Clinical Genomics in Endocrinology

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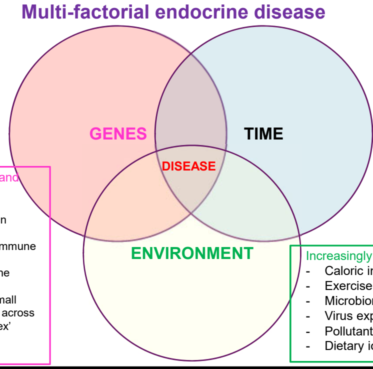
2025 Conti Symposium on Veterinary Continuing Education
Current Concepts and Controversies in Clinical Genomics

RVC

Multi-factorial endocrine disease



Many genes of known and unknown function:

- Monogenic mutations in receptors or channels
- MHC variation in autoimmune endocrine disease
- Oncogenes in endocrine cancer
- Cumulative effect of small number of 'risk alleles' across many genes in 'complex' diseases

Increasingly well characterised:

- Caloric intake and diet
- Exercise
- Microbiome
- Virus exposure
- Pollutants and EDCs
- Dietary iodine

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Endocrine disorders

- Overproduction of hormones
  - Hyperthyroidism
  - Cushing's (hyperadrenocorticism)
  - Hyperaldosteronism
  - Insulinoma
  - Hypersomatotropism (Acromegaly)
  - Hyperparathyroidism
- Deficiency (relative or absolute):
  - Hypothyroidism
  - Diabetes mellitus
  - Addison's (hypoadrenocorticism)

> Overproduction – lack of response to normal signals, and expansion of the endocrine organ
  - Hyperplasia (nodule)
  - Tumour (benign or malignant)

> Deficiency – lack of response to normal signals, and expansion of the endocrine organ
  - Autoimmune destruction
  - Antibodies blocking signalling
  - Gland destroyed by infection, tumour, surgery or radiation

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SUMMARY

- Canine Diabetes Mellitus
  - Genetic basis of human diabetes
  - Investigating canine diabetes genetics
- Feline Hyperthyroidism
  - Can we predict which cats will become hyperthyroid?
  - Acquired genetic mutations in the feline thyroid gland
- Canine insulinoma
  - Using single-cell transcriptomics to understand a rare cancer

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The Veterinary Journal 270 (2021) 105611
Contents lists available at ScienceDirect
The Veterinary Journal
journal homepage: www.elsevier.com/locate/tvjl

Invited review

Genetics of canine diabetes mellitus part 1: Phenotypes of disease

Alice L. Denyer[a], Brian Catchpole[a], Lucy J. Davison[b,c,*],
Canine Diabetes Genetics Partnership[1]

The Veterinary Journal 270 (2021) 105612
Contents lists available at ScienceDirect
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Review

Genetics of canine diabetes mellitus part 2: Current understanding and future directions

Alice L. Denyer[a], Brian Catchpole[a], Lucy J. Davison[b,c,*],
Canine Diabetes Genetics Partnership[1]

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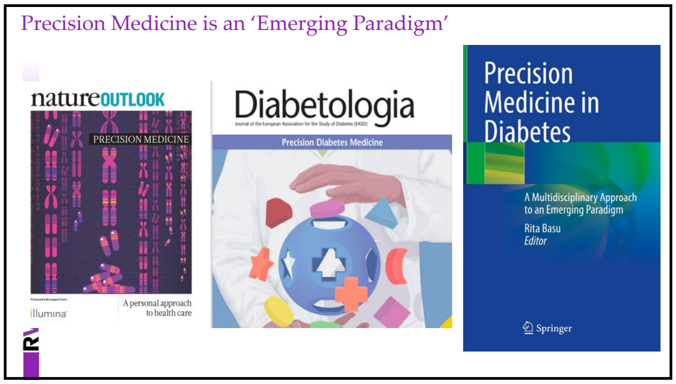
Thursday, 7 June 2007

Wellcome Trust Case Control Consortium *Nature* 2007

There are now >75 genetic regions associated with type 1 diabetes and >200 regions associated with type 2 diabetes in humans

Most cases of canine diabetes are likely to have a similarly 'complex' genetic basis


Precision Medicine is an 'Emerging Paradigm'
nature OUTLOOK
PRECISION MEDICINE
A personal approach to health care
illumina
Diabetologia
Precision Diabetes Medicine
Precision Medicine in Diabetes
A Multidisciplinary Approach to an Emerging Paradigm
Rita Basu
Editor
Springer


THE LANCET
Diabetes & Endocrinology
Log in
COMMENT | VOLUME 6, ISSUE 8, P594-595, AUGUST 01, 2018
Precision medicine in KCNJ11 permanent neonatal diabetes
Siri Atma W Greeley • Lisa R Letourneau • Louis H Philipson
Open Access • Published: June 04, 2018 • DOI: https://doi.org/10.1016/S2213-8587(18)30138-4
Excellent clinical response to oral sulphonylureas
Neonatal diabetes mellitus – assumed to be "type 1" autoimmune and insulin dependent
Poor or erratic response to injectable insulin therapy
Clinical whole genome sequencing (WGS)
Mutation in KCNJ11 identified (a potassium channel involved in insulin release in pancreatic beta cells)
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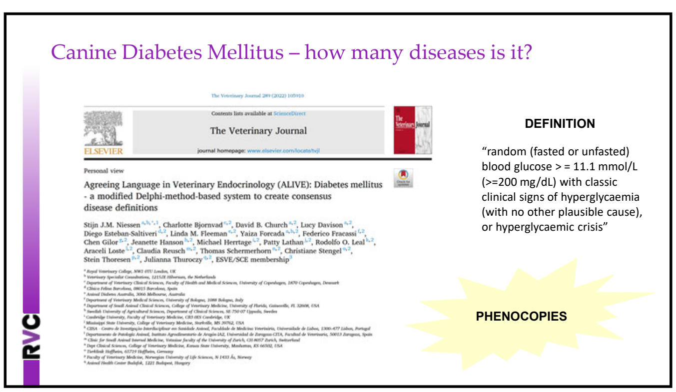
Canine Diabetes Mellitus – how many diseases is it?
The Veterinary Journal 289 (2022) 105910
Contents lists available at ScienceDirect
The Veterinary Journal
journal homepage: www.elsevier.com/locate/tvjl
ELSEVIER
Personal view
Agreeing Language in Veterinary Endocrinology (ALIVE): Diabetes mellitus - a modified Delphi-method-based system to create consensus disease definitions
Stijn J.M. Niessen, Charlotte Bjornvad, David B. Church, Lucy Davison, Diego Esteban-Saltiveri, Linda M. Fleeman, Yaiza Forcada, Federico Fracassi, Chen Gilor, Jeanette Hanson, Michael Herrtage, Patty Lathan, Rodolfo O. Leal, Araceli Loste, Claudia Reusch, Thomas Schermerhorn, Christiane Stengel, Stein Thoresen, Julianna Thuroczy, ESVE/SCE membership
DEFINITION
"random (fasted or unfasted) blood glucose > = 11.1 mmol/L (>=200 mg/dL) with classic clinical signs of hyperglycaemia (with no other plausible cause), or hyperglycaemic crisis"
PHENOCOPIES
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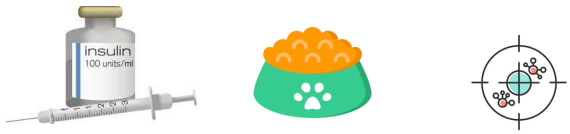
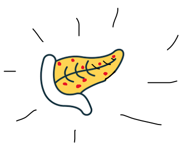


What will genetics reveal?



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Epidemiology supports a strong genetic risk in canine diabetes

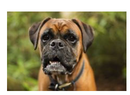
Table 2 Descriptive and univariable logistic regression results

Variable	Case (%) $n = 409$	Control (%) $n = 818$	Odds Ratio	95% CI[a]	Category *P*-value	Variable *P*-value
Purebred status						0.051
Crossbred	92 (22.5%)	226 (27.7%)	Base			
Purebred	317 (77.5%)	591 (72.3%)	1.15	1.00–1.32	0.051	
Breed ≥ 10 dogs and/or ≥ 5 case dogs						< 0.001
Crossbred	88 (21.5%)	204 (24.9%)	Base			
Tibetan Terrier	9 (2.2%)	2 (0.2%)	10.43	2.21–49.27	0.003	
Border Terrier	21 (5.1%)	10 (1.2%)	4.87	2.20–10.76	< 0.001	
Cairn Terrier	5 (1.2%)	3 (0.4%)	3.86	0.90–16.52	0.068	
Miniature Schnauzer	10 (2.4%)	6 (0.7%)	3.86	1.36–10.96	0.011	
West Highland White Terrier	53 (13.0%)	32 (3.9%)	3.84	2.32–6.36	< 0.001	
Yorkshire Terrier	30 (7.3%)	23 (2.8%)	3.02	1.66–5.50	< 0.001	
Bichon Frise	11 (2.7%)	15 (1.8%)	1.70	0.75–3.85	0.203	
Cavalier King Charles Spaniel	16 (3.9%)	22 (2.7%)	1.69	0.84–3.36	0.138	
Jack Russell Terrier	32 (7.8%)	51 (6.2%)	1.45	0.88–2.42	0.148	
Border Collie	13 (3.2%)	23 (2.8%)	1.31	0.63–2.70	0.465	
Cocker Spaniel	13 (3.2%)	26 (3.2%)	1.16	0.57–2.36	0.684	
Purebred (other)	71 (17.4%)	269 (32.9%)	0.90	0.61–1.33	0.597	
Labrador Retriever	25 (6.1%)	76 (9.3%)	0.76	0.45–1.28	0.304	
Lhasa Apso	4 (1.0%)	13 (1.6%)	0.71	0.23–2.25	0.564	
Staffordshire Bull Terrier	12 (2.9%)	56 (6.9%)	0.50	0.25–0.97	0.041	
Springer Spaniel – unspecified	2 (0.5%)	12 (1.5%)	0.39	0.08–1.76	0.219	
Golden Retriever	1 (0.2%)	9 (1.1%)	0.26	0.03–2.06	0.201	
Boxer	1 (0.2%)	11 (1.35)	0.21	0.03–1.66	0.139	

Heeley et al. Canine Medicine and Genetics (2020) 7:6
https://doi.org/10.1186/s40575-020-00087-7
Canine Medicine and Genetics
RESEARCH Open Access

Diabetes mellitus in dogs attending UK primary-care practices: frequency, risk factors and survival

Angela M. Heeley[1*], Dan G. O'Neill[1], Lucy J. Davison[2], David B. Church[2], Ellie K. Corless[1] and Dave C. Brodbelt[1]



Canine Diabetes GENETICS PARTNERSHIP

The Canine Diabetes Genetics Partnership is an interdisciplinary consortium formed to discover and understand genetic variants contributing to canine pancreatic beta cell health and disease

Petplan CHARITABLE TRUST

Dechra

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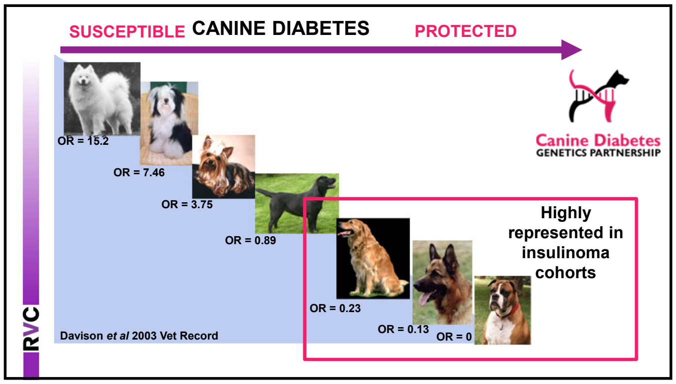
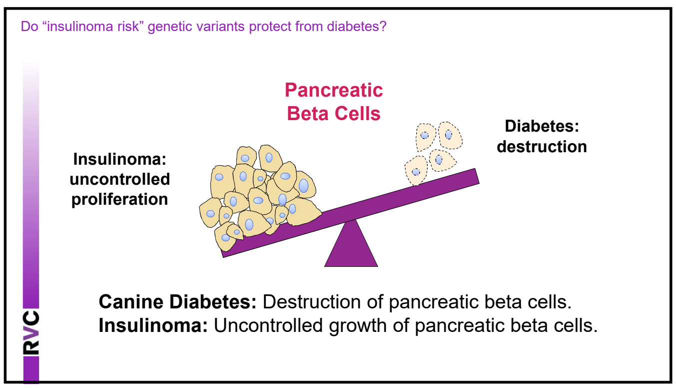

SUSCEPTIBLE
CANINE DIABETES
PROTECTED
Canine Diabetes
GENETICS PARTNERSHIP
OR = 15.2
OR = 7.46
OR = 3.75
OR = 0.89
OR = 0.23
OR = 0.13
OR = 0
Highly represented in insulinoma cohorts
Davison et al 2003 Vet Record
RVC


Do "insulinoma risk" genetic variants protect from diabetes?
Pancreatic Beta Cells
Insulinoma: uncontrolled proliferation
Diabetes: destruction
Canine Diabetes: Destruction of pancreatic beta cells.
Insulinoma: Uncontrolled growth of pancreatic beta cells.
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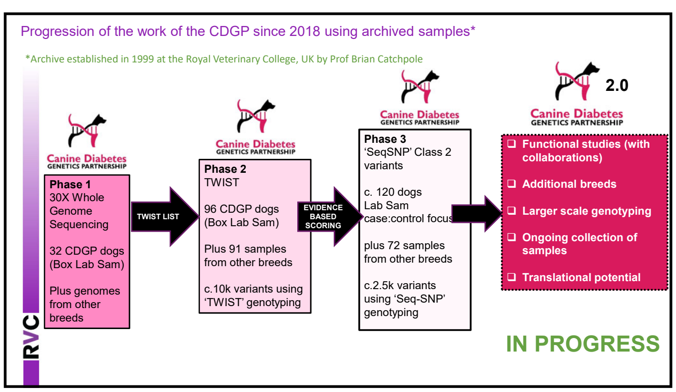
Progression of the work of the CDGP since 2018 using archived samples*
*Archive established in 1999 at the Royal Veterinary College, UK by Prof Brian Catchpole
Canine Diabetes
GENETICS PARTNERSHIP
Phase 1
30X Whole Genome Sequencing
32 CDGP dogs (Box Lab Sam)
Plus genomes from other breeds
TWIST LIST
Phase 2
TWIST
96 CDGP dogs (Box Lab Sam)
Plus 91 samples from other breeds
c.10k variants using 'TWIST' genotyping
EVIDENCE BASED SCORING
Phase 3
'SeqSNP' Class 2 variants
c. 120 dogs
Lab Sam
case:control focus
plus 72 samples from other breeds
c.2.5k variants using 'Seq-SNP' genotyping
2.0
Functional studies (with collaborations)
Additional breeds
Larger scale genotyping
Ongoing collection of samples
Translational potential
IN PROGRESS
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What attributes give a genetic variant (SNP) a 'high' evidence score for further evaluation?

- Statistics:
  - High frequency in high diabetes risk breed(s)
  - Distinct in high diabetes risk breed(s)
  - Low frequency or absence in low diabetes risk breed(s) and insulinomas
  - P value of case / control analysis within a breed
  - P value of case / control analysis in the whole cohort
- Plausible link to disease
  - Tier 1: direct link to disease
  - Tier 2: gene / pathway relevant to disease
- Impact
  - Coding sequence
  - Predicted effect on gene function or splicing

CLUSTER COMPUTING

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How can genetic variants contribute to risk in a complex disease?

1. High-frequency & fixed variants in a breed

- providing an overall increased susceptibility of the whole breed to the disease (may or may not be exclusive to the breed)

2. Variants in a subset of individuals with the breed

- modifying susceptibility to the disease within a breed (i.e. seen in more cases than controls within a breed)

3. Low-frequency or unique variants

- modifying risk of the disease in individual dogs or cats

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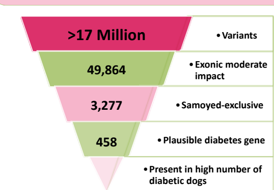
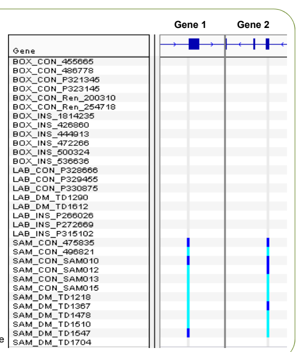
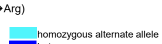
Samoyed Diabetes



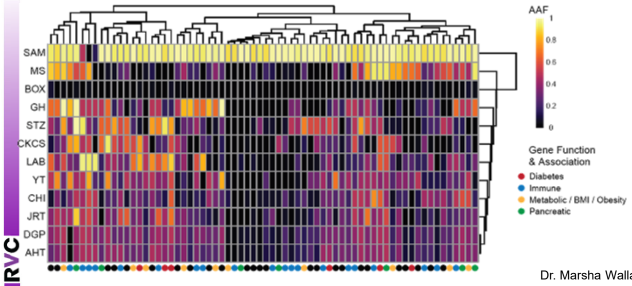
Gene 1
- Missense (p.Val→Gly)
- regulation of insulin receptor signalling pathway

Gene 2
- Missense (p.Arg→Lys); (p.Gly→Arg)
- response to insulin





"Class 1" : Examples of candidate variants making the whole Samoyed breed at increased risk of diabetes



Dr. Marsha Wallace

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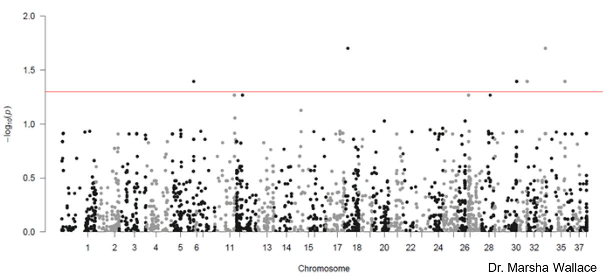
"Class 2" : Within breed GWAS: are certain dogs within each breed at increased risk?



Dr. Marsha Wallace

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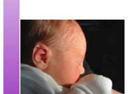
THE LANCET
Diabetes & Endocrinology
Log in
COMMENT | VOLUME 6, ISSUE 8, P594-595, AUGUST 01, 2018
Precision medicine in *KCNJ11* permanent neonatal diabetes
Siri Atma W Greeley • Lisa R Letourneau • Louis H Philipson
Open Access • Published: June 04, 2018 • DOI: https://doi.org/10.1016/S2213-8587(18)30138-4

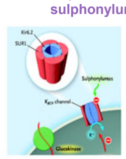
Excellent clinical response to oral sulphonylureas



Neonatal diabetes mellitus – assumed to be "type 1" autoimmune and insulin dependent

Poor or erratic response to injectable insulin therapy

Clinical whole genome sequencing (WGS)



Mutation in *KCNJ11* identified (a potassium channel involved in insulin release in pancreatic beta cells)

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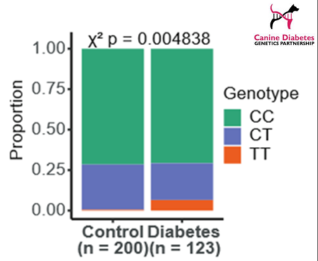
Class 3 (Monogenic diabetes) variant in the same gene (KCNJ11) in Labrador retrievers

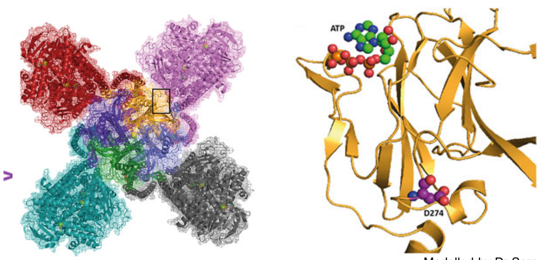
- 200 non-diabetic Labrador retrievers **– 1 homozygote**
- 123 Labrador retrievers with diabetes (adult onset) **– 8 homozygotes**
- Not (yet) seen in any other breeds



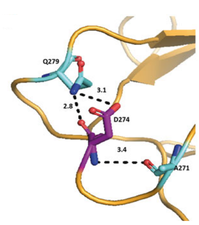
These data are supportive of possible monogenic recessive inheritance of DM associated with the mutation rs851344999 (D274N) in *KCNJ11* in the Labrador retriever

Dr. Marsha Wallace
Manuscript in preparation
Patent submitted

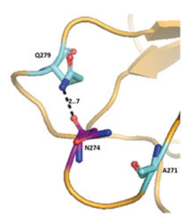
KCNJ11 encodes a subunit of the K_{ATP} channel expressed in beta cells, and involved in the electrophysiological process of insulin release



Modelled by Dr Sara Falcone



Reference:
D (Aspartic Acid) at position 274



Diabetes-associated:
N (Asparagine) at position 274

Would diabetic dogs with this mutation benefit from sulphonylurea drugs like humans?

Can we prevent diabetes occurring in these dogs?

Modelled by Dr Sara Falcone

SUMMARY

- Canine Diabetes Mellitus
  - Genetic basis of human diabetes
  - Investigating canine diabetes genetics
- Feline Hyperthyroidism
  - Can we predict which cats will become hyperthyroid?
  - Acquired genetic mutations in the feline thyroid gland
- Canine insulinoma
  - Using single-cell transcriptomics to understand a rare cancer

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www.nature.com/scientificreports

scientific reports

Check for updates

OPEN

Transcriptomic analysis reveals a critical role for activating $G_s\alpha$ mutations in spontaneous feline hyperthyroidism

Thomas K. Hiron[1,2], Joana Aguiar[1,3], Jonathan M. Williams[4], Sara Falcone[2], Paul A. Norman[1], Jonathan Elliott[5], Robert C. Fowkes[5,6], Harriet M. Syme[1] & Lucy J. Davison[1,2]✉

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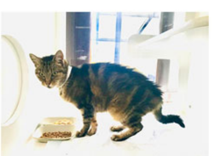

10% of cats over the age of 10 years are hyperthyroid

Hyperthyroidism is less common in color-point breed cats

- **Can we use clinical genetics to predict which cats will get hyperthyroidism?**
- **Can we use genetics or transcriptomics to understand the pathogenesis of hyperthyroidism so we can design more targeted treatments?**

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Multifactorial additive risks in development of feline HTH

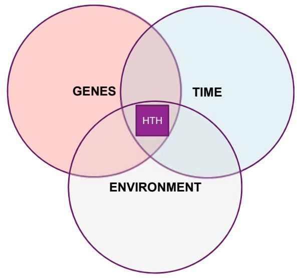
What do we mean by "genetics"?

- ✓ Inherited (germline) variation

AND

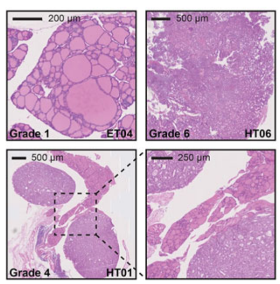
- ✓ Acquired (somatic) mutations within individual cells in the thyroid

NEW TREATMENT TARGETS



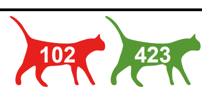
What is actually happening in the feline thyroid?

- Feline hyperthyroidism shares several histopathological and clinical similarities with human toxic multinodular goitre (TMG).
- The major risk factors for TMG, besides advanced age and female sex, are iodine deficiency and **acquired mutations** in the genes encoding TSHR or Gsα.

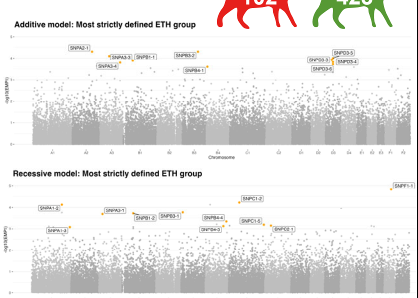


Feline euthyroid (ET) and hyperthyroid (HT) thyroid tissue: Hiron et al 2024

Discovery GWAS results: **Case-control**



- Using a SNP chip
- **A total of 71 variants associated with feline hyperthyroidism (nominal significance) were identified.**
- 15 variants were repeatedly associated with hyperthyroidism across different association tests.



Paul Norman PhD student – manuscript in preparation

ONGOING WORK

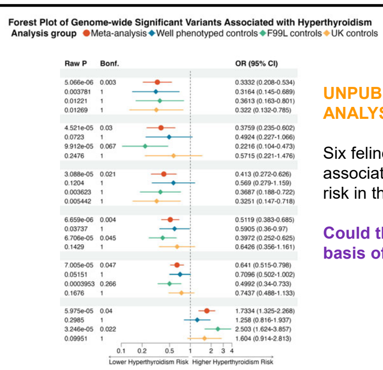
The most promising variants have been prioritised, using a bespoke bioinformatics pipeline for "evidence scoring".

DNA has been extracted from archived blood samples from a further 144 cases and 263 controls from the RVC geriatric cat clinic, for targeted sequencing at 673 selected variants, using a technology called Seq-SNP

Analysis is ongoing in the form of a meta-analysis from the original SNP-chip GWAS data and the new targeted sequencing data – more data to be published 2025-2026

NEW TREATMENT TARGETS?

Paul Norman PhD student



UNPUBLISHED PRELIMINARY ANALYSIS:

Six feline variants are significantly associated with feline hyperthyroidism risk in the meta-analysis

Could these eventually form the basis of a clinical test?

Manuscript in preparation

Paul Norman
Marsha Wallace

Multifactorial additive risks in development of feline HTH

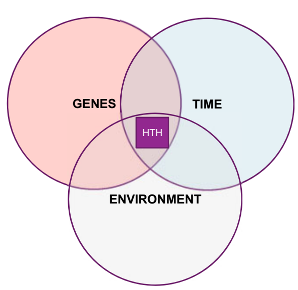
What do we mean by "genetics"?

- ✓ Inherited (germline) variation

AND

- ✓ **Acquired (somatic) mutations within individual cells in the thyroid**

NEW TREATMENT TARGETS



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OPEN

Transcriptomic analysis reveals a critical role for activating $G_s\alpha$ mutations in spontaneous feline hyperthyroidism

Thomas K. Hiron[1,2], Joana Aguiar[1,3], Jonathan M. Williams[4], Sara Falcone[2], Paul A. Norman[1], Jonathan Elliott[5], Robert C. Fowkes[5,6], Harriet M. Syme[1] & Lucy J. Davison[1,2]

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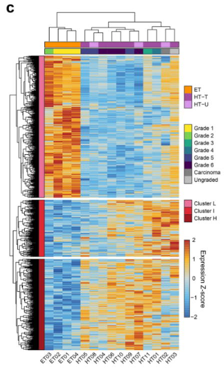


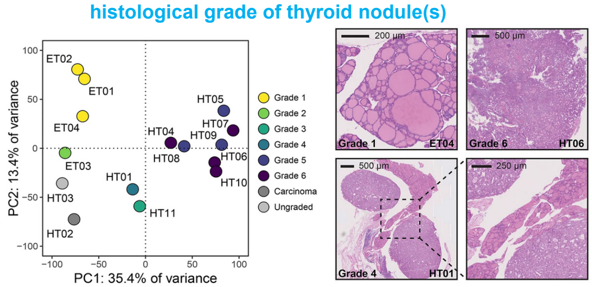
Study design (Hiron et al 2024)

Thyroid tissue histopathology and RNA sequencing

Sample ID	Reason for collection	Age at collection	Sex	Breed	T4 at diagnosis (nmol/L)	T4 at collection (nmol/L)	TSH (ng/mL)	Thyroid status	Treatment status	Treatment duration (days)
ET01	euthanasia	15y 3m	MN	DLH	-	18.8	0.05	euthyroid	-	-
ET02	euthanasia	9y 6m	FN	DSH	-	7.3	0.06	euthyroid	-	-
ET03	euthanasia	17y 5m	MN	DSH	-	35.9	0.07	euthyroid	-	-
ET04	euthanasia	15y 2m	FN	DSH	-	20	0.07	euthyroid	-	-
HT01	euthanasia	15y 6m	MN	DSH	77.6	86.6	-	hyperthyroid	treated	1539
HT02	euthanasia	20y	FN	DLH	82.5	91.2	-	hyperthyroid	untreated	-
HT03	euthanasia	15y 1m	FE	DSH	251	107	-	hyperthyroid	treated	77
HT04	thyroidectomy	10y 8m	FN	DSH	299	4.1	-	hyperthyroid	treated	88
HT05	thyroidectomy	9y 2m	MN	DSH	261	-	-	hyperthyroid	treated	31
HT06	thyroidectomy	12y 7m	FN	DSH	138	-	-	hyperthyroid	treated	48
HT07	euthanasia	12y 7m	FN	DSH	237	-	-	hyperthyroid	untreated	-
HT08	thyroidectomy	14y 2m	FN	DSH	170	-	-	hyperthyroid	untreated	-
HT09	euthanasia	21y 8m	MN	DLH	43.9	15.7	<0.03	hyperthyroid	treated	1343
HT10	thyroidectomy	12y 11m	MN	DSH	>300	-	-	hyperthyroid	treated	21
HT11	euthanasia	15y	FN	DSH	169	4	-	hyperthyroid	treated	263

Joana Aguiar PhD student
Dr Tom Hiron

Gene expression profile by RNA-Seq correlates with histological grade of thyroid nodule(s)



Which genes might be involved?

Hyperthyroid cats have low or no TSH

Looking for **acquired** mutations in thyroid nodules, that might explain why thyroid hormone is still made and secreted in hyperthyroid cats, even when TSH is low

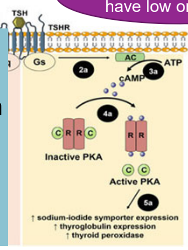


Figure from: Pereira, Sofia & Lobato, Carolina & Monteiro, Mariana. (2020). Cell Signaling Within Endocrine Glands: Thyroid, Parathyroids and Adrenal Glands. 10.1007/978-3-030-44436-5_3.

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Acquired mutations in feline hyperthyroidism: The TSH receptor (*TSHR*)

- Watson *et al.* reported mutations in exon 10 of TSHR, encoding the transmembrane and intracellular domains, in thyroid nodules from 28/50 HT cats
- **We saw this mutation, and some additional mutations in *TSHR* – but in both hyperthyroid and euthyroid cats**

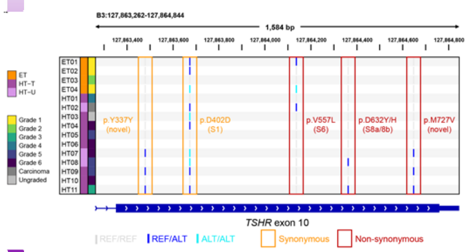
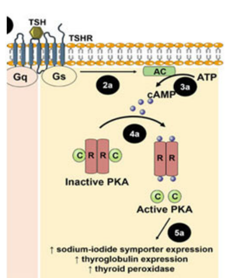


Figure: Genotypes of *TSHR* variants detected in RNA-seq reads from HT and ET samples. Genomic coordinates are for the felCat9 reference genome (see Methods). Variants are labelled with the resulting amino acid substitution in TSHR, and with the variant ID from Watson et al. where applicable.

- ***GNAS*** is the gene encoding the alpha subunit of Gs (**Gsα**), which is **critical in downstream signalling from TSHR**
- Peeters *et al.* detected Gsα mutations in 4/10 HTH cats at two different sites.
- **We also detected these two mutations in hyperthyroid cats in our RNA-Seq data**
- We also found a third, novel mutation in *GNAS* in thyroid tissue from cats with hyperthyroidism.



Pereira et al 2020

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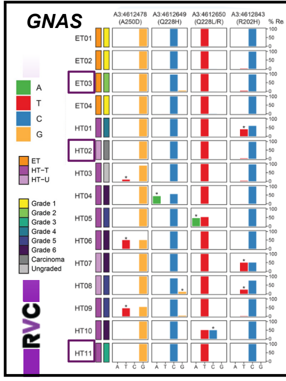
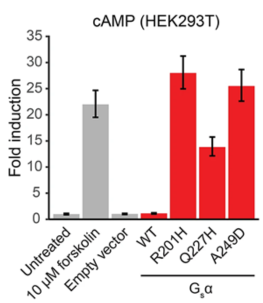


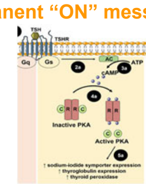
- **In exons 8–10 of *GNAS*, (encoding $G_s\alpha$), we detected acquired missense variants in 9/11 thyroid samples from HTH cats**
- **None of these variants were detected in thyroid samples from euthyroid cats or in blood samples from HTH cats**

Nucleotide frequencies in mapped RNA-seq reads at variant positions in *GNAS* (ENSFCAT00000040256). Alternative alleles called by GATK are marked with *. The first 2 mutations have been previously reported.



Hiron *et al* 2024

The acquired mutations in $G_s\alpha$ in feline hyperthyroidism lead to constitutive signalling (cAMP production) = a permanent "ON" message



Pereira *et al* 2020

WHAT DOES THIS MEAN?

- ☑ The $G_s\alpha$ variants detected in feline thyroids in this study are acquired mutations
- ☑ These mutations result in constitutive $G_s\alpha$ activation and elevated intracellular cAMP
- ☑ This makes the mutations a likely causal factor in feline hyperthyroidism

The question remains:

Why and how do mutations arise in feline thyroid glands?

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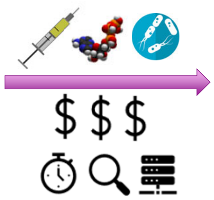
DNA sequence

Without comparative information and expert analysis, this is of limited value



This will look different for each person

Precision Medicine

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SUMMARY

- Canine Diabetes Mellitus
  - Genetic basis of human diabetes
  - Investigating canine diabetes genetics
- Feline Hyperthyroidism
  - Can we predict which cats will become hyperthyroid?
  - Acquired genetic mutations in the feline thyroid gland
- Canine insulinoma
  - Using single-cell transcriptomics to understand a rare cancer

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Wallace *et al. Veterinary Oncology* (2025) 2:13
https://doi.org/10.1186/s44356-025-00026-3

Veterinary Oncology

RESEARCH Open Access

Single-cell transcriptomic analysis of canine insulinoma reveals distinct sub-populations of insulin-expressing cancer cells

M. D. Wallace[1,2], M. E. Herrtage[3], R. Gostelow[1], L. Owen[3], L. Rutherford[1], K. Hughes[3], A. Denyer[4], B. Catchpole[4], C. A. O'Callaghan[5] and L. J. Davison[1,2*]

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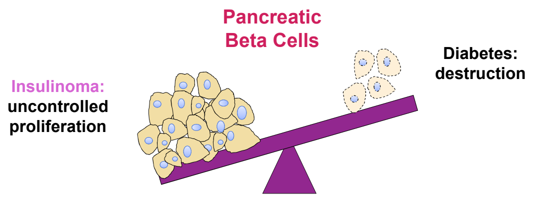

Canine Diabetes: Destruction of pancreatic beta cells.
Insulinoma: Uncontrolled growth of pancreatic beta cells.

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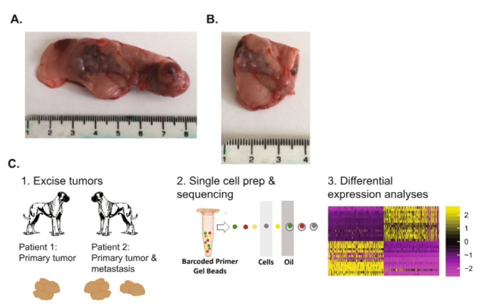
10X single-cell transcriptomics of two canine insulinomas



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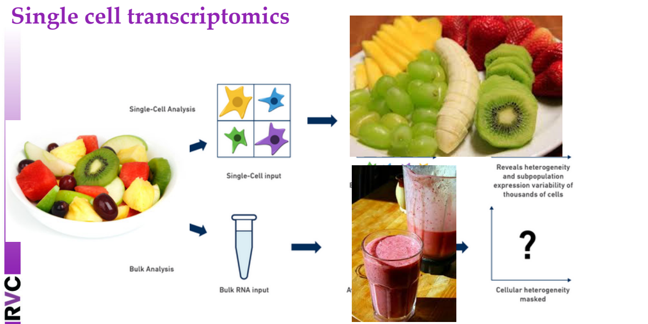
Single cell transcriptomics



https://community.10xgenomics.com/t5/10x-Blog/Single-Cell-RNA-Seq-An-Introductory-Overview-and-Tools-for/ba-p/5

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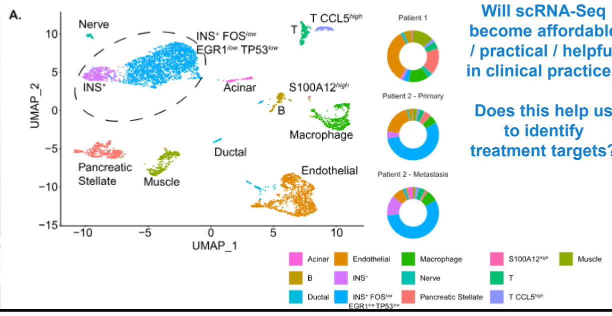
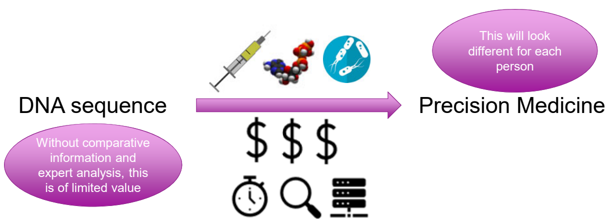
Unexpectedly, two different populations of cells were expressing insulin



Will scRNA-Seq become affordable / practical / helpful in clinical practice?

Does this help us to identify treatment targets?



Clinical Genomics in Endocrinology

THANK YOU FOR YOUR ATTENTION – QUESTIONS?

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2025 Conti Symposium on Veterinary Continuing Education
Current Concepts and Controversies in Clinical Genomics