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Screening of Candidates Genes of Diabetes Mellitus Type 1 in Dog by Bioinformatics Translational Study

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Abstract. National Center for Biotechnology Information (NCBI) is an extensively impacted genetic database for big data analysis for bioinformatics studies in all organisms. At the same time, Human-Mouse: Disease Connection (HMDC) is a complete database for mutated gene information in many human and mouse disease models. Diabetes mellitus (DM) type 1 is a common and deadly degenerative disease in dogs, so looking for candidate genes for type 1 DM)genetic markers in dogs is essential. This study aimed to search for candidate genetic markers of DM type 1 in dogs by comparing human and mouse model databases through bioinformatics studies. This study used the HMDC database to find candidate genes of type 1 DM genetic markers with endocrine system disease limitations, then continued to check the accession number and similarity of nucleotide identity from each genetic marker, comparing dogs, humans, and mice. The results identified as many as seven candidate genes for DM type 1 genetic markers in dogs out of 16 candidate genes for DM type 1 humans and mice models. This study concluded that utilizing NCBI and HMDC tools could find the candidate genes for DM type 1 genetic markers in dogs. The findings contribute to molecular diagnostic demand in veterinary medicine, especially for dogs' DM disease.

Keywords bioinformatics, diabetes mellitus, genetic markers, pet animal, translational research

Introduction

NCBI (National Center of Biotechnology Information) is a big data database of molecular data often used for medical genetic research through bioinformatics (1). In addition to NCBI, HMDC (Human-Mouse: Disease Connection) is a big data database for genetic mutation information in human diseases or disease models in mice. NCBI and HDMC are open sources so researchers can utilize them efficiently and for free (2). However, information related to genetic mutations related to animal diseases does not yet have a comprehensive database, so bioinformatics studies to examine in silico genetic mutations in pet diseases are needed. One degenerative disease often appearing in pets is diabetes mellitus (DM) (3). HDMC has a complete genetic disorder database that characterizes type 1 diabetes mellitus in humans and mice. Type 1 DM occurs due to damage to the endocrine part of the pancreas caused by genetic mutations (4).

DM is common in medium and old-age dogs, with the prevalence of DM incidence in the world population around 0.2%-1.2%, and certain dog breeds have a genetic predisposition, such as Samoyeds, Tibetan Terriers, Cairn Terriers, and other breeds can easily suffer from DM (5). Data in America, 2012, as many as 165,000 dogs had diabetes, and about 1/10 dogs with DM must be euthanized yearly. In addition, the cost of DM treatment in dogs is estimated at $ 70 per month for insulin costs alone, not included in the cost of medication and other treatments (6).

Therefore, the research gap that will be answered through this study is that there has been no bioinformatics study for detecting candidate genetic markers DM type 1 in dogs. This study aims to conduct big data research analysis of genetic markers that characterize the incidence of type 1 DM in dogs through bioinformatics studies using NCBI and HDMC. In this study, the investigator found seven candidate genes of DM type 1 genetic markers in dogs for early detection through bioinformatics studies that can be applied to molecular diagnostics and genetic epidemiology in degenerative diseases in dogs, especially diabetes mellitus

Materials and Methods

The research material required two significant database sources, NCBI and HMDC. HMDC is used to look for genetic abnormalities in type 1 DM in human and animal mice models as genetic markers with endocrine system disease filter limitations. NCBI is required to search the DM 1 genetic marker database profile in dog species and nucleotide blasting analysis to identify the percentage of identity between dogs, humans, and mice. This study used 16 genetic markers of type 1 DM specific to endocrine system disease, namely 1) angiotensin I converting enzyme (ACE), 2) acid phosphatase 1 (ACP1), 3) advanced glycosylation end-product specific receptor (AGER), 4) Allograft Inflammatory Factor 1 (AIF), 5) autoimmune regulator (AIRE), 6) aldehyde dehydrogenase 2 family member (ALDH2), 7) apolipoprotein C3 (APOC3), 8) apolipoprotein M (APOM), 9) B cell scaffold protein with ankyrin repeats 1 (BANK1), 10) Butyrylcholinesterase (BCHE), 11) Betacellulin (BTC), 12) Cbl proto-oncogene B (CBLB), 13) C-C motif chemokine ligand 5 (CCL5), 14) C-C motif chemokine receptor 2 (CCR2), 15) C-C motif chemokine receptor 5 (CCR5), and 16) CD28 molecule (CD28), as listed in **Table 1.**

Searching for DM type 1 genetic markers in humans and mice on HMDC

Diagnosing DM type 1 genetic markers at HDMC was conducted at https://www.informatics.jax.org/diseasePortal website address. Then, we chose a search keyword based on the name of the disease with the keyword diabetes mellitus type 1 **(Fig.1)**. The results of the database search from HDMC gave the results that the genes have mutations in DM type 1 in humans and mice and filtered specifically in endocrine system disease, then obtained 16 genetic markers DM type 1 related to endocrine system disease **(Fig 2)**.

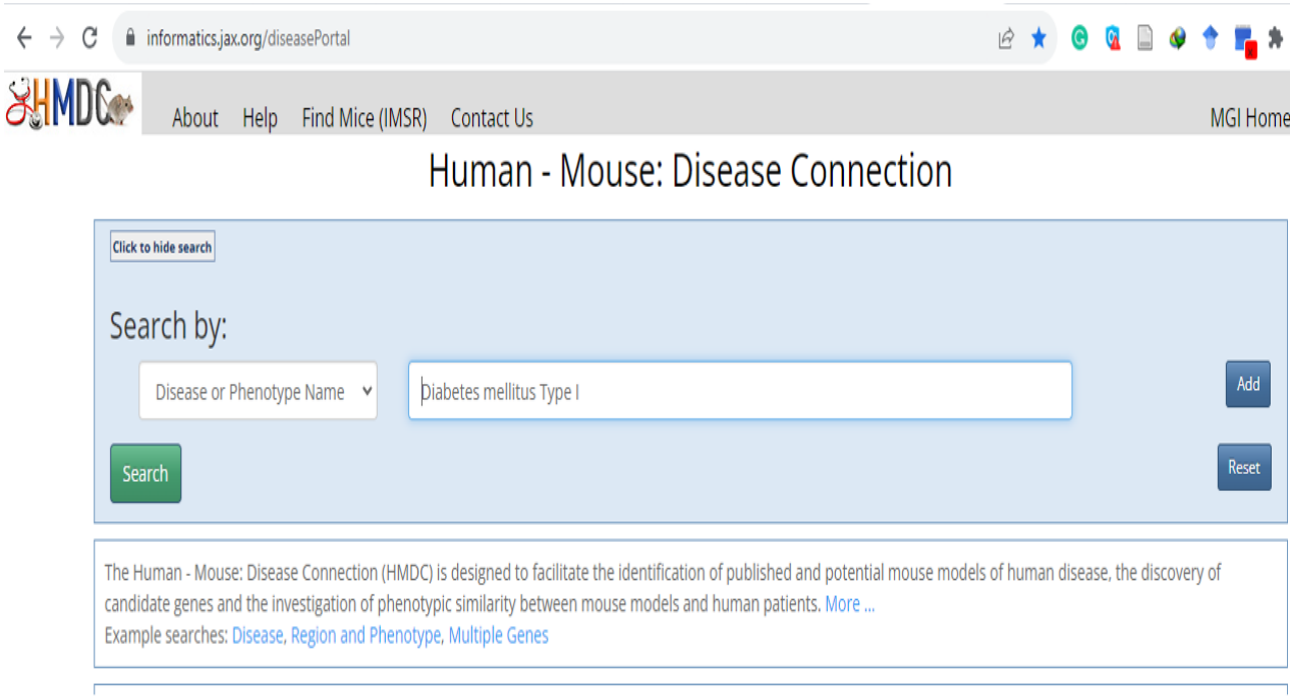
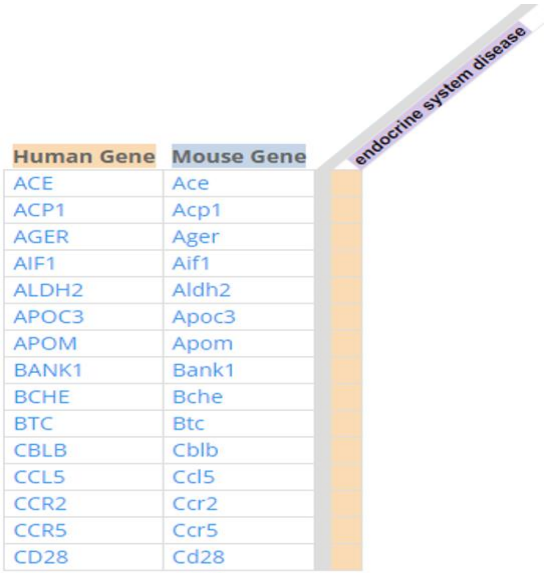


Figure 1. HMDC display for browsing of genetic mutation databases in specific diseases in human and animal mouse models



Human Gene	Mouse Gene
ACE	Ace
ACP1	Acp1
AGER	Ager
AIF1	Aif1
ALDH2	Aldh2
APOC3	Apoc3
APOM	Apom
BANK1	Bank1
BCHE	Bche
BTC	Btc
CBLB	Cblb
CCL5	Ccl5
CCR2	Ccr2
CCR5	Ccr5
CD28	Cd28

Figure 2. The results of the DM type 1 genetic markers filter related explicitly to endocrine system disease.

Detection of the presence of a database of DM type 1 genetic markers in dogs in NCBI

HMDC search results in the form of 15 DM type 1 genetic marker related to endocrine system disease,

then each genetic marker was traced to the existence of DM type 1 genetic marker in dogs through the NCBI website (https://www.ncbi.nlm.nih.gov/) through an advanced search on genes with gene name filters and dog organism names, namely "Canis lupus familiaris" **(Fig 3)**. The search results were then continued the orthologs table for browsing humans (Homo sapiens), mice (Mus musculus), and dogs (Canis lupus familiaris) **(Fig 4)** to obtain the nucleotide accession number and amino acid length of each DM type 1 genetic marker.

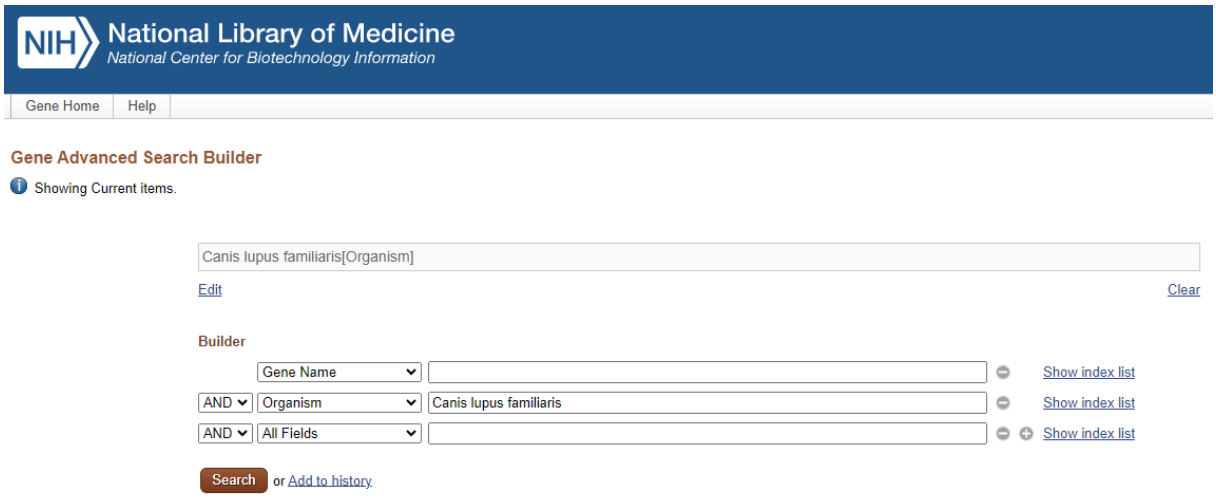


Figure 3. Searching the database of DM type 1 genetic markers in dogs through NCBI

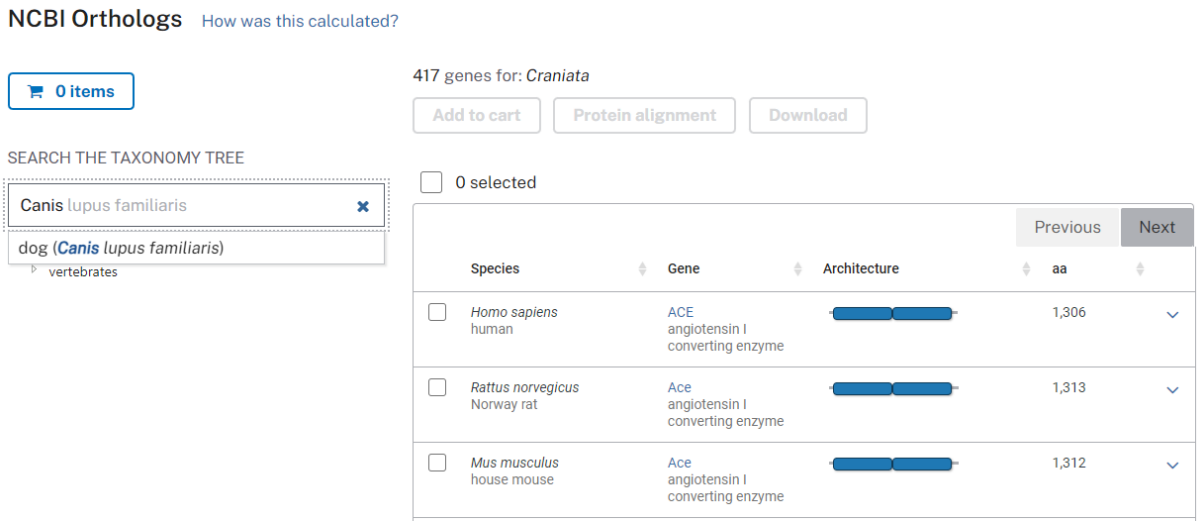


Figure 4. Filtering NCBI orthologs of specific genes in NCBI based on the type of organism

Examining the percentage of identity nucleotide DM type 1 genetic markers

The next stage was to check the similarity of nucleotide sequence related to the results of tracing

genetic markers DM type 1 in dogs compared to databases in humans and mice through BLAST nucleotide with align two sequences in NCBI **(Fig 5)**. The information on accession numbers of each genetic marker from humans, mice, and dogs was recapitulated from previous steps.

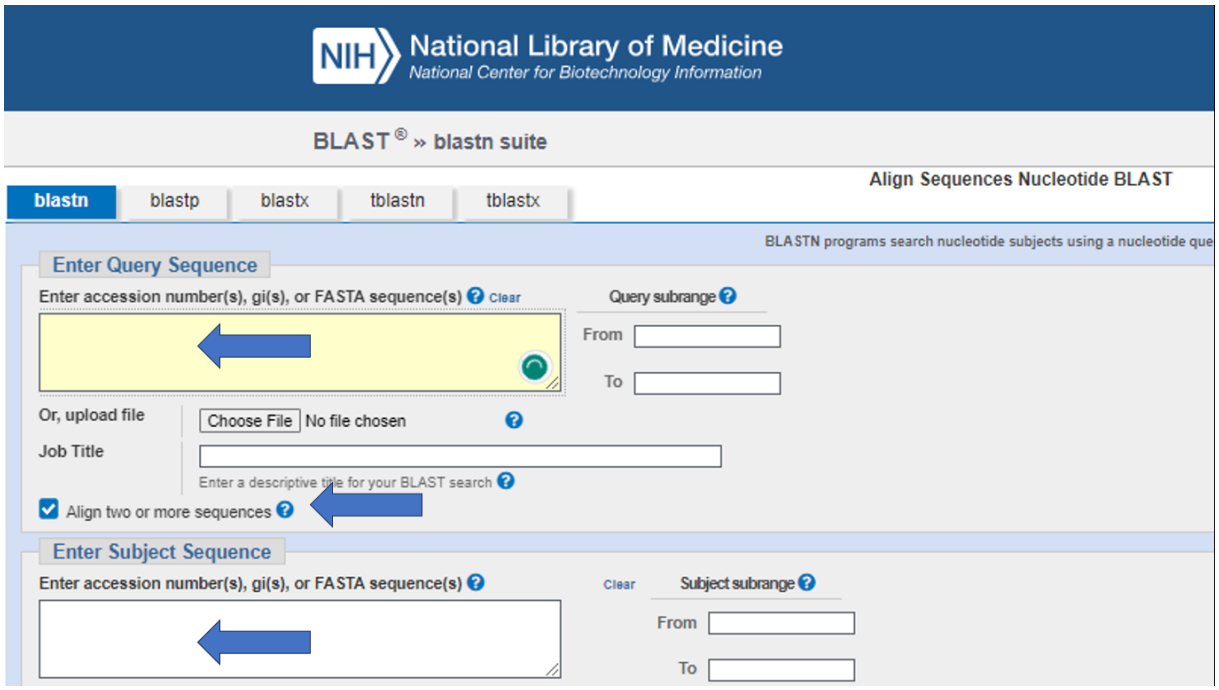


Figure 5. Percentage identity of nucleotide genetic markers DM type 1 screening in dogs, humans, and mouse model animals using BLAST nucleotide NCBI. Input the accession number of each genes by humans versus dog or mouse versus dog (blue arrow).

Data analysis.

Data on each DM type 1 genetic marker's profile and similarity was analyzed comparatively among humans, mice, and dogs with DM type 1 endocrine system disease. The results of the analysis are displayed in tabular form and explained comparatively.

RESULTS

The presence and comparison of DM type 1 genetic markers in dog

The results of a database search of DM type 1 genetic markers in dogs based on information from a database of human and animal models of mice in DM type 1 with endocrine system disease limitations

showed that there were 16 genetic markers. Details of the profiles of the 16 genetic markers in humans, mice, and dogs are presented in **Table 1.**

Table 1. Profile of 16 genetic markers of DM type 1 endocrine disease in humans, mouse, and dog

No	Gene Name	Acronym	Accession number of transcript and length of the amino acid		
			Human database	Mouse database	Dog database
1	angiotensin I converting enzyme	ACE	NM_000789.4 (1,306 aa)	NM_207624.6 (1,312 aa)	XM_038546924.1 (1,317 aa)
2	acid phosphatase 1	ACP1	NM_004300.4 (158 aa)	NM_021330.4 (158 aa)	XM_038453310.1 (158 aa)
3	advanced glycosylation end-product specific receptor	AGER	NM_001136.5 (404 aa)	NM_007425.3 (402 aa)	NM_001048081.3 (404 aa)
4	Allograft Inflammatory Factor 1	AIF1	NM_001623.5 (147 aa)	NM_019467.4 (147 aa)	XM_532072.7 (147 aa)
5	autoimmune regulator	AIRE	NM_000383.4 (545 aa)	NM_009646.2 (552 aa)	XM_022413324.2 (584 aa)
6	aldehyde dehydrogenase 2 family member	ALDH2	NM_000690.4 (517 aa)	NM_009656.4 (519 aa)	XM_848535.6 (521 aa)
7	apolipoprotein C3	APOC3	NM_000040.3 (99 aa)	NM_023114.4 (99 aa)	NM_001003369.2 (100 aa)
8	apolipoprotein M	APOM	NM_019101.3 (188 aa)	NM_018816.2 (190 aa)	XM_038553524.1 (235 aa)
9	B cell scaffold protein with ankyrin repeats 1	BANK1	NM_017935.5 (785 aa)	NM_001033350.3 (783 aa)	XM_038444246.1 (774 aa)
10	Butyrylcholinesterase	BCHE	NM_000055.4 (602 aa)	NM_009738.3 (603 aa)	NM_001313861.2 (602 aa)
11	Betacellulin	BTC	NM_001729.4 (178 aa)	NM_007568.5 (177 aa)	XM_038452061.1 (181 aa)
12	Cbl proto-oncogene B	CBLB	NM_170662.5 (982 aa)	NM_001033238.1 (938 aa)	XM_545087.7 (983 aa)
13	C-C motif chemokine ligand 5	CCL5	NM_002985.3 (91 aa)	NM_013653.3 (91 aa)	NM_001003010.2 (91 aa)
14	C-C motif chemokine receptor 2	CCR2	NM_001123396.4 (360 aa)	NM_009915.2 (373 aa)	**Unavailable**
15	C-C motif chemokine receptor 5	CCR5	NM_001394783.1 (352 aa)	NM_009917.5 (354 aa)	**Unavailable**
16	CD28 molecule	CD28	NM_006139.4 (220 aa)	NM_007642.4 (218 aa)	NM_001003087.2 (221 aa)

The search results found two genetic markers (2/16) of DM type 1 endocrine system disease, namely CCR2 and CCR5, were not available in the dog genetic database, and 14 other genetic markers (87.5%) were found in dogs and had amino acid lengths that did not differ much between humans, and mice.

The percentage identity of DM type 1 genetic markers among humans, mice, and dog

The similarity of nucleotide DM type 1 genetic marker (endocrine system disease) in dogs in humans and mice has been analyzed BLAST nucleotide on 14 types of DM type 1 genetic marker **(Table 1)**. The results of the nucleotide genetic markers similarity test are presented in **Table 2**. In this research, the researcher uncovered seven promising genes linked to Type 1 DM in dogs, using bioinformatics methods. These genes are potential markers for early detection, offering valuable applications in the fields of molecular diagnostics and the genetic study of degenerative diseases, particularly diabetes mellitus, in canines.

The analysis showed that one genetic marker (1/14) of type 1 DM from dogs, CD28 molecules, had no significant resemblance to that in humans. However, as many as six canine DM type 1 genetic marker (42.86%), including ACP1, AGER, AIF1, APOC3, BCHE, and BTC, did not have significant similarities in mouse DM type 1 disease models. While seven genetic markers (50%) in canine DM type 1, namely ACE, AIRE, ALDH2, APOM, BANK1, CBLB, and CCL5, have similarities in genetic markers from humans and mice models with a percentage of similarity above 70%. Therefore, we believe these seven genetic markers are reliable for candidate DM type 1 genetic markers for early detection of DM type 1 in dogs.

Table 2. Percentage identity dari DM type 1 genetic markers among human, mouse and dogs using BLAST nucleotide NCBI.

Percentage identity*			Organism		
Genetic markers		Organism	Human (Homo sapiens)	Mice (Mus musculus)	Dog (Canis lupus familiaris)
1	angiotensin I converting enzyme (ACE)	Human		83.21%	87.26%
		Mice	83.21%		83.35%
		Dog	87.26%	83.35%	
2	acid phosphatase 1 (ACP1)	Human		86.75%	84.12%
		Mice	86.75%		**No sig. identity**
		Dog	84.12%	**No sig. identity**	
3	advanced glycosylation end-product specific receptor (AGER)	Human		81.99%	84.20%
		Mice	81.99%		**No sig. identity**
		Dog	84.20%	**No sig. identity**	
4	allograft inflammatory factor 1 (AIF1)	Human		85.16%	86.88%
		Mice	85.16%		**No sig. identity**
		Dog	86.88%	**No sig. identity**	
5	autoimmune regulator (AIRE)	Human		77.69%	82.20%
		Mice	77.69%		78.11%
		Dog	78.11%	82.20%	
6	aldehyde dehydrogenase 2 family member (ALDH2)	Human		86.97%	85.71%
		Mice	86.97%		85.38%
		Dog	85.71%	85.38%	
7	apolipoprotein C3 (APOC3)	Human		**No sig. identity**	84.79%
		Mice	**No sig. identity**		**No sig. identity**
		Dog	84.79%	**No sig. identity**	
8	apolipoprotein M (APOM)	Human		**No sig. identity**	85.91%
		Mice	**No sig. identity**		82.55%
		Dog	85.91%	82.55%	
9	B cell scaffold protein with ankyrin repeats 1 (BANK 1)	Human		78.20%	82.61%
		Mice	78.20%		75.42%
		Dog	82.61%	75.42%	
10	Butyrylcholinesterase (BCHE)	Human		80.17%	88.51%
		Mice	80.17%		**No sig. identity**
		Dog	88.51%	**No sig. identity**	
11	Betacellulin (BTC)	Human		**No sig. identity**	84.18%
		Mice	**No sig. identity**		No sig. identity
		Dog	84.18%	**No sig. identity**	
12	Cbl proto-oncogene B (CBLB)	Human		88.28%	91.53%
		Mice	88.28%		87.83%
		Dog	88.28%	91.53%	

Discussion

This study has found seven genetic markers that can be used for early detection of DM type 1 in dogs, namely ACE, AIRE, ALDH2, APOM, BANK1, CBLB, and CCL5. These results contrast with previous research by Short et al., which showed that cytokine-related inflammatory genes strongly influence the incidence of diabetes in dogs (7). The previous study examined the incidence of SNP (Single Nucleotide Polymorphism) in several genes, including IFNγ, IGF2, IL-10, IL-12β, IL-6, insulin, PTPN22, RANTES, IL-4, IL-1α, and *TNFα in dogs confirmed with diabetes*. This study used bioinformatics studies based on genetic mutation databases in DM type 1 with endocrine system disease filters in humans and mice models in HDMC, which then searched the gene database in dog organisms at NCBI so that the genetic markers found in this study are very relevant as translational research between humans, mice, and dogs. Therefore, these seven genetic markers are considered for early detection of DM type 1 in dogs because they have a percentage of identity above 70% between humans, mice, and dogs.

Each genetic marker above is associated with endocrine system disorders in type 1 diabetes mellitus. The ACE gene (angiotensin I converting enzyme) encodes the enzyme angiotensin involved in regulating vascular pressure and electrolyte balance (8). The existence of diabetes mellitus conditions is characterized by hyperglycemia that disrupts blood pressure and electrolyte balance, causing disruption of this gene (9).

The AIRE (autoimmune regulator) gene is a transcript regulator coding gene that forms nuclear bodies and binds to the CREB transcriptional coactivator binding protein (10,11). This protein plays an essential role in immunity by regulating the expression of autoantigens. Type 1 diabetes mellitus is characterized by pancreatic beta cell damage due to autoimmune reactions from beta cells becoming autoantigens (12). Mutation changes in the AIRE gene can be a marker of autoimmune reactions due to autoantigens (13).

The ALDH2 gene (aldehyde dehydrogenase 2 family member) encodes the aldehyde dehydrogenase group enzyme. The enzyme aldehyde dehydrogenase is an enzyme that appears in the oxidative pathway of alcohol metabolism (14) The condition of DM type 1 causes glucose not to enter the cells so that cells cannot use glucose for metabolism ((15) so the energy source uses fat, which has a by-product in the

form of alcoholic compounds, namely glycerol, causing the condition of diabetes ketoacidosis (16). The amount of glycerol that accumulates causes interference with the ALDH2 gene. For the same reason, the increased use of fat in DM conditions can cause interference with the APOM gene (apolipoprotein M), the gene encoding apolipoprotein (17) These proteins are found to be associated with high-density lipoproteins, low-density lipoproteins, and triglyceride-rich lipoproteins related to fat transport. In type 1 diabetes mellitus, lipoprotein profile disturbances occurred (18)

The BANK1 gene (B-cell scaffold protein with ankyrin repeats 1) is a B-cell-specific scaffold protein-encoding gene that functions in the B-cell receptor for calcium mobilization from intracellular stores. This protein also promotes lyn-mediated tyrosine phosphorylation of inositol 1,4,5-trisphosphate receptors(19). Changes in the activity of the BANK1 gene were reported to be associated with pathogenesis in type 1 DM. This gene activity is related to type 1 DM, considered an autoimmune disease involving B lymphocyte cell activity, so the BANK1 gene is involved in B cell regulation in the incidence of type 1 DM (20).

The CBLB gene (Cbl proto-oncogene B) encodes E3 ubiquitin-protein ligase that causes proteosome-mediated protein degradation by transferring ubiquitin from an E2 ubiquitin-conjugating enzyme to a substrate (21) The protein encoded for this gene also regulates the immune response by activating receptors on the T-cell receptor, B-cell receptor, and high-affinity immunoglobulin epsilon receptor. Therefore, the CBLB gene is essential in the innate and adaptive immune response (22) In addition, the CCL5 gene (C-C motif chemokine ligand 5) is also involved in activating the immune response process related to pancreatic beta cell damage in DM type 1. The CCL5 gene is a chemokine-coding gene that is an essential protein in immunoregulatory and inflammatory processes (23) The chemokine subfamily CC plays a role as a blood monocyte chemoattractant, memory T helper cells, and eosinophil (24). The CBLB gene and CCL5 gene are involved in immune responses related to autoimmune processes. Type 1 DM is a very closely related autoimmune mechanism process in which pancreatic beta cells are killed by immune cells themselves (12)

Based on the discussion, the investigator suggested that seven genetic markers (ACE, AIRE, ALDH2,

APOM, BANK1, CBLB, and CCL5) as candidates for type 1 DM genetic markers in dogs related to the pathway of DM type 1 as autoimmune disease. In addition, further studies can be carried out on checking for gene mutations in dogs confirmed to have diabetes mellitus.

Conclusions

This research concluded with these points:

1. A total of 14 data for DM type 1 genetic markers with endocrine system disease in dogs, namely ACE, ACP1, AGER, AIF1, AIRE, ALDH2, APOC3, APOM, BANK1, BCHE, BTC, CBLB, CCL5, and CD28 with the number of amino acids are not much different.
2. Only 50% of candidates for DM type 1 genetic markers related to endocrine system disease in dogs, namely ACE, AIRE, ALDH2, APOM, BANK1, CBLB, and CCL5 have high identity nucleotides to those of humans and mouse models.

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