GENES ASSOCIATED WITH PRODUCTION AND HEALTH IN FARM ANIMALS

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In the early 1990s in the European Union and Poland alike, special research projects (i. e. PiGMaP, BovMaP, ChickenMaP) were launched in order to gather as much information on the farm amimals genome as possible (Archibald et al., 1991; Komisarek et al., 1998; Korwin-Kossakowska et al., 1998). The aim of these projects was also to make gene maps that pinpoint the structure (DNA nucleotide sequences) and, more importantly, the location of genes on specific chromosomes. The coverage on these maps is now sufficient to allow researchers to conduct quantitative trait loci (QTL) linkage analyses. QTL linkage analyses involve using a genomic scan. Often F2 or backcross families are used and genotypes are obtained for many (>75) markers evenly spaced across the genome. Several such experiments are underway and beginning to produce interesting and useful results. Candidate gene and comparative mapping approaches have also been successful in identifying major genes affecting several traits. Candidate gene analysis is when we choose a gene based on the physiology of the trait. The candidate gene is assumed to affect trait performance. Comparative gene analysis allows us to find "positional candidate genes" in the regions associated with possible QTL. To date, several major genes have been found with the candidate gene approach (Rothschild, 2007).

Genes associated with meat quality in pigs

FAT1 gene

The first major gene of a quantitative trait (FAT1) for fatness and growth in pigs was localized on chromosome 4 by using a wild boar intercross (Andersson et al., 1994). This gene region on chromosome 4 in the pig is homologous to parts of human chromosome 1 and 8. The latest comparative mapping results between humans and pigs indicate that the QTL is located in a region homologous to HSA1q (q arm of human chromosome 1 pair) (Berg et al., 2002).

Ryanodine receptor (RYR1) gene

The ryanodine receptor (RYR1) gene, responsible for pig sensitivity to stress, has received the most study. Pig sensitivity to stress is due to C1843-T transition (resulting in the conversion of amino acid arginine into cysteine) in the RYR1 gene. The product of a gene showing such mutation leads to calcium release unit in the endoplasmic reticulum of skeletal muscles. An analysis of meat quality made by MacLennen and Phillips (1992) showed that under intense stress conditions, a rapid glycogen disintegration leads to increase of lactic acid content in the muscle cells of the mutated gene carriers. In consequence the level of muscle acidification increases. At slaughter, such animals are a source of PSE (pale, soft, exudative) pork (Essen-Gustavsson et al., 1992). On the other hand, studies of pigs heterozygous for the RYR1 genotype (Pedersen et al., 2001) demonstrated that they were characterized by 4-5% higher meat content and 14% lower fat content in carcass compared to mutation-free pigs. These studies indicate that the RYR1 gene exerts an important influence on parameters of meat quality and carcass meatiness. For this reason, this gene is regarded as one with a major effect on these two traits. Analysis of the pig genome physical map made it possible to localize the RYR1 gene on chromosome pair 6 in the q1.1→1.2 region.

Acid meat (Hampshire) gene (RN – Rendement Napole)

Another gene controlling pig meat quality, regarded as a major effect gene, is the dominant acid meat (Hampshire) gene (RN^{-}). Unfavourable RN^{-} gene increases the glycogen level as assessed by glycolytic potential and branching enzyme activity in the myofibres, giving rise to a lowered protein content, ultrastructural abnormalities and resulting in decreased technological abilities associated with high lactic acid levels postmortem (Monin and Sellier, 1985; Lebret et al., 1999; Huang et al., 2004).

The presence of a mutated allele in the genome causes meat processors even greater losses than PSE meat. The meat of pigs with RN^{-}/- genotype is also observed to contain less protein than the meat of animals without the mutated gene (Monin et al., 1992). Previous studies showed that the RN gene is located between the markers SW120 and SW936 on the porcine chromosome 15 (Milan et al., 1995; Mariani et al., 1996; Reinsch et al., 1997). Further studies showed that

the incidence of acid (Hampshire) meat is conditioned by a point mutation (G→A) at codon 200 (changing arginine to glutamine) of the PRKAG3 gene. This gene was localized on chromosome pair 15 in the q2.4→2.5 region, between microsatellite sequences S1006 and S1007 (Milan et al., 2000). It should be noted, however, that the RN⁻ gene has so far been identified only in European and American Hampshire pigs (Miller et al., 2000).

Growth hormone (GH) gene

The developing pig is particularly sensitive to treatment with growth hormone (GH), which increases the average daily weight gain (Etherton et al., 1987), enhances protein accretion and reduces fat deposition (Campbell et al., 1989).

The growth hormone gene is localized on chromosome pair 12 (in the p1.4 region) (Larsen et al., 1995). In the 1990s several experiments were carried out to identify polymorphic variants of this gene and to determine the most favourable haplotype controlling carcass fatness (Schellander et al., 1994; Pierzchała et al., 1999). Of slightly different nature were the studies of Kopchik and Cioffi (1991) showing that introduction of an exogenous growth hormone gene into pig organisms results, among others, in increased intensity of protein synthesis, which in turn makes it possible to increase weight gains by 10-20% while reducing fat in tissues by 30-40%, and allows a 15-30% higher fattening efficiency compared to the control animals.

The GH gene pathway contains various interdependent genes, such as insulin-like growth factor I (IGF1), pituitary-specific transcription factor I (PIT1), growth hormone releasing hormone (GHRH), growth hormone receptor (GHR) and other genes. These genes are potential candidate markers because of their important physiological effects associated with economic traits (Franco et al., 2005).

The GHRH gene product is released by the hypothalamus and acts on the adenophosphyse to stimulate of secretion of growth hormone. Growth hormone-releasing hormone is a member of a superfamily of structurally related peptide hormones that includes vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), secretin, and glucagons (Rekasi et al., 2000).

Insulin-like growth factor 2 (IGF2) gene

The first gene detected in pigs to be characterized by expression in the form of parental imprinting, was the IGF2 gene, localized on chromosome pair 2 in the p1.7 region, in the close neighbourhood of the microsatellite sequence SWC9 (Rejduch et al., 2004). The IGF2 gene is expressed only within the line of boars, which makes possible restrictive selection for carcass lean (Nezer et al., 1999). Moreover, Swedish as well as Polish studies showed that (G→A) transition in intron 3-G3072A of the gene (in conservative region of CpG islet) is related to an increase of about 10-20% in the muscle weight in pigs.(Van Laere et al., 2003; Oczkowicz et al., 2008).

Other IGFs

The IGF system consists IGF1, IGF2 and their receptors and also of six binding proteins (IGFBP-1 to –6). The IGFBPs can modify IGF activity by binding IGFs and preventing IGF receptor activation. Up to now, the best known is the inhibiting influence of IGFBP-2, IGFBP-3 and IGFBP-5 expression on muscle differentiation in pigs (Green et al., 1994; James et al., 1996; Dunaiski et al., 1999).

MyoD genes family

Basing on a knowledge of molecular mechanisms controlling myogenesis (muscle development) several candidate genes may be selected as potentially affecting carcass meat content. In this reason MyoD family genes encoding factors of muscle regulatory are very good genes for carcass meat deposition. MyoD family consist an several structural and functional genes: myogenin- MYOG - located on 9q2.1→2.6 of pig chromosome (Ernst et. al., 1998), miogenic factor 3 - MYF3 (MYOD1) – located on 2p1.4→1.7 region (Čepica et.al. 1999), miogenic factor 5 – MYF5 – located on 5q2.5 region (Soumillion et. al., 1997) and, miogenic factor 6; herculin MYF6 (earlier named MRF4) – located on 5q2.4→2.5 between microsatellite DNA sequence SW378 and most distal marker SW967 (Vykoukalova et. al., 2003). The PCR-RFLP analysis showed the point mutations in MYOG in intron 2, MYF3 in intron 1 and exons 2 and 3 and MYF5 in intron 2. Application of the SNP-PCR technique made possible to show the polymorphism of MYF6 gene in intron 1 and exons 2 and 3 (Knoll et. al., 1997; Soumillion et. al., 1997; Stratil and Čepica 1999; te Pas et. al., 1999; Vykoukalova et. al., 2003).

The results of the studies performed on different breed and lines (Kurył et. al., 2002; Cieślak et. al., 2002) predict to suggestion that the mutation in coding as well as non-coding region of MYOG, MYF3 and MYF5 genes is the mechanism changed the value of meat quality. For this reason is very interesting to answer if the polymorphism in the regions of herculin (MYF6) is connected with carcass meat and fat deposition trait.

Genes associated with production and reproduction in cattle and sheep

Diacylglycerol acyltransferase (DGAT1) gene

The diacylglycerol O-acyltransferase (DGAT1) is a microsomal enzyme that catalyzes the final step of triglyceride synthesis. The latter was recently achieved for a QTL on chromosome 14 with a pronounced effect on milk fat content. It was shown that the QTL variation is most likely caused by a nonconservative base substitution in the candidate gene DGAT1 changing lysine to alanine (K232A) in the enzyme diacylglycerol O-acyltransferas (DGAT) (Winter et al., 2002). In particular, the allele encoding the lysine 232 variant proved to be efficient with regard to milk fat synthesis.

Lacorte et al. (2006) estimated the frequency of the DGAT1 K232A polymorphism in the main Zebu and Taurine breeds in Brazil as well as in Zebu x Taurine crossbreds, Holstein, and Gyr x Holstein. The highest frequency of the A allele was found in the Holstein sample (73%) followed by Gyr x Holstein F1 (39%). Brazilian Holstein and Gyr x Holstein F1 showed a very high frequency of the A allele. The Authors showed association between presence of A allele in DGAT1 locus and milk traits, e.g., milk production, fat and protein yield and fat and protein content in Brazilian cattle.

Mascular hipertrophy (MH) gene

Work on Belgian Blue cattle revealed that an 11 base pair (bp) deletion within the bovine myostatin gene (GDF8) is associated with the double-muscled phenotype seen in this breed. Investigations focusing on other European breeds known to show double-muscling identified several mutations within the coding region of the gene associated with the double-muscled phenotype in different breeds. The number of mutations found suggest that myostatin is highly variable within beef cattle. Variations that alter the structure of the gene product such that the protein is inactivated are associated with the most pronounced form of double-muscling as seen in the Belgian Blue cattle.

The similar map positions of the myostatin gene and the mh locus and the identification of the other kind of mutation (cysteine to tyrosine substitution) in the myostatin gene of two different double-muscled cattle breeds (Belgian Blue and Red Angus) suggest that this mutation Is also responsible for the double muscling phenotype (McPherron and Lee, 1997).

Callipyge (CLPG) gene in sheep

Genetic strategies to improve the profitability of sheep operations have generally focused on traits for reproduction. However, natural mutations exist in sheep that affect muscle growth and development, and the exploitation of these mutations in breeding strategies has the potential to significantly improve lamb-meat quality. The best-documented mutation for muscle development in sheep is callipyge (CLPG), which causes a postnatal muscle hypertrophy that is localized to the pelvic limbs and loin. Enhanced skeletal muscle growth is also observed in animals with the Carwell (or rib-eye muscling) mutation, and a double-muscling phenotype has been documented for animals of the Texel sheep breed. However, the actual mutations responsible for these muscular hypertrophy phenotypes in sheep have yet to be identified, and further characterization of the genetic basis for these phenotypes will provide insight into the biological control of muscle growth and body composition (Lien et., al 1999).

The callipyge (CLPG) locus was mapped to a chromosome segment of approximately 400 kb which was shown to contain four genes (DLK1, GTL2, PEG11 and MEG8) that are preferentially expressed in skeletal muscle and subject to parental imprinting in this tissue (Cockett et al., 2001).

Booroola fecundity gene (FecB)

The autosomal Booroola fecundity gene (FecB) mutation in sheep increases ovulation rate and litter size, with associated effects on ovarian physiology and hormone profiles. Analysis (Montgomery et, al 1995) of segregation in twelve families (379 female progeny) identified linkage between the mutation, two microsatellite markers (OarAE101 and OarHH55) and epidermal growth factor (EGF) from human chromosome 4q2.5. The marker OarAE101 was linked to secreted phosphoprotein 1 (SPP1, which maps to chromosome 4q21−23 in man) in the test pedigrees and independent families . The identification of linkage between the FecB mutation and markers from human chromosome 4q is an important step towards further understanding the control of ovulation rates in mammals.

Genes associated with health in farm animals

Fucosytransferase (FUT1) gene in pig

Enterotoxigenic Escherichia coli F18(ECF18) is a main pathogen that causes edema disease and post-weaning diarrhoea in piglets, and al-fucosytransferase (FUT1) gene has been identified as a candidate gene for controlling the

expression of the receptor for ECF18 bacteria. Two alpha (1,2) fucosyltransferase genes (FUT1, FUT2) on porcine chromosome 6q11 have been identified and are closely linked to the blood group inhibitor (S) and Escherichia coli F18 receptor (ECF18R) loci.

The typical clinical symptoms of oedema disease are neurological signs such as ataxia, convulsions and paralysis. At post-mortem examination, oedema is typically present at characteristic sites such as eyelids and forehead, stomach wall and mesocolon. The occurrence of these illnesses in the whole population is quite high, about 15%, and the mortality among the sick animals is about 90%. The disease is associated with the colonization of the small intestine with toxigenic Escherichia coli strains of a limited number of serotypes: O138, O139, O141, O147, O157, O16, O108. The mutation in four Polish pig breeds: Polish Large White, Polish Landrace, Zlotnicka White and autochtonous Zlotnicka Spotted was analysed by Klukowska et al (2001). High frequency of $M307^{a}$ mutation at FUT1 locus, causing resistance to oedema disease, in an autochtonous Polish pig.

Prion protein gene (PrP)

In mammals, the PrP gene is a highly conservative nucleotide sequence. Localized on the p arm of chromosome 20, the PrP gene in humans is composed of 16000 base pairs and divided into 2 exons, with the whole open reading frame (ORF), i.e. the protein encoding sequence, being located on exon 2 (Tao et al., 2005). Between exons 1 and 2, the human PrP contains a sequence corresponding to exon 2 of mice and sheep ("three-exon" species). It is known that this exon determines the structure of protein molecule encoded by a gene. The greater the differences in the structure of PrP genes in different species, i.e. in the amino acid composition of proteins encoded by them, the more difficult it is to transmit infection to another species via the prion protein. For cattle and humans, the difference is as much as 30 codons (Carlson et al., 1988). In the encoding fragment of the gene in cattle, two types of polymorphism were detected: C→T transition in the 3'-flanking region of exon 3 and polymorphism of octopeptide repeats (5 and 6) associated with duplication/deletion in the ORF region (Seabury et al., 2004).

The PrP gene in sheep has been mapped on chromosome 13 (13q15) (Iannuzzi et al., 1998). It consists of 31412 base pairs including three exons (52, 98 and 4028 nucleotides) and two introns (2421 and 14031 nucleotides) that interrupt these. The non-coding 3'UTR region is 3246 bp long. Repeat elements account for 57.1% of the gene sequence (Lee et al., 1998). Only the third exon is translated and the open reading frame contains 256 codons (766 bp). Post-translational processing results in the generation of PrP prion protein (PrP^{C}) composed of 210 amino acids (33-35 kDa) with two glycosylation sites. Most often, the PrP gene polymorphism is found in the C-terminal domain.

Twenty-five polymorphic codons have been described to date in the ovine PrP gene in the open-reading frame (Goldmann et al., 2005). The PrP gene polymorphism in sheep was first observed over the entire sequence (Hunter et al., 1997; Maciulis et al., 1992). However, most study has been devoted to the occurrence of polymorphism in the PrP coding region and its association with disease susceptibility, resistance and time of incubation (DeSilva et al., 2003; Goldmann et al., 2005; Maciulis et al., 1992). To date, amino acid polymorphism has been found in 23 codons: Q101R, M112T/I, G127V/A/S, A136V/T, M137T, S138N/R, L141F, H143R, R151C/G/H, Y152F, R154H, R167S, P168L, Q171R/H/K, Y172D, Q175E, N176D/K, H180Y, Q189L/R, T195S, T196S, R211Q and P241S (DeSilva et al., 2003; Goldmann et al., 2005; Maciulis et al., 1992). Several silent mutations were also detected in codons 83, 138, 231 and 237 (Baylis and Goldmann, 2004).

Few studies have explored PrP gene polymorphism in pigs. To date, description has been made of 4 SNPs that cause no change in the amino acid sequence and one change (G → C) in codon 4 of the gene. However, due to the considerable importance of pigs in breeding, and the recent use of pigs as donors of organs in xenotransplantation, it seems very important to identify the structure and function of the PrP gene in this animal species.

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