Institutionen för husdjursgenetik

Genetic association of Canine Lymphocytic Thyroiditis (CLT) with DLA class II in Giant Schnauzer and Hovawart dogs

by

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Handledare:
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Examensarbete 297
2007

Examensarbete ingår som en obligatorisk del i utbildningen och syftar till att under handledning ge de studerande träning i att självständigt och på ett vetenskapligt sätt lösa en uppgift. Föreliggande uppsats är således ett elevarbete och dess innehåll, resultat och slutsatser bör bedömas mot denna bakgrund. Examensarbete på D-nivå i ämnet husdjursgenetik, 20 p (30 ECTS).

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Agrovoc: Canine lymphocytic thyroiditis, Cytotoxic T lymphocyte-associated 4, Dog leukocyte antigen, Major Histocompatibility Complex, Autoimmunity

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Abstract

Canine Lymphocytic Thyroiditis (CLT) resembles naturally occurring lymphocytic thyroiditis in White Leghorn chickens and Hashimoto's thyroiditis in man. It is a common autoimmune endocrine disease in dogs which is a result of destruction of the thyroid glands. Many autoimmune diseases show associations with the major histocompability complex (MHC) class II alleles.

Within the canine Major Histocompatibility Complex (*DLA*) some of the class II genes are highly polymorphic. In this study an evaluation of the association between *DLA* class II haplotype and the risk for developing CLT has been performed by sequencing the polymorphic exon 2 form the genes *DLA-DRB1*, *DLA-DQA1* and *DQB1*.

Two high-risk breeds for developing CLT, Giant Schnauzer and Hovawart, have been analysed from a total of 198 dogs. Included in the study were 35 healthy controls, 3 borderline cases and 87 CLT-positive dogs.

Results show that Giant Schnauzers carrying the haplotype *DRB1*01201DQA1*00101DQB1*0020* have an increased risk to develop CLT, cases 22.5% versus controls 4.5%.

This with an odds ratio = 6.0667 and with a p value = 0.015401 which shows that the increased risk to develop CLT is statistically significant.

In Hovawart dogs the risk haplotype *01201*00401*013017* was present in 45 % (cases 43% versus controls 50%) of the total dogs analyzed. In this breed there was no evidence for an increased risk to develop CLT for dogs with this haplotype.

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1. Abbreviations

CLT	Canine lymphocytic thyroiditis
CTLA4	Cytotoxic T lymphocyte-associated 4
DLA	Dog leukocyte antigen
GS	Giant Schnauzer
GWA	Genome-wide Association
HLA	Human leukocyte antigen
HW	Hovawart
LYP	Lymphoid tyrosine phosphatase
MHC	Major Histocompatibility Complex
T3	Thyronin
T4	Thyroxin
TgAA	Thyroglobulin autoantibody
TSH	Thyroid stimulating hormone

2. Introduction

The major histocompatibility complex (*MHC*) class II genes are strong genetic risk factors for many autoimmune diseases including Lymphocytic Thyroiditis in canines. Two dog breeds, Giant Schnauzer (GS) and Hovawart (HW), which shows an increased risk for developing the disease, were included in the study.

A genetic association between canine lymphocytic thyroiditis (CLT) and the *DLA-DRB1*01201* allele has already showed to be an increased risk factor.[1]

The aims of this study is to extend the *DLA-DRB1* study by also determine the nucleotide sequence of the polymorphic exon 2 for *DLA-DQA1* and *–DQB1* genes and then evaluate whether there is an association between DLA class II haplotype and the risk for developing CLT.

2.1 Autoimmunity

The immune system's task is to protect the body against foreign organisms and material. Therefore it is essential to know what is self (autoantigen) and what is foreign (non-self) to the body. Autoimmunity is the failure of an organism to completely recognize what is self and what is foreign to the body. This results in an immune response against its own cells and /or tissue.[2]

Most immunodeficiency diseases results from a defective gene which results in an elimination or mutation in one or more components in the immune system. This can effect T- or B-lymphocyte development, phagocyte function and components of the complement system.

Self tolerance is normally controlling and preventing autoimmune diseases.[3] During development, self and non-self antigens are presented by MHC class I and II molecules to T-lymphocytes. Those T-cells that interact get a protective signal that prevents apoptosis. Those that have not reacted with MHC go through cell death. This process is known as positive selection. During negative selection, the surviving thymocytes are tested for affinity for MHC molecules on antigen presenting cells. Only those with a low to moderate affinity are able to mature.[4]

Despite this process, some self-reacting lymphocytes do mature and can be activated and cause autoimmune diseases, also not all self antigens are expressed during development.[3]

Autoimmune diseases can be classified into two types, organ-specific or systemic. In organ-specific autoimmune diseases the autoimmunity is only expressed in a certain organ compared to systemic, where many tissues in the body are affected. Table 1a and b shows organ-specific and systemic autoimmune diseases in humans and which autoantigen that is recognized.[2]

Table 1a. Organ-specific autoimmune diseases in humans.[2]

Autoantigen	Disease	Target organ
TSH receptors (hGT)	Grave's disease	Thyroid glands
Thyroid peroxidise	Hashimoto's thyroiditis	Thyroid glands
Myelin sheets	Multiple Sclerosis	Central nervous system
Beta cells (IA-2, GAD, GM2-1)	Type 1 diabetes mellitus	Pancreas

Table 1b. Systemic autoimmune diseases in humans.[2]

Autoantigen	Disease
Joints, skin, blood vessels, heart, lungs and muscles	Rheumatoid arthritis
Cells in skin, kidney and brain	Systemic lupus erythematosus
Skin and intestine	Scleroderma
Salivary glands, tear glands and joints	Sjögren's syndrome

Autoimmune diseases are a result of multiple factors, both genetic and environmental.
Most of the genes that are predisposing factors affect autoantigen availability, apoptosis, signalling pathways, cytokine expression and expression of co-stimulatory molecules.[3]

2.2. Canine Lymphocytic Thyroiditis

Canine hypothyroidism is a common endocrine disease of dogs and approximately half of all cases are caused by lymphocytic thyroiditis, which is similar to Hashimoto's thyroiditis in man and lymphocytic thyroiditis in White Leghorn chickens. The disease is characterized by an increase of infiltration of autoreactive T cells and other activated lymphocytes in the thyroid gland, autoantibodies against proteins from the thyroid gland and high concentrations of thyroid stimulating hormones (TSH).[5]

2.2.1. Hypothyroidism

Hypothyroidism is a result of destruction of the thyroid gland. The thyroid gland is located in the neck, above the larynx and its main function is to produce thyroxin (T4) that regulates the metabolism. If the T4 levels in the blood are too low the pituitary glands is stimulated to produce TSH by hypothalamus that produces TRH.[6] Secretion of TSH stimulates secretion of T4 and triiodothyronine (T3). When the T4 and T3 levels increase the TSH secretion is inhibited by negative feedback.[7] See Figure 1.

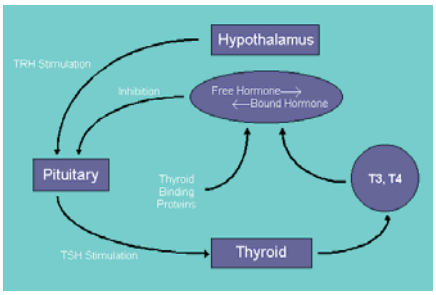

Figure 1. Regulation of thyroid hormones through a negative feedback mechanism[8] (Cargill. J. et al. 2005. *Hypothyroidism article*).

The physiology of thyroid glands is the basics for all tests for hypothyroidism. The cause of hypothyroidism can be classified as primary, secondary or tertiary. At the primary causes, the levels of T4 and T3 are low but the TSH secretion is increased which is associated with the thyroid glands. Secondary causes are associated with a deficiency of TSH and pituitary glands and tertiary causes with a TRH deficiency from hypothalamus. CLT is an autoimmune disease that is associated with the primary

causes where the thyroid glands are infiltrated with lymphocytes that destroy the thyroid cells that produce T4. Therefore a large amount of free T4 is circulating in the bloodstream and also an increase of TSH can be shown. [6]

2.2.2. Symptoms

The thyroid gland regulates the cell metabolism. The hormones produced by the thyroid glands are necessary for embryonic development, stimulate protein and enzyme synthesis and also protein and fat metabolism. Therefore, a dysfunction in the thyroid glands produces a wide range of different symptoms. More than 75 % of the thyroid glands need to be destroyed to develop symptoms. Since the cellular metabolism is decreasing with an absence of thyroid hormones the first symptoms can be tiredness and inactivity. Also reproduction and the central nervous system can be affected. A weight gain, depression, weakness and freezing are other clinical sign of a decrease in metabolism. Dermatological changes can also be observed. The fur becomes dry or fat and oily.[9]

2.2.3. Clinical diagnosis

Diagnosis requires laboratory testing where the T4 and TSH assays provide the most accurate information. Both increases in the T4 levels and TSH provide good evidence for CLT. Amount of T3 is not by itself a good indicator because the secretion does not decrease significant. Thyroglobulin autoantibodies (TgAA) occur frequently in dogs diseased with CLT. Therefore analysis for the presence of these autoantibodies is also performed during clinical diagnosis.[7]

2.3. MHC class II

In humans, three gene regions have shown to be particularly involved in autoimmune diseases: The human leukocyte antigen (*HLA*) class II region, the gene encoding cytotoxic T lymphocyte-associated 4 (*CTLA4*) and the gene encoding lymphoid tyrosine phosphatase (*LYP*).[10] Among these, most autoimmune diseases show associations with MHC class II alleles. This is not surprising since autoimmune responses involve the ability for T cells to recognise a particular antigen and this is dependent on the MHC genotype.[3]

The *HLA* class II region is a part of the *MHC* and is located on chromosome 6p21. Alleles and haplotypes of *DQB1*, *DQA1* and *DRB1* have shown to either predispose or protect for many autoimmune diseases.[10]

Hashimoto's thyroiditis shows an association with the *HLA-DR5* haplotype with a relative risk of 3.2.[3] Because of that it is interesting to also study this gene in dogs diseased with CLT.

The canine Major Histocompatibility Complex (*DLA*) is located on chromosome 12 and can as in other mammalian species be divided into class 1, 2 and 3 regions. The structures of *DLA* class II genes are similar to humans. The DLA region contains one functional gene at each locus i.e. *DQA1*, *DQB1* and *DRB1* (which are orthologs to human). The *DQB1*, *DQA1* and *DRB1* loci are in high linkage disequilibrium and haplotypes can therefore be used as genetic risk factors. *DQA1* and *DQB1* are located very close to each other and in complete LD and recombination between them has never been observed.

Within the *DLA* class II complexes, the genes are highly polymorphic. The latest report documents 61 *DLA-DRB1* alleles, 18 *DLA-DQA1* alleles and 47 *DLA-DQB1* existing alleles.[12]

2.4. Giant Schnauzer and Hovawart as model breeds

The domestic dog, *Canis familiaris,* is an excellent model species having over 400 recognized breeds in which to study complex inherited diseases. These breeds are phenotypically diverse and each represents a closed breeding population. Several autoimmune diseases exist in dogs and can be compared to humans in both symptoms and inheritance. This is due to the genetic bottleneck caused by breed creation.[13]

A higher incidence for hypothyroid diseases have been reported for Dobermans, Great Danes, Irish Setter , Miniature Schnauzer , Boxers, Golden Retrievers, Dachshunds, Shetlands Sheepdogs, Pomeranians, Cocker Spaniel and Airedale Terriers[14]. Giant Schnauzer and Hovawart are two dog breeds that previously not have been reported as being high risk breeds. The overall prevalence in the Swedish GS and HW population was shown to be 14.0 % versus 13.7 % for CLT.[14]

3. Material and methods

3.1. Study material

Blood samples from two high-risk breeds Giant Schnauzer and Hovawart are available from the registry at the Swedish Kennel Club. Two birth cohorts (1992 and 1995) at 7-8 and 4-5 years of age, respectively, were collected and analysed. Clinical and diagnostic information is available for 198 dogs and is summarized in supplementary Table S1. A total of 35 controls (GS=22; HW=13), 3 borderline cases (GS=3; HW=0) and 87 CLT-positive cases (GS=58; HW=29) were included in the study.

3.2. Clinical diagnosis

Each dog in the study was classified by strict inclusion and exclusion criteria. TSH levels above 29mgU/l and TgAA concentration at ≥150% compared to a negative control serum were used as inclusion criteria. Exclusion criteria were TSH levels below 20mgU/l and TgAA concentration below 100% compared to a negative control serum. Borderline cases were dogs with TSH levels between 20-29mgU/l and TgAA concentration between 100-150% compared to a negative control serum.

3.3. Extraction of genomic DNA

Genomic DNA was extracted from 200 µl blood using a salt extraction method. The concentration and quality of the DNA were measured by NanoDrop ND-1000 spectrophotometer 3.1.0.

3.4. PCR amplification

PCR was performed according to protocol developed by Lorna Kennedy, Manchester University. PCR reactions was performed using 20ng DNA in a 20µl reaction containing 1x PCR buffer as supplied by Qiagen (with no extra Mg^{2+}), Q solution (Qiagen), final concentrations of 0.1µM for each primer, 200µM each dNTP, with 2 units of Taq polymerase, (Qiagen HotStarTaq). For primers used to amplify *DLA-DRB1*, *DQA1* and *DQB1* respectively, see table 2. All primers are intronic and locus specific. Both M13 and T7 tailed primers were used for labelling the PCR products. Better results were generated for *DQA1* with tailed M13 primers and for *DRB1* and *DQB1* with T7.

Table 2. Primers used to sequence DLA-DRB1, DQA1 and DQB1. (10)

Primer	Primer sequence 5'-3'	Product size
DRB1 R	(T7)TGT GTC ACA CAC CTC AGC ACC A	303 bp
DQA1 R	GGA CAG ATT CAG TGA AGA GA	345 bp
DQB1 F	(T7)CTC ACT GGC CCG GCT GTC TC	300 bp
T7	TAA TAC GAC TCA CTA TAG GG	
M13	TGT AAA ACG ACG GCC AGT[15]	

A standard Touchdown PCR protocol was used for all amplifications, which consisted of an initial 15 minutes at 95°C, 14 touch down cycles of 95°C for 30 seconds, followed by 1 minute annealing, starting at 62°C (*DRB1*), 54°C (*DQA1*) 73°C (*DQB1*) and reducing by 0.5°C each cycle, and 72°C for 1 minute. Then 20 cycles of 95°C for 30 seconds, 55°C (*DRB1*), 47°C (*DQA1*) 66°C (*DQB1*) for 1 minute, 72°C for 1 minute plus a final extension at 72°C for 10 minutes.

3.5. Nucleotide sequence analysis

Sequencing was performed by Lark Technologies DNA sequencing services (LARK, Texas and England). Sequencing was only made in one direction, reverse for *DRB1* and *DQA1* and forward for *DQB1*.

3.6. Data analysis

The sequence data were analyzed by using the Macintosh software, MatchTools and MatchToolsNavigator (AppliedBiosystems, CA, USA), also used for assigning the alleles. The sequences were firstly read in the program MatchToolsNavigator and compared to an already prepared consensus sequence.[12] Each polymorphic site was viewed and manually examined. When the sequence had been corrected, the sequence was put in the program MatchTools. A reference sequence library was already created[6] and used to compare obtained sequence data with. MatchTools then provides a report of the closest matching allele.

3.7. Statistical analysis

Statistical analyses were performed using VassarStats[16] using a 2x2 Contingency Table to investigate if the results were statistically significant. Cases and controls were divided into presence or absence of the allele and the total number of individuals in each group was calculated. Then a comparison was made to the total number of alleles in each group. Odds Ratios (OR), Relative Risk (RR) and p-values were calculated for each haplotype in both Giant Schnauzer and Hovawart. Both the odds ratio and the relative risk compare the likelihood of an event between two groups. The estimation of the RR can be calculated using the formula:

$RR = (a/c)*k / (b/d)*k = (a/c)/(b/d) = ad/bc$

A RR close to 1 implies no risk for those who are carrying the allele to develop the disease. RR values above 1 show an increased risk and below 1 a lower risk for developing the disease. A stronger association is seen the further away from 1 the number is calculated. To determine if the association is significant p-values are calculated. A p-value < 0.05 shows statistical significance.

For the χ^2 test Yates continuity correction values were used. χ^2 tests are performed to imply that the observed data did not arose by chance.[19]

4. Results

4.1. Clinical diagnosis

Diagnostic criteria of all available samples are found in Table 3 and supplementary Table S1.

Table 3. Diagnostic criteria and status of presented samples in Hovawart and Giant Schnauzer[1].

Diagnosis code	Diagnostic criteria	Presented samples	Status
1	TgAA≥199 and TSH ≥39	14	Case
2	TgAA≥199	19	Case
3	TSH≥39	23	Case
4	CLT diagnosed and under treatment	9	Case
5	200>TgAA>149 and 40>TSH> 29	0	Case
6	200>TgAA> 149	14	Case
7	40>TSH> 29	8	Case
8	TSH<20, TgAA<100, T4 5-25, age >8years when analysed	28	Control
9	TSH<20, TgAA<100, T4 5-25, exact age not available	7	Control
10	150>TgAA> 100 and 29>TSH> 20	3	Borderline case
?	Can not be classified	73	-
Blank	Values are missing	6	-

4.2. Data analysis

Supplementary Table S1 shows all haplotypes generated. Table 4A shows the haplotype frequency for cases and controls in Giant Schnauzer and table 4B in Hovawart. The *01201*00101*00201* haplotype shows an increased risk (cases 22.5% versus controls 4.5%) for Giant Schnauzer to develop CLT.

Table 4A. Haplotype frequency within cases and controls for Giant Schnauzer.[1]

Haplotype (*DRB1*DQA1*DQB1*)	Haplotype frequency (%) Cases and Controls (160)	Haplotype frequency (%) Cases (116)	Haplotype frequency (%) Controls (44)
*00101*00101*00201*	**28**	**26**	**32**
*00601*00401*01303*	**11.5**	**8.5**	**18**
*00901*00101*008011*	**1.5**	**0**	**4.5**
*01201*00101*00201*	**17.5**	**22.5**	**4.5**
*01301*00101*00201*	**8**	**9.5**	**4.5**
*01301*00301*00501*	**22.5**	**24**	**18**
*02301*00301*00501*	**9.5**	**7**	**16**
*09401*00401*01303*	**0**	**0**	**0**
*09501*00101*00201*	**0**	**0**	**0**
*01501*00601*00301*	**2**	**1.5**	**2**

Table 4B. Haplotype frequency within cases and controls for Hovawart.[1]

Haplotype (*DRB1*DQA1*DQB1*)	Haplotype frequency (%) Cases and Controls (84)	Haplotype frequency (%) Cases (58)	Haplotype frequency (%) Controls (26)
*00201*00901*00101*	**19**	**24**	**7.5**
*01101*00201*01302*	**6**	**3.5**	**11.5**
*01201*00401*013017*	**45**	**43**	**50**
*01301*00101*00201*	**13**	**15.5**	**7.5**
*01301*00101*00802*	**1**	**0**	**4**
*01501*00601*00301*	**6**	**5**	**7.5**
*01501*00601*04901*	**1**	**0**	**4**
*01501*00601*049v*	**3.5**	**1.5**	**7.5**
*01501*00601*02301*	**1**	**1.5**	**0**
*03001*00601*00301*	**3.5**	**5**	**0**

[1] Representing cases (diagnosis code 1-6) versus controls (diagnosis code 8 and 9).

4.3. Statistical analyses

Odds Ratios and p-values were calculated for each allele in both Giant Schnauzer and Hovawart, see supplementary table S2A and S2B. The 2x2 Contingency table for *DLA-DRB1*01201DQA1*00101DQB1*00201* in Giant Schnauzer shows an increased risk with an odds ratio = 6.0667 and p = 0.015401 for developing CLT. See table 4.

Table 5. 2x2 Contingency table for *DLA-DRB1*01201DQA1*00101DQB1*00201* in Giant Schnauzer.[1]

Antigen	*01201*00101*00201* +	*01201*00101*00201* -	Total
Case	26	90	116
Control	2	42	44
Total	28	132	160

[1] Representing cases (diagnose code 1-6) versus controls (diagnose code 8 and 9).

Risk ratio: 4.931
Odds ratio: 6.0667
X^2: 5.87
p = 0.015401

5. Discussion

The aims of this study were to determine the nucleotide sequence of the polymorphic exon 2 from three *DLA* loci i.e. *DLA-DRB1, DQA1* and *DQB1* and then evaluate the association between *DLA* class II haplotype and the risk for developing CLT. In GS the *01201*00101*00201* haplotype shows an increased risk (cases 22.5% versus controls 4.5%) with an odds ratio = 6.0667 and p = 0.015401 for developing CLT.

In HW the risk haplotype *01201*00401*013017* was present in 45 % (cases 43% versus controls 50%) of the total dogs analyzed.

The haplotype *01301*00101*00201* also shows an increased risk (cases 15.5% versus controls 7.5%) for developing CLT. This indicates that *DRB1* is not the genetic risk factor. Instead *DQA1* and *DQB1* could be the genetic factors in the *MHC* that leads to an increased risk for developing the disease. Nucleotide sequence alignment of the *DQA1*00401* with *DQA1*00101* sequences revealed that there is only three amino acids differences between the two alleles (Fig. 2). The consensus sequence shows where differences are located. The observed amino acid substitutions are non-conservative. At position X, there is an asparagine to tyrosine change. Aspargine is hydrophilic and thyrosine is hydrophobic. At position X, arginine which has basic side-chains is changed for a threonine with hydrophilic side-chains. Finally, at position X, methionine is changed for a leucine. Both have hydrophobic side-chains. Since this is rather large changes within the hypervariable regions, the antigen binding site is likely to be influenced by these amino acid replacements. If the haplotype *01201*00401*013017* is a risk haplotype, the *DQA1* region may not be involved in the risk for developing CLT. Instead *DRB1* would be the risk factor. But if *01301*00101*00201* is a risk haplotype *DQA1 and DQB1* would be the risk factor.

Figure 2. Alignment between *DQA1*00401* and *DQA1*00101* (EMBOSS, PrettyPlot).

In GS, the haplotype *00601*00401*01303* may be protective (cases 8.5% versus controls 18%). However, too few samples carrying this haplotype were found and the protective association is only suggestive.

Inbreeding predisposes for autoimmune diseases. Variation in MHC is important and is not maintained in inbred dogs. Therefore, CLT is so common in both Giant Schnauzer and Hovawart.

A gender difference in Hashimoto's thyroiditis can be shown in humans where women have a four to five times higher risk than men to develop the disease. This can imply that sex hormones are involved in the development of the human disease. In contrast, our results corroborate the lack of gender effect for CLT risk.[16]

Recombination has never been observed between DQA1 and DQB1. Therefore one can assume the haplotype if the allele at the *DRB1* locus and either of *DQA1* or *DQB1* is known. Sequencing is therefore not necessary for all three loci.

A genome-wide association mapping (GWA) can be performed in future studies to identify additional genes contributing to the disease. The dog genome sequence of a boxer covering 97% of the genome and approximately 19.300 genes were determined.[18] Sequence comparison between additional dog breeds resulted in identification of ~2.5 million SNPs. From this a 27,000 SNP array has been developed for a GWA mapping. To perform this analysis more CLT cases and healthy controls are required. Power calculations have indicated that at least samples from 100 individuals in each category are needed for a disease with 5-fold increased risk i.e. similar to that of CLT. At present time, a total of 87 cases and 35 controls have been collected.[18]

Obtained information about the disease-causing genes can then be used in selective breeding practice in an effort to reduce the frequency of CLT. E.g. a particular MHC in combination with other genes can be a disease-causing combination. By not breed on these dogs, healthier dogs can be created.

These results also give us a better knowledge about MHC, antigen presentation and why a particular MHC gives an increased risk for developing CLT.

6. Acknowledgement

First I would like to thank my supervisor Göran Andersson for guidance, inspiration and the overall support with my project.

I would also like to thank Lorna Kennedy for the help with the PCR, teaching me the software MatchTool and MatchTool Navigator and helping me analyse the sequences. Special thanks to Erik Bongcam-Rudloff for the help with installing MatchTool and MatchTool Navigator and Katarina Stensham for overall help with my project.

Finally I would like to thank the whole department of Animal Breeding and Genetics at SLU for giving me the opportunity to perform my bachelor thesis there.

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8. Supplementary tables

8.1. Table S1. Clinical and diagnostic information for all dogs.

Sample Number	Disease code	Breed	*DRB1*	*DQA1*	*DQB1*	*DRB2*	*DQA2*	*DQB2*	TgAA (%)	T4 (mgU/l)	TSH (mgU/l)
2.29.001	8	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	82	23	12
2.29.002	8	Hovawart	*01201*	*00401*	*013017*	*01301*	*00101*	*00802*	70	22	10
2.29.003	?	Hovawart	*01201*	*00401*	*013017*	*01501*	*00601*	*?*	34	31	13
2.29.004	8	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	66	25	10
2.29.005	?	Hovawart	*01301*	*00101*	*00201*	*01501*	*00601*	*00301*	87	27	15
2.29.006	6	Hovawart	*01201*	*00401*	*013017*	*01501*	*00601*	*00301*	165	20	11
2.29.008	8	Hovawart	*01501*	*00601*	*00301*	*01501*	*00601*	*049v*	99	16	15
2.29.013	?	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	83	34	11
2.29.017	?	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	75	28	15
2.29.018	8	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	64	13	8
2.29.019	3	Hovawart	*01201*	*00401*	*013017*	*01301*	*00101*	*00201*	159	102	243
2.29.020	4	Hovawart	*01201*	*00401*	*013017*	*01301*	*00101*	*00201*	122	21	9
2.29.021	?	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	96	27	19
2.29.022	8	Hovawart	*01301*	*00101*	*00201*	*01501*	*00601*	*00301*	86	16	17
2.29.025	8	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	88	25	11
2.29.026	8	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	68	16	15
2.29.027	4	Hovawart	*01201*	*00401*	*013017*	*01301*	*00101*	*00201*	129	22	14
2.29.028	?	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	90	27	14
2.29.029	8	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	97	20	12
2.29.031	3	Hovawart	*01201*	*00401*	*013017*	*01501*	*00601*	*049v*	105	16	47
2.29.032	?	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	75	32	17
2.29.035	8	Hovawart	*01101*	*00201*	*01302*	*01201*	*00401*	*013017*	90	25	16
2.29.036	?	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	66	30	7
2.29.037	3	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	87	6	175
2.29.038	8	Hovawart	*01101*	*00201*	*01302*	*01201*	*00401*	*013017*	72	22	13
2.29.041	?	Hovawart	*01501*	*00601*	*00301*	*01501*	*00601*	*049v*	97	30	13
2.29.044	8	Hovawart	*01101*	*00201*	*01302*	*01501*	*00601*	*049v*	84	23	16
2.29.045	8	Hovawart	*01301*	*00101*	*00201*	*01501*	*00601*	*04901*	94	19	11
2.29.059	3	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	163	25	87
2.29.081	3	Hovawart	*01201*	*00401*	*013017*	*01501*	*00601*	*00301*	84	19	49
2.29.082	3	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	100	0	127
2.29.087	1	Hovawart	*01101*	*00201*	*01302*	*01201*	*00401*	*013017*	297	0	60
2.29.089	1	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	225	39	55
2.29.105	2	Hovawart	*00201*	*00901*	*00101*	*03001*	*00601*	*00301*	>200	11,2	14
2.29.106	1	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	POS	19,7	>200
2.29.107	1	Hovawart	*00201*	*00901*	*00101*	*03001*	*00601*	*00301*	POS	11,5	780
2.29.108	3	Hovawart	*00201*	*00901*	*00101*	*01501*	*00601*	*00301*	NEG	11,3	>200
2.29.109	1	Hovawart	*01301*	*00101*	*00201*	*01301*	*00101*	*00201*	POS	9,9	>200
2.29.110	3	Hovawart	*00201*	*00901*	*00101*	*00201*	*00901*	*00101*	NEG	7,5	125
2.29.111	3	Hovawart	*01201*	*00401*	*013017*	*01201*	*00401*	*013017*	NEG	7,3	93
2.29.112	7	Hovawart	*01201*	*00401*	*013017*	*03001*	*00601*	*00301*	NEG	5,7	35
2.29.113	3	Hovawart	*01301*	*00101*	*00201*	*01301*	*00101*	*00201*	NEG	21,9	355

2.29.114	3	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	NEG	10,9	>200
2.29.115	7	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	NEG	8	31
2.29.116	6	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	GRÅ	8,6	29
2.29.117	3	Hovawart	*01201*	*00401*	*013017*	*01301*	*00101*	*00201*	NEG	8,2	55
2.29.118	1	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	225	5,8	55
2.29.119	7	Hovawart	*01201*	*00401*	*013017*	*01301*	*00101*	*00201*	NEG	7	33
2.29.120	2	Hovawart	*00201*	*00901*	*00101*	*01201*	*00401*	*013017*	POS	11,5	38
2.29.121	3	Hovawart	*01201*	*00401*	*013017*	*01501*	*00601*	*02301*	NEG	7,2	40
2.29.122		Hovawart	*01201*	*00401*	*013017*	*01501*	*00601*	*049v*			
2.45.225	2	Hovawart	*01101*	*00201*	*01302*	*01201*	*00401*	*013017*	254	26	22
2.45.007	?	Riesen	*00601*	*00401*	*01303*	*00601*	*00401*	*01303*	125	27	17
2.45.008	4	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	135	19	12
2.45.009	?	Riesen	*02301*	*00301*	*00501*	*02301*	*00301*	*00501*	117	22	16
2.45.010	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	112	26	15
2.45.011	6	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	167	25	33
2.45.013	?	Riesen	*00601*	*00401*	*01303*	*01201*	*00101*	*00201*	103	18	14
2.45.014	6	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	171	26	17
2.45.015	8	Riesen	*00601*	*00401*	*01303*	*00901*	*00101*	*008011*	88		15
2.45.017	?	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	85	34	13
2.45.018	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	129	23	16
2.45.019	2	Riesen	*00101*	*00101*	*00201*	*01501*	*00601*	*00301*	258	4	14
2.45.021	?	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	139	19	15
2.45.022	?	Riesen	*01201*	*00101*	*00201*	*01301*	*00101*	*00201*	143	28	0
2.45.023	?	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	144	27	15
2.45.025	?	Riesen	*00601*	*00401*	*01303*	*00901*	*00101*	*008011*	127	22	16
2.45.026	6	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	171	14	13
2.45.027	?	Riesen	*00601*	*00401*	*01303*	*01201*	*00101*	*00201*	106	24	0
2.45.028	?	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	125	29	12
2.45.030	?	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	100	20	23
2.45.032	2	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	382	14	8
2.45.033	?	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	110	15	10
2.45.034		Riesen	*00601*	*00401*	*01303*	*00901*	*00101*	*008011*			
2.45.035	?	Riesen	*01201*	*00101*	*00201*	*01301*	*00101*	*00201*	96	14	24
2.45.038	2	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	220	27	21
2.45.039	4	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	110	29	15
2.45.040	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	65	19	26
2.45.041	?	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	75	18	24
2.45.042	8	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	58	20	17
2.45.043	?	Riesen	*00601*	*00401*	*01303*	*00601*	*00401*	*01303*	130	16	12
2.45.045	8	Riesen	*00601*	*00401*	*01303*	*00601*	*00401*	*01303*	90	19	15
2.45.046	8	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	83	14	16
2.45.047	6	Riesen	*01301*	*00101*	*00201*	*01301*	*00101*	*00201*	173	26	0
2.45.049	7	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	81	25	36
2.45.050	?	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	113	21	9
2.45.052	8	Riesen	*00601*	*00401*	*01303*	*00601*	*00401*	*01303*	63	14	10
2.45.054		Riesen	*02301*	*00301*	*00501*	*02301*	*00301*	*00501*			
2.45.055	8	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	76		13
2.45.057	?	Riesen	*00601*	*00401*	*01303*	*00601*	*00401*	*01303*	121	18	20

2.45.058	8	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	83	17	0
2.45.059	4	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	99	21	0
2.45.062	?	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	57	26	22
2.45.063	8	Riesen	*01301*	*00101*	*00201*	*01301*	*00301*	*00501*	57	24	12
2.45.065	4	Riesen	*01201*	*00101*	*00201*	*01301*	*00101*	*00201*	97	6	13
2.45.068	?	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	119	16	10
2.45.071	8	Riesen	*01301*	*00101*	*00201*	*02301*	*00301*	*00501*	89	19	11
2.45.074	8	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	76	11	16
2.45.075	8	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	70	18	21
2.45.078	6	Riesen	*01201*	*00101*	*00201*	*01301*	*00301*	*00501*	160	10	14
2.45.079	?	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	110	18	7
2.45.080	1	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	255	14	84
2.45.081	?	Riesen	*01301*	*00301*	*00501*	*09401*	*00401*	*01303*	148	10	10
2.45.082	8	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	98	13	16
2.45.084	6	Riesen	*01201*	*00101*	*00201*	*01201*	*00101*	*00201*	165	2	23
2.45.085	?	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	101	18	20
2.45.095	?	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	102	14	20
2.45.097	8	Riesen	*01301*	*00301*	*00501*	*02301*	*00301*	*00501*	57	17	19
2.45.099	2	Riesen	*00601*	*00401*	*01303*	*01301*	*00101*	*00201*	216	6	21
2.45.103	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	121	20	12
2.45.104	?	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	101	21	11
2.45.106	10	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	101	14	26
2.45.109	4	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	144	5	12
2.45.110	4	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*			
2.45.132		Riesen	*01201*	*00101*	*00201*	*01301*	*00301*	*00501*			
2.45.133	2	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	329	6	14
2.45.135	3	Riesen	*01301*	*00301*	*00501*	*01301*	*00301*	*00501*	NEG	5,5	88
2.45.136	?	Riesen	*01201*	*00101*	*00201*	*01201*	*00101*	*00201*	107	21	0
2.45.137	?	Riesen	*01201*	*00101*	*00201*	*01201*	*00101*	*00201*	110	20	11
2.45.138	?	Riesen	*01201*	*00101*	*00201*	*02301*	*00301*	*00501*	90	44	13
2.45.139	3	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	109	10	46
2.45.140	?	Riesen	*01201*	*00101*	*00201*	*01201*	*00101*	*00201*	106	6	21
2.45.144	?	Riesen	*00601*	*00401*	*01303*	*00601*	*00401*	*01303*	99	32	12
2.45.150	2	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	381	22	32
2.45.153	?	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	72	29	0
2.45.161	?	Riesen	*01301*	*00301*	*00501*	*01501*	*00601*	*00301*	64	26	11
2.45.164	2	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	389	16	30
2.45.167	?	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	120	17	12
2.45.169	4	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	112	20	9
2.45.171	1	Riesen	*01301*	*00301*	*00501*	*01301*	*00301*	*00501*	POS	4,7	123
2.45.173	?	Riesen	*01301*	*00301*	*00501*	*01501*	*00601*	*00301*	93	26	9
2.45.175	?	Riesen	*00601*	*00401*	*01303*	*02301*	*00301*	*00501*	116	19	15
2.45.179	?	Riesen	*00601*	*00401*	*01303*	*01201*	*00101*	*00201*	88	40	10
2.45.180	?	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	86	18	26
2.45.183	?	Riesen	*00101*	*00101*	*00201*	*01301*	*00101*	*00201*	145	13	17
2.45.186	10	Riesen	*00101*	*00101*	*00201*	*01301*	*00101*	*00201*	101	10	26
2.45.189	6	Riesen	*01201*	*00101*	*00201*	*02301*	*00301*	*00501*	167	15	11
2.45.196	6	Riesen	*01201*	*00101*	*00201*	*01201*	*00101*	*00201*	151	21	0

2.45.197	?	Riesen	*01301*	*00101*	*00201*	*01301*	*00301*	*00501*	100	13	20
2.45.206	2	Riesen	*01201*	*00101*	*00201*	*01201*	*00101*	*00201*	1377	34	17
2.45.207	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	64	46	14
2.45.214	?	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	101	28	10
2.45.215	?	Riesen	*01301*	*00301*	*00501*	*01501*	*00601*	*00301*	105	34	9
2.45.217	1	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	302	5	56
2.45.218	2	Riesen	*01201*	*00101*	*00201*	*01201*	*00101*	*00201*	449	15	31
2.45.221	?	Riesen	*01301*	*00301*	*00501*	*01301*	*00301*	*00501*	122	22	19
2.45.222	3	Riesen	*00601*	*00401*	*01303*	*01301*	*00301*	*00501*	81	10	41
2.45.223	7	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	52	30	36
2.45.224	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	130	17	10
2.45.227	1	Riesen	*01201*	*00101*	*00201*	*01301*	*00301*	*00501*	1436	5	54
2.45.228	?	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	121	25	21
2.45.229	2	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	NEG	2,4	49
2.45.235	10	Riesen	*00101*	*00101*	*00201*	*01501*	*00601*	*00301*	131	16	22
2.45.239	6	Riesen	*01301*	*00301*	*00501*	*01501*	*00601*	*00301*	152	20	0
2.45.241	2	Riesen	*01201*	*00101*	*00201*	*01201*	*00101*	*00201*	200	16	0
2.45.244	2	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	592	19	0
2.45.246	?	Riesen	*00101*	*00101*	*00201*	*01301*	*00101*	*00201*	73	28	18
2.45.247	?	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	130	13	16
2.45.248		Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*			
2.45.249	?	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	107	30	8
2.45.250	1	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	1106	2	58
2.45.251	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	108	20	12
2.45.252	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	101	18	8
2.45.253	9	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	81	24	11
2.45.254	9	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	54	20	12
2.45.256	9	Riesen	*01301*	*00301*	*00501*	*01501*	*00601*	*00301*	91	4	15
2.45.265	9	Riesen	*00601*	*00401*	*01303*	*00901*	*00101*	*008011*	97	23	17
2.45.267	7	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	89	28	38
2.45.271	9	Riesen	*00101*	*00101*	*00201*	*00101*	*00101*	*00201*	92	23	13
2.45.272	?	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*	82	26	13
2.45.288	6	Riesen	*01201*	*00101*	*00201*	*02301*	*00301*	*00501*	GRÅ	7	26
2.45.289	2	Riesen	*00101*	*00101*	*00201*	*01301*	*00101*	*00201*	POS	2,7	<14
2.45.290	7	Riesen	*01301*	*00301*	*00501*	*01301*	*00301*	*00501*	NEG	8	32
2.45.291	2	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	POS	5	22
2.45.292	8	Riesen	*01201*	*00101*	*00201*	*02301*	*00301*	*00501*	NEG	11,6	<14
2.45.293	?	Riesen	*00601*	*00401*	*01303*	*00601*	*00401*	*01303*	NEG	7,3	<14
2.45.294	1	Riesen	*01301*	*00101*	*00201*	*01301*	*00301*	*00501*	POS	14	163
2.45.295	?	Riesen	*00601*	*00401*	*01303*	*01201*	*00101*	*00201*	NEG	5,1	<14
2.45.296	?	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	NEG	5,9	24
2.45.297	3	Riesen	*01201*	*00101*	*00201*	*02301*	*00301*	*00501*	GRÅ	4,6	49
2.45.298	1	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	POS	1,4	45
2.45.299	?	Riesen	*00101*	*00101*	*00201*	*01301*	*00101*	*00201*	NEG	20,7	<14
2.45.300	8	Riesen	*01301*	*00301*	*00501*	*02301*	*00301*	*00501*	NEG	8	<14
2.45.301	9	Riesen	*00101*	*00101*	*00201*	*02301*	*00301*	*00501*	NEG	16,5	<14
2.45.302	3	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	NEG	2,4	49
2.45.303	?	Riesen	*00601*	*00401*	*01303*	*01301*	*?*	*?*	NEG	2,8	19

2.45.304	9	Riesen	*00101*	*00101*	*00201*	*01301*	*00301*	*00501*	NEG	12,5	17
2.45.305	6	Riesen	*01201*	*00101*	*00201*	*01301*	*00101*	*00201*	GRÅ	6,4	27
2.45.306	2	Riesen	*01301*	*00101*	*00201*	*01301*	*00301*	*00501*	POS	6,3	19
2.45.307	?	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	NEG	4,9	19
2.45.308	?	Riesen	*01301*	*00101*	*00201*	*01301*	*00301*	*00501*	NEG	4	23
2.45.309	?	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	NEG	7,7	26
2.45.310	2	Riesen	*01301*	*00101*	*00201*	*01301*	*00301*	*00501*	POS	5,5	29
2.45.311	?	Riesen	*01201*	*00101*	*00201*	*01301*	*00301*	*00501*	NEG	6,3	20
2.45.312	6	Riesen	*01201*	*00101*	*00201*	*01301*	*00301*	*00501*	GRÅ	8,5	23
2.45.313	?	Riesen	*01201*	*00101*	*00201*	*01301*	*00301*	*00501*	NEG	5,4	20
2.45.314	3	Riesen	*01301*	*00301*	*00501*	*01301*	*00301*	*00501*	NEG	5,5	88
2.45.315	7	Riesen	*01201*	*00101*	*00201*	*01301*	*00101*	*00201*	NEG	3,7	38
2.45.316	3	Riesen	*01201*	*00101*	*00201*	*01301*	*00301*	*00501*	NEG	4,6	83
2.45.317	3	Riesen	*00101*	*00101*	*00201*	*01201*	*00101*	*00201*	NEG	4,7	40
2.45.318	1	Riesen	*01301*	*00301*	*00501*	*01301*	*00301*	*00501*	POS	4,7	123
2.45.319	3	Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*		10,2	54
2.45.320	3	Riesen	*00601*	*00401*	*01303*	*01301*	*00101*	*00201*		24,9	>200
2.45.321		Riesen	*00101*	*00101*	*00201*	*00601*	*00401*	*01303*			

8.2. Table S2A. Giant Schnauzer 2x2 Contingency tables

Antigen	*00101*00101*00201* +	*00101*00101*00201* -	Total
Case	31	85	116
Control	14	30	44
Total	45	115	160

Risk ratio: 0.8399
Odds ratio: 0.7815
X^2: 0.2
p = 0.654721

Antigen	*00601*00401*01303* +	*00601*00401*01303* -	Total
Case	10	106	116
Control	8	36	44
Total	18	142	160

Risk ratio: 0.4741
Odds ratio: 0.4245
X^2: -
p = -

Antigen	*00901*00101*008011* +	*00901*00101*008011* -	Total
Case	0	116	116
Control	2	42	44
Total	2	158	160

Risk ratio: 0
Odds ratio: 0
X^2: -
p = -

Antigen	*01201*00101*00201* +	*01201*00101*00201* -	Total
Case	26	90	116
Control	2	42	44
Total	28	132	160

Risk ratio: 4.931
Odds ratio: 6.0667
X^2: 5.87
p = 0.015401

Antigen	*01301*00101*00201* +	*01301*00101*00201* -	Total
Case	11	105	116
Control	2	42	44
Total	13	147	160

Risk ratio: 2.0862
Odds ratio: 2.2
X^2: -
p = -

Antigen	*01301*00301*00501* +	*01301*00301*00501* -	Total
Case	28	88	116
Control	8	36	44
Total	36	124	160

Risk ratio: 1.3276
Odds ratio: 1.4318
X^2: 0.35
p = 0.554113

Antigen	*02301*00301*00501* +	*02301*00301*00501* -	Total
Case	8	108	116
Control	7	37	44
Total	15	145	160

Risk ratio: 0.4335
Odds ratio: 0.3915
X^2: -
p = -

Antigen	*09401*00401*01303* +	*09401*00401*01303* -	Total
Case	0	116	116
Control	0	44	44
Total	0	160	160

Risk ratio: 0
Odds ratio: 0
X^2: -
p = -

Antigen	*09501*00101*00201* +	*09501*00101*00201* -	Total
Case	0	116	116
Control	0	44	44
Total	0	160	160

Risk ratio: 0
Odds ratio: 0
X^2: -
p = -

Antigen	*01501*00601*00301* +	*01501*00601*00301* -	Total
Case	2	114	116
Control	1	43	44
Total	3	157	160

Risk ratio: 0.7586
Odds ratio: 0.7544
X^2: -
p = -

8.3. Table S2B. Hovawart 2x2 Contingency tables

Antigen	*00201*00901*00101* +	*00201*00901*00101* -	Total
Case	14	44	58
Control	2	24	26
Total	16	68	84

Risk ratio: 3.1379
Odds ratio: 3.8182
X^2: -
p = -

Antigen	*01101*00201*01302* +	*01101*00201*01302* -	Total
Case	2	56	58
Control	3	23	26
Total	5	79	84

Risk ratio: 0.2989
Odds ratio: 0.2738
X^2: -
p = -

Antigen	*01201*00401*013017* +	*01201*00401*013017* -	Total
Case	25	33	58
Control	13	13	26
Total	38	46	84

Risk ratio: 0.8621
Odds ratio: 0.7576
X^2: 0.12
p = 0.729034

Antigen	*01301*00101*00201* +	*01301*00101*00201* -	Total
Case	9	49	58
Control	2	24	26
Total	11	73	84

Risk ratio: 2.0172
Odds ratio: 2.2041
X^2: -
p = -

Antigen	*01301*00101*00802* +	*01301*00101*00802* -	Total
Case	0	58	58
Control	1	25	26
Total	1	83	84

Risk ratio: 0
Odds ratio: 0
X^2: -
p = -

Antigen	*01501*00601*00301* +	*01501*00601*00301* -	Total
Case	3	55	58
Control	2	24	26
Total	5	79	84

Risk ratio: 0.6724
Odds ratio: 0.6545
X^2: -
p = -

Antigen	*01501*00601*04901* +	*01501*00601*04901* -	Total
Case	0	58	58
Control	1	25	26
Total	1	83	84

Risk ratio: 0
Odds ratio: 0
X^2: -
p = -

Antigen	*01501*00601*049v* +	*01501*00601*049v* -	Total
Case	1	57	58
Control	2	24	26
Total	3	81	84

Risk ratio: 0.2241
Odds ratio: 0.2105
X^2: 0
p = 0

Antigen	*01501*00601*02301* +	*01501*00601*02301* -	Total
Case	1	57	58
Control	0	26	26
Total	1	83	84

Risk ratio: ∞
Odds ratio: ∞
X^2: -
p = -

Antigen	*03001*00601*00301* +	*03001*00601*00301* -	Total
Case	3	55	58
Control	0	26	26
Total	3	81	84

Risk ratio: ∞
Odds ratio: ∞
X^2: -
p = -