Insights and challenges from a decade of studying autoimmune diseases in dogs

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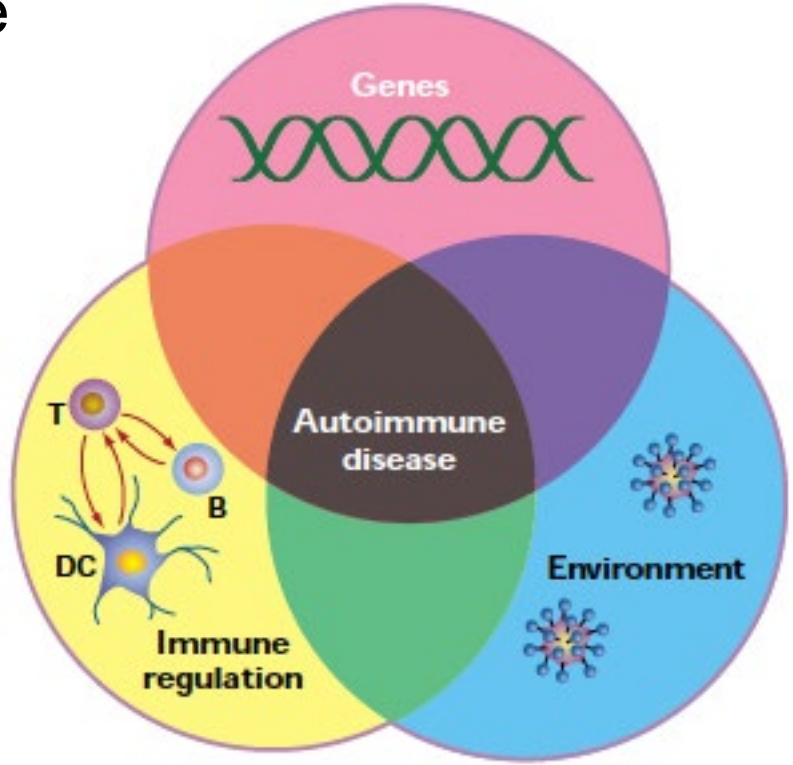
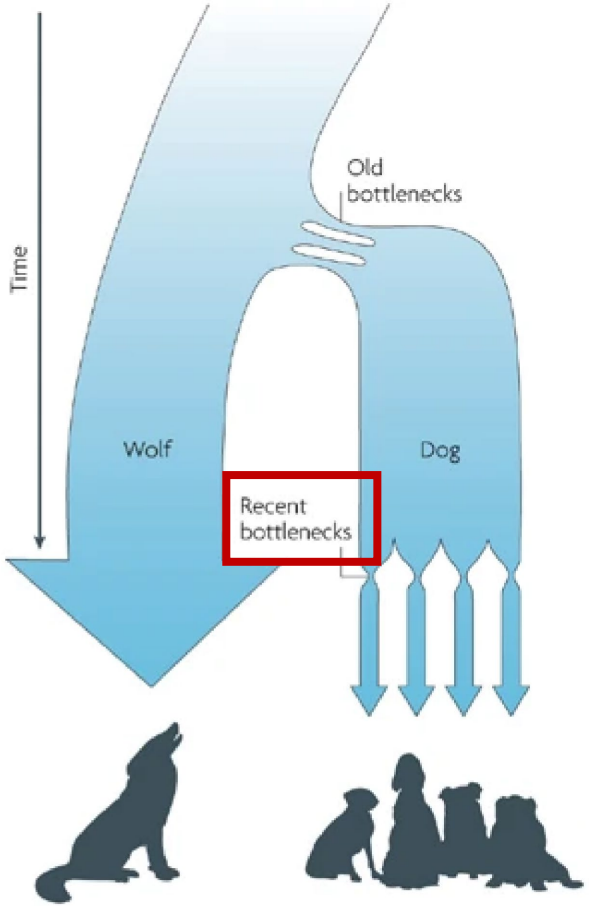
Why study autoimmune diseases in dogs?

- Common, and often severe, medical problems
- Can be highly similar to human diseases
  - Supports a “One Health” approach to medicine
- Occur spontaneously
- Advantageous genetic model?



Source: Ermann, J., Fathman, C. Autoimmune diseases: genes, bugs and failed regulation. Nat Immunol 2, 759–761 (2001). https://doi.org/10.1038/ni0901-759

Dogs as a genetic model



Recent bottlenecks

- Hundreds, not thousands, of years ago
- Intense “artificial” selection for physical and behavioral traits
- Limited genetic diversity within a breed
- Certain diseases become overrepresented within a breed

Source: Karlsson, E., Lindblad-Toh, K. Leader of the pack: gene mapping in dogs and other model organisms. Nat Rev Genet 9, 713–725 (2008). https://doi.org/10.1038/nrg2382

Breed-specific immune-mediated diseases

- Addison's disease
- Sebaceous adenitis

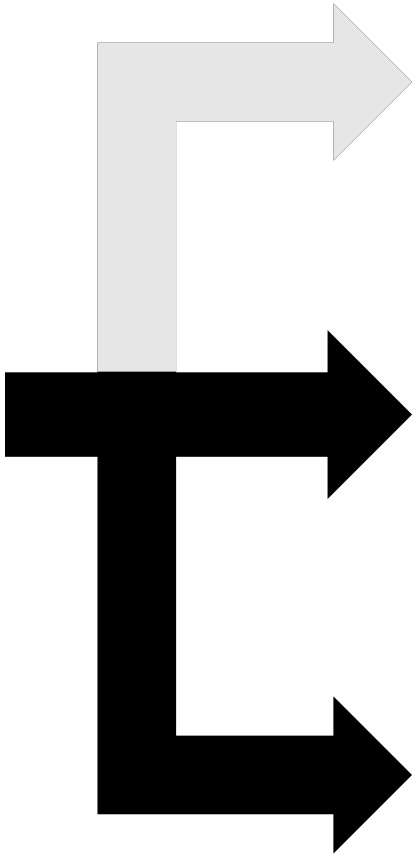
- Diabetes
- (Hyperlipidemia)

- Autoimmune hemolytic anemia
- Immune-mediated thrombocytopenia
- Dry eye

- Exocrine pancreatic insufficiency
- Perianal fistulas
- Chronic superficial keratitis (Pannus)

Source: American Kennel Club

Implications for health and disease



Mendelian diseases

- Popular sires, bottleneck effects
- ~500 Mendelian diseases in dogs have associated single point variants

Polygenic diseases

- Common alleles in uncommon combinations
- Mappable with common tools, require larger populations

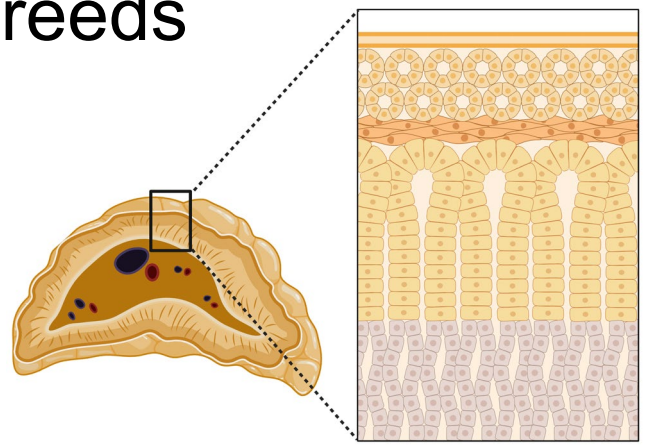
Fixed disease predisposition

- All dogs within a breed are predisposed
- Requires non-traditional genetic approaches and functional evidence

Areas of research focus

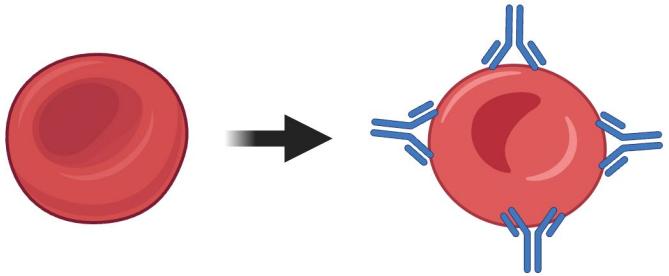
Addison's disease

- Autoimmune disorder affecting the adrenal cortex
- Inherited in dogs and humans, highly overrepresented in certain breeds



Autoimmune hemolytic anemia

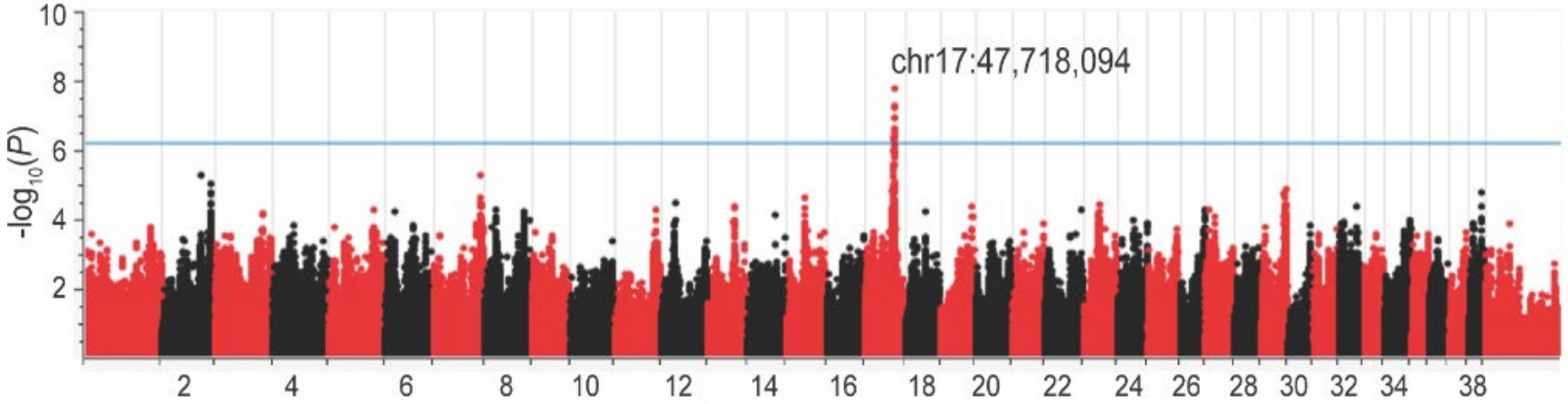
- Immune-mediated attack on circulating red blood cells
- ~100x more common in certain Spaniel breeds



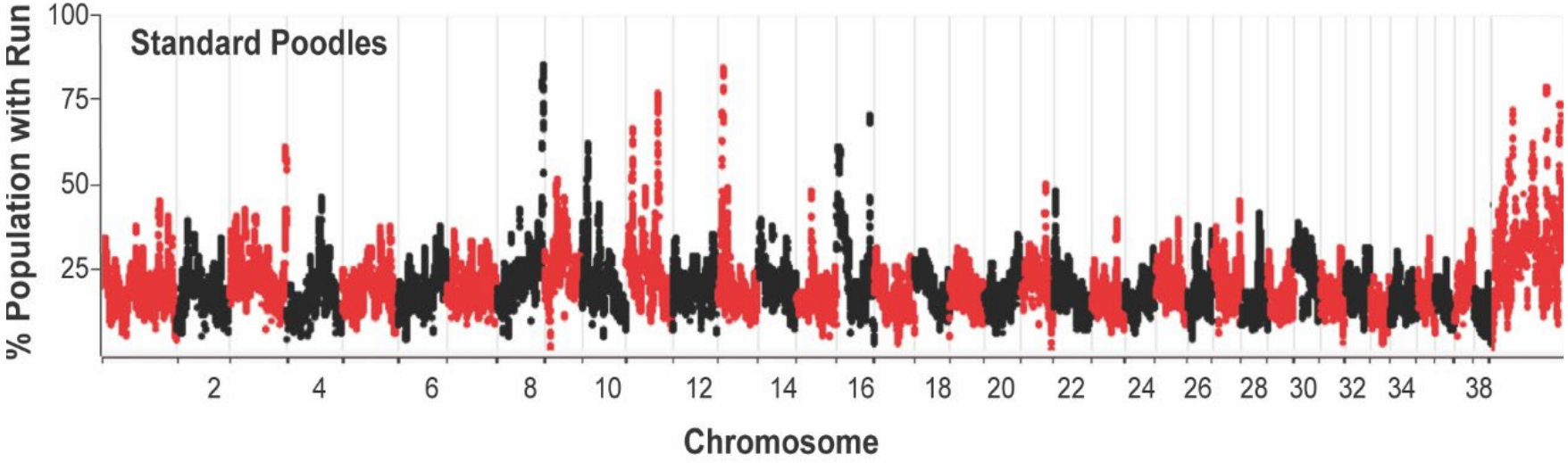
Source: Biorender.com

Addison's genetics findings

Traditional GWAS

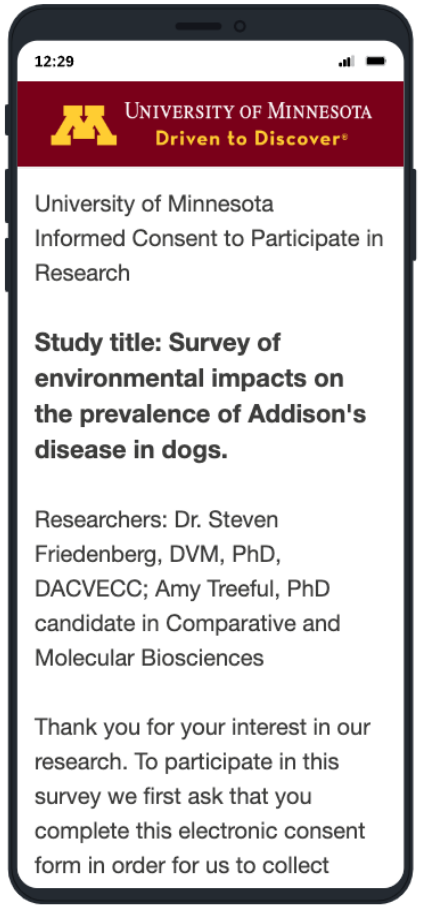


Runs of homozygosity: Fixed effects



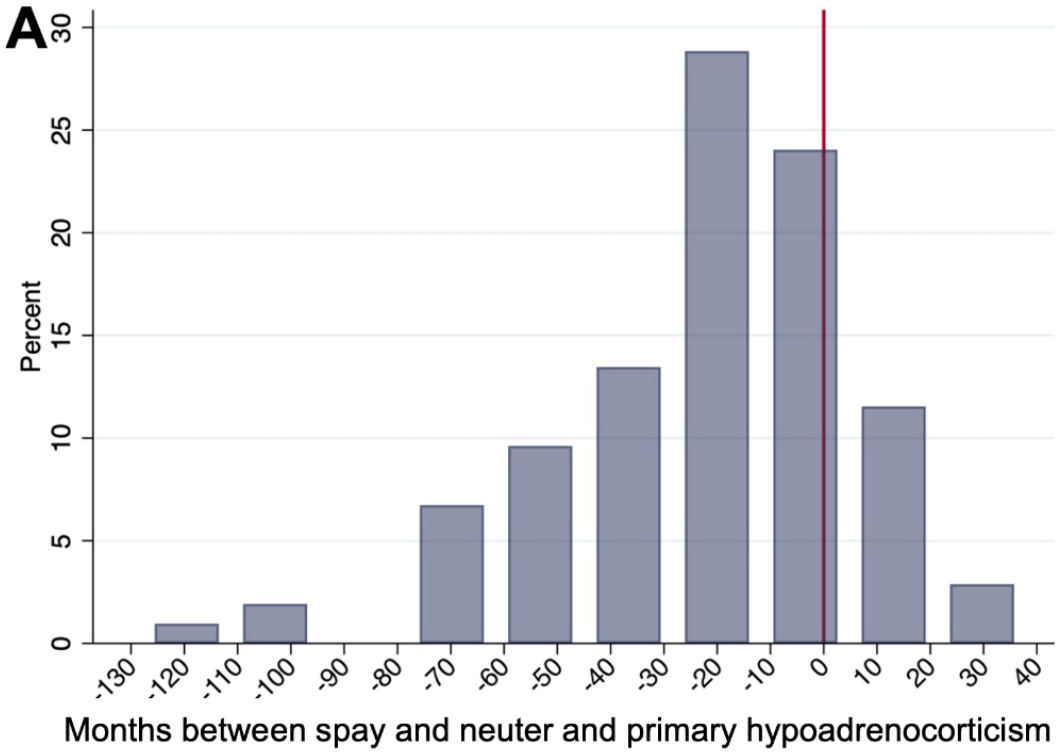
Addison's environmental risk factor survey

- Standard Poodle and Portuguese Water Dog owners in the US and Canada
- 358 cases; 4,689 controls
- ~50 questions
- Broad range of environmental exposures
- Overlay of soil, air quality, and water quality data from EPA



Spaying/neutering may play a key role

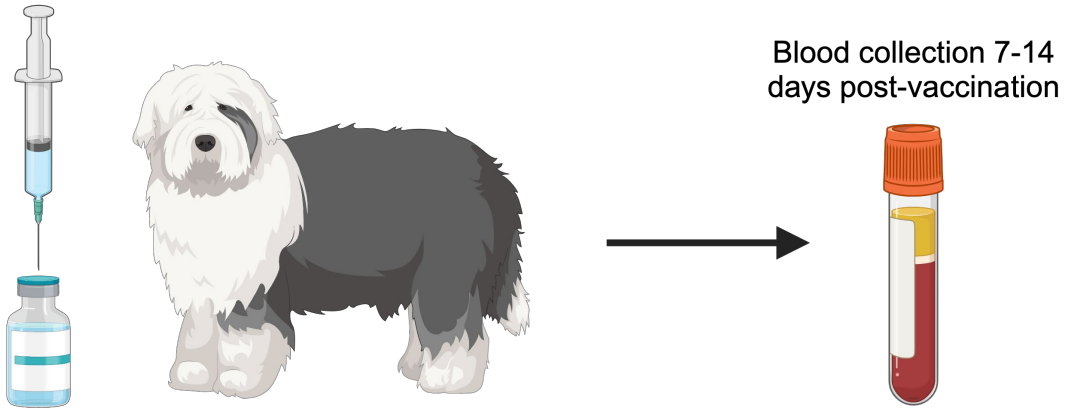
Variable	Adjusted OR (95% CI)	Adjusted *P* value
Neutered		
Yes	6.0 (2.6-13.9)	$P < .001$
Spayed		
Yes	2.5 (1.4-4.5)	$P = .003$



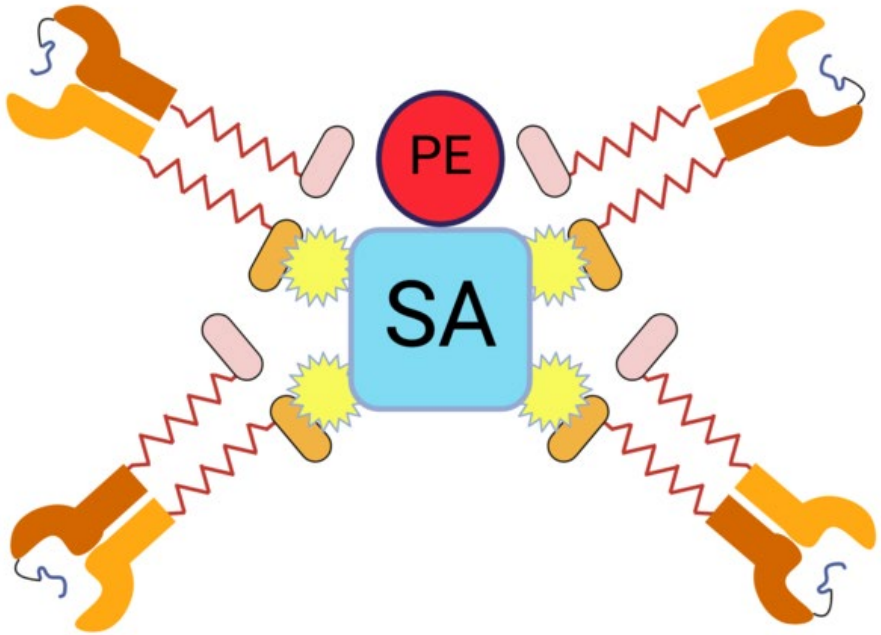
Source: A case-control survey study of environmental risk factors for primary hypoadrenocorticism in dogs, AE Treeful, KM Searle, DM Carroll, KJ Yost, AL Hedger, SG Friedenberg. Journal of veterinary internal medicine 37 (6), 2073-2083

Getting beyond genetics

Rabies vaccination model system



MHC Tetramers



Challenges

1. Limited funding for canine research
2. Minimal coordination on development of dog genetics resources
3. Lack of immunology tools vs. other species
4. Difficult to collect precious research samples across fragmented industry

Acknowledgements

Lab members

- Amy Treeful
- Jonah Cullen
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- Anna Hedger

Collaborators

- Leigh Anne Clark
- Kelly Searle
- Dana Carroll
- Kathleen Yost

Mentors

- Rory Todhunter
- Kate Meurs
- Marc Jenkins
- Jamie Modiano
- Kristin Hogquist

Questions?

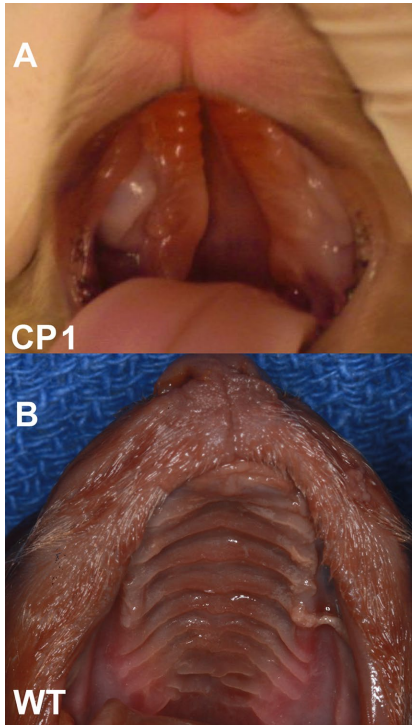
APPENDIX

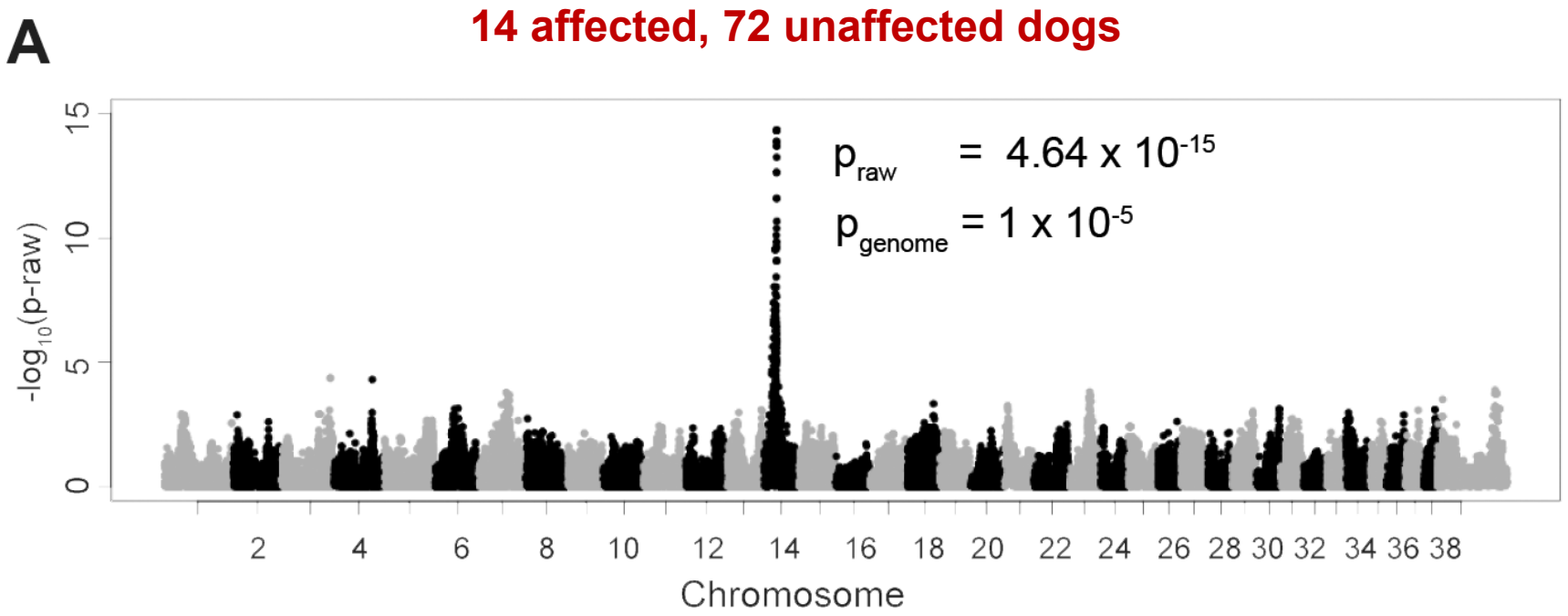
Canine dermatomyositis

- Mapped to variants in 3 genes
  - Dog leukocyte antigen
  - PAN2
  - MAP37CL
- Epistatic effects
- Only affected breeds have high frequencies of all three alleles

Source: Evans JM, Noorai RE, Tsai KL, Starr-Moss AN, Hill CM, Anderson KJ, Famula TR, Clark LA. Beyond the MHC: A canine model of dermatomyositis shows a complex pattern of genetic risk involving novel loci. PLoS Genet. 2017 Feb 3;13(2):e1006604. doi: 10.1371/journal.pgen.1006604. PMID: 28158183; PMCID: PMC5315411.

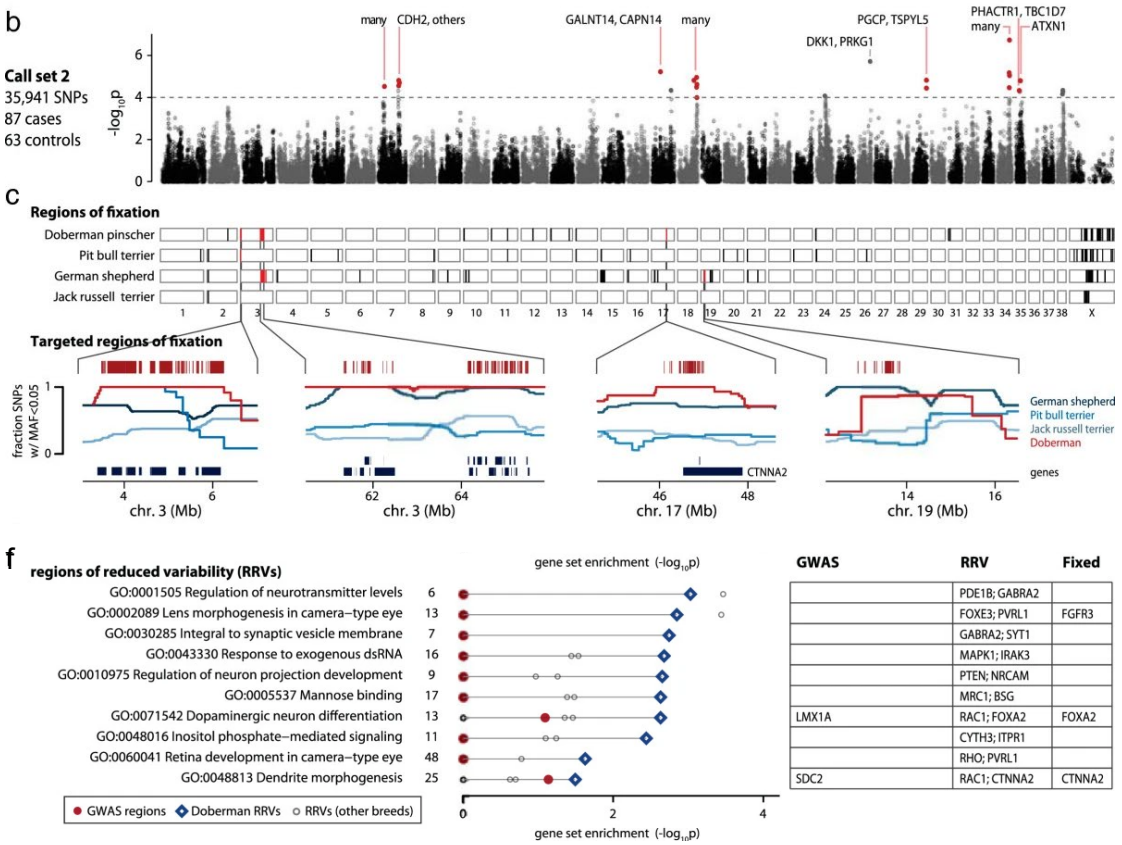
Cleft palate in Tollers





Source: Wolf ZT, Leslie EJ, Arzi B, Jayashankar K, Karmi N, et al. (2014) A LINE-1 Insertion in DLX6 Is Responsible for Cleft Palate and Mandibular Abnormalities in a Canine Model of Pierre Robin Sequence. PLOS Genetics 10(4): e1004257. https://doi.org/10.1371/journal.pgen.1004257

OCD in Doberman Pinschers



- 87 cases, 63 controls
- Identified 119 conserved variants overrepresented in cases across GWAS and fixed regions
- Many of these variants clustered in four genes implicated in brain synapse function

Source: Tang, R., Noh, H.J., Wang, D. et al. Candidate genes and functional noncoding variants identified in a canine model of obsessive-compulsive disorder. Genome Biol 15, R25 (2014). https://doi.org/10.1186/gb-2014-15-3-r25