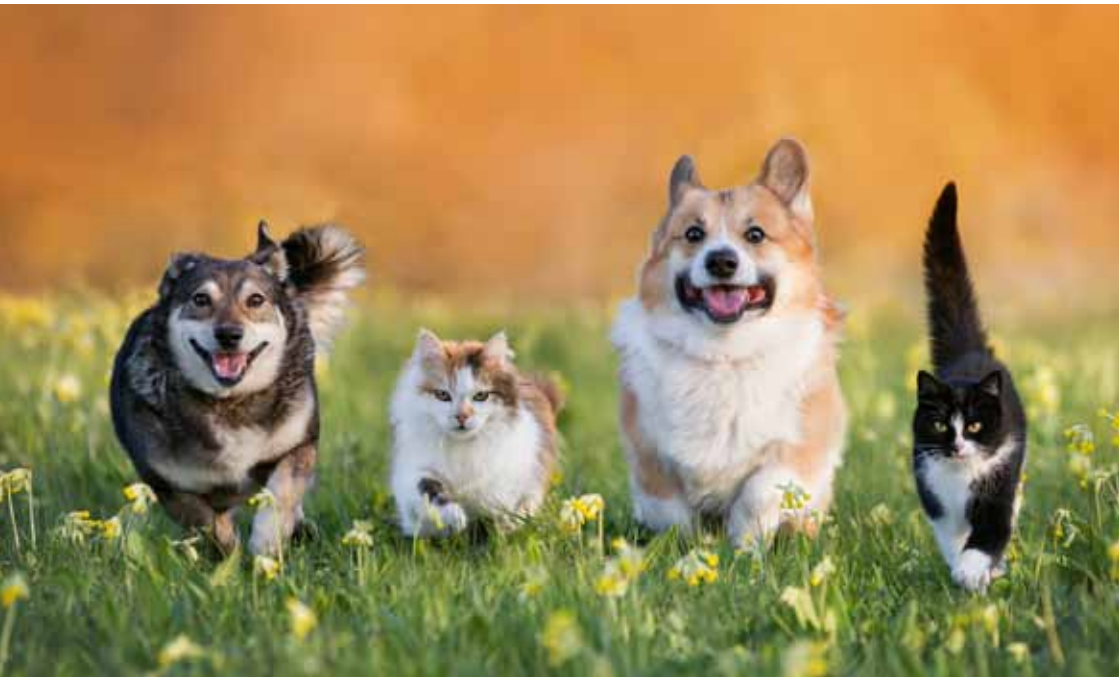
Programme & Abstracts

12th International Conference on

Canine and Feline Genetics and Genomies

ICCFGG2024
Helsinki – Finland

Contents



Welcome to the 12th International Conference on Canine and Feline Genetics and Genomics

Helsinki is the capital and most populous city in Finland. It is located on the shore of the Gulf of Finland and serves as the seat of the Uusimaa region in southern Finland. More than 675,000 people live in the municipality, and 1.6 million in the metropolitan area. Helsinki is a vibrant city and the country's most significant center for politics, education, finance, culture, and research.

This International Conference has a tradition of alternating between Europe and the United States, and the Helsinki conference follows the successful meeting in Huntsville, Alabama, US, in 2022. The conference has evidenced many breakthroughs and milestones in the fields of canine and feline genetics, including the development of outstanding resources for genetic, genomic, and functional genomics research coupled with exciting studies in inherited diseases, cancer, behavioral and morphological traits, evolutionary biology, genome architecture and related areas in dogs and cats.

This time in Helsinki, we have planned a full plate of fascinating presentations based on 115 submitted abstracts. We will skip the workshop day – preceding the official conference - to avoid overlapping presentations and have spread the official program over the 3,5 days. The Scientific Organizing Committee has selected 40 for oral presentations, with all other abstracts being presented at one of the three poster sessions. Additionally, fifteen posters from mostly young scientists will be highlighted in poster flash talks.

We also have two inspiring keynote speakers: Aarne Palotie, MD, PhD, is the research director of the Human Genomics program at the Institute for Molecular Medicine Finland (FIMM) at the University of Helsinki. His research utilizes the unique Finnish population and health care to improve our understanding of the genetic component underlying common diseases. Guillaume Bourque is a Professor in the Department of Human Genetics at McGill University, and his research interests are in comparative and functional genomics with a particular emphasis on applications of next-generation sequencing technologies and transposable elements.

The social program includes a Sunday night reception at the Little Finland and, on Tuesday, June 11, a gala dinner at the Restaurant Saaristo, located on the Klippan island in front of South Harbour. Saaristo is one of Helsinki's most imposing and traditional restaurants, and it includes a short boat trip to get there.

Again, we are very grateful to our main sponsor, Nestle Purina, who has supported and made this event possible for the last 20 years. My team and I look forward to welcoming you to Helsinki and enjoying an exciting and collaborative scientific conference.

Enjoy the conference, and welcome to Helsinki!

Best wishes,

Hannes Lohi

Nestlé PURINA. Nestlé Research

On behalf of Nestlé Purina PetCare Company, we are pleased to welcome you to Helsinki, Finland for the 12th International Conference on Canine and Feline Genetics and Genomics. Nestlé Purina PetCare Company is honored to sponsor this prestigious scientific gathering, continuing our tradition of supporting advancements in pet health since the conference's inception. We trust that this event will continue its tradition of excellence in sharing and promoting scientific advancements that help dogs and cats live longer and healthier lives.

We extend our gratitude to the scientific committee for their dedication to maintaining the conference's high standards. Special thanks go to the local organizing committee for their tireless efforts in ensuring a smooth event. Our appreciation extends to all supporters and contributors who have made this conference possible. We are especially thankful to the researchers and presenters for their invaluable contributions to enhancing the lives of pets.

With over a century of experience in animal nutrition research, Purina is committed to pioneering petcare innovations. Our global team of over 400 scientists and experts, along with our eight dedicated research and development centers and facilities, continues to lead way in advancing pet nutrition.

Through collaborations with researchers worldwide and innovative partnership in academia and industry, we strive to drive breakthroughs in petcare. We look forward to the opportunities for knowledge exchange and future collaboration at this conference.

Thank you for joining us in Helsinki. Your participation is crucial to driving scientific progress in the field of pet genetics and genomics. Together, we can anticipate exciting breakthroughs that will positively impact the lives of pets worldwide.

Sincerely,

Johnny Li, Ph.D.
Senior Principal Scientist
Nestlé Purina Research

Ebenezer Satyaraj, Ph.D.
Director of Molecular Nutrition
Nestlé Purina Research

Conference Ethics

The International Canine and Feline Genetics and Genomics Conference encourages scientists to present and discuss preliminary data prior to scientific publication. Presentation of research findings is a major factor for the success of the conference. In order to maintain conference integrity and participation, we stress that information presented here should be treated as preliminary work and out of respect for the authors, should only be used with the authors' permission.

In order to maintain the high quality of the conference we would like to inform all attendees of the following policies:

- We ask that new information obtained at this conference will not be used, for either research or commercial purposes, without permission from the authors.
- The abstracts in the conference program booklet cannot be cited.
- Publication of studies presented here in peer-reviewed journals is of course highly encouraged.

Breaches of confidentiality and common sense ethics will ultimately interfere with the pre-publication free flow of information and discussion expected of our conference and endangers the spirit of the conference.

We all thank you for your understanding and attention to this matter.

Conference committees

Scientific organizing committee

Hannes Lohi, University of Helsinki, Finland
Jennifer Meadows, University of Uppsala, Sweden
Jeffrey Schoenebeck, Roslin Insitute, Scotland, UK
Christophe Hitte, University of Rennes, France
Greg Barsh, Hudson Alpha, US
Adam Boyko, Cornell University, US
Eva Furrow, University of Minnesota, US
Leigh Anne Clark, University of Georgia, US
Claire Wade, University of Sydney, Australia
Qinghong (Johnny) Li, Nestle Purina Research, US

Local organizing committee

Hannes Lohi, University of Helsinki and Folkhälsan Research Center
Marjo Hytönen, Folkhälsan Research Center and University of Helsinki
Mikko Peltonen, Faculty of Veterinary Medicine
Nanna Mourujarvi-Rosenlöf, University of Helsinki
Confedent International

Presentation awards

The scientific organizing committee will select six graduate or postdoctoral student talks and posters (3+3) for best presentation awards (250€ each) in the conference.

PURINA Institute

Advancing Science for Pet Health

At the **Purina Institute**, we believe science is more powerful when it's shared. That's why we're on a mission to unlock the power of nutrition to help pets live better, longer lives. A global professional organization, the **Purina Institute** shares Purina's leading-edge research, as well as evidence-based information from the wider scientific community, in an accessible, actionable way so veterinary professionals are empowered to put nutrition at the forefront of pet health discussions to further improve and extend the healthy lives of pets through nutrition.

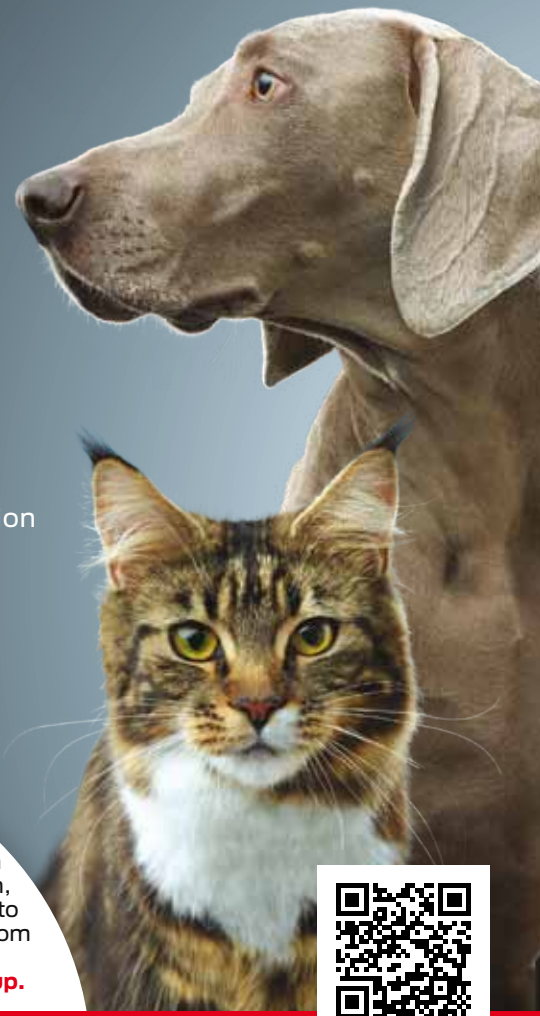
Partnering
With Global Thought Leaders

Sharing
Groundbreaking Research

Connecting The Most
Innovative Minds In Pet Health

Shaping
The Nutrition Conversation

Facilitating
The Exchange Of Knowledge



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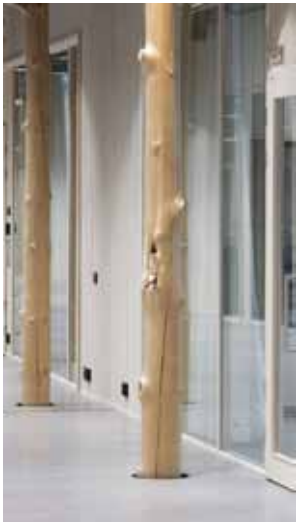
visit www.PurinaInstitute.com.

Sponsors

Little Finlandia

The event center Little Finlandia opened its doors in March, 2022, by the sea at Karamzininranta 4. Little Finlandia is located in a scenic park on the shores of Töölönlahti Bay. Easy and frequent public transport connections from the airport, bus and train stations. Tram and bus stops are in the immediate vicinity of the house. The city center is within walking distance, and there are several parking garages for those arriving by car.

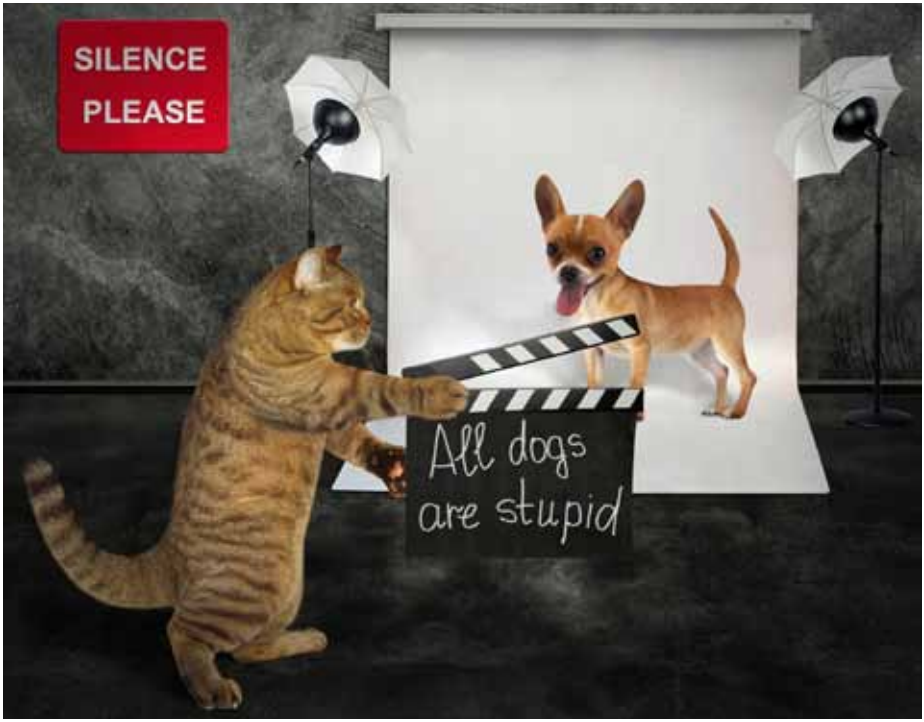


Little Finlandia is a temporary event space and cafe in overlooking the Töölönlahti Bay. It serves as a temporary substitute for the city's congress centre, Alvar Aalto's renowned Finlandia Hall, which is currently closed for refurbishment.

The most striking feature of the building is the 95 pine trees that support it. These trees were felled without damaging their branches and pressure-washed to remove the bark with minimal further processing. The design proves that, alongside the trunk, the thinner crown section of a pine tree can also be used for construction, not just as pulpwood.

What is less obvious about Little Finlandia is that the entire building is reusable, transportable and fully recyclable. Once the renovation work on Finlandia Hall is complete, Little Finlandia will be transported elsewhere and re-assembled with a new purpose. With an expected lifespan of 50 years, the building lends itself to many uses including as a school or a day-care centre.

Architects Jaakko Torvinen, Havu Järvelä and Elli Wendelin were still students at Aalto University when they designed Pikku-Finlandia together with Architects NRT and Professor Pekka Heikkinen in collaboration with the City of Helsinki and Finlandia Hall.



GENERAL INFORMATION

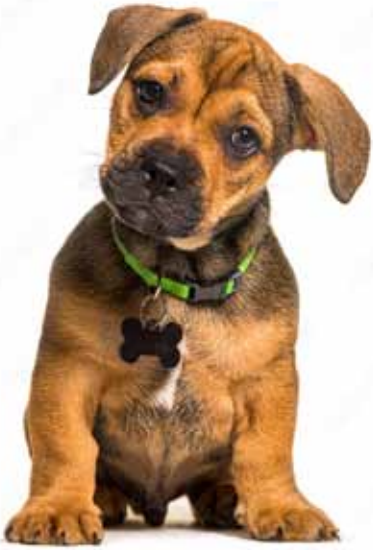
Venue
Little Finlandia
Karamzininranta 4
00100 Helsinki
Finland

Registration & information desk
Registration & information desk is located in the Little Finlandia lobby.

Opening hours:

Sunday 9 June	08.00 – 20.00
Monday 10 June	08.00 – 12.00
Tuesday 11 June	08.00 – 12.00

Name badges
Please collect your name badge from the Registration & information desk on your arrival.
Name badge must be worn during conference, including the official social events.



Coffee & lunch breaks
Coffee and lunch mentioned in the programme are included to all registered attendees.

Exhibition & Posters
Exhibition and posters are located in meeting room Kelo. Posters should be mounted on Sunday morning and removed at the end of the conference on Wednesday 12th.

Wifi
There is free WiFi for guests at Little Finlandia. The network name is Pikku-Finlandia and the password is Finlandia2024.

Public transportation
Helsinki has a very well functioning public transportation. Ticket for the public transportation (bus, tram, metro, train) needs to be purchased in advance, either from a vending machine, or from the HSL app.
The HSL Journey Planner is an easy way to plan your travel (https://www.hsl.fi/en).

Parking
Parking is available at a separate fee, and the 650-space car park is operated by Aimo Park. The drive to the parking garage takes place via Karamzininranta.

Sightseeing
While in Helsinki, you might want to explore
Visit www.myhelsinki.fi/en for great tips.

Contact
ICCFGG 2024 Participant services
Confedent International
iccfgg2024@confedent.fi
+358 50 325 4956

SOCIAL EVENTS

Reception at Little Finlandia
Date: Sunday 9 June, 2024
Time: 18.00 – 20.00
Venue: Little Finlandia (Karamzininranta 4, 00100 Helsinki)
Dresscode: Casual

Welcome Reception is held at the conference venue, Little Finlandia. Meet colleagues, enjoy light snacks and a drink!

Gala Dinner
Date: Tuesday 11 June
Time: meet at 18.40 at Restaurant Saaristo pier, dinner at 19.00 – 24.00
Venue: Restaurant Saaristo (address: island Klippan, 00140 Helsinki)
Dresscode: Smart casual

ICCFGG 2024 Gala Dinner will be celebrated in Restaurant Saaristo. Restaurant Saaristo is located on Island Klippan, on the south side of Olympia-terminal. A boat serves from pier located on the south side of Olympia-terminal, by the street Ehrenströmintie (next to the Peace Statue). Short sea journey takes only few minutes.
Gala Dinner is included in the registration fee to all registered attendees but requires pre-registration. If you have not registered for the Gala Dinner in advance, please check with the Registration & Information desk for available tickets.

12th ICCFGG program, June 9-12, 2024, Helsinki, Finland

Sunday 8:00-18:00

8:00-12:00 Registration and poster mounting

10:00-10:15 Welcome and introduction

Hannes Lohi, University of Helsinki and Folkhälsan Reserach Center
Johnny Li, Nestle Purina
Olli Peltoniemi, Dean, Faculty of Veterinary Medicine, University of Helsinki

10:15-11:55 **Session: Disease genetics** Chairs: *Eva Furrow and Lucy Davison*

- 10:15-10:35 The genetic architecture of canine blood phenotypes, *Adam Boyko*
- 10:35-10:55 A feline model of human LDLR-dependent atherosclerosis, *Marjo Hytönen*
- 10:55-11:15 Meta-analysis of canine obesity GWAS: identifies novel obesity genes in multiple dog breeds, *Liang Ming*
- 11:15-11:35 GWAS in Labrador retrievers identifies novel obesity genes in dogs and humans, *Eleanor Raffan*
- 11:35-11:55 GWAS and selection signatures indicate involvement of synaptic genes in Addison's disease, *Elizabeth Greif*

11:55-13:25 **Lunch**

13:25-15:05 **Session: Genetics of neurological disorders and longevity** Chairs: *Leigh Anne Clark and Jacquelyn Evans*

- 13:25-13:45 A study of over 15,000 dogs identifies the major locus for canine non-generalized tonic-clonic seizures, *Tiina Harmas*
- 13:45-14:05 Idiopathic epilepsy in the Border Collie: identifying common and rare genetic risk factors, *Christopher Jenkins*
- 14:05-14:25 Complicated structural variant causes familial adult-onset ataxia in Toy Poodles, *Keijiro Mizukami*
- 14:25-14:45 Increasing the dimensionalities of canine compulsive disorder with factor and genetic analyses, *Katarina Tengvall*
- 14:45-15:05 Exploring the genetics of longevity with the Dog Aging Project, *Elinor Karlsson*

15:05-15:45 **Coffee break**

15:45-16:15 **Poster flashtalks** Chair: *Marjo Hytönen*

Suspected autosomal recessive primary ciliary dyskinesia in a colony of Labrador Retriever guide dogs, *Katy M Evans*

Polymyositis in Kooiker dogs is associated with a 39 kb deletion upstream of the IL21/IL2 genes, *Peter Leegwater*

A Chromosome-Scale Assembly of a Domestic Cat Felis catus of American Shorthair Breed, *Yasukazu Nakamura*

Homozygous DSG4 missense variant in a Cavalier King Charles Spaniel with hair shaft dystrophy, *Jana Gresova*

An inherited Robertsonian translocation in Entlebucher mountain dogs reduces Fertility, *Claude Schelling*

16:15-18:00 **Poster session 1 & Coffee break**

18:00- 20:00 Reception at Little Finlandia

Monday 8:30-16:30

8:00-12:00 Registration

8:30-8:45 Announcements

8:45-10:45 **Session: Genetics of morphology and disease**
Chairs: *Jeff Schoenebeck and Suvi Mäkeläinen*

8:45-9:05 Within clade genome sequence analysis from 389 breeds identifies new genes controlling morphologic variation, *Heidi Parker*

9:05-9:25 A genotype first approach for discovery of trait-associated variants in dogs, *Reuben Buckley*

9:25-9:45 Lessons from genome-wide association studies using data from electronic medical Records, *Jonas Donner*

9:45-10:05 Short-spine dogs: a modern and historical phenotype definitively characterized, *Kari Ekenstedt*

10:05-10:25 Determination of the genetic etiology of bilateral anterior hemimelia in the Chihuahua, *Danika Bannasch*

10:25-10:45 Functional investigation of felid color pattern mechanisms in transgenic mice, *Kelly A McGowan*

10:45-11:15 **Coffee break**

11:15-12:15 **Keynote, Aarno Palotie**, Finngen project, Chair: *Hannes Lohi*

12:15-13:30 **Lunch**

13:30-14:00 **Poster flashtalks,** Chair: *Tomas Bergström*

EFNB3 frameshift variant in Weimaraner dogs with synchronous bunny-hopping Gait, *Cleo Schwarz*

Novel candidate genes for retinal degeneration in dogs and humans, *Sara Mikkonen*

PAX3 haploinsufficiency in Maine Coon cats with dominant blue eyes and hearing loss, *Gabriela Rudd Garces*

Gene variants identified and associated with polycystic kidney disease in Siberian and Neva Masquerade cats, *Åsa Ohlsson*

Identification of an RBCK1 splice site donor variant in Basset Hounds with glycogen storage disease, *Jeanna Blake*

14:00-15:30 **Poster session 2 & Coffee break**

15:30-17:10 **Session: Gene regulation**
Chairs: *Jennifer Meadows and Chris Kaelin*

15:30-15:50 Canine brain atlas: epigenetic and single nuclei transcriptome profiling across eleven dog brain regions, *Matthew Christmas*

15:50-16:10 Gene Expression Patterns in Dog and Wolf Brain Regions, *Faezeh Mottaghitalab*

16:10-16:30 Enhancer-mediated gene regulation in the dog genome, *Carsten Daub*

16:30-16:50 The canine eQTL project: the role of gene expression in shaping canine body size, *Reuben Buckley*

16:50-17:10 Transcriptomic and Intervention Evidence Reveals Domestic Dogs as a Promising Model for Anti-inflammatory Investigation, *Min Zeng*

Adjourn, enjoy Helsinki!
SAB meeting 19:00-21:00

Tuesday 8:30-17.00

8:00-12:00 Registration
8:30-8:45 Announcements

8:45-10:25 **Session: Evolution and population genetics**
Chairs: *Adam Boyko and Leslie Lyons*

8:45-9:05 Genetic analysis of 60,000 domestic cats reveals fine-scale population structure and its geographic origins, *Jason Huff*
9:05-9:25 A 3,500-year Human-Leopard Cat Commensalism Preceded the Arrival of Domestic Cats in China, *Yu Han*
9:25-9:45 Comparative functional analysis of SINEs in canines and felines, *Emily Koch*
9:45-10:05 Remapping to a Greenland Wolf assembly normalizes canine Divergence, *Anthony Nguyen*
10:05-10:25 Ancient genomes reveal the evolutionary history of Australian Dingoes, *Lachie Scarsbrook*

10:25-10:55 **Coffee break**

10:55-12:15 **Session: Population genetics and genome biology**
Chairs: *Johnny Li and Xu Wang*

10:55-11:15 The genomic history of Arctic sled dogs from past to present, *Heather Huson*
11:15-11:35 Ancient mitochondrial genomes reveal northwest China as crossroad in Eurasia of dog dispersal, *Shaojie Zhang*
11:35-11:55 A phylogenetic estimate of the rate of retrotransposition in canines, *Matthew Blacksmith*
11:55-12:15 A role for host genetic-microbe interactions in canine inflammatory bowel disease, *Jeffrey Brockman*

12:15-13:45 **Lunch**

13:45-14:15 **Poster flashtalks,** Chair: *Noora Salokorpi*

A single nuclei characterization of dorsal root ganglia to study canine degenerative myelopathy, *Wes Warren*
The evolutionary genomics of wildcats in northwest China and their admixture with local domestic cats, *Shu-Jin Luo*
The GOLDogs project: genomics of longevity in dogs, *Thomas Derrien*
Characterization of canine oral melanoma and histiocytic sarcoma cell lines: Resources for rare human cancers, *Benoit Hedan*
Dipping a paw in the fishbowl: diving into the genetic risk factors of feline Diabetes, *Jessica Hayward*

14:15-16:00 **Poster session 3 & Coffee break**

16:00-16:45 **Keynote, Guillaume Bourque**, Genomics 2.0: why a pangenome graph is better for genetic and epigenetic analyses,
Chair: *Christophe Hitte*

19:00-24:00 **Gala Dinner**

Wednesday 8:30-13:00

8:30-8:45 Announcements

8:45-10:05 **Session: Cancer Genetics** Chairs: *Claire Wade and Bianca Haase*

- 8:45-9:05 Comparative analysis of non-coding constraint mutations in canine and human osteosarcoma, *Raphaela Pensch*
- 9:05-9:25 Canine diffuse large B-cell lymphoma: a comprehensive study of coding And non-coding regions using whole-genome sequencing, *Anna Darlene van der Heiden*
- 9:25-9:45 Bayesian analysis and selection scans for gastric cancer identify multiple risk loci, *Jacquelyn Evans*
- 9:45-10:05 Reference Genome and Annotation for Canine Transmissible Venereal Tumor, *Brian Davis*

10:05-10:45 **Session: Genetics of eye disorders** Chair: *Christophe Hitte*

- 10:05-10:25 An RCN1 frameshift mutation is associated with rapidly progressive, adult-onset cataracts in Miniature American Shepherds, *Shawna Cook*
- 10:25-10:45 A novel form of inherited retinal degeneration in Lagotto Romagnolo dogs, *Thomas Simon*

10:45-11:15 **Coffee break**

11:15-12:35 **Special session: new technologies and approaches**
Chair: *Greg Barsh*

11:15-11:35 Utilization of Pangenome Graphs for Identification of Novel Variation in Canidae, *Brian Davis*

11:35-11:55 Induced Pluripotent Stem Cells to Model Gene Function in Dogs, *Jeffrey Schoenebeck*

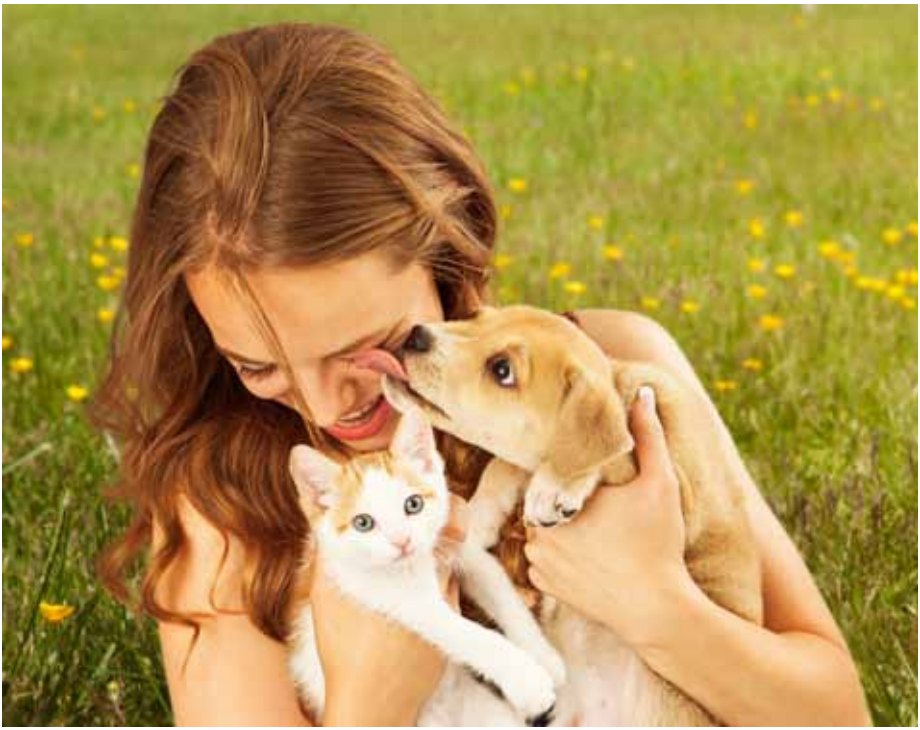
11:55-12:15 Leveraging community science for canine cancer: developing genetic screening and genomic selection tools in dogs, *France Chen*

12:15-12:35 Biological age clocks predict health trajectory and mortality risk in dogs, *Alix Zollinger*

12:35-12:50 Awards

12:50-13:00 Closing remarks

13:00-13:30 **Lunch**



Keynote speakers

Aarno Palotie

Professor Aarno Palotie, M.D., Ph.D. is the research director of the Human Genomics program at the Institute for Molecular Medicine Finland (FIMM), HiLife. He is also a faculty member at the Center for Human Genome Research at the Massachusetts General Hospital in Boston and associate member of the Broad Institute of MIT and Harvard. He has a long track record in human disease genetics. He has hold professorships and group leader positions at the University of Helsinki, UCLA and Wellcome Trust Sanger Institute. He has also been the director of the Finnish Genome Center and Laboratory of Molecular Genetics in the Helsinki University Hospital.

Aarno Palotie's research utilizes the unique Finnish population and health care to improve our understaning of the genetic component underlying common diseases. He has chaired several large international research consortia, like the Sequencing Initiative Suomi, SISu (www.sisuproject.fi) combining all Finnish sequences for a data resource and variant catalogue, the SUPER project (www.superfinland.fi) collecting and studying genetics in over 10 000 Finnish psychosis patients, the International Headache Genetics Consortium (IHGC, www.headachegenetics.org) and the Northern Finland Intellectual Disability (NFID) study. He is the Scientific Director of the large FinnGen project (www.finngen.fi) that combines the genome and national health record data from 500 000 Finnish participants. The project is partnered by Business Finland (The Finnish innovation fund), thirteen international pharma companies, Finnish Universities, University Hospitals, the Institute for Health and Welfare and the Blood Transfuson service. He has published over 700 articles and book chapters.

FINNGEN

Guillaume Bourque

Dr. Guillaume Bourque is a Professor in the Department of Human Genetics at McGill University, a Canada Research Chair in Computational Genomics and Medicine and the Director of Bioinformatics at the McGill Genome Center. He leads the Canadian Center for Computational Genomics and the Epigenomics Mapping Center at McGill. He is also a Principal Investigator at the Institute for the Advanced Study of Human Biology (ASHBi) of Kyoto University. Dr. Bourque is on the Scientific Steering Committee of the International Human Epigenome Consortium (IHEC) and on the Steering Committee of the Global Alliance for Genomics and Health (GA4GH). He leads the CFI-funded SecureData4Health computational platform and a new CIHR-funded project called the Pan-Canadian Genome Library, which will allow for easier analysis and sharing of genomic data across the country. His research interests are in comparative and functional genomics with a special emphasis on applications of next-generation sequencing technologies and transposable elements. His papers have been cited 39,911 times and his h-index is 71 (source Google scholar).

Bourque Lab

PRESENTATION ABSTRACTS

The genetic architecture of canine blood phenotypes

Adam Boyko[1], Jessica Hayward[1]
[1]Cornell University

Blood phenotypes gathered from blood chemistry and CBC panels are invaluable tools to aid clinical decision-making. They can also vary substantially due to genetic factors, leading to missed diagnoses or unnecessary treatments if these factors are not considered when interpreting lab values. In humans, half of all blood lab values have significant heritability ($h \geq 0.5$), mainly from rare loci with large effect sizes and common loci with small effect sizes.

Using dense genotyping and lab values from 3000 Golden Retrievers enrolled in the Golden Retriever Lifetime Study, we evaluated whether genetics influenced blood phenotypes in the breed. Two lab values—ALT and amylase—had previously been associated with large-effect QTLs in dogs but no previous studies have examined the genetic architecture of blood phenotypes in a large, single-breed cohort.

Surprisingly, half of the lab values had significant genetic associations ($p < 5 \times 10^{-8}$), usually from a single common (MAF > 20%), highly significant ($p < 1 \times 10^{-11}$), large-effect QTL. This was true not just for ALT and amylase but also for alkaline phosphatase, total bilirubin, total T4, mean corpuscular volume, mean corpuscular hemoglobin, creatine kinase, triglycerides, eosinophils and monocytes. We identify candidate genes for each association and show that reference ranges vary significantly for these values depending on genotype. We also discuss the opportunity for canine blood phenotype QTLs to power Mendelian randomization studies and whether any of these variants partially explain the increased risk of cancer in Golden Retrievers.

A feline model of human LDLR-dependent atherosclerosis

Marjo Hytönen[1,2,3], Veera Karkamo[4], Sruthi Hundi[1,2,3], Heidi Anderson[5], Maria Kaukonen[1,2,3], Niina Airas[1], Ilona Kareinen[1], Hannes Lohi[1,2,3]
[1]Department of Medical and Clinical Genetics, University of Helsinki, [2]Department of Veterinary Biosciences, University of Helsinki, [3]Folkhälsan Research Center, [4]Production and Companion Animal Pathology Section, Finnish Food Authority, [5]Wisdom Panel, Mars Petcare Science & Diagnostics

Atherosclerosis is a chronic inflammatory vascular disease initiated by the accumulation of LDL-derived cholesterol on the arterial inner surface. It is the leading cause of mortality in humans worldwide; however, the disease is almost non-existent in animals, including cats. We have recently discovered a spontaneous atherosclerosis in the Korat cat breed. The affected cats presented with severe hypercholesterolemia and clinical signs of congestive heart failure, finally leading to death. Severe atherosclerosis with primary and secondary histopathological lesions resembling those in human patients was observed at autopsy. As the affected cats were closely related, we hypothesized the condition to be genetic. We used whole genome sequencing to identify a loss-of-function variant in the low-density lipoprotein receptor (LDLR) gene. Pathogenic LDLR variants are the most common cause of severe familial hypercholesterolemia in humans. Genotyping the LDLR variant in an additional cohort of Korat cats confirmed its segregation and revealed new affected cats for clinical follow-ups. This is the first report of a spontaneous atherosclerosis animal model with an LDLR variant. Gene test will enable improved veterinary diagnostics and better breeding choices in the Korat breed in future. Meanwhile, the affected Korats might also provide a model for CRISPR-Cas9-mediated DNA base editing therapeutics, as our in silico analyses demonstrate that the feline LDLR variant is an ideal target for testing ABE-mediated base editing in vitro and in vivo.

Meta-analysis of canine obesity GWAS: identifies novel obesity genes in multiple dog breeds

Liang Ming[1], Natalie Wallis[1,2], Enoch Alex[1], David Sargan[3], Tanguy Mareau[1], Eleanor Raffan[1,2]
[1]University of Cambridge Department of Physiology Development and Neuroscience,
[2]Wellcome-MRC Institute of Metabolic Science,
[3]University of Cambridge Department of Veterinary Medicine

Obesity in dogs significantly impacts quality of life, with different breeds showing varying susceptibility. Previous research has identified certain genetic mutations as associated with obesity. However, the majority of the genetic landscape responsible for canine obesity remains to be characterized.

This study aims to explore the genetic factors contributing to canine obesity through conducting meta-analysis of GWAS for body condition scores performed in different dog breeds.

A total of 1685 dogs of four breeds (Labrador retrievers, golden retrievers from The Golden Retriever Lifetime Study, pugs, and French bulldogs) were included, selected for their varied susceptibility to obesity. GWAS for body condition scores were performed using GEMMA and GCTA, and summary statistics were meta-analysed using METAL. Systematic comparisons were performed to understand the genetic architecture of this complex trait. Candidate obesity genes and variants were explored.

Successful meta-analysis identified novel obesity-associated loci and candidate genes. As anticipated, some associations were private to one breed and others common to multiple breeds. The data illustrates that multibreed studies performed using relatively sparse genomic array data are likely to increase the power to identify true associations relevant to multiple breeds but will be unlikely to detect true positive associations that are related to variants private to only a subset of or one breed in a meta-analysis.

The data illustrates both the value and pitfalls of using meta-analysis in stratified populations and provides insight into the complex genetic architecture of obesity in future work.

GWAS in Labrador retrievers identifies novel obesity genes in dogs and humans

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Obesity is a common complex disease with far reaching effects on the health of humans and dogs. It is highly heritable, yet the understanding of obesity genetics is incomplete, and no existing genome-wide study has successfully investigated canine obesity. We undertook a genome wide association study for obesity in just 241 Labrador retrievers and identified multiple novel obesity genes. We identify DENND1B as a previously unrecognised obesity gene in dogs and humans and demonstrate how DENND1B regulates activity of MC4R, a key hypothalamic receptor involved in energy homeostasis. We show candidate canine obesity genes are associated with both common and rare forms of human obesity, identifying patients with undiagnosed monogenic obesity. A polygenic score for obesity predicted obesity and associated phenotypes in related but not unrelated dog breeds. We demonstrate polygenic background interacts with environmental exposure to diet and exercise to mediate disease outcome and that polygenic risk affects penetrance of a known obesity mutation. Thus, we have identified novel obesity-related genes in dogs and humans and have created the first ever PRS for canine obesity. This demonstrates the benefits of studying complex disease in non-traditional animal models such as the dog. Findings of this study inform both human and veterinary medicine, and improve the understanding of this complex, stigmatised disease.

GWAS and selection signatures indicate involvement of synaptic genes in Addison's disease

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Addison's disease, or primary hypoadrenocorticism, is an endocrine disorder caused by a failure of the adrenal cortex to produce essential hormones, primarily cortisol and aldosterone. In humans, Addison's disease is most often immune-mediated, marked by autoantibodies against 21-hydroxylase and strong associations with the major histocompatibility complex. In dogs, the etiology of the disease is unclear, but gonadectomy increases risk at least 3-fold. Dogs have a higher incidence of Addison's disease compared to humans, and the disease is overrepresented in certain breeds, indicating a genetic etiology. We generated high-coverage genomes from 39 Standard Poodles, including 26 with Addison's disease, and incorporated them into a multibreed reference panel. Imputation of low-coverage sequences resulted in over 1 million high quality single nucleotide variants used to perform a GWAS with 93 neutered Standard Poodles (56 cases, 37 controls). We identified a significant association with a locus harboring genes related to neuronal and synapse function. Using cross-population extended haplotype homozygosity (XP-EHH) testing to compare cases with controls, we detected a selection signature over this locus. Additional loci identified through XP-EHH and runs of homozygosity analyses were enriched for genes related to synapse organization and plasticity. Many of these genes are highly expressed in regions of the brain that influence neurons in the hypothalamic-pituitary-adrenal (HPA) axis. These results suggest a role for the neuroendocrine system in canine Addison's disease, which has not been previously reported.

A study of over 15,000 dogs identifies the major locus for canine non-generalized tonic-clonic seizures

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Dogs with idiopathic epilepsy (IE) have a lowered threshold for seizures, including generalized tonic-clonic (GTC) and focal seizures (FS). In some breeds, like Labrador Retrievers (LR), paroxysmal dyskinesia (PD) causes episodes which may resemble FS. Despite the genetic susceptibility of IE in many breeds, the contributing variants remain largely unknown. We aimed to identify the major loci and common variants associated with the risk of IE and PD in dogs by performing large-scale GWAS in two cohorts. The first cohort included 280 LR categorized based on their diagnoses (IE vs PD) and episode types (GTC vs non-GTC) and 460 controls. The second multi-breed cohort included ~5,000 dogs with reported seizures and 10,000 controls from > 100 breeds. Analyses in both cohorts revealed a 27.8 kb risk haplotype overlapping ADAM23 on CFA 37. The risk haplotype was associated with non-GTC seizures and PD in LR, but not with GTC seizures. WGS analyses revealed two non-synonymous exonic variants in ADAM23 within the same coding triplet in exon 12. Preliminary functional studies in cell cultures suggest an effect of these variants on ADAM23 interaction with LGI1, previously implicated in epilepsy. We also continue Bayesian analyses, which suggest additional associated loci and candidate genes. This is the largest GWAS of canine epilepsy, which will help us better understand the genetic background of the most common neurological disease in dogs.

Idiopathic epilepsy in the Border Collie: identifying common and rare genetic risk factors

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The Border Collie (BC) is one of the breeds most commonly and severely affected by idiopathic epilepsy (IE), though little is known regarding the genetic factors that may increase this breed's susceptibility.

We conducted a genome-wide association study (GWAS) meta-analysis including up to 123 cases and 187 controls utilising three array-genotyped study sets and used genotype imputation to increase the resolution to whole genome level. Cases were BC diagnosed with IE with at least a tier I level of confidence; controls were BC over the age of 8 years reported by owners to have never had a seizure. We tested 28 SNPs in an independent BC replication set (up to 288 cases and 372 controls), identifying three SNPs (two on chromosome 11, one on chromosome 16) showing evidence of a reproducible association with IE. Whole genome sequence (WGS) analysis of 12 cases and five controls, and follow-up genotyping in the replication set, enabled fine-mapping of the three IE-associated regions.

Separately, we searched for rare, common, and fixed risk variants directly through WGS analysis of 12 cases compared against 59 dogs of 35 different breeds not known to have a high prevalence of epilepsy. Following filtering for candidacy and subsequent follow-up in our extended case-control set, we identified common variants, and rare case-specific variants.

These findings provide evidence that IE in the BC is a heterogeneous disease with higher and low impact DNA variants contributing to risk and will help improve our understanding of the aetiology of IE.

Complicated structural variant causes familial adult-onset ataxia in Toy Poodles

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It is important to identify causative genes and variants of canine genetic diseases not only for diagnosis and prevention through genetic testing but also to gain insight into pathogenesis and treatment as a spontaneous model of homologous human diseases. In this study, we found that Toy Poodles showed progressive neurological signs, including adult-onset ataxia, and identified variants causing the disease. Pedigree analysis of affected Toy Poodles revealed familial aggregation, suggesting the existence of a genetic factor in the disease. A genome-wide search for relevant regions identified a region likely to contain the causative gene. Sequencing analysis of the affected dog revealed the presence of a complex structural variant in the area consisting of two large deletions (49k-bp and 1.7k-bp), one duplication (971-bp), one insertion (69-bp), and five short indels (<10-bp), which contained the entire length of a protein-coding gene. Gene expression analysis in the cerebrum and cerebellum confirmed the complete gene expression loss in the affected dogs. Complete loss of the gene homologous in humans is known to cause an extremely rare inherited neurodegenerative disease. Since the only existing animal model of the disease is the mouse model, the dog identified in this study is the first large animal model. In addition, identifying the causative variant will facilitate the diagnosis of the disease in Toy Poodles, and genetic testing of breeding dogs will avoid the birth of dogs that develop the disease.

Increasing the dimensionalities of canine compulsive disorder with factor and genetic analyses

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Canine compulsive disorder (CCD) is a proxy for human obsessive-compulsive disorder (OCD), sharing similar symptoms including repetitive behaviours. OCD is both phenotypically and genetically heterogeneous, and while genome-wide association studies (GWAS) estimate the heritability of 23%, sample sizes of >5,700 human patients remain significantly underpowered. CCD genetic studies have offered insight for OCD, but these relied on small numbers of purebred dogs, phenotyped for single repetitive behaviours. There is a clear need to increase sample size and phenotype characterization.

We explore CCD using samples from the Darwin's Ark dataset (N~25,000 dogs), now with expanded behavioural question sets. Exploratory factor analysis of 14 behavioural questions resulted in an optimal 3-factor solution. The factor scores were then extracted for the subset of Gencove low-pass sequenced (N=3,044) and Axiom Array genotyped (N=411) samples. All data were remapped to the UU_Cfam_GSD_1.0/ROS_Cfam_1.0_chrY_contigs reference genome and imputed using the Dog10K reference panel. The resulting dataset includes 3,455 samples and ~9.9 million SNVs (MAF ≥1%).

Focusing on Factor 1 of 3 - Repetition Severity (4 questions; N=2,507), we explain 27% of genetic heritability (SE 0.07, $p<1x10-8$), with a significant GWAS peak ($p<5x10-8$) overlapping multiple regulatory signals (high Zoonomia phyloP), including Epic Dog brain-specific enhancer elements. Together, this implicates the regulation of higher-order cognitive control (cerebellum) and decision-making processes (cerebrum) in canine repetitive behaviours. Ongoing efforts aim to refine this peak, and others, using the single nuclei Canine Brain Atlas and targeted conformation experiments to link putative enhancers to their gene targets.

Exploring the genetics of longevity with the Dog Aging Project

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Pet dogs are a natural model for aging, but investigating the complex interaction between inherited genetics and lifestyle and environmental factors requires very large sample sizes. The Dog Aging Project is a U.S. based study of aging that has collected dense genotyping data (from low-pass sequencing and imputation) and longitudinal environmental data for 7,628 dogs. We have tested ~11 million common dog variants (frequency > 1%) for association with hundreds of phenotypes. About 25% of traits have heritabilities exceeding 0.2. The five most heritable traits are all related to weight and weight gain. With this scale of data, even modestly heritable traits yield significant associations. We find significant associations for "Dog eats anything" (N=4437, heritability of 0.22) in three genes connected to appendicular lean mass, body mass index, and triglyceride levels in humans: WSCD2 (p=3.5e-9), MTAG4C (p=5.6e-9) and NAALADL2 (p=3.8e-8). In the subset of dogs assayed for mobility (N=2321), which is one of the best predictors of longevity in humans, we find suggestive associations (p<1e-6) to cellular processes implicated in human aging, including GBE1 (involved in glycogen accumulation) and the mTOR pathway regulator SH3BP4. These first genomewide association results from the Dog Aging Project demonstrate the power of dogs for investigating the genetics of aging. To share these results and maximize their impact, we are developing an interactive website based on the human PheWeb interface for exploring the Dog Aging Project results (broad.io/dogPheWeb).

Within clade genome sequence analysis from 389 breeds identifies new genes controlling morphologic variation

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Diverse genetic backgrounds and confounding population structure can disguise functional alleles and inflate the effect of associated alleles in analyses of complex traits. By examining traits within single clades, rather than across all breeds, the effect of genetic background is reduced, and new loci accounting for missing heritability can be identified. Phylogenetic analysis in a dataset of 2751 dogs from 389 breeds and varieties reveals that doubling the number of breeds does not double the number of clades, rather, it expands existing clades. Each large clade is made up of breeds that originate from a common ancestor and share multiple and, in many cases, distinct traits. Thus, within each clade a range of variation for many types of single traits is represented. Body size provides an excellent example. Of the six largest clades, five display a nearly 10-fold range in breed-standard body weight and up to a 5-fold range in breed height, encompassing nearly the full range of sizes found across all breeds. Each GWAS for body size within a clade produces unique patterns of association, identifying both known variants and new size loci. For instance, within the Mastiff clade, standard breed weights range from 10kg-90kg. Clade GWAS identifies the strongest association in a locus on chr32 near a gene involved in human dwarfism. Association with this gene and locus have not been previously identified for canine body size. We propose this approach as a method for identifying missing heritability associate with multiple types of morphological traits across breeds.

A genotype first approach for discovery of trait associated variants in dogs

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Genetic association analyses typically follow a phenotype first approach, where individuals are grouped according to phenotypic variation to test for genotype associations. In a genotype first approach, individuals are instead grouped according to a specific genotype to test for associated phenotypes. Successful implementation of this approach requires identification of variants with a phenotypic impact and genotyped cohorts where additional phenotyping can be performed. Here, we apply the genotype first approach to a combined cohort of over 2,000 dogs representing approximately 200 phylogenetically distinct breeds to identify potential new genotype-phenotype relationships. Dog breeds are an apt system to test this approach as breed membership can indicate an individual's morphological characteristics and risk for certain diseases. To prioritize variants with potential phenotypic impacts, we measured variant impact on gene function and the functional importance of affected genes, where functional importance was calculated according to human gene constraint of dog-human orthologs. We also considered breed frequency and specificity of genetic variants to focus on breed related phenotypes. Amongst a set of 3,000 high priority genes, we identified 20 candidate variants in 18 different breeds. Depending on breed characteristics and gene roles of where candidate variants were found, we proposed candidate traits for potential genotype-phenotype relationships. Next, we recruited mixed breed dogs that shared candidate traits with selected breeds for whole genome sequencing to further investigate potential genotype-phenotype relationships. Our work shows how analysis of genotype data within a large cohort of diverse breeds can drive investigation of previously overlooked phenotypes.

Lessons from genome-wide association studies using data from electronic medical records

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Understanding the genetic risk factors behind complex canine disorders in particular is likely to require large across-breed datasets with thousands to tens of thousands of cases. The integration of panel genetic testing using high density genotyping platforms into veterinary practice presents an unparalleled opportunity to perform genetic investigations into a wide range of conditions by linking clinical and genetic data.

The Wisdom Panel genetic panel test, run on a custom-designed Illumina Infinium 100K SNP microarray, was introduced into the routine screening protocol at Banfield Pet Hospital clinics across the United States in 2018. We have leveraged this prospective cohort of more than 1 million dogs with both genotype and electronic medical record (EMR) data available as an opportunity to evaluate the association of genetic variants and veterinarian-diagnosed medical disorders using genome-wide association studies (GWAS).

We show that the often more loosely defined phenotypes found in EMRs can yield relevant insights, but sample size is critical for success. We further find that many common disorders in dogs may be partially driven by the same variants underlying certain physical traits, suggesting pleiotropic effects. Finally, we illustrate the value of GWAS in mixed breed populations, or how breed structure can occasionally be a hindrance to risk locus identification if disorder or trait loci are fixed within breeds.

We conclude that EMR-based GWAS hold great promise for understanding the genetic etiology of canine disease, when appropriate learnings are considered.

Short-spine dogs: a modern and historical phenotype definitively characterized

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The canine condition collectively referred to as "short-spine syndrome" has been recognized since at least the 17th century, when it was called a "monster of fox and dog." This phenotype occurs spontaneously and sporadically, with global incidences. We identified eleven modern-day short-spine dogs, which each have severe and rare axial skeletal malformations. The bony features of canine "short spine syndrome" remain undescribed and the genetic underpinnings have never been investigated. Careful phenotyping including gross examination together with radiographic interpretation by a board-certified veterinary radiologist demonstrated that the "short spine" phenotype is not cohesive, but rather represents a spectrum of vertebral dysplasias, variably including kyphoscoliosis, decreased vertebral number, vertebral fusion, and segmentation defects. Eight of the 11 dogs were subjected to high coverage whole-genome sequencing, with the genes driving this phenotype successfully identified in six cases. Deleterious canine variants are in genes associated with human skeletal dysplasias, including spondylocostal dysostosis (LFNG, DLL3, and MESP2), brachyolmia (PAPSS2), and a murine rib-vertebrae phenotype (DLL1). Fascinatingly, two unrelated dogs with very disparate breed backgrounds (hound mix and a German Shepherd Dog) had the exact same 48bp deletion variant, suggesting either that this mutation has occurred independently multiple times or that it is very rare and ancient. These special dogs represent spontaneous models to better inform our understanding of vertebral segregation and development across mammalian species.

Determination of the genetic etiology of bilateral anterior hemimelia in the Chihuahua

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Bilateral anterior hemimelia is the congenital absence of the majority of the bones of the thoracic limbs and has been reported in the Chihuahua as an autosomal recessive disorder. Affected dogs can have variable expressivity; however, cases collected for this study all had shortened humeri and an absence of the bones and limb distal to the humerus. The pelvic limb distal phalanges were variably affected, but the pelvic limbs were otherwise spared. Intrigued by an inherited variant that only affected thoracic limb development, we identified 13 cases from shelters and rescue organizations and utilized GWAS and WGS to investigate the cause. A significant association was identified on chromosome 13, and a 2.1 Mb homozygous region was identified in 12 cases that included the RSPO2 gene. Limb deformities affecting all four limbs in humans and Holstein cattle are caused by loss of function mutations of RSPO2, leading us to predict that the Chihuahua variant is likely regulatory. Six affected chihuahuas were whole genome sequenced (WGS), and no protein-coding variants were identified in RSPO2 or within the homozygous interval. The WGS alignments are being analyzed for structural variants. SNVs and small indels that fit a recessive model are being genotyped in silico in publicly available datasets. Candidate variants will be genotyped in 7 additional cases and 50 control Chihuahuas with normal thoracic limbs. The identification of the variant responsible will enhance our understanding of RSPO2 gene regulation and the determination of the developmental difference between thoracic and pelvic limbs.

Functional investigation of felid color pattern mechanisms in transgenic mice

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Variation in periodic color pattern is a distinctive and charismatic feature of domestic cats whose underlying basis is not well understood. We identified two genes, Taqpep and Dkk4, that alter pattern element shape, size, and spacing in domestic cats and wild felids. Taqpep encodes a transmembrane aminopeptidase whose loss-of-function causes dark tabby markings to expand; Dkk4 encodes a long-range inhibitor of Wnt signaling whose loss of function causes dark tabby markings to become smaller. Our previous work with fetal cat skin collected from feral cat spay-neuter clinics showed that both genes act early in embryogenesis before hair follicle development. To better understand the underlying mechanisms, we generated an allelic series of Taqpep mutant mice using CRISPR-Cas9 genetic engineering and compared cutaneous pattern formation (color pattern in cats, hair follicle pattern in mice) in wild-type and Taqpep-mutant embryos. We find that (1) cutaneous pattern initiation is non-random and occurs at similar anatomic sites in both species, (2) pattern expansion is analogous in the two species, and (3) the role of Taqpep in pattern establishment is similar in mice and cats. Thus, aspects of cutaneous pattern formation in the two species are convergent, and additional studies in mice may yield insight into the molecular pathways that control pattern variation in felids.

Canine brain atlas: epigenetic and single nuclei transcriptome profiling across eleven dog brain regions

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The brain is the most complex mammalian organ and its function underlies many species-specific traits. Understanding the molecular organisation and complexity of the dog brain at regional, cellular and subcellular levels allows insight into the mechanisms underpinning homeostasis, behaviour, disease and the effects of domestication. We introduce the Canine Brain Atlas to aid researchers in addressing these questions, surveying brain tissues from four beagles across the cerebrum (seven regional tissues), brain stem (two regional tissues), hypothalamus, and cerebellum (one tissue each).

Using bulk brain tissues we performed ATAC-seq, CUT&RUN and Hi-C to assay open chromatin, histone marks, and chromatin conformation respectively. We identified candidate cis-regulatory elements (cCREs) and used comparisons with non-brain tissues in the Epic Dog and BarkBase projects to identify likely brain-specific cCREs. Transcriptomic profiling of the same tissues allowed us to identify regional isoform use and associate tissue-specific expression with the epigenetic profiles.

We systematically surveyed cells across the dog brain tissues using single-nucleus RNA sequencing, sampling ~750,000 individual nuclei. Our analysis identified 26 gene expression superclusters that reflect cell type, brain region heterogeneity, and follow cell lineage commitment. Recent advances in the generation of brain atlases for multiple species (e.g., human, mouse, pig) allow us to highlight similarities in brain expression patterns among species. Unique patterns identified in our data may reflect distinctive features of the dog brain, providing a more complete understanding of the specifics of its biology.

Gene Expression Patterns in Dog and Wolf Brain Regions

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This study aimed to uncover the gene expression patterns within the dog and wolf brains to improve our understanding of gene dynamics and differences within brain regions between dogs and wolves. We leveraged an extensive STRT2-based dataset from the Dog Genome Annotation (DoGA) project, comprising 383 dog samples and 259 wolf samples across 22 brain regions. The analysis revealed approximately 26,000 expressed genes, with the highest expression levels observed in the telencephalon, neurohypophysis, and prefrontal cortex, while the lowest expression levels were noted in the temporal and parietal lobes. Approximately 16% of genes exhibited high expression across all brain regions. Unsupervised principal component analysis demonstrated that samples were grouped according to their distinct brain regions, indicating clear patterns of gene expression variability across different anatomical areas. Differential expression analysis found that approximately 5% of genes were specific to different brain regions and ~3000 genes (11%) are differentially expressed between dogs and wolves. We will present and discuss the observed differences between dog and wolf brains and their possible links to behavioral traits as a foundation for further research in dog domestication and behavioral research.

Enhancer mediated gene regulation in the dog genome

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Dogs are an interesting model organism for a variety of human diseases, due to their high cognitive abilities, shared living environment and a large variety of phenotypes in highly inbred individuals. Even two decades after the establishment of the reference genome for dogs, regulatory regions have only been described in a small amount of tissues. The DoGA consortium applied CAGE-seq on 37 tissues collected from 10 different dogs, resulting in 116 samples to study their transcriptome and regulatory regions. We identified and characterised promoter expression resulting in ~55,000 promoters, with ~24,000 hitherto unannotated regions. Furthermore, we catalgoue ~21,000 active enhancer regions. When comparing the expression in different tissues, ~9,000 promoter and ~12,000 enhancer regions are enriched in a specific tissue. Using the distance and co-expression of promoter and enhancer candidates, we find that 44% of our enhancers are linked to at least one promoter region. We compared the sequence of our dog enhancers with human enhancers identified in FANTOM5 and found 435 conserved enhancers. Finally, 66 of the conserved enhancers were also linked to the same orthologous, indicating that the regulatory structure is conserved as well.

The canine eQTL project: the role of gene expression in shaping canine body size

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Most genetic variation that shapes morphological diversity in dogs is non-coding and therefore difficult to assess. To overcome this, we initiated the canine eQTL project. Bulk RNA-seq and low-pass WGS data was collected and analyzed for 143 canine testes samples. To control for cell-type heterogeneity in bulk RNA-seq data, we performed cell-type deconvolution with human single cell testes expression profiles to estimate cell-type composition of dog samples. Inclusion of cell-type covariates to our analysis led to the identification of an additional 1,138 eGenes. To identify genes potentially regulating morphological traits, we performed colocalization analysis for 28 breed height and weight loci. Loci on CFA7 and CFA34 were supportive of eQTL colocalization. The CFA7 locus was associated with SMAD2 expression and the CFA34 locus was associated with IGF2BP2 expression. Increased expression of each gene was associated with increased canine body size. Finally, we investigated eQTL activity within a 1 Mb CFAX locus that is associated with proportionately large breed size. Previously associated genes, IRS4 and ACSL4, showed no significant expression change in the presence of the large breed size allele. Instead, the large breed size allele was associated with decreased expression of AMMECR1 and CHRDL1, novel candidates for regulating canine body size. The canine eQTL project has identified a total of 1,838 eGenes and has helped identify novel gene candidates for canine traits. As this resource grows, it will continue to facilitate identification of target genes from GWAS and provide a framework for comparing genetic architecture across species.

Transcriptomic and Intervention Evidence Reveals Domestic Dogs as a Promising Model for Anti-inflammatory Investigation

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Domestic dogs have great potential to expand our understanding of the determinants of aging. To understand the aging pattern of domestic dogs and evaluate whether they can be used as an aging model, we performed RNA sequencing on white blood cells from domestic dogs aged 1 to 9 years and treated aged dogs with classical anti-aging approaches. We obtained 30 RNA sequencing libraries and identified 61 age-associated genes with dynamic changes, the majority of which were related to metabolism and immune function, which may be predominant biomarkers for aging in dogs. We next treated aged dogs with canine mesenchymal stem cells , nicotinamide mononucleotide, and rapamycin to determine whether and how they responded to the anti-aging interventions. The results showed that these treatments can significantly reduce the level of inflammatory factors (IL-6 and TNF-α). MSCs effectively improved the heart functions of aged dogs. Three key potential age-related genes (PYCR1, CCRL2 and TOX) were reversed by MSC treatment, two of which (CCRL2 and TOX) are implicated in immunity. Overall, we profiled the transcriptomic pattern of domestic dogs and revealed that they may be a good model of aging, especially in anti-inflammatory investigations.

Genetic analysis of 60,000 domestic cats reveals fine-scale population structure and its geographic origins

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BACKGROUND: Domestic cats reproducing without intentional human guidance constitute the vast majority of cat populations worldwide. However, little is known about their population genetics. We present a study of cats from Wisdom Panel, the largest companion animal genomics platform to date.

RESULTS: Surprisingly, we identify fine-scale structure throughout regional and global populations, with Wisdom's extensive coverage of the United Kingdom and North America. Domestic cats were first introduced to North America more than 400 years ago, and regional populations therein reflect founding admixtures of Old World populations, revealing a rich tapestry of their origins.

Individual alleles with evidence of geographic differentiation include blood type, genetic diseases and traits. Genetic differentiation is sufficient to allow geolocation of individual cats, revealing the geographic origins of several pedigreed breeds. Clear examples are evident where alleles carried through from a broader geographic population to the founding of a pedigreed breed, thus explaining some diseases and traits characteristic of certain breeds.

By investigating the possibility of local adaptation, we identify factors associated with candidate genes for further investigation of selection. Additionally, we use genetics to reveal multiple scales of migration: from individuals to populations, along with factors that may influence migration dynamics.

CONCLUSIONS: An understanding of fine-scale population structure informs the origins and dynamics of the genetic landscape of domestic cats with implications for veterinary medicine. Additional population studies will increase understanding of cats worldwide and complement studies across dogs and humans by providing a distinct facet through which to understand recent history and evolution.

A 3,500-year Human-Leopard Cat Commensalism Preceded the Arrival of Domestic Cats in China

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We investigated the paleogenomic and archeological dynamics of small felids in anthropogenic landscapes of China and illuminated an approximately 3,500-year remarkable commensal relationship between leopard cats (Prionailurus bengalensis) and ancient human settlements. This symbiosis persisted as early as 5,500 BP and appeared to have attenuated around 1,800 BP, concurrent with the breakdown of the Han Dynasty (2,156 -1,730 BP) and agricultural dwindling. Subsequent to the waning presence of human-associated leopard cats, the first occurrence of domestic cats (Felis catus) in China likely transpired between the 7th to 8th centuries during the Tang Dynasty (1,332-1,043 BP), introduced primarily from the eastern Mediterranean coast via the ancient Silk Road and ascended to prominence with expansive geographical distribution and long-term genetic stability. The most ancient domestic cat of China thus far was excavated from Shaanxi around 1,220 BP with a reconstructed morphology including short hair and white spotting based on 16× whole genome sequencing. These ancient genomic revelations spanning 5,500 years of China's history demonstrate a momentous turnover of commensal species involving cats from two different genera and provide an enriched understanding of the human-felid interactions across the world.

Comparative functional analysis of SINEs in canines and felines

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Mobile elements contribute to mammalian genetic diversity through their ability to insert into new genomic locations via retrotransposition. Short INterspersed Elements (SINEs) require proteins encoded by Long INterspersed Elements (LINEs) for retrotransposition. For example, evidence suggests that human Alu RNA structure is important for ribosomal localization, allowing Alu RNA to hijack the nascently translated LINE-encoded reverse transcriptase protein to promote its genomic integration. Whereas primate specific Alu elements are derived from the 7SL RNA gene, the majority of mammalian SINEs are derived from tRNA genes. tRNA secondary structures are well established; however, the structure and functionally important domains of tRNA-derived SINEs require elucidation. The ancestral Carnivore-specific SINE (i.e., SINEC), present in Canidae and Felidae, is derived from a lysine tRNA. Genome comparisons have identified tens of thousands of dimorphic canine-specific SINEs (SINEC_Cf) sequences. Analysis of the feline genome (felCat9) also revealed high frequency of dimorphic feline-specific tRNA derived SINEs (SINEC_Fc), suggestive of recent activity. Here, we demonstrate that engineered SINEC_Cf and SINEC_Fc elements are active in a cell culture-based retrotransposition assay. To investigate the relationship between tRNA-derived SINE structure and function, we determined the secondary structure of SINEC_Cf RNA using a chemical probing technique (SHAPE-MaP), which revealed SINEC_Cf RNA structure differs from the canonical tRNA cloverleaf structure. Mutations that alter the SINEC_Cf RNA secondary structure, as well as compensatory changes, identified features important for SINEC_Cf retrotransposition. Additional structural analysis of SINEC_Cf and SINEC_Fc RNAs will determine whether Carnivore-specific SINEs have retained similar secondary structures to facilitate their retrotransposition.

Remapping to a Greenland Wolf assembly normalizes canine divergence

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For over 15 years, canine genetics research relied on a reference assembly from a Boxer breed dog named Tasha (i.e, canFam3.1). Recent advances in long-read sequencing and genome assembly have led to the development of numerous new, high-quality assemblies from diverse canines. These assemblies represent notable improvements in completeness, continuity, and the representation of gene promoters and gene models. Although genome graph and pan-genome approaches have promise, most genetic analyses in canines rely upon the mapping of Illumina sequencing reads to a single reference. The Dog10K consortium, and others, have generated deep catalogs of genetic variation through an alignment of Illumina sequencing reads to a reference genome obtained from a German Shepherd Dog named Mischka (i.e, canFam4, UU_Cfam_GSD_1.0). However, alignment to a breed-derived genome introduces bias in genotype calling across samples. We and others have identified a potential reference bias in some ancient DNA datasets, and similar concerns have been raised for other types of analyses. Examination of the Dog10K SNP call set shows that samples have a wide range of SNP differences relative to the German Shepherd reference. To explore this, we have reprocessed the Dog10K dataset of 2,000 samples using the assembly of a Greenland wolf (mCanLor1.2). We efficiently performed remapping and variant calling using a GPU-implementation of the bwa and GATK tool set. The resulting call set removes the variability in genetic differences across samples. We further describe structural differences between the Greenland wolf and Mischka assemblies. The variant datasets will be made publicly available.

Ancient genomes reveal the evolutionary history of Australian dingoes

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In Australia, self-sustaining populations of indigenous dogs (dingoes) evolved in isolation for millennia, until the arrival of European dogs onboard the First Fleet. After 1788, the presence of foreign dogs within Aboriginal Encampments, and colonial persecution of indigenous cultural practices, led to a shift in the utilisation of dingoes by First Nations Australians. In contrast, early European farmers reportedly cross-bred dingoes to working breeds to improve their durability and performance in the harsh Australian climate. To quantify the extent and impact of colonial persecution and admixture in the recent history of dingoes and Australian dog breeds, we generated low-coverage (1- to 2-fold) genomes from 13 pre- and 6 post-European contact dingoes from the Nullarbor Plain, and an extinct 19th century Australian Greyhound, as well as 35 high-coverage (over 10-fold) genomes from contemporary populations across Australia. Wild dingoes can be broadly separated into western and south-eastern populations, with finer-scale geographic structuring persisting over the last 2,500 years. Significant shifts in the diet and genomic diversity of dingoes, however, immediately followed the arrival of the First Fleet, highlighting the rapid and widespread impacts of European colonisation. Although most post-contact dingoes possess some degree of non-indigenous (i.e. European) ancestry, this largely reflects admixture events at-least 20 generations in the past. Furthermore, some Australian breeds have detectable levels of dingo ancestry, which validates historical claims.

The genomic history of Arctic sled dogs from past to present

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Genomic and paleontological evidence support continuity in the Arctic ancestral lineage of dogs for at least 9,500 years. Here, we use the Siberian Husky as a model system to investigate the genomic legacy of the Eurasian Arctic lineage and model the deep population history using genome-wide SNPs. Our dataset (n=355) compared Arctic breeds including Siberian Husky, Alaskan Malamute, Alaskan Sled Dog, Chukotka Sled Dog, and Greenland Sled Dog with West Eurasian breeds. We found significant population structure in the Siberian Husky related to their usage as pet, show, or sled dog, and pervasive European breed introgression mainly in dogs that participate in sled races. In contrast, we found no evidence for significant European admixture in show dogs, but lower effective population size and higher levels of inbreeding. Additionally, we found fewer potentially harmful variants in Siberian Husky show and sled dogs compared to the pet population. Finally, using fossil calibrations, we estimated genome-based divergence times and suggest the existence of at least two distinct lineages of Arctic dogs in ancient Eurasia 11,800 years ago. Since we found significant ancient wolf admixture in the Zhokhov/Greenland Sled Dog lineage, but not in modern Siberian dog lineages, we suggest gene flow from wolves may have been used to increase size, freighting, and hunting ability of some dogs while also maintaining smaller, efficient sledding dogs during the climate chaos and megafaunal extinctions at the end of the Pleistocene. Understanding the genomic evolution of Arctic dogs will help to preserve these evolutionarily unique lineages.

Ancient mitochondrial genomes reveals northwest China as crossroad in Eurasia of dog dispersal

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The dog is the earliest animal domesticated by humans, and the migration history of dogs can provide us with important clues about human activities. Dogs may be domesticated in southern East Asia and migrating around the world with humans. With the development of new technologies, the use of ancient DNA to study the spatiotemporal dynamic changes of ancient dog populations has become an important research direction. East Asia is an important domestication center, but the lack of ancient dog DNA research and data here, which restricts the study of the global migration history of dogs. We collected ancient dog remains from nine Neolithic to Iron Age sites in northwestern China, and through ancient DNA technology, we successfully extracted and sequenced 15 samples, and finally obtained 15 high-quality dog mitochondrial sequences. The ages of these samples range from 1800 to 5000 years ago, which can well represent the ancient dog population in northwestern China. Our mitochondrial analysis results show that ancient dogs in northwestern China have a rich maternal genetic background, with three unique haplotypes from ancient Europe, ancient East Siberia, and ancient southern China, suggesting that this region may have been an important dog mixing center in ancient. Our results illustrate the importance of ancient DNA technology in the study of dog history and the necessity of ancient DNA research in East Asia.

A phylogenetic estimate of the rate of retrotransposition in canines

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Long INterspersed Element-1 (LINE-1) retrotransposons use a "copy and paste" mechanism, termed retrotransposition, to mobilize throughout the genome. During retrotransposition, the LINE-1 encoded proteins (ORF1p and/or ORF2p) preferentially bind their encoding mRNA (termed cis preference), but can also bind Short INterspersed Elements (SINE) RNAs and mRNAs in trans. Components of the resultant ribonucleoproteins (RNPs) gain access to the nucleus, where the ORF2p endonuclease and reverse transcriptase activities mediate LINE-1 integration by target-site primed reverse transcription. LINE-1 mediated insertions have diagnostic hallmarks including: 3' poly(A) tails, short (~7-20 bp) flanking target site duplications (TSDs), and integration into a LINE-1 endonuclease cleavage sequence. Although numerous polymorphic LINE-1-mediated insertions have been identified in canines, the rate of LINE-1-mediated retrotransposition requires elucidation. Here, we identified polymorphic LINE-1, SINE, and retrocopy insertions in genome assemblies from five breed dogs, a dingo, and a Greenland wolf (mCanlor1.2). The average dog differs from the Greenland wolf at 5,170 LINE-1, 26,523 SINE, and 694 retrocopy loci, and most loci possess a TSD and/or Poly(A) tail. By combining pairwise comparisons of LINE-1-mediated insertions with an estimate of the number of generations since the divergence of each dog and the Greenland Wolf, we estimate the rate of LINE-1, SINE, and retrocopy formation as 1/100, 1/20, and 1/693 births, respectively. Retrocopy formation rates in canines far exceed those in humans, while LINE-1 retrotransposition rates remain similar. Thus, we propose canine LINE-1s may possibly exhibit reduced cis-preference relative to human LINE-1s, resulting in an increased rate of canine retrocopy formation.

A role for host genetic-microbe interactions in canine inflammatory bowel disease.

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Estimates suggest that a substantial fraction of the gut microbiome is heritable, indicating that host-microbe interactions could be important in microbiome-associated diseases like inflammatory bowel disease (IBD). IBD is a common gastrointestinal condition in dogs causing recurrent episodes of diarrhea and/or vomiting. While pathogenic microbes can cause acute cases, chronic cases of IBD may involve disruption of the normal commensal microbiota, leading to gut microbiome dysbiosis and subsequent inflammation. Commensal microbiota in the gut are a collection of microbes that have evolved to function synergistically with one another and the host to perform a multitude of functions including maintaining the integrity of the gut mucosa and immunomodulation. Metagenomic analysis of a cohort of 922 dogs representing over 100 breeds and collected from multiple geographic locations, indicates that the bacterium, Collinsella intestinalis, is one of the commensal bacteria in dogs. The level of C. intestinalis is over five fold lower in dogs clinically diagnosed with chronic IBD compared to breed, age and sex matched healthy controls. A genome wide association study has identified a locus on chromosome 19 associated with C. intestinalis levels across the 922 dog cohort. A candidate gene in the locus, HS6ST1, plays a role in the biosynthesis of heparan sulfate, a glycosaminoglycan (GAG), which is an important carbohydrate source for a number of bacteria. HS6ST1 is also associated with variance in the gut microbiome composition of humans. Variants of his gene may play a role in the development of IBD in dogs.

Comparative analysis of non-coding constraint mutations in canine and human osteosarcoma

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Osteosarcoma (OSA) is a common bone cancer in dogs and serves as a valuable model for the corresponding human cancer, which is rare and hence harder to study. Protein-coding mutations have been extensively analyzed in cancer. Non-coding mutations have also been recognized as cancer drivers, however, their involvement in canine OSA and their translational relevance remain unexplored. In this study, we applied an evolutionary constraint approach combining tumor/normal whole-genome sequencing of 116 canine patients with constraint scores derived from the 240 mammals in the Zoonomia project to predict the functional impact of non-coding mutations in OSA. Furthermore, our findings in the canine cohort were compared to somatic variants from 38 human patients from the International Cancer Genome Consortium. We identified non-coding constraint mutations (NCCMs) in evolutionarily conserved positions and extracted genes with an enrichment of NCCMs in their regulatory regions. Our candidate gene set included multiple cancer-related genes and exhibited a significant overrepresentation of genes transcriptionally regulated by RUNX2, a protein critical for skeletal development and osteoblast differentiation. Several genes including the oncogene SOX2 showed a strong NCCM enrichment in both the human and canine dataset and their NCCMs emerged as potential novel non-coding drivers in OSA. Our findings highlight the power of evolutionary constraint in identifying novel candidate drivers that might be used to develop better diagnostic, prognostic and treatment strategies in the future. Moreover, our study emphasizes the significance of canine OSA as a reliable model for studying the human disease.

Canine diffuse large B-cell lymphoma: comprehensive study of coding and non-coding regions using whole-genome sequencing

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Diffuse large B-cell lymphoma (DLBCL) is a highly common and aggressive lymphoid malignancy in dogs and humans. Although prior research on canine DLBCL (cDLBCL) has contributed greatly to veterinary oncology and demonstrated the dog's value as a comparative animal model, most studies have been conducted using whole-exome sequencing, limiting the focus to the regions targeted by exome capture. This project aims to expand our knowledge of cDLBCL and identify novel driver genes, biomarkers, and therapy targets by performing a comprehensive analysis of coding and non-coding regions, leveraging whole-genome sequencing data from 70 canine tumour/normal samples. Our coding mutation analysis revealed 23 recurrently mutated genes, of which 10 are involved in histone modifications. Notably, H3C8 harboured a H3K27M mutation hotspot predicted to dysregulate gene expression, which correlated significantly with reduced progression-free survival. Non-coding mutation analysis utilised evolutionary constraint scores from the Zoonomia project to pinpoint highly conserved regions of likely regulatory importance. We identified 96 candidate genes enriched with non-coding constraint mutations (NCCMs) and performed a similar analysis on 41 human DLBCL (hDLBCL) samples, cross-referencing the results. Ten NCCM-enriched genes were shared between dogs and humans, including BCL6, BCL7A, and BACH2, which are known to be of importance in hDLBCL but whose role in cDLBCL is unclear. Our findings highlight the prevalence of coding mutations in epigenetic genes, designate H3C8 as a potential prognostic marker, and further assert the dog's utility as a comparative animal model for human cancer. Functional studies to determine how NCCMs may influence tumorigenesis are currently ongoing.

Bayesian analysis and selection scans for gastric cancer identify multiple risk loci

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Gastric adenocarcinoma ranks among the top five cancers diagnosed in humans and has poor treatment options and a high mortality rate. Canine gastric cancer is clinically and histologically similar with both human tumor subtypes occurring in the Belgian Tervuren and Belgian Sheepdog (Groenendael), breeds that are disproportionately diagnosed with this disease. To identify genomic loci associated with gastric cancer, we collected 200 cases and 270 controls from North America and Europe. SNP array data generated on the Illumina 173k, Illumina 220k, and Affymetrix 670k platforms were separately imputed to the whole genome sequence level with a multibreed reference panel consisting of 1,143 dogs, including 33 Belgian Tervuren and Sheepdogs. The merged dataset comprised over 5 million variants with imputation quality scores and minor allele frequencies greater than 0.9 and 0.05, respectively. Imputed data were analyzed using a Bayesian approach (BayesR) and cross population extended haplotype homozygosity (XP-EHH) selection scans. We identified seven loci with moderate effect size on gastric cancer phenotype, including a well-known cancer locus as well as novel associations, some of which are under selection in these breeds. This study highlights the complex genetic architecture of gastric cancer in Belgian shepherd breeds and its relevance as a model for the genetically heterogeneous human disease counterpart.

Reference Genome and Annotation for Canine Transmissible Venereal Tumor

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Canine Transmissible Venereal Tumor (CTVT) represents a unique paradigm in cancer biology due to its transmissible nature within canids. CTVT is known to be one of the few naturally occurring transmissible cancers, which raises intriguing questions about its ability to bypass host immune defenses and its evolutionary journey across dog populations globally. This study aims to document the genomic characteristics and definitive isoform-specific gene expression using long read sequencing technology. We generated 200x Pacific Biosciences circular consensus sequencing data, and high-depth Hi-C chromatin conformation capture data which were used to assemble a chromosome-level reference genome for CTVT. We also generated over 80 gigabases of full-length isoform sequencing data (IsoSeq) to characterize the complete complement of genes that are expressed and identify those that are ablated in this novel allograft. Using our canid pangenome as a basis, we identify tens of thousands of somatic structural mutations and ancestral genomic instability not documented using short read data. Combining this with IsoSeq afforded the ability to see the erosion of genic regions and pseudogenization of a large portion of previously protein coding genes. Investigation of immune evasion focused on the modulation of immune checkpoint molecules, antigen presentation pathways, and cytokine signaling. Our study not only advances the understanding of CTVT's genomic structure and gene expression, but also contributes to the broader knowledge of cancer evolution and immune interactions in transmissible cancers, which could help pave the way for novel therapeutic strategies and preventive measures in veterinary oncology.

An RCN1 frameshift mutation is associated with rapidly-progressive, adult-onset cataracts in Miniature American Shepherds

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Hereditary cataracts are one of the leading causes of blindness in dogs. Previously, a single nucleotide HSF4 deletion was associated with an incompletely penetrant, dominant cataract in Australian Shepherds; this allele is also present in the closely-related Miniature American Shepherd (MAS). A MAS family was recently identified with adult-onset, rapidly-progressive cataracts and all affected individuals were homozygous wild-type for the HSF4 deletion. The cataracts developed between the ages of 3 and 5 years and required corrective surgery due to loss of sight within months of diagnosis. Pedigree analysis supported a completely penetrant autosomal recessive mode of inheritance. High coverage whole-genome sequencing (WGS) data were generated for four affected dogs and two MAS controls (older than 8 years of age with healthy eyes per a board-certified veterinary ophthalmologist). The high-coverage data were downsampled and merged with 220k Illumina SNP array data from 70 additional MAS clear of eye disease. GWAS (n = 76 dogs) revealed an approximately 20 Mb associated CFA18 window for which affected dogs shared a unique run of homozygosity. Within this window, a 2-bp frameshift deletion was identified in the RCN1 (reticulocalbin 1) gene. Genotyping of additional related dogs demonstrated this variant perfectly segregated with the cataract phenotype. RCN1 has not been previously associated with cataracts in humans, although RCN1 variants cause cataracts and abnormal lens morphology in murine models. This work highlights the utility of spontaneous canine models for identifying phenotype-associated novel genes; unexplained hereditary cataracts in people should include sequencing of RCN1.

A novel form of inherited retinal degeneration in Lagotto Romagnolo dogs

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Inherited retinal degenerations (IRDs) are a heterogeneous group of diseases causing visual impairment and blindness. Age of onset as well as rate of progression varies considerably between different forms of IRDs. Most IRDs show an autosomal recessive mode of inheritance but there are also examples of autosomal dominant and x-linked inheritance. In humans, almost 300 genes have been identified. For the majority of clinically affected dogs, the genetic cause of IRD remains unknown and less than 40 genes have so far been identified.

In the breed Lagotto Romagnolo, several cases of IRD with unknown genetic cause have been observed. Ophthalmic examination, including optical coherence tomography (OCT) and electroretinography (ERG), was performed in affected Lagotto Romagnolo dogs. Morphologically, bilateral neuroretinal thinning, mainly affecting the outer retina, was observed. The degeneration was more advanced peripherally than centrally. Rod-driven ERGs were relatively more reduced than cone-driven, suggesting a diffuse rod-cone degeneration.

We sequenced the genomes of a family including the unaffected parents and an affected offspring as well as its affected half-sibling. After mapping and variant calling, we applied conditional filtering, assuming an autosomal recessive mode of inheritance. This led to the identification of a candidate gene with 20 exons and a premature stop codon in exon 4. In screening a larger cohort of 80 dogs, it was shown that all homozygous dogs were clinically affected. The effect the nonsense variant is currently being investigated on mRNA expression as well as on protein level and the results will be presented.

Utilization of Pangenome Graphs for Identification of Novel Variation in Canidae

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Current approaches to comparative genomics rely on aligning fragmented sequence data to a highly curated, single haplotype reference genome. The primary drawback to this approach is that a single reference cannot represent population diversity. This can lead to incorrect conclusions drawn from genomic data in that both false positive and false negative variant calls result from reference bias, which is particularly problematic for structural variants. To combat this discrepancy when inferring variants, we have generated the largest Canidae pangenome from domestic dog, grey wolf, coyote and fox genomes using both unpublished and published reference assemblies. Currently at 50 haplotypes pangenome graphs were built using an in-house German shepherd as a reference and reference-free for optimum variant discovery. Consisting of over 20 breeds, as well as wolf, coyote, and fox individuals, and reference genomes for canine cancer, we observe a considerable drop in reference bias (the ability to capture genome variation in haplotypes not represented by a linear reference) when aligning short read data, even for breeds unrepresented by reference individuals. Structural variants implicated in disease processes were also detected for the first time. In addition, using pangenome graphs across Canidae, we can identify structural variants present post-domestication, and reliably observe genome evolution across canids. We propose that pangenome-based variant discovery approaches be developed in dogs as in other species. This approach shows great promise, though tools and resources are needed to bring its full potential mainstream so it can be adopted by genetics researchers to improve their variant discovery.

Induced Pluripotent Stem Cells to Model Gene Function in Dogs

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Dog population genetics studies have revealed a myriad of genetic variants that are associated with disease and traits. However, the leap from variant 'association' to 'causality' is extremely challenging, especially when cases are rare and access to biological material for characterisation is limited. Induced pluripotent stem cells (iPSCs) are an essential and inexhaustible biological resource for circumventing these limitations. As a self-renewing population of cells amenable to genetic manipulation and lineage differentiation, iPSCs are an ideal tool to explore the effects of genetic variation conspecifically. Currently, the production of canine iPSCs from adult cells is inefficient and reproducibility is poor. Here we describe our progress to overcome these limitations. Using transposon-based, doxycycline regulatable reprogramming factors, we attempted to reprogramme skin fibroblasts derived from a Labrador retriever, the same dog sequenced to produce the ROS_Cfam_1.0 genome assembly. Theorising that a major limitation to reprogramming success was the proliferative capacity of starting adult cells, we overexpressed SV40 large T antigen to create the cell line LAB1-Tag. Critically, this cell line is immortalised in a doxycycline-dependent manner and sequence-based inference of karyotypes indicates LAB1-Tag is normal. Unlike their primary parental cells, LAB1-Tag cells were competent to produce putative iPSC colonies following transfection with a cocktail of reprogramming factors. We will provide updates on our ongoing iPSC characterisation that describe our iPSCs' pluripotency and competence to differentiate.

Leveraging community science for canine cancer: developing genetic screening and genomic selection tools in dogs

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Genomic sequencing technologies applied to canine cancer research offer insight into cancer risk variants and pathways underlying cancer biology, benefiting both dogs and humans. Sequencing approaches can also be applied towards directly reducing heritable risk factors for cancer in dogs through genomic selection.

Utilizing longitudinal data from 5000+ dogs in the Golden Retriever Lifetime Study and the International Working Dog Registry (IWDR), we investigate germline risk factors in canine hemangiosarcoma and assessed feasibility of genomic selection in at-risk retriever breeds. This builds on our prior work in identifying hemangiosarcoma risk variants and applying genetic selection to complex traits in working dogs. By incorporating genomic approaches into existing genetic selection programs for working dogs, we aim to demonstrate the reduction of hemangiosarcoma incidence over time.

Supporting this effort, we have collaborated with Gencove to develop a powerful and cost-effective genotyping approach combining low pass whole genome sequencing with a targeted panel of 300+ canine trait associated loci, facilitating high density genotyping while unlocking new tools for genetic selection in dogs. We have validated coverage and variant calling using 30X sequences from both single breed and mixed ancestry dogs. Leveraging our canine community science platform at Darwin's Ark, we will further enhance these technologies for broader application in canine research and breeding programs.

Ultimately, we aim to align our genomic discovery research efforts with application of genomic selection in dogs, thereby advancing comparative genomics and oncology research while also reducing heritable canine disease.

Biological age clocks predict health trajectory and mortality risk in dogs

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Companion animals play a significant role in our lives, and, like humans, undergo aging and are subject to age-related diseases and loss of quality of life. However, unlike humans, pets are unable to communicate their physical well-being. Thus, reliable aging metrics are invaluable to ensure optimal care of aging pets. Differences in physiology, genetics, nutrition, and lifestyle limit the generalization of aging biomarkers between species. In particular, algorithms for biological age trained for humans are difficult to translate to pets. However, the methodologies and approaches can be applied to any species, provided the right training dataset is available. Using a unique, internal longitudinal dataset with health records from 829 dogs spanning over 12 years, we developed two new canine-specific aging clocks. Our canine PhenoAge based on blood markers whereas our second-generation epigenetic clock, canine EpiAge, is based on targeted EM-seq and trained on canine PhenoAge estimates. Applying these algorithms to samples from a unique 14-year life-long diet restriction study with dogs, we showed that restricted caloric intake lowers biological age, an effect that can be quantified at midlife, years before a difference in survival is observed. Thus, in dogs, biological age clocks based on either blood markers or epigenetics can help predict health trajectories for use in research and veterinary practice.

POSTER ABSTRACTS

#1
Genetic Counseling in Veterinary Medicine: towards an evidence-based definition for the small animal practice

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Poster session 1

Background: In human medicine, questions regarding heritable disorders are dealt with by clinical geneticists and genetic counselors and both the field, their roles and the tools they use are well-defined. Even though the prevalence of diseases is far higher and scientific literature agrees on expectations towards an increased importance, this does not seem to be the case in veterinary medicine.

Methods: Comparing human genetic counseling definitions with veterinary literature and clinical data, a stepwise analysis was used that lead to a set of three potential definitions (i.e. on what genetic counseling is, who provides it and which tools are used) that fullfill four criteria (i.e. definitions have to be clear, minimally sufficient, complete and valid).

Results: The concise veterinary genetic counseling definition is: "Genetic counseling is the process of helping animal owners and breeders understand – and adapt to – the medical, psychological, familial implications of genetic contributions to disease." Genetic counseling in small animal practice is currently provided by veterinarians and the tools that are used, can be divided in five categories. The signalment of the patients revealed that both cats and dogs accross various breeds, the two sexes and all age categories were represented.

Conclusion: These definitions are derived from human and veterinary literature, and an evaluation based on patient data has demonstrated that these definitions meet all the criteria of a correct definition. With these definitions and case descriptions, our aim is to contribute to the formal foundation of genetic counseling in veterinary medicine.

#2
Novel rare variants found in English Cocker Spaniel with early retinal degeneration

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Poster session 2

Progressive retinal atrophy (PRA) is a hereditary condition observed in dogs, including the English Cocker Spaniel (ECS) breed, where a recessive variant in PCRD accounts for most of the cases.

A male blue roan ECS developed blindness at two years of age. Both parents were tested clear for 26 known variants associated with retinopathies. The retina of both eyes appeared devoid of blood vessels and hyperreflective, leading to the diagnosis of early-onset retinal degeneration. No other clinical signs were detected. The genome of the case and the two parents were sequenced and the polymorphisms, small indels, and large structural variants called compared against the Dog10k database.

We found 24 exclusive indels and SNPs. Of these, two were coding variants heterozygous in the parents and homozygous in the case: one AA exchange and one frameshift, both involving genes with a degree of expression in the retina. Additionally, we detected one non-coding exclusive structural variant.

This study underscores the complex genetic underpinnings of PRA in ECS, highlighting the potential involvement of novel genetic variants beyond PCRD mutations. Genotyping of a large score of controls is necessary to confirm the segregation of either the exclusive variants with the phenotype.

Detection of novel variants is crucial for preserving breed health and assisting breeders confronted with the challenge of producing blind dogs despite their diligent testing efforts.

#3
GWAS in Golden Retrievers Identifies Potential Candidate Obesity Genes

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Poster session 3

Canine obesity represents a significant veterinary health challenge, often linked to inadequate management by owners. However, the varying prevalence of obesity across different breeds suggests that genetic factors also play a crucial role. Despite existing heritability estimates indicating that 40-70% of obesity can be attributed to genetics, many of the causal variants involved are yet to be identified. In dogs, historical population bottlenecks and intense selective breeding practices have made gene mapping easily tractable. Therefore, the aim of this study is to elucidate the genetic underpinnings of obesity in a population of Golden Retrievers, an obesity-prone breed.

In this study, we used data from the Golden Retriever Lifetime Study (GRLS) to perform a genome-wide association study (GWAS) for obesity, identifying multiple associated loci with obesity. Downstream analyses revealed potential candidate canine obesity genes. These genes were explored further in the STRING database for protein-protein interaction, PANTHER database for overrepresented pathways and Human Protein Atlas for tissue-specific enrichment data.

Our findings narrowed down the list of plausible candidate genes to KCNJ1, KCNJ16, SYT1, WDR35, TTC32, PCDH17, PCDH15, and SLC12A8. Additionally, we identified four biological pathways that were overrepresented in our data: Cadherin signalling pathway, Synaptic vesicle trafficking, Integrin signalling pathway, and Wnt signalling pathway.

In conclusion, this study provides novel insights into potential candidate genes and pathways associated with canine obesity. These findings are a pivotal step towards an improved understanding of the genetic basis of obesity in dogs, which may, in time, transform preventive strategies and therapeutic interventions across species.

#4

Machine learning-driven morphological segmentation of canine diffuse large B-cell lymphoma (DLBCL) and reactive lymphoid hyperplasia

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Poster session 1

Background: DLBCL is the commonest and one of the most aggressive lymphoma in dogs with 20% survival rate 1-year post-diagnosis, despite treatment. Compared to its human homolog, there is a significant knowledge gap in the genomic, transcriptomic and histopathological characterisation of canine DLBCL. The aim of this project is to bridge this gap and ultimately generate tools to provide better diagnosis, prognostication and stratification in DLBCL patients by investigating genomics, transcriptomics and tissue morphology. This abstract focuses on exploring tissue segmentation on histopathological slides using machine learning (ML).

Aim: To determine if transfer learning (TL) and unsupervised ML (USML) approaches can segment whole slide images (WSI) to highlight clinically relevant regions.

Methods: Canine lymph node were submitted for diagnosis. HE-stained FFPE lymph nodes were scanned at 20× magnification. The model was trained on 138,000 images extracted from 59 DLBCL cases and 68 reactive lymphoid hyperplasia (RLH) cases.

Results: TL was employed to extract features vectors. Using dimensionality reduction and USML clustering, images were grouped based on their features vectors. The model was tested on 'never-seen' WSI, generating a heatmap overlaid on the original WSI to produce visual representations of tiles based on clustering. The heatmap generated distinct patterns that differentiate DLBCL from RLH.

Conclusions: Results suggest that canine DLBCL and RLH WSIs can be segmented using TL and USML, potentially providing tools that carry clinical relevance at histopathologic diagnosis. This will help ensure that dogs with DLBCL or RLH are provided with the most appropriate treatment at diagnosis, improving prognosis.

#5

Identification of an RBCK1 splice site donor variant in Basset Hounds with glycogen storage disease

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Flashtalk session 2

Glycogen storage diseases (GSDs) are rare, typically inherited, disorders caused by various defects in glycogen metabolism enzymes, generally resulting in the accumulation of glycogen in several tissues. Recently, two adult Basset Hound (BH) littermates were diagnosed with GSD via postmortem histopathology, with excess glycogen manifesting in both cardiac and smooth muscle. Using whole genome sequencing, a homozygous splice site donor variant was identified in exon 8 of RBCK1, a gene which encodes an E3 ubiquitin ligase, in both littermates. The presumptive loss of the splice site donor is predicted to result in premature termination in the mid-domain of the protein. Screening for the variant in related (n = 7) and unrelated (n = 124) BHs identified one additional affected littermate and five familial heterozygous carriers. No variant alleles were present in the unrelated BH population, establishing the novelty of the identified mutation. Variants in RBCK1 have previously been associated with polyglucosan body myopathy, a type of GSD characterized by skeletal muscle myopathy, cardiomyopathy, and polyglucosan accumulation in humans. To date, no reported variants in RBCK1 have been identified in dogs or other large animals associated with GSD, making this the first spontaneous large animal model of GSD due to a defect in RBCK1. The findings of this study add to the mutational spectrum of GSDs in dogs, permitting broader genetic testing for early diagnosis and for disease prevention through targeted breeding strategies.

#6

Exploring the Genetic Basis of Startle Disease in a Family of Old English Sheepdogs.

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Poster session 3

A 2-week-old litter of three Old English Sheepdog puppies presented with episodic generalized muscle hypertonia and cyanosis triggered primarily by touch and noise since the onset of ambulation. Clinical and neurological examinations, as well as electromyography, showed no abnormalities, and limited bloodwork was within normal limits. Due to the lack of response to therapy and the progression of clinical signs, the puppies were euthanized. A full necropsy of the central and peripheral nervous system revealed microscopic perineuronal incrustations in the spinal cord, suggestive of ischemia or neuronal necrosis, potentially related to the severe episodes of apnea and cyanosis.

Whole exome sequencing (WES) of the nuclear family, containing the affected pups and both the parents, revealed a truncating variant in the SLC6A5 gene, with affected individuals being homozygous for the variant and the parents being heterozygous.

In a population study, an additional 17 unrelated Old English Sheepdogs and a previous litter of the sire were screened. This testing revealed two unaffected dogs carrying the variant in a heterozygous state, comprising one genetically related and one unrelated dog. The latter finding suggests that the SLC6A5 truncating variant is segregating within the breed, raising concerns about potential carriers and their contribution to future generations.

Our study underscores the critical role of genetic counselling in breeding programs to identify carriers, make informed breeding decisions, and ultimately mitigate the impact of Startle Disease in this breed. These findings offer valuable insights for breeders, veterinarians, and geneticists aiming to enhance Old English Sheepdogs' health and welfare.

#7

A new flavor of feline coat coloration, "salmiak," is identified in Finnish domestic cats

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Poster session 1

Background: Cats with a distinctive white hair pattern of unknown molecular cause have been discovered in the Finnish domestic cat population. Based on the unique appearance of these cats, we have named this phenotype salmiak ("salty licorice").

Aim: The aim of this study was to investigate the genetic basis of the salmiak phenotype in domestic cats.

Methods: We employed a commercially available Wisdom Panel™ test for felines to genotype four salmiak-colored cats, assessing the presence of known variants associated with white-haired phenotypic loci. Whole-genome sequencing was performed on two salmiak-colored cats to identify candidate causal variants in the KIT gene.

Results: Panel DNA test analysis for coat color revealed the absence of all known variants associated with white-haired phenotypic loci in the tested cats. Whole-genome sequencing identified a large ~95 kb deletion located ~65 kb downstream of the KIT gene in the salmiak cats. PCR genotyping of additional 180 domestic cats confirmed the homozygous derived variant genotype fully concordant with the salmiak phenotype. We propose designating the newly identified variant as w^sal for "w salmiak".

Conclusions: Our findings suggest that the salmiak coat color phenotype in domestic cats is associated with a novel genetic variant of the KIT gene designated as w^sal.

#8

The feline variant classification guideline (FVCG): an objective tool to evaluate the genetic variant pathogenicity

Fréderique Boeykens[1], Marie Abitbol[2], Jessica J. Hayward[3], Åsa Ohlsson[4], Heidi Anderson[5], Jens Häggström[4], Ingrid Ljungvall[4], Leslie A. Lyons[6], Maria Longeri[7], Mark D. Kittleson[8], Elvio Lepri[9], Tommaso Vezzosi[10,11], Luc Peelman[1], Caroline Dufaure de Citres[12], Pascale Smets[1], Frank van Steenbeek[13,14], **Bart Broeckx**[1,14]
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Poster session 2

Background: the correct classification of a variant as pathogenic is important as breeding decisions based on invalid DNA tests can lead to the incorrect exclusion of animals and potentially compromise the long-term health of a population. In human medicine, the American College of Medical Genetics and Genomics guideline (ACMGG) provides a framework for variant classification. However, questions on the transferability to veterinary medicine have been raised.

Aim: to develop a cohesive variant classification guideline that can be used by the community for feline Mendelian disorders to classify variants in categories based on scientific evidence.

Methods: a stepwise approach was adopted in which experts were individually asked to evaluate the ACMGG and propose new criteria. Next, these evaluations were jointly discussed and led to the "feline variant classification guideline" (FVCG). The FVCG and ACMGG are benchmarked for a set of variants that were unanimously considered pathogenic by at least three independent experts.

Results: from the original 28 criteria in the ACMGG, seven were removed, seven adapted and 14 retained. One criterion was added. Together, this led to 22 criteria in the FVCG. Sixty pathogenic variants are used for benchmarking.

Conclusions: half of the ACMGG criteria were deemed unsuitable in its current form. New criteria have been developed and their performance is assessed. This collaborative approach led to a tool that can provide guidance to researchers, clinical geneticists, and laboratories to objectively determine when sufficient evidence is present to consider a feline Mendelian variant pathogenic.

#10
Analysis of LINE-1 expression in dogs

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Poster session 1

Transposable elements account for 34% of the canine genome. The largest group of TE are self-replicating LINE-1 (L1) elements, which comprise ~18% of the canine genome. The vast majority of L1 elements have accumulated mutations or have 5' truncations rendering them non-functional. The canine L1 is ~6 kb in length and codes for two proteins, ORF1p and ORF2p, which mediate its retrotransposition. CanFam3.1 has ~ 250 full-length L1 with intact open reading frames (L1-IORF) that are putatively active. Active L1 can mediate the retrotransposition of L1, cellular mRNA (to form retrogenes), and SINE elements. Thus, L1 is responsible for ~10% of the phenotype-causing variants identified in dogs. We hypothesize that the full repertoire of active L1 within an individual or a breed could shape the health of the breed. We identified full-length L1-IORF from canFam4, canFam5, canFam 6, ROS_Cfam_1.0, UNSW_CanFamBas_1.2, and mCanLor1.2, which varied from 21-554. While there was overlap in L1 between assemblies, only 32-37% were shared across canFam 4, 5 and 6 genome assemblies. Using neonatal brain samples, cytoplasmic mRNA was isolated, followed by strand-specific L1 cDNA synthesis, and PCR products encompassing the open reading frames of transcribed L1 were cloned and sequenced. Thirty-seven percent of the expressed L1 had full-length open reading frames in both proteins and 43% of the transcribed L1-IORF were not identified as L1-IORF in any genome assembly (<0.12% sequence difference). We identify striking differences in the number of different L1 elements expressed between individual dogs.

#11
The prevalence of ABCB1-1Δ in a clinical veterinary setting: to test or not to test?

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Poster session 2

Background: Multidrug sensitivity is an autosomal recessive disorder in dogs caused by a 4-bp deletion in the ABCB1 gene, often referred to as the ABCB1-1Δ variant. The deletion results in a truncated P-glycoprotein, an efflux-transporter expressed on the endothelium in the blood-brain barrier. Dysfunction thereof causes adverse reactions to certain drugs when given in otherwise safe doses. Though most dogs known to be at risk are of the collie lineage, the variant has also been described in several seemingly unrelated breeds.

Aim: As it is generally advised to genotype dogs at risk before treating them, the possible risk of not testing for multidrug sensitivity prior to treatment was assessed in a clinical setting.

Methods: The ABCB1-1Δ variant allele frequency was determined in a cohort of 286 dogs from the veterinary clinic using qPCR or Sanger sequencing. This frequency was compared to the allelic frequency in 599 samples specifically sent in for genetic testing.

Results: While the allelic frequency in the sample routinely tested dogs was high (21.6%) and in line with general reports, the allelic frequency in the clinical setting was low (0.2%), demonstrating a discrepancy between dogs sent in for genetic testing and the clinical population.

Conclusions: The frequency of the disease-causing variant in the general clinical population was low, therefore, the risk of encountering a dog displaying multidrug sensitivity despite not genotyping seems to be low. As the variant was only found in an at-risk breed, the current recommendation of routinely genotyping at-risk breeds before treatment seems justified.

#12
Extension Locus Recessive Allele Discovered in Novel Breed

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Poster session 3

The AKC accepted coat colors for Boxers are fawn and brindle, either of which can also have white markings, and a black mask. Recently, a litter of Boxer puppies was born with a subset of individuals exhibiting a novel, full-body, cream-colored coat phenotype (together with white markings). DNA was obtained from the entire litter, sire, and dam. Both commercial breed-determination genetic test kits as well as internal principal components analysis (using all publicly available Boxer SNP data) demonstrate that the cream dogs are, indeed, purebred Boxers. Whole genome sequence (WGS) was generated (n = 5 cream, n = 2 related, non-cream), with SNP-array loci down sampled to combine with existing Boxer SNP data (n = 22). GWAS identified a strongly significant locus directly encompassing the MC1R gene, and WGS indicated that the cream Boxers were homozygous recessive at the E Locus. There are no previous reports of "ee" Boxers, meaning that the "e" allele must be extremely rare in the breed; however, this particular family had a high level of inbreeding, explaining in part the novel phenotype. Interestingly, there also exists a range in pheomelanin dilution between the cream boxers, from nearly white to practically fawn, indicating the likely existence of one or more additional contributing variant(s), which is being further explored. Besides the intense curiosity of dog breeders and the public about novel canine coat colors, understanding the genetic drivers of this uncommon phenotype will add to the knowledge of pigment production across all mammalian species.

#13

A genetic purr-spective: exploring disease and parentage testing in the Maine Coon and British Shorthair

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Poster session 1

Background: The Maine Coon (MCO) and British Shorthair (BSH) are Europe's most genetically tested cat breeds.

Aim: This study explores allele frequency changes, breeder-prioritized diseases, and the applicability of ISAG parentage SNPs to monitor and preserve genetic diversity of these breeds.

Methods: Genetic disease test results of samples submitted to LABOKLIN (Germany) between 2013 and 2023 were investigated for allele frequency changes. Additionally, nineteen Belgian MCO and twenty-two BSH were genotyped for 117 parentage SNPs, including the 101 ISAG SNPs. Multidimensional scaling (MDS) plots were generated to visualize relatedness between individuals. Inbreeding coefficients based on homozygosity rate (Fhom) and pedigree information (up to 10 generations, Fped) were compared using Pearson's correlation coefficient (r).

Results: In the period between 2013 and 2023, the frequency of the causal allele for hypertrophic cardiomyopathy decreased substantially from 18.4% to 5.2% in the MCO, while the pyruvate kinase deficiency-causal variant showed minimal reduction (from 10.1% to 8.3%). BSH saw a 5-fold increase in polycystic kidney disease tests in the last decade, with a relatively constant allele frequency of around 1.5%. We found a positive correlation between Fhom and Fped ($r = 0.348$, $p = 0.038$) and the MDS plots generally confirmed the pedigree information.

Conclusion: DNA tests can efficiently reduce deleterious allele frequencies. However, the limited decrease in pyruvate kinase deficiency and stagnation in polycystic kidney disease suggest breeders can benefit from genetic counseling to further improve breeding practices. Utilizing parentage SNPs shows promise in monitoring and preserving genetic diversity.

#14
Serum miR-30b, miR-502 and miR-331 are upregulated in Labrador retrievers with hepatic copper accumulation

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Poster session 2

Background: Copper associated hepatitis is a hereditary disease in Labrador retrievers with a complex genetic background. Currently, liver biopsies are needed for diagnosis and treatment monitoring. A non-invasive serum biomarker for elevated hepatic copper levels could partially replace these liver biopsies. MiRNAs are potential biomarkers increasingly studied for their diagnostic potential in hepatobiliary disease. The aim of this study was to identify copper-specific microRNA biomarkers.

Aim: To identify serum miRNAs associated with hepatic copper levels in Labrador retrievers.

Animals: Client owned Labrador retrievers with normal hepatic copper levels and increased hepatic copper levels retrospectively selected from a patient database.

Material and methods: In this retrospective case-control study the expression of 277 miRNAs in blood serum were analyzed in Labrador retrievers with normal hepatic copper levels (n=5) and elevated hepatic copper levels (n=5) using real-time PCR based array technology. MiRNAs upregulated in the high hepatic copper group were analyzed with real-time qPCR in a replication cohort of 13 Labrador retrievers with normal hepatic copper levels and 18 with elevated hepatic copper levels.

Results: Five out of the 277 serum miRNAs were significantly upregulated and were analyzed in the replication cohort. miRNAs miR-30b (fold-change 2.17, p-value = 0.00035), miR-502 (fold-change 1.59, p-value = 0.022) and miR-331 (fold-change 1.39, p-value = 0.046) were also upregulated in the replication cohort.

Conclusion: Serum miR-30b, mir-502 and miR-331b are upregulated in Labrador retrievers with hepatic copper accumulation. These miRNAs are potential copper specific biomarkers for the diagnosis and treatment monitoring of copper associated hepatitis in dogs.

#15
The GOLDogs project: Genomic Of Longevity in Dogs

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Flashtalk session 3

The dog model represents a unique mammalian system to decipher the (epi-)genetic bases of various phenotypes, including longevity. It has already been shown that in dogs, the breed average lifespan is inversely correlated with breed average body weight, with smaller dogs living longer than larger dogs. But the combined contribution of small (SNVs - Single Nucleotide Variants) and large genomic variations (SVs – Structural Variations) influencing dog aging remains to be explored. In the GOLDogs project, we aim to produce an exhaustive catalog of both small and large genetic variations through low-pass sequencing of 25 dog breeds, including 20 dogs per breed (10 with an extreme longevity & 10 with a median longevity, specific to each breed). To this resource, we will combine long-read sequencing and genome assemblies of 100 dogs representing these 25 breeds, with 4 dogs per breed, all collected through the Cani-DNA BRC network of French practitioner (https://igdr.univ-rennes.fr/en/crb-cani-dna) and sequenced in collaboration with France Génomique (https://www.france-genomique.org/projet/goldogs/) and our in-house IGDRion long-read sequencing facility (https://igdr.univ-rennes.fr/en/igdrion). We will present the preliminary results of the project including GWAS and long-read sequencing bioinformatic analyses of the first samples. Altogether, we hope that the GOLDogs resource will not only be useful to study longevity in dogs, but also to get insights on the genomic diversity of dog populations and to map all forms of genetic variations to a phenotype of interest, with the fascinating example of longevity.

#16
Genetic Mechanisms Underlying Disorders of Sexual Development in Dogs

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Poster session 1

Normal development of gonads and other sex-determined characteristics are complex genetically regulated processes that form the foundation for animal reproduction. Our current understanding about the genetic control of normal sex development is largely based on molecular and functional analyses of human patients or mouse models with various disorders of sex development, while knowledge about the genetics of sex development in most animals is limited. Disorders of Sex Development (DSD) represents numerous categories such as intersex, hermaphroditism, pseudohermaphroditism, and sex reversal with phenotypes including gonadal dysgenesis and a spectrum of intersex or ambiguous sex conditions. Most cases have cytogenetically normal male or female karyotypes and are broadly classified according to sex chromosome complement as XX and XY DSDs. Further sub-categorization is based on specific gonadal or hormonal abnormalities, and the presence of SRY. We explore the genetics of DSDs in domestic dogs using whole genome sequencing (WGS) of 60 karyotypically normal individuals displaying a wide array of reproductive abnormalities including azoospermic SRY+ XY males, XX females with ovarian dysgenesis, phenotypically female XY SRY+ males, XX females with one ovary and one testis, and true hermaphrodites of both sexes. We compared the genomes of these cases with a catalog of over 3000 other whole genome sequences to identify rare mutations and found deleterious variants in implicated pathways such as meiosis, spermiogenesis, steroidogenesis, as well as hormone production and receptor function. These findings parallel our work to understand DSDs in other species and demonstrate the essential and highly conserved mechanisms controlling mammalian reproduction.

#17
TENM4 de novo variant in a Lagotto Romagnolo dog with tremor and cerebellar ataxia

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Poster session 2

Different neurological disorders with progressive ataxia exist in the Lagotto Romagnolo breed. Clinical signs are variable, as is the severity and age of onset, suggesting heterogeneity. Only a single AGTD4-related form of progressive cerebellar ataxia (CA) has been studied at the molecular level. We sequenced 22 genomes from closely related and unrelated Lagotto Romagnolo dogs of different ages suffering from loss of coordination or confirmed CA to elucidate possible genetic causes. One affected is a living 8-year-old female who was first presented with head tremor at the age of 2. Two years later, neurological examination confirmed persistent head tremor and MRI showed atrophy of the cerebellum and cortex. WGS was performed on this dog and its unaffected parents. Assuming monogenic recessive inheritance, no private homozygous protein-changing variant was observed. Alternatively, the presence of possible de novo variants was assessed. Two heterozygous private protein-changing variants, absent in both parents, were found, and confirmed by Sanger sequencing. We postulate that the private heterozygous TENM4 missense variant (XM_038568485.1:c.845G>A, XP_038424413.1:p.(Ser282Asn)) affecting a highly conserved domain and absent in >3000 controls is the candidate causal pathogenic variant for the observed phenotype. The TENM4 gene encodes a transmembrane protein predominantly expressed in neurons. Heterozygous variants in TENM4 have been reported in human patients with dominantly inherited forms of essential tremor. We provide the first evidence that independent de novo mutations contribute to the heterogeneity of CA in the Lagotto Romagnolo breed and may explain sporadic occurrence of canine CA.

#18
Suspected autosomal recessive primary ciliary dyskinesia in a colony of Labrador Retriever guide dogs

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Flashtalk session 1

Over a 23 year period, 11 litters were born in a guide dog breeding program in which one or more puppies developed characteristic respiratory clinical signs around 2 weeks of age. These included nasal discharge, chronic rhinitis and recurrent upper respiratory tract infections which sometimes progressed to bronchopneumonia. Mycoplasma cynos was often found on culture, but no primary diagnosis was determined until early 2023 by electron microscopy. Nasal biopsy samples from one affected dog revealed changes suggestive of primary ciliary dyskinesia. Pedigree analysis revealed a likely autosomal recessive inheritance pattern, tracing back to one common ancestor. Genome-wide association studies of 8 cases and 20 case-related control dogs revealed a single significantly associated region on canine chromosome 2 from 62,624 to 11,674,110 (P-val <= 7.65E-06). This region encompasses the SPAG6 (sperm-associated antigen 6) gene (10,737,260 – 10,787,547 bp) which has been suggested to play a role in ciliary dyskinesia in mouse knockout studies as well as being proposed as a mechanism in humans. A 'risk haplotype' of strongly associated SNPs was also identified. All the cases were homozygous for the risk haplotype. This enabled more accurate identification of carriers in our breeding program. Identification of carriers based on pedigree analysis, then risk haplotype, has allowed successful avoidance of producing more affected puppies. Next steps include whole genome sequencing of several parents of known cases, cases, unaffected littermates and unaffected unrelated dogs to determine a causative mutation.

#19
The utilization of the Vezzoni modified Badertscher distension device in breeding programs

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Poster session 1

Canine hip dysplasia (CHD) is a common orthopedic condition influenced by genetic and environmental factors. Current breeding programs utilize ventrodorsal hip-extended (VDHE) radiographs, but their accuracy in assessing hip joint laxity is limited. This study assesses the efficacy of the Vezzoni modified Bädertscher distension device (VMBDD) technique, measuring hip joint laxity with the laxity index (LI), as a screening tool in two breeding programs: a Belgian population of assistance dogs (population A) and a French population of guide dogs (population B). Bayesian statistical methods revealed high heritability estimates for LI in both populations (0.80 in A, 0.82 in B). Combining VMBDD with VDHE for parent screening significantly reduced LI and CHD prevalence in offspring. In population A, screening both parents with VMBDD resulted in an average LI decrease of 0.04 ($P<0.05$). In population B, screening one or both parents with VMBDD reduced average LI by 0.04 ($P<0.05$) and 0.05 ($P<0.01$), respectively. Screening both parents with VMBDD in addition to VDHE lowered CHD odds by 82.5% ($P<0.05$) in population A and 72.3% ($P<0.05$) in population B when screening one parent. In population B, when screening both parents with VMBDD, not a single case of CHD was observed in the offspring. This study suggests that the VMBDD technique holds significant potential for substantially decreasing CHD prevalence, making it an invaluable tool for breeding programs.

#20
Homozygous DSG4 missense variant in a Cavalier King Charles Spaniel with hair shaft dystrophy

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Flashtalk session 1

Canine hair shaft dystrophy is characterized by hair shaft malformations. We performed clinical, histopathological, ultrastructural and genetic analyses on a Cavalier King Charles Spaniel exhibiting hair shafts with bulb-like structures at the tips of the hair shafts leading to fragility and subsequent breakage. Clinically, localized alopecia affected the head, tail, and abdomen, while sparing the back and trunk. Microscopic examinations confirmed the typical morphology of so-called lanceolate hairs. Whole-genome sequencing data of the affected dog were compared to 960 genetically diverse canine genomes. By filtering for variants that were present only in the affected dog but absent from the control genomes, a homozygous missense variant in the DSG4 gene was identified, XM_038541813.1:c.491T>C or Chr7:58,103,242A>G (UU_Cfam_GSD_1.0 reference genome assembly). This variant is predicted to lead to a substitution of a highly conserved leucin to a proline, XP_038397741.1:p.(Leu164Pro). DSG4 encoding for desmoglein 4 is a known candidate gene for hair shaft dystrophy in humans, cats, and several other species. DSG4 is essential for cellular signaling during the transition phase from proliferation to differentiation in the developing hair, and its alteration is hypothesized to contribute to the hair shaft abnormalities. In light of the knowledge on DSG4 variants in other species, our data strongly suggest that the identified DSG4 variant caused the hair shaft dysplasia in the investigated Cavalier King Charles Spaniel. This is the first report of a pathogenic DSG4 variant in dogs. The findings enable the development of genetic testing to preclude the breeding of further affected individuals.

#21
Whole genome sequencing to explore variation in mineral-and-bone disorder in chronic kidney disease cats

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Poster session 3

Introduction: Chronic kidney disease-mineral and bone disorder (CKD-MBD) develops due to phosphate retention and causes CKD progression and mortality, but its severity varies amongst patients. Fibroblast growth factor-23 (FGF-23), a novel biomarker, increases early in CKD-MBD.

Objective: Explore genetic variants associated with CKD-MBD severity in CKD cats.

Materials and Methods: Fourteen client-owned DSH cats with azotaemic IRIS stage 2 CKD (n=7 High FGF-23 1477-5673pg/ml, n=7 Low FGF-23 142-230pg/ml) fed a commercial renal diet underwent whole genome sequencing (WGS) at 30X coverage (Illumina platform). A bespoke bioinformatics workflow was used for quality control (FASTQC), mapping to the reference genome FelCat9 (BWA), variant calling (GATK 4), allele frequency calculation and statistics (PLINK), and annotation. Alternate allele frequencies were compared to the Feline 99 Lives dataset. Variants were prioritised using evidence including: predicted impact, presence in genes with known renal/bone function, and alternate allele frequency statistics in the high and low FGF-23 groups ($p<0.3$).

Results: Evidence-based prioritisation identified >10,000 variants of interest; 355 were particularly relevant due to being in genes associated with human CKD or rickets, being moderate or high impact or differences in their alternate allele frequencies between groups. Variants found in genes encoding for FGF-23, the vitamin D receptor, a kidney phosphate transporter and DMP1 (regulator of local FGF-23 expression), may prove valuable as diagnostic or therapeutic targets.

Conclusion: WGS has identified exciting novel candidate variants associated with high versus low FGF-23 concentrations. A follow-up targeted sequencing study of 10,000 variants in 180 CKD cats (known FGF-23 status) is underway.

#23
Investigation of cell-free DNA and paired tumor-normal samples in dogs with hepatocellular carcinoma

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Poster session 2

Background: Hepatocellular carcinoma (HCC) is the most common primary liver tumor of dogs. Surgical excision is the standard of care, however, feasibility depends on tumor subtype, size, and location. Diagnosis of HCC is challenging and usually occurs later in the illness. Thus, a more specific, accurate, and less invasive test is needed to aid HCC diagnosis.

Aim: The broad aim of this study is to investigate cell-free DNA (cfDNA) as a biomarker for the diagnosis and progression of canine HCC. We hypothesize that the majority of the circulating cfDNA in the blood of canine HCC patients is derived from the HCC tumor itself.

Methods: Longitudinal cfDNA samples were collected from HCC dogs to compare the amount of circulating cfDNA to the clinical manifestations of the disease. Further, paired tumor-genomic DNA samples were collected from nine dogs. These underwent whole genome sequencing and a somatic variant calling pipeline to identify variants present in the liver tumors but not in the germline of each individual. Resulting variants were annotated and compared across all nine individuals to identify shared HCC variants.

Results: Our results show the relationship between the amount of cfDNA in the blood and biochemical markers of disease (ALT, ALP), suggesting that cfDNA is a good prognostic marker for HCC. The paired tumor-normal samples identified shared HCC variants, which will be used to compare to cfDNA sequencing.

Conclusions: This study provides preliminary data for the long-term goal of developing a non-invasive liquid biopsy test for earlier detection of canine HCC.

#24

Dipping a paw in the fishbowl: diving into the genetic risk factors of feline diabetes

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Flashtalk session 3

Background: Diabetes mellitus (DM) is a complex genetic disease commonly seen in domestic cats, especially older and overweight cats. Unlike dogs, cats more commonly develop non-insulin-dependent diabetes, caused by a diminished sensitivity to insulin. Managing DM requires lifestyle changes, daily medication, and significant costs to owners. Several studies have identified loci associated with DM, but these have all used low density genotype platforms.

Aim: Here, we use a custom feline Affymetrix array of 2 million genome-wide SNPs, the largest dataset to our knowledge, to identify loci significantly associated with feline DM.

Methods: We genotyped 172 diabetic cats and 750 unaffected cats, sourced predominantly from the Cornell University Hospital for Animals, but also including 286 samples from Australia. Where possible, we collected date of birth, sex, breed, weight, and body condition score on these cats.

Quality control was performed, and a genome-wide association study was conducted.

Results: After quality control, we had approximately 1.35 million SNPs remaining. Our analysis identified significant associations on chromosomes D1 and C1, which have not previously been found in cats. The C1 locus includes the gene PIK3R3, which is part of the phosphatidylinositol 3-kinase (PI3K) family of enzymes, that form a central part of the insulin signaling pathway.

Conclusions: Feline diabetes is a relatively common disease that has a significant impact on the lives of cats and their owners. Identification of genetic risk factors can help with screening to prevent development of disease and to reduce the frequency in the domestic cat population.

#25

Breed-specific genetic bottlenecks reveal new information about breed formation in the context of global events

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Poster session 1

By definition, established breeds are limited in the introduction of new genetic material, resulting in frequent bottlenecks. We aim to detect breed-specific genetic bottlenecks and determine how they correlate with defining moments in breed formation, popular media, and historical events. Two datasets totaling 207 breeds were used: 1) Illumina CanineHD SNP positions for 2,373 dogs (202 breeds) and; 2) whole genome sequence from 274 dogs (37 breeds). Known birth years (1984-2021) allowed for calculation of accurate bottleneck timepoints. Generation interval was calculated from pedigree data of 25 breeds and timepoints were detected using ASCEND.

Breed-specific bottlenecks can be attributed to popular sire effects and are present throughout most modern breeds. Bottlenecks spanning large periods of time have smaller effects that those that happen quickly, often with strong implications for breed health. Some signals overlapped with recognition by national registries e.g., Tibetan Spaniel in 1983, or establishment of a breed outside its country of origin, e.g., importation of the Bulgarian Shepherd to the USA in 2004. Severe bottlenecks were detected for both the Old English Sheepdog and the Bulldog during years of rapid increases in popularity. The film release "The Shaggy Dog" in 1959 preceded such a bottleneck (1962-71), and AKC registered sheepdogs increased from 252 to 10,511. The Bulldog, symbolizing wartime resilience, also experienced a bottleneck at the end of WWII, with AKC registrations increasing from 1,533 in 1944 to 4,225 in 1947. These accounts reflect only a few of the hundreds of breed histories written in the canine genome.

#26
The Golden Retriever Lifetime Study: a resource for genetic research

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Poster session 2

The Golden Retriever Lifetime Study is the largest, most comprehensive longitudinal veterinary cohort study, following 3,044 Golden Retrievers in the contiguous United States. The primary aim of the study is to investigate risk factors for cancer and other common diseases in dogs, with an emphasis on lymphoma, osteosarcoma, hemangiosarcoma, and high-grade mast cell tumors. Rolling enrollment of dogs aged 6 months through 2 years was conducted from 2012–2015. Extensive owner- and veterinarian-completed annual questionnaires obtain information about lifestyle, environmental exposures, physical activity, reproductive history, behavior, diet, medications, and diagnoses. Dogs also have annual veterinary examinations and biospecimen collection (whole blood, serum, hair, nails, feces, urine) for laboratory analysis and biobanking. The cohort was genotyped using a 1.1 million marker Axiom array. As of February 2024, 407 hemangiosarcomas, 177 lymphoma/leukemias, 36 high-grade mast cell tumors, and 21 osteosarcomas have been diagnosed. Additionally, many other disorders common in Golden Retrievers have been diagnosed, including otitis externa, atopy, hypothyroidism, cataracts, and orthopedic disorders. A subset of questionnaire data and all our genotyping data are freely available to researchers through our Data Commons site (https://datacommons.morrisanimalfoundation.org). We also provide a tutorial for conducting genome-wide association studies using our genotyping data. Researchers can apply to access additional data and/or biospecimens through our request for proposal process. This study is an instrumental resource for studying genetic and environmental risk factors for canine health conditions.

#27

Analysis of plasma-derived exosomal microRNAs as potential biomarkers for canine idiopathic epilepsy

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Poster session 3

Exosomes are small extracellular vesicles released by cells that encapsulate diverse molecules, including microRNAs (miRNAs). These miRNAs, known for their pivotal role in gene regulation processes, have been shown as promising targets for convulsion management. Within the cargo of exosomes, these regulatory molecules hold potential as biomarkers for epilepsy, a prevalent neurological disorder in dogs, with its idiopathic form being the most commonly diagnosed. In this study, exosome samples were isolated from plasma of 23 dogs, 9 dogs with epilepsy responsive to treatment, 6 dogs with drug-resistant epilepsy, and 8 control dogs. Plasma exosomes were characterised by electron transmission microscopy, nanoparticle tracking analysis, and dot blotting, showing in the latter a strong positive signal in exosome markers TSG101, FLOT1, ICAM, ALIX, CD81 and ANXA5. The RNA content of exosomes was isolated, and miRNA quantification was performed by quantitative real-time PCR. Seven circulating miRNAs previously described as potential diagnostic or prognostic biomarkers for epilepsy were evaluated. We observed a significant downregulation in miR-16, miR-93-5p, miR-142, miR-574, and miR-27 levels in dogs with refractory epilepsy compared to the control group. In drug-sensitive epileptic dogs, miR-142 levels were also significantly lower in comparison to healthy dogs. Moreover, a decreased expression of miR-16, miR-93-5p, and miR-574 and an upregulation of miR-132 were found in drug-sensitive epileptic dogs compared to the drug-resistant group. Our results present plasma-circulating exosomes as a useful source of epileptic biomarkers, highlighting the potential of miRNAs as prognostic and diagnostic biomarkers of canine idiopathic epilepsy.

#28
MITF promoter length polymorphism association with Irish spotting in Great Danes

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Poster session 1

Background: Irish spotting is a heritable phenotype in several breeds of dogs resulting from variable length polymorphisms in the promoter of microphthalmia-associated transcription factor (MITF). The length polymorphism results from the independent expansion of 3 homopolymer regions thus multiple alleles result in the same fragment length. Irish Spotting is characterized by white on the neck, chest, and underside/belly. Karlson et al 2007 reported that promoter lengths ≤ 32 bp are not associated with the Irish Spotting phenotype whereas promoter lengths ≥ 35 bp are.

Aim: Determine if the length polymorphism in the MITF promoter is correlated with the Irish spotting pattern in Great Danes.

Methods: A diagnostic assay was developed to determine the size of the MITF promoter expansion but cannot differentiate which homopolymer was expanded. 197 Great Dane dogs were photographed, scored for Irish spotting, and genotyped.

Results: 137/137 Great Danes dogs with the Irish spotting pattern type had 35/35 or 35/36 genotypes at the MITF promoter. No homozygous 36 individuals were identified despite representing 26% of the alleles in the cohort. The lack of homozygous 36 individuals is consistent in over 5,000 Great Danes tested at the VGL.

Conclusions: In Great Danes the 35 bp promoter fragment appears correlated with the Irish spotting phenotype and appears recessive when paired with an allele less than 35 bp. 35/36 Great Danes also demonstrate the Irish spotting pattern but 36/36 individuals were not observed. The 36 bp fragment may not be causal for Irish spotting in the Great Dane.

#29

Microflora-produced uremic toxins and their renal transporters gene expressions in cats with chronic kidney disease

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Poster session 2

Background: Chronic kidney disease (CKD) is characterized by gut dysbiosis and an accumulation of uremic toxins (UTs). Several organic anion transporters (OATs) play an important role in the urinary UT eliminations in humans and rodents. In cats, only indoxyl sulfate has been previously associated with CKD. No OATs have been reported in cats.

Aims: Quantification of circulating uremic toxins, renal tissue OATs gene expressions

Methods: Serum and urine samples from 2 cohorts of cats: Cohort 1 of 41 colony cats, including 28 control and 13 CKD stage 2; Cohort 2 of 30 privately-owned cats, equally split between 3 groups of control, CKD stage 2, and 3. Renal cortex (n=24) and medulla (n=21) from CKD and non-CKD cats euthanized for humane reasons unrelated to the study. OATs gene expressions were measured by RNA-seq and RT-qPCR and compared between control and across CKD groups.

Results: Serum concentrations of trimethylamine N-oxide, indoxyl sulfate, p-cresol sulfate, and phenyl sulfate were increased in stage 2 in cohort 1, and stages 2 and 3 in cohort 1+2 when compared to control (all $P<0.05$). Humans and cats share 90.9% and 78.9% protein sequence identities in OAT1 and OATP4C1, respectively. Gene expressions of OAT1 and OATP4C1 were downregulated by more than two-fold in both cortex and medulla from CKD cats (all $P<0.05$).

Conclusions: Changes in serum and urine uremic toxins in colony cats were independently validated in privately-owned cats. OATs are highly conserved across species and likely play a similar role in tubular UT excretions in cats.

#30
Comprehensive screening of 55 pharmacogenes in ~3200 dogs reveals significant burden of likely pathogenic variants

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Poster session 3

Genetic variations in pharmacogenes can significantly impact drug metabolism, efficacy, and toxicity, leading to variations in treatment outcomes. Accounting for genetic diversity in these genes across different breeds is vital for optimizing drug therapies and ensuring safety. There is limited information available. In this study, we aim to identify pathogenic variants in the protein-coding regions of known important pharmacogenes and study their diversity in a set of 2900 whole genomes and 300 whole exomes, including 375 breeds worldwide. We listed 69 very important pharmacogenes from PharmgKb and retrieved 55 canine orthologs using Ensembl biomart. We screened the protein-coding regions of those 55 PGx genes in ~3200 publicly available genomes for variants, which were groups based on the variant pathogenicity according to Sift.

In the preliminary analysis we found 6477 coding variants in these genes, of which 42% were protein changing / non-silent variants. Among these 92% were had minor allele frequency <= 0.01, depicting an abundance of rare variants in these genes, like in humans. Our data contains multiple samples with previously reported PGx variants such as MDR1 delta mutation, CYP1A2 poor metabolizer mutation and CYP2D15 variants relating to reduced enzyme activity. Our ongoing analyses also include 684 samples from 404 trios, enabling us to investigate the prevalence of de novo events. Our comprehensive pharmacogenomics screening reveals the likely pathogenic variant landscape of pharmacogenes across breeds. It lays a foundation for future studies to prioritize and target the most important pathways and drugs for better treatment and care of dogs.

#31
Characterization of canine oral melanoma and histiocytic sarcoma cell lines: resources for rare human cancers

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Flashtalk session 3

Mucosal melanomas (MM) are a subtype of human melanoma, primarily located in the oral, nasopharyngeal or ano-vaginal spheres. Although rare in humans, they are highly severe, with a 5-year survival rate of only 20-25%. Similarly, histiocytic sarcoma (HS) is an extremely rare tumour in human, but is very aggressive without any standard treatments. Dogs, with specific breed predispositions, naturally develop these cancers, sharing clinical, histological, genetic and therapeutic features remarkably similar to their human counterparts. Owing to the BRC Cani-DNA (https://igdr.univ-rennes.fr/en/crb-cani-dna), we developed 29 canine tumour cell lines (15 MM and 14 HS) derived from tumoral tissues to better characterize their biology and to provide the community with a useful resource for developing new treatments.

To genetically characterize these cell lines, we performed whole exome sequencing and low-pass sequencing to identify coding Single Nucleotide Variants and Structural Variations. For a subset of these cell lines, we also used our long-read sequencing IGDRion facility (https://igdr.univ-rennes.fr/en/igdrion) to quantify known and novel genes (both coding and long non-coding), thereby providing transcriptomic signatures of MM and HS at the levels of genes and alternative isoforms.

From a functional point of view, the sensitivity of these lines was assessed by IC50 tests with a dozen of molecules, as well as their tumorigenicity in immunodeficient mice. This approach enables the correlation of targeted therapies with somatic alterations.

Overall, we hope this new resource will help for the development of specific therapies for these rare but aggressive cancers, with mutual benefits for veterinary and human medicine.

#32
Revisiting a cold case of dwarfism in Dalmatians

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Poster session 2

Skeletal dysplasias represent a heterogeneous group of inherited diseases causing abnormalities in cartilage and bone, and resulting in varying degrees of short stature and dwarfism. In humans, 771 different types of skeletal dysplasias, associated with 552 genes, have been identified to date. Several dog breeds suffer from different types of these disorders. To our knowledge, the first cases of Dalmatians with autosomal recessive skeletal dysplasia were observed in the early 80's in Sweden, and several affected litters were born during the 80's and 90's. By the time, the phenotype was carefully investigated using radiological and histopathological examinations. Now, 30 years later, we have revisited the investigations and sequenced the genomes of samples collected in 1992. We identified a strong candidate variant leading to a premature stop codon in the gene protein kinase cGMP-dependent 2 (PRKG2). The variant is predicted to trigger nonsense-mediated mRNA decay, a cellular process removing too short gene products and preventing the production of truncated protein products. Mutations in the PRKG2 gene cause a corresponding human disease, acromesomelic dysplasia, affecting the growth of the lower arms and legs of young children. Moreover, a PRKG2 splice-site mutation has previously been reported in Dogo Argentino with disproportionate dwarfism. Recently, there has been new reports of chondrodysplasia in Dalmatians and we have now screened over 250 Dalmatians, including three affected dogs. All three affected and none of the unaffected individuals were homozygous for the nonsense variant, suggesting that this cold case of dwarfism in Dalmatians has now been solved.

#33
The genetics of class 2 malocclusion in husky dogs

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Poster session 3

A class II malocclusion or overbite often leads to damage to the upper palate due to misalignment of the canines, causing discomfort in affected dogs. There has been an increasing incidence of overbites reported in certain breeding lines of Siberian huskies and related sled dog breeds. The affected dogs appear to exhibit a combination of an elongated maxilla and a shorter mandible. Based on phenotypic similarities, we hypothesize that these dog populations share the hereditary background predisposing them to class II malocclusion. The aim of this study was to use pedigree data to deduce the most likely mode of inheritance of this condition and to identify genetic locations associated with class II malocclusion through DNA profiling with the Illumina Canine HD SNP Array. The pedigree data indicated a possible autosomal recessive inheritance pattern. However, the SNP data of 11 cases and 161 controls did not confirm a simple mode of inheritance. A population structure analysis of 172 dogs showed a high level of stratification, which confounds a genome wide association study at this point. We are expanding the study cohort at a global level to enable reliable identification of risk loci.

#34

Small RNA-sequencing profiling of serum samples from dogs with canine idiopathic epilepsy

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Poster session 1

Epilepsy is the most common chronic neurological disease in dogs, being idiopathic epilepsy (IE) the most prevalent form. The cause of IE remains unknown. The difficulty of an early diagnosis coupled with the resistance of some animals to anti-seizure drugs, makes necessary the development of more accurate and faster diagnostic methods. In this regard, the identification of readily accessible biomarkers, such as circulating small non-coding RNAs, would help to improve IE diagnosis and prognosis. In the present study, a small-RNA sequencing analysis of serum samples from 33 dogs (12 healthy control dogs, 12 dogs with IE sensitive-to-treatment and 11 dogs with IE refractory-to-treatment) was performed. Among the different types of small non-coding RNA identified, the two more abundant types in serum samples were microRNAs (miRNAs) and transfer RNAs (tRNAs). No differential expressed miRNAs were found between the different groups, but an overall increase in tRNAs was observed in epileptic dogs compared to controls. More studies will be conducted in order to identify the exact tRNAs increased in the epileptic group, and to validate their possible use as IE biomarkers.

#35
Epidemiological study reveals disease-breed association in domestic cats

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Poster session 2

During the process of animal domestication and breeding, genetic diseases have accumulated, often exhibiting heritability and breed associations. Investigating the causal genes and mutations contributing to these genetic diseases necessitates the establishment of a model based on disease-breed association, typically examined through Genome-Wide Association Studies (GWAS). In this study, we analyzed medical record data collected for seven years (2015 to 2022) provided by the Veterinary Medical Center, University of Tokyo (UT-VMC). After meticulous data wrangling and converting Japanese records into English using disease glossary, Fisher's exact test was implemented to identify potential disease-breed association. Our findings reveal several disease-breed pairs with strong positive association, which are likely to be caused by a single major factor. Rank tests were also applied to subtables to focus on groups of related diseases and detect the disease-disease association. The results demonstrate high association between certain diseases, which indicates similar etiopathogenesis within the group of diseases. These findings enhance our comprehension of disease prevalence in domestic cats and inform the establishment of disease models. Notably, Bengal cat, a recent breed rising in popularity based on distant hybridization between Leopard cat (Prionailurus bengalensis) and American domestic cats mainly, exhibits intriguing disease susceptibilities: remarkable disease resistance to renal problems alongside vulnerability to hypertrophic cardiomyopathy (HCM) and related diseases. This unique disease profile suggests Bengal cat as a valuable model for comparative genomics to study complex diseases in parallel with traditional methods.

#36

The curly tail of ancient dogs; the polygenic adaptation evidence in the domestication history

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Poster session 3

The domestic dog, a descendant of wolves, has been a human's close ally for about 15,000 years. While we don't know exactly when or where they were first domesticated, they likely came from a now-extinct wolf species and were tamed in several places worldwide. Dogs stand out from their wild relatives with unique physical traits, like their tail and ear shapes, and their friendly behavior. To understand how dogs evolved from wolves, we studied genetic changes that might explain these differences. First, we obtained published dog genomic data, including 53 wild canines, and used genomic principal component analysis (PCA) and ADMIXTURE analysis to identify genetically basal dog breeds. For the precise population structure inference, Patterson's f4 statistics and qpgraph are used. Then we aimed to identify traits selected during the dog domestication process by detecting positively selected variants and phenotypes between wild canines and the basal group. For this purpose, we conducted a genome-wide association study (GWAS) for behavioral and physical phenotypes obtained from the authorized database. To detect positive selection on polygenic phenotypes, we also tested the systematic difference of phenotype-associated SNPs between wild canines and the basal group. Furthermore, we conducted several tests for detecting not only the genetic drift but also selection signals. Our study resulted in detecting polygenic evidence of the domestication history of dogs.

#37

Detection of structural variants in PacBio long read sequences from a family of Bearded Collies.

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Poster session 1

We previously reported on a Bearded Collie family with a suspected new familial cancer syndrome. Roughly 50% of the offspring of the founder female were affected with a highly infiltrative diffuse astrocytoma of gliomatosis cerebri growth pattern (GCGP). We hypothesize that the cancer syndrome is caused by a de novo mutation that happened in the founder female or the germline of one of its parents. So far, short read sequencing data has not revealed a plausible candidate causal variant. We therefore obtained PacBio Revio long-read sequencing data at 8x – 25x coverage from 5 family members, comprising the healthy parents of the founder female, a healthy and an affected offspring of the founder female, and the healthy sire of the offspring. We searched for structural variants and potentially newly arise structural variants in the family using both alignment and graph based methods. For alignment based methods, we compared 3 different aligners minimap2, nglmr and winnowmap. In addition, three different callers Sniffles2, cuteSV3 and vulcan were used to identify structural variants. The software svim-asm that includes an initial assembly followed by an alignment to a reference was also used to call structural variants. For graph based methods, we used hifiasm assembled genomes to build a pan-genome graph and call structural variants. Of these 98,164 and 66,146 structural variants were called by read and assembly based methods. A total of 74,334 variants were called by graph based methods. We will present the advantages and disadvantages of each of these detection strategies.

#38
Novel candidate genes for retinal degeneration in dogs and humans

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Flashtalk session 2

The unique evolutionary history of the domestic dog has enriched many disease-causing variants into specific breeds, making them excellent models to study inherited diseases, such as progressive retinal atrophy (PRA), resembling human retinitis pigmentosa. We studied two breeds, Finnish Lapphund (FL) and Karelian Bear Dog (KBD), both affected by PRA with unknown genetic causes.

To unravel the genetic cause of previously unexplained FL and KBD PRA cases, we established clinical study cohorts of 26 and 44 eye-examined dogs, respectively. Eight FLs and 13 KBDs had been diagnosed with PRA before 2 and 5 years of age, respectively, and the rest were unaffected controls.

Genome wide association studies mapped a recessive locus in CFA27 in FLs and CFA30 in KBDs. Whole genome sequencing of selected FL cases and controls revealed a 21 kb deletion in the ETNK1 gene, overlapping exon 2. The variant was confirmed in additional 348 FLs. In the KBDs, whole-genome sequencing revealed a case-specific frame-shift deletion in the exon 4 of the NR2E3 gene, most likely leading to nonsense-mediated decay. Variant screening in additional 715 KBDs confirmed autosomal recessive inheritance with a carrier frequency of 18%. To date ETNK1 variants have not been associated with retinal degeneration in any species, while NR2E3-related retinal disease in humans is well-documented, although to our knowledge this is the first time it is being reported in dogs.

This study describes two new spontaneous dog models to study retinal biology and pathology and establishes ETNK1 as a novel candidate gene for retinal degeneration.

#39

Insights into the Leonberger genome derived from massive whole-genome sequencing data

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Poster session 3

Leonbergers, a giant dog breed originating in Germany in the 1850s, have shown an increased prevalence of certain health conditions, e.g. neurodegenerative disorders, hypothyroidism, hemangiosarcoma, osteosarcoma, cardiac, and eye diseases. To shed light on the genetic basis of these complex traits, we conducted whole-genome sequencing (WGS) on a representative cohort of 90 Leonbergers. This included 47 Leonbergers diagnosed with polyneuropathy and/or laryngeal paralysis (LPN), of which only 7 were affected by previously described LPN variants.

Short-read WGS data aligned to the UU_Cfam_GSD_1.0 reference assembly was explored for variants (including SNPs, indels, and structural variants) enriched in Leonbergers in comparison to 1413 genomes of 255 different dog breeds from the DBVDC dataset. We prioritized protein-changing variants with estimated high or moderate impact to identify new alleles involved in developing LPN. Additionally, variant allele frequencies in a panel of 2365 developmental disorder and 410 lethal genes were investigated to identify heterozygous carriers of lethal mutations.

Our analysis of this large single-breed cohort resulted in a comprehensive variant catalog, encompassing both common and rare alleles within the Leonberger population. In so doing, we uncovered plausible novel candidate variants potentially associated with LPN, hypothyroidism, eye disease, cryptorchidism, or renal dysplasia. These results provide valuable insights into the basis of the breed's apparent predisposition to inherited diseases and will facilitate the discovery of yet unreported phenotypic traits. The list of likely disease-associated variants provides a foundation for future studies aimed at the development of genotyping strategies to improve the overall health and well-being of Leonbergers.

#41

Inbreeding genomics and inbreeding depression in the Finnish gray wolf

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Poster session 2

Inbreeding is a common problem in small and closed populations. It can cause lowered fitness by increasing the homozygosity of harmful alleles, i.e., by unmasking mutational load. The Finnish wolf population went through a severe population bottleneck in the 19th century, and the population size started to increase in the 1990s. In the 21st century, the population size has fluctuated between 150 and 300 individuals. However, the number of breeding individuals is considerably lower, and dispersal from the neighbouring Russian population seems relatively low. Here, we first use genome data from Finnish wolves to study the realized inbreeding levels between 1994–2016 and the timing of past inbreeding events, and then use this inbreeding information to examine whether there is inbreeding depression in the probability of acquiring an alpha status or being infected by *Trichinella* or *Echinococcus* parasites.

We estimated genomic inbreeding using runs of homozygosity (FROH) and realized genetic load by estimating the proportion of homozygous deleterious loci of all loci. We found that genomic inbreeding has mildly increased over time, but the mean level of inbreeding is still low. A few individuals showed clear evidence of recent inbreeding based on the length of homozygous-by-descent segments. Our preliminary results suggest that the fitness of inbred individuals may be reduced, as we found some evidence that more inbred individuals are less likely to become breeding alpha individuals than less inbred individuals. However, we did not find strong evidence of inbreeding depression in parasite prevalence or abundance.

#42
The Evolutionary Genomics of Wildcats in Northwest China and their Admixture with Local Domestic Cats

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Flashtalk session 3

The wildcat (Felis silvestris) comprises a group of small felids in Eurasia and Africa, including two taxa living in Northwest China, or the Asiatic wildcat (F. s. ornata) and the Chinese Mountain cat (F. s. bieti). Other nonmenclature systems propose the Asiatic wildcat as a subspecies of F. lybica while maintain independent species status in the Chinese Mountain cat. In addition, the absence of reproductive barrier and the presence of large number of free-ranging domestic cats also raise the prospect of disrupted genomic integrity in the co-existing wildcats, an issue with profound conservation implications. To resolve the taxonomic controversy in these endangered wildcat taxa and to reveal the status of genomic admixture between wildcat and domestic cats, we assemble whole genome sequencing data covering all F. silvestris lineages for phylogenomic analysis and generate population genomic data from Asiatic wildcats (~20), Chinese Mountain cats (~50) and uncertain wildcats with suspected admixed origin (~10) in northwest China as well as sympatric local domestic cats (>100). The study provides an initial assessment of the genetic background, hybridization, and evolutionary history among the wildcat lineages in the ancient Silk Road region of Northwest China and promises to set the scientific foundation needed for Felidae conservation in the region.

#43

Polymyositis in Kooiker dogs is associated with a 39 kb deletion upstream the IL21/IL2 genes

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Flashtalk session 1

An inflammatory myopathy with characteristics of polymyositis is prevalent in the 'Nederlandse Kooikerhondje' dog breed. A genome wide association study of 33 cases and 106 controls indicated the involvement of a region on chromosome 19 containing the cytokine gene pair IL21 and IL2 (praw = 2.1*10-14). Next generation DNA sequencing revealed that 8 cases shared a 39 kb deletion, situated 10 kb upstream of IL21. Of the 102 cases with available DNA, 66 were homozygous, 34 were heterozygous and only 2 cases were clear of the deletion. The frequency of the deletion allele in a random sample of the Kooiker dog breed was 0.25. Postulating causality, the penetrance of the disease phenotype was estimated at 5-15% for homozygous dogs and 0.5-2% for dogs that are heterozygous for the deletion. Leukocytes of affected, untreated dogs that were homozygous for the deletion overexpress IL21 and IL2 after stimulation with mitogens. We suggest that elements located 10 – 49 kb upstream of the IL21/IL2 gene pair play an important role in the regulation of the canine genes and that deletion of these elements is a risk factor for inflammatory myopathy in Kooiker dogs. Our results imply that distant variants upstream of IL21 could also be important for human autoimmune diseases that were found to be associated with the IL21/IL2 chromosome region.

#44

Gene variants identified and associated with polycystic kidney disease in Siberian and Neva Masquerade cats

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Flashtalk session 2

Polycystic kidney disease (PKD) is a progressive disease associated with renal cysts that destroy renal integrity and function. Recently cases of PKD have been observed in the Siberian (SIB) and Neva Masquerade (NEM) breeds that do not appear to be caused by the previously described gene variant in Persian cats. The aim of this study was to evaluate the presence of renal cysts in the SIB/NEM breeds in Sweden, and to identify potential genetic variants associated with the cysts. Ultrasound examinations of 1072 unique cats were evaluated and 50 cats with PKD were identified. Pedigree investigation indicated that the disease was inherited in a dominant form. Blood samples from two females (an 8-year-old NEM and a 15-year-old SIB) with PKD and similar pedigree background were chosen for whole genome long-read sequencing. Evaluation of the mapped reads identified variants of interest in PKD1, PKD2 and PKHD1, of which four variants were subsequently screened for in a larger cohort of 75 cats, including 16 with confirmed PKD. The variants in PKD1 and PKD2 account for the penetrance of the disease, but it cannot be ruled out that one variant in PKHD1 influence age of onset and progression rate. None of the identified variants have previously been described in cats. In conclusion, two dominant forms and one potential recessive gene variant were identified and associated with PKD in a Swedish population of SIB/NEM and should likely be accounted for in breeding decisions among the feline breeders.

#45

Canine Obesity: Owner Management Effort and Outcome Differ According to genetically determined Food Motivation

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Poster session 3

Canine obesity is commonly dismissed as the consequence of lax diet and exercise management, and the influence of genetics is frequently overlooked.

We determined Obesity/Overweight Probability (OP) according to breed from the health records of 1.1 million purebred dogs, and information on eating behaviour and owner management of diet and exercise of >14,000 dogs, using a previously validated questionnaire. Breed average Food Motivation Score (FMS) was calculated, accounting for differences in the breed distributions of sex, neuter status and age.

There was a strong positive correlation between the breed OP and breed average FMS ($r=0.71$, $p=4.48\times10^{-8}$) with over half the variability in breed OP explained by differences in breed average FMS ($R2=0.5053$, $p=4.48\times10^{-8}$). In individual level data, FMS had the greatest significant positive effect on Body Condition Score (BCS), compared to conventional risk factors, with differences of up to 15% of adiposity ($BCS=1.64/9$, $p<2\times10^{-16}$) attributable to this factor alone.

The population was then stratified on FMS tertiles, using food motivation as a surrogate for genetic risk for obesity based on the breed-average results. This showed the effect of biological (age, sex, neutering) and environmental factors (exercise, food availability) differed according to underlying risk, with higher-risk dogs being particularly influenced by both groups of risk factors.

These data shed light on how genetically determined eating behaviours are a powerful driver of weight gain in pet dogs and are highly heritable. Control of environmental access to food and activity are of particular importance in high-risk individuals.

#46
Integrated landscape of renal metabolism in cats with chronic kidney disease

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Poster session 1

Background: The kidney is a highly metabolic organ rich in mitochondria, and its ability to produce ATP is compromised by chronic kidney disease (CKD). As a result, the kidneys adapt to alternative energy substrates, and increase their size and oxygen consumptions, which contributes to excess ROS and hypoxia.

Aim: Characterization and integration of multi-omics data

Methods: Serum samples from 2 cohorts of cats: cohort 1 included 31 CKD and 25 control cats from colony; cohort 2 included 30 privately-owned cats equally split between 3 groups, control, stages 2 and 3. Renal cortex (n=24) and medulla (n=21) tissues from CKD and non-CKD cats euthanized for humane reasons unrelated to the study.

Serum samples underwent untargeted metabolomics, while renal tissues were analyzed with RNA-seq transcriptomics, PCR and proteomics to compare between control and CKD groups.

Results: Serum concentrations of 250 and 114 metabolites were different between groups in cohorts 1 and 2 (FDR<0.05, FC>1.5), respectively, of which 76 were common. 1072 and 1016 differentially expressed genes (FDR<0.05, FC>2), and 146 and 363 differentially expressed proteins (FDR<0.15, FC>1.5), were identified from medulla and cortex, respectively. Despite plasma elevations in free fatty acids, acylcarnitines and Krebs Cycle intermediates, renal tissue's NAD+ biosynthesis and capacities to oxidize key energy substrates were reduced in CKD. The homocysteine degradation pathway to replenish cysteine pool and glutathione biosynthesis were also downregulated. Additionally, markers for inflammation and fibrosis were upregulated, but downregulated for tryptophan-kynurenine pathway by CKD.

Conclusions: Our findings unveil profound metabolic reprogramming and abnormalities in feline CKD.

#47

Comparison of kooikerhondje pedigrees and maternal and paternal haplotypes

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[1]Independent research

Poster session 2

The Kooikerhondje is a relatively small and new breed. The first Kooikerhondjes were registered in the 1940s in the Netherlands, and all registered Kooikerhondjes can be found in the same database. Therefore, it is possible to construct pedigrees for every recent dog back to the founders of the breed.

Modern DNA testing offers the opportunity to investigate the reliability of pedigrees of registered purebred dogs. This has been explored by gathering information on maternal and paternal haplotypes from 114 Kooikerhondjes available in the freely accessible Embark data on the Internet. These pieces of information have been compared to the pedigree data of the same dogs.

The haplotypes of the dogs were mainly consistent with the information in the pedigrees. However, the haplotypes of the 11 dogs did not match the pedigree. More investigation is needed to determine whether these discrepancies originate from issues related to sampling, errors in sample analysis, or problems in breeding practices or dog registration.

It should be noted that data from all dogs are based on their Embark profile (pedigree name and registration number if provided). This does not guarantee that the sample used for the Embark results was definitely from the dog described in the profile. It would be interesting to compare if similar results are obtained from samples taken by veterinarians as well. However, 10% incorrect information is quite a lot. Does this affect the use of pedigrees in scientific research and breeding?

#48
Low-pass whole-genome mapping reveals genetic loci associated with ONH in miniature poodle

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Poster session 3

Optic nerve hypoplasia (ONH) is a congenital defect characterized by the abnormal or development of the optic nerve. About 0.8% of poodles, particularly miniature varieties are affected with ONH, with a suspected genetic background. We analyzed through GWAS 52 canine low-pass whole-genome sequences (WGS) including 22 cases and 30 controls. All dogs involved in the study were clinically ascertained by veterinary ophthalmologists. After quality control, a total of 6,691,505 SNPs were retained for analyses. We used haplotype-based GWAS using population-based case-control studies. GWAS was performed using a mixed linear model with PCA as a fixed variate and kinship as random and implemented in GEMMA (v.0.98.5).Our haplotype based GWAS revealed that ONH is a complex trait, and that multiple loci are likely to be important. Three chromosomes, CFA4, CFA22 and CFA25 were identified to harbor putative risk loci for ONH. At these loci, the load of risk haplotypes was significantly different between cases and controls. For instance, at CFA22, 9 cases share homozygous haplotypes, in contrast to only 1 control exhibiting homozygous haplotype. While cases have a higher frequency of candidate homozygous haplotypes than controls, the complex nature of the trait and imperfect segregation make us suspect that multiple factors must coincide for ONH development in miniature poodles. Our study shows that ONH is a polygenic disease to which many loci and genetic factors contribute. Refinement of the risk loci with whole-genome sequencing data will help identify causal variants and genes contributing to ONH.

#49

Population and health analysis in the worldwide population of the Dutch Kooikerdog

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Poster session 1

The Dutch Kooikerdog is a breed with a small population size for which thorough pedigree and clinical data were kept for dogs born between 1942 and 2023.

The aim of this study was to investigate the effects of selection against hereditary diseases on the population dynamics, including disease incidence, allelic frequencies, genotypic variation and inbreeding in the breed.

All data generated from this study will be used in future selection procedures and breeding advice to improve the breed's genetic health, and to identify potential threats to the purebred dog population.

The records of 37,851 dogs were analyzed. The breed showed an average coefficient of inbreeding of 33% (sd = 4), and an average longevity of 10 years, with the most common causes of death being old age and cancer. Allelic frequencies and incidence of diseases that were selected against, has progressively decreased in the breed.

This selection did not lead to an increased coefficient of inbreeding, nevertheless effective population size should continuously be taken into account in responsible selection strategies.

#50
Development of a computational pipeline to estimate SNP-based heritability

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Poster session 2

Genomic heritability estimates the proportion of phenotypic variance that can be explained by genetics. Estimating heritability informs breeders on the potential impact of selective breeding and provides researchers with insights into the genetic architecture of a trait. This knowledge aids downstream analyses like genome-wide association studies. Several computational tools estimate heritability, however, there is no streamlined pipeline that takes phenotypic data, genomic data, and covariates to produce a single, accessible report of heritability estimates across multiple programs.

We built a computational pipeline using snakemake that: filters a VCF for single-nucleotide polymorphisms (SNPs), performs quality control using PLINK, creates genomic relationship matrices (GRMs), and estimates heritability using restricted maximum likelihood as implemented in Genome-wide Complex Trait Analysis (GCTA). Currently, the pipeline creates two GRMs, an additive GRM that is the GCTA default and a weighted additive GRM that considers linkage disequilibrium (LD) weighted relatedness using Linkage Disequilibrium Adjusted Kinships (LDAK), and returns two estimates of heritability per phenotype (with and without LD weighting). We have tested the pipeline using several subsets of a cohort of 1,210 assistance dogs with >50 behavioral phenotypes and low-pass whole-genome sequencing of ~18 million genetic markers.

We are currently focused on adding additional GRM types calculated in the snpReady package in R, including dominance relatedness and non-linear relatedness. In addition, we are creating a step that selects the optimal GRM using deviance information criteria (DIC) for the genomic data that will then return a heritability estimate that utilizes the best GRM.

#51
Immune Mediated Polymyositis In The Dutch Kooiker Dog

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Poster session 3

Within the Dutch Kooiker dog (het Nederlandse Kooikerhondje), one of nine Dutch dog breeds, we have described earlier, an inflammatory myopathy that presents itself with clinical signs of primarily dysphagia, locomotion problems, or a combination of both. The first cases emerged in 1972 and up to now over 170 affected Kooiker dogs, originating from various countries, have been identified. The outcome of this disease was in most cases fatal as affected dogs died withing 2 years after diagnosis. We further investigated and characterized the histopathological changes in muscle tissue and immunophenotyped the inflammatory infiltrates. FFPE-fixed muscle biopsies from 39 Kooiker dogs were included and evaluated histopathologically according to a tailored classification scheme for skeletal muscle inflammation. Immunophenotyping revealed primarily lymphohistiocytic infiltrates, with CD3+ T-cells being the predominant inflammatory cell type, accompanied by CD8+ cytotoxic T-cells. The concurrent expression of MHC-II class molecules on myofibers suggests their involvement in initiating and maintaining inflammation. Additionally, CD20+ B-cells were identified, though in lower numbers compared to T-cells, and IBA-1 positive macrophages were frequently seen. These findings suggest a breed-specific subtype of polymyositis in Kooiker dogs, akin to other breeds. The study sheds light on the immune response activation, combining adaptive and innate mechanisms, contributing to our understanding of polymyositis in this breed.

#52
Mt-ND5 DNA variability in wildcats living in Central Italy Protected Areas

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Poster session 1

The European wildcat (Felis silvestris silvestris, Schreber 1777) is a medium-sized felid distributed heterogeneously throughout Europe: from the Iberian Peninsula to the Caucasus and up in north in Scotland. Despite the generally stable trend of the population, it is included in the "strictly protected" species in Europe. In Italy, the reserved behavior of this felid together with its small distribution, particularly in the central regions of the peninsula, has prevented the collecting of data, hence little is known about its demographic situation and genetic status. This study provides a preliminary view of the genetic variability of the European wild cat, based on 21 tissue samples of dead subjects neighboring or inside Central Italy Protected Areas. These individuals were phenotypically classified as wildcats by experts (park guards and/or veterinarians) and the DNA of their samples was extracted. Preliminary analyses on mitochondrial NADH subunit 5 (MT-ND5) by sanger sequencing have been conducted. A total of four haplotypes have been identified having: 71% a DW1 (Domestic Wildcat hybrid) haplotype, 14% a DW4 haplotype, 10% a W (Wildcat) haplotype and 5% (one individual) a D3 (Domestic) haplotype. Overall, the Haplotype diversity (HD) was 0.48095 with a Nucleotide diversity (π) = 0.00318 (computed using DNASP version 6.12.03). Furthermore, a meta-analysis has been conducted by comparing these results with those reported by other authors in these Italian regions. The results align, to some extent, with the reported introgression of domestic cat genes into European wildcat populations, which is occurring along with habitat loss and fragmentation.

#53

Transcriptomic characterisation of hypertrophic cardiomyopathy in British Shorthair (BSH), Birman and Domestic Shorthair (DSH) cats

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Poster session 2

Hypertrophic cardiomyopathy (HCM) is the most common heritable heart disease in cats affecting ~15% of cats. Feline HCM is characterised by primary left-ventricular myocardial hypertrophy and is associated with increased risk of congestive heart failure, aortic thromboembolism and sudden cardiac death. The prevalence of HCM and lack of treatments to modify the disease process demonstrates the importance of studies aiming to understand the genetics and underlying mechanisms of HCM susceptibility. To date there are limited feline HCM genomic studies and only 5 HCM-associated variants. Moreover, the transcriptomic signature of feline HCM remains largely unknown.

This study used RNA-sequencing and perform differential expression and enrichment analysis to identify the transcriptomic profile of HCM in BSH, Birman and DSH cats and provided the first examination of the HCM transcriptome in BSH and Birman cats. Identified DEGs were interrogated based on known HCM/cardiomyopathy-associations, function and roles in potentially relevant pathways and networks. Additionally, GWAS were performed to identify genomic markers associated with HCM-susceptibility.

DEGs were identified within and across breeds. Overrepresentation analysis indicated enrichment for genes with roles in cell signalling and organisation, ion transport and binding, IGF and EGF-related terms and some immune/inflammation related terms. Networks and pathways analysis highlighted fibrosis, cell growth and proliferation, inflammatory and immune response-related and other cell signalling and organisational pathways. GWAS results suggest HCM behaves as a complex, polygenic disease.

Further investigation is required to validate candidate genes and pathways. These candidates could lead to development of novel diagnostic tests and drug-treatment targets.

#54
Heritability of impactful assistance dog behaviors for children with autism informed by family needs

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Poster session 3

Autism Assistance Dogs (AADs) are trained to aid individuals with Autism Spectrum Disorder (ASD) by preventing elopement, interrupting repetitive behaviors, and applying deep pressure. Their support also alleviates stress for family members through enhanced safety and improved socio-emotional wellbeing. While selective breeding has improved the consistency of assistance dog (AD) behavior, the underlying genetic architecture and genomic heritability of behaviors associated with AD failure are unknown. To determine which dog behaviors are most impactful, we surveyed 637 families with ASD children and found dog insecurity (r2: -0.41, $p < 0.001$), resource guarding (r2: -0.29, $p < 0.001$), and dog-directed fear/aggression (r2: -0.39, $p < 0.001$) had the strongest negative associations with measures of child-dog attachment. Aspects of these family-reported measures are routinely captured via trainer-completed behavioral assessments at Canine Companions, the largest AD organization in the US. Heritability (SNPh2) of these behaviors was estimated using restricted maximum likelihood implemented in LDAK and GCTA with a linkage disequilibrium-weighted relationship matrix using ~10 million genetic markers in 297 ADs from Canine Companions (98 AADs, 99 other ADs, and 100 behavioral releases). The behaviors with the highest SNPh2 were excitability (0.45, se = 0.21, $p = 0.007$), responsiveness (0.37, se = 0.17, $p < 0.001$), response to physical exam (0.28, se = 0.17, $p = 0.005$), and activated with stress (0.27, se = 0.18, $p = 0.02$). Ongoing work includes collection of additional AADs to build a genomic predictive model for early detection of likely failures to improve AAD success rates.

#56
PAX3 haploinsufficiency in Maine Coon cats with dominant blue eyes and hearing loss

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Flashtalk session 2

This study investigates the dominant blue eyes (DBE) trait linked to hearing impairment in variable white-spotted Maine Coon cats. Fifty-six animals descending from two different DBE lineages: Dutch line and Topaz, were sampled. They comprised 47 cats from the Dutch bloodline, including 9 green-eyed and 30 blue-eyed cats, with some individuals exhibiting symptoms of deafness, and eight stillborn kittens. Samples from the Topaz linage included nine related blue-eyed animals. A brainstem auditory evoked potential test (BAER) revealed a reduced to absent response to auditory stimuli and absent physiological waveforms in the DBE animals. We sequenced the genome of two affected cats and searched for variants in eight candidate genes for auditory-pigmentary disorders: PAX3, MITF, SOX10, KITLG, EDN3, EDNRB, KIT, and SNAI2. This search yielded three private protein-changing candidate variants in the genes EDN3, KIT and PAX3. The genotype-phenotype co-segregation was exclusively observed for the PAX3 variant within animals from the Dutch lineage. This mutant allele was absent from 461 control genomes and 241 additionally genotyped green-eyed Maine Coons. We considered the PAX3 variant as the most plausible candidate – a heterozygous nonsense 1 bp substitution in the sixth exon of PAX3 (NC_051841.1: g.205,787,310G>A, XM_019838731.3:c.937C>T, XP_019694290.1:p.Gln313*), predicted to result in a premature stop codon. PAX3 variants were previously reported to cause auditory-pigmentary syndrome in humans, horses, and mice. Together with the comparative data from other species, our findings strongly suggest PAX3:c.937C>T as the most likely candidate variant for the observed phenotype in a subset of the DBE Maine Coon cat population.

#57

Deciphering the function of a non-coding variant associated with a canine sensory neuropathy

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Poster session 3

Canine acral mutilation syndrome is a neurological disease severely impacting the quality of life and has been documented for decades as part of inherited sensory neuropathy in various breeds. The affected dogs show loss of pain sensation in the distal extremities, which leads to intense licking, biting, and self-mutilation of digits. We have already identified a mutation shared by four hunting dog breeds, and located ~ 90 kb upstream of the Glial cell-line Derived Neurotrophic Factor gene (GDNF), in an intergenic region with genetic marks corresponding to a regulatory region. GDNF is a neurotrophic factor essential for the development and maintenance of sensory neurons. Our goal is now to explore how this mutation impacts the regulation of GDNF expression using different functional approaches such as EMSA, reporter assay, Western blot and cell cultures. Our first results indicate that this mutated region could be an enhancer that impacts GDNF expression, as well as two long non-coding RNAs in its neighborhood. In addition, we observe that the "affected" allele seems to disrupt the binding of a protein complex that could contain transcription factors. Since GDNF is implicated in human neurological diseases such as Parkinson's disease (but not yet associated to sensory neuropathies), our findings will provide new knowledge about this gene and its regulatory mechanisms. Thus, this work highlights potential candidate regions to screen in human patients.

#58
Evaluation of candidate genes for cryptorchidism in Australian racing greyhounds

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Poster session 1

The Australian racing greyhound has a high prevalence of cryptorchidism (failure of testes to descend to the scrotum). In this study, candidate genes that are associated with the development of the gubernaculum and/or have a functional role in testicular migration were selected. These genes were evaluated using Illumina whole genome sequences from four Australian racing greyhounds (2 affected bilateral cryptorchid males, 1 normal male and 1 female) and 106 dogs of various other breeds. Candidates included: Androgen receptor (AR), Collagen type II α 1 (COL2A1), Estrogen receptor 1 (ESR1), High mobility group AT-hook 2 (HMGA2), Insulin-like 3 (INSL3), MID1 interacting protein 1 (MID1IP1), Oxytocin receptor (OXTR), and Relaxin/insulin-like family peptide receptor 2 (RXFP2). Variants in candidate regions (gene +/- 1Mb) were extracted from a multiple individual variant call file (N=110 dogs) using Tabix and an across breed association was performed in Plink. 213 statistically significant variants were identified. The 100 top associated variants from candidate regions were taken forward. Three candidate genes demonstrated greyhound-enriched associations among the top 100 associations that were consistent with possible Mendelian inheritance of the disorder: RXFP2, COL2A1 and ESR1. Using the variant annotation integrator tool, predicted functional consequence of the greyhound-enriched variants from these genes was assessed. Potential LINE/SINE insertions were also explored.

#59
Herd protection dog behavior is mainly influenced by environmental factors

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Poster session 2

The number of wolf packs roaming Swiss alpine regions has increased during the last ten years. This represents a problem for sheep-keeping in high-altitude alps during the summer. Sheep are an easy prey for wolves and attacks often result in numerous dead or severely injured animals. The best protection against predators would be a high electric fence. However, installing and maintaining fences is costly and may not be compatible with all types of alps.

As an alternative the Swiss government supports and supervises the breeding of herd protection dogs which stay with the sheep around the clock and should fend off predators. The requirements for this complex behavior of herd protection dogs are challenging. They must fend off predators aggressively, but the aggression cannot be acted out towards mountain walkers and/or their companion animals.

Before a dog can be used as a herd protection dog, he must pass an exam. For this, the dog is placed with a small herd of sheep on an alp and the movements of the herd, and the dog are monitored by transponders.

We used a general linear model to identify factors which influence the outcome of exams. Sex, breed, parents, examinator, breeder, and instructor were independent variables. The only significant factors identified were breeder and instructor indicating that the behavior is rather influenced by environmental factors than by genetics. As a conclusion, more emphasis on the quality of rearing/education may increase the number of dogs showing the required behavior.

#60
Stability of canine retrogenes by an extensive pedigree analysis

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Poster session 3

Dog genome contains a high frequency of structural variation (SV), such as retrogenes and mobile elements. Retrogenes are processed copies of other genes. This duplication mechanism produces an intronless copy of the parental gene randomly in the genome. This action may make additional functional copies of existing genes with phenotypic consequences. Examples of canine retrogenes include the fibroblast growth factor 4 (FGF4) retrogenes in chromosomes 18 and 12, resulting in shorter limbs and elevated risk of intervertebral disc disease.

A recent study of ~2000 dog genomes discovered retrogene insertions from 926 parent genes. Our primary goal is to utilize our extensive pedigree cohort of 429 trios (n=698 dogs across 45 breeds) to understand the stability of the retrogenes and other structural variants. We have used Delly, TEBreak, and Manta to call retrogenes and compare the results with different tools. We have found 821 parent genes within our samples, of which 605 are the same discovered in a recent study. Our examples include the known FGF4 retrogenes.

A preliminary trio analysis in a subset of the identified retrogenes indicates that approximately 80% are inherited from parent to offspring, suggesting that the majority of them are stable. Ongoing analyses will combine results of different tools in our massive pedigree dataset and is expected to reveal new retrogenes with possible clinical significance and provide new insights into the genome biology of retrogenes and other structural variants in the dog genome.

#61
A Chromosome-Scale Assembly of a Domestic Cat Felis catus of American Shorthair Breed

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Flashtalk session 1

Our study introduces Anicom American Shorthair 1.0 (AnAms1.0), a novel high-quality cat genome assembly derived from the American Shorthair breed. AnAms1.0 offers an enhanced representation of the general cat population, facilitating precise identification of genetic variations. Combining multiple advanced genomics technologies, including PacBio long-read sequencing and sequence scaffolding based on long-range genomic information obtained from Hi-C and optical mapping data, AnAms1.0 achieved improved contiguity and accuracy in genome assemblies. Through this assembly, we identified over 29 million repetitive and 15 thousand structural variations, along with more than 1,800 novel protein-coding genes. Underscoring the assembly's potential for elucidating normal and disease-related phenotypes in domestic cats, our findings are publicly accessible on Cats-I (https://cat.annotation.jp/), a platform established to foster the accumulation and sharing of genomic resources for uncovering unknown genetic traits and advancing veterinary medicine.

#62
EFNB3 frameshift variant in Weimaraner dogs with synchronous bunny-hopping gait

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Flashtalk session 2

We investigated three Weimaraner puppies from a litter of eleven that presented with hind limb weakness and a synchronous bunny-hopping gait at the age of four weeks. All three dogs were euthanized due to the unfavorable prognosis. The initial pathological examination was unremarkable. Combined linkage and autozygosity mapping delineated a 43.2 Mb critical interval. Whole genome sequencing data of the three cases were compared to 1491 control genomes and revealed a private homozygous frameshift variant in EFNB3 encoding ephrin-B3. Ephrin-B3 is a transmembrane ligand for Eph receptor tyrosine kinases which mediate various developmental processes, including axon guiding in the nervous system. During neurodevelopment, ephrin-B3 prevents contralateral corticospinal axons from re-crossing the spinal cord midline, thus allowing for unilateral motor control. The identified variant, XM_038536724.1:c.643_644dup introduces a premature stop codon and is predicted to result in the truncation of 14% of the wild-type open reading frame, XP_038392652.1:p.(Ala216fs*79). Genotypes of 130 additional unaffected Weimaraner dogs were consistent with a monogenic autosomal-recessive mode of inheritance and identified additional heterozygous carrier animals. The existing functional knowledge of EFNB3 together with our findings suggest the identified variant as the potential causative variant for the observed phenotype. So far, comparable phenotypes have only been documented in genetically engineered mice. We provide the first report of an EFNB3-related neurodevelopmental disorder in dogs. It remains to be seen whether a similar EFNB3-related disorder involving loss of independent left-right movement coordination also occurs in human patients.

#63
Genetic correlation between mentality traits based on behavioral assessment and questionnaire information in dogs

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Poster session 3

A new behavior and personality assessment in dogs (BPH) was created in Sweden in 2012. Since the start of BPH, questionnaire data based on an extended version of C-BARQ has been collected describing the everyday behavior of dogs. Our aim was to estimate genetic correlations between mentality traits based on BPH or questionnaire data for 5 breeds: Golden Retriever, Labrador Retriever, Lagotto Romagnolo, Nova Scotia Duck Tolling Retriever, and Rhodesian Ridgeback. Average number of observations ranged from 863 to 2462 for BPH traits and from 509 to 839 for questionnaire traits. About 372 to 486 BPH-trait observations also had questionnaire information. From BPH, five traits were defined: Sociability, Playfulness, Non-social fearfulness (NSF), Aggressiveness, and Boldness. From the questionnaire, 18 traits were defined, mainly related to interest, aggression and fear directed towards humans or dogs. Consistently positive (+) or negative (-) genetic correlations were found for Sociability and Boldness with Dog-directed interest (DDI), Stranger-directed interest (SDI), Human-directed play interest (HDPI) (+), Stranger-directed aggression (SDA), and Stranger-directed fear (SDF) (-). Playfulness was consistently correlated with HDPI, Trainability, Energy (+), SDA, and SDF (-). NSF was mainly correlated with the non-social fear questionnaire trait. Aggressiveness was consistently correlated with SDA, SDF, NSF (+), and SDI (-). The results confirm that behaviors measured at BPH are genetically correlated to relevant behaviors in everyday life.

#64
Genetic background of hyperdontia in German Shorthair Pointers

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Poster session 1

Hyperdontia is a globally recognized trait expressing an excess number of teeth. It is a clinical feature associated with several rare human disorders, including cleidocranial dysplasia and Gardner syndrome. Yet, especially, the genetic background of non-syndromic supernumerary teeth is still marginally recognized. We observed closely related German shorthair pointers (GSP) with spontaneous supernumerary permanent incisors without other associated clinical signs. The affected dogs have one to four extra incisors, and the morphology of these is observed to be relatively similar to incisors in normal permanent dentition. Supernumerary teeth can cause pain if expressed in an abnormal location in the dental arch and are usually surgically removed.

We established a cohort of seven affected closely related GSP and performed whole genome sequencing to identify the genetic cause. The variant analysis and validation of candidate variants are ongoing. Identifying causal variant of hyperdontia in the GSP breed would enable us to develop a genetic test for breeding purposes to manage and prevent hyperdontia in the GSP breed. The findings could further explain the tooth development and the genetic background of non-syndromic hyper

#67
Intragenic MFSD8 duplication in Small Swiss Hounds with neuronal ceroid lipofuscinosis

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Poster session 1

We investigated two Small Swiss Hound littermates both of whom developed signs of progressive ataxia, hypermetria, and disorientation around the age of twelve months. In MRI, the cerebellar gray matter appeared generalized thinned to barely visible and the transition from gray to white matter was indistinct. Both dogs had to be euthanized due to neurological deterioration. Pathology of one dog confirmed a concentric gray matter atrophy based on neuronal depletion and ongoing degeneration associated with significant neuronal accumulation of yellowish autofluorescent material within the perikarya. The clinical signs and pathological changes were consistent with a diffuse degenerative polioencephalopathy as a consequence to neuronal ceroid lipofuscinosis (NCL).

Linkage analysis and autozygosity mapping in both affected dogs, their unaffected parents and one unaffected littermate delineated a critical interval of 45 Mb. Whole genome sequencing data of one of the affected littermates revealed a homozygous 18,819 bp duplication in MFSD8 located in the critical interval. The variant can be designated as NC_049240.1:g.13,811,543_13,830,361dup. The breakpoints of the duplication are located in intron 3 and exon 12 and the duplicated allele is unlikely to produce a functional transcript or protein. MFSD8 is a known candidate gene for NCL7 in humans and animals alike. Pathogenic variants have so far been described in Chihuahuas and Chinese Crested dogs. While its exact function is not completely understood, MFSD8 is known to encode an integral lysosomal transmembrane protein. Our results enable the development of a genetic test to avoid further unwanted mating of carriers.

#68

The genetic epidemiology of hemangiosarcoma in the Golden Retriever: How cohort-changes impact study-power

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Poster session 2

Background: The Morris Animal Foundation's Golden Retriever Lifetime Study (GRLS) identified Hemangiosarcoma (HSA) as the most frequent cancer diagnosis. Golden Retrievers from the United States are more prone to developing HSA compared to other breeds, suggesting a hereditary basis.

Aim: To identify regions of the genome associated with the development of HSA.

Materials and methods: Over 3,000 Golden Retrievers (6 months - 2 years) were enrolled from 2012 to 2015, and cancer diagnoses were recorded over time. Dogs were genotyped on the Axiom™ Canine HD Array.

Results: Male sex was associated with the development of HSA, therefore, GWAS were performed with correction for sex and population stratification. The oldest dogs in the cohort study have currently reached the age of ±14 years. Initially, 9 years was chosen as cut-off age for controls. However, the median age of HSA diagnosis in the cohort was 9.5 years (range 3.6 to 12.9 years). Therefore, the age limit was increased to 11 years. In 2023, 216 dogs were diagnosed with HSA, and results from GWAS did not reach genome wide significance. In 2024, the number of cases increased to 407 and 125 dogs that were initially defined as controls developed HSA. These changes in the cohort resulted in a clear increase in power.

Conclusion: Choosing the correct age for controls influences power and is important for the identification of true signals in GWAS, whilst studying cancer phenotypes in a cohort-population analysis.

#69
Unveiling the canine detective: labrador retriever genome assembly for advancing detection dog genetics

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Poster session 3

Detection canines are specially trained dogs with capability to detect chemical substances or biological specimens. Labrador retrievers and German wirehaired pointers are among the best breeds suitable for detection work. We sequenced the genome of a male labrador retriever, an elite detection dog bred and trained at Auburn University Canine Performance Sciences colony. A total of 80× PacBio Revio HiFi sequences, 53× Omni-C, and 41× Illumina short reads were generated. Initial assembly resulted in 204 contigs in haplotype 1 and 184 contigs in haplotype 2. Chromosome-level assembly was achieved with Omni-C data, and the best representative set of chromosomes was manual selected from the two haplotypes. Additional gap filling was performed based on megablast results and information a female dog assembly in the same colony. The final genome assembly is 2.47 Gbp in length with 65.1 Mbp contig N50. The 38 acrocentric autosomes and metacentric X chromosome have assembled centromeric regions, with telomeric sequences at both chromosome termini and only 7 internal gaps. The assembled Y chromosome is 19.5 Mbp with no gap, including a PAR region of 6.5 Mb. Genome completeness and accuracy (96.0% complete, 1.9% duplicated, 1.3% fragmented, 2.7% missing BUSCOs) are comparable to other labrador retrievers' assemblies. A total of 6.7 million SNVs and 123 thousand structural variations have been identified in the genome. We reported the first genome of an elite detection dog, which will serve as the proper reference genome for future genetic mapping of the behavioral phenotypes associated with detection dog performance.

#70
An inherited Robertsonian translocation in Entlebucher mountain dogs reduces fertility

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Flashtalk session 1

A good reproduction rate is a central element for any breeding program. Structural and numerical chromosomal aberrations are well documented causes of reduced fertility or infertility in mammals and may cause abnormal sexual development. Animals with reduced litter sizes reduce the selection potential in a population.

A healthy bitch of the Entlebucher mountain dog breed was suspected to be sub-fertile. Although she had three litters with three different sires – the litter sizes with one, two and three puppies were clearly below the average litter size of 5.4 puppies in this breed. A cytogenetic analysis (DAPI, FISH) showed that the bitch was a carrier of a Robertsonian translocation involving chromosome 1 and one of the smallest chromosomes. The aberration was present in all analyzed cells. The owner of a female offspring planned to breed with this dog. After a cytogenetic analysis it was clear that the offspring had inherited the translocation from her mother. Additionally, other breeding dogs of this population were recognized to carry the translocation.

Carriers of balanced Robertsonian translocations are difficult to recognize because they usually have a normal phenotype, but often produce unbalanced gametes which can result in monosomic or trisomic zygotes. Therefore, it is strongly advised not to breed with such animals. The present case emphasizes the need to examine sub-fertile dogs, and, if proven to be carrier of a chromosomal aberration, they should be no longer used for breeding.

#71
Using citizen science to map congenital heart disease in the Basenji

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Poster session 2

At the request of the Basenji Club of New South Wales (Australia) we are investigating the inheritance of cardiac valvular defects in the Basenji. Submitted electronic array data include five heart affected animals from the same family pedigree. The affected animals exhibit a range of valvular defects affecting tricuspid, aortic and pulmonic valves. A further four animals in the analysis have heart murmurs that are possibly related to the same condition. Illumina canine genotyping array data from a total of 43 Basenjis have been contributed to the analysis.

Genome-wide association analysis has identified one marker on chromosome 33 that is associated with genome-wide significance (chr33_5069201, Praw=8.058e-07, Pgenome=0.04331) (canFam3.1). A further eight markers in the vicinity are among the top 50 associated markers and four have near genome-wide significance.

The associated region includes the genes Coproporphyrinogen Oxidase (CPOX); ST3 Beta-Galactoside Alpha-2,3-Sialyltransferase 6 (ST3GAL6); and Discoidin (DCBLD2). Among these positional genes, reduced expression of DCBLD2 is implicated in human calcific aortic valve disease (CAVD) and mitral valve disease. Next steps in our analysis will involve obtaining whole genome sequence from an affected individual to identify the potential causative variant(s).

#72

A single nuclei characterization of dorsal root ganglia to study canine degenerative myelopathy

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Flashtalk session 3

Canine degenerative myelopathy (DM) is a naturally occurring adult-onset neurodegenerative disease with no known treatment and is considered a disease model for ALS. Dogs homozygous for a common missense variant superoxide dismutase 1 gene (SOD1) are at elevated risk for developing DM. However, it appears that there are additional unidentified factors underlying the incomplete penetrance of the SOD1 mutation. The earliest clinical sign in DM affected dogs is an asymmetric general proprioceptive ataxia of the pelvic limbs. The first order neurons of the proprioceptive pathways lie within in the dorsal root ganglia (DRG). We hypothesize that altered function of lumbar DRG neurons is at least partially responsible, therefore we have generated single nucleus RNA sequence (snRNAseq) data of lumbar DRGs from healthy control dogs and dogs with DM. We identified 16 transcriptionally unique clusters with corresponding cell types. Among these cell types were the so-called p75NTR++ glial cells previously only identified in DRGs from rats. We have also generated spatial images of individual genes that uniquely differentiate multiple cell types including various neuronal subtypes. Estimates of differentially expressed genes (DEGs) show unique cell type specific effects of the DM condition, such as higher APOE expression in certain neuron cell types. Our study is the first to characterize the molecular features of cell types in the DRG of dogs with advanced DM. These DEGs unique to cell type could lead to expanded comparative clinicopathological assessments, which may translate to human neurodegenerative diseases and advance therapeutic approaches

#73

New molecular insight into the tumor microenvironment of canine hepatocellular carcinoma

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Poster session 1

Hepatocellular carcinoma (HCC) is frequently resistant to chemotherapy and radiation, and response to immunotherapy remains low in human patients. Despite HCC being uncommon in dogs, defining the tumor microenvironment, especially the immune cell subtypes and somatic mutations that are present, could define core targets for development of novel therapeutics. We performed whole exome sequencing (WES) of HCC tumors and matched normal tissue to identify somatic mutations in 10 dog HCC tumors, and single nucleus RNAseq (snRNA-Seq) analysis to identify tumor-infiltrating immune cell types in 2 dogs. Following the classification of all somatic variants according to their influence on protein structure, 645 variants remained in total, each assigned an impact prediction score. Comparing this small cohort to the human HCC COSMIC database, we identified a few genes with frequent incidences of missense variants. For the Catenin Beta 1 gene, CTNNB1, that is mutated in 22% of human HCC patients, we find missense mutations in half of the dog HCC tumors. Using snRNAseq data, the infiltration of immune cell types was assessed in two 13-year-old mixed breed dogs diagnosed with HCC by histological examination. Seven major cell types were discerned after manual annotation: T cells, endothelial cells, hepatocytes, macrophages, malignant cells, proliferating cells, and stellate cells. Cell-cell interaction analysis of human and canine HCC additionally identified cross-species commonalities for tumor-associated macrophages. Initial cross-species comparative analyses of HCC have defined common, potentially core mechanisms that may inform future therapeutic targeting and supports expansion of additional comparative multi-omic studies in canine and human HCC.

#74
Going feral: genomic drivers of cat feralization in Australia

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Poster session 2

Australian explorers and colonists have brought with them a range of animal species, including rats, mice, cats, goats, horses, and cattle. Many of these species have dispersed widely across the continent and most have strong detrimental effects on many native animals and plants. Cats were not only introduced to Australia for companionship but were intentionally dispersed to control a rodent and rabbit plague in the late 19th century. The intentional release of domestic cats led to a rapid proliferation of the species throughout Australia, with over 124 endangered Australian native species currently under direct pressure from feral cat predation and diseases. In addition to their impact on native wildlife, toxoplasmosis associated with feral cats is estimated to cause an agricultural loss of $12 million annually.

The genomic processes that have enabled the domestic cat to successfully transition from domestic to feral and establish itself as an apex predator in Australia are yet to be described. We explore genomic differences between domestic and feral cats. To date we have accumulated 66 feral cat samples from areas distant from population centres in the Northern Territory (n=11) and Queensland (n=55) and genomic DNA was extracted and genotyped on the Infinium iSelect 63K Feline genotyping array. A genome-wide association study will be performed to assess feral cat population structure and to identify genomic regions that significantly diverge between domestic and feral populations. The genetic data will be integrated into spatial maps to identify signatures of selection across the heterogeneous Australian landscape.

Open University of the University of Helsinki has launched two free multidisciplinary and interactive lay public courses targeted at anybody interested in dogs and cats and their owners' health, behavior, and personality relationships with their pets. The participants will also get a heavily discounted code to order the leading gene panel test for their pets to understand the particularities of their genomes. Enjoy the journey!