

Mapping of quantitative trait loci for reproductive traits in pigs

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This paper reviews the major approaches used to map quantitative trait loci (QTL) and current knowledge about QTL affecting reproductive trait loci in pigs. Three different approaches, i.e. functional candidate gene analyses, genome-wide linkage studies (GWLS) and genome-wide association studies (GWAS) have been used to map QTL in pigs. The interest and limits of each of the three approaches are discussed. Candidate genes and QTL have been reviewed based on PigQTLdb at <http://www.animalgenome.org>. A total of 29 candidate genes affecting reproductive traits located on 14 autosomes have been considered. Some of them are well established results, but most results originate from single studies of limited scale and need to be confirmed. Several thousands of QTL affecting 15 male and 15 female reproductive traits have been identified on 17 and 19 different chromosomes, respectively, using GWLS. Yet, the majority of them are only putative QTL and few QTL regions overlap between studies. Epistatic interactions between QTL appear as rather important in the single study investigating the effects of epistasis on pig reproductive traits. A large number of QTL distributed over almost all pig chromosomes have been identified in the single GWAS study published so far for pig reproductive traits. Use of sequence data, of more complex genetic models and of integrative biology approaches should be considered for more thoroughly investigating the genetic architecture of pig reproductive traits in the future.

Introduction

The development of genomics in the last 25 years has revolutionized the research methods and tools in genetics and, more generally, in biology. This revolution has been largely driven by the human genetics area. Considerable resources have indeed been mobilized to decipher the human genome and its variations. The huge progress obtained in humans has largely contributed to the advancement of livestock genetics and genomics due to both technological leaps (genotyping, microarrays, sequencing, bioinformatics...) and to the input of comparative genomics on the knowledge of animal genomes.

Genomics has not only allowed the whole sequence of most livestock genomes to be deciphered, but has also allowed to get a much better understanding of the genetic architecture of complex traits. An increasing number of polymorphisms responsible for variations in simple Mendelian traits (e.g. Andersson and Plastow 2011), or having major effects on quantitative traits (Milan, *et al.* 2000, Van Laere, *et al.* 2003) have been or are about to be identified. Several thousands of Quantitative Trait Loci (QTL) associated with phenotypic variations have been mapped on livestock genomes (e.g. Bidanel and Rothschild 2002). In parallel, the other

“omics” technologies, i.e. transcriptomics, proteomics and metabolomics, are powerful tools to better understand the functioning of animal genomes, identify gene and metabolic networks involved in key biological functions, and contribute to the ambitious goal of bridging the gap between genotype and phenotype.

Reproduction is a major biological function in all animal species. Although pig is known to have a very high reproductive efficiency, with fertility rates close to 90% and average numerical productivities that approach or exceed 30 piglets / sow / year, reproduction traits, especially prolificacy, are essential components of the economic efficiency pig production systems. Litter size has been a major component of the breeding goal in major pig dam lines over the last 20 years. Rather large genetic gains, in the order of 30 to 40% of the mean, have obtained on litter size at birth in several pig populations (Guéry, *et al.* 2009, Tribout, *et al.* 2003) despite the low heritability of this trait.

Nevertheless, these gains remain limited by the low heritability, the late and sex-limited expression of reproductive traits. These limitations can be circumvented by using marker-assisted (MAS) or genomic selection (GS) methods, which are thus likely to be of high interest to improve the efficiency of selection for these traits. Additionally, reproductive traits are strongly influenced by non-additive genetic effects, as shown by the large heterosis values obtained in crosses between pig breeds (Bidanel 2011). A better understanding of gene interactions underlying these non additive effects is also of high interest to improve the efficiency of livestock breeding and management. This paper reviews the results obtained over the last 20 years on the genetic architecture of reproductive traits in pigs and discusses challenges and opportunities offered in the coming years by recent high throughput genomic tools.

Methods to investigate the genetic architecture of complex traits.

The methods used to investigate the influence of genes on phenotypic variability have been closely related to available genetic and genomic tools. The oldest methods, based on the polygenic infinitesimal model, use pedigree and phenotype information to estimate genetic parameters, i.e. the genetic part of phenotypic (co)variances. Even if they are outside the scope of this article, it should be noted that these methods are still very useful in animal breeding, and are a necessary first step of the analysis of a new trait so as to make sure it is at least partly genetically determined. Several reviews of genetic parameters of reproductive traits are available in the literature (see Bidanel 2011 for the most recent one). We will consequently not present them, but just point out that most of the reproductive traits have low to moderate heritability values.

The next step, since DNA polymorphism has become accessible, has been to relate variations at the DNA level to phenotypic variation. Several methods have been used depending on the available technologies and resources. The first one is to identify a gene involved in a biological function, find one or several polymorphisms in this gene, and then test the effects of these polymorphisms on traits characterizing the biological function investigated. This approach is known as functional candidate gene (FCG) analysis. FCG analyses have the great merit of being rather inexpensive and simple to implement. This is probably the main reason why this approach has been widely used by a large number of research teams since the publication of the article of Rothschild, *et al.* (1996) on the effects of the estrogen receptor gene on litter size.

FCG analyses conversely have several important limits. First, the functional importance of a gene does not imply that variations of its sequence result in variations at the phenotypic level. The vast majority of FCG analyses actually leads to non significant results. When significant results are obtained, the polymorphisms investigated have a “significant” probability of being the

causative polymorphism, particularly if it has been selected on the basis of functional arguments (e.g. it changes the structure of the translated protein). In practice, causal polymorphisms have rarely been identified using FCG analyses. In most cases, the polymorphisms investigated are likely to be only markers in linkage disequilibrium (LD) with the causal mutation, which can have nothing to do with the gene under investigation. In such a situation, the estimated effect of the polymorphism is an “apparent” effect, which is a function of the effect of the causal polymorphism and of its linkage disequilibrium with the marker.

In spite of its limitations, FCG analysis can be very interesting within population, as LD often extends over short distances. In this situation, a significant effect means that there is probably a causal polymorphism close to the marker. This is conversely not relevant when the LD extends over large distances, as in crosses between populations or in newly formed synthetic lines (Zhao, *et al.* 2003). In all cases, using single marker results from a FCG analysis in a marker or candidate gene assisted selection program appears as rather risky. If MAS is considered as a method of interest, it is much wiser to have two or more markers flanking the causal polymorphism to optimize the efficiency of MAS. Yet, direct selection for the causal polymorphism when it has been identified (i.e. gene assisted selection) or genomic selection, which appear as more powerful methods than MAS, should be preferred when possible.

The positional FCG analysis is a commonly used variant of the FCG approach. Its principle is to find functional candidate genes within the confidence interval of a QTL position. It is a potentially quite powerful approach if the confidence interval of the QTL is rather small. It is much more difficult when QTL have been detected in an F2 design between divergent breeds for the above-mentioned reasons of LD extent over large distances (Zhao, *et al.* 2003), unless strong functional arguments exist in favor of a gene / a polymorphism.

The other approaches are not based on functional arguments, but on the associations between closely linked markers / genes. They allow whole-genome QTL mapping to be performed, provided that a network of markers covering the genome is available, and are often used in this way. Two major types of methods have been used depending on marker technologies available.

In the 1990s, microsatellites were the first type of markers covering the entire genome that could be amplified using polymerase chain reaction and then genotyped on a large scale at a reasonable cost using automated sequencers. They led to the establishment of the first genetic maps of the entire genome (Archibald, *et al.* 1995, Rohrer, *et al.* 1996) and the establishment of a large number of QTL mapping programs (Bidanel and Rothschild 2002, Hu, *et al.* 2013). As microsatellite density is insufficient to give access to within-population LD, microsatellite based QTL mapping programs are based on within-family linkage disequilibrium, which requires designs with large half-sib families, or on F2 or backcross populations issued from crosses between divergent populations which are assumed to be fixed for different QTL alleles.

These microsatellite based programs have led to the detection of thousands of QTL, including a few hundred of QTL for reproductive traits. Their location often remains inaccurate, with confidence intervals of several centimorgans, and the generalization of the results to commercial populations is not straightforward. Yet, some studies have shown, for production traits, that QTL detected in crosses between divergent breeds can also be segregating in commercial populations (Evans, *et al.* 2003, Sanchez, *et al.* 2010). Fine-mapping programs have been developed by several teams (Berg, *et al.* 2006, Campbell, *et al.* 2003, Riquet, *et al.* 2011), but only one (Campbell, *et al.* 2003) dealt with reproductive traits. Moreover, apart from the identification of intron3 G3072A-IGF2 locus as a causative polymorphism for carcass fatness (Van Laere, *et al.* 2003), they have not yet led to the identification of causal polymorphisms.

Since the mid-2000s, the dramatic progress achieved in genome sequencing technologies has allowed to take advantage of a new type of markers, single nucleotide polymorphisms (SNP).

Several millions of SNP are available throughout the genome, so that very dense genetic maps can easily be built. At the same time, the development of DNA chips has made it possible to genotype animals for tens of thousands (Ramos, *et al.* 2009), or even hundreds of thousands of markers (a 800,000 SNP chip is currently available in cattle) at a very low cost. This DNA chip technology has allowed the development of selection based on genetic marker indexes, i.e. genomic selection (GS). It also gives the opportunity to have a much more accurate mapping of QTL and to go further in the knowledge of the genetic architecture of complex traits. A mean coverage of 20 markers / morgan can indeed be expected with a 60,000 SNP chip, which is dense enough to have access to within-population LD in most pig populations. These SNP chips thus make it possible to perform whole-genome association studies (GWAS) directly in commercial populations. Optimal designs for GWAS are based on a large number of small nuclear families, which is favorable to ensure a good representation of the whole population. Genetic parameters can easily be estimated to ensure that there is enough genetic variation for association studies. Finally, they can easily be used as a first step towards the development of a reference population for genomic selection. In contrast, reference populations from genomic selection programs are highly valuable resources for the analysis of the genetic architecture of traits of interest, provided that the data are available to research teams.

Yet, in spite of their higher statistical power, QTL detected by GWAS are far from explaining the whole genetic variation of the traits investigated. This problem, known as the “missing heritability” problem in the human genetics literature, can be due to the insufficient size of experiments, which make it possible to identify only QTL with moderate to large effects, but also to the fact that the additive effects of individual genes cannot explain the whole genetic variation of a trait, which may also be due to genetic interactions or epigenetic effects (Slatkin, 2009; Zuk *et al.* 2012).

Effects of candidate genes on reproductive traits

Candidate genes with significant effects on reproductive traits that were available in pig QTL database (<http://www.animalgenome.org/cgi-bin/QTLdb/SS/index> - accessed on January 2013) are given in Table 1. Most of the oldest references are pure FCG analyses, while some of the most recent references (Balcells, *et al.* 2011a, Balcells, *et al.* 2011b, Coster, *et al.* 2012) are positional FCG analyses based on previous QTL mapping designs. Pure FCG analyses first dealt with genes clearly involved in reproductive physiology, such as ESR, FSHB, FSHR, GNRHR, PRLR,... Genes that were less obviously involved in reproduction were then investigated, particularly for positional analyses. It has to be noted that a rather important fraction of the results are based on single study on a rather limited number of animals and should be interpreted with some caution. Results for some genes are based on larger samples of animals and / or involve several independent studies (e.g. ESR1, LEP, PRLR, ...), so that there is a very high probability that there is a causal mutation inside or in the vicinity of the gene. The polymorphisms investigated have not been shown to be causative. In the case of ESR1, population dependent effects even strongly suggest that at least one of the polymorphisms investigated is not causal.

The effects on reproductive traits of known major genes have also been investigated. The ryanodine receptor (also called halothane sensitivity or Hal) locus (Fujii, *et al.* 1991) and the PRKAG3 (or RN) locus (Milan, *et al.* 2000) have been shown to have no or very limited effects on reproductive traits. Significant effects of the halothane gene region were reported in some studies, but they were probably due to a linked gene rather than Hal locus itself (Sellier, *et al.* 1987). QTL affecting reproduction traits have indeed been detected in the vicinity of both the HAL and RN genes (Tables 2 and 3), so that apparent effects of Hal and RN on reproductive traits would occur in case of linkage disequilibrium with the QTL. An effect of the IGF2-Intron3-

Table 1a. Candidate genes associated with reproductive traits in pigs (1/2)

Gene ¹	SSC	Polymorphism (location)	Trait ²	Population ³	Genotyped pigs (N)	Reference
ESR1	1	PvuII site (Intron)	TNB, NBA	MS x SL; LW	161; 1079	(Rothschild, et al. 1996)
			TNB, NBA	LW	4262	(Short, et al. 1997)
			TNB, NBA	LW x MS	275	(Van Rens, et al. 2002)
ESR2	1	C/T (Exon 5) g.672C>T (exon 1) g.35756T>C (intron 1) A/G (Exon 5)	TNB, NBA	LW	1030	(Goliassova and Wolf 2004)
			TNB, NBA	LW	226	(Horogh, et al. 2005)
			TNB, NBA	CL	408	(Munoz, et al. 2007)
			MOT, PDR, NRR	PI, PI x HA	300	(Gunawan, et al. 2011)
			NBA	(LWxLR)xLe PI, PI x HA	129	(Buske, et al. 2006a)
PAX5	1	C / T (intron 9)	SCON, MOT, VOL, PDR, NBA	PI x HA	100	(Gunawan, et al. 2012)
			AP	DU/LR x CW	376	(Kuehn, et al. 2009)
EPOR	2	Intron 4	Uterine capacity	4 way cross	402	(Nonneman, et al. 2006, Vallet, et al. 2005)
FSHB	2	FSHBMS microsatellite (5' flanking region)	TNB, NBA	YO x ER	289	(Li, et al. 1998)
			NW, LWW, GL	LW x MS	-	(Li, et al. 2008)
IGF2	2	Intron 3 g.3072G>A	NW, LWW	LW, LR	9260	(Stinckens, et al. 2010)
miR-27a	2	SNP (T / C)	TNB, NBA	LW, DIV	142, 140	(Lei, et al. 2011)
FSHR	3	SNP at positions 74, 532, 1166	OR	DU x MS	248	(Sato, et al. 2011)
CD9	5	SNP at positions 74, 532, 1166 g.358A>T (intron 6)	MOT, PDR, ASR	PI, PI x HA	340	(Kaewmala, et al. 2011)
FUT1	6	Exon 2	TNB, NBA	PBP	104	(Buske, et al. 2006b, Horak, et al. 2005)
			TNB, NBA	(LWxLR)xLe	123	
LCK	6	A/G substitution at the position of 1127-bp of mRNA	TNB, NBA	LW, LR	100, 100	(Yonggang and Xueshan 2012)
LEPR	6	Intron 2, exons 2, 18	TNB, NBA	YO; DU	62; 246	(Chen, et al. 2004b)
RNF4	6	C / T (Intron 5)	TNB, NBA	QP	159	(Niu, et al. 2009)
BF	7	Intron 1	TNB, NBA	(LWxLR)xLe	123	(Buske, et al. 2005)
DIO3	7	SNP ASGA0037226	TNB, NBA, LWB	2 LW lines	689 + 1050	(Coster, et al. 2012)

¹ESR1, ESR2 = Estrogen receptor 1 and 2, respectively; PAX5 = Paired box 5; EPOR = Erythropoietin receptor; FSHB = Follicle Stimulating Hormone beta; IGF2 = Insulin-like growth factor 2; miR-27a = micro RNA 27a; FSHR = Follicle Stimulating Hormone receptor; CD9 = Cluster-of-differentiation antigen 9; FUT1 = Fucosyl transferase 1; LCK = Lymphocyte-specific protein tyrosine kinase; LEPR = Leptin receptor; RNF4 = Ring finger protein 4; BF = Properdin; DIO3 = deiodinase, iodothyronine, type III.

²AP = Age at puberty; GL = gestation length; LWB = litter weight at birth; LWW = litter weight at weaning; NBA = Number born alive; NW = Number born alive; NW = number weaned; OR = ovulation rate; NRR = non return rate; TNB = Total number born; ASR = abnormal spermatozoa rate; SCON = sperm concentration; MOT = sperm motility; VOL = semen volume; PDR = plasma droplet rate;

³CL = composite line; CW = composite white; DIV = diverse populations; DU = Duroc; ER = Erhualian, HA = Hampshire; Le = Leicoma; LR = Landrace; LW = Large White; MS = Meishan; PBP; Prestice Black Pied; PI = Piétrain; QP = Qingping; SL = Synthetic line; YO = Yorkshire.

Table 1b. Candidate genes associated with female reproductive traits in pigs (2/2)

Gene ¹	SSC	Polymorphism (location)	Trait ²	Population ³	Genotyped pigs (N)	Reference
GNRHR	8	3'UTR	OR	MS x LW	200	(Jiang, et al. 2001)
LIF	8	Exon 3	NBA	LR; LW	850; 604	(Spotter, et al. 2009)
MAN2B2	8	D28521:c.1574A>G	OR	CW x MS	600	(Campbell, et al. 2008)
OPN	8	Intron	TNB, NBA	CL	519	(Korwin-Kossakowska, et al. 2002)
AKR1C2	10	Ile16Phe (N1179 in coding region)	AP, OR	¼ MS	191	(Nonneman, et al. 2006)
NAT9	12	A/G mutation position 699-bp of mRNA	TNB	LW, LR	100, 100	(Jiugang, et al. 2012)
NOS2	12	SNP c.2192C > T	TNB, NBA	IB x MS	255	(Fernandez-Rodriguez, et al. 2010)
ITIH cluster	13	ITIH-1 : 2 SNP ITIH-3 : 4 SNP ITIH-4 : 4 SNP	TNB, NBA	IB x MS	255	(Balcells, et al. 2011b)
MUC4	13	DQ124298:g.243A>G	NBA	IB x MS	347	(Balcells, et al. 2011a)
ROPN1	13	T/C mutation position 536 bp of mRNA	TNB, NBA	LW, LR	100, 100	(Lan, et al. 2012)
RBP4	14	Intron	TNB, NBA NBA	CL LR; LW	1300 850; 604	(Rothschild, et al. 2000) (Spotter, et al. 2009)
EphA4	15	Exon 3, 2 SNP	TNB, NBA	LR, YO, DU	765	(Fu, et al. 2012)
PRLR	16	Alu site	TNB, NBA NBA	LW; MS; LR CL	400;261; 416 273	(Vincent, et al. 1998) (Drogemuller, et al. 2001)
LEP	18	Exon 3 Exon 3 Intron 1	TNB, NBA TNB, NBA TNB, NBA	MS x LW/ LR CL YO; LR DU	55 to 77 519 62; 170 246	(Van Rens, et al. 2003, Van Rens and Van der Lende 2002) (Chen, et al. 2004a, Korwin-Kossakowska, et al. 2002) (Chen, et al. 2004a)

¹AKR1C2 = Aldo keto reductase 1C2; EphA4 = erythropoietin-producing hepatocellular A4; GNRHR = Gonadotropin releasing hormone receptor; ITIH = inter-alpha-trypsin inhibitor; LEP = Leptin LIF = Leukemia inhibitory factor; MAN2B2 = mannosidase 2B2; MUC4 = Mucin 4; NAT9 = N-acetyltransferase 9; NOS2 = inducible nitric oxide synthase; OPN = Osteopontin; PRLR = Prolactin receptor; RBP4 = Retinol binding protein 4; ROPN1 = Rhoophilin associated protein 1.

²AP = Age at puberty; NBA = Number born alive; OR = ovulation rate; TNB = Total number born;

³CL = composite line; CW = composite white; DU = Duroc; IB = Iberian pig; LR = Landrace; LW = Large White; MS = Meishan; PI = Piétrain; YO = Yorkshire.

Table 2. QTL for male reproductive traits

Trait	Pig chromosome	Population ¹	Size	% variance	Reference
Ejaculation duration	6, 17	DU x ER	177	7.7 to 7.9	(Xing, et al. 2009)
Ejaculation times	6, 16, 17	DU x ER	177	5.9 to 11.8	(Xing, et al. 2009)
Epididymal weight at					
- 90 days of age	2	DU x ER	347	4.5	(Ren, et al. 2009)
- 180 days of age	3, 4, 10, 13, 15	LW x MS	487	1.9 to 4.3	(Bidanel, et al. 2001)
- 300 days of age	3, 7	DU x ER	347	4.5 to 27.3	(Ren, et al. 2009)
Length of bulbo-urethral glands	1, 3, 7, 13	LW x MS	485	3.3 to 5.1	(Bidanel, et al. 2001)
Plasma FSH level	3, 10, X	WC x MS	315	Np ²	(Rohrer, et al. 2001)
	X	WC x MS	132	np	(Ford, et al. 2001)
Plasma testosterone level	7, 13	DU x ER	347	7.3 to 14.3	(Ren, et al. 2009)
Semen volume	3, 15, 18	DU x ER	177	7.9 to 8.6	(Xing, et al. 2009)
Seminiferous tubular diameter					
- at 90 days	5, 13, 14, X	DU x ER	347	8.4 to 14.8	(Ren, et al. 2009)
- at 300 days	16	DU x ER	347	14.8	(Ren, et al. 2009)
Seminal vesicles Weight	1, 3, 4, 7, 11, 15, 16, X	LW x MS	481	2.5 to 21.8	(Bidanel, et al. 2001)
Daily sperm production	X	WC x MS	132	np	(Ford, et al. 2001)
Sperm abnormality rate	4, 9	DU x ER	177	8.8 to 11.8	(Xing, et al. 2009)
Sperm concentration	17	DU x ER	177	9.5	(Xing, et al. 2009)
Sperm motility	4	DU x ER	177	6.3	(Xing, et al. 2009)
Sperm pH value	2, 6, 9	DU x ER	177	5.7 to 9.8	(Xing, et al. 2009)
Testicular weight at :					
- 60 days	3, X	DU x MS	449	5.0 to 9.0	(Sato, et al. 2003)
- 90 days	1, X	DU x ER	347	9.1 to 20.6	(Ren, et al. 2009)
- 180 days	4, 7, 10, 13, 17, X	LW x MS	487	3.5 to 19.6	(Bidanel, et al. 2001)
- 220 days	X	WC x MS	315	np	(Rohrer, et al. 2001)
	X	WC x MS	132	np	(Ford, et al. 2001)
- 300 days	1, 5, 7, X	DU x ER	347	4.8 to 14.7	(Ren, et al. 2009)

¹DU = Duroc; ER = Erhualian, LW = Large White; MS = Meishan; WC = White European breed cross

²np = not provided

G3072A mutation (Van Laere, et al. 2003) on sow prolificacy has recently been reported (Stinckens, et al. 2010) but, to our knowledge, it is not yet known whether it is a direct or an apparent effect of G3072A mutation.

QTL affecting reproductive traits

The main features of male and female reproductive trait QTL reported in in pig QTL database (<http://www.animalgenome.org/cgi-bin/QTLdb/SS/index> - accessed on January 2013) are

Table 3a. QTL for female reproductive traits (1/2)

Trait	Pig chromosome	Population ¹	Size	% variance	Reference
Age at puberty	1, 4, 6, 7, 13	LW x MS	476	3.0 to 10.0	(Bidanel, et al. 2008)
	7, 8, 12	LW x LR	295	2.7 to 9.7	(Cassady, et al. 2001)
	15	LW x LR	295	np ²	(Holl, et al. 2004)
	1, 10	WC x MS	344	np	(Rohrer, et al. 1999)
	1, 7, 8, 17	DU x ER	454	2.0 to 8.0	(Yang, et al. 2008)
Ovulation rate	4, 5, 7, 9, 13	LW x MS	502	3.9 to 5.9	(Bidanel, et al. 2008)
	9	LW x LR	295	3.4	(Cassady, et al. 2001)
	4, 8, 13, 15	LW x LR	114	5.1 to 10.9	(Rathje, et al. 1997)
	3, 8, 9, 10, 15	WC x MS	344	np	(Rohrer, et al. 1999)
	3	DU x MS	234	np	(Sato, et al. 2006)
	7, 8, 15	YO x MS	104	np	(Wilkie, et al. 1999)
	8	YO x MS	108	17.4	(Braunschweig, et al. 2001)
	8	WC x MS	600	np	(Campbell, et al. 2003)
Weight of ovaries	4, 6, 7, 9, 12, 13, 14, 15, 18	LW x MS	502	2.3 to 7.0	(Rosendo, et al. 2012)
Number of embryos	9, 12, 18	LW x MS	468	2.8 to 7.2	(Bidanel, et al. 2008)
Uterine capacity	8	WC x MS	187		(Rohrer, et al. 1999)
Uterine horn length	1, 5, 6, 7, 9, 11, 12, 13	LW x MS	465	2.7 to 9.2	(Rosendo, et al. 2012)
Uterine horn weight	1, 2, 4, 5, 7, 9, 12, 13, X	LW x MS	465	2.3 to 4.5	(Rosendo, et al. 2012)
Reproductive tract weight	1, 5, 9, 12, 14, 18, X	LW x MS	465	1.8 to 4.6	(Rosendo, et al. 2012)
Gestation length	1, 9, 15	YO x MS	104	9.4 to 23.6	(Wilkie, et al. 1999)
	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, 18	LW, LW x LR	683	np	(Onteru, et al. 2012)
Number mummified	2, 6, 12	LW x LR	279	np	(Holl, et al. 2004)
	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, X	LW, LW x LR	683	np	(Onteru, et al. 2012)

¹DU = Duroc; ER = Erhualian, IB = Iberian pig; LR = Landrace; LW = Large White; MS = Meishan; WC = White European breed cross; YO = Yorkshire

²np = not provided

summarized in Tables 2 and 3, respectively. The limited number of QTL mapping programs for male reproductive traits have been performed using crosses between early maturing Chinese and American / European breeds. Most QTL have a rather low to moderate effect (less than 10% of trait variance), except on chromosome X, where QTL explaining up to 20% of the variance of several traits, i.e. testicular weight, seminal vesicles weight and seminiferous tubular diameter, have been detected. Alleles from Chinese breeds increase testes weight at young ages, but tend to reduce it at older ages. The *SERPINA7* gene, which regulates the availability of thyroid hormones within tissues has been reported as an interesting positional candidate for this QTL by Ren, et al. (2009), but its potential implication remains to be investigated. No

Table 3b. QTL for female reproductive traits (2/2)

Trait	Pig chromosome	Population ¹	Size	% variance	Reference
Total number born	11	LW x LR	279	5.1	(Cassady, <i>et al.</i> 2001)
	7, 12, 14, 17	LW/LR x MS	269	2.7 to 8.8	(De Koning, <i>et al.</i> 2001)
	8	LW x MS	152	np ²	(King, <i>et al.</i> 2003)
	7, 15	DU x ER	299	2.8 to 4.3	(Li, <i>et al.</i> 2009)
	13, 17	IB x MS	881	np	(Noguera, <i>et al.</i> 2009)
	6	YO x MS	104	np	(Wilkie, <i>et al.</i> 1999)
Number of stillborn	1, 2, 3, 4, 6, 7, 8, 9, 12, 13, 14, 15, 16, 17, 18	LW, LW x LR	683	np	(Onteru, <i>et al.</i> 2012)
	5, 13	LW x LR	279	7.9	(Cassady, <i>et al.</i> 2001)
	12, 14	LW x LR	279	np	(Holl, <i>et al.</i> 2004)
	7, 8	DU x ER	299	3.7 to 5	(Li, <i>et al.</i> 2009)
	6, 11, 14	LW, LR		np	(Tribout, <i>et al.</i> 2008)
	4	YO x MS	104	np	(Wilkie, <i>et al.</i> 1999)
Number born alive	1, 2, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18	LW, LW x LR	683	np	(Onteru, <i>et al.</i> 2012)
	11	LW x LR	279	np	(Cassady, <i>et al.</i> 2001)
	6, 15	DU x ER	299	3.7 to 5	(Li, <i>et al.</i> 2009)
	13, 17	IB x MS	881	np	(Noguera, <i>et al.</i> 2009)
	7, 16, 18	LW, LR		np	(Tribout, <i>et al.</i> 2008)
	1, 2, 3, 4, 6, 10, 11, 12, 13, 14, 15, 16	LW, LW x LR	683	np	(Onteru, <i>et al.</i> 2012)
Removal parity	1, 5, 8, 9, 11, 12, 13, 14, 16	LW, LW x LR	818	np	(Onteru, <i>et al.</i> 2011)
Nonproductive days / herd life	9, 12, 14, 17, X	LW, LW x LR	818	np	(Onteru, <i>et al.</i> 2011)

¹DU = Duroc; ER = Erhualian; IB = Iberian pig; LR = Landrace; LW = Large White; MS = Meishan; WC = White European breed cross; YO = Yorkshire

²np = not provided

fine mapping of autosomal QTL has been carried out as yet and the localization interval of the QTL remains very large (generally above 20 cM).

QTL for female reproductive traits are shown in Table 3. They were all detected using GWLS except in the recent GWAS results of Onteru, *et al.* (2011; 2012) which will be discussed later. The most heritable traits, i.e. age at puberty ovulation rate and uterine dimensions have the largest number of QTL. QTL for age at puberty have been detected on 10 different chromosomes, with overlapping confidence intervals from independent studies on SSC1, on SSC7 in the SLA complex region and at the extremity of the short arm of SSC8. QTL for ovulation rate have been detected on 9 different chromosomes, with QTL from independent studies located on two different regions of SSC8, the first one in the centromeric region (Wilkie, *et al.* 1999), the second one in the telomeric part of SSC8 short arm.

The position of the 2 SSC8 QTL has been refined by, respectively, Braunschweig, *et al.* (2001) and Campbell, *et al.* (2003). Campbell, *et al.* (2008) proposed the mannosidase 2B2 (*MAN2B2*) locus as a positional candidate, but the causal polymorphism does not seem to have been identified so far. A C/G substitution in the 3' UTR of a functional candidate locus, i.e. *GNRHRH*, located in the centromeric part of SSC 8, was found to affect ovulation rate by Jiang, *et al.* (2001).

QTL affecting litter size traits have been detected on 13 different chromosomes with microsatellite markers, but most of them are only putative results and the overlap between studies is rather limited. Indeed, overlaps between confidence intervals concern the results of Bidanel, *et al.* (2001), Wilkie, *et al.* (1999) and Li, *et al.* (2009) on SSC 6, of De Koning, *et al.* (2001), Tribout, *et al.* (2008) and Li, *et al.* (2009) on SSC 7, of Bidanel, *et al.* (2001), Wilkie, *et al.* (1999) and Noguera, *et al.* (2009) on SSC 13 and, finally, of De Koning, *et al.* (2001) and Noguera, *et al.* (2009) on SSC 17. Some overlaps with FCG results can also be found. The *LEPR* locus is located in the confidence interval of the above mentioned SSC 6 QTL. The SSC 7 QTL are located in the vicinity of the properdin locus (*BF*). The prolactin receptor locus (*PRLP*) is located on SSC 16, close to the confidence interval bound of the QTL affecting number born alive mapped by Tribout, *et al.* (2008).

The papers of Onteru, *et al.* (2011; 2012) are, to our knowledge, the only ones who report QTL results based on the PorcineSNP60 BeadChip. They found a very large number of QTL that are located much more accurately than previous results. Most of them correspond to new QTL regions. Even if they have to be confirmed by other independent studies, these results are a clear illustration of the high detection power of dense sets of SNP markers. They also show that the genetic architecture of complex traits such as reproductive traits depends on larger numbers of loci than was expected 10 years ago.

Finally, it should be emphasized that the simple additive models that have been used so far are unlikely to correctly describe the complex gene interaction pathways underlying the genetic architecture of traits that are known to have a high degree of complexity. Noguera, *et al.* (2009) used a more complex model involving two-QTL with interaction models and found not less than 18 epistatic QTL affecting number born alive. A lot of work remains to be done using more complex models on larger data sets. Additional major challenges for the future include: 1) the use of sequence data in QTL mapping studies; 2) the integration of transcriptome, proteome and metabolome data for both improving QTL mapping power and more getting a much better understanding the complex pathways underlying complex biological functions such as reproduction; 3) to model gene functioning and enter the area of predictive biology.

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