Genetic Diseases in Dogs and Humans

Duchenne Muscular Dystrophy, Copper Toxicosis, and Narcolepsy

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Duchenne Muscular Dystrophy

Background: Golden Retriever Muscular Dystrophy (GRMD) in dogs and Duchenne Muscular Dystrophy in humans are characterized by on-going muscle fiber necrosis and regeneration

Causes: X-linked recessive mutation / deletion in *DMD* gene that encodes for dystrophin, a vital protein for supporting muscle fiber strength and preventing muscle fiber injury

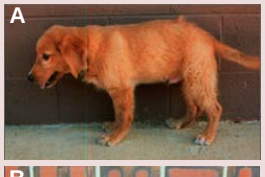
Dogs: RNA processing error from single point mutation → early termination of translation and truncated dystrophin

Humans: mutations or deletions in DMD gene

Symptoms: elevated creatine kinase (CK) levels at birth (indicating abnormal muscle degradation), progressive deterioration of muscles

Dogs: gait abnormalities ("bunny" shuffle), muscle atrophy, fibrosis, contractures, cardiomyopathy

Humans: muscle fatigue, learning difficulties, loss of mobility, breathing difficulties and heart disease by 20



Affected Golden Retriever at (A) 3 months and (B) 6 months (NCDMD 2014)

(A) Affected child using hands to push body up due to lower limb weakness (Gower's Sign). (B) Necrotic muscle cells replaced by fibrous and fatty tissue (Pestronk 2013)

Treatment: no cure; treatment aims to control symptoms and improve quality of life

Dogs (experimental):

- Gene Therapy: repair mutation, reintroduce gene via plasmid
- Cell-Based Therapy: transplant stem cells

Humans: physical therapy, insulin-like growth factor, cardiac drugs, corticosteroids, aminoglycoside antibiotics

Copper Toxicosis

Background: 'Copper Toxicosis' in dogs (especially Bedlington terriers) and 'Wilson's disease' in humans results in toxic levels of copper in the liver and other organs

Causes: autosomal recessive mutation in copper metabolism genes *COMMD1* or *ATP7B*

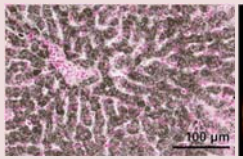
Dogs: loss of function mutation in *COMMD1*

Humans: loss of function mutations in *ATP7B*

Symptoms: liver inflammation → necrosis → cirrhosis

Dogs: liver most affected. Often no signs initially; differences in severity depending on breed; lethargy, vomiting, icterus, hepatic encephalopathy

Humans: liver, brain, and cornea affected. Kayser-Fleischer rings in eyes; neurological issues (anxiety, schizophrenia, depression); abnormal serum ceruloplamin concentrations



Copper in liver cells of a 3-year-old female Bedlington Terrier (Fieten 2012)

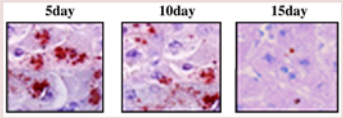
Reddish-brown Kayser-Fleischer ring in the right eye (Sullivan 2002)

Treatment: fatal if untreated

- life-long treatment with chelating agents D-penicillamine and 2,3,2-tetramine causes copper excretion in urine
- zinc compounds to inhibit GI absorption of copper, especially for presymptomatic or pregnant patients

Dogs: selective breeding: test for disease at 1 year old (liver biopsy/DNA test) and exclude diseased dogs

Humans: chelating agents often do not aid in recovery from neurological defects (could worsen the condition)



Progression of treatment with D-penicillamine and Andrographoliode (AG) in a rat model, copper is stained red (Roy 2011)

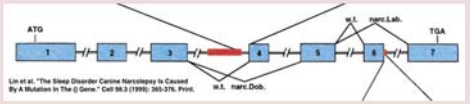
Narcolepsy

Background: a life-long chronic brain disorder that disturbs the general circadian rhythm

Causes: Deficit in the hypocretin signaling pathway causing abnormal hypothalamic function

Dogs: Mutation/deletion in Hcrtr2 (hypocretin receptor 2) → loss of protein function

Humans: No mutation in gene noted; most likely acquired by destruction of hypocretin synthesizing cells



Hcrtr2 mutation in dogs (Lin 1999)

Symptoms: cataplexy following emotional stimuli, excessive daytime sleepiness, disrupted REM sleep

Dogs: develops between 4 weeks and 6 months

Humans: develops between age of 7-25

Catalepsy in a Doberman (Nishino 2007)

Loss of hypocretin cells in humans (Thannickal 2000)

Treatment: no cure, CNS stimulants to increase wakefulness, avoid cataplexy triggers

Dogs: methoxamine or H3 antagonists for cataplexy

Humans: sodium oxybate; tricyclic antidepressants for cataplexy; daytime naps

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