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The association between canine hip dysplasia and *CHST14* pseudogene polymorphisms

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ABSTRACT

Canine Hip Dysplasia (CHD) is a multifactorial developmental disorder with complex polygenic hereditary characteristics. The purpose of this study was to determine the association between CHD and polymorphisms in the Carbohydrate Sulfotransferase-14 *(CHST14)* pseudogene, which is an active gene in humans and has a role in extracellular matrix stability and is related to Ehlers-Danlos Syndrome. There were 62 dogs included in this research: 46 in the experimental and 16 in the control group. DNA sequence analysis of *CHST14* pseudogene revealed four SNPs, two SNPs in exon 1 and two SNPs in the 3' untranslated region (UTR). Both SNPs in the 3' UTR were found to be associated with the disease ($P<0.05$). The novel CHD-associated SNP found in this study is located near the target sites of cfa-miR-212 and cfa-miR-8793. cfa-miR-212 also targets *TPM2, FBN2* and *FGF23*. cfa-miR-8793 targets *SULF1*. These genes play various roles in the development of the musculoskeletal system. Associated variations in 3' UTR might alter the miRNA decoy activity of the *CHST14* pseudogene and therefore affect the expression of the genes involved in cartilage and joint metabolism. Potential candidate genes in the biochemical pathways of the musculoskeletal system and their association with CHD should be explored further for a comprehensive understanding of this complex polygenic disorder in dogs.

Key words: hip dysplasia; *CHST14;* miRNA target; SNP; pseudogene; dog

Introduction

Canine Hip Dysplasia (CHD) is one of the most common developmental orthopaedic disorders in dogs worldwide. The pathophysiological process is similar to developmental dysplasia of the hip (DDH) and secondary osteoarthritis in humans. CHD and human DDH, two multifactorial and polygenic disorders, are moderately hereditary (TODHUNTER et al., 2003). Phenotype-based breeding methods have not been successful in decreasing CHD incidence. In this respect, additional diagnostic methods have been developed to uncover the genetic basis of CHD, and to create predictive models by determining various single nucleotide polymorphism (SNP)

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combinations as genetic markers (BARTOLOME et al., 2015).

Carbohydrate sulfotransferase *(CHST)* genes have a major part in glycosaminoglycan (GAG) synthesis. Studies on dogs revealed a relationship between a SNP near the *CHST3* gene and CHD (BARTOLOME et al., 2015). The enzyme encoded by *CHST3* takes part in the sulfation process. Another member of this family, *CHST14*, maintains stabilization of the dermatan sulphate in humans. Impaired *CHST14* activity causes epimerization/sulfation imbalance (TROWBRIDGE and GALLO, 2002). Loss of dermatan-4-sulfotransferase-1 (D4ST1) encoded by *CHST14* in humans reveals a different GAG composition in the fibroblasts, and results in destabilization of the extracellular matrix (ECM). These effects are prominent in Ehlers-Danlos syndromes, with clinical manifestations such as excessive elasticity of skin, joint hypermobility and general connective tissue fragility (DÜNDAR et al., 2009; KOSHO et al., 2010).

The canine *CHST14*, located in CFA30, was updated to a pseudogene in the recent Ensembl Annotation Release 107 (CUNNINGHAM et al., 2022). While it has been announced that *CHST14* is a novel pseudogene in dogs, it can still have a regulatory function in relation to CHD development. Most pseudogenes are transcriptionally silent, but several pseudogenes have been reported to have functions at RNA or protein level. The functions of pseudogenes can be categorized as natural antisense suppression, RNA interference, gene competition, and coding peptides (WEN et al., 2012). Pseudogenes can also regulate gene expression by acting as microRNA decoys (PINK et al., 2011).

In this study, we aimed to determine the polymorphisms of canine *CHST14*, a novel pseudogene, and analyse the association between these variants and CHD susceptibility.

Materials and methods

Samples. The case and control groups in the study were composed of 46 dogs with CHD and 16 healthy dogs, which were brought to the Surgery Department of the Faculty of Veterinary Medicine, Istanbul University-Cerrahpasa, between 2014 and 2016 (the study was approved by Istanbul University Animal Research and Ethics Committee with the protocol number 2014/68). DNA samples were obtained from the DNA collection of the Biochemistry Department of the Faculty of Veterinary Medicine, Istanbul University-Cerrahpasa. Data from 62 dogs (breed, age, gender and hip dysplasia score) were recorded.

Canine hip dysplasia was diagnosed according to physical and radiological examination findings. Ventro-dorsal hip radiographs were taken and the Norberg Angle was measured. Hip dysplasia scores were determined on the basis of the Norberg Angle, according to the FCI Fédération Cynologique Internationale (FCI) scoring criteria.

Polymerase chain reaction and sequencing. The *CHST14* gene was amplified and sequenced. The designed primers and their annealing temperatures are given in Table 1. Polymerase chain reaction amplifications were performed in a reaction volume of 25 µL using 1 U HotStartTaq polymerase, 2-2.5 µL 10XPCR buffer (100 mM KCl, 20 mM Tris HCl (pH=8.0), 0.1 mM

Table 1. Primers used in PCR and sequencing

Primer name	Primer sequence (5'-3')	Annealing temperature
CHST-F	ATGGAGATGAGCCACTGGTCAA	57 °C
CHST-R	AAGCCTTCACAAGGATTCCA	57 °C
Seq 3 (F)	ACAGCACTACTTCAAGTTCCT	57 °C
Seq 4 (F)	TGCCCCACGGGCCCT	62 °C
Seq 5 (F)	ACTGTGCCGTCCACCACTT	61 °C

Ethylenediaminetetraacetic acid (EDTA), 0.5 mM Phenylmethylsulfonyl fluoride (PMSF), 1 mM DTT, 50% glycerol), 2.5 mM $MgCl_2$, 50-100 ng genomic DNA, 100 µM dNTP and 10 pmol of each primer. Amplifications were carried out with an initial denaturation at 95°C for 1 min; 30 cycles of 95°C for 20 sec, primer-specific annealing temperature for 40 sec, 72°C for 4 min; and a final extension at 72°C for 7 min. After the purification of the PCR products, sequencing was performed using an ABI-3100 sequencer (PE Biosystems, Germany) and the BigDyeTM terminator cycle sequencing kit (ThermoFisher Scientific, USA).

DNA sequences were aligned using ClustalW in MEGA X software (KUMAR et al., 2018). SNPs were determined on the basis of the comparison of the samples and the reference sequence of canine *CHST14* (GenBank accession number NC_051834).

Statistical analysis. Statistical analysis was performed using the SPSS 25.0 program (IBM CORP, 2011). The allele frequencies and genotype frequencies of the SNPs in the case and control groups were calculated. Binary logistic regression analyses were applied in order to investigate the association between SNPs and CHD susceptibility. For the alleles and genotypes of each SNP, crude odds ratios (OR) and odds ratios, adjusted for age, breed and sex, were estimated with a 95% confidence interval. ORs with a 95% interval were calculated using the minor allele as the reference group. For regression analysis, the dogs were grouped according to their breeds (medium-small pure breeds, large pure breeds and mixed breeds), and ages (≤ 12 months, 13-84 months and ≥84 months). Breeds were grouped according to the Fédération Cynologique Internationale breeds nomenclature system (FCI, 2013). Binary logistic regression analysis was also performed with age, breed and sex alone, to determine the effects of these variables, other than SNPs. The statistical significance level was determined as $P<0.05$.

Bioinformatics. The miRNAs which are predicted to target the *CHST14* pseudogene were listed using the miRDB database (CHEN and WANG, 2020) and the TargetScanHuman 8.0 database (AGARWAL et al., 2015; MCGEARY et al., 2019). The miRNA target sites in 3'UTR of the *CHST14* pseudogene were also determined using TargetScanHuman 8.0 to investigate the effects of CHD-associated SNPs on miRNA seed sequences. Other potential target genes of the miRNAs were also predicted using miRDB and TargetScanHuman 8.0. The functions of these genes were taken from the UniProt Knowledgebase (UniProtKB) (UNIPROT, 2021). The target genes with functions which might be related to CHD were chosen.

Results

DNA sequence analysis revealed four SNPs in the *CHST14* gene. Two variants (C/G and T/C polymorphisms) in exon 1 and two variants (C/G and C/T polymorphisms) in 3' UTR of the *CHST14* pseudogene were identified. Minor allele frequencies and the association of SNPs with hip dysplasia are given in Table 2. Minor allele frequencies in total varied between 0.14 and 0.49. Association analysis adjusted for breed, age and sex showed that two SNPs in 3'UTR of the *CHST14* were significantly related to CHD ($P<0.05$). Crude ORs, adjusted ORs and adjusted P-values are given in Table 2. The G allele of rs851616627 and the T allele of the novel SNP in 3' UTR might be accepted as risk alleles. When all the SNPs and other factors were analysed together, no statistically significant effect of breed, age and sex was determined on CHD susceptibility. However, according to the regression analysis with variables other than SNPs, the risk for CHD was higher in large purebred dogs than in mixed breeds (Table 3).

According to the miRDB and TargetScan 8.0 databases, there is a total of 11 miRNAs targeting 3' UTR of the canine *CHST14*, namely: cfa-miR-124, cfa-miR-8793, cfa-miR-544, cfa-miR-9, cfa-miR-8795, cfa-miR-140, cfa-miR-8796, cfa-miR-590, cfa-miR-8847, cfa-miR-193a and cfa-miR-212. To investigate the possible interaction between these miRNAs and two CHD-associated SNPs (rs851616627 and the novel SNP found in this study), the distances between the miRNA seeds and the SNPs were determined on the basis

Table 2. The association between *CHST14* polymorphisms and canine hip dysplasia

SNP	Genome position	Allelles	Minor allele	Minor allele frequency		Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted P-value
				Total	CHD			
rs852536290	30: 7.640.710	G/C	C	0.45	0.47	0.780 (0.345-1.763)	0.568 (0.226-1.427)	0.229
rs852245958	30: 7.642.721	C/T	T	0.49	0.51	1.377 (0.590-3.213)	1.323 (0.520-3.369)	0.557
rs851616627	30: 7.642.918	C/G	G	0.41	0.49	3.818 (1.419-10.270)	3.316 (1.161-9.469)	0.025*
Novel SNP	30:7.643.323	C/T	T	0.14	0.18	6.889 (0.875-54.250)	12.458 (1.271-122.105)	0.030*

SNP: single nucleotide polymorphism, CHD: canine hip dysplasia

Table 3. The effects of the breed, age and sex of the dogs on canine hip dysplasia

Factors	Groups	P-values	OR	OR (95% CI)
Breed	Mixed		1 (Ref.)	
	Small-medium	0.095	0.164	0.020-1.373
	Large	0.030*	0.205	0.049-0.861
Age	≥84 months		1 (Ref.)	
	13-84 months	0.347	0.510	0.126-2.071
	≤ 12 months	0.343	1.858	0.516-6.684
Sex	Female		1 (Ref.)	
	Male	0.986	1.008	0.403-2.523

Table 4. The distances between the CHD-associated SNPs and miRNA seed regions

CHD-associated SNP	Predicted miRNA	Distance from seed region
rs851616627	cfa-mir-8847	58 nt upstream
Novel SNP	cfa-mir-8796	26 nt upstream
	cfa-mir-8793	32 nt upstream
	cfa-mir-124	42 and 62 nt upstream
	cfa-mir-212	6 nt downstream
	cfa-mir-8795	63 nt downstream
	cfa-mir-9	67 nt downstream
	cfa-mir-193a	70 nt downstream

of the ROS_Cfam_1.0, whole genome shotgun sequence (accession number: NC_051834.1). The SNP rs851616627 was found to be near the cfa-miR-8847 seed region, and the novel SNP was found to be near the seed regions of seven miRNAs, namely: cfa-mir-8796, cfa-mir-8793,

Table 5. Other potential target genes and their functions

miRNA	Gene Symbol	Gene Description	Gene Function (UniProtKB)
cfa-miR-124	FLOT2	flotillin 2	regulation of myoblast differentiation
	SBNO2	strawberry notch homolog 2	osteoclast differentiation
	PLEKHM3	pleckstrin homology domain containing M3	myoblast differentiation, skeletal muscle differentiation
cfa-miR-8793	SULF1	sulfatase 1	heparan sulphate proteoglycan metabolic process, glycosaminoglycan binding, bone, cartilage, chon drocyte development
cfa-miR-9	TGFBI	transforming growth factor beta induced	collagen binding, extracellular matrix binding, integrin binding
	DSE	dermatan sulphate epimerase	dermatan sulphate metabolic process, chondroitin sulphate metabolic process
	FBN1	fibrillin 1	integrin binding, heparin binding, skeletal system development, sequestering of BMP in extracellular matrix, sequestering of TGF beta in extracellular matrix
	TNC	tenascin C	neuromuscular junction development
cfa-miR-193a	SYNM	synemin	form a linkage between desmin, and the extracellular matrix, and provides an important structural support in muscle
	ACVR1	activin receptor type-1	bone, heart, cartilage, nervous, and reproductive system development and regulation
cfa-miR-212	TPM2	tropomyosin 2	binding to actin filaments in muscle and non-muscle cells. regulation of vertebrate striated muscle contraction
	GDF11	growth differentiation factor 11	skeletal system development
	FBN2	fibrillin 2	Regulation of the early process of elastic fiber assembly, regulation of osteoblast maturation
	FGF23	fibroblast growth factor 23	regulator of vitamin-D metabolism, osteoblast differentiation and matrix mineralization

cfa-mir-124, cfa-mir-212, cfa-mir-8795, cfa-mir-9 and cfa-mir-193a. The distances between the CHD-associated SNPs and the seed regions are shown in Table 4. Five of these miRNAs target 14 genes in total, which are involved in metabolic pathways such as extracellular matrix organization, myoblast differentiation, collagen binding, integrin binding, heparan and dermatan sulphate metabolic processes, and bone, cartilage and muscle development (Table 5).

Discussion

CHD is a common hereditary disorder mainly affecting large-sized dog breeds. Due to its complex nature, the genetic background of CHD has remained unclear. Previous studies have revealed multiple loci associated with CHD, and many candidate genes in different pathways. In this case-control study, we performed an association analysis between CHD and the canine *CHST14* pseudogene. There are abundant data regarding the results of mutations in the human *CHST14*

gene. DÜNDAR et al. (2009) reported impaired chondroitin and dermatan sulphate balance in individuals with Ehlers-Danlos musculocontractural type-1 syndrome, characterized by loss of the activity of the D4ST1 enzyme, encoded by the *CHST14* gene in humans. An autosomal recessive disease in humans, the Adducted-Thumb Clubfoot Syndrome (ATCS), develops due to a mutation in the *CHST14* gene (MIZUMOTO et al., 2017).

This is the first association study in the literature analyzing the relationship between the *CHST14* pseudogene and CHD. According to the association analysis, two SNPs in 3' UTR were found to be significantly associated with CHD. Pseudogenes are one of the miRNA sponges, also called ceRNAs or miRNA decoys, which competitively bind the miRNAs of other target genes. Due to the reduction in the activity of the related miRNA, expressions of other target genes are upregulated (ZHANG et al., 2021). The *CHST14* pseudogene might act as an miRNA decoy and release some genes involved in metabolic pathways related to CHD, from the miRNA control. The miRNAs, cfa-miR-124, cfa-miR-8793, cfa-miR-544, cfa-miR-9, cfa-miR-140, cfa-miR-193a, cfa-miR-212 and cfa-miR-590, that the *CHST14* transcript can bind, were found to be regulating factors in the extracellular matrix organization, myoblast differentiation, collagen binding, integrin binding, heparan and dermatan sulphate metabolic processes, and bone formation.

In this study, we found a significant association between two SNPs in 3' UTR of the *CHST14* and CHD. These SNPs might have an effect on the function of miRNAs which have seed regions near them. The SNPs located in 3′ UTRs could alter miRNA target sites, but the entire 3′ UTR sequence could also affect miRNA function in addition to miRNA targeting (HU and BRUNO, 2011). Previous studies suggested that 3′ UTR sequences outside of the seed sequences might play a role in miRNA targeting by controlling the accessibility of the miRNA or local RNA structure (GRIMSON et al., 2007). The distance between two SNPs and the miRNA seed regions in 3' UTR of *CHST14* varies between 6 and 70 nucleotides. The nearest SNP (six nucleotides) to the cfa-miR-212 target site is the novel one, which was found to be associated with CHD. cfa-miR-212 targets four other genes involved in the musculoskeletal system. *TPM2* plays a role in the regulation of muscle contraction. *FBN2* and *FGF23* are involved in osteoblast maturation differentiation. GDF11 has a part in skeletal system development. The novel SNP is also located 32 nucleotides upstream from the seed region of cfa-miR-8793. This miRNA targets *SULF1*, which has a role in bone, cartilage and chondrocyte development by glycosaminoglycan binding. The novel SNP might affect the cfa-miR-212 and cfa-miR-8793 targeting the *CHST14* pseudogene, and thus alter its miRNA sponge effect and change the expression profiles of the genes mentioned above. These changes might lead to CHD susceptibility in dogs. Other potential target genes of the miRNAs have target sites near the two CHD-associated SNPs, and their functions are shown in Table 5. Further studies are needed to uncover the specific mechanisms. With future studies confirming these data in different dog populations, *CHST14* variations may be found to have the potential to be used as preventive markers against hip dysplasia in dog breeding.

In conclusion, we found two SNPs in the 3' UTR of the canine *CHST14*, which have a significant association with CHD. We think that these variants might alter the miRNA decoy process of the *CHST14* pseudogene, and therefore change the expression of other candidate genes involved in cartilage and joint metabolism.

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SAŽETAK

Displazija kuka u pasa (CHD) multifaktorski je razvojni poremećaj sa složenim poligenskim nasljednim značajkama. Cilj istraživanja bio je ustanoviti povezanost između CHD-a i polimorfizama pseudogena ugljikohidratne sulfotransferaze 14 (*CHST14*), koji je aktivan gen u ljudi i sudjeluje u stabilnosti izvanstaničnog matriksa te je povezan s Ehlers-Danlosovim sindromom. U istraživanje su uključena 62 psa, među kojima je 46 pasa svrstano u eksperimentalnu skupinu, a 16 pasa u kontrolnu skupinu. Sekvenciranje DNA pseudogena *CHST14* pokazalo je četiri pojedinačna nukleotidna polimorfizma (SNP), dva u eksonu 1 i dva u netranslatiranoj regiji 3' (UTR). Utvrđeno je da su oba SNP-a u UTR 3' povezana s bolešću ($P<0,05$). Novi SNP povezan s displazijom kuka u pasa u ovom istraživanju smješten je blizu ciljnih mjesta cfa-miR-212 i cfa-miR-8793. cfa-miR-212 također je usmjeren na gene *TPM2*, *FBN2* i *FGF23* dok je cfa-miR-8793 usmjeren na gen *SULF1*. Ovi geni imaju različite uloge u razvoju mišićno-koštanog sustava. Varijacije koje su povezane u UTR 3' mogu promijeniti miRNA aktivnost pseudogena *CHST14* i tako utjecati na ekspresiju gena uključenih u metabolizam hrskavice i zglobova. Potrebno je dodatno istražiti potencijalne kandidatne gene u biokemijskim mehanizmima mišićno-koštanog sustava i njihovu povezanost s displazijom kuka radi sveobuhvatnog razumijevanja ovog složenog poligenskog poremećaja u pasa.

Ključne riječi: displazija kuka; *CHST14*; ciljna miRNA; SNP; pseudogen, pas