Pharmacogenomics in the Canine Patient

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What is pharmacogenomics?[1,3,10]

- Pharmacogenomics is the study of how genetic makeup determines response to a drug.
- If a dog is not responding to a drug, there could be underlying metabolic conditions leading to lower levels of drug in the dog's system.
- Toxicities are sometimes seen in dogs because they lack proteins responsible for excretion or degradation of a drug.
- Pharmacogenomics is driving the new practice of Personalized Medicine.
- Personalized Medicine is the practice of picking medications that will be more likely to provide good outcomes or avoiding drugs with high probabilities of toxicities or drug interactions.
- Personalized medicine can save owners money since they won't be trying drugs on a trial-and-error basis (or will do so to a lesser extent).
- Personalized medicine can also hasten treatment for progressive diseases such as cancer and epilepsy.

Relationship between humans and dogs[3]

- Dogs are model organisms for human genetic disease.
- Dogs and humans share environments, are exposed to the same toxins, share lifestyles, and often share the same diseases as their human companions.
- Dogs and humans share 85% of their genetic makeup.
- By studying genetic diseases in dogs, we can extrapolate how genetics and epigenetics (how genes are expressed rather than coded for) will affect treatment in humans.
- Because detailed pedigrees are often kept for dogs and they have shorter gestation periods and lifespans than humans, we can follow heritable diseases and mutations more readily.

Medications affected by genes in the dog

Ivermectin [4,9]

Current Use: Commonly used as an antiparasitic to treat and prevent heartworms, microfilarial keratitis and ectoparasites,
Affected gene: MDR1
Outcome: A 4 base-pair deletion leads to a premature stop codon. This means that p-glycoprotein (p-gp) will be dysfunctional and drugs can cross the blood-brain-barrier into the CNS, leading to toxicities.
Commonly Affected Breeds: Herding breeds (especially Collies)

Sildenafil [1,5]

Current Use: Pulmonary hypertension, congenital idiopathic megaesophagus, Eisenmenger's syndrome, MMVD
Affected gene: PDE5A
Outcome: A change between glutamine to lysine leads to lower cGMP levels, which is the target of sildenafil treatment. This leads to poor efficacy and worse outcomes in dogs with this mutation

Propofol [2,7,8]

Current Use: General anesthesia
Affected gene: CYP2B11
Outcome: CYP2B11 is expressed at lower levels and drug clearance is decreased. Dogs recover slowly from anesthesia.
Commonly Affected Breeds: Some Sighthounds (especially Greyhounds)

Doxorubicin [6]

Current Use: Chemotherapy
Affected gene: MDR1
Outcome: Toxicities at normal doses of chemotherapy, especially myelosuppression and GI toxicities
Affected breeds: Herding breeds (especially Collies)

Future Directions[1,2,3,8]

- Studying treatment of significant humans diseases in dogs and seeing positive outcomes from intervention with personalized medicine may change the way human medicine is practiced.
- Studying disease that often take long periods of time to come up with the perfect "cocktail" of treatments, such as epilepsy, may lead to shorter periods of time between diagnosis and successful treatment.
- Studying pharmacogenetic response to medications such as chemotherapy may improve our understanding of cancer and how it responds to treatment.

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