Family of melanocortin receptor (MCR) genes in mammals—mutations, polymorphisms and phenotypic effects

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Abstract The melanocortin receptor gene family consists of five single-exon members, which are located on autosomes. Three genes (MC2R, MC4R and MC5R) are syntenic in the human, mouse, cattle and dog genomes, while in the pig, the syntenic group comprises MC1R, MC2R and MC5R. Two genes (MC1R and MC4R) have been extensively studied due to their function in melanogenesis (MC1R) and energy control (MC4R). Conservative organisation of these genes in five mammalian species (human, mouse, cattle, pig and dog), in terms of the encoded amino acid sequence, is higher in the case of MC4R compared to MC1R. Polymorphisms of these two genes are responsible or associated with variation of pigmentation (MC1R) and adipose tissue deposition (MC4R). Polymorphic variants in MC1R, causing coat colour variation, were described in humans and domestic mammals (cattle, horse, pig, sheep, dog), as well as farm red and arctic foxes. The MC4R gene is very polymorphic in humans and it is well known that some variants cause monogenic obesity or significantly contribute to the development of polygenic obesity. Such relationships are not so evident in domestic mammals; however, at least one missense substitution (298Asp>Asn) in the porcine MC4R significantly contributes, at least in some breeds, to fat tissue accumulation, feed conversion ratio and daily weight gain. Knowledge on the phenotypic effects of polymorphisms of MC2R, MC3R and MC5R in domestic mammals is scarce, probably due to the small number of reports addressing these genes. Thus, further studies focused on these genes should be undertaken.

Keywords MC1R · MC2R · MC3R · MC4R · MC5R · Pig · Cattle · Horse · Dog

Introduction

Receptors of melanocortins are encoded by a gene family consisting of five members (MC1R–MC5R). The encoded receptors bind four ligands: α-, β- and γ-melanocyte-stimulating hormone (α-, β-, γ-MSH) and the adrenocorticotropic hormone (ACTH). Among them, MC1R binds preferentially α-MSH, while MC2R binds ACTH. Expression of the MCR genes is tissue-specific: MC1R is mainly expressed in melanocytes, MC2R in the adrenal cortex, MC3R and MC4R in the nervous system, and MC5R in sebaceous glands and other tissues, e.g. the brain, muscles, lung and kidney (Yang 2011).

The physiological role of the melanocortin receptors has been previously reviewed several times (Cone 2006; Eves and Haycock 2010; Yang 2011). Also, the effect of their mutations and polymorphisms in humans was reviewed, especially with regard to cutaneous pigmentation, MC1R (Dessinioti et al. 2011), and obesity, MC3R (Tao 2010b) and MC4R (Santini et al. 2009; Tao 2010a; Loos 2011).

The MCR genes, mainly MC1R and MC4R, were also extensively studied in domestic mammals. Polymorphism of these genes was analysed in terms of coat colour variability or the association with production traits related to fat tissue deposition and feed conversion ratio. These studies have not been reviewed to date. Thus, this article is focused on studies of the MCR gene family polymorphisms in domestic mammals.

Comparative organisation of the MCR genes

The MCR genes contain only a single exon and the encoded number of amino acids varies from 296 (MC2R) to 332 (MC4R). All these genes are located on autosomes (Table 1). Some of them (MC2R, MC4R and MC5R) are located on a single chromosome: 18 in humans and the mouse, 24 in cattle and 1 in the dog. In the case of the pig karyotype, the location is slightly different, since the MC1R, MC2R and MC5R genes
reside on chromosome 6, but not MC4R, which is not syntenic with MC2R and MC5R. This difference reflects chromosome rearrangements which took place during pig karyotype evolution (Goureau et al. 1996).

A comparison of the coding sequences of the two most frequently studied MCR genes (MC1R and MC4R) revealed a higher evolutionary conservatism of the MC4R protein (Tables 2 and 3). In the case of the MC1R protein, the amino acid similarity varied between 74.0 % (mouse vs. dog) and 83.6 % (cattle vs. dog), while for MC4R, it varied between 90.7 % (mouse vs. cattle) and 96.1 % (pig vs. dog). A comparison of nucleotide sequences revealed practically the same level of similarity. For MC4R, it ranged between 75.1 % (mouse vs. cattle) and 85.3 % (pig vs. cattle), while for MC4R, it was between 84.0 % (mouse vs. cattle) and 91.3 % (human vs. pig).

Knowledge on the genetic variants of melanocortin receptor genes and their phenotypic effects is most advanced for the MC1R and MC4R genes, and to a lesser extent for MC3R. Two other genes (MC2R and MC5R) were occasionally studied.

**MC1R**

The melanocortin receptor type 1 is mainly involved in melanogenesis. Thus, its polymorphism was studied in terms of its effect on hair and skin colour in humans and coat colour in animals. It is estimated that human cutaneous pigmentation (skin, hair and eye) is controlled by approximately 120 genes, but a crucial role in this process is played by MC1R, for which over 100 missense polymorphisms were identified (Dessinioti et al. 2011). Among these variants, functional and/or phenotypic effects were described only for 15 of them.

Coat colour is an important characteristic of breeds in domestic animal species. Thus, it is not surprising that the MC1R gene has been extensively studied. Altogether, 16 causative polymorphisms in seven species (pig 5, dog 3, cattle 2, sheep 2, arctic fox 2, horse 1 and red fox 1) were identified (Table 4). The polymorphic sites were located in extracellular (6), transmembrane (5) or intracellular (5) domains.

In cattle, the black/red coat colour depends on two polymorphic sites, which give a series of three alleles: $E^+$, $E^+$ and $e$. The $E^D$ (p.99Pro) and $E^+$ wild type (p.99Leu) substitutions are located in the first extracellular loop of the MC1R protein and are responsible for black coat colour and a combination of red or reddish brown/black coat colours, respectively (Klungland et al. 1995). Interestingly, the same mutation was observed in Asian pigs and variant $E^D$ (p.99Pro) also caused black coat colour, while the wild allele ($E^+$) facilitates the full expression of both pheomelanin and eumelanin (Kijas et al. 1998). The third allele ($e$) of the bovine MC1R gene was created by a deletion of guanine nucleotide at position 310/311, resulting in a premature stop codon, instead of the presence of tyrosine at the 155 position in the polypeptide (the second intracellular loop). The homozygotes ($ee$) produce pheomelanin only (Joerg et al. 1996).

In the pig, five polymorphic sites were identified. Interestingly, the genetic background of black colour is different in Asian and European breeds. In Asian breeds, black coat colour depends on the occurrence of the above-mentioned $E^D$ allele (p.99Pro), while in European breeds, the black coating is controlled by the $E^D$ allele (p.121Asn) (Kijas et al. 1998). Red coat colour is caused by a recessive $e$ allele. In this allele, two substitutions are present (p.164Val and p.243Thr), which are located in the fourth and sixth transmembrane domains, respectively. It is not clear if one or both substitutions are responsible for this coat colour (Kijas et al. 1998). Furthermore, the $E^P$ allele responsible for black spotting on the red or white background was identified (Kijas et al. 2001). This phenotype is a consequence of two C nucleotide insertions, at the position of the 67 nucleotide, leading to the frameshift and premature stop codon.

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**Table 1** Chromosomal location of the MCR genes in mammalian species

| Gene  | Human | Mouse | Pig   | Cattle | Dog   |
|-------|-------|-------|-------|--------|-------|
| MC1R  | 16    | 8     | 6     | 18     | 5     |
| MC2R  | 18    | 18    | 6     | 24     | 1     |
| MC3R  | 20    | 2     | 17    | 13     | 24    |
| MC4R  | 18    | 18    | 1     | 24     | 1     |
| MC5R  | 18    | 18    | 6     | 24     | 1     |

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**Table 2** Identity (%) of the nucleotide (above the diagonal) and amino acid (below the diagonal) sequences of the MC1R gene in five mammalian species

| Species | Human (953 nt*) | Mouse (947 nt) | Pig (963 nt) | Cattle (953 nt) | Dog (952 nt) |
|---------|-----------------|----------------|-------------|----------------|-------------|
| Human (317 aa**) | 76.9            | 84.6           | 82.7        | 81.9           |             |
| Mouse (315 aa) | 75.9            | 74.6           | 75.1        | 75.6           |             |
| Pig (320 aa) | 78.5            | 72.4           | 85.3        | 82.9           |             |
| Cattle (317 aa) | 81.4            | 74.6           | 82.6        | 81.3           |             |
| Dog (317 aa) | 80.4            | 74.0           | 82.0        | 83.6           |             |

* nucleotide, ** amino acid

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**Table 3** Identity (%) of the coding sequence (999 nucleotides, above the diagonal) and the encoded polypeptide (323 amino acids, below the diagonal) in five mammalian species

| Species | Human | Mouse | Pig | Cattle | Dog |
|---------|-------|-------|-----|--------|-----|
| Human   | 87.2  | 91.3  | 87.2| 88.4   |     |
| Mouse   | 93.4  | 87.8  | 84.0| 86.8   |     |
| Pig     | 95.8  | 94.0  | 88.5| 89.5   |     |
| Cattle  | 92.8  | 90.7  | 94.0| 87.2   |     |
| Dog     | 95.2  | 94.3  | 96.1| 93.1   |     |

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* nucleotide, ** amino acid
| Species         | Polymorphism | Function → phenotype | References |
|-----------------|--------------|----------------------|------------|
| Dog             | C916T        | Arg306Stop           | Newton et al. (2000) |
|                 |              |                      | E (wild type) → g.916CC and g.916CT → p.306Arg and p.306Stop → brown/black coat | |
|                 |              |                      | e → 916 TT → p.360Stop → red/yellow coat | |
|                 |              |                      | Breeds: Golden Retriever, Yellow Labrador, Irish Setter | |
| G233T           | Gly78Val     | E<sup>G</sup>→g.233TT and g.233CT → p.78Val or p.78Gly/p.78Val phenotype → grizzle or domino | Everts et al. (2000) |
| A790G           | Met264Val    | E<sup>M</sup>→g.790GG or g.790AG → p.264Val or p.264Met → black melanistic mask | Schmutz et al. (2003) |
| Cattle          | T296C        | p.Leu99Pro           | Klungland et al. (1995) |
|                 |              |                      | E<sup>D</sup>→g.296CC → p.99Pro→ dominant black coat colour | |
|                 |              |                      | E<sup>E</sup>→g.296TT → p.99Leu→ wild type→ combination of red or reddish brown and reddish black coat colour | |
|                 |              |                      | e→p.155* | |
| Sheep           | T218A        | p.Met73Lys           | E<sup>E</sup>D→g.218AA and g.361AA→ dominant black phenotype | Våge et al. (1999) |
|                 | G361A        | p.Asp121Asn          | Breeds: Norwegian Dala | |
| Horse           | C901T        | p.Ser83Phe           | Marklund et al. (1996) |
|                 |              |                      | EE→g.901CC→ p.83Ser→ non-chestnut | |
|                 |              |                      | Ee→g.901CT→ p.83Ser/ p.83Phe→ non-chestnut | |
|                 |              |                      | ee→g.901TT→ p.83Phe→ chestnut | |
| Pig             | T296C        | p.Leu99Pro           | Kijas et al. (1998) |
|                 |              |                      | E<sup>+</sup> (wild type)→ g.296TT→ p.99Leu allows full expression of both pheomelanin and eumelanin | |
|                 |              |                      | E<sup>E</sup>D1→g.296C→ p.99Pro→ dominant black | |
|                 |              |                      | Breeds: Asian | |
|                 |              |                      | E<sup>E</sup> (wild type)→ g.491C→ g.727G→ p.164Val→ red coat colour | |
|                 |              |                      | e→ g.491 T g.727-A→ p.164 Val p.243 Thr→ red coat colour | |
|                 |              |                      | nt67insCC Codon 23 | |
|                 |              |                      | E<sup+E</sup> (wild type)→ g.67 68CC→ p.23 Ala | Kijas et al. (2001) |
|                 |              |                      | E<sup>+</sup>→black spotting on red or white background | |
| Red Fox         | T373C        | Gly5Cys              | Våge et al. (1997) |
|                 |              |                      | E<sup>E</sup>→g.373C→ p.125Arg→ Alaskan silver coating | |
| Arctic Fox      | G13T         | Cys125Arg            | Våge et al. (2005) |
|                 | T839G        | Phe280Cys            | p.5Cys and p.280Cys→ blue coating | |

**Table 4 (continued)**

| Species         | Polymorphism | Function → phenotype | References |
|-----------------|--------------|----------------------|------------|
| Dog             | C916T        | Arg306Stop           | Newton et al. (2000) |
|                 |              |                      | E (wild type) → g.916CC and g.916CT → p.306Arg and p.306Stop → brown/black coat | |
|                 |              |                      | e → 916 TT → p.360Stop → red/yellow coat | |
|                 |              |                      | Breeds: Golden Retriever, Yellow Labrador, Irish Setter | |
| G233T           | Gly78Val     | E<sup>G</sup>→g.233TT and g.233CT → p.78Val or p.78Gly/p.78Val phenotype → grizzle or domino | Everts et al. (2000) |
| A790G           | Met264Val    | E<sup>M</sup>→g.790GG or g.790AG → p.264Val or p.264Met → black melanistic mask | Schmutz et al. (2003) |
| Cattle          | T296C        | p.Leu99Pro           | Klungland et al. (1995) |
|                 |              |                      | E<sup>D</sup>→g.296CC → p.99Pro→ dominant black coat colour | |
|                 |              |                      | E<sup>E</sup>→g.296TT → p.99Leu→ wild type→ combination of red or reddish brown and reddish black coat colour | |
|                 |              |                      | e→p.155* | |
| Sheep           | T218A        | p.Met73Lys           | E<sup>E</sup>D→g.218AA and g.361AA→ dominant black phenotype | Våge et al. (1999) |
|                 | G361A        | p.Asp121Asn          | Breeds: Norwegian Dala | |
| Horse           | C901T        | p.Ser83Phe           | Marklund et al. (1996) |
|                 |              |                      | EE→g.901CC→ p.83Ser→ non-chestnut | |
|                 |              |                      | Ee→g.901CT→ p.83Ser/ p.83Phe→ non-chestnut | |
|                 |              |                      | ee→g.901TT→ p.83Phe→ chestnut | |
| Pig             | T296C        | p.Leu99Pro           | Kijas et al. (1998) |
|                 |              |                      | E<sup>+</sup> (wild type)→ g.296TT→ p.99Leu allows full expression of both pheomelanin and eumelanin | |
|                 |              |                      | E<sup>E</sup>D1→g.296C→ p.99Pro→ dominant black | |
|                 |              |                      | Breeds: Asian | |
|                 |              |                      | E<sup>E</sup> (wild type)→ g.491C→ g.727G→ p.164Val→ red coat colour | |
|                 |              |                      | e→ g.491 T g.727-A→ p.164 Val p.243 Thr→ red coat colour | |
|                 |              |                      | nt67insCC Codon 23 | |
|                 |              |                      | E<sup+E</sup> (wild type)→ g.67 68CC→ p.23 Ala | Kijas et al. (2001) |
|                 |              |                      | E<sup>+</sup>→black spotting on red or white background | |
| Red Fox         | T373C        | Gly5Cys              | Våge et al. (1997) |
|                 |              |                      | E<sup>E</sup>→g.373C→ p.125Arg→ Alaskan silver coating | |
| Arctic Fox      | G13T         | Cys125Arg            | Våge et al. (2005) |
|                 | T839G        | Phe280Cys            | p.5Cys and p.280Cys→ blue coating | |
Studies on the molecular background of coat colour variation in canids revealed 22 polymorphic sites: ten in the dog, eight in the red fox, three in the arctic fox and one in the Chinese raccoon dog (Nowacka-Woszuk et al. 2013). Among them, six are responsible for coat colour: three in dogs, two in arctic foxes and one in red foxes (Table 4). In dogs, four main alleles were identified: E (wild type), EG, EM and e. The recessive e allele was independently identified by two teams (Newton et al. 2000; Everts et al. 2000). It is a C>T transition at the 916 nucleotide position, causing a premature stop codon, instead of arginine at the 306 position of the encoded polypeptide. The missense variant (p.306STOP, allele e) leads to a reduction of the cytoplasmic tail of the receptor and, as a consequence, results in red/yellow coat colour in dogs. This allele was found in three breeds: Golden Retriever, Yellow Labrador and Irish Setter. The EG (p.78Val) allele produces the so-called “grizzle” phenotype in Saluki and the “domino” phenotype in Afghan Hound breeds (Dreger and Schmutz 2010). The occurrence of a black melanistic mask in 12 dog breeds is controlled by the EM allele, p.264Val (Schmutz et al. 2003). Polymorphisms in the canine MC1R gene are located in the intracellular C-terminal extension (allele e), the second transmembrane domain (EG) and the third extracellular loop (EM). Analysis of data collected from commercial and research Canadian laboratories, performing DNA tests to detect coat colour alleles in dogs, revealed the occurrence of the e and EM alleles also in other breeds: the German Wirehaired Pointer, German Shorthaired Pointer and the Great Dane, while the EM allele occurred in the Basset Hound, Boxer and the Chinese Shar-Pei (Schmutz and Melekhovets 2012). Interestingly, the authors described white dogs with the e/e genotype in the Chow, German Shepherd Dog, Miniature Schnauzer and Puli breeds instead of the expected red or yellow coat colour. It was suggested that an interaction of an unknown gene with the e/e genotype causes elimination of the red pigment.

In red foxes, the E4 allele (p.125Arg), responsible for Alaskan silver coating, was reported by Våge et al. (1997). This coat colour is widely distributed in farm red foxes. Studies on the MC1R polymorphism in the arctic fox revealed two non-synonymous substitutions (p.Gly5Cys and p.Phe280Cys) in a highly conserved region of the protein, which is associated with a constitutive activation of the receptor (Våge et al. 2005). The p.5Cys (extracellular N-terminus) and p.280Cys (third extracellular loop) variants were observed in blue coat variants, which are rare in wild populations (3–5 %) and very frequent in farm populations. Until now, only one silent polymorphism in the coding sequence of the MC1R gene (g.759C>T) was identified in the Chinese raccoon dog (Nowacka-Woszuk et al. 2013).

MC2R

MC2R, also known as the adrenocorticotropic hormone receptor gene (ACTHR), encodes a receptor for the hormone, which plays a crucial role in the regulation of glucocorticoid secretion. The adrenocorticotropic hormone (ACTH) selectively activates the MC2R and induces glucocorticoid production and its secretion in the adrenal cortex, especially in zona fasciculata (Mountjoy et al. 1992; Cone and Mountjoy 1993). Recent studies revealed that small single-pass transmembrane proteins, called melanocortin receptor accessory proteins (MRAP and MRAP2), are essential for the expression of the melanocortin receptor type 2 and its transport to the plasma membrane (for reviews, see Webb and Clark 2010; Novoselova et al. 2013).

A crucial insight into the role of MC2R comes from knockout mice (Chida et al. 2007). The authors showed that it causes neonatal lethality of the majority of such mice. It was also concluded that MC2R knockout mice is a useful model for a rare, autosomal human hereditary disease, familial glucocorticoid deficiency (FGD). Altogether, 25 missense mutations in the human MC2R associated with FGD were identified. A majority of these mutations result in an unsuccessful protein traffic to the cell surface (Webb et al. 2009). Furthermore, some of the human MC2R polymorphisms (e.g. g.-184A, rs2186944) have a protective effect against heroin addiction in the Spanish population (Proudnikov et al. 2008). Moreover, four SNPs (rs1893219, rs1893220, rs2186944 and g.-2T>C) showed an association with responsiveness to ACTH therapy in some types of epileptic encephalopathy, infantile spasms. The TCCT haplotype results in an increased expression of MC2R and a stronger response to ACTH (Liu et al. 2008; Ding et al. 2010). The g.-2T>C mutation is also associated with higher levels of dehydroepiandrosterone, androstenedione and plasma ACTH in children with premature adrenarche (Lappalainen et al. 2008). Taking the above-mentioned data into consideration, it is rather unlikely that functional polymorphisms of the MC2R gene may significantly contribute to the phenotypic variability of production traits in livestock. Thus, it is not surprising that studies on the MC2R polymorphism in domestic animals are very scarce. According to the Single Nucleotide Polymorphism Database (dbSNPs; NCBI Platform), only 11 SNPs in dogs, four in pigs and none in cattle, sheep and horse were identified. In the pig, the MC2R locus was mapped within a QTL region for intramuscular fat content and back fat thickness (Jacobs et al. 2002). The authors showed that the distribution of a silent T>G substitution is different (P<0.01) in some pig breeds.

MC3R

The MC3R gene, similarly to the MC4R gene, plays a crucial role in energy homeostasis (Begriche et al. 2011), but associations of its polymorphisms/mutations with human obesity are not as evident as in case of the MC4R (Tao 2010a). In domestic mammals, this gene was studied only very rarely. In the porcine MC3R, two silent SNPs (522C>T and 549C>T) were described by Civánová et al. (2004). Further studies of one of these SNPs (549C>T), carried out on a small sample
(n = 101) of Czech Large White sows, revealed its association with the estimated breeding value for average daily weight gain (Weisz et al. 2011).

Extensive studies on the MC3R gene in four species of the family Canidae (dog, red fox, arctic fox and Chinese raccoon dog) showed a variable level of its polymorphism (Skorczyk et al. 2011). In total, 16 polymorphisms were described and a dog) showed a variable level of its polymorphism (Skorczyk et al. 2011). In total, 16 polymorphisms were described and a majority of them were found in the 5′-flanking (8) and 3′-flanking (2) regions. The MC3R gene of the red fox (eight polymorphic sites) and the Chinese raccoon dog (six polymorphisms) appeared to be the most polymorphic. In the dog, only two polymorphisms were observed, while the arctic fox was monomorphic. Association studies carried out in red foxes (n = 376) for two polymorphisms (silent substitution c.957A>C and c.*185C>T in the 3′-flanking region), revealed a significant relationship with body weight.

MC4R

The melanocortin receptor type 4 is a well known, major controller of food intake and energy expenditure (for reviews, see Adan et al. 2006; Tao 2010a). Thus, the MC4R gene has been considered as a candidate for human obesity. Altogether, more than 150 variants were identified in this gene (Tao 2009; Loos 2011). The variants are classified into five groups according to the phenotypic effects they evoke (Tao 2009). Class I contains mutations causing defective protein synthesis or its accelerated degradation, resulting in dramatically decreased expression. Class II mutations cause receptor retention inside a cell, probably due to a misfolding of the receptor. Class III represents variants which are present on the cell surface, but their binding capacity or ligand affinity are impaired. Variants causing defective signalling properties (decreased efficacy and/or potency) are categorised as class IV. Variants causing unknown effects form class V. Among the known variants, there are two (Val103Ile and Ile251Leu) which are considered as having a protective role against obesity (Loos 2011). However, sometimes, this effect is not pronounced, especially if small populations are analysed (Nowacka-Woszuk et al. 2011). On the other hand, extensive genome-wide association studies (GWAS) revealed that an SNP located close to the MC4R gene is associated with a predisposition to polygenic obesity. This variant (rs17782313), mapped 188 kb downstream of the gene (Loos et al. 2008), shows a strong association with an elevated BMI (for a review, see Xi et al. 2012).

Association of the MC4R gene variants with human obesity have initiated studies on the relationship with fat tissue accumulation in livestock species. The most extensive studies were carried out in the pig, resulting in the identification of eight polymorphic sites (Table 5). Among them, the missense substitution c.1426G>A (Asp298Asn) was the most extensively studied in terms of its association with production traits, mainly fatness, feed intake and feed conversion ratio. This polymorphism was identified by Kim et al. (2000a) and was originally named c.892G>A.

The Asp298Asn substitution is located in a highly conserved motif within the seventh transmembrane domain. Functional studies revealed that both polymorphic forms of MC4R bind its agonist with similar affinity. However, signal generation should be studied more carefully, since Kim et al. (2004) reported the Asp298 variant’s inability to generate signals, in contrast to Fan et al. (2008), who proved a similar signalling force for both variants. In a majority of studies, it was claimed that allele Asp298 is strongly associated with lower back fat thickness, higher lean meat percentage, slower growth rate and lower feed intake, while the Asn298 allele exhibit lower meat redness and a higher content of saturated fatty acids compared to the GG homozygote. Further studies revealed that allele frequencies differ greatly among pig breeds and lines, probably due to long-term artificial selection. For example, pigs representing lines of the same breed and raised for fresh meat production showed an increased Asp298 allele frequency when compared to those bred for cured ham and loin production (Burgos et al. 2006). Despite those promising reports, some of the subsequent studies failed to confirm an association of Asp298Asn SNP

### Table 5 Genetic variants identified in the porcine MC4R gene. Positions numbered according to NM_214173 (positions in brackets numbered according to AB021664)

| Location     | Position | Effect                                      | References               |
|--------------|----------|---------------------------------------------|--------------------------|
| Proximal     | c.-780C>G | Possible disruption of transcription factor binding site | Fan et al. (2009)        |
| promoter     |          |                                             |                          |
| Proximal     | c.-746CA | (6, 7)                                      | Fan et al. (2009)        |
| promoter     | c.-702delC|                                             | Fan et al. (2009)        |
| Proximal     | c.-135C>T | Possible disruption of transcription factor binding site | Fan et al. (2009)        |
| 5′UTR        |          |                                             |                          |
| Exon 1       | c.175C>T | Leu59Leu                                    | Ovilo et al. (2006)      |
|              | (c.706C>T)|                                             |                          |
| Exon 1       | c.707G>A | Arg236His                                   | Meidtner et al. (2006)   |
| Exon 1       | c.892G>A | Asp298Asn                                   | Kim et al. (2000a)       |
| Putative     | c.*430A>T|                                             | Fan et al. (2009)        |
| 3′UTR        |          |                                             |                          |
Table 6  Effects of the missense substitution c.892G>A (presently described as c.1426G>A) causing amino acid substitution (Asp298Asn) on pig production traits

| Trait                       | Effect of allele G (Asp) compared to allele A (Asn) | Breed                                                                 | References                             |
|-----------------------------|------------------------------------------------------|-----------------------------------------------------------------------|----------------------------------------|
| Average daily gain          | ↓                                                    | Duroc                                                                | Kim et al. (2006)                      |
|                             |                                                      | Pietrain × Mangalitsa                                                | Meidtner et al. (2006)                 |
|                             |                                                      | Lithuanian White                                                    | Jokubka et al. (2006)                  |
|                             |                                                      | Large White                                                         | Houston et al. (2004)                  |
|                             |                                                      | Polish Landrace                                                     | Stachowiak et al. (2005)               |
|                             |                                                      | Italian Large White; Duroc                                          | Davoli et al. (2012)                   |
|                             |                                                      | Pulawska breed                                                      | Piórkowska et al. (2010)               |
|                             |                                                      | Landrace × Large White × Pietrain                                   | Van den Maagdenberg et al. (2007)      |
|                             |                                                      | Berkshire × Yorkshire                                               | Fan et al. (2009)                      |
| Lean meat content           | ↑                                                    | Duroc                                                                | Kim et al. (2006)                      |
|                             |                                                      | Italian Large White                                                 | Davoli et al. (2012)                   |
|                             |                                                      | Pulawska breed                                                      | Piórkowska et al. (2010)               |
|                             |                                                      | Landrace × Large White × Pietrain                                   | Van den Maagdenberg et al. (2007)      |
|                             |                                                      | Lithuanian White                                                   | Jokubka et al. (2006)                  |
|                             |                                                      | Duroc                                                                | Davoli et al. (2012)                   |
|                             |                                                      | DIv2 line                                                           | Chao et al. (2012)                     |
| Back fat thickness          | ↓                                                    | Landrace; Large White; Large White × Duroc; Large White × Meishan   | Kim et al. (2000a)                     |
|                             |                                                      | Yorkshire                                                           | Fan et al. (2010)                      |
|                             |                                                      | Large White                                                         | Houston et al. (2004)                  |
|                             |                                                      | Italian Large White; Duroc                                          | Davoli et al. (2012)                   |
|                             |                                                      | Pulawska Breed; Polish Large White                                  | Piórkowska et al. (2010)               |
|                             |                                                      | Landrace × Large White × Pietrain                                   | Van den Maagdenberg et al. (2007)      |
|                             |                                                      | Landrace × Large White × Taihu                                      | Ovilo et al. (2006)                    |
|                             |                                                      | DIv2 line                                                           | Chao et al. (2012)                     |
| Average feed intake/daily  | ↓                                                    | Pietrain × Mangalitsa                                               | Meidtner et al. (2006)                 |
| feed intake                 |                                                      | Landrace; Large White; Large White × Duroc; Large White × Meishan   | Kim et al. (2000a)                     |
|                             |                                                      | Large White                                                         | Houston et al. (2004)                  |
|                             |                                                      | Pulawska breed                                                      | Piórkowska et al. (2010)               |
| Growth rate                 | ↓                                                    | Landrace; Large White; Large White × Duroc; Large White × Meishan   | Kim et al. (2000a)                     |
| Feed conversion ratio       | ↓                                                    | Italian Large White                                                 | Davoli et al. (2012)                   |
|                             | ↑                                                    | Duroc                                                                | Davoli et al. (2012)                   |
| Tenth rib back fat          | ↓                                                    | Yorkshire                                                           | Fan et al. (2010)                      |
| thickness                   |                                                      | Berkshire × Yorkshire                                               | Fan et al. (2009)                      |
|                             |                                                      | Lithuanian White                                                    | Jokubka et al. (2006)                  |
|                             |                                                      | Duroc                                                                | Schwab et al. (2009)                   |
| Ham weight                  | ↓                                                    | Italian Large White, Duroc                                          | Davoli et al. (2012)                   |
|                             | ↑                                                    | Pulawska breed                                                      | Piórkowska et al. (2010)               |
in the \textit{MC4R} gene with performance and quality traits in pigs (Schwab et al. 2009; Munoz et al. 2011) or reported breed-related differences in the observed effects (Stachowiak et al. 2005; Davoli et al. 2012). It is possible that this mutation might not be the causative one, only closely related to the real quantitative trait nucleotide (QTN), or there might be an epistatic interaction (Bruun et al. 2006).

Another missense substitution (707A>G, Arg236His) was detected in Pietrain, Vietnamese pigs and Berkshire × Yorkshire crossbreds (Kim et al. 2004; Meidtner et al. 2006; Fan et al. 2009). Animals carrying a minor allele A are fatter and grow more slowly than those carrying allele G. According to Fan et al. (2009), this polymorphism co-segregates with four other SNPs (−780C>G in promoter, −135C>T in 5′UTR, 175C>T synonymous substitution in exon 1 and *430A>T in putative 3′ UTR), forming three haplotypes, which exhibit a significant association with average back fat thickness and average daily weight gain. As predicted by the in silico study, the occurrence

| Table 6 (continued) | Trait | Effect of allele G (Asp) compared to allele A (Asn) | Breed | References |
|---------------------|-------|--------------------------------------------------|-------|-----------|
| Live weight at 140 days | ↑ | Landrace × Large White × Taihu | Otto et al. (2006) |
| Colour | Brighter | Pietrain-based crossbreed | Otto et al. (2007) |
| Drip loss | ↑ | Landrace × Large White × Taihu | Otto et al. (2007) |
| Intramuscular fat | ↑ | Polish Landrace, Duroc, Pulawska breed, Duroc; Polish Landrace | Davoli et al. (2012) |
| Saturated fatty acids content | ↓ | Landrace × Large White × Pietrain | Piórkowska et al. (2010) |
| Saturated fatty acids content | ↓ | Landrace × Large White × Taihu | Stachowiak et al. (2005) |

| Table 7 Genetic variants of the bovine MC4R gene and their association with production traits |
|---------------------|-------|-------|-----------|
| Position | Effect on | Breed | References |
| −293C>G | Body weight | −293C/−129A | Nanyang, Qinchuan, Jiaxian Red, Jinnan | Zhang et al. (2009) |
| −129A>G (linked SNPs) | Average daily gain | −129A | Jinxian Red, Jinnan |
| −129A>G | Live weight | G↑ | Qinchuan cattle | Liu et al. (2010) |
| 927C>T | Marbling | T↑ | Hanwoo cattle | Seong et al. (2012) |
| 989G>A | Back fat grade | A↑ | Angus, Holstein | McLean and Schmutz (2011) |
| Ser330Asn | Length of longissimus dorsi area | G↑ | Angus, Holstein | McLean and Schmutz (2011) |
| 1069C>G | Back fat thickness | C↑ | Hanwoo cattle | Seong et al. (2012) |
| Leu 286Val | Marbling | G↑ | Simmental, Angus, Hereford, Charolais, Limousine, Qinchuan, Luxi, Jinnan | Huang et al. (2010) |
| 1343C>A | Carcass weight | C↑ | Qinchuan cattle | Liu et al. (2010) |
| 1786C>T | Live weight | T↑ | Qinchuan cattle | Liu et al. (2010) |
| 1343C>A | Back fat thickness | A↑ | Hanwoo cattle | Seong et al. (2012) |
| 1786C>T | Back fat thickness | C↑ | Hanwoo cattle | Seong et al. (2012) |
of −780C>G and −135C>T SNPs may disrupt several transcription factor binding sites. The influence of these polymorphisms may be an explanation for the above-mentioned inconsistent data on the Asp298Asn association with production traits (Fan et al. 2009).

In the bovine MC4R gene, 17 polymorphic sites were discovered and, among them, 13 were silent mutations and four were missense substitutions. They occurred in the following positions: −293C>G, −193A>T, −192 T>G, −129A>G (Zhang et al. 2009), −84 T>C (Liu et al. 2010), 19C>A, 20A>T, 83 T>C, 128G>A (Huang et al. 2010), 709G>A (Val166Met) (Seong et al. 2012), 747G>A, 927C>T (Valle et al. 2004), 1069C>G (Leu286Val) (Thue et al. 2001), 1343C>A, 1786C>T (Seong et al. 2012), 145Val>Ala and 172Ala>Thr (Haegeman et al. 2001). A majority of them were reported only once, of which six were reported to be associated with production traits (Table 7). The most extensively studied substitution was 1069C>G, for which strong associations with back fat thickness, marbling, carcass and live weight were reported (Huang et al. 2010; Liu et al. 2010; Seong et al. 2012).

Studies of the canine MC4R gene revealed the presence of four SNPs, −637G>T, 777 T>C, *33C>G (Skorczyk et al. 2007) and 868C>T (van den Berg et al. 2010). Among them, only one SNP resulted in amino acid substitution, namely, 637G>T, changing valine to phenylalanine at position 213 (Skorczyk et al. 2007; van den Berg et al. 2010). Analysis of this polymorphism disclosed no association with morphological measures (van den Berg et al. 2010), probably because ligand binding and signalling abilities are not disturbed when compared to the wild variant of the MC4R gene (Yan and Tao 2011). Further studies focused on 5′UTR revealed the presence of two novel indels and three novel SNPs (Nowacka-Woszuk et al. 2012).

Table 8 Polymorphisms of the MC5R gene and their phenotypic effects in humans and pigs

| Species | Position | Studied traits | Effect on | Variant present in breed/population | References |
|---------|----------|----------------|-----------|-------------------------------------|------------|
| Humans  | 849C>G   | Skin condition, acne vulgaris | Association not found | Negro, South Indian, Japanese, Polynesian, Caucasian | Hatta et al. (2001) |
|         | Ala81Ala |                |           | Negro, South Indian, Japanese, Polynesian, Caucasian |            |
|         | Asp108Asp |                |           | Negro, Inuit, Japanese, Caucasian |            |
|         | Ser125Ser |                |           | Caucasian |            |
|         | Thr248Thr |                |           | Negro, South Indian, Japanese, Polynesian, Caucasian |            |
|         | PsI, PvulI | Obesity | BMI, fat mass, resting metabolic rate | Caucasian (Canada) | Chagnon et al. (1997) |
|         | 185G>T   | Obesity | BMI | Caucasian (Finland) | Valli-Jaakola et al. (2008) |
|         | 849C>G   | Type 2 diabetes | Type 2 diabetes | Caucasian (Finland) | Valli-Jaakola et al. (2008) |
|         | Phe209Leu | Mental disorders | G allele predisposes to schizophrenia and bipolar disorder | Caucasian (USA), African American | Miller et al. (2009) |
| Pigs    | 303A>G   | Fatness traits | Average daily gain, feed intake, feed conversation G ↑ | Large White × Landrace | Kovácik et al. (2012) |
|         | Ala109Thr |                |           | Landrace, Duroc | Kim et al. (2000b) |
|         |          | Fat deposition, carcass quality traits | No association studies performed | Berkshire, Duroc, Hampshire, Landrace | Emnett et al. (2001) |
|         |          | Fat deposition, carcass quality traits | – | Berkshire | Emnett et al. (2001) |
|         |          | Fat deposition, carcass quality traits | Tenth rib back fat thickness | Hampshire | Emnett et al. (2001) |
|         |          | Fat deposition, carcass quality traits | Meat colour and tenderness | Landrace | Emnett et al. (2001) |
|         |          | Fat deposition, carcass quality traits | Intramuscular fat percentage | Yorkshire, Chester White | Kim et al. (2000b) |
Among these polymorphisms, there was an 11-bp indel within a putative upstream open reading frame (uORF). This indel segregated with four SNPs, forming two haplotypes. Association studies ($n=381$) did not show any relationship of the haplotypes with body weight.

**MC5R**

The **MC5R** gene is expressed in the central nervous system and in a variety of peripheral tissues, especially in the skin. The encoded protein is involved in different physiological processes, including lipid metabolism, exocrine function (Yang et al. 2013) and proinflammatory activity (Jun et al. 2010). Together with other members of the melanocortin receptor family, the **MC5R** expression down-regulates leptin secretion in the in vitro cultured adipocytes (Hoggard et al. 2004; Norman et al. 2003), as well as mediates in the interleukin 6 (IL6) production (Jun et al. 2010). Because a high level of the IL6 circulating in blood correlates with insulin resistance (Kristiansen and Mandrup-Poulsen 2005), and leptin takes part in regulating food intake and energy expenditure, melanocortin receptor 5 is a functional candidate gene for obesity in humans or fatness in domestic animals. Also An et al. (2007) demonstrated the involvement of MCR subtype 5 in inducing fatty acid oxidation in skeletal muscles.

Despite a broad range of functions, only several polymorphisms of the **MC5R** gene were described in both humans and the domestic animals (Table 8). In the pig genome, the **MC5R** gene was mapped closely to marker S0059, which is within a QTL for fatness and meat quality. Several reports confirmed an association between porcine back fat thickness or feed intake and polymorphic variants of the **MC5R** gene (Kováčik et al. 2012; Emmett et al. 2001). Also, in humans the **MC5R** polymorphisms were reported to be associated with obesity (Chagnon et al. 1997; Valli-Jaakola et al. 2008). Due to a variety of physiological processes involving **MC5R**, it was also studied in relation to skin condition, metabolic and mental disorders. As a result of these studies, associations with type 2 diabetes, schizophrenia and bipolar disorder were documented (Valli-Jaakola et al. 2008; Miller et al. 2009).

**Conclusion**

Studies on the melanocortin receptor gene family revealed numerous functional variants, especially in the **MC1R** and **MC4R** genes. It is not surprising that extensive polymorphism of the **MC1R** gene exists in humans and domestic mammals, since skin or coat colour is a variable trait in human ethnic groups, as well as in domestic animal breeds. Thus, further studies on **MC1R** gene polymorphism in domestic animals demonstrating a unique coat colour should be continued. On the other hand, the **MC4R** gene is highly polymorphic in humans (more than 150 variants) and much less polymorphic in domestic mammals. A low level of **MC4R** polymorphism in pigs and cattle may reflect a selection pressure on the decrease of fat tissue content in a carcass. Comparative studies on the polymorphism of this gene, which will include breeds predisposed to adiposity (e.g. pigs of Mangalica and Ossabaw breeds), could verify this hypothesis. Since the role of **MC3R** polymorphism in the development of human obesity is not clear, it seems reasonable to extend studies of this gene in domestic animals, mainly in pigs and dogs, which are considered as valuable model organisms for human hereditary diseases. Finally, we showed that knowledge on the polymorphism of the remaining genes of the **MC** family (**MC2R** and **MC5R**) is scarce, even in humans. It seems that **MC5R** is worthy of further study due to its potential role in lipid metabolism and may bring new insight to knowledge on the association with adipose tissue accumulation in mammals. Finally, the application of functional genomic approaches, including epigenetic modification of **MC3R**, **MC4R** and **MC5R** genes in domestic animals, may elucidate their potential role in the phenotypic variability of production traits related to fatness, daily gain of body mass and feed conversion ratio.

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