Man's Best Friend Solves Human Neuropsychiatric Diseases

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In "Genetics: Pet Project," David Cyranoski (2010) describes researchers looking to man's best friend to solve problems related to human neuropsychiatric diseases. An estimated 77.5 million dogs in the U.S. have some form of behavioral disorder (p. 1037). According to U.K. geneticist Jonathan Flint, "[Dogs] are the only naturally occurring models of psychiatric disorders, and perfect for genetic mapping and cloning." It has been difficult to pinpoint genes causing psychiatric disorders in humans due to genome complexity, but dogs' genomes make it easy to find the genes responsible (p. 1036).

Success stories show that studies in dogs can reveal answers in humans. For decades, researchers studied DNA in narcoleptics to find the genes responsible for the sleep disorder. Emmanuel Mignot, a sleep researcher at Stanford University School of Medicine, began using classical genetic techniques to breed narcoleptic Dobermanns, who are prone to the disorder, to trace the inheritance patterns of the disease. It took Mignot ten years to uncover the mutation that caused narcolepsy; a gene called hypercretin receptor 2, which regulates the brain's uptake of the neurotransmitter hypercretin (a.k.a. orexin). Mignot did not find the same mutation in the corresponding human gene, but he discovered changes in the hypercretin pathway. He began measuring hypercretin in cerebrospinal fluid and learned that it was nonexistent in narcoleptics. Researchers are now narrowing the search for human gene mutations that cause hypercretin depletion and narcolepsy (p. 1037).

Since Mignot's studies have been published, the canine genome has been sequenced so that researchers can efficiently compare the genomes of hundreds of dogs by looking at single

nucleotide polymorphisms (SNPs). SNPs are single-letter changes in genomes that act as markers for inherited blocks of DNA. Genome-wide association studies (GWAS) using these markers are much simpler in dogs than in humans, because individual breeds share larger DNA blocks than those shared by any two humans. Therefore, researchers can study far fewer SNPs and individuals to find a block of DNA that associates reliably with a disease. GWAS have proved successful in finding the genes for several dog traits that are relevant to human diseases. Results show that once a mutation (related to a disease) is found in dogs, 90% of the cases involve the same gene in humans (p. 1037). However, for GWAS to be successful, canines must have *exactly* the same disorder as that being studied (p. 1038).

Compulsive disorders may be among the first successes. Over 60 studies on genes in mice thought to be linked to obsessive-compulsive disorder (OCD) failed (p. 1037). Due to the high incidence of OCD in canines (tail-chasing in bull terriers, and excessive chewing or licking in Dobermanns, German shepherds, Great Danes, and golden retrievers), studies revealed a link between canine OCD and a region on the dog's chromosome 7 (p. 1038). It was found that 60% of Dobermanns that obsessively chewed had the deviation, compared to 22% with no indication of OCD (p. 1038).

Further studies include those conducted by European dog-genetics initiative LUPA, a $15.4M project aimed at studying single-gene and complex disorders including cancer, cardiovascular disease, and neurological disorders by genotyping 10,000 dogs (p. 1037). Moreover, LUPA is trying to clarify diagnosis to identify neurological disorders consistently. LUPA is also focusing on aggression in spaniel breeds in hopes of identifying gene mutations related to human bipolar disorder, schizophrenia, and other mental disorders involving aggression (p. 1038).

Regardless of whether dog studies improve or prevent human disease, they certainly help canines. Breeders can focus on screening and more selective breeding to eliminate undesirable behavioral traits, thereby relieving dogs of their suffering (p. 1038).

Reference

Cyranoski, D. (2010). Genetics: Pet project. *Nature 466*, 1036-1038. doi:10.1038/4661036a.

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