

Canine Models of Human Diseases

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A recent paper by Grall *et al.* published in *Nature Genetics* (2012;44:140-9) and highlighted in *Science* (2012;335:271), reminds us of the value of spontaneous diseases of animals, particularly dogs, to our understanding of human disease genetics and pathophysiology and to the development of therapeutic interventions. Physicians concerned principally with clinical medicine, who may have more difficulty grasping One Health principles calling for closer ties with the veterinary medical community, may be especially interested in the illustration provided by this publication.

Grall *et al.* describe a spontaneous disease in golden retriever dogs that clinically resembles a form of congenital ichthyoses in humans. Ichthyoses include both nonsyndromic ichthyosis vulgaris and various syndromic forms associated with a noncutaneous abnormalities (e.g., Netherton syndrome, Chanarin-Dorfman syndrome, Sjogren-Larsson syndrome, and Refsum's disease). The genetic basis of ichthyoses and other rare diseases in humans is difficult to study because of the inability to collect enough families affected by a single clinical entity. In contrast, dogs are subject to intensive in-breeding used to select for desirable traits, and in consequence have developed a number of breed-specific congenital disorders. Dog breeds thus represent a unique model for identifying genetic linkages responsible for disease expression. Multiple breed-specific forms of ichthyoses have been described, and the genetic basis of a few of these have been identified: e.g. Norfolk terriers [mutation in the KRT10 (Keratin 10) gene], and Jack Russell terriers [insertion in the TGM1 gene, a gene associated with human ichthyosis also].

In the recent paper by Grall *et al.* a homozygous mutation in PNPLA1 was identified in golden retrievers with hereditary nonepidermolytic retention ichthyosis, a disease that has recently spread throughout the breed due to repeated in-breeding of champion dogs. The authors then studied 46 consanguineous human families with congenital ichthyoses in which previous genetic studies had failed to find a causative mutation. In two families with multiple affected siblings, homozygous mutations in PNPLA1 were found. The study showed that mutations in PNPLA1, the result of autosomal recessive segregation during in-breeding, were responsible for a similar clinical disorder in dogs and humans.

This is not a unique example, and indeed there are numerous reports of spontaneous hereditary diseases of dogs serving as important models for human hereditary diseases, often with homologous single-gene defects. A few examples may be cited, including: Progressive retinal atrophy (PMA) in dogs is the canine equivalent of retinitis pigmentosa in humans; other retinopathies, such as Leber congenital amaurosis; X-linked myotubular myopathy in Labrador retrievers; inherited glycogen storage disease in Maltese terriers analogous to human von Gierke disease (mutation in glucose-6-phosphatase- ; and trapped neutrophil syndrome in border collies, a model for Cohen's syndrome in humans.

The practical value of these genetic homologies and canine models for human medicine is immense, because the gene defects, once identified and understood, can be used for

diagnosis and genetic counseling, and for the design of specific interventions, including gene therapy. The genetic bottlenecks introduced in the practice of selective breeding of dogs has revealed much about the genetic basis of human disease, and represents a field of study of invaluable consequence to human medicine. The relevance to One Health is clear.

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