

## The Human/Canine Connection

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The release of the canine genome sequence has brought more attention to dogs as a “powerful biomedical model,” Dr. Breen said. One result has been a larger number of people asking for a definition of a domestic dog.

Citing a passage from Rudyard Kipling’s *Just So Stories*, Dr. Breen said the relationship between humans and canines can be traced back 30,000 to 50,000 years. Some of the earliest surviving records of that relationship date back to ancient Egypt, where pictographs on gravestones and coffins showed different dog breeds associating with members of the nobility.

Dr. Breen showed a print from the world’s first official dog show, conducted by the Kennel Club of England in 1873. “We can now start to see that many of the dogs that were around did not resemble the ancient breeds,” he said. “Instead of breeding dogs primarily for their function, we started to breed for their phenotype,” as a growing leisure class began inbreeding and linebreeding for specific characteristics that they favored.

The bond between dogs and humans “really took force when dogs became members not only of our households, but of our families,” Dr. Breen said. Dog owners take their companions everywhere. Dogs are trained to understand humans, and many still serve their owners as intruder alarms, as they have over the millennia.

Dog owners have joked for many years about their physical similarities to their pets. With the release of the canine genome sequence, there is now evidence that dogs and humans are 85%–100% similar at the genetic level.

“My perception as a geneticist is that we’re all just mammals, and as mammals we’re all just differential rearrangements of the same collection of ancestrally related genes,” Dr. Breen said. “We all have the same genes, and we all have about 20,000 of them,” so the only difference is in the way the genes interact and are expressed.

Part of what makes canine research powerful is the potential for “multiple generations on the ground at the same time. We can’t do that for humans.” An important consequence of linebreeding is that the same ancestors appear multiple times in the same purebred pedigree, often showing up in both the maternal and paternal line.

“It’s not surprising that our dogs are now being described in a politically correct way as ‘genetically challenged,’” with many breeds facing a serious reduction in their genetic variability. High levels of inbreeding lead to smaller litters and reduced fecundity, outcomes that Dr. Breen described as nature’s way of slowing down the process. As

researchers, veterinarians, breeders, and owners all learn how to prolong life and health, the dogs breed more, and genetic problems can be perpetuated.

After 300–400 years of selective breeding practices and severely reduced variability, dogs are presenting with genetic diseases that affect every body system. Dr. Breen said 25% of purebreds in the United States are either affected by or carriers of a serious genetic disease. By contrast, in the much more genetically diverse human population, a 1% risk of genetic disease is considered shocking and worthy of medical attention.

“This is why I always like to regard the canine genome as man’s new best friend,” Dr. Breen said. He cited narcolepsy and Lafora’s disease, one of five known inherited progressive epilepsy syndromes, as examples of human conditions better understood as a result of canine genetic research. Researchers working with the Doberman isolated the narcolepsy gene and are testing a therapy that could help 250,000 Americans if it proves to be effective on dogs.

In Dr. Breen’s specialty area, canine cancer, “we have shown quite irrefutably that dogs and humans present with the same chromosome aberrations, the same genetic lesions, in corresponding cancers.” He said he has spoken to human cytogeneticists who initially questioned the genetic link; after checking further, they reported back that the anomaly was very rare. “That’s because the technology is just not capable of finding these aberrations in humans.”

After coexisting with dogs for tens of thousands of years, Dr. Breen said humans have two good reasons to study canine genetic disease. The first is that breeding programs are responsible for many canine diseases. The second is that canine research can help health researchers understand human biogenetic disease. “The irony is that the keys to unlocking these intriguing puzzles may be sitting, walking, and sleeping right beside us,” so that the emotional bond between dogs and humans “is ever so much fortified by the biomedical relationship that we share.”

### *Discussion*

A participant said more research on specific targets would be needed before human gene therapies can be adapted for use with canine cancer patients. Dr. Breen said a key challenge for canine health research is to demonstrate a strong enough biomedical relationship between humans and dogs to “raise eyebrows with Big Pharma and make them interested.”

Dr. Breen agreed with the participant’s statement that researchers need more information on biology. “That’s why I wholeheartedly support the mission of CHF, because I don’t have to justify the dog as a model,” he said. “I’ve gone on record that studying dog cancers over the next five to 10 years will yield more cancer-associated genes than working in the same field in humans,” thereby benefiting dogs first before the results move back to humans.

At another participant's invitation, Dr. Breen announced that he and Dr. Jaime Modiano had just secured a five-year, \$1-million grant from the US National Institutes of Health (NIH) to study lymphoma genes in dogs and associate the results back to human cancer research. "NIH doesn't fund projects unless they think they're going to win," he said. A five-year grant in tight financial times is a testament to CHF's foresight in funding the initial research that led to the grant.

A participant recalled researchers' commitment in the mid-1960s to "conquer cancer" within 10 years. At the time, he said, NIH scientists saw no value in dogs as a model for understanding human cancer. Now, "we may be able to go light years ahead in understanding human cancer by understanding dog cancer."

A participant emphasized the genetic damage that results when popular sires are overused in breeding programs. "People should go back and point this out to their kennel clubs," Dr. Breen said. "The damage is unbelievable, and you won't know about it for two or three generations, until these dogs start crossing back" through the pedigrees.