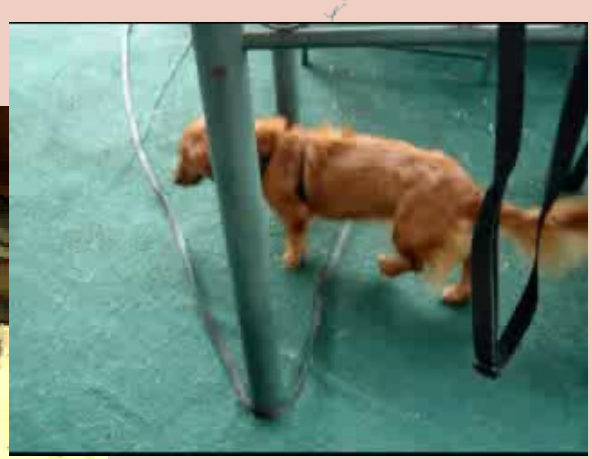
Dennis O'Brien DVM PhD

Canine Neurodegenerative Diseases

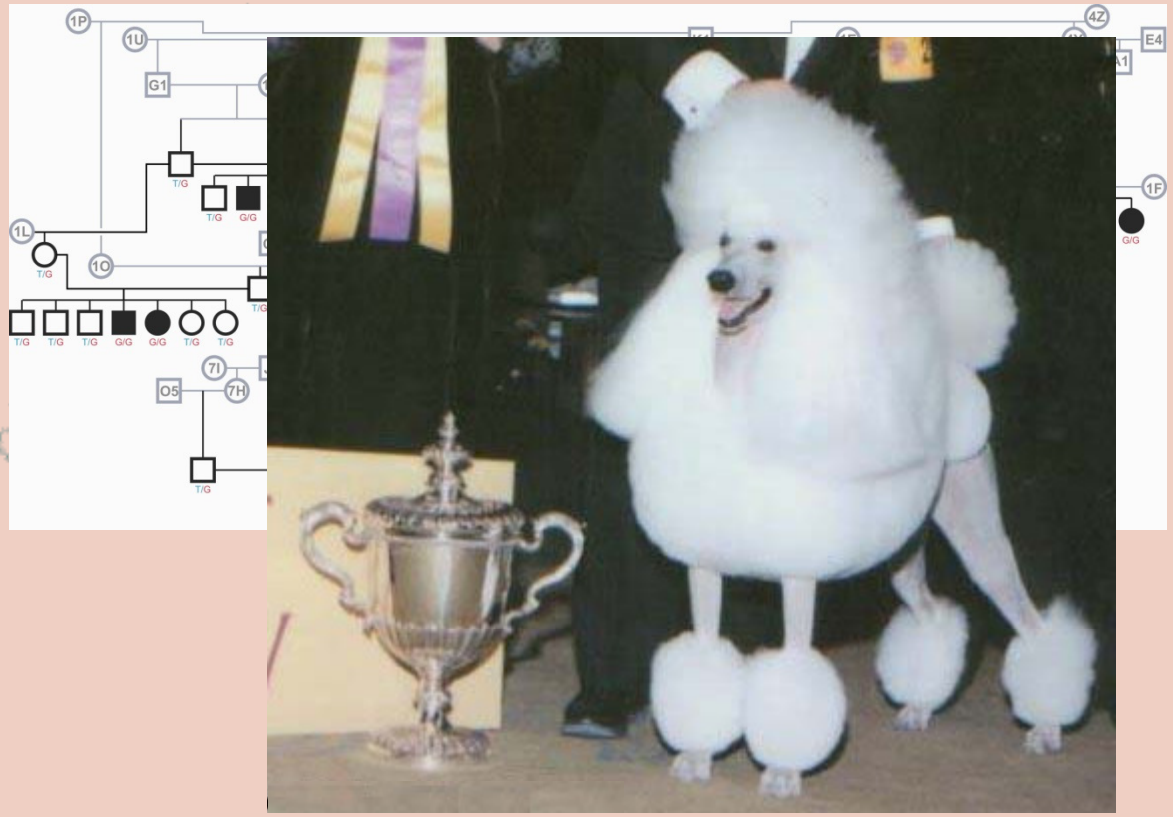
Comparative Neurology Program

Canine Neurodegenerative Disease



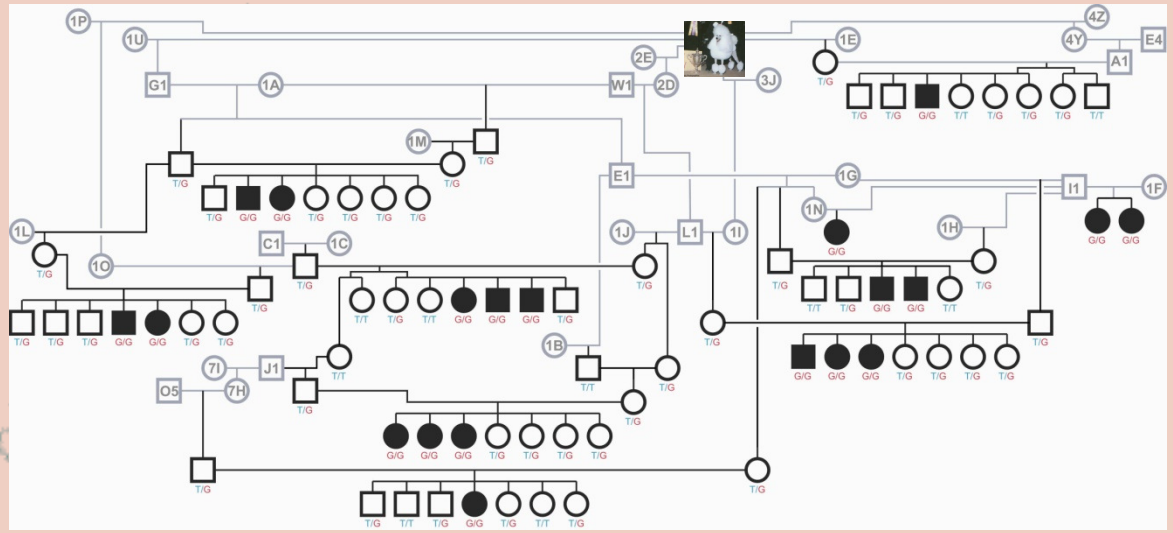
- Why are they common?
- Why is a dog better than a mouse?

Mutations happen



- Popular sire gets widely used
- Some disease-causing recessive genes with the desirable ones
- Bad dogs happen to good breeders

Mutations happen



- Unique opportunity to study genetics of neurologic disease
- Motivated breed club

  ~25% of litter affected
- Pedigrees & DNA available
- Several generations in a few years

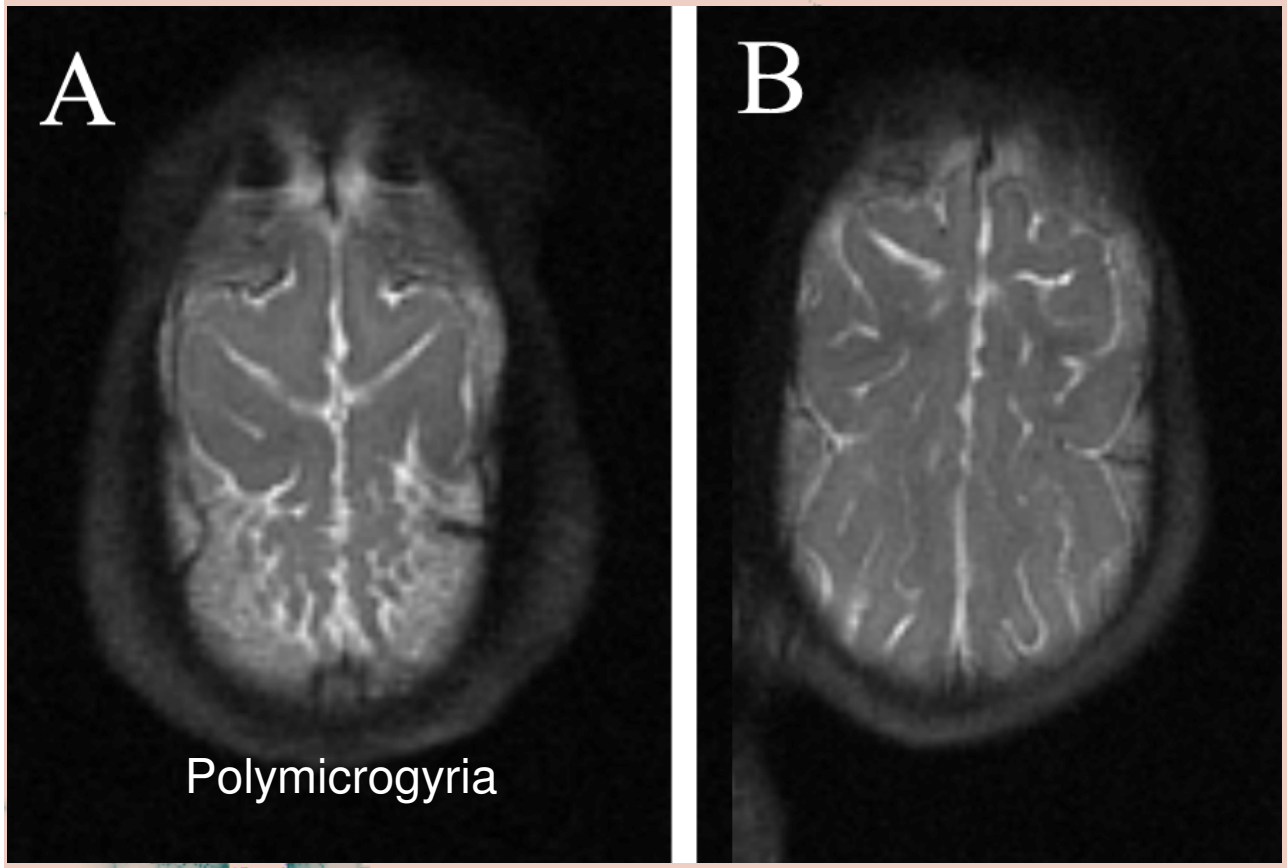
Genome-wide association map

- Compare affected to normal
- Map the mutation responsible

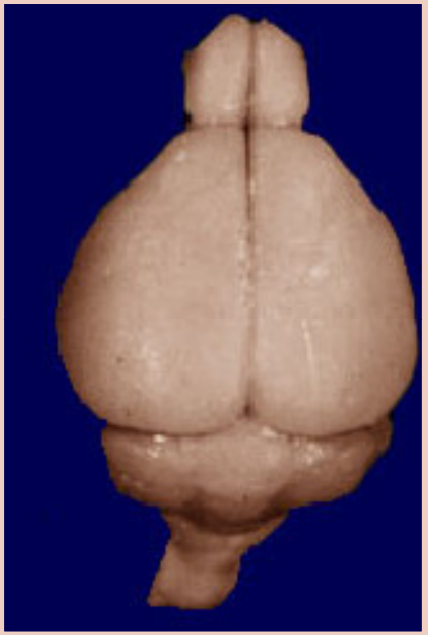
Knockout mouse

Polymicrogyria

- ***Poly*** - many
- ***micro*** - small
- ***gyria*** - turns



Mouse



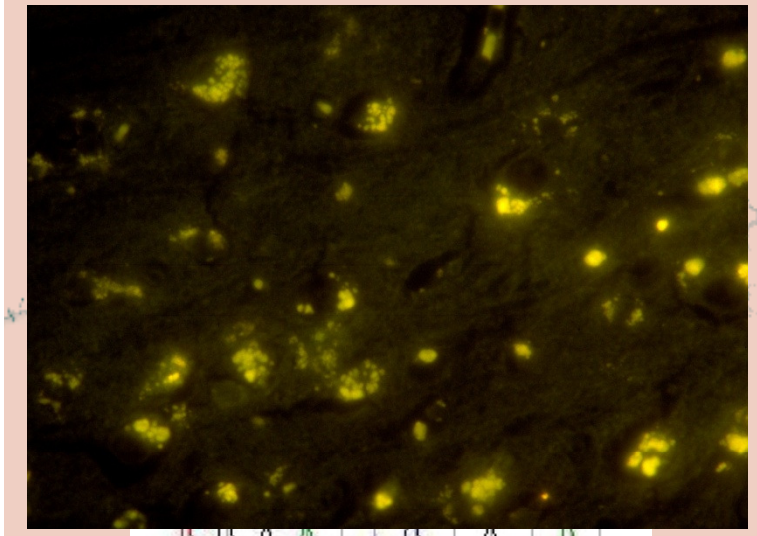
University of Wisconsin Brain Collection

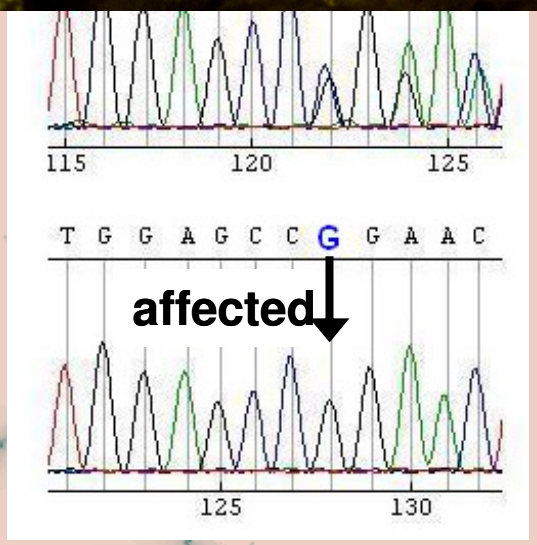
Journal Vet Internal Med 23(4):871-4, 2009

Frodo

- Normal until 7 months of age
- Loss of vision
- Ataxia & hypermetria
- Personality change
- Myoclonic seizures
- Died at 12 months

Ceroid lipofuscinosis-Batten disease





- Lysosomal storage disease
- Tripeptidyl peptidase 1 (CLN2)
  - Single base-pair deletion
  - Frameshift → premature stop
  - No enzyme activity

Mol Gen Metab 89:254-60, 2006

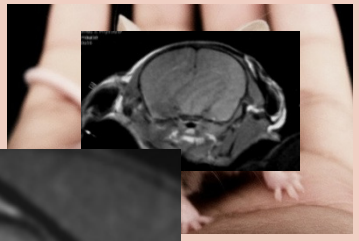
Translation

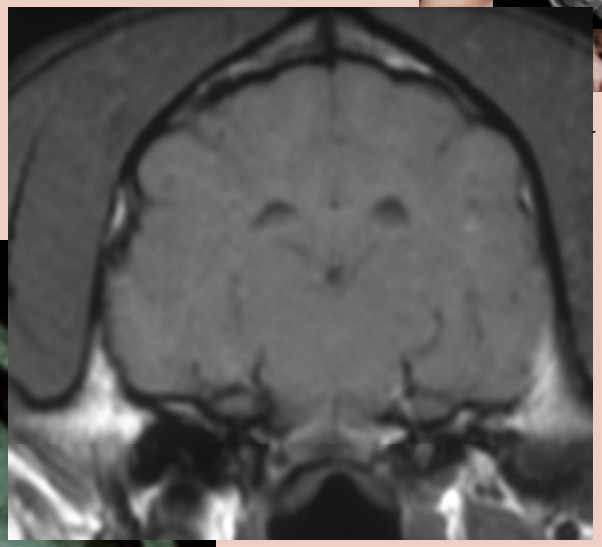
- Rodent model → human disease

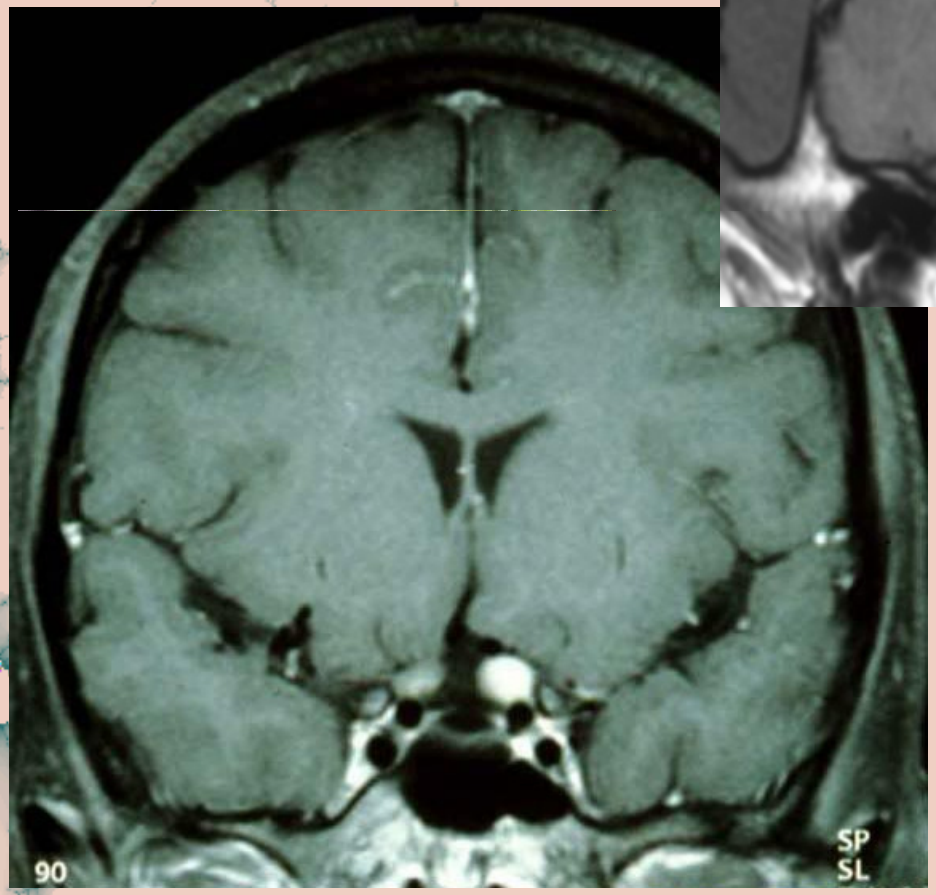
CLN2 knockout mouse

Translation

- Rodent model → human disease

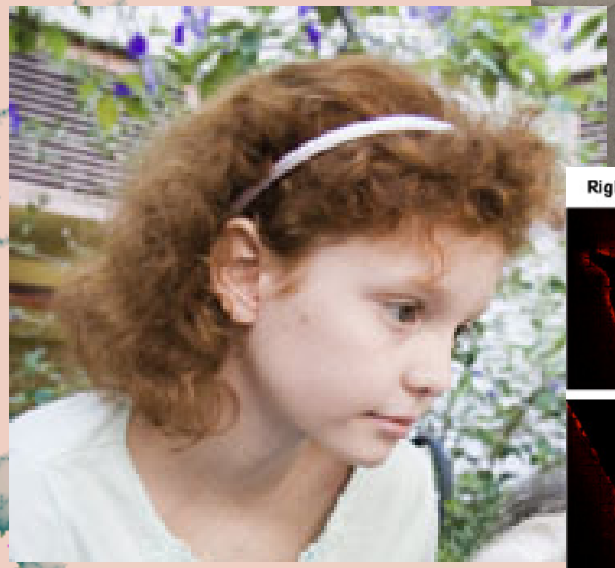


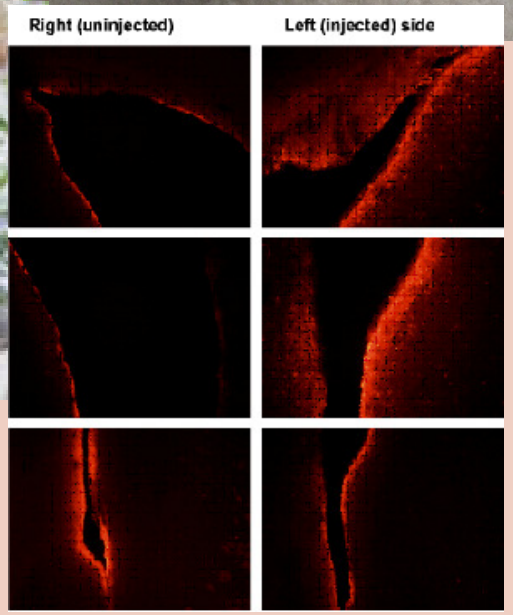




Translation

- Rodent model → canine disease → human disease





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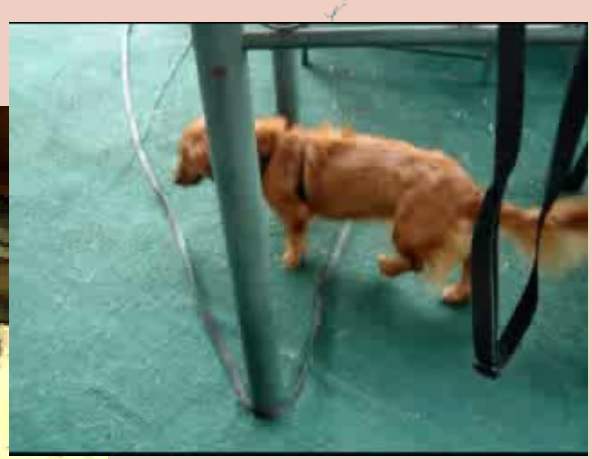

Canine Neurodegenerative Disease

A Bridge from Clinic to Bench to Health for Humans & their Companions

Comparative Neurology Program

Dennis O'Brien DVM PhD

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Department of Veterinary Medicine & Surgery
Gayle Johnson & George Rottinghaus
Veterinary Medical Diagnostic Laboratory
Jerry Taylor & Bob Schnabel
MU Animal Sciences Research Center
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Mason Eye Institute
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Kirsten Lindblad-Toh & Claire Wade
The Broad Institute of Harvard & MIT
Elaine Ostrander
National Human Genome Research Institute
James Weber
NHLBI Mammalian Genotyping Service
Bev Davidson
University of Iowa
Peter Lobel & Istvan Sohar
Rutgers University
Urs Giger
University of Pennsylvania

Comparative Neurology Program

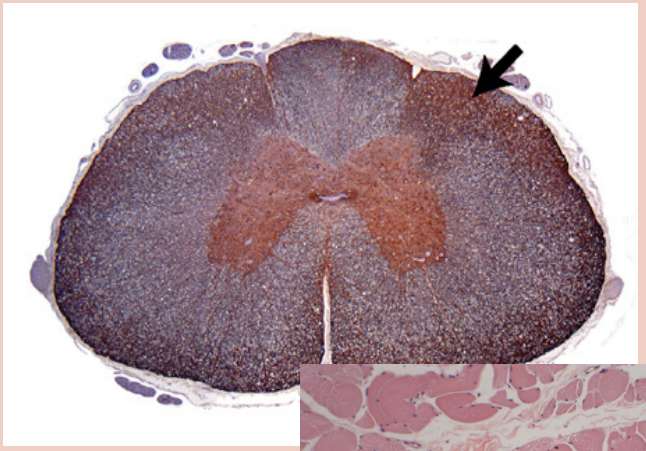
Thanks to the AKC-CHF, NINDS, BDRSA, & the breed clubs for support and the breeders, owners & veterinarians for assistance

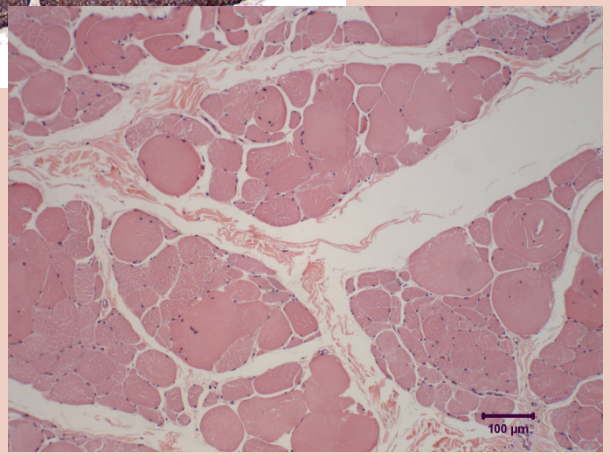
Questions?

Comparative Neurology Program

Degenerative Myelopathy

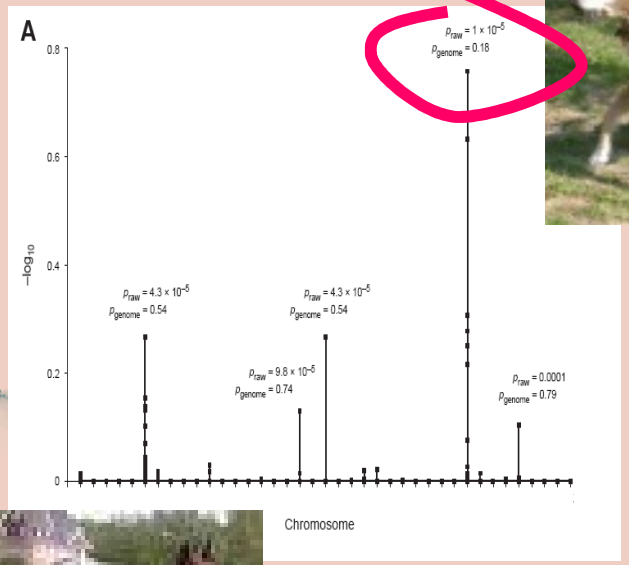
- Older dogs (> 8 years)
- Progressive paralysis





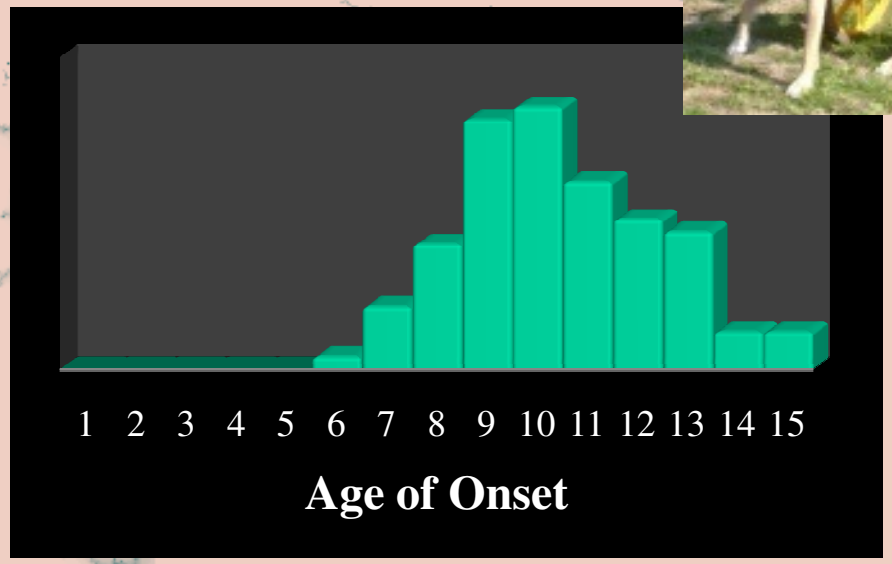
J Vet Internal Med 21:1323-31, 2007

Mutation in *SOD1* gene



- Familial amyotrophic lateral sclerosis (ALS)

Mutation in *SOD1* gene

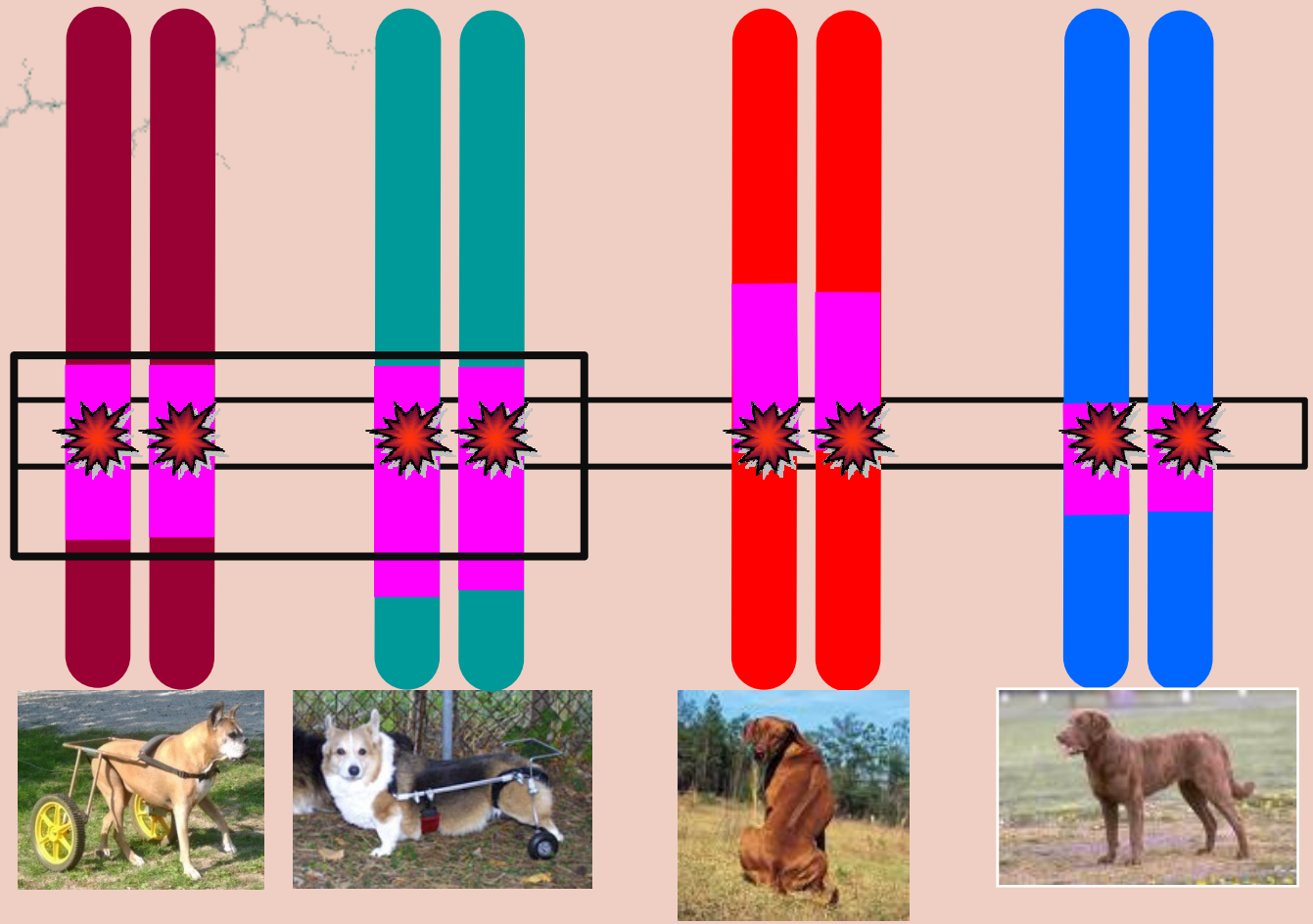


- A
  i
- J
- Inter
  strategies

Ancestral haplotype

Fine mapping

- Similarities with affected dogs of other breeds



Canine disease

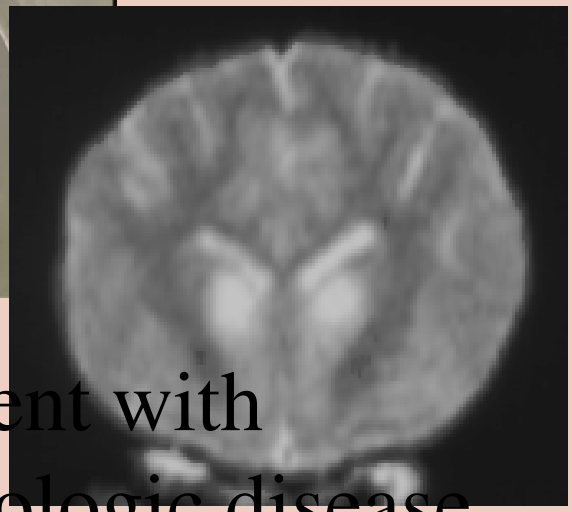
- Shared evolution & environs

Canine disease

- Present with neurologic disease

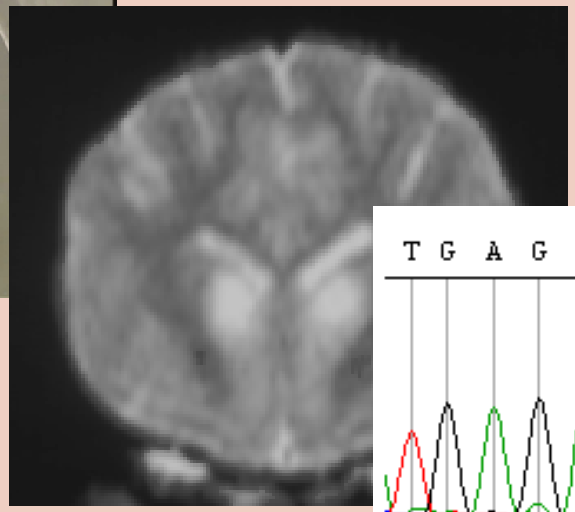
- Shared evolution & environs

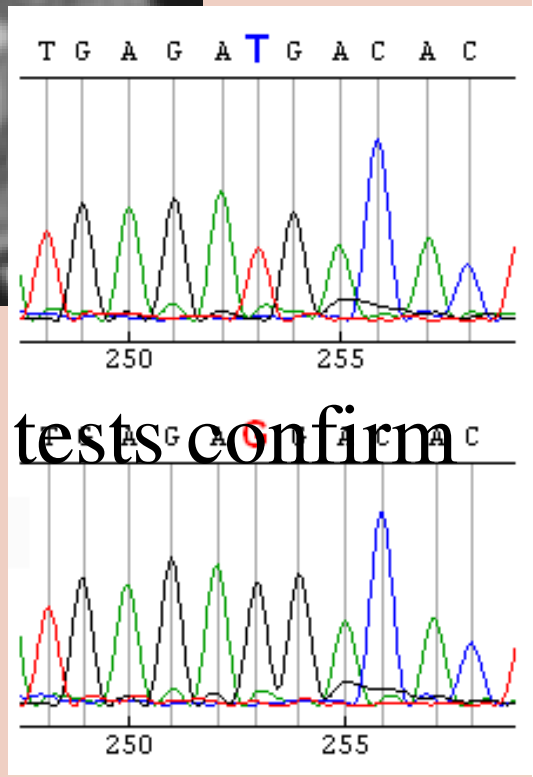
Canine disease



- Present with neurologic disease
  - Diagnostic tests confirm

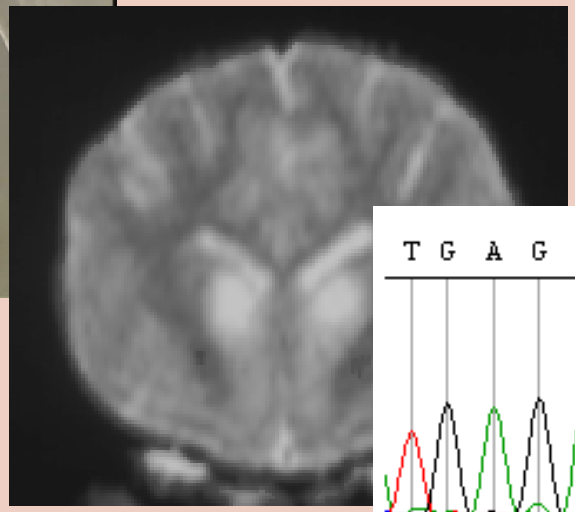
Canine disease

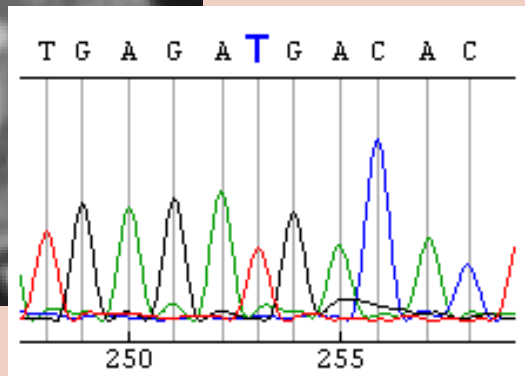


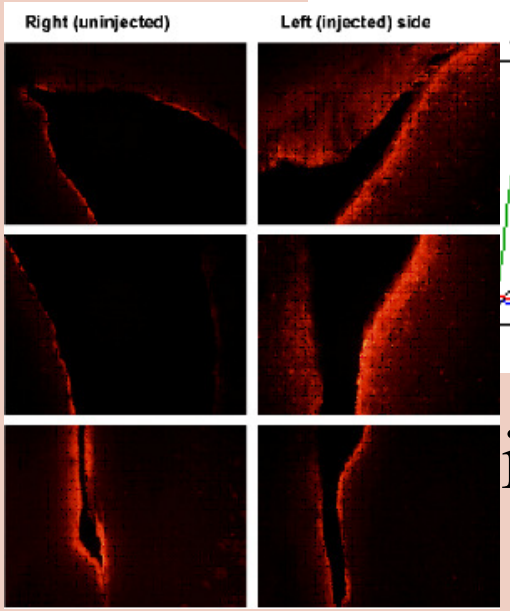


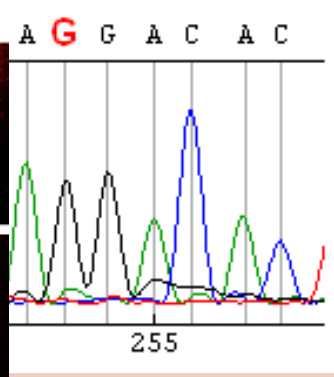
- Diagnostic tests confirm
- Gene discovery

Canine disease





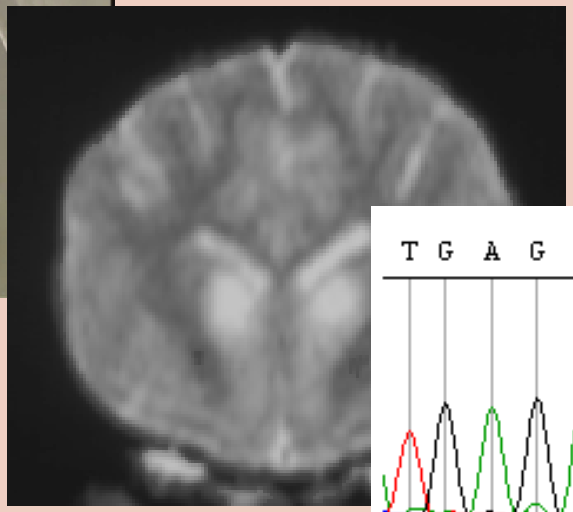


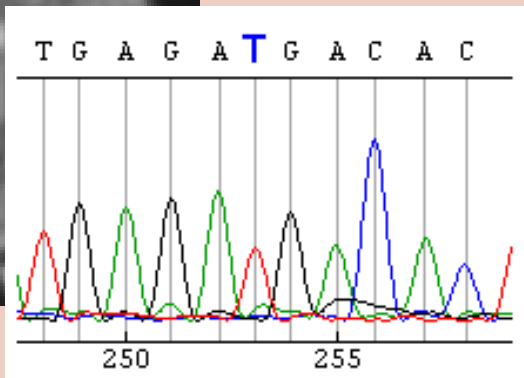


- Model for pathogenesis & therapy

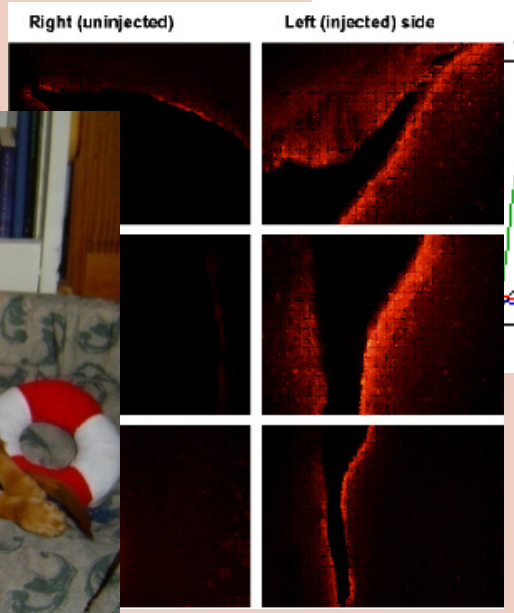
iscovery

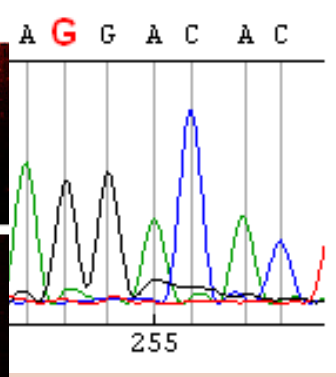
Canine disease



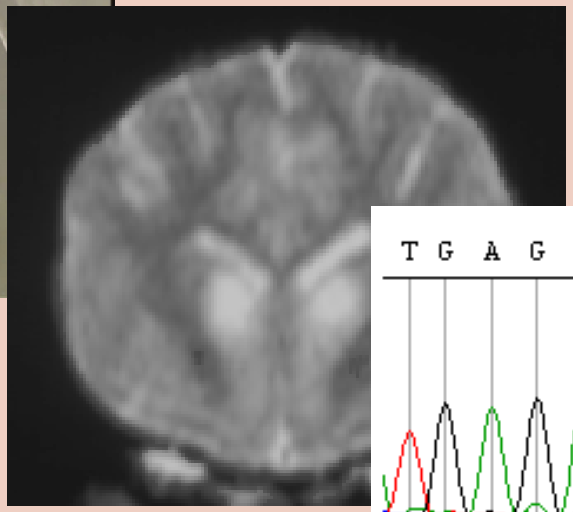


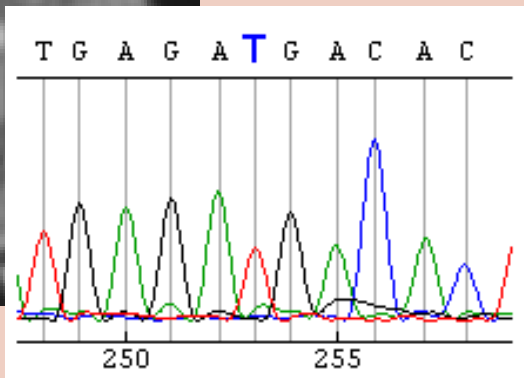
- Translation to patients





Canine disease





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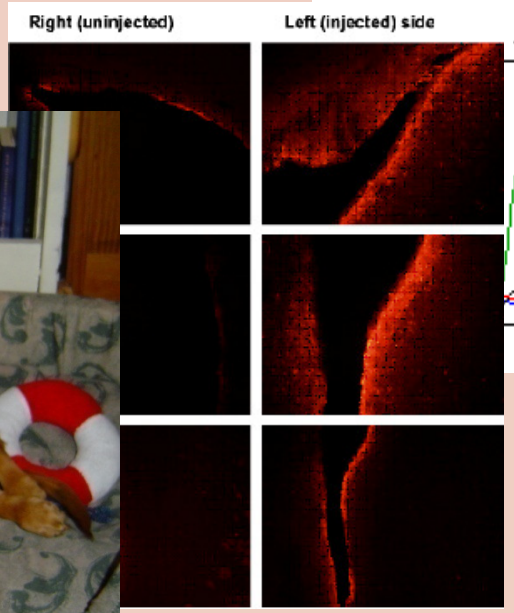
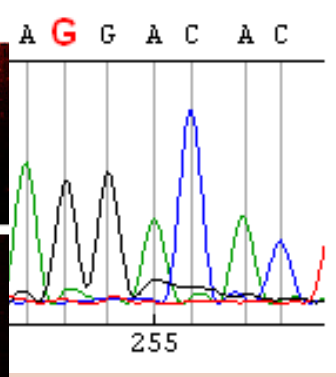


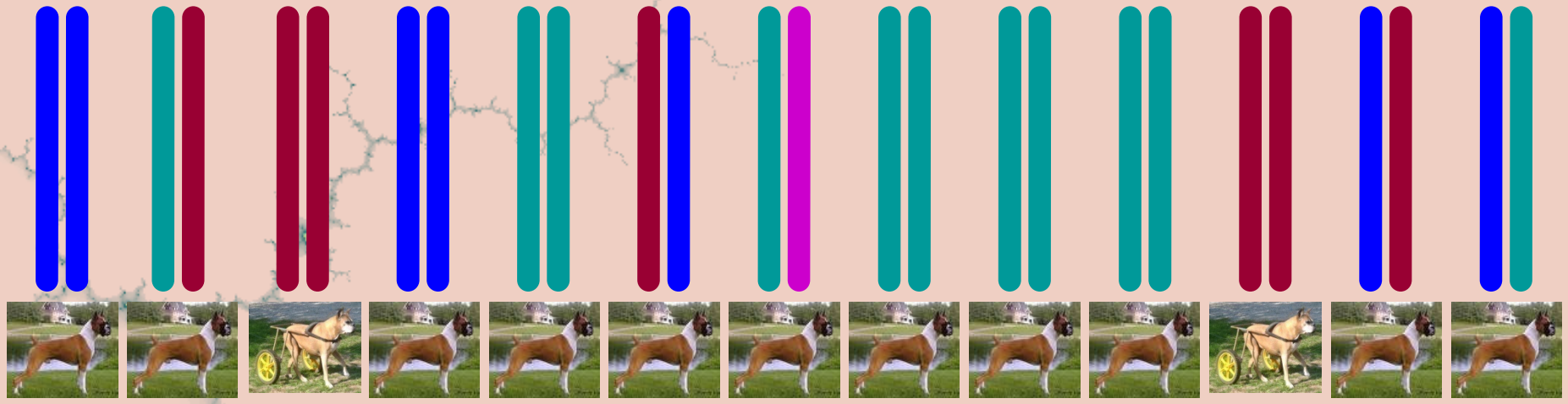


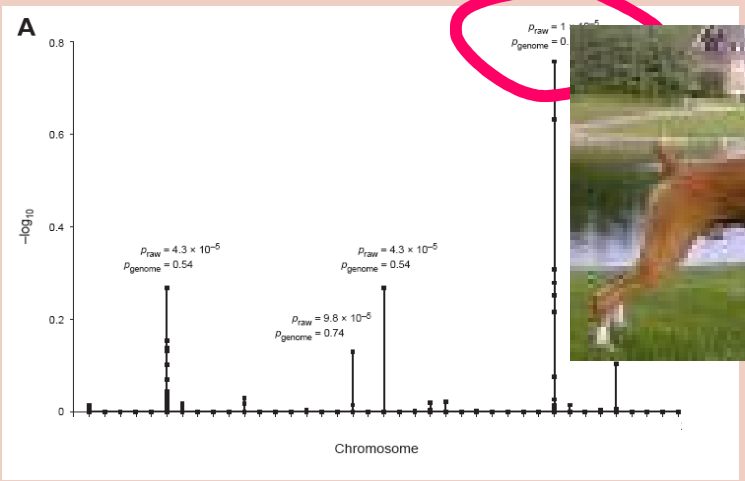
Within a population

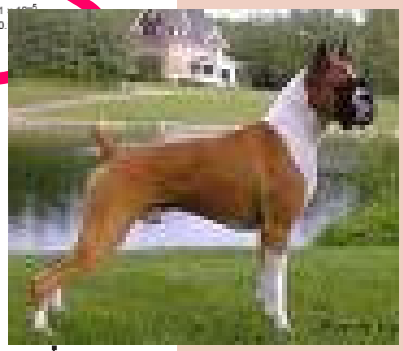
- Different combinations for a chromosome

Association with disease?

- Difference between normal and affected dogs

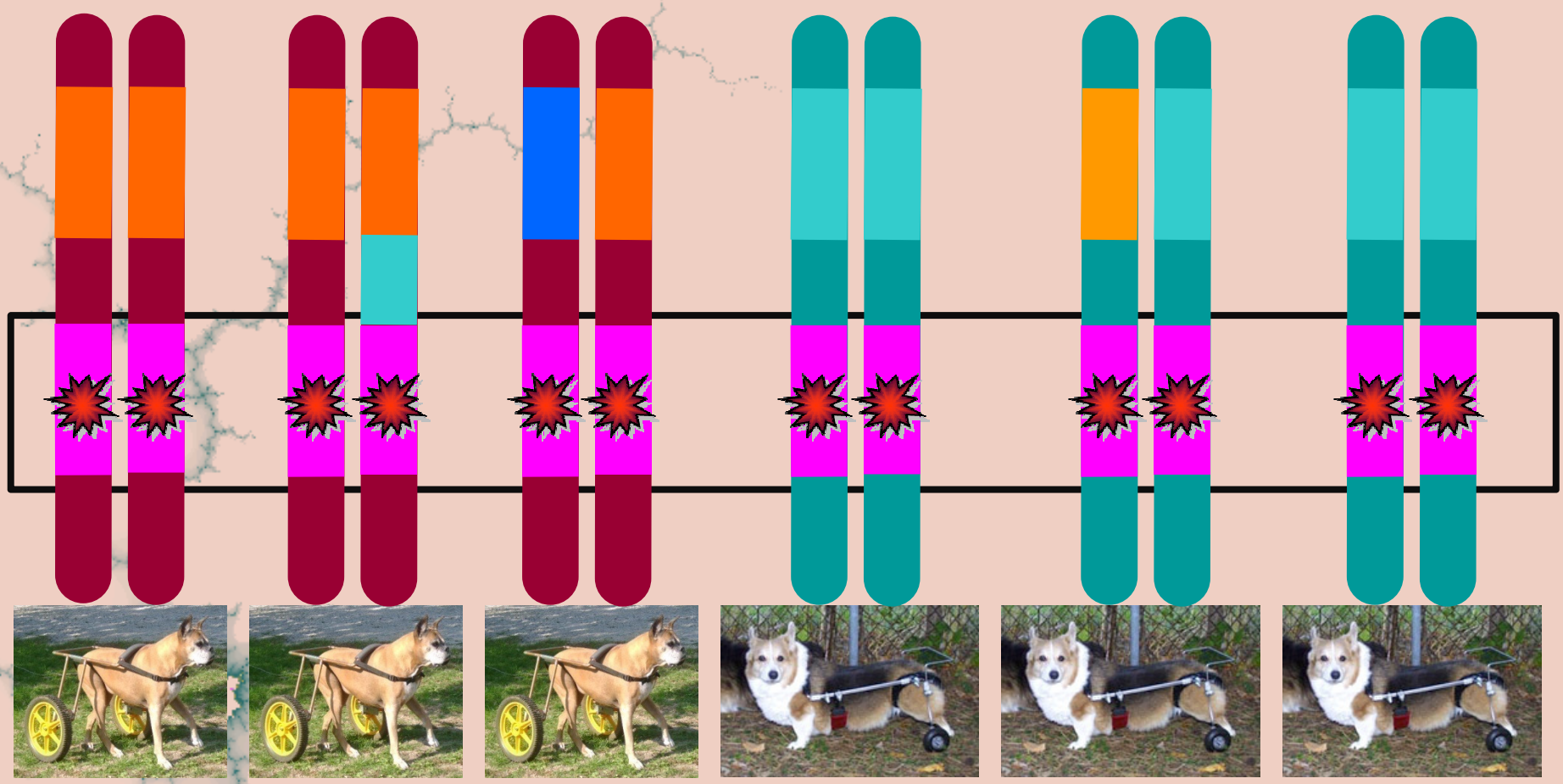






Fine mapping

- Similarities with affected dogs of other breeds

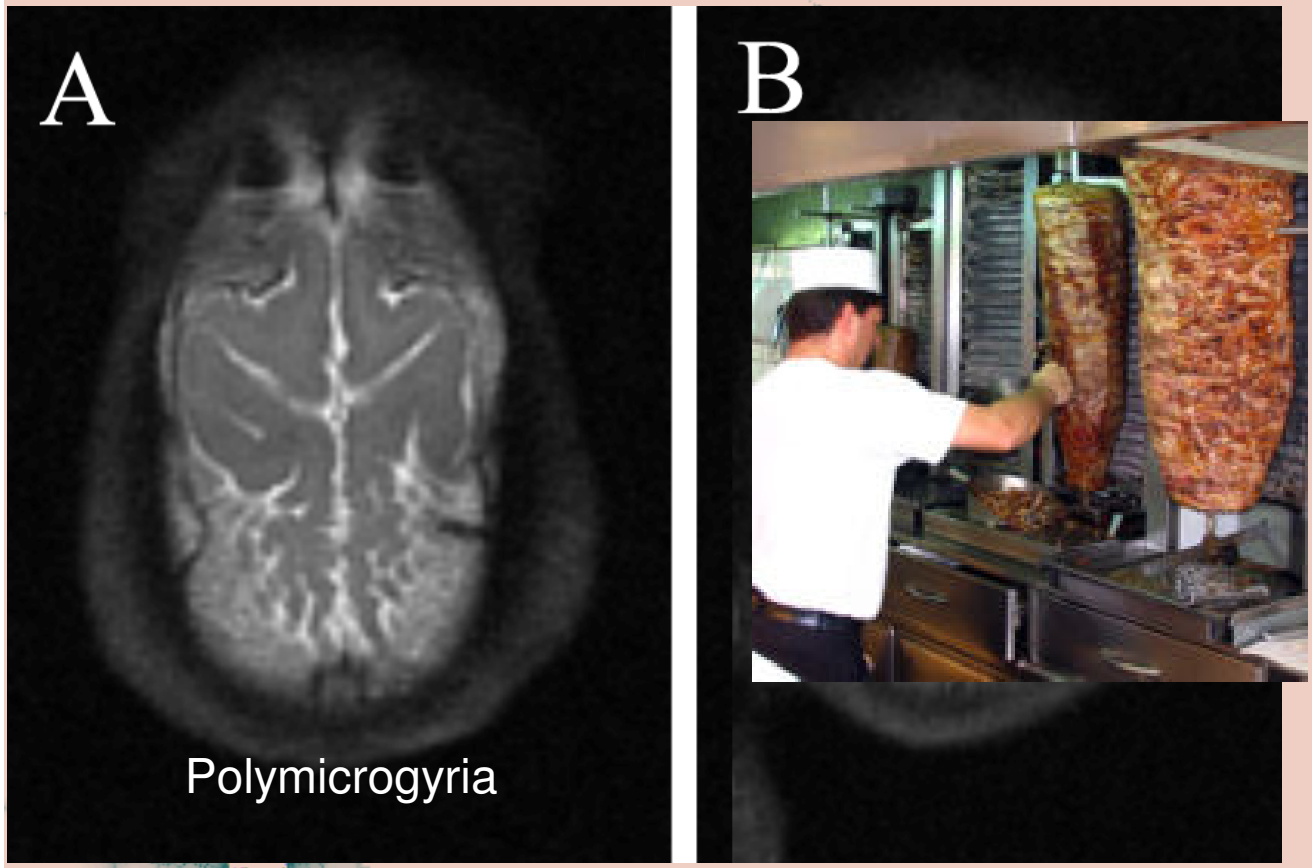


Objectives

- Translation from spontaneous disease to lab studies & back again
- How spontaneous disease can be utilized
- Genetic disease can teach us about acquired diseases
- Fruitful collaborations
- Value of large animal model (polymicrogyria?)
- Establish breeding colony
- Utilize clinical population

Polymicrogyria

- ***Poly*** - many
- ***micro*** - small
- ***gyria*** - turns



Mouse

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