardy-Weinberg equilibrium should be expected for loci with impact on traits under selection (GOLIÁŠOVÁ and WOLF, 2004). Because of the lack of any homozygous BB sows in our population, a completing statement concerning a potential association between ESR2 genotypes and litter size is strictly speaking not feasible. An explanation of our results could be, that the BB genotype has been excluded from this population over years. To our knowledge, up to now, there is only one association study concerning the influence on litter size of the ESR2 gene

(MUÑOZ et al., 2004) and no significant association was found by these authors, probably due to low animal numbers.

An additional improvement of the presented two-tail analysis would be, to extend litter size characterization by including a fifth or even a sixth litter in order to improve the reliability of phenotypes, but under our experimental conditions, this was not possible. Even if it is rather unlikely that sows of the high performance group show few offspring in the following litters or reversely, this cannot be excluded even if environmental parameters were highly standardized. In such a case, the grouping of the selected sows could be false for a few individuals, leading to problematic results with regard to an association between the frequencies of genotypes in one of the two performance groups. Therefore, a conclusion of the methodical point of view concerning two-tail analyses is generally, to characterize the phenotype as exact as possible as it is easily feasible for carcass and meat quality parameters, for example.

In a two-tail analysis, one is looking for dissimilarities for genotype distribution between two performance groups with regard to a special phenotype. However, if commercial sow populations are used, as it was the case in this study, there is often the problem that one genotype is not, or only present with extremely low animal numbers. Therefore, a comparison between rare genotypes cannot be evaluated with sufficient statistical power. Under such circumstances, statements concerning associations between phenotype and genotype are problematically. The more phenotyped animals for a certain genotype are available, the better is the expressiveness for an association between genotype and phenotype. For further research, a planned mating test would be an improvement in order to obtain more balanced genotype frequencies in the basic population (ROTHSCHILD et al., 1996). If there is a strong association between genotype and phenotype, a significant imbalance for genotypes between the two performance groups (tails) can be expected. However, planned matings are hardly imaginable when cooperating with commercial sow farms, so, in our opinion, it is essential to revert to populations, which are kept under controlled and standardized laboratory circumstances, or, even better to revert to resource populations. Considering all these facts, selection progress is mainly achieved, if firstly a beneficial polymorphism is detected for a desirable trait, and secondly, rare genotypes are detected which improve the performance in order to increase this genotype in the population.

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Author's address

Dipl.-Agr. Biol. BERND BUSKE*, Dr. agr. INA STERNSTEIN,
Dr. agr. MONIKA REIßMANN, PD Dr. habil. PETER REINECKE,
Prof. Dr. habil. GUDRUN BROCKMANN
Humboldt-University of Berlin, Agricultural and Horticultural Faculty,
Institute of Animal Sciences, Department of Breeding Biology and Molecular Genetics,
Invalidenstr. 42
10115 BERLIN
GERMANY

*Corresponding Author, E-mail: bernd.buske@staff.hu-berlin.de