

Pig Leanness, Insulin Like Growth Factor 2 (IGF2) gene status of pigs in South Africa – Literature Review

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Introduction

The challenge facing the South African pig industry is to breed leaner pigs. There are about 350 commercial pork producers in South Africa. About 50% of the production is used for processing products such as sausages, bacon and other products. There is great scope in South Africa to increase pork production and consumption. The genetics of pig breeding is studied intensively in order to produce pork for human consumption that is mainly free of fat. IGF2-gene plays an important role in muscle growth in pigs

Growth is a complex biological phenomenon controlled by a complex of endo-, para- and autocrine control mechanisms. This has been studied in depth in most farm animals and it has been shown that the insulin growth factor complex (IGF) plays a critical role in growth regulation, together with insulin, thyroid hormones, steroids and the growth hormone. IGF's are growth-promoting peptides, which are structurally homologous with insulin. Their biological effects are also similar to that of insulin that is synthesized only in the pancreatic islets of Langerhans, while IGF's are synthesized in tissues throughout the body (Nedbel *et al.*, 2000). The effect of growth hormone on growth, myogenesis and some metabolic pathways is mediated by IGF's 1 and 2. IGF2-gene plays an important role in muscle growth in pigs and has potential to assist pig breeders by using genotypic information in the selection programmes. The effects of the gene on muscle mass and leanness are of the same magnitude as that reported for the halothane gene (MH gene) but without the undesirable effects on meat quality. IGF2 is an imprinting gene, paternally expressed, i.e. only the allele from the father is expressed in the progeny. This imprinting inheritance mode of the gene was reported by several studies (Buys, 2003; van Laere, 2003; van Maagdenberg, 2007). The IGF2 gene has an effect on the production of lean meat. Boars tested for IGF2 can be used to either increase or decrease back fat. Boars with IGF2 +/+ genotypes can be used to increase lean yield, while those with IGF2 -/- genotype can be used to decrease lean yield. The IGF2 gene can also be used to produce pork with the desired level of leanness from fatter sows. Based on its physiological function, IGF2 has been considered a candidate gene for a

quantitative trait locus (QTL) in pigs affecting muscularity.

The best-described example of a gene affecting meat quality in pigs is the well-known *HAL* gene (Christian, 1972) but the gene is associated with pale, soft, exudative (PSE) meat. The Rendement Napole (RN) gene and the Melanocortin Receptor (MC4R) gene have been also shown to bear mutations relevant to meat quality (lower muscle and reduced water holding capacity). A number of QTL's have been reported on almost all chromosomes affecting growth; carcass and meat quality traits (drip loss, water-holding carcass). A QTL effect for muscle mass and fat deposition, expressed only in boars, was found to be caused by a single base pair mutation near the IGF2 gene.

Pig breeds can be classified as genetically lean and genetically obese (Wood, 1984). The two extreme examples are the Duroc (genetically obese) and Pietrain (genetically lean). Breeding a leaner pig decreases the ratio between fat deposition and lean deposition. Consequently, fat quality is negatively affected. Currently, there is interest in the intra muscular fat content of pigs since higher intramuscular fat levels are associated with improved eating quality of pork (Bejerholm and Barton-Gade, 1986; Jakobsen, 1992, de Vries *et al.*, 1998). Intramuscular fat content is strongly influenced by genetics. For example, the Duroc has more intramuscular fat than other breeds (Barton-Gade, 1987).

The test for IGF2 gene allows for knowing if the pig has the gene for leanness or fatness and accurately detects the genetic mutation associated with meat quality. Both genotypes can be useful to breeders allowing them to make informed decisions for selection of breeding stock.

The effects of this gene on lean meat content and back fat thickness (BFT) of pigs were reported by several studies but we do not know if it has an effect on meat tenderness, juiciness and taste.

A study to determine the incidence of the IGF2 gene amongst the breeding boars in South Africa and to determine whether the IGF2 gene has an effect on meat quality such as tenderness, juiciness and taste is thus imperative for the South African pork industry.

A previous study on South African pig population indicated a low frequency of the *HAL* gene. IGF2 has potential to increase leanness of the carcass and a commercial test is available. The aim of this study is to evaluate the frequency of the IGF2 gene in the stud and commercial population in SA and study the effect of the gene on carcass

quality traits such as pH, BFT and water-holding capacity.

Literature overview

Effects of IGF2 gene on lean meat content and backfat thickness of pigs

Identification of IGF2

Initial studies on finding a QTL for IGF2 was performed using a candidate gene approach. In a study by Andersson-Eklund *et al.* (1998) used an intercross between wild boar and Large White domestic pigs were used for QTL mapping. A QTL on the short arm of chromosome 2 with moderate effect on muscle mass was detected using conventional Mendelian inheritance model. The data was reanalyzed by Jeon *et al.* (1999) for the presence of an imprinting effect and an imprinted QTL (paternally expressed) was detected on the distal tip of chromosome 2 in pigs (SSC2) that has effects on lean meat content. The QTL indicated 15.4% of F2 phenotypic variance of longissimus muscle area, 14% of heart weight and 10.4% of backfat depth. The results indicated that the paternally expressed QTL locates at the same position as IGF2. This result and the fact that both the gene and the QTL were imprinted, made IGF2 gene a possible candidate for the QTL effect. Jeon *et al.* (1999) found that the allele in the Large White at the IGF-2 linked QTL was associated with larger muscle mass and reduced BFT, but that this QTL had no notable effect on abdominal fat.

The IGF2 linked QTL was also found in experimental crosses of Pietrain and Large White pig breeds, in a study on 1032 F2 progeny (Nezer *et al.*, 1999). The QTL mapping based on this experiment detected a significant QTL at the distal end of the short arm of chromosome 2, influencing muscle mass and fat deposition (BFT, back fat % and fat cut %). The results founded by Nezer *et al.* (1999) also confirmed that the QTL at the end of SSC2 was imprinted and paternally expressed. Therefore, IGF2 gene was regarded as a potential candidate for the QTL at the distal end of SSC2. The effects on muscle mass and fat deposition were major and of the same magnitude as that reported for the halothane gene (ryanodine receptor 1 gene). Two loci together explained 50% of the Pietrain-Large White difference for muscularity and leanness. No evidence for interaction between the QTL at IGF2 gene and Halothane gene locus was found. Sequence analysis (Nezer *et al.* (1999) found a single nucleotide mutation, G to A transition in IGF2, which increased lean yield by 2.7% (Meadus, 2000).

The QTL at IGF2 and FAT1 on chromosome 4 (Andersson *et al.* 1994) were the two

QTL's with the greatest effect on body composition and fatness, present in the wild boar-Large White cross. The QTL at IGF2 controlled mainly muscle mass whereas FAT1 had a major effect on fat deposition (Jeon *et al.* 1999). The two QTL loci explains 33% variance for lean meat content in ham, 31% for percentage of lean meat and bone in back, and 26% for average depth of backfat. The IGF2 microsatellite was also found to be highly polymorphic, with three alleles among wild boars founders and an additional two alleles among eight Large White founders (Jeon *et al.* 1999). It is important to have markers with as many alleles as possible. The more variation amongst the microsatellite markers, the larger the exclusion probability. This high polymorphism provides excellent potential for improving lean meat content of pigs by selection.

According to Sheller *et al.* (2002), IGF2 explains 25% of the phenotypic variation of leanness in experimental crosses. However, it does not influence daily weight gain and pH of meat. Lee *et al.* (2001) tested the presence of the imprinted QTL at IGF2 based a F2 population of 512 pigs from cross between Berkshire and Yorkshire breeds. The hypothesis made reconfirmed that the IGF2 gene is an imprinting gene in pigs and constitutes an important QTL for muscle mass and fat deposition. The test reached the genome-wide threshold ($p < 0.01$) for average BFT and loin-eye area. The favorable alleles showed in the Yorkshire breed, when transmitted through the sire, reduced average back fat by 0.1 cm and increased loin-eye area by 1.0 cm², when compared to Berkshire alleles.

A QTL scan in a porcine experimental population based on Duroc and Berlin Miniature pigs was reported by Wimmers *et al.*, (2006) to identify QTL for microstructural muscle properties as well as biophysical parameters of meat quality and traits related to body composition, ie. pH and lean meat content. The proportion of slow and fast twitch fibres has been related to insulin resistance, as well as fat catabolism (Simoneau *et al.*, 1997). Regions with significant QTL for muscle fibre traits or significant QTL for meat quality were detected on several chromosomes (SSC1, 2, 3, 4, 5, 13, 14, 15 and 16). Loci controlling lean meat content segregated on SSC6. The results presented in the study indicated that loci affecting meat color and meat quality traits, such as related to water binding capacity, like pH value and conductivity, segregate in many populations including commercial breeds and are located on the p-arm of SSC3. A QTL for meat color was reported on SSC13.

A genome scan was performed in a F2 experimental cross bred population using a

marker set covering more than 80% of the porcine linkage map (USDA-MARC v2, ArkDB) (<http://www.thearkdb.org/>) for traits related to muscle fibre type composition and meat quality applying line-cross and half-sib analysis. The study showed that microstructural properties of pig muscle and meat quality are governed by genetic variation at many loci distributed throughout the genome.

De Koning *et al.*, (1999) described a total genome scan by using experimental cross between Meishan and Large White. The traits examined in that study were BFT in intramuscular fat content. The study indicated significant QTL on SSC7 for back fat and suggestive QTL's for both intramuscular fat and back fat on SSC2. Further investigation of these regions was performed with two different models in a study by (Rattink *et al.*, 2000). Imprinting analysis revealed a genome-wise, significant, paternally expressed QTL on SSC2. The results suggested that this QTL is different from the previously reported paternally expressed QTL for muscle mass and fat deposition on the distal tip of SSC2. Evans *et al* (2003) and De Koning *et al* (2003) analyzed the Large White commercial population for the presence of the QTL, but inconsistent results for fatness traits were obtained in the IGF2 region.

Association between IGF2 gene and lean meat

Van Laere *et al.* (2003) reported that a G to A transition in IGF2 gene is the causative quantitative trait nucleotide. This single nucleotide mutation adds approximately 3-4% more lean meat to pigs. The link of the mutation with the desired phenotype is 100%, regardless the origin of the pedigree (Buys, 2003). It allows for the selection of carcass leanness based directly on the functional nucleotide at the DNA level.

Confirmation of IGF2 in selection

Actual breeding trials confirmed that the use of IGF2 gene to increase uniformity of pork leanness is not just a theoretical potential. One example of these was illustrated in a trial where terminal sires homozygous for the favorable allele at the IGF2 gene were selected (Sheller *et al.* 2002) and investigated whether the IGF2 gene can be used in commercial selection programs in order to increase uniformity of commercial pigs without influencing meat quality. From this trial, the pigs from selected boars were leaner and more uniform compared to those from unselected boars. The BFT was reduced by 2.3 mm. Average lean meat percentage, ham percentage and loin percentage increased by 1.98%, 0.31% and 0.43% respectively. The meat quality traits, pH after 24 hours and meat color, were also compared. Offspring from selected boars

and those from unselected boars had the same pH value (5.77 to 5.78 measured after 24 hours), and lightness (44.57 to 43.08) also within the optimal range. The investigation concluded that the selection of homozygous terminal sires with the favorable allele at IGF2 gene increased the uniformity and carcass leanness in market pigs without influencing meat quality, in particular the water holding capacity.

Oczkowicz *et al.* (2009) reported that the frequency of the IGF2 gene mutation was evaluated between Polish Landrace and Large White pigs. The aim of the study was to compare body composition, growth performance and meat quality traits between the two breeds, carrying the A/A and G/G genotypes in the IGF2 gene. The results obtained were consistent with previous reports (Sheller *et al.*, 2002), showing that the A allele is common in breeds subjected to strong selection for lean meat content. The association study revealed that the A allele increased the weight of loin, weight of ham, carcass meat percentage, and decreased average backfat thickness. Highly significant effects of the IGF2 mutation on body composition traits were observed, as well as significant effects on growth performance, but only in the Polish Landrace. No significant effects for meat quality traits, average backfat thickness, carcass meat percentage, pH after slaughter, pH after 24 hours, intramuscular fat percentage and meat color were observed.

The influence of the IGF2 gene mutation on meatiness has been confirmed by other authors in various pig populations (Estelle *et al.* 2005). However, the association between the IGF2 mutation and growth performance and meat quality traits are not clear to date. In the study conducted by Estelle *et al.* (2005), the objective was to investigate the IGF2 substitution effect in a Large White outbred population and in an Iberian x Landrace F2 cross. The results showed that the substitution had significant effects on fatness and growth. It was also evident that there were other QTL's segregating in pig chromosome 2, which still had valuable mutations to be discovered, other than the IGF2 substitution for carcass weight and pH after 24 hours. Jungerius *et al.* (2004) also reported that the IGF2 substitution explains a backfat thickness QTL. The study demonstrated that the IGF2 mutation also controls the paternally expressed QTL for backfat thickness in a cross between Meishan and European Whites. In the study by Jungerius *et al.* (2004), a comparison of backfat thickness measured by Hennessy grading probe (HGP) and by ultrasound measurement (USM) was made. The results of the QTL analyses for both the techniques were highly consistent. A paternally expressed QTL was shown in the analysis of the HGP data. A possible second QTL

was only observed with the HGP, this would be a QTL for a characteristic that is measured only by HGP and not by USM, example, the third layer of backfat. Total backfat consists of three layers of which the third (inner) layer develops at a later stage of growth and in European commercial lines is underdeveloped. A very thin third-layer of fat may be difficult to detect by BFT-USM. As a result, in some cases BFT-USM only represents the thickness of two layers of fat, while BFT-HGP measures the total amount of fat in all three layers.

Three genotypes were evaluated for leanness and overall carcass quality was reported by Eggert *et al* (1997). Line 1 [Large White sires x (Large White-Landrace) dams], Line 2 [Dekalb Pietrain sires and Dekalb (Large White-Landrace) dams] are lean pigs of comparable backfat thickness. Line 3 [synthetic terminal sires x (Yorkshire-Landrace) dams] is a commercial terminal cross representing average U.S. pigs for leanness. Standard carcass measurements, depths of the individual backfat layers (outer, middle and inner) were taken at the tenth rib. Line 3 showed the most backfat at every midline and fat depth measurement. Although lines 1 and 2 were comparable in total tenth rib fat depth, their backfat was unevenly distributed between the individual layers. Line 1 showed more outer layer backfat and less inner layer backfat when compared to Line 2. In an attempt to obtain leaner animals, Line 1 may have been selected for slower maturing backfat layers which have resulted in softer carcass fat. There was no difference in color or firmness of the *longissimus dorsi* between the lines. Line 1 produced the largest loin eye area and the least inner layer backfat. Line 2 had higher marbling scores which is associated with having more inner layer backfat, than Line 1. The total belly thickness, the middle layer belly fat and the outer lean streak was less for Line 1 than the other two lines. The thinner, leaner bellies of Line 1 was also less firm. Thin, soft bellies can result in difficult slicing and processing.

Association between ryanodine receptor (RYR1) and pork leanness

The ryanodine receptor (RYR1) gene, also known as the “halothane” gene had been intensely studied. In a survey conducted by Soma *et al* (2005), to determine the MH-gene status of pigs in nucleus herds and AI stations in South Africa indicated that from a total of 439 boars tested, 421 tested normal (NN) for the MH-gene and 17 were carriers (Nn). Only one individual showed recessive (nn). The breeds comprised SA Landrace, Large White, Duroc, Pietrain, Chester, Kolbroek and synthetic lines. It was evident that the presence of the MH gene is low in the South African seed stock herds. In the second phase of the study, the incidence of the MH-gene amongst pigs at the abattoirs

was investigated. The results indicated a low incidence of the MH-gene and that the incidence of PSE meat reported was due to other factors such as heat, handling and transport, and not the presence of the MH-gene amongst the South African pig population. Pig sensitivity to stress is due to the C1843-T transition in the RYR1 gene. The product of a gene showing such mutation leads to calcium release in the endoplasmic reticulum of the skeletal muscles at a rate that is equivalent to twice that of normal muscle. A meat quality analysis conducted by MacLennan and Phillips (1992), showed that under intense stress conditions, a rapid glycogen disintegration leads to increase of lactic acid content in muscle cells of the mutated gene carriers. Consequently the level of muscle acidification increases. The affected animals are a source of pale, soft, exudative (PSE) pork. In other studies pigs heterozygous for the RYR1 genotype demonstrated that they were characterized by 4-5% higher meat content and 14% lower fat content in carcass as compared to mutation-free pigs. Elimination of this gene from pig populations resulted in improvement of meat quality because PSE meat was simultaneously eliminated. The recessive allele is associated with more lean meat. It is this association that has allowed the gene frequency to be increased initially through selection for increased muscularity. These studies indicate that the RYR1 gene exerts an important influence on parameters of meat quality, that is, drip loss and pH, and carcass meat. The RYR1 gene is thus regarded as one with a major effect on these two traits.

Hamilton *et al* (2000) investigated the effect of the Halothane and Rendement Napole genes on carcass and meat quality characteristics (pH, color and water-holding capacity) of pigs. Animals were classified according to their halothane genotype, normal and carrier (NN and Nn). Color, firmness and marbling were assessed. Carrier animals had shorter carcasses than normal (NN) animals. There was no difference in backfat thickness amongst the genotypes. Carrier pigs had lower pH than normal animals, higher Minolta color scores and drip loss values. Decreased water-holding capacity and paler pork color has been reported by other studies (Leach *et al.*, 1996). There was no difference between the Halothane genotypes for the chemical fat content of the longissimus muscle. The results of this study highlighted that the Halothane gene independently have negative effects on muscle color and water-holding capacity.

Interaction between Ryanodine receptor (RYR1) gene and IGF2 gene

Muscle tissue is mainly composed of muscle fibres. Muscle growth potential in pigs is related to the total number of fibres (Dwyer *et al*, 1993; Stickland & Goldspink, 1973),

which is known to be fixed before birth. Hyperplasia and hypertrophy are responsible for the increase in total muscle mass and are the result of proliferation, differentiation and the fusion of myoblasts and satellite cells that are controlled by a number of regulatory factors. Insulin-like growth factor system is one these regulatory factors. The result of the IGF2 mutation on muscle growth and lean meat content may be associated with effects on biochemical and histochemical muscle fibre characteristics, and can allow for better understanding the role of IGF2 on muscle growth. The effects of the RYR1 genotype on carcass and meat quality traits have been widely described (Fuji *et al*, 1991). The mutations associated with increased lean meat content but also with malignant hyperthermia. This results in a higher incidence of pale, soft and exudative meat in nn, and to a lesser extent in Nn pigs, compared to normal (NN) pigs. The regulation of muscle growth has to be better understood to improve performance traits without compromising animal health and meat quality. The interaction between RYR1 and IGF2 genes is thus critical in pig breeding programs.

A study reported by van den Maagdenberg *et al* (2008), aimed to investigate the effect of the IGF2 mutation on biochemical and histochemical muscle fibre characteristics in relation to the RYR1 genotype (Nn vs. NN). No effect of the IGF2 or the RYR1 genotype on muscle fibre type composition was found. However, a two-way interaction between IGF2 and RYR1 genotype or gender on fibre type composition was observed. In the study, the mutation in the RYR1 did not influence birth weight, average daily gain, lean meat content or average daily lean meat growth, although an increased percentage of carcass weight and *Longissimus* muscle cross-sectional area were found in Nn animals. Muscle IGF2 expression does not appear to be the only factor explaining muscle growth, because NN animals had less muscle than their heterozygous counterparts, despite their higher IGF2 mRNA expression. Further investigation is necessary to understand the interaction between the IGF2 mutation and RYR1 genotype.

The effect of the IGF2 paternal allele (Apat and Gpat animals that inherited the mutant and wild type paternal allele of interest) were evaluated on carcass and meat quality traits in Nn and NN genotypes and to rule out possible unfavorable correlated responses of the IGF2 mutation and to examine the interaction between these two major genes (van den Maagdenberg *et al*, 2008). The IGF2 genotype did not influence the meat quality traits measured on the carcass post mortem and only a small influence on meat quality was found. The lean meat content was approximately 5% higher in animals that inherited the mutation in the IGF2 gene from their father and consequently, the

average daily lean meat growth was higher compared to wild type Gpat animals. The difference in lean meat percentage was due to a lower fat thickness. Greater drip losses and water losses were apparent for Nn animals compared to the NN animals. The red colour of the meat from Nn animals was more stable compared to the meat from NN animals. The study re-confirmed that the IGF2 mutation is associated with a strong effect on carcass traits of economic importance, as was shown by other studies with other breeds (Jeon et al., 1999 for an intercross between the Wild Boar and Large White; Nezer et al., 1999, Large White and Pietrain intercross; Estelle et al., 2005, in a Large White outbred population and an Iberian x Landrace cross). The results obtained indicated that the IGF2 gene had a role in both fat and muscle deposition, without negative effects on meat color and drip loss. The recessive RYR1 gene in the heterozygous animals showed lower backfat thickness and shorter carcass length in this study. In contrast with the mutation in the IGF2 gene, the results indicated that the higher lean meat percentage in Nn animals was solely due to an increased muscle growth without an effect on backfat thickness. In contradiction with the IGF2 mutation, the RYR1 genotype had a more negative effect on meat quality, such as meat color, water holding capacity and tenderness. It was clear that the mechanisms behind the increased leanness are different. Similarly, the different physiological mechanisms associated with these mutations are responsible for either no effect on meat quality or a detrimental effect in the case of the IGF2 and RYR1 mutation, respectively. The role of the RYR1 gene in postmortem metabolism is thought to occur from increased cytosolic calcium levels which delays postmortem metabolism (Depreux, Grant & Gerrard, 2002), and this accelerated metabolism of the carbohydrate reserves that is related to PSE development. The muscle pH is lower when the temperature of the carcass is still high, with higher protein denaturation and higher drip losses as a result. While the increased leanness due to the RYR1 genotype is connected more with increased muscle hypertrophy and better carcass conformation, the IGF2 mutation leads to increased leanness which is associated with reduced fat deposition.

Factors Influencing Fat Quality in Pigs

Breed or Race

The genotype and feeding regime determines the quality attributes of fat regarding content, composition and uniformity as well as oxidative stability (Rosenvold *et al*, 2003). Pig genetics accounts for at least 30% of the variation in meat quality (De Vries, as cited by Andersen). The influence of genetics on pork quality comprises differences among breeds as well as differences amongst animals within the same breed. Wariss *et al*

(1990) indicated that the tendency of lean breeds to have poorer fat quality was due to their leanness and thinner subcutaneous fat layer instead of other inherent breed differences.

Sex and Gender

Moss (1992) indicated that differences exist between male and female animals and sex status (castrated or entire) animals. Uncastrated male pigs have more lean meat per carcass and better feed conversion ratios than castrates. The difference in sex hormone metabolism between males and females are responsible for thinner subcutaneous fat layers in males compared to females. Bruwer et al (1991), indicated that castrate carcasses contained the most fat, gilts were intermediate and boars had the highest lean meat content.

Conclusions:

Genomic information is increasingly becoming integrated into quantitative genetic practice. A number of DNA markers are used in pig improvement programs. These programs combine molecular genetics with quantitative genetic methodologies to increase the accuracy of selection for complex breeding objectives in commercial environments. Selection criteria focusing mainly on a single area of performance, such as meat quality while disregarding the potential negative effects on growth or carcass quality could create a negative trend for the economic performance of the animal. Genotype by environment interactions ($G \times E$) are particularly important to pig improvement programs, including genetics of meat quality, as progeny of individuals raised, tested and slaughtered under "ideal" genetic nucleus or "meat lab" conditions have to perform under varying commercial production and plant environments. Genetic correlations between purebred and crossbred performance for economically important traits in the pig can deviate significantly from unity, and not all improvement predicted will be realized when crossbred animals are evaluated in a commercial system. Future success for the pig industry will require efficient growth with good quality meat or perhaps optimizing meat quality at the lowest production costs. The initiation of IGF2 testing in South Africa thus becomes imperative for South African commercial pork producers and the industry at large.

Recommendations

Considering the effect of the IGF2 gene, it thus becomes imperative to ascertain the status of the IGF-2 gene in breeding boars amongst the South African pig breeds (SA Landrace, Duroc, Large White).

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