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Advances in the Research of AMPK and its Subunit Genes

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Abstract: AMP-activated kinase (AMPK) is a heterotrimeric complex composed of three subunits and is the core energy sensor of the cell. The AMPK activity is important for survival during periods of stress and starvation and also has implications in type II diabetes, obesity, metabolic syndrome, longevity and cancer, etc. The activation of AMPK is triggered through binding of Adenosine Monophosphate Activated Proteins (AMP) to the Bateman domains of the gamma subunit, leading to increased phosphorylation of the threonine 172 on the alpha subunit by inducing allosteric activation and inhibiting dephosphorylation. AMPK and its subunits have been the focuses of many researchers dealing with genetic and metabolic issues. The study makes a comprehensive review on the structure, function, distribution, enzyme activity, the genetic mutation and other aspects of AMPK and its subunit genes, with the aim to outline main aspects of present researches on AMPK and its subunits in animal genetics.

Key words: AMP-activated protein kinase, subunit, energy metabolism, genetic mutation

INTRODUCTION

It has been over forty years since when first identified and reported the kinase HMG2CoA (Hardie *et al*., 1998; Ferrer *et al*., 1985). The following researchers found that this kinase could be easily activated by AMP and called it AMP-activated protein kinase (AMPK) (Natsuume-Sakai *et al*., 1978; Kemp *et al*., 1999). However, AMPK is mainly activated by an elevation of intracellular 5'-AMP with arsenite and heat shock in stress responses (Corton *et al*., 1994). It is now regarded as a key energy sensor or switch in cellular metabolism regulation responding to stress signaling (Allard *et al*., 2007). Reports on HMG-CoA reductase regulation also reinforced the concept of AMPK functioning in metabolic stress responses (Sato *et al*., 1993). When it is activated, the AMPK complex will switch on ATP-generating pathways and switch off ATP-consuming pathways. This allows the cellular energy balance to be restored (Hardie *et al*., 2003).

AMPK belongs to the family of serine-threonine protein kinases and self-forms a heterotrimeric complex. Usually, it consists of a catalytic subunit (alpha) and two non-catalytic subunits (beta and gamma) (Mitchelhill *et al*., 1994; Carling *et al*., 1994; Stapleton *et al*., 1994). Co-expression of the non-catalytic beta and gamma subunits is demanded for the optimal activity of the alpha subunit (Dyck *et al*., 1996). AMPK phosphorylates a number of enzymes involved in the lipid metabolism control, such as HMG-CoA reductases, acetyl-CoA carboxylases and hormone sensitive lipases (Hardie, 1992). In mammals, two or three isoforms of each AMPK subunit are often encoded by distinct genes and may be combined at least 12 different heterotrimers whose expression patterns differ among various tissues (Sanders *et al*., 2007; Stapleton *et al*., 1996, 1997; Thornton *et al*., 1998). AMPK is certainly one of the well-known sensors perceiving changes in cellular energy metabolism (Lizcano *et al*., 2004). In response to metabolic stress depleting ATP, AMPK rapidly switches on catabolic processes and switches off ATP-consuming metabolic pathways to provide some ATP (Lage *et al*., 2008; Carling, 2004). It maintains the dynamic metabolism equilibriums between the cellular energy supply and demand by affecting the metabolic links. It is well-known that AMPK is activated by an increase in the cellular AMP: ATP ratio after ATP depletion and the classic function of AMPK is to maintain energy homeostasis in modulating metabolic pathways (Sanders *et al*., 2007). However, recent studies have revealed an expanded role for the kinase AMPK in regulating cell growth and proliferation, cell membrane polarity and mitochondrial biogenesis, etc. (Steinberg and Kemp, 2009). AMPK also plays a critical role in cellular

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responses to diverse physiologic and pathologic stresses like diabetes and obesity. It emerges to be a potential therapeutic target for treatment of diabetes, cancer and cardiovascular disease. For instance, Adipocyte AMPK could be targeted to modulate obesity-related adipokine production associated with clinical insulin resistance and breast cancer cell proliferation (Joseph *et al*., 2011). The pharmacological activation of AMPK by metformin has proven to be a beneficial therapeutic approach for the treatment of type II diabetes and atherosclerosis. Therefore, AMPK and its subunits have been the focuses of researchers dealing with genetic and metabolic issues. The present work makes a comprehensive review on the research advances and application aspects of AMPK and its subunit genes in animal genetics.

Structure and function of AMPK subunits: AMPK belongs to the serine-threonine kinase superfamily existing extensively in eukaryotic cells. The AMPK complex was a kind of hetero-triplicate protein composed of three subunits, namely alpha, beta and gamma. Among these subunits, alpha functions as the catalytic subunit, beta and gamma serves as the regulatory subunits. Moreover, many sub-types of subunits were found to be encoded by distinct genes, such as alpha 1 and alpha 2, beta 1 and beta 2, gamma 1, gamma 2 and gamma 3.

In the enzyme composition, alpha subunit is the kinase catalytic site responsible for the ATP phosphoric acid base group to be passed to target proteins. It contains two main functional ends or areas (i.e. N and C) and alpha subunit might combine with the beta and/or gamma subunits at the C terminal region. The N end is the core catalytic part of alpha subunit, while the C end is the allosteric part responsible for the combination and activity regulation of AMP (Hudson *et al*., 2003). The N end of beta subunit was followed by two conservative domains, i.e. KIS and ASC and the KIS domain was a functional glycogen-binding domain (Hudson *et al*., 2003), but the ASC domain was incapable to form stable and active complex tripolymers (Polekhina *et al*., 2003). In the gamma subunit, there are four serial duplicate cystathionine b-synthase (CBS) domains responsible for the protein connection of AMPK with AMP, while the beta subunit acts as a scaffold and brackets the alpha, gamma subunits with its anchoring domains of KIS and ASC, respectively (Winder and Thomson, 2007). AMPK would be activated via phosphorylatio when the AMPKK (AMP-activated protein kinase kinase) was revitalized. The detailed binding site is the first 172 threonine in the AMPK alpha subunit. Reports showed that the alpha 1 subunit was located in the cytoplast and the alpha 2 subunit was positioned in the karyon (Dyck *et al*., 1996). These results suggested that the AMPK alpha 2 complex might regulate nuclear gene expression with phosphorylated nuclear transcription factors.

In mammalian cells, the catalytic alpha subunit of AMPK has no activity because of its self-inhibition region, e.g. the 313-392 amino acid residues in alpha 1 subunit, but the subunit inhibitory mechanism is not reported and clearly defined. By means of molecular biology technology, such as gene deletion or missing, site-directed mutation, structural simulation and RNAi experiments, it was found that a conservative residual fragment of the 313–335 residues in the alpha helix was crucial to keep the self-inhibition activity of alpha 1 subunit (Chen *et al*., 2009). It was further pointed out that the inner Leu-328 and the outer Val-298 residues of the self-restraint activity region could stabilize the self-inhibition active conformation through hydrophobic interactions in human and animal carcinoma cells (Jin *et al*., 2007; Chen *et al*., 2009).

AMPK heterotrimeric complex: AMPK is present in all tissues as a heterotrimeric complex consisting of a catalytic alpha subunit and the regulatory beta and gamma subunits (Xiao *et al*., 2007; Witczak *et al*., 2008). Both beta and gamma subunits are required for the optimal activity of alpha-catalytic subunit (Chen *et al*., 1999). Multiple genes exist for each of the subunits (alpha1, alpha2, beta1, beta2, gamma1, gamma2, gamma3), enabling the expression of less than 12 heterotrimer combinations which are expressed in tissue-specific manners (Mahlapuu *et al*., 2004). In addition, alternative splice variants exist for alpha1 and gamma2 which further increases the potential diversity of the AMPK heterotrimers. In human skeletal muscle, the majority of AMPK complexes contain both alpha2 and beta2 subunits. Among these alpha2/beta2 complexes, 20% associate with gamma3 and the remaining alpha1/beta2 and alpha2/beta2 associate with gamma1 (Wojtaszewski *et al*., 2005). In mice skeletal muscle, gamma3- and gamma2 AMPK is mainly expressed in the fast-twitch glycolytic Extensor Digitroum Longus (EDL) muscle compared to the slow-twitch oxidative soleus muscle (Barnes *et al*., 2004; Mahlapuu *et al*., 2004), whereas in gastrocnemius muscle, gamma1, gamma2 and gamma3 are evenly expressed (Barnes *et al*., 2004; Mahlapuu *et al*., 2004).

Tissue-specific expression of AMPK subunit genes: The distribution of AMPK subunits varies and their expressions were reported tissue-specific. There are two kinds of alpha and beta subunit isomers in skeletal muscle tissues, namely alpha 1 and alpha 2 and beta 1 and beta 2,

but the gamma subunits differentiate into three isomers. Alpha 1 subunit highly exists in kidneys, liver, lungs, heart and brain, while alpha 2 subunit dominates ~80% of all the AMPK trimers and is more likely distributed in skeletal muscle tissues, heart and liver. Beta 1 subunit shows high expression and mainly lied in the liver, while Beta 2 subunit is primarily found in the skeletal muscle. Gamma 1 and gamma 2 subunits are also widely distributed, while gamma 3 subunit appears specifically in skeletal muscle tissues. Among mouse, rat, cattle, goat and human tissues, the gamma subunits of AMPK showed a sequence homology and/or genetic conservative property measured with cDNA and amino acid fragment (Stapleton *et al*., 1997). In fact, there were more than 12 different combinations of AMPK subunits and different cellular types of the AMPK compound were found. It is more likely to be involved the selection of downstream target proteins.

In mammals, the AMPK heterotrimers developed into a protein complex and mainly expressed in a tissue-specific manner. At present, although the literatures provided the primary information on the distribution and structure and biochemical characteristics of various heterotrimers, the functional and biological significances of this diversity were not clear. Moreover, there are few studies investigating the heterotrimer distributions of AMPK complexity in human and animal skeletal muscle tissues (Treebak *et al*., 2009; Birk and Wojtaszewski, 2006; Wojtaszewski *et al*., 2005). However, together with mutation and knock-out models, these data gave us some important research clues to the diverse biological functions of AMPK complexity in different types of cells and tissues. Among the subunit isomers, the gamma 3 isoform is of particular interest because it's very selectively expressed in white skeletal muscle tissues (Mahlapuu *et al*., 2004; Barnes *et al*., 2004; Yu *et al*., 2004). Furthermore, the gamma 3 isoform makes up the only human heterotrimer being activated with high intensity exercise (Birk and Wojtaszewski, 2006; Treebak *et al*., 2007) and the expression level of gamma3 protein differs with training status, age and sex (Frosig *et al*., 2004; Mortensen *et al*., 2009; Wojtaszewski *et al*., 2005). Besides the tissue specific expression manner, the gamma 3 isoform is also selectively distributed in complex partners who was only found being presented in complex with alpha2 and beta2 in white mouse muscle Extensor Digitorum Longus (EDL) and at very low levels in the red soleus muscle (Treebak *et al*., 2009). Although all the seven subunits are widely expressed in human and animal skeletal muscle, coimmuno-precipitation analyses reveal that only three complexes seem to exist in human vastus lateralis muscle tissues, i.e. alpha2-beta2-gamma1 (65%), alpha1-beta2-gamma1 (15%) and alpha2-beta2-gamma3 (20%) (Birk and Wojtaszewski, 2006; Wojtaszewski *et al*., 2005). This distribution of AMPK complexes is very similar to expression manner in the mouse EDL muscle tissues (Treebak *et al*., 2009).

Regulation of AMPK activity: AMPK is got activated by alterations of the AMP: ATP ratios in response to energetic stress and requires the phosphorylation of site Thr172 in the catalytic subunit's activation loop (Hardie *et al*., 1999). Once activated, AMPK will induce ATP-generating catabolic pathways including glucose metabolism and fatty acid oxidation and at the same time inhibit ATP consuming anabolic pathways including cholesterol, fatty acid and triacylglycerol synthesis (Hardie *et al*., 1999, 2003; Hardie., 2007). The AMPK complex activity is regulated by nutrients (mainly glucose and amino acids) (Leclerc and Rutter, 2004; Bungo *et al*., 2011), hormones, calcium and metformin (Doustar *et al*., 2012) and cellular stress etc. AMPK coordinates these signals via phosphorylation of numerous targets involved in glucose uptake and its subsequent utilization by tissues, ATP-generating and consumption, such as fatty acid oxidation and protein synthesis (Xue and Kahn, 2006).

Presently, three upstream kinases have been identified as activators of AMPK, i.e. the tumor suppressor LKB1, calcium/calmodulin-dependent protein kinase (CaMKK) and TGF-beta-activated kinase-1 (TAK1) (Hong *et al*., 2003, 2005; Momcilovic *et al*., 2006). Generally speaking, the AMPK complex activity is regulated at the level of allosteric activation by adenine nucleotides and of direct phosphorylation by upstream activating kinases, including LKB1, CAMKK2 and TAK1, etc. (Lizcano *et al*., 2004; Hawley *et al*., 2003; Woods *et al*., 2003). Reversible phosphorylation at site Thr172 within the activation loop of alpha subunit is the mainly activator of AMPK (Oliveira *et al*., 2012). Besides phosphorylation, AMPK can also be directly activated by AMP and ADP that bind to the gamma subunit, which is important for maintaining AMPK activity (Sanders *et al*., 2007; Oakhill *et al*., 2011; Xiao *et al*., 2011). The binding of AMP and ADP to the gamma subunit was thought to induce a conformational change in the kinase domain which protects the AMPK Thr172 site from dephosphorylation by protein phosphatase 2 A and C (PP2A and C) (Sanders *et al*., 2007; Oakhill *et al*., 2011). The other two upstream kinases, LKB1 and Ca2+/CaM-dependent protein kinase kinase (CaMKK), have been shown to phosphorylate AMPK Thr172 site in mammalian cells too (Hawley *et al*., 2003; Woods *et al*., 2003).

LKB1 is also a heterotrimer complex with regulatory proteins STRAD and MO25. The LKB1 tumor suppressor kinase is an activator of AMPK. Recent studies reported that LKB1 and AMPK controlled the cellular polarity and inhibited the breast carcinogenesis from invertebrates to mammals (Nagalingam *et al*., 2012). Taken from literatures, LKB1 and AMPK are regarded as two key components of an epithelial polarity pathway, i.e. the LKB1-AMPK pathway. This molecular complex link between polarity and metabolism may constitute an ancient stress-response protective mechanism that was co-opted for tumor suppression. Unfortunately, there are presently only few reports.

AMPK and obesity inducing and fatty acid uptaking: AMPK was reported activated in response to metabolic stresses such as muscle contraction or hypoxia and modulated by hormones and cytokines that affect whole-body energy balance, such as leptin, adiponectin, resistin and ghrelin (Hardie, 2003; Hardie *et al*., 2003). Tissue or cellular high ATP content, a reflection of high cellular energy status, will antagonize the binding of AMP to the gamma subunit and this allows the AMPK modulating system to act as a sensor of cellular energy status (Hardie, 2008). Therefore, AMPK was first discovered as a sensor of cellular energy status in eukaryotic cells. AMPK, this fuel-sensing enzyme, is often activated by phosphorylation when a cellular stress increases the AMP: ATP ratio due to increased ATP depletion (muscle contraction) or limited generation of ATP (e.g. hypoxia). Consequently, AMP production (e.g. exercise). Activation of AMPK usually leads to the concomitant inhibition of energy-consuming biosynthetic pathways not required for survival and to the activation of metabolic pathways regenerating ATP (Richter and Ruderman, 2009).

The role of AMPK in mediating energy metabolism is mainly controlled by two upstream kinases, i.e. LKB1 and/or CaMKK kinase b (CaMKKb) in response to baicalin (Ma *et al*., 2012). Now, there are some new evidences for the role of AMPK in fatty acid assimilating or steroid hormone biosynthesis in starvation conditions. Generally speaking, starvation induces stress and the following energy deprivation to maintain proper cell functions. Hirsch *et al*. (2012) showed that starvation growth conditions shift steroidogenesis of human adrenal NCI-H295R cells towards the androgen production attributable to decreased HSD3B2 expression and activity and increased CYP17A1 phosphorylation and 17,20-lyase activity. They concluded that starvation-mediated increase of androgen production in NCI-H295 cells seem not to be mediated by AMPK signaling. However, the AMPK activation could enhance androgen production through a specific increase in CYP17A1-17,20 lyase activity (Hirsch *et al*., (2012). So far, many increased rates of long-Chain Fatty Acid (LCFA) uptaking have been observed in skeletal muscle tissues of obese individuals (Bonen *et al*., 2004; Yavari, 2008), as well as obese (Shamsadin *et al*., 2001; Coort *et al*., 2004; Han *et al*., 2007; Holloway *et al*., 2009) and diabetic in Zucker rats (Smith *et al*., 2007; Bonen *et al*., 2009). This provides a plausible mechanism accounting for the intramuscular lipotoxic environment implicated in peripheral muscle and insulin resistance in addition to elevated levels of circulating plasma free fatty acids (Boden, 2003). Fortunately, three types of transport proteins have been identified now, i.e. a protein of 40 kDa peripheral FABPPM located on the outer leaflet of the plasma membrane (Stremmel *et al*., 1985; Schwieterman *et al*., 1988; Isola *et al*., 1995), fatty acid transport proteins of 63 kDa (FATP1-6) with at least six trans-membrane domains (Schaffer and Lodish, 1994; Hirsch *et al*., 1998; Gimeno *et al*., 2003) and a highly glycosolated protein of 88 kDa (FAT/CD36) with at least two transmembrane domains (Abumrad *et al*., 1993). Though research has shown a role for FATP1 and four in LCFA transport (Kim *et al*., 2004; DiRusso *et al*., 2005), less is known about the regulation of the FATP protein family in response to physiological stimuli, obesity and insulin resistance, etc. Therefore, AMPK may be important for regulation of fatty acid uptake in response to pharmacological agents, the AMPK independent pathways are required for regulating this process during exercise.

AMPK gene mutations in animal genetics researches: AMPK (AMP-activated Kinase) is activated by changes in the intracellular AMP: ATP ratio when ATP consumption is stimulated by contractile activity and AICAR and metformin compounds that increase glucose transport in mammalian muscle cells. AMPK is invariably regarded as the master metabolic switch and mediates the observed increase of glucose uptake in mammal locomotory muscle during exercising. Therefore, researchers have widely investigated the possible role of AMPK in the regulation of glucose metabolism and its association with meat quality in skeletal muscle tissues of some vertebrates, including human, goat, cattle, mouse, rat, chicken and fish (Irrcher *et al*., 2008; Beck Jorgensen *et al*., 20009; Magnoni *et al*., 2012; Wilson *et al*., 2012).

The genetic mutations and effects of AMPK and its subunits have been the research focuses of disease resistant and meat quality regulation in domestic animal genetics too. Different from ordinary candidate genes of reproducing characters, such as the pituitary specific

transcription factor POU1F1 (Jiang *et al*., 2004), prolactin and prolactin receptor genes (Jiang *et al*., 2005, 2009; Jiang and Geng, 2011), parathyroid hormone genes (Jiang *et al*., 2010) and the β2-Adrenergic Receptor (Han *et al*., 2011) and Alkaline Phosphatase loci (Orunmuyi *et al*., 2007), at present, there was little gene polymorphism found of AMPK subunit genes in domestic animals and fowls due to the complicated cases of energy balance and its molecular linking network (Arain *et al*., 2010a, b; Jafarnejad and Sadegh, 2011; Afolayan *et al*., 2012). However, the AMP-activated protein kinase gamma subunit was frequently referred.

Meat quality traits are always the hotspots to researchers in domestic animal genetics (Malkawi and Gharaibeh, 2004; Das *et al*., 2007; Ganabadi *et al*., 2009; Arain *et al*., 2010a, b; Wongsuthavas *et al*., 2011; Jafarnejad and Sadegh, 2011; Joseph *et al*., 2011; Olajide 2012; Hossain *et al*., 2012). Since Lief andesson and his coworkers identified and characterized the AMPK gamma 3 mutations associated with excess glycogen content in pig skeletal muscle (Milan *et al*., 2000; Andersson, 2003), it has been a hotspot topic to find out gene mutations of AMPK subunits and its association with meat quality in domestic animals (Andersson, 2001, 2009; Andersson and Georges, 2004). There were many interesting reports in pig (Ciobanu *et al*., 2001; Roux *et al*., 2006), chicken (Zhao *et al*., 2006; Bungo *et al*., 2011), cattle (Granlund *et al*., 2011) and goats (Jin *et al*., 2012) and other animals. Our group has also been on the way of researching the gene mutational effects on meat quality in domestic animals and fowls. For instance, Zhao *et al*. (2006) surveyed and reported the relevance of single-nucleotide polymorphisms in the 5' end and exons of the PRKAG3 (AMPK gamma 3) gene loci in two commercial and three Chinese indigenous chicken breeds. In this study, two single-nucleotide polymorphisms (SNPs) in the 5'-end of PRKAG3 gene and 10 SNPs in exons 3, 4, 9 and 11 in the PRKAG3 gene were identified among the five chicken breeds and the result showed a significant association between the mutations of PRKAG3 and chicken meat quality. Jin *et al*. (2012) made an analysis of PRKAG3 gene variation and its association with carcass quality of goat breeds. They investigated the polymorphism of goat PRKAG3 gene and its distribution patterns in different goat breeds. They found that two mutation loci in the 5' regulatory region, C-525A and C-225T, located at -525 and -225 bp upstream of the start codon of the PRKAG3 gene and two mutation loci in the exon 13, T90C and C102T, located at 90 bp and 102 bp of the exon 13. They concluded with statistics that the lipoidosis ability of goat breeds may be associated with C-525A and C-225T loci of PRKAG3 gene. Chen *et al*. (2012) analyzed the polymorphisms of Goat THRSP gene in Chinese indigenous goat breeds to identify polymorphism loci of goat THRSP gene associated with the goat lipogenesis ability and ecological factors. Recently, we designed primers for the PCR reactions of AMPK subunit gamma isoform genes, PRKAG1, PRKAG2 and PRKAG3, among different chicken lines, followed with single-nucleotide polymorphism analysis. There are many point mutations identified, including one insert and three mis-sense mutations. With correlation analysis, we found these mutations were significant relevant to the carcass quality traits among chicken lines (unpublished data). Moreover, Li (2007) showed many meaningful results from studies on genetic polymorphisms in mice and Japanese rabbits and gene differentially expressing experiments in corresponding skeletal muscle and fat tissues. For instance, there was a 1944 site G→A mutation in mice AMPK alpha 2 (PRKAA2) gene loci, but the mutation was synonymous so that no effect on the increase or loss of fat and muscle and body weight detected (Li, 2007). However, there was a non-synonymous mutation between the Japan's great ear and the wild populations. It was an inserting mutation at the 8731 site in the ninth exon of AMPK alpha 2 (PRKAA2) gene loci, which was significant related with the changes of rabbit fat and muscle and weight. Another mutation of PRKAG 2 gene loci is at the 3429 site inserted with A resulting a terminating codon and the protein sequence composed of 1143 amino acid residues, but it was statistically uncorrelated with fat and muscle and body weight loss (Li, 2007). Moreover, there was a point mutation (A→ G) at the 1754 site in the fourth exon of AMPK alpha 1 (PRKAA1) gene loci between the Japan's great ear rabbit and the wild groups, resulting a shorten protein encoded with a Lys → Arg change at sequence site 585 (Li, 2007). This mutation resulted many carcass performances differences of intramuscular fat content, live weight and eviscerated yield. In addition, there was an inserting mutation at the 1531 site with C in the AMPK gamma 1 (PPKAG 1) gene loci between the Japan's great ear rabbit and the wild groups and no difference of similar growth and carcass performances was reported or found among the homozygous mutations or genotypes (Li, 2007). Up to day, the AMPK alpha 2 gene loci is properly a good choice whose genetic SNP can be used as fat markers in animal genetic selecting and breeding, while the usage of SNP polymorphisms of AMPK Alpha 1 gene loci should be further explored. Researchers (Xiao *et al*., 2007; Witczak *et al*., 2008) also found that the missense mutation of human PRKAG2 gene loci encoding AMPK gamma 2 subunit was involved in the pathogenesis of familial preexcitation syndrome. This mutant changed the

amino acid residue at the 302 site in gamma 2 subunit from arginine to glutamic acid. This result was also observed in the site-directed mutagenesis experiment of AMPK gamma 2 subunit (PRKAG2) gene fragments (Sanders *et al*., 2007; Kilimann *et al*., 2005). However, there are currently not enough polymorphism data of AMPK gamma subunit gene and other gene loci for future animal genetics researches.

CONCLUSION

The importance of AMPK and its subunits in regulating fatty acid metabolism and genetic effect of mutation has been highlighted in this review. Given that disturbances in the metabolic pathways contribute to variations of fat and muscle and daily gain during animal growth and development, it is critical to survey and understand the underlying mechanisms, detect and exploit novel mutations or single nucleotide polymorphism s, in order to develop new strategies for genetically improving animal products and serve for molecular breeding. AMPK subunit genes could be good genetic markers in animal genetics researches. Further efforts supporting this idea are needed to be future investigated.

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