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ANIMAL GENETICS REVIEW

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

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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

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

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 *MC1R*, 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.

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

Table 3 Identity (%) of the coding sequence (999 nucleotides, above the diagonal) of the *MC4R* gene and the encoded polypeptide (323 amino acids, below the diagonal) in five mammalian 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	

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^D, 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^{D1} (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^{D1} allele (p.99Pro), while in European breeds, the black coating is controlled by the E^{D2} 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.

Table 4 Polymorphic variants of the *MC1R* gene influencing coat colour in domestic animal species

Species	Polymorphism		Function→ phenotype	References
	Nucleotide	Amino acid		
Dog	C916T	Arg306Stop	*E* (wild type)→ g.916CC and g.916CT→ p.306Arg and p.306Arg/ p.306Stop→ brown/black coat *e* → 916 TT → p.360Stop → red/ yellow coat Breeds: Golden Retriever, Yellow Labrador, Irish Setter	Newton et al. (2000) Everts et al. (2000)
	G233T	Gly78Val	E^G→g.233TT and g.233CT → p.78Val or p.78Gly/p.78Val And $a^t a^t$ in *ASIP* gene phenotype → grizzle or domino Breeds: Saluki, Afghan Hound	Dreger and Schmutz (2010)
	A790G	Met264Val	E^M→g.790GG or g.790AG → p.264Val or p.264Val/ p.264Met → black melanistic mask *E* → g.790AA → p.264Met → dogs without black melanistic mask Breeds: Akita, Bullmastiff, Great Dane, German Shepherd, Bouvier, Whippet, English setter, Dachshund, Doberman pinscher, Cocker spaniel, Miniature poodle, Irish setter	Schmutz et al. (2003)
Cattle	T296C	p.Leu99Pro	E^D→g.296CC→ p.99Pro→ dominant black coat colour E^+→g.296TT→ p.99Leu→wild type→ combination of red or reddish brown and reddish black coat colour	Klungland et al. (1995)
	G310/311 delG	p.Tyr155*	*ee*→p.155* (premature stop codon)→red coat colour	Joerg et al. (1996)
Sheep	T218A G361A	p.Met73Lys p.Asp121Asn	Order of dominance:→$E^D > E^+ > e$ E^D→g.218AA and g.361AA→ p.73Lys and p.121Asn→ dominant black phenotype Breeds: Norwegian Dala	Våge et al. (1999)
Horse	C901T	p.Ser83Phe	*EE*→g.901CC→ p.83Ser→ non-chestnut *Ee*→g.901CT→ p.83Ser/ p.83Phe→ non-chestnut *ee*→g.901TT→ p.83Phe→ chestnut	Marklund et al. (1996)
Pig	T296C	p.Leu99Pro	E^+ (wild type)→ g.296TT→ p.99Leu allows full expression of both pheomelanin and eumelanin E^{D1}→g.296C→ p.99Pro→ dominant black Breeds: Asian	Kijas et al. (1998)
	G361A	p.Asp121Asn	E^+ (wild type)→ g.361GG→ p.121Asp E^{D2}→g.361 AA→ p.121Asn→ dominant black Breeds: European	Kijas et al. (1998)
	C491T G727A	p.Ala164Val Ala243Thr	E^+ (wild type)→ g.491C g.727G→ p.164Ala p.243Ala *e* → g.491 T g.727-A→p.164 Val p.243 Thr→red coat colour	Kijas et al. (1998)
	nt67insCC	Codon 23	E^+ (wild type)→ g.67_68CC→ p.23 Ala E^P→black spotting on red or white background	Kijas et al. (2001)
Red Fox	T373C	Gly5Cys	E^A→g.373C→ p.125Arg→ Alaskan silver coating	Våge et al. (1997)
Arctic Fox	G13T T839G	Cys125Arg Phe280Cys	p.5Cys and p.280Cys→ blue coating	Våge et al. (2005)

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), E^G, E^m 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 E^G (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 E^m 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 (E^G) and the third extracellular loop (E^M). 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 E^M alleles also in other breeds: the German Wirehaired Pointer, German Shorthaired Pointer and the Great Dane, while the E^M 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 E^A 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 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.

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 promoter	c.-780C>G	Possible disruption of transcription factor binding site	Fan et al. (2009)
Proximal promoter	c.-746CA (6_7)		Fan et al. (2009)
Proximal promoter	c.-702delC		Fan et al. (2009)
5′UTR	c.-135C>T	Possible disruption of transcription factor binding site	Fan et al. (2009)
Exon 1	c.175C>T (c.706C>T)	Leu59Leu	Ovilo et al. (2006)
Exon 1	c.707G>A	Arg236His	Meidtner et al. (2006)
Exon 1	c.892G>A (c.1426G>A)	Asp298Asn	Kim et al. (2000a)
Putative 3′UTR	c.*430A>T		Fan et al. (2009)

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 had the opposite effects, i.e. higher fat deposition and faster growth, which seems to be a result of greater feed intake (Table 6). Association studies on meat quality traits and fatty acid composition were also performed (Table 6). For example, Ovilo et al. (2006) concluded that animals homozygous for 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 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)
		Puławska 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)
		Puławska 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)
		DIV_2 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)
		Puławska 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)
	↑	DIV_2 line	Chao et al. (2012)
Average feed intake/daily feed intake	↓	Pietrain × Mangalitsa	Meidtner et al. (2006)
		Landrace; Large White; Large White × Duroc; Large White × Meishan	Kim et al. (2000a)
		Large White	Houston et al. (2004)
		Puławska breed	Piórkowska et al. (2010)
Growth rate	↓	Landrace; Large White; Large White x Duroc; Large White × Meishan	Kim et al. (2000a)
Feed conversation ratio	↓	Italian Large White	Davoli et al. (2012)
	↑	Duroc	Davoli et al. (2012)
Tenth rib back fat thickness	↓	Yorkshire	Fan et al. (2010)
		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)
	↑	Puławska breed	Piórkowska et al. (2010)

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	Ovilo et al. (2006)
Colour	Brighter	Pietrain-based crossbreed	Otto et al. (2007)
	Darker	Landrace × Large White × Taihu	Ovilo et al. (2006)
Drip loss	↑	Pietrain-based crossbreed	Otto et al. (2007)
Intramuscular fat	↑	Polish Landrace	Stachowiak et al. (2005)
		Duroc	Davoli et al. (2012)
		Puławska breed, Duroc; Polish Landrace	Piórkowska et al. (2010)
	↓	Polish Large White	Stachowiak et al. (2005)
		Landrace × Large White × Pietrain	Van den Maagdenberg et al. (2007)
Saturated fatty acids content	↓	Landrace × Large White × Taihu	Ovilo et al. (2006)

in the *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 7 Genetic variants of the bovine *MC4R* gene and their association with production traits

Position	Effect on		Breed	References
−293C>G	Body weight	−293C/	Nanyang, Qinchuan, Jiaxian Red, Jinnan	Zhang et al. (2009)
−129A>G (linked SNPs)	Average daily gain	−129A↑		
−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	A ↑	Angus, Holstein	McLean and Schmutz (2011)
Ser330Asn	Grade fat Length of longissimus dorsi area Lean meat	G ↑	Angus, Holstein	McLean and Schmutz (2011)
1069C>G	Back fat thickness	C ↑	Hanwoo cattle	Seong et al. (2012)
Leu 286Val			Simmental, Angus, Hereford, Charolais, Limousine, Qinchuan, Luxi, Jinnan	Huang et al. (2010)
	Marbling Carcass weight Live weight	G↑	Qinchuan cattle	Liu et al. (2010)
1343C>A	Back fat thickness	A↑	Hanwoo cattle	Seong et al. (2012)
1786C>T	Back fat thickness Marbling	C↑ T↑	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 Phe209Leu	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	
	PstI, PvuII	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 Phe209Leu	Type 2 diabetes	Type 2 diabetes	Caucasian (Finland)	Valli-Jaakola et al. (2008)
		Mental disorders	G allele predisposes to schizophrenia and bipolar disorder	Caucasian (USA), African American	Miller et al. (2009)
Pigs	303A>G Ala109Thr	Fatness traits	Average daily gain, feed intake, feed conversation G ↑	Large White × Landrace	Kováčik et al. (2012)
		No association studies performed	–	Landrace, Duroc	Kim et al. (2000b)
		Fat deposition, carcass quality traits	Tenth rib back fat thickness	Berkshire, Duroc, Hampshire, Landrace	Emnett et al. (2001)
		Fat deposition, carcass quality traits	Meat colour and tenderness	Berkshire	Emnett et al. (2001)
		Fat deposition, carcass quality traits	Meat quality index	Hampshire	Emnett et al. (2001)
		Fat deposition, carcass quality traits	Intramuscular fat percentage	Landrace	Emnett et al. (2001)
	841C>T	No association studies performed	–	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; Emnett 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 *MCR* 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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