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W Locus Alleles of the *KIT* Gene in Turkish Van Cats and Their Association with Certain Phenotypes

Van Kedilerinde *KIT* Geninin *W* Lokus Allelleri ve Bazı Fenotiplerle İlişkileri

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ÖZET

Amaç: Van kedisi dünyada özel kedi ırkları arasıdadır. Van kedilerinin en önemli karakteristik özellikleri beyaz, ipeksi tüyleri ve farklı göz renkleridir. Kedilerde *KIT* geninin *W* lokusu beyaz tüy için önemli bir lokus olarak bulundu. Fakat, Van kedilerinin *W* lokusu hakkında yeterli bir bilgi bulunmamaktadır. Bu çalışmanın amacı Van kedilerinde *W* lokus allelerinin genotipik dağılımını ve belirli fenotipik özellikler ve alleller arasındaki ilişkiyi belirlemekti.

Materyal ve Metot: Van Yüzüncü Yıl Üniversitesi Van Kedisi Araştırma ve Uygulama Merkezinde Yetiştirilen 48 Van kedisi bu çalışma için seçildi. DNA izolasyonları ağız sürüntülerinden gerçekleştirildi ve bu kedilerin *W* lokus genotiplemesi PCR ile yapıldı. Ki-kare testi, alleller ve belirli fenotipler arasında ilişkiyi belirlemek için yapıldı.

Bulgular: Kedilerin %41.67, %22.92, %18.75 ve %16.67'sinin sırasıyla *W/W*, *W/w*$^+$, *w*$^+$/*w*$^+$ ve *W/w*^{s} genotipini taşıdığıdı görüldü. *W* lokus allellerinin frenkansları *W*, *w*$^+$, *w*^{s} için sırasıyla %61.45%, %30.21 ve %8.33 olarak bulundu. Göz rengi, baş beneği ve tüy uzunluğunu içeren fenotipler ile belirlenen genotipler arasında bir ilişki saptanamadı.

Sonuç: Van kedileri *W* lokusda beyaz (*W*), beyaz beneklenme (*w*^{s}) ve yabanıl tip (*w*$^+$) alleleri taşıyabilir. *W* lokus allelleri ile göz rengi, baş beneği ve tüy uzunluğu arasında iliştkinin olmaması bu kedilerin genetik yapısını anlamak için diğer genetik varyasyonlara yönlenilmesi gerektiğini işaret etmektedir.

Anahtar Kelimeler: Van kedisi, *KIT* geni, *W* lokus, *FERV1*.

ABSTRACT

Objective: Turkish Van cat is a special cat breed in the world. The most important characteristics of the Turkish Van cats are the white and silky fur, and different eye colors. *W* locus of the *KIT* gene was found to be an important locus for white fur in cats. However, there is not enough information about the *W* locus of Turkish Van cats. The aim of this study was to determine the genotypic distribution of *W* locus alleles in Turkish Van cats and the association between alleles and certain phenotypes.

Material and Method: 48 Turkish Van cats bred in Van Yüzüncü Yıl University Van Cat Research and Application Center were selected for this study. DNA isolations were carried out from oral swaps and *W* locus genotyping of these cats was done by PCR. The Chi-square test was used to determine the association between the alleles and certain phenotypes.

Results: It was shown that 41.67%, 22.92%, 18.75% and 16.67% of cats carried *W/W*, *W/w*$^+$, *w*$^+$/*w*$^+$and *W/w*^{s}, genotype respectively. Frequencies of *W* locus alleles were found to be 61.45%, 30.21%, 8.33% for *W*, *w*$^+$, *w*^{s}, respectively. An association between detected genotypes and the phenotypic characters including eye color, head spotting, and hair length, could not be established.

Conclusion: Turkish Van cats can carry white (*W*), white spotting (*w*^{s}), and wild-type (*w*$^+$) alleles in the *W* locus. No association between *W* locus alleles and eye color, head spotting, and fur length indicates other genetic variations should be addressed to understand the genetic background of the cats.

Keywords: Turkish Van cat, *KIT* gene, *W* locus, *FERV1*.

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INTRODUCTION

Turkish Van cat is a local cat breed of Turkey and exists in Van province since ancient times (Figure 1). The characteristic properties of Turkish Van cats are white fur and different eye color (Figure 1a). Eye color of Turkish Van cats can be one eye blue and the other amber (yellow and its tones) which is called odd eyes, both eyes blue or both eyes amber

(Robinson, 1983; Şenler, 1986; Odabaşıoğlu and Ateş, 2000) (Figure 1b). Furthermore, Turkish Van cats can have tiny black or grey spots on their heads and tails, which are known Van patterns among the white cat breeds (Cooper et al., 2006; Strain, 2017; Çelik, 2019). A sad state of these lovely cats is that they can suffer from deafness like other white cat breeds with blue eyes. The incidence of deafness in Turkish Van cats was found to be 14.33% in a recent study (Çelik, 2019). Since the Turkish Van cats are very important for Van province and Turkey, Van Cat Research and Application Center was founded by Van Yüzüncü Yil University. The cats have been bred in this unit since 1998 (Figure 2). It should be noted that this unit is open for both researchers and cat fancies and is visited by thousands of people every year.

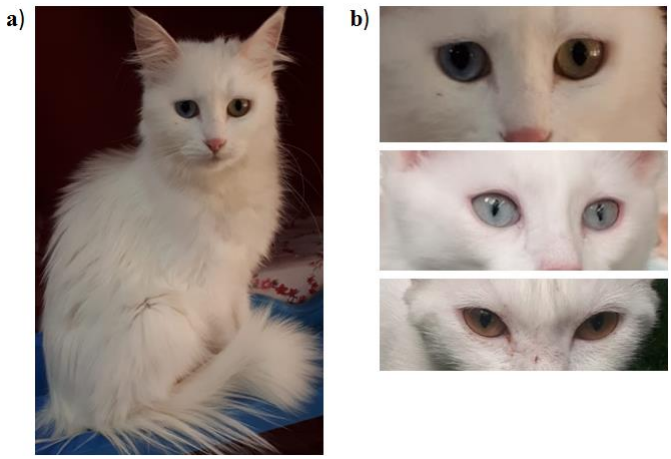

Figure 1. Phenotypical feature of Turkish Van cats.
a) General phenotypic profile of Turkish Van cats.
b) Eyes color characteristics of Turkish Van cats.

Figure 2. Van Yüzüncü Yıl University Van Cat Research and Application Center.

It was known from early reports that there is a positive correlation between deafness and having both white fur and blue eyes (Darwin, 1894; Bamber, 1933). White fur color and blue-eye combination are associated with congenital deafness in dogs, cats, and lots of mammalians. Cross-eyed syndrome is observed with partial albinism in Siamese cats (Webb and Cullen, 2010; Stelow et al., 2016). Researchers are working on the breeds and pedigrees to explore the genetic bases of fur or coat color patterns of mammals whose color combinations, spots, stripes, patches, and swirls, as genetic markers, to solve the inheritance of the genetic syndromes and the behaviors (Ishida et al., 2006; O'Brien et al., 2008; Eizirik et al., 2010).

White cats' characteristics are similar to Waardenburg's syndrome in humans. Waardenburg's syndrome is characterized by congenital sensorineural hearing loss syndrome associated with pigmentary disturbances of the eyes, hair, and skin. The genetic basis of this syndrome has been well-studied and some pathogenic mutations are found in the six of the genes: *PAX3*, *MITF*, *EDN3*, *EDNRB*, *SOX10,* and *SNAI2.* The mutations in these genes can cause the different types of this syndrome in different frequencies (Read and Newton, 1997; Pingault et al., 2010). However, the research on white cats is highly limited.

Molecular genetic mechanisms of the fur color and pigmentation of felines have a highly complex nature including lots of polymorphisms, long terminal repeat (LTR), and mutations in many different genes (Ishida et al., 2006). The linkage was identified between this characteristic white coat-blue eye combined phenotypes and the variations in the particular genes including *MITF*, *PMEL*, *KIT*, *EDNRB*, *CDH23*, *TYR*, and *TRPM1* in many mammalian species such as dogs, cats, horses, cows etc. (Strain, 2015).

A study showed different length of insertions of *Feline Endogenous Retrovirus 1 (FEVR1)* into the intron 1 of *KIT* gene, in feline chromosome B1, causing both *Dominant White* (*W*) and *White spotting* (w^s) alleles and affecting the feline coat patterns (David et al., 2014). The inserted sequences are copies of the

endogenous retroviral genomes. The insertion and integration of full-length 7125 bp *FEVR1* in *KIT* gene in the host genome cause the white spotting coat pattern whereas insertion of *FERV1* long terminal repeat (LTR) whose length is 623 bp into the same point causes the Dominant White pattern. It is reported that these endogenous retroviral genome sequences had come from ancestral infections and integrated into the genome (Song et al., 2013; David et al., 2014; Montague et al., 2014; Frischknecht et al., 2015; Strain, 2015). The orthologue of the Feline *KIT* gene found in the human genome is named *KIT* or c-*KIT*. It is a proto-oncogene for organisms and the products of the gene have a role for fetal development. The expression of the *KIT* gene is constitutionally maintained in particular cell types which are hemopoietic stem cells, mast cells, intraepithelial lymphocytes, germ cells, melanocytes, and interstitial cells of Cajal, and the product of the gene has a role as a growth factor receptor in these cells (Lammie et al., 1994; Gibson and Cooper, 2002; Morini et al., 2004). Besides, some cases of cutaneous mastocytosis, which is a hyperpigmentation-related disease, and Piebaldism which is a trait with the absence of melanocytes in affected regions of the skin and hair come out with the mutation of *c-KIT* gene in humans (Thomas et al., 2004; Bodemer et al., 2010; Kambe et al., 2010).

Researches on the syndromic association of these phenotypes in the cats are the result of the action of a *Dominant White (W)* locus, which is single autosomal dominant. *Dominant White (W)* locus demonstrates complete penetrance for suppression of pigmentation in the coat and incomplete penetrance for deafness and hypopigmentation of the iris (Bergsma et al., 1971). A recent study showed that none of the Turkish Van cats with the spot on their head had deafness. Also, it was reported that the observation of the highest deafness was very high in those with both blue eyes (Çelik, 2019).

The aim of this study was to determine the existence and frequency of *W* locus alleles of *KIT* gene in Turkish Van cats bred in Van Yüzüncü Yıl University Van Cat Research and Application Center and to evaluate the association between the presence of the particular alleles with eyes colors, head spotting, and hair length.

MATERIALS and METHODS

Sampling

The present study contained 48 Turkish Van cats bred in Van Yüzüncü Yıl University Van Cat Research and Application Center. The phenotypical characteristics of the chosen cats are shown in Table 1.

Table 1. The phenotypical characters of the Turkish Van Cats selected for this research.

Category	Variables	Cohort (N=48)
Gender	Males	33.33%
	Females	66.67%
Eyes Color	Blue-Blue	50.00%
	Amber-Blue	50.00%
Spotting on Head	Presence	27.08%
	Absence	72.92%
Hair Length	Short	25.00%
	Medium	4.17%
	Long	70.83%

DNA isolation

DNA isolations were carried out from the oral swaps taken from 48 Turkish Van cats. The study was approved by the Animal Researchers Local Ethics Committee of Van Yüzüncü Yıl University (Approval 28.04.2022, 2022/4-22 and 2022/11-16). Oral swap DNA isolation kit was used for DNA extractions (Hibrigen, Turkey). DNA isolations were carried out by following the manufacturer's protocols. Isolated DNA samples were stored at -20°C until PCR set-up.

Genotyping

To detect Dominant White (*W*), White spotting (w^s) and wild-type (w^+) alleles of the *KIT* gene, a previously described PCR-based genotyping method was carried out (David et al., 2014). *KIT* primer pairs F: 5'-ATTTTGAGATCTGCAACACCCCTTC-3' and R:

5′-TCCTCCACCTTCAGACCTAAGTTC-3′ were used to determine wild-type and white alleles of the *KIT* gene. For the wild-type allele, 171 bp amplicon length was expected, while the amplicon length would be 793 bp for the white allele. For detection of the white spotting allele, FERV F: 5′-GTCTTGGGGATCCCGGACGA-3′ and KIT R: 5′-TCCTCCACCTTCAGACCTAAGTTC-3′ primer pairs were used. In the PCR reaction with these primer pairs, 732 bp PCR product was expected for the white spotting allele. The primers were modified from the previously published study (David et al., 2014). The primer properties were also checked as described previously (Arslan, 2020).

PCR reaction contained 4 µl of 5xPCR master mix (FIREPol Master Mix, 7.5 mM $MgCl_2$, Solis Biodyne), 300 nM of each primer pair, 13.8 µl of PCR grade water, and 1 µl of DNA (~50 ng) sample for both w^+/W alleles and w^s alleles, separately. PCR cycling conditions were as follows: 5 min at 95 °C was followed by up to 35 cycles of 20 s at 95 °C, 40 s at 55 °C, and 1 min at 72 °C for both reactions. After that, agarose gel electrophoresis was performed with 2% agarose gel. Agarose gel was prepared as described previously (Arslan et al., 2021). For pre-casting staining of 150 ml gel, 5 µl fluorescent dye (DSView, DSBIO) was used. Electrophoresis was carried out at 90 volts (V) for 80 min.

Analysis

The Chi-square and Fisher's exact test were applied to investigate the association between detected alleles and genotypes of *W* locus of the *KIT* gene with different categorical variables. Statistical analyses were carried out by using R software (R version 4.0.2) (R Core Team, 2020). Statistical significance was determined at a p-value of 0.05. The allele frequency (F %) was determined as a percentage calculated by dividing the absolute count of each allele by the total number of alleles in each group.

RESULTS

The PCR products belonging to the *KIT* gene *W* locus alleles of the selected cats were resolved in agarose gel electrophoresis and the cats' genotypes were determined (Figure 3). According to the gel electrophoresis results, *W/W*, W/w^s, W/w^+ and w^+/w^+ genotypes were determined in the studied cats.

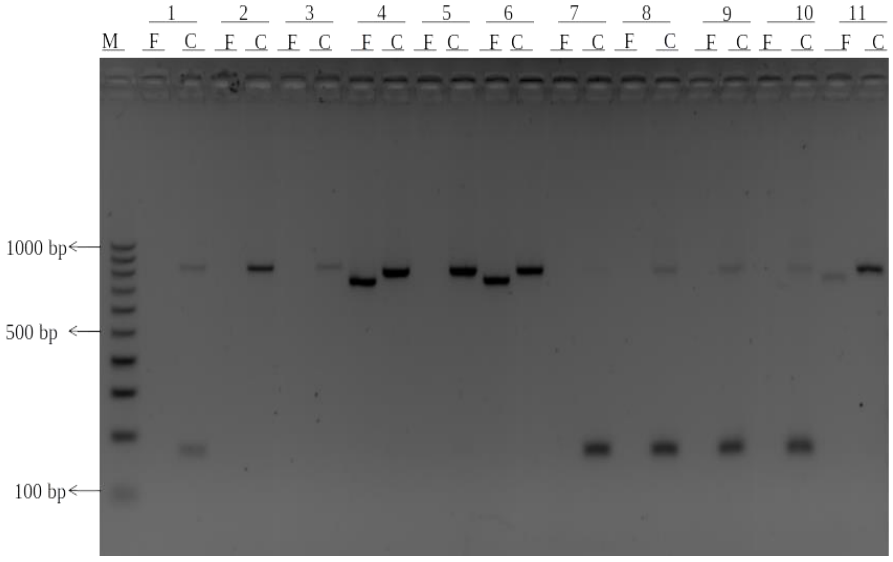

Figure 3. Agarose gel electrophoresis results of PCR analysis of *W* locus alleles of the *KIT* gene in Turkish Van cats. M indicates DNA marker (100-1000 bp). F indicates PCR products obtained from FERV forward and KIT reverse primers, and C indicates PCR products obtained by KIT primer pairs. 1, 8, 9 and 10 lines indicate W/w^+genotypes. 2, 3 and 5 lines indicate *W/W* genotypes. 4, 6 and 11 lines indicate W/w^s genotypes. Line 7 indicates w^+/w^+ genotype.

Genotypic and allelic distributions were shown in Figure 4. It was observed that most of the cat population had a homozygous *W/W* genotype (Figure 4a). Allele frequency of the White allele was the highest (61.46%), whereas white spotting allele frequency was the lowest (8.33%) in cats (Figure 4b). The frequency of the wild-type allele was found to be 30.21% (Figure 4b).

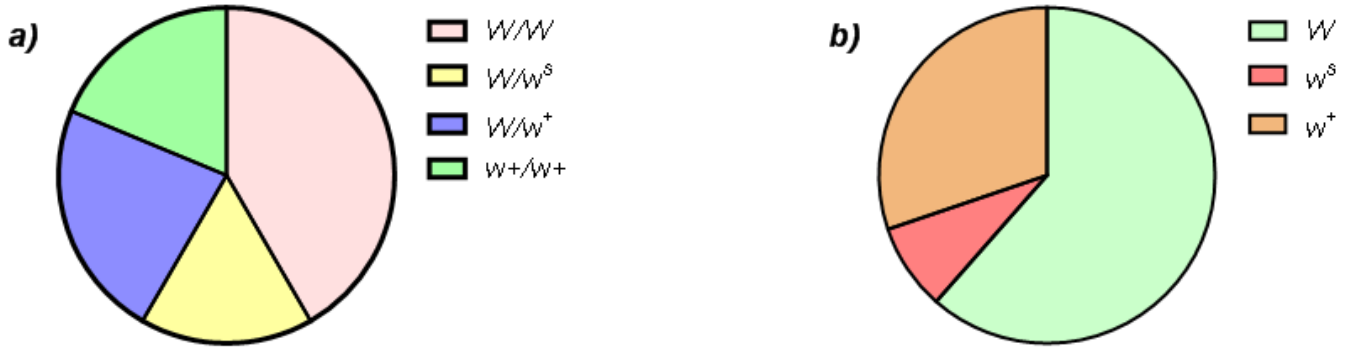

Figure 4. Distribution of genotypes and alleles of *W* locus of the *KIT* gene in cats. a) Genotypic distribution of Turkish Van cats. b) Allele frequencies of *W* locus alleles of *KIT* gene in Turkish Van cats.

The association between the genotype of the cats and the phenotypic features including eye color, head spotting, hair length was investigated by statistical calculations. It was found that 60.42% of the cohort had homozygous and 39.58% of this cohort had heterozygous genotype for *W* locus on the *KIT* gene. 41.76% of the cats had *W/W* with the highest frequency of genotypes and 18.75% of the cats had w^+/w^+ homozygous genotypes. 22.92% of the cats had W/w^+ and 16.67% of the cats had W/w^s heterozygous genotype. The frequency of *W*, w^+, w^s were 61.46%, 30.21%, 8.33%, respectively (Table 2-4).

Half of the cats with *W/W* (20.83%) genotype had amber-blue eyes, and the other half had blue eyes. In addition, the same ratio observed for cats with W/w^s genotype for eye color character. Besides, half of the cats with w^s allele (8.33%) had amber-blue eyes, and the other half had blue eyes. Approximately the same number of cats had amber-blue and blue eyes which had *W* and w^+ alleles (Table 2). No scientifically significant association was detected between *W* locus alleles and eye colors, indicating that eye color is not associated with *W* locus alleles of the *KIT* gene in Turkish Van cats.

Table 2. Genotypic and allelic distribution of *W* locus of *KIT* gene in Turkish Van cats according to the eyes color, and their association.

		Eye Colors N (%)		
Genotype	**Cohort N=48 (%)**	**Amber-Blue**	**Blue-Blue**	**p-Value**
W/W	20 (41.67%)	10 (20.83%)	10 (20.83%)	0.610
W/w^+	11 (22.92%)	7 (14.58%)	4 (8.33%)	
w^+/w^+	9 (18.75%)	3 (6.25%)	6 (12.50%)	
W/w^s	8 (16.67%)	4 (8.33%)	4 (8.33%)	
Allele	**N=96 (%)**	**Amber-Blue**	**Blue-Blue**	**p-Value**
W	59 (61.46%)	31 (32.29%)	28 (29.17%)	0.793
w^+	29 (30.21%)	13 (13.54%)	16 (16.67%)	
w^s	8 (8.33%)	4 (4.17%)	4 (4.17%)	

33.33% of the cats with *W/W* genotype had smooth head fur (with the highest genotype frequency), and 2,58% of the cats with *W/w*^{s} genotype had spotting on head fur (with minimum genotype frequency). Besides, the allele frequency of the cats with smooth head fur with the *W* allele was 47,92% and the frequency of the cats with spotting on head fur with *w*^{s} allele was 1.04%. It was determined that *W* locus genotype was not found to be associated head spotting pattern of cats. Allelic evaluation of this trait was also carried out, but no association was detected between *W* locus alleles of the *KIT* gene and head spotting pattern (Table 3).

Table 3. Genotypic and allelic distribution of *W* locus of the *KIT* gene in Turkish Van cats according to head spotting pattern, and their association.

		Head Spotting N (%)		
Genotype	**Cohort N=48 (%)**	**Spotting**	**Non-Spotting**	**p-Value**
W/W	20 (41.67%)	4 (8.33%)	16 (33.33%)	0.358
W/w^{+}	11 (22.92%)	4 (8.33%)	7 (14.58%)	
w^{+}*/w*$^{+}$	9 (18.75%)	4 (8.33%)	5 (10.42%)	
W/w^{s}	8 (16.67%)	1 (2.08%)	7 (14.58%)	
Allele	**N=96 (%)**	**Spotting**	**Non-Spotting**	**p-Value**
W	59 (61.46%)	13 (13.54%)	46 (47.92%)	0.099
w^{+}	29 (30.21%)	12 (12.50%)	17 (17.71%)	
w^{s}	8 (8.33%)	1 (1.04%)	7 (7.29%)	

Among the studied cats, cats with *W/W* genotype and long hair were the highest number. There was no cat with *w*$^{+}$*/ w*$^{+}$, *W/w*^{s} and medium hair in the cohort. Allele frequency of the cats with *W* allele and long hair was 44,79%. Genotype and hair length association analysis showed that *W* locus of the *KIT* gene was not associated with hair length in Turkish Van cats (p>0.05). Also, Association between alleles of *KIT* gene and hair length was performed, and the results indicated that there was no association between *W* locus alleles and hair length (p>0.05) (Table 4).

Table 4. Genotypic and allelic distribution of Turkish Van cats according to hair length pattern, and their association.

		Hair Type N (%)			
Genotype	**Cohort N=48 (%)**	**Long Hair**	**Medium Hair**	**Short Hair**	**p-Value**
W/W	20 (41.67%)	15 (31.25%)	1 (2.08%)	4 (8.33%)	0.458
W/w^{+}	11 (22.92%)	9 (18.75%)	1 (2.08%)	1 (2.08%)	
w^{+}*/w*$^{+}$	9 (18.75%)	6 (12.50%)	0 (0.00%)	3 (6.25%)	
W/w^{s}	8 (16.67%)	4 (8.33%)	0 (0.00%)	4 (8.33%)	
Allele	**N=96 (%)**	**Long Hair**	**Medium Hair**	**Short Hair**	**p-Value**
W	59 (61.46%)	43 (44.79%)	3 (3.13%)	13 (13.54%)	0.518
w^{+}	29 (30.21%)	21 (21.88%)	1 (1.04%)	7 (7.29%)	
***w*^{s}**	8 (8.33%)	4 (4.17%)	0 (0.00%)	4 (4.17%)	

DISCUSSION

Even though white cats are attractive due to their phenotypic patterns such as white fur and different eye color, they can suffer from deafness. The genes *MITF*, *PMEL*, *KIT*, *EDNRB*, *CDH23*, *TYR*, and *TRPM1* were identified and associated with deafness or white pigmentation patterns in many mammalian species such as cat, dog, horse, pig, cow, ship (Strain, 2015). A previous study highlighted that *FERV1* insertion of the *KIT* gene, which encodes the mast/stem cell growth factor tyrosine kinase receptor, was associated with white, white spotting, and deafness in cats (David et al., 2014). There was very limited knowledge about *W* locus of the *KIT* gene in Turkish Van cats. In the current study, for the first time, the genotype of the *KIT* gene in Turkish Van cats, which is a white cat breed, was studied in the high number of cats bred in Van Yüzüncü Yıl University Van Cat Research and Application Center.

The first report related to *W* locus of the *KIT* gene of Turkish Van cats came from David et al. (2014)' study. In the study, there were only two Turkish Van cats (n=2) among the studied cat breeds (n=270) and they found that *W* locus of *KIT* gene in these cats were homozygous white spotting alleles (w^s/w^s). In the present study, we studied 48 Turkish Van cats, and it was found that the most frequent genotype was homozygous white (*W/W*) (41.67%) (Figure 4). In contrast to the article by David et al. (2014), we did not detect any of the homozygous white spotting (w^s/w^s) genotypes in our Turkish Van cat study cohort. Furthermore, white spotting allele frequency was found to be lowest (8.33%), and wild type allele frequency (30.21%) was found to be higher than white spotting allele frequency (Figure 4). This result indicates that Turkish Van cats can carry all of the alleles, and their phenotypical patterns might not be dependent on the *W* locus of the *KIT* gene.

David et al. (2014) have reported an association between blue iris and *W* genotype. However, in the present study, we didn't establish any association between genotype or alleles of *W* locus and eye color in Turkish Van cats (Table 2). This situation may be specific to Turkish Van cats since David et al. (2014)' study contained a range of cat breeds and there were only two Turkish Van cats in their study. On the other hand, different genetic factors could have a role for the blue iris color in Turkish Van cats. Therefore, the iris color of Turkish Van cats can be affected by distinct genetic factors rather than the *W* locus of the *KIT* gene.

Another characteristic of Turkish Van cats is head spotting (or piebald) which is known as Van pattern among the white cats breeds (Cooper et al., 2006; Strain, 2017). Head spotting of Turkish Van cats has been associated with no-deafness (Çelik, 2019). Therefore, this character can be used for selective breeding to decrease the prevalence of deafness. We investigated the association between head spotting and genotype and allele *W* locus of the *KIT* gene but we could not find a relationship (Table 3). Similar to eye color characteristics, other genes can take the role to determine this pattern in Turkish Van cats.

Hair length can be a highly variable feature in cats' nature. It is well-known that different variations of the *fibroblast growth factor 5 (FGF5)* gene cause the different hair length in some species including cats (Shaffer et al. 2021). It was shown that the c-kit expression in certain cells in hair follicul implicated stem cell factor for regenerating hair bulbs (Randall, 2008). The *KIT* gene may influence on hair length. However, there is no research related to the *KIT* gene and hair length in cats. Therefore, in this study, we also evaluated the association between *W* locus alleles and hair length. However, we could not find an association between hair length and *W* locus alleles of the *KIT* gene ($p > 0.05$) (Table 4).

To conclude, Turkish Van cats can carry white, white spotting and wild-type alleles in the *W* locus of the *KIT* gene. Eye color, head spotting and hair length of Turkish Van cat could not be affected by *W* locus alleles of the *KIT* gene. Other genetic factors may be addressed to understand the genetic background of the cats' phenotypes.

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Conflict of interest

The authors declare that there is no conflict of interest.

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