MOLECULAR GENETICS OF COAT COLOUR IN PIGS

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ABSTRACT

Coat colour in *Sus scrofa* has been the matter of pioneering genetics studies carried out at the beginning of the last century. Since then, classical genetics studies have assumed that several loci affect this trait in pigs. With the advent of molecular genetics it was possible to identify genes and mutations affecting coat colours and patterns in pigs. Variability in several genes have been shown to affect pigmentation in this species. However, only two of them might play major roles in determining coat colour variation in Mediterranean pig breeds or populations: melanocortin 1 receptor (*MC1R*, *Extension* locus) and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*, *Dominant White* locus). Other genes (*ASIP*, *TYRP1*, *EDNRB*, *KITLG* and *OCA2*) might affect coat colour in few breeds/populations or could modify the effect of the two major genes. Polymorphisms in the *MC1R* and *KIT* genes can be also used to authenticate mono-breed products obtained from local pig breeds.

Key words: Coat colour / *MC1R* / *KIT* / Polymorphisms / Pig breeds

1 INTRODUCTION

One of the first phenotypic traits that has been modified during the domestication process in livestock and that differentiate wild ancestors between the domesticated animals is the coat colour. It is assumed that the occurrence of coat colours different from those of the wild animals is the first sign of domestication in an animal species. Subsequent selection processes have largely determined the current within-species variability for this trait. In pigs, domestication and selection have produced a large variety of coat colours and patterns that are characteristics of different breeds and populations (Porter, 1993; Legault, 1998). Coat colour in *Sus scrofa* has been the matter of pioneering genetics studies carried out at the beginning of the last century, just after the re-discovery of the Mendel's laws (Spillman, 1906, 1907). Since then, classical genetics studies have assumed that several loci affect this trait in pigs and comparative analyses among species attempted to establish homolo-gies between these loci across mammals (Searle, 1968). With the advent of molecular genetics it was possible to identify genes and mutations affecting most of the coat colours and patterns in pigs. In this review we will briefly summarize what is currently known in this species, focusing also on practical applications that might be useful to characterize and authenticate pork productions in the Mediterranean area.

2 MOLECULAR AND MORPHOLOGICAL BASIS OF COAT COLOUR IN MAMMALS

To understand which genes and how genes are involved in determining coat colour differences, it is important to give an overview of the biochemical and morphological mechanisms determining pigmentation. Pigmentation in all mammals (including the pig) is due to the presence or absence of melanins in the hair and in the skin. Melanins are pigments that derive from the en-

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zymatic oxidation of the tyrosine amino acid. Two types of melanins are synthesized: eumelanins (black/brown pigments) and pheomelanins (yellow/red pigments). Pigmentation is essentially determined by the distribution of these two pigments producing a black/brown and a yellow/red colour, respectively. Metabolic pathways leading to the synthesis of these two types of melanins are mostly known. The key enzyme of this process is tyrosinase, that catalyses the two first metabolic steps starting from the hydroxylation of tyrosine to dihydroxyphenylalanine (DOPA) and followed by the oxidation of this metabolite into DOPAquinone. Moreover, eumelanins derive from DOPAchrome metabolites, while pheomelanins are produced by 5-S-cysteinylDOPA metabolites (Prota, 1992). Melanins are synthesized and accumulated within melanosomes, which are organelles of the cytoplasm of specialized cells, the melanocytes, lying between derm and epiderm. Melanosomes are transferred into the hair during their growing up, by means of an exocytosis process. During embryo development, melanocytes, starting from the neural crest, migrate in the different parts of the body, conferring pigmentation on the areas where they are present. In the areas where melanocytes are missing, white spots appear giving the characteristic spotting or white patterns of some breeds. Moreover, in some parts of the body pigmentation can be modified depending on a more or less reduced melanocytes activity.

3 MAIN LOCI AFFECTING COAT COLOUR VARIABILITY IN PIGS

From this short presentation it is possible to predict that a large number of genes may affect coat colour in mammals. For example, in mice more than 300 loci have been shown to affect pigmentation. Variability in several genes have been shown to affect pigmentation also in pigs (Table 1). However, only two of them might play major roles in determining coat colour variation in Mediterranean pig breeds or populations: melanocortin 1 receptor (*MC1R*, *Extension* locus) and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*, *Dominant White* locus). Other genes (*ASIP*, *TYRP1*, *EDNRB*, *KITLG* and *OCA2*) might affect coat colour in few

Table 1: Genes affecting or associated with different coat colours in pigs

Gene name	Gene symbol	Locus	SSC[1]	No. of alleles[2]	Molecular events[3]	Breeds/ populations[4]	References
Melanocortin 1 receptor	*MC1R*	*Extension*	6	>10	Missense mutations; 2-bp insertion	Many	Kijas *et al.* (1998; 2001); Fang *et al.* (2009)
v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	*KIT*	*Dominant White*	8	Many	Copy number variation; splice mutation; unknown	Many	Johansson Moller *et al.* (1996); Marklund *et al.* (1998); Giuffra *et al.* (1999); Pielberg *et al.* (2001); Fontanesi *et al.* (2010); Rubin *et al.* (2012)
Agouti signaling protein	*ASIP*	*Agouti*	17	2 (?)	Unknown	Mangalitza	Drögemüller *et al.* (2006)
Tyrosinase related protein 1	*TYRP1*	*Brown*	1	2 (?)	6-bp deletion	Tibetan, Kele, Dahe	Ren *et al.* (2011)
Endothelin receptor beta	*EDNRB*	*Spotting*	11	4 (?)	Missense mutations; unknown	Jinhua, Gloucestershire Old Spot, Xiang; Chinese belted pigs	Okumura *et al.* (2006; 2010); Ai *et al.* (2013); Wilkinson *et al.* (2013)
KIT ligand	*KITLG*	-	5	2 (?)	Missense mutations; unknown	Berkshire, Jiangquhai	Okumura *et al.* (2008; 2010); Wilkinson *et al.* (2013)
Oculocutaneous albinism II	*OCA2*	*Pink eyed dilution*	15	2 (?)	Missense mutations; unknown	Duroc	Fernández *et al.* (2006)

[1] *Sus scrofa* chromosome. [2] No. of alleles with effect or putative effect on coat colour (including wild type). Question marks indicate that other alleles might be present whose effect should be clarified. [3] Molecular events that create different alleles with effect or putative effect on coat colour. [4] Breeds or populations in which mutated alleles have been described.

breeds/populations or could modify the effect of the two major genes (Table 1).

3.1 *MC1R* VARIABILITY

The *Extension* locus was initially characterized at molecular level in mice. This locus encodes for the melanocortin 1 receptor (*MC1R*), also known as melanocyte stimulating hormone receptor (Robbins *et al.*, 1993), which is a transmembrane proteine of the G-protein-coupled receptors family. Mutations in this gene affect pigmentation in a large number of vertebrates, including the pig (Kijas *et al.* 1998; 2001).

The *MC1R* gene is probably the better characterized coat colour gene in *Sus scrofa*. It is constituted by a single coding exon of about 950 bp that has been sequenced in a large number of pig breeds with different coat colours (Kijas *et al.* 1998; 2001; Fang *et al.*, 2009). Five allelic groups have been reported so far: wild type alleles (E^+); dominant black alleles (E^{D1} and E^{D2}); the black spotted alleles (E^P); the recessive red e allele. The wild type E^+ alleles have been identified in wild boar populations. The only European breed that carries the E^+ allele is Mangalitza. Sequence data showed that the Dominant black *Extension* allele (E^D) identified by classical genetics studies is constituted by two different *MC1R* gene sequences identified as E^{D1} and E^{D2} (actually three different sequences that differ from few synonymous mutations are considered for the E^{D1} allele; Fang *et al.*, 2009). The former sequence may be of Asian origin whereas the latter sequence may be of European origin. These two groups of E^D sequences are distinguished from all other alleles by a few missense mutations that might activate the *MC1R* function, resulting in eumelanin production. The black spotted alleles E^P were probably originated from the E^{D2} allele and produce black spotted phenotypes on a white or red background. These alleles are characterized by a 2-bp insertion in the coding sequence that somatically reverts into a normal and functional gene that produces an E^{D2} classical phenotype in coloured spotted regions (Kijas *et al.*, 2001). The recessive red allele (e), derived by two other missense mutations, has been observed in the Duroc. These mutations or just one of them might compromise substantially the function of the *MC1R* transmembrane protein, leading to the production of pheomelanic pigments and red coat colour in animals homozygous for the e allele. The *MC1R* gene has been characterized by sequencing or genotyping pigs from a few local Mediterranean breeds, like the Italian Cinta Senese and Nero Siciliano breeds (Russo *et al.*, 2004; Fontanesi *et al.*, 2010), Alentejano and Bisaro from Portugal and Negro Canario from Spain (Ramos *et al.*, 2003; Fang *et al.*, 2009). Many other auto-

chthonous breeds remain to be characterized at this locus even if it could be possible to infer their genotype at the *Extension* locus based on previous results obtained for other European breeds.

3.2. *KIT* VARIABILITY

The *KIT* gene encodes the mast/stem cell growth factor receptor. This is a large protein with an extracellular domain consisting of 5 Ig-like domains, a transmembrane region, and a tyrosine kinase domain (Ray *et al.* 2008). *KIT* plays key roles in melanogenesis, erythropoiesis, spermatogenesis and T cell differentiation (Besmer *et al.* 1993; Yoshida *et al.* 2001). Its functional role in melanogenesis derives from its involvement in driving the melanocyte migration from the neural crest along the dorsolateral pathway to colonize the final destination in the skin (Besmer *et al.* 1993).

Extended variability at the *KIT* gene is responsible for the allelic series of the *Dominant White* (I) locus (Table 2; Johansson Moller *et al.*, 1996; Marklund *et al.*, 1998); Giuffra *et al.*, 1999; Pielberg *et al.*, 2001; Fontanesi *et al.*, 2010; Rubin *et al.*, 2012). The recessive wild type allele "*i*" is constituted by a normal single copy *KIT* gene that is associated with a solid or wild type coat colour. The Dominant White coat colour of several important commercial breeds, like Large White and Landrace, is determined by the duplication of the *KIT* gene (copy number variation) and by the presence of a splice mutation in intron 17 in one of the duplicated copies, that causes the skipping of exon 17 (allele I^1). The duplicated region is of about 450-kb. To complicate the allelic series at this locus, the number of *KIT* gene copies could be more than two but in all cases at least one copy should carry the splice mutation on intron 17. These Dominant white alleles are indicated with I^2, I^3, etc., with different numbers of detected copies. In the I^2 and I^3 alleles, the splice mutation is in one or two copies of the three-copies gene forms, respectively (Pielberg *et al.* 2002). There are other evidences that support the presence of alleles with a larger number of copies and combinations with the splice mutation (Johansson *et al.* 2005; our unpublished data). The presence of another Dominant white allele, I^L, has been hypothesised. This allele should carry a single copy of a mutated *KIT* gene (with splice mutation) that should be lethal if homozygous (Pielberg *et al.* 2002; Johansson *et al.* 2005). Two normal *KIT* copies are present in the I^P allele that causes the presence of pigmented regions (patches) in white pigs. The I^{Be} allele, a single copy *KIT* gene with a regulatory mutation, determines the belted phenotype of the Hampshire and Cinta Sense pigs (Giuffra *et al.*, 1999; Fontanesi *et al.*, 2010). Other two dupli-

Table 2: KIT alleles and their effects

Allele symbol	Allele name	No. of KIT copies	No. of splice mutations	Intron 18 deletion	Effect	Breeds/ Populations
i	Wild type	1	0	No	Wild type (solid coat colour)	Many- mainly local breeds
I^1	Dominant white	2	1	Yes	White	Large White, Landrace, Belgian Landrace
I^2	Dominant white	3	1	Yes	White	Large White, Landrace, Belgian Landrace
I^3	Dominant white	3	2	Yes	White	Large White, Landrace, Belgian Landrace
I^P	Patch	2	0	Yes	Black spots on white background	Pietrain (Large White, Landrace, Belgian Landrace)
I^L	Lethal	1	1	?	?	?
I^{Be}	Belt	1	0	No	white belt at level of shoulders and forelegs	Hampshire, Cinta Senese
I^{Rn}/I^d	Roan/Dilute	1	0	Yes	Grey – white and coloured hairs intermingled	Local populations (Large White, Landrace, Belgian Landrace)

cated regions (4.3-kb duplication located about 100-kb upstream of the *KIT* gene; and 23-kb duplication located about 100-kb downstream the gene, which in turn contains another duplication of 4.3-kb) have been identified in Hampshire and might be involved in determining the belted phenotype in this breed (Rubin *et al.*, 2012). Another allele with a single copy of the *KIT* gene without the splice mutation and, possibly, determining a spotted phenotype, has been hypothesized to segregate in white pig populations (Johansson *et al.* 2005). This allele has been named I^{Be^*}, suggesting that might be similar to the I^{Be} allele or it is the same allele but in a different genetic background. Earlier classical genetics studies on coat color segregation between and within populations suggested the presence of an additional allele (I^d also indicated as I^{Rn}), giving a gray-roan phenotype and dominant over the *i* allele (Hetzer 1948; Lauvergne and Canope 1979). Markers in the *KIT* gene (including an indel in intron 18: *intron18-g.29_32delAGTT*) were used to demonstrate that the I^d allele is determined by a single *KIT* copy gene with another putative regulatory mutation in a grey-roan Sicilian pig population (Fontanesi *et al.*, 2010).

3.3   OTHER GENES

Polymorphisms in other genes have been associated with coat colour in different pig populations. However, their effects seems restricted to few breeds. In addition, in most cases the causative mutations have not been identi-fied or demonstrated yet. In particular, Drögemüller *et al.* (2006) have demonstrated that the a^t allele at the *Agouti* locus is associated with the markers in the agouti signalling protein (*ASIP*) gene in the Mangalitza breed. However, the causative mutation, supposed to be a regulatory mutation, has not been identified yet. A 6-bp deletion in the tyrosinase related protein 1 (*TYRP1*) gene is responsible for the Brown coat colour locus in Chinese pig populations (Ren *et al.*, 2011). Variability in the endothelin receptor beta (*EDNRB*) gene has been shown to be associated with spotted or belted phenotypes in a European pig breed (Gloucestershire Old Spot) and in several Chinese breeds (Bamaxiang, Dongshan, Ganxi, Jinhua, Rongchang, Shaziling and Tongcheng) (Okumura *et al.*, 2006, 2010; Ai *et al.*, 2013; Wilkinson *et al.*, 2013). Polymorphisms in the *KIT* ligand (*KITLG*) gene might be involved in determining the typical coat colour pattern of the Berkshire breed similar to what is also present in the Jiangquhai breed (Okumura *et al.*, 2008, 2010; Wilkinson *et al.*, 2013). Fernandez *et al.* (2006) investigated the oculocutaneous albinism II (*OCA2*) gene in Iberian Duroc pigs and identified polymorphisms that could explain variability in colour intensity in animals of this breed. This gene is the product of the Pink-eyed dilution coat colour locus. A quite large number of other coat colour genes selected according to their role in affecting pigmentation in mice, have been studied in pigs (Okumura *et al.*, 2010). However, variability in these genes might not be involved in determining variability of coat colour phenotypes in different pig breeds. Additional studies

might be needed to evaluate their role as modifier or the major coat colour loci.

4   USE OF POLYMORPHISMS IN COAT COLOUR GENES FOR PORK AUTHENTICATION

Due to the recent increase of the market of local and typical products, a large number of local breeds have been rediscovered by farmers who have established consortia with the aim to protect, valorise and characterise the products obtained from local populations. As the meat obtained from these pigs are usually sold at a higher price than that of commercial pigs, there is the need to guarantee pig farmers as well the consumers about the authenticity of the meat through the production chain by means of traceability and authenticity systems (D'Alessandro *et al.*, 2007). To verify the information reported on the product labels, DNA systems based on the analysis of coat colour genes have been applied. The systems use polymorphisms in the *MC1R* and *KIT* genes as several mutations are fixed in breeds/populations with different coat colours. However, coat colour cannot be observed on meat products and these markers can indirectly identify the colour of the animals, and in turn identify or exclude the breed of origin of the pork products. Usually, local pig breeds are coloured and should be homozygous for the *i* allele at the *Dominat white* locus. The duplication breakpoint test (Giuffra *et al.*, 2002) can identify if meat comes from pigs that carry alleles with duplicated *KIT* genes. This test can be easily applied to exclude that the meat has been produced with white pigs instead of coloured (local) pigs. The use of polymorphisms in the *MC1R* gene can establish if meat comes from Duroc or Wild Boars to complement results obtained with analyses of the *KIT* gene.

5   CONCLUSIONS

Variability in several genes contributes to explain difference of coat colours and patterns between and within pig breeds and populations. Two major genes (*MC1R* and *KIT*) with many alleles are the most important determinant of this phenotypic trait in pigs. Characterization of variability in coat colour genes may contribute to evaluate biodiversity in local pig populations. Analysis of polymorphisms in these two genes can be also used for breed authentication of pork products. Several other genes have been shown to affect coat colour in a few breeds. However, other studies should be carried to understand their role in affecting coat colour in this species.

6   ACKNOWLEDGMENTS

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