Canine Neurodegenerative Diseases

Comparative Neurology Program

Dennis O’Brien DVM PhD
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

• Experimentally remove gene from mouse
• Model how gene causes disease & treatment
• Doesn't always work
Polymicrogyria

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

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
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Questions?
Degenerative Myelopathy

- Older dogs (> 8 years)
- Progressive paralysis

Mutation in \textit{SOD1} gene

- Familial amyotrophic lateral sclerosis (ALS)
Mutation in *SOD1* gene

- At risk population
- Age of Onset
- Identify additional risk factors
- Intervention 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

• Gene discovery

• Diagnostic tests confirm

• Gene discovery

http://www.archbase.com/fayuin/
Canine disease

- Model for pathogenesis & therapy
Canine disease

- Translation to patients
Canine disease

- Translation to patients
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