Canine melanoma study identifies genetic basis of disease, potential drug targets

September 7 2018, by Steve Yozwiak

Credit: Translational Genomics Research Institute

As a veterinarian, Dr. Carolyn Duregger is familiar with the telltale signs of canine melanoma. So when she gave her own dog, Parker, a routine oral examination, the 1-centimeter-diameter discolored lump in the pup's upper right gums took her breath away.

"It's an aggressive cancer with poor prognosis that I've seen many times. My stomach dropped. I literally gasped," said Dr. Duregger, recalling the moment she realized her fluffy, 9-year-old Wheaten terrier might be in big trouble.

Dr. Duregger surgically removed the cancerous lump, and started Parker on radiation and an immunotherapy drug. But these measures don't always last, which is why she whole-heartedly supports the molecular-level precision medicine research led by the Translational Genomics Research Institute (TGen), an affiliate of City of Hope.

In the most comprehensive study of its kind, TGen and its collaborators from across the nation used multiple genomic analysis techniques to identify several gene mutations that could be the keys to what drives melanoma in dogs. Following the path from human melanoma, the findings of recurring molecular changes in canine melanoma can help veterinary physicians pinpoint potential new treatments for dogs. Likewise, human physicians will view these changes in light of the type of melanoma that occurs in non-sun exposed areas (as in the case of Parker) in the mouth, or other mucosal surfaces.

Researchers specifically identified mutations in a gene called PTPRJ, a tumor suppressor gene, according to the multi-year study published today in the journal *PLOS Genetics*.

"This mutational landscape of canine melanoma resembles that seen in human melanoma subtypes found in sun-shaded areas of the body, such as the nose and mouth, which remain difficult to treat. This similarity means that we have a genetic bridge across which understanding of the disease in either species can inform the other," said Dr. Will Hendricks, a TGen Assistant Professor of Integrated Cancer Genomics, and the study's lead author.

While melanoma is commonly associated with skin cancer, different types of melanoma can originate in different parts of the body, and it often spreads to the lungs, lymph nodes, bones and brain.

Researchers looked at 37 canine tumors and 17 control samples from a variety of dog breeds, and used several genomic analysis tools, including: whole genome sequencing, RNA sequencing, array comparative genomic hybridization, single nucleotide polymorphism array, and targeted Sanger sequencing analyses.

"Malignant melanoma is a significant cause of death among domestic dogs, and also provides a powerful comparative model for melanoma among humans," said Dr. Jeffrey Trent, TGen President and Research Director, and the study's senior author. "Overall, these data inform biological comparisons between canine and human melanoma, while suggesting actionable targets for both."

The study found mutations in the PTPRJ tumor suppressor gene in seven of the tumors, and cancer-activating mutations in the RAS gene in nine of the tumors, in addition to changes in the genes MDM2 and TP53.

"Our genetic understanding of canine melanoma now allows us to continue to work to understand melanoma biology, and serves as a roadmap to developing and evaluating new treatment strategies," Dr. Hendricks said.

The study examined several dog breeds with a propensity for melanoma, including Cocker Spaniels, an English Cocker Spaniel and a Labrador retriever. The paper—Somatic inactivating PTPRJ mutations and dysregulated pathways identified in canine malignant melanoma by integrated comparative genomic analysis—notes that an expanded study of breed-specific groups will be critical for further understanding of melanoma among dogs.

More information: William P. D. Hendricks et al. Somatic inactivating PTPRJ mutations and dysregulated pathways identified in canine malignant melanoma by integrated comparative genomic analysis, *PLOS Genetics* (2018). DOI: 10.1371/journal.pgen.1007589