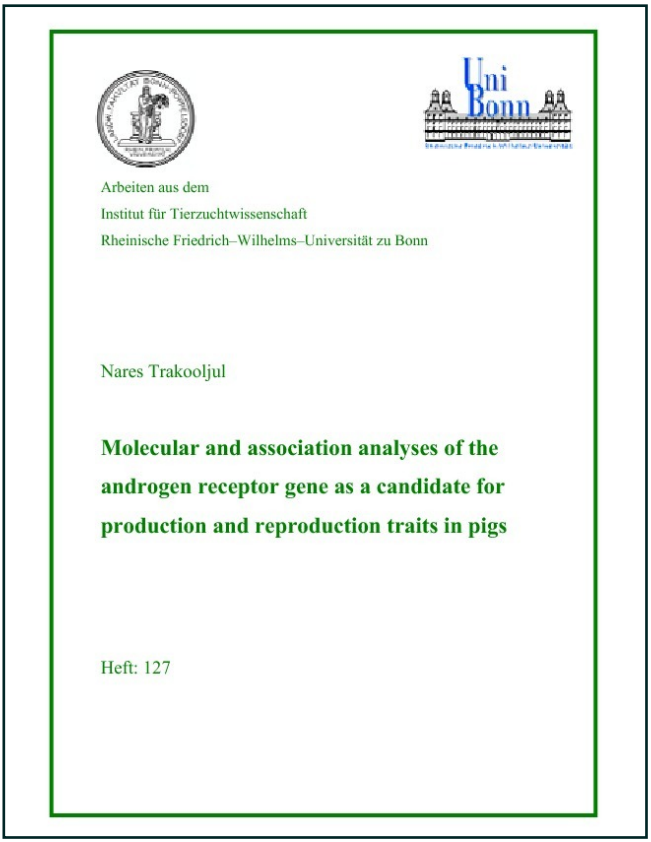
Molecular and association analyses of the androgen receptor gene as a candidate for production and reproduction traits in pigs



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1 Introduction

Genome research is showing a tremendous progress in mapping and characterization of quantitative trait loci (QTL) that control phenotypic variation of various important traits in human, model animals and farm animals. Continuing molecular analysis of economic important traits is leading to a better understanding of quantitative trait genetics. Like in other species, rapid advances in pig genomics and functional gene discovery have been made (Rothschild 2003). The strategy widely applied in QTL detection is genome scaning based on linkage mapping with anonymous DNA markers and subsequent positional cloning. Genetic markers that are being discovered to be linked to traits can be used to enhance the genetic improvement of breeding stock through marker-assisted selection (Dekkers and Hospital 2002).

The current status of QTL mapping in pigs shows that several QTLs for a variety of traits including growth, fat deposition, meat quality, reproduction as well as disease resistance have been mapped on nearly all chromosomes in divergent breed crosses and commercial breeds (Bidanel and Rothschild 2002). QTL mapping identifies chromosome regions with influences traits of interest by mapping of the trait/linked marker. Fine mapping can help in this step to restrict the region of interest and functional gene candidates can be potentially selected. Besides, rapid developing of human-pig comparative map and increase of the gene number mapped to pig chromosomes hold great promises of the candidate gene approach as a powerful method to detect major genes underlying trait loci.

This study proposed the androgen receptor gene (*AR*) as a potential functional positional gene candidate for production and reproduction traits in pigs since the porcine *AR* is located within a QTL-region for carcass traits, abdominal fat, back fat thickness and intramuscular fat content (Knott et al. 1998, Rohrer and Keele 1998, Harlizius et al. 2000, Rohrer 2000) and it functions as a nuclear transcription factor being involved in diverse physiological developments of e.g. male and female reproductive tissues (Drews et al. 2002, Slomczynska et al. 2001, Tripepi et al. 2000). The pig *AR* has been recently assigned to the X (q13) chromosome (Seifert et al. 1999). However, molecular information particularly of the gene, promoter and polymorphisms was not well defined

in the pig. In addition, gene expression and phenotype/genotype association analyses will provide better understanding of the gene functions and effects on traits of interest.

Therefore, the objectives of the present study were:

I. Sequencing of the porcine *AR* and promoter

II. Detection of polymorphisms

III. Investigation of the *AR* mRNA expression profile and genotype-associated differential transcript level

IV. Association analyses between the *AR* genotype and selected traits including uterus traits, number of normal and inverted teats as well as fatness traits

2. Literature review

2.1 Candidate gene approach

Over recent years, a number of QTL mapping programs in pigs have been developed. Many regions of the genome with QTLs have been identified for various economic traits for example growth, fat deposition, meat quality, reproduction and disease resistance (Bidanel and Rothschild 2002). Advances in molecular biology and genetics result in a wealth information e.g. identification of genes and single nucleotide polymorphisms (SNP), comprehensive genetic linkage maps, high-resolution physical maps using radiation hybrid panels as well as comparative maps linked to human or mouse genome. These promise the candidate gene approach as a powerful tool to identify major genes affecting economically important traits. In addition to a high-resolution fine mapping, a prior knowledge of genes and their functions is also necessary to select a potential candidate gene related to a trait and to reduce the number of considered genes.

The candidate gene approach can be very powerful and can detect loci even with small effects. However, results from candidate gene analyses must be interpreted with caution because spurious results can occur due to linkage disequilibrium (LD) to linked- or nonlinked- causative genes. A genome scan will always find a map location of trait locus with a major effect. However, it will fail to detect trait loci with smaller effects if it does not reach stringent significance thresholds (Andersson 2001).

The candidate gene study has been currently paid more interest due to an increase of known new genes across species. Examples of candidate gene analyses in pigs are given in table 2.1. Variation of significant results and therefore referring its reproducibility seem to be widely discussed primarily on specific genetic background of test population and heritability of a given trait. On the other hand, untraceable association may also refer to characteristics of used marker which could be only a linked locus rather than a causative variant.

Table 2.1 Candidate gene analyses in pigs

Chromosome	Candidate genes	Affecting traits	Test population	Reference
1p24-25	Estrogen receptor	litter size, back fat thickness	MS-SL, LW-SL LW-ComL	Rothschild et al. 1996, Short et al. 1997
1q22-27	Melanocortin 4 receptor	backfat, daily gain, feed intake	LR-SL, LW-SL, LW x D	Kim et al. 2000
2p17	Insulin like growth factor 2	muscle development and body composition	WB x LW, PI x LW	Jeon et al. 1999, Nezer et al. 1999
4	A-FABP	intramascular fat content and growth rate	D	Gerbens et al. 1998
6p	Melanocortin receptor 1	coat color	WB, MS, LW, PI, H, D, WB x LW	Kijas et al. 1998
6q11-12	Ryanodine receptor 1	malignant hyperthemia, high lean meat content	PI	Fujii et al. 1991
6q11	FUT1	susceptibility to E. coli F18	Swiss LR, LW	Meijerink et al. 1997

B is abbreviated for Bergshire, ComL for commercial lines, D for Duroc, H for Hamshire, LR for Landrace, LW for Large White, MS for Meishan, PI for Pietrain, SL for synthetic lines, WB for Wild Boar, and Y for Yorkshire.

Table 2.1 continued

Chromosome	Candidate gene	Affecting trait	Test population	Reference
8p12	KIT	dominant white	WB x LW, LR, LW, H, D, MS, PI	Johansson Moller et al. 1996, Marklund et al. 1998
8q1.1-1.2	GNRHR	number of corpora lutea	MS x LW	Jiang et al. 2001
13	PIT-1	fatness traits	MS x D, MS x H, MS x LR, MZ x LR, LW, LW x LR	Yu et al. 1995, Stancekova et al. 1999
14	Retinol-binding protein 4	litter size	LR-SL, LW-SL, D x LW	Rothschild et al. 2000
15	PRKAG3 gene	glycogen content in muscle, meat quality	H, B x Y	Milan et al. 2000, Ciobanu et al. 2001
16q2.2-2.3	Prolactin receptor	litter size, age at first estrus, number of teat	LW-, MS-, LR-SL, MS x LW	Vincent et al. 1998, van Rens and Lende 2002
18q13-21	Leptin	feed intake, growth rate, fatness	LR, LW	Kennes et al. 2001, Jiang and Gibson 1999

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