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Association of the FTO gene with obesity and cancer in dogs

Dina Bedik, Gizem Kırmızıoğlu, Iraz Akış

1. Istanbul University-Cerrahpasa, Veterinary Faculty, Department of Biochemistry, 34500 Istanbul, TURKEY

Bedik, D. ORCID: 0000-0002-4088-3827; Kırmızıoğlu G., ORCID: 0000-0002-6422-0139; Akış, Akad, I. ORCID: 0000-0001-7330-103X

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ABSTRACT

Nowadays, obesity is one of the most serious problems that significantly affect health in both human and animal populations. Fat mass and obesity-associated gene (FTO), increases the risk of obesity and other metabolic diseases such as cancer, with taking part in many complex molecular pathways. On the other hand, environmental and genetic factors cause changes in FTO gene variants and expression levels, which result in phenotypic differences. Advanced knowledge on the genetic basis of human FTO gene and its association with cancer and obesity, has paved the way for the investigation of FTO gene in animals as well. In this review, we summarized current state of knowledge about the FTO gene, which is considered as an important marker of obesity in humans, as well as obesity, cancer and the association of FTO polymorphisms with these diseases in dogs by considering humans with other animal species. Understanding the molecular background of the FTO gene in dogs will be leading to the development of individual treatment methods and prediction of possible phenotypic effects in other species.

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Introduction

Obesity is defined by the World Health Organization (WHO) as an excessive or abnormal increase in fat mass that can lead to diseases such as cancer, cardiovascular disease, or diabetes mellitus (Phillips, 2013). The morbidity of this disease increases year by year in many countries and threatens human health (Ng et al., 2013). Especially in the past 20 years, increased sedentary lifestyle and excessive consumption of high-calorie foods have caused an increment in the prevalence of overweight and obesity in people approximately 3 times. Thus, obesity has become a major problem in both developed and developing countries (Finucane et al., 2011; Haidar and Cosman, 2011). The fact that studies have reported that more than 1.9 billion adults were overweight in 2016, of whom 650 million were obese, and this number is expected to increase to 1.12 billion by 2030, clearly highlights the seriousness of the obesity problem. (WHO, 2023).

The inordinate accumulation of adipose tissue leading to obesity is a growing problem in both animal populations and humans (Switonski and Mankowska, 2013). According to the 2009-2010 National Pet Owners Survey conducted by Pet Products Manufacturers Association there are 77.4 million purebred and crossbred dogs in USA with 39% of households have at least 1 dog and 24% of them have 2 dogs. Considering this the increase in body weight of pets, especially animals such as cats and dogs that share the same environment with humans, it is usual to be positively correlated with the owner's Body Mass Index (BMI) and to encounter the problem of obesity for these animals (Nijland et al., 2010; Davis and Ostrander, 2014). In addition, after it was reported that 22% of dogs visiting veterinary clinics were overweight and 1% were obese in 1991, the number of overweight dogs increased to 34-59% and obese dogs to 5-10% in about 20 years, this proves that obesity is a year by year growing problem in dogs as well as in humans (Kronfeld et al., 1991; McGreevy et al., 2005; Colliard et al., 2006; Lund et al., 2006; Courcier et al., 2010).

In this review, it is aimed to explain obesity and cancer diseases in dogs, which are one of the pets that share the common environment with humans, and to explain the molecular basis of the FTO gene in dogs, which can cause these diseases.

*Corresponding Author: Dina Bedik
E-mail: dina.bedik@ogr.iuc.edu.tr

Obesity in dogs

Dogs are considered overweight when their body weight exceeds 15% of the optimal weight, and they are considered obese when it exceeds 30% (German, 2006). The reproductive and health status of dogs is significantly affected in the presence of obesity. Furthermore, obesity also leads to the triggering of some diseases such as fatty liver, metabolic syndrome, heart diseases, bone disorders, and cancer, or an increased risk of developing these diseases (Switonski and Mankowska, 2013).

In addition to environmental factors such as nutrition, gonadal status, and inadequate physical activity, individual genetic factors such as age, breed, and gender also play a role in the emergence of the obesity problem (Robertson, 2003; Courcier et al., 2010; Hess and Bruning, 2014).

Between 30% and 70% of common obesity is inherited (Huđek et al., 2017). Gene-dependent obesity can be monogenic, syndromic, oligogenic, or polygenic. However, obesity is mostly a polygenic condition. The mechanism underlying polygenic obesity is quite complex and is based on the intricate interactions between the gene itself and the gene-environment relationship (Huvenne et al., 2016). Studies have shown that while there is no significant gender-obesity relationship in mostly unneutered dogs, spayed animals, especially females, tend to be more prone to obesity. Additionally, it has been noted that the risk of obesity increases with age (Robertson, 2003; Lund et al., 2006; Courcier et al., 2010).

The difference between breeds is one of the most significant genetic factors influencing obesity prevalence in dogs. Depending on age, body composition, which is the ratio of fat body mass (FBM) to lean body mass (LBM), varies between breeds (Speakman et al., 2003). In a study by Speakman et al. (2003) comparing metabolism and body composition in three different dog breeds based on age, it was noted that FBM and LBM were not age-related in Labrador and Papillon breeds, while FBM increased with age in Great Dane breed. The same study also indicated that resting metabolic rate (RMR) decreased with age in all three dog breeds examined. Another study suggested that the varying predisposition of obesity between breeds could be attributed to changes that occur during the selection process in genes related to fat metabolism associated with body composition and fat mass (Jeusette et al., 2010). Population studies have reported that Beagles, Cocker Spaniels, Dachshunds, Rottweilers, Shetland Sheepdogs, Dalmatians, and Retrievers are prone to obesity, supporting the hypothesis proposed by Jeusette et al. (Kronfeld et al., 1991; Colliard et al., 2006; Lund et al., 2006). This situation indicates the interbreed predisposition differences demonstrate that in some breeds the gene pool contains DNA polymorphisms that may be responsible for obesity (Switonksi and Mankowska, 2013).

Cancer disease in dogs and its relationship with obesity

Cancer is an extremely serious disease in dogs, affecting approximately 4 million dogs annually and being the most common cause of death in dogs of all ages, particularly those over the age of 10 (David and Ostrander, 2014; Gardner et al., 2016). While 50% of older dogs are diagnosed with cancer, one-fourth of these cases result in death (Bronson, 1982; Vail and MacEwen, 2000; Adams et al., 2010; Dobson, 2013; ACF, 2023).

Registrations regarding cancer in dogs are predominantly retrospective due to the inherent nature of the disease, and they are often limited to a defined patient population (Bronson, 1982; Dobson et al., 2002). In a retrospective necropsy study conducted by Bronson (1982) on 2,002 dogs, it was reported that 45% of dogs aged 10 and above, and 23% of dogs of all ages, died due to cancer and this disease was one of the leading causes of death in dogs. Data from the Genoa Animal Tumor Registry suggests an estimated cancer incidence in dogs ranging from 99.3 to 272.1 cases per 100,000 dogs (Merlo et al., 2008).

There are many differences among breeds regarding predisposition to specific types of cancer. For instance, breeds like Boxers, Golden Retrievers, French Bulldogs, Boston, and Rat Terriers are severely prone to the brain and central nervous system cancers, while this risk is low in Cocker Spaniels and Doberman Pinchers. Additionally, meningiomas are more common in dolichocephalic (long-nosed) breeds, while brachycephalic (flat-nosed) breeds are more prone to gliomas (Song et al., 2013). As multiple dog breeds are at risk for the same type of cancer, these breeds are likely to share an underlying genetic predisposition (Davis and Ostrander, 2014).

Obesity has been reported to increase the risk of at least 13 different types of cancer, including esophageal adenocarcinoma, colon cancer, endometrial cancer, kidney cancer, hematopoietic cancers, and postmenopausal cancers in humans (Calle and Kaaks, 2004; Goodwin and Stambolic, 2015). According to a study conducted in the USA, in 2003, 14% of men and 20% of women who died from cancer, particularly colon, rectum, esophagus, kidney, pancreas, gallbladder, ovary, endometrium, liver, prostate, and hematological malignancies, were overweight or obese (Calle et al., 2003).

There are several mechanisms that can explain the relationship between obesity and increased cancer risk. Obesity is associated with the compensatory increase of hyperinsulinemia in the production of insulin resistance and growth factors. This first stimulates mitogenesis and consequently carcinogenesis, multiple signaling pathways, oxidative stress, and inflammatory processes (Sarfstein et al., 2013). In an epidemiological study linking obesity and cancer, it was reported that the cancer risk in obese women is 50% higher than in women with normal weight (Calle and Kaaks, 2004).

History of the FTO gene

The FTO gene, identified through Genome-Wide Association Studies (GWAS), is considered the most powerful predictor of polygenic obesity today. It can influence the development of obesity by regulating fatty acid transport and fat metabolism and is the first obesity-related gene to be described. (Loos and Bouchard, 2008; Loos and Yeo, 2014). This gene was first cloned through exon capture analysis in mice with the 'fused toes (Ft)' mutation in 1999, and it was identified as one of the six genes deleted in these mice (Peters et al., 1999). Since homozygous mice with the Ft mutation displayed severe developmental anomalies resulting in embryonic death and heterozygous mice exhibited syndactyly and thymic hyperplasia, scientists initially considered that this gene might be associated with programmed cell death (Van Der Hoeven et al., 1994; Fischer et al., 2008). It was stated that the observed phenotype in mice occurred as a result of a 1.6 Mb deletion in chromosome 6, and three of the six deleted genes belonged to the IrxB (Irx3, Irx5, Irx6,) cluster of Iroquois family genes, while the other three had no known function, i.e. dysfunctional. Thus, the first of the genes were named Ft1 (later Fts), the second was named Phantom (Ftm) due to technical difficulties in its characterization, and the third was named Fatso (later FTO) because of the fact that mice with Ft mutation did not have any signs of obesity both metabolically and phenotypically, only because of the size of the gene (Fischer et al., 2008; Larder et al., 2011). However, in 2007, the FTO gene was identified as an obesity susceptibility gene through GWAS, and single nucleotide polymorphisms (SNPs) located in intron 1 were reported to be strongly associated with BMI, body fat ratio, waist circumference, hip circumference, and energy intake (Dina et al., 2007; Frayling et al., 2007; Scuteri et al., 2007). As a result, the gene in question was named a fat mass and obesity-associated (FTO) gene (Lan et al., 2020).

According to current genomic research, the FTO gene is found only in vertebrates and a few types of marine algae, along with highly conserved nucleotide and amino acid sequences, but not in invertebrates, fungi, and green plants (Robbens et al., 2008). Furthermore, the FTO protein is thought to have a similar function among all vertebrates as it is conserved with 85% sequence similarity between humans, mice, sheep, cattle, and horses (Fredriksson et al., 2008).

Association of FTO gene with obesity

The association between the FTO gene and obesity was first reported with GWAS, detecting that there are approximately 500,000 autosomal SNPs in a population of individuals with type 2 diabetes (T2D) in the UK (Frayling et al., 2007). In this study, an SNP (rs9939609) that has a strong relationship with both T2D and increased BMI was identified in the 1st intron of the gene in question was identified, and it was considered that this SNP caused a predisposition to diabetes by affecting the body weight. The authors noted that individuals homozygous for the risk allele (A) of this SNP were approximately 3 kg heavier than those homozygous for the non-risk allele (T), and these individuals have a 1.7 times higher risk of obesity. The association of FTO gene variants with obesity and other diseases is shown in Table 1 and Table 2.

After the publication of the initial study, the association of the FTO gene with obesity was primarily confirmed in European populations, and other SNPs such as rs9930506 (Scuteri et al., 2007), rs1121980 (Dina et al., 2007), and rs8050136 (Stratigopoulos et al., 2008) were identified.

Later, studies expanded to include populations from Africa, the Americas (such as Mexican-Mestizo), Afro-Americans, and Asia (such as Han Chinese and indigenous Oceanian), and the association of FTO variants with other metabolic diseases, particularly with obesity and T2D, across other ethnicities was evaluated (Ohashi, 2007; Li et al., 2008; Villalobos-Comparán et al., 2008; Hassanein et al., 2010; Li et al., 2013). Accordingly, in the study conducted by Hassanein et al. (2010) investigating the FTO locus in an African population, the strongest association with obesity was not observed with the SNPs rs9939609 or rs8050136, which are frequently examined in European populations, but rather with two less characterized SNPs, rs3751812 and rs9941349. Furthermore, in a study investigating the risk of Polycystic Ovary Syndrome (PCOS) associated with the rs9939609 variant of the FTO gene, Chinese women, as PCOS (741) and control group (704), were evaluated. The results of the study in which the samples were divided into 2 groups, obese PCOS patients and non-

Table 1. Association of FTO gene intronic variants with obesity and other diseases in humans (Reviewed from Hernández-Caballero and Sierra-Ramírez, 2015, Köksal, 2019, Kucher, 2020)

Locus	Location	Diseases	Description
rs9939609	Intron 1	Obesity	It causes an increase in BMI.
		T2DM	It causes T2DM development unrelated to BMI.
		PCOS	BMI unrelated studies have been reported to have a stronger effect.
		Endometrium Cancer	AA genotype increases the risk of endometrial cancer.
		Pancreas Cancer	There is a risk of pancreatic cancer in the A allele (BMI unrelated) and the AT genotype (BMI associated).
		Colorectal Cancer/ Adenoma	Associated with BMI.
		Lung Cancer	The AA genotype reduces the risk of lung cancer. (BMI related)
		Kidney Cancer	The AA genotype increases the risk of kidney cancer.
		Prostate Cancer	The A allele causes high-grade prostate cancer. (BMI related)
		Cardiovascular Disease	The A allele increases the risk of coronary heart disease, heart attack, and atrial fibrillation. (BMI related)
rs17817449	Intron 1	Obesity	It causes an increase in BMI.
		Colorectal Cancer/ Adenoma	G allele reduces the risk of colorectal adenoma. (BMI related)
		Breast Cancer	There is a risk of ER+ breast cancer. (BMI unrelated)
rs3751812	Intron 1	Obesity	The T allele causes an increase in BMI.
rs1421085	Intron 1	Obesity	It causes an increase in BMI.
		T2DM	Associated with BMI.
		PCOS	BMI unrelated studies have been reported to have a stronger effect.
rs9930506	Intron 1	Obesity	The A allele causes an increase in BMI.
rs8050136	Intron 1	Obesity	It causes an increase in BMI.
		T2DM	It causes T2DM development unrelated to BMI.
		Pancreas Cancer	There is a risk of pancreatic cancer in the AC genotype. (BMI related) There is a risk of pancreatic cancer in T2DM patients who are carriers of the A allele.
		Prostate Cancer	Polymorphisms reduce the risk of prostate cancer.
		Colorectal Cancer/ Adenoma	The A allele reduces the risk of colorectal adenoma. (BMI related)
rs7202116	Intron 1	Obesity	It causes an increase in BMI.
rs8043757	Intron 1	Obesity	The T allele causes obesity.
rs9928094	Intron 1	Obesity	A/G alleles cause extreme obesity.
rs9941349	Intron 1	Obesity	The T allele causes extreme obesity.
rs1558902	Intron 1	Obesity	A/T alleles cause obesity.
rs1121980	Intron 1	Obesity	A/T alleles cause extreme obesity.
		Breast Cancer	There is a risk of breast cancer in T/C alleles. (BMI unrelated)

Table 2. Association of non-obesity-related intronic variants of the FTO gene with other diseases in humans (Reviewed from Hernández-Caballero and Sierra-Ramírez, 2015, Köksal, 2019, Kucher, 2020)

rs7185735	Intron 1	T2DM	A/G alleles cause T2DM. (BMI related)
rs9936385	Intron 1	T2DM	The C allele causes T2D. (BMI related)
rs12933928	Intron 1	Melanoma	It increases the risk of melanoma.
rs6499640	Intron 1	Endometrial Cancer	There is a risk of endometrial cancer in the A allele. (BMI unrelated)
rs1477196	Intron 1	Breast Cancer	There is a risk of breast cancer in the GG genotype (BMI-related)
rs62048402	Intron 1	Breast Cancer	There is a risk of breast cancer in the A allele.
rs56094641	Intron 1	Nephropathy	The G allele causes nephropathy in patients with T2DM.
rs7187250	Intron 1	Cardiovascular Disease	It causes mineral density in the heel bone.
rs8044769	Intron 1	Osteoarthritis	The T allele causes osteoarthritis. (BMI related)
rs9930333	Intron 1	Osteoarthritis	G/T alleles cause osteoarthritis of the hip and knee. (BMI related)
rs9940128	Intron 1	Metabolic Syndrome	The A allele causes metabolic syndrome. (BMI related)
rs11642841	Intron 2	T2DM	The A allele causes T2DM.
rs11075995	Intron 2	Breast Cancer	There is a risk of ER- breast cancer. (BMI unrelated)
rs12932428	Intron 7	Melanoma	The risk of melanoma is increased.
rs12599672	Intron 7	Melanoma	The risk of melanoma is increased.
rs1125338	Intron 8	Melanoma	The risk of melanoma is increased.
rs16953002	Intron 8	Melanoma	It causes melanoma risk in the A allele (BMI unrelated)
rs56077980	Intron 8	Breast Cancer	There is a risk of breast cancer in the CT genotype.
rs7195994	Intron 8	Rheumatoid Arthritis	The A allele causes rheumatoid arthritis.
rs7187423	Intron 8	Rhinitis	It is associated with seasonal allergic rhinitis.

obese PCOS patients, revealed the relationship of the aforementioned variant with not only obesity but also non-obese cases in Chinese women (Li et al., 2013). Contrary to the initial studies that interpreted FTO's influence on obesity to potentially lead to metabolic diseases like T2D by affecting BMI (Frayling et al., 2007), this situation indicates that FTO might contribute to susceptibility to certain metabolic diseases independently of its effect on weight gain and that environmental or other genetic factors could lead to distinct relationships between the FTO gene and ethnic groups (Larder et al., 2011).

Function of the FTO gene

The physiological function of the FTO gene is not yet fully understood. Frayling et al. (2007) referred to the FTO gene as “a gene with an unknown function in an unknown pathway”. In sequence analysis, the FTO protein was predicted to have a double-stranded β-helix structure homologous to members of the non-heme Fe (II) and 2-oxoglutarate (2-OG) oxygenase superfamily (Clifton et al., 2006; Ozer and Bruick, 2007). Through advanced bioinformatics analyses, Gerken et al. (2007) revealed that the FTO gene encodes Fe(II)/2-OG dependent demethylase, which is the ninth protein found in mammals from the alpha-ketoglutarate dependent dioxygenase (AlkB) family, which is Escherichia coli DNA repair enzyme. Due to its homologous sequence with proteins from the AlkB family, this protein is also referred to as ALKBH9. Based on this, it has been hypothesized that FTO plays a significant role in DNA repair and post-translational modifications. Additional experiments have determined that FTO signals the cellular presence of oxygen, is functionally involved in fatty acid metabolism and energy metabolism, and has a role in the catalysis of nucleic acid demethylation (Han et al., 2010). In a study

2010). In a study conducted a few years later by Jia et al. (2012), it was stated that N6-methyladenosine (m6A) in nuclear RNA is the primary substrate of FTO. Therefore, FTO was initially described as the first RNA demethylase, opening the door for further research into both RNA epigenetic modifications and the functions of FTO proteins in the subsequent years (Wei et al., 2018).

While the FTO gene can influence the proliferation and differentiation of adipocytes, the FTO protein can regulate the growth and development of adipocytes as a transcriptional co-activator (Qiong, 2010; Ronkainen et al., 2015; Chen et al., 2017). It also plays a regulatory role in biological processes such as the regulation of animal β-cell function and oxidative stress (Bravard et al., 2011; Russell and Morgan, 2011). On the other hand, as the FTO gene regulates adipocyte differentiation and causes obesity, mutations in this gene may also affect growth characteristics in animals (Wang et al., 2021). For instance, in a study focused on Italian Duroc pigs, it has been indicated that the g.276T> G polymorphism in the pig FTO gene is closely associated with adipose tissue characteristics, marbleization, backfat thickness, and intramuscular fat content (Fontanesi et al., 2009). Another study investigating the relationship between FTO gene variants and growth and carcass characteristics in cattle indicated that the FTO gene had a significant impact on growth and carcass characteristics in Simmental and Brown cattle in the Slovenian population. In a statistical analysis conducted between these traits and 34 SNPs in the FTO gene, it was reported that there is a significant correlation between FTO variants and the percentage of lean muscle mass (Jevsinek Skok et al., 2016). Moreover, in a study focusing on the effects of insertion/deletion (InDel) polymorphisms in the FTO gene on fat tail size and growth traits in the Tong sheep, a breed famous for its fat-tailed characteristics in China, as a result of fat tail diameter and body measurements, a total of 10 InDel loci were identified in 75 sheep, 4 (InDel 4,5,7,8) of which were significantly correlated with tail fat accumulation, and 8 (InDel 1,2,3,4,5,7,8,10) were significantly associated with certain growth characteristics (Wang et al., 2021). In addition, there are studies reporting that genetic variations in the FTO gene can also affect growth characteristics in chickens and rabbits (Jia et al., 2012; Zhang et al., 2013).

Data from numerous human studies have suggested an association between various FTO risk alleles and increased energy intake. In the conducted studies, it has been reported that cases with at least one risk-free allele showed an increase in food consumption, more frequent eating, impaired satiety, and loss of eating control compared to individuals with homozygous risk-free allele (Speakman et al., 2008; Haupt et al., 2009; Tanofsky-Kraff et al., 2009; Wardle et al., 2009). In detailed analyses on this subject, the observed increase in energy intake among risk allele carriers is attributed to an increased tendency towards high-fat, energy-dense foods, rather than an increase in the quantity of consumed food (Cecil et al., 2008; Timpson et al., 2008). Furthermore, the role of the FTO gene in regulating energy balance and energy expenditure has been confirmed through experiments conducted on mice and rats (Fischer et al., 2009; Fredriksson et al., 2008). For example, a study conducted by Fischer and colleagues (2009) demonstrated that the absence of the FTO gene in knock-out mice leads to a drastic reduction in both fat tissue and lean body mass, resulting in postnatal growth retardation. Considering the studies, it is understood that the energy balance of the FTO gene is more effective on the "input" side (Larder et al., 2011). In a study examining the FTO gene locus for milk fat characteristics in Holstein dairy cattle, it has been reported that the FTO region regulates not only milk fat yield but also the total energy content of milk (Zielke et al., 2013).

Animal models

Animal models are crucial for understanding the role and effects of FTO in different anatomical regions (Larder et al., 2011). This gene is strongly expressed in the hypothalamus, the region of the brain that controls appetite behavior (Gerken et al., 2007; Stratigopoulos et al., 2008). In mice, the expression of the FTO gene in the hypothalamus increases after feeding with a high-fat diet (Tung et al., 2010). Due to the different amounts of transcripts obtained in the regions of the brain that control food intake, depending on food intake and deprivation, it has been suggested that the role of FTO in regulating body weight depends on the activity of FTO protein in these regions of the brain (Fredriksson et al., 2008). In studies on pigs and sheep, it has been reported that FTO expression is significantly higher in the cortex, hippocampus and hypothalamus regions of the brain (Madsen et al., 2009; Sebert et al., 2010). Other studies on pigs have proven that FTO is associated with intramuscular fat and average daily gain (Fan et al., 2009; Fontanesi et al., 2009). Furthermore, it has been reported that the FTO gene is widely expressed in several tissues and organs involved in the control of energy metabolism and cardiovascular function in animals, including adipose tissue, liver, pancreas,

kidney, brain, skeletal muscle, and heart (Stratigopoulos et al., 2008; Wåhlén et al., 2008; Madsen et al., 2009).

Mouse experiments are used to understand the anatomical role of the FTO gene as well as its metabolic effects. For example, in the study by Church et al. (2009) on mouse model, were studied the metabolic effects and expression level of the human FTO gene, for this, were used mice with a dominant missense mutation (I367F), which causes a reduced body weight and fat mass phenotype. As a result, it was mentioned that physical activity and food intake did not change in mutant mice, but the metabolic rate was high. Also, in mutant mice, fat and carbohydrate metabolism was increased and mutant mice fed with a high-fat diet had lower fat mass than the wild-type. According these results, it is stated that mice are a model for the human phenotype and may provide evidence that the FTO gene may be one of the underlying causes of obesity.

Besides mouse experiments, dogs are also important biomedical models (Lequarré et al., 2011). Knowledge of powerful molecular tools such as sequence of the canine genome, marker genome maps, haplotype distribution or SNPs, facilitate the identification of monogenic hereditary diseases associated with quantitative traits or gene mutations responsible for polymorphisms in humans as much as dogs (Breen, 2008). In particular, dog obesity attracts attention as a model, because many hereditary diseases seen in humans have similarities in different dog breeds and also differences that may arise from the gene-environment interactions are minimised due to their presence in the same living place with humans (Tsai et al., 2007; Ricci and Bevilaqua, 2012).

FTO gene in dogs

The canine FTO gene (Gene ID: 478125) is a protein-coding gene located on chromosome 2 with a length of 416.31 kb (428.861 nt) (NCBI, 2023). In total, there are 4.767 variants in all regions including SNPs and InDel, and the majority of these variants (4.428) are localizated in introns. There are a total of 9 protein-coding FTO transcripts (from 428 to 620 aminoacids) ranging in length from 4797 to 1485 bp (Ensembl, 2023). This gene, enables metal ion binding and activates mRNA N6-methyladenosine dioxygenase, oxidative DNA demethylase and transferase activities in biological process. Also, it is involved in DNA dealkylation, RNA repair, oxidative single-stranded DNA demethylation, oxidative single-stranded RNA methylation and regulation of multicellular organism growth (GO Annotations, 2023).

The alpha-ketoglutarate-dependent dioxygenase protein, which is encoded by the FTO gene and uses Fe (II) as a cofactor, is localized in the nucleus, nuclear speckle and cytoplasm of the cell, performs a number of molecular functions and takes part in biochemical processes (Wei et al., 2018).

Roles of canine FTO protein

The canine FTO protein acts as an RNA demethylase, mediating the oxidative demethylation of different types of RNA such as messenger RNA (mRNA), transfer RNA (tRNA) and small nuclear RNA (snRNA) and as a regulator of fat mass, adipogenesis and energy homeostasis (Gerken et al., 2007; Jia et al., 2008; Mauer et al., 2017). Also, it shows demethylase activity against m6A RNA, which is the most common modification of mRNA, especially in higher eukaryotes. This demethylation mediated by FTO, regulates expression levels of certain target genes by affecting the expression and stability of mRNA (Mauer et al., 2017). Among the genes targeted by the FTO gene in humans are Ghrelin, SRSF2, CCNA2 and CDK2, which can cause obesity; ASB2, RARA, ADAM19, EPHA3, KLF4, CDKN2A, BRCA2, TP53I11, BNIP3, MZF1, USP7, PKM2, MERTK, BCL-2, PD-1, CXCR4, and SOX10, which can be associated with various types of cancer (Reviewed from Lan et al., 2020 Table 1). Furthermore, FTO protein is also demethylates m6A in U6 small nuclear RNA (U6 snRNA) and it mediates demethylation of the N6,2'-O-dimethyladenosine cap (m6A(m)), which is located in the 5' cap, by demethylating m6A at the second transcribed position of mRNA and U6 snRNA (Mauer et al., 2017). This process ensures mRNA stabilization by increasing the sensitivity to uncapping. Also, FTO functions as a tRNA demethylase by removing N1-methyladenine (m1A) from tRNAs. In mRNA, FTO regulates dopaminergic activity in the midbrain through its ability to demethylate m6A (Hess et al., 2013). In addition, it is able to repair alkylated DNA and RNA by oxidative demethylation. FTO executes this by demethylating single-stranded RNA containing 3-methyluracil (3-meU) and single-stranded DNA containing 3-methylthymine (3-meT), as well as its low demethylase activity towards single-stranded DNA containing 1-methyladenine or 3-methylcytosine (3-meC) (Jia et al., 2008). However, the mentioned ability of repairing DNA and RNA is not definitively established in vivo (Gerken et al., 2007; Jia et al., 2008). It has no detected activity against double-stranded DNA as well (Jia et al., 2008).

The FTO protein causes the development of obesity by affecting the m6A levels of hormones related to nutrition (Lan et al., 2020). Furthermore, it contributes to the regulation of body size and fat accumulation by playing a role in the regulation of

adipogenesis, fat mass and body weight (Fischer et al., 2009; Church et al., 2009; Church et al., 2010; Hess et al., 2013; McMurray et al., 2013). Thus, it regulates both thermogenesis and the differentiation of brown and white fat cells (Church et al., 2009; Fischer et al., 2009).

Association of the canine FTO gene with obesity and cancer

Studies on the canine FTO gene are quite limited. Grzes et al. (2011) studied on the FTO and insulin-induced gene 2 (INSIG2), which are two candidate genes associated with fat accumulation in four species of Canidae family including dog, red fox, Arctic fox, and raccoon dog. In this study, a comparative genomic analysis was perfomed on the mentioned genes and as a result, a total of 29 SNPs were identified with 13 of them located in the FTO gene. Two of the analyzed 29 SNPs were determined to be missense in dogs and these SNPs were further investigated in 14 different dog breeds. As a result of the investigations, the presence of the variant identified as missense mutation in exon 1 (23C>T, Thr>Met) was reported in 5 dogs representing different breeds, including Labrador and Golden Retriever. In addition, 2 synonymous mutations, one in the FTO gene and the other one in the INSIG2 gene, were used for association studies in red foxes. In conclusion, it has been indicated that both genes are potential candidates for growth and adipose tissue development in canids. On the other hand, Grzemski et al. (2019) investigated the association of the FTO and Iroquois homeobox protein 3 (IRX3) gene with obesity in Labrador dogs. For this purpose, polymorphisms were investigated in 32 Labradors and also 165 Labrador dogs were used to examine the orthologous regions of these genes with humans. However, none of the identified 12.217 polymorphisms were reported to be significant in lean and obese dogs. The study concluded that FTO and IRX3 genes are not indicators of obesity in Labrador dogs.

Although there is no other published study on the canine FTO gene, it has been stated that dogs can be used as valuable models in genetic studies particularly related with cancer which is one of the most important diseases that obesity increases the risk of it, since they often experience spontaneous diseases and can develop many types of cancer observed in humans. Also, considering that domestic dogs are divided into more than 175 breeds and these breeds show similar phenotypic characteristics, it was mentioned that the breed barrier may enhance the utility of the dog model, especially in genetic studies that consider breed-based cancer susceptibility expressed by few genes (Switonski and Mankowska, 2013; Davis and Ostrander, 2014).

FTO Gene and cancer relationship

FTO proteins play a role in adipogenesis as well as in tumorigenesis with their m6A-dependent demethylase activity. In this way, FTO is highly expressed in many cancer tissues by acting as an oncogene and participating in the regulation of the malignant phenotype of cancer cells (Lan et al., 2020). In the study by Cui et al. (2017), it was reported that high levels of m6A promote the growth, self-renewal of glioblastoma stem cells (GSCs) and tumor development in these cells. Furthermore, several studies have reported that SNPs in the FTO gene are associated with breast cancer risk (Kaklamani et al., 2011; Zhang et al., 2014; Hernández-Caballero and Sierra-Ramírez, 2015).

Following the first publications showing the association between variants of FTO gene and obesity, researchers have started questioning and exploring the existence of the relationship between these variants and cancer risk in obese people from various ethnic groups (Hernández-Caballero and Sierra-Ramírez, 2015). In the study conducted by Brennan et al. (2009) on 7,000 people from Central and Eastern Europe, the rs9939609 variant of the FTO gene was investigated, however, it was reported that the A allele was associated with a low risk of lung cancer, while the risk of kidney cancer showed minimal increase. Subsequently, Lewis et al. (2010) suggested in their study that the A allele of the same variant is a protective factor against prostate cancer, reducing the possibility of low-grade cancer but potentially increasing the possibility of high-grade cancer. In 2011, an association between obesity and pancreatic cancer have been suggested and in two case-control studies of the non-Hispanic white population and the European population, the A allele of the rs8050136 variant was shown to be significantly associated with pancreatic cancer (Pierce et al., 2011; Tang et al., 2011). Besides the rs8050136A variant, Tang et al. (2011) were also studied on rs9939609A. In both variants a decreased risk of pancreatic cancer was observed in people with normal BMI, and an increased risk in people with high BMI (Tang et al., 2011). In the following years, the association of rs9939609 variant with pancreatic cancer risk was investigated in the Japanese population and it was reported that the TT genotype had a 1.5 times higher risk of pancreatic cancer than the TA genotype (Lin et al., 2013).

In relation to endometrial cancer and breast cancer, Delahanty et al. (2011) examined the relationship between obesity and endometrial cancer

risk in Chinese women and they revealed a strong association between the FTO SNPs they studied and endometrial cancer, but the association was not related to BMI. In another study conducted in the same year, it was reported that there is a significant association between the rs1477196 variant and breast cancer, predominantly in individuals of Caucasian descent (Kaklamani et al., 2011). In addition, in a study which the FTO SNPs rs1121980 and rs9939609 were analyzed in Brazilian population, it was reported that the risk of developing breast cancer was 4,9 times higher when the rs17782313 variant of melanocortin receptor-4 (MCR4) and these FTO SNPs were found in combination (da Cunha et al., 2013). In the study conducted by the GenoMEL consortium (2013), it was stated that SNPs located in an intron of the FTO gene unrelated to obesity, such as intron 8, may be associated with the risk of developing cancer. Later, in 2015, the study by Tan et al., examining the expression of the FTO gene in the breast tissue of Chinese women stated that FTO was overexpressed in cancerous breast tissue compared to healthy breast tissue.

Conclusions

The results obtained from all the mentioned studies on association of the FTO gene with obesity and cancer suggest that the relationship between cancer development, being overweight and having some FTO polymorphisms is based on ethnic origins as well as some genetic and environmental factors. Hence, it is clear that there is a multifactorial relationship between FTO variants and cancer disease rather than a simple association. In addition, the size and quality of the working group raise concerns about the reliability of certain results in these studies. For example, in a study that examines gender comparison, the ethnic backgrounds of individuals may hide the differences between genders. The character of the tumor in cancer diseases is another factor that influences the relationship between the polymorphic variants of FTO. Especially in studies focusing on breast cancer, the nature of tumors in the working group, whether they are spontaneous, hereditary or estrogen receptor status (ER+/-) should be considered (Hernández-Caballero and Sierra-Ramírez, 2015). Furthermore, in studies, the interaction of individual genes with the FTO gene or protein, the existence of an effective FTO pathway and the impact of FTO expression on other genes should be taken into consideration (Popović et., al., 2023).

Although excessive fat accumulation primarily promotes tumor growth rather than initiating cancer, it is essential to understand the underlying factors of obesity development. Even though the polymorphisms in intron 1 have been reported to be associated with obesity in studies, further investigations are needed to reveal their relationship with cancer. In addition, the reported association of polymorphisms in intron 8, which are not related to obesity, with cancer suggested that FTO polymorphisms may cause cancer with a mechanism other than obesity and opened a new field of research (Hernández-Caballero and Sierra-Ramírez, 2015). When the obtained results are evaluated, FTO gene and its intronic polymorphisms are likely to be associated with cancer as well as obesity.

In contrast to studies on human FTO gene, researches on the FTO gene in animals are quite limited. Since the identification of the FTO gene as an obesity gene, studies have mainly focused on farm animals such as pigs, cattle, sheep, and chickens. Regarding to pet animals, dogs have been studied in only two studies while cats have never been studied. The reason for this is probably the fact that the number of farm animals is high because they are usually keep in herds and use in breeding, also, their genetic origins can be followed easily thanks to selective breeding programs and certain traits such as tail fat, milk fat, back fat and intramuscular fat content are highly important in terms of the quality of food obtained from these animals. Furthermore, there are no studies conducted on the FTO gene in animals regarding diseases such as cancer and cardiovascular diseases, which are associated with an increased risk due to obesity. On the other hand, mice and chickens have been used as models in studies of the human FTO gene. Understanding the molecular basis of the FTO gene in dogs will provide an opportunity to develop individualized treatment strategies for diseases related to this gene. Also, considering that especially Beagle breed dogs are predicted to show phenotypes similar to the phenotypic characteristics caused by variations in the human FTO gene in terms of BMI and metabolic traits (Akey et al., 2010), the knowledge about the phenotypic effects of variations in dogs will pave the way for investigating the genetic origin of variations in both dogs and humans.

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