

NEWS

# Dog pedigrees unearth genes for psychiatric disease

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**Model behavior:** Bull Terriers, some of which compulsively chase their tails and stare off into space, might help find the genetic causes of autism.

For the title of best animal models, lab rats may be facing some competition from man's best friends: dogs.

Canines and humans get many of the same diseases, and often respond to the same drug treatments. Dogs also tend to mimic the symptoms and pathology of human disease much more closely than rodents do.

"Understanding the underlying genetics in dogs is almost certain to enlighten us about the human condition," notes **Elaine Ostrander**, chief of the Cancer Genetics Branch at the National Human Genome Research Institute.

Because dogs are purposely inbred for specific traits and are extremely well characterized, scientists have long used their pedigrees to study cancer and other biological diseases. But researchers are just beginning to use dogs as models of psychiatric and behavioral conditions, including obsessive-compulsive disorder (OCD) and autism.

In a January report, for instance, scientists pinpointed a genetic hotspot for compulsive behavior by screening a conspicuous subgroup of Doberman Pinschers: those that repetitively suck their flanks. The findings were published in *Biological Psychiatry*<sup>1</sup>.

The gene may also drive compulsive behaviors in other dog breeds and other species, the

researchers say.

"We think this gene will also be the same one involved in human OCD," notes investigator **Nicholas Dodman**, director of the animal behavior clinic at Tufts University in Massachusetts. "This is really just the beginning of using [dog] behaviors to study behaviors of humans."

The gene encodes a protein, cadherin 2, that helps form connections between brain cells. Researchers have recently implicated this family of proteins in other mental disorders. For instance, a report in the same issue of the journal links cadherin 7 to bipolar disorder<sup>2</sup>; a large study last year **tied two other cadherins to autism**, which often includes repetitive behaviors<sup>3</sup>.

With such robust corroborating evidence, the dog study throws a bone to researchers studying people with OCD. The disorder runs in families but has largely mysterious genetic origins, making it difficult to understand its biological underpinnings.

"This particular study has leap-frogged ahead of the human studies," says **Paul Arnold**, who was not involved in the new work.

In 2007, dozens of investigators around the world, including Arnold, launched a genome-wide association study of about 1,600 people with OCD and their families. The researchers are searching the data for common genetic variants that increase risk of OCD.

"We haven't had any really clear-cut genetic animal models of OCD. The fact that they have used this model to identify a gene that makes sense, mechanistically — that's pretty exciting," says Arnold, a staff psychiatrist at the Anxiety Disorders Clinic at the Hospital for Sick Children in Toronto.

Studies of dog genetics have exploded since 2005, when scientists decoded the canine genome<sup>4</sup>. Ostrander's lab — one of the largest focused on this work — has discovered genes related to cancer<sup>5</sup>, eye disease<sup>6</sup> and morphology, such as short legs<sup>7</sup> and curly hair<sup>8</sup>.

Fewer efforts have looked at dog genes to study brain conditions, but those findings are also encouraging. For instance, by studying dogs with narcolepsy, **Emmanuel Mignot's** lab at Stanford University isolated genes for hormones, called orexins, that turned out to play a role in humans with sleep disorders<sup>9</sup>.

In 2005, an international group of researchers identified a mutation in dogs with epilepsy, and showed that animals carrying the mutation are good models of Lafora disease, a form of epilepsy that is seen in teenagers<sup>10</sup>. And **Samuel Wang**, associate professor of neuroscience at Princeton University, is using images of dog brains to investigate whether the size of various brain regions correlates with specific behavioral characteristics, such as intelligence or aggressiveness.

The new genetic study is the first to focus on more subtle behaviors reminiscent of those seen in psychiatric disorders.

"We've known for a long time that at least a small subset of the neuropsychiatric disorders that we see in humans we see in dogs as well. Now's the time to tackle those," says Ostrander. "I think this will be the first of many such papers that we'll see."

## Fine pedigrees:

The new study began one day in the late 1980s, when Dodman attended a dog-training class at Tufts' veterinary school. He was training a 1-year-old white, male Bull Terrier. The dog's owner approached him after class and asked if he knew anything about tail-chasing behavior in the breed. Coincidentally, Dodman had recently stumbled upon a case report about tail-chasing.

Dodman took the man upstairs to his office to look at the paper more closely, and discovered that it described a 1-year-old white, male Bull Terrier.

"Here they were displaying absolutely identical behaviors. And I went, oh my god, this is genetic," Dodman recalls.

He began collecting blood samples of Bull Terriers. In 2000, he met **Edward Ginns**, director of the Molecular Diagnostics Laboratory at University of Massachusetts.

Interested in the genetic underpinnings of depression, Ginns had for years studied isolated groups of people, such as the Amish, or ethnic groups with fairly homogeneous genetic roots, such as Ashkenazi Jews. Because these groups are genetically similar, differences between individuals with and without a specific disease are relatively easy to spot.

"But one disadvantage of pedigrees is they're very hard to find. And even if you find them, it's difficult to exquisitely characterize the symptoms," Ginns says. "So it was of high interest to me that Nick had this dog population."

The duo formed a collaboration focused on finding an animal model for repetitive behaviors, and cast a wide net. Dodman passed out flyers at dog shows and gave lectures about the research to breed clubs. Eventually, he collected hundreds of samples from Bull Terriers and Dobermans — which often suck on their hindquarters or on blankets — as well as purebred horses and Siamese cats, which can also show repetitive behaviors.

"Early on, of course, they were just stuck in the fridge, waiting for the technology to catch up," Dodman says.

By 2007, researchers had created a gene chip that could identify common genetic variants in the canine genome, called single-nucleotide polymorphisms (SNPs), from blood samples.

## Exciting genes:

The new study reports their SNP comparison of 94 Dobermans that sucked either on their flanks or on blankets, or on both, and 73 Dobermans that did not show any repetitive behaviors. They found that dogs with compulsive behaviors tend to carry SNPs on a particular spot on canine chromosome 7 that contains the cadherin 2 gene.

Cadherin 2 is abundant in the hippocampus and cerebellum. It is active early in brain development, when nerve cells are forming connections, called synapses, with each other.

"It was very thrilling to find that we hit a neurological gene that sits at the synapse and has to do with transmission of signals in the brain," says **Kerstin Lindblad-Toh**, co-director of the Genome Sequencing and Analysis program at the Broad Institute in Massachusetts who led the canine genome project. "That makes it a very believable hit, and could be the start of unraveling a very important pathway for what happens in OCD."

Ginns is also excited about the clinical applications of the finding. "When you start a genome-wide scan, the anticipation is, 'Gee, if you're lucky you'll see something that might be almost significant'," he says. "When you run into something like this, which is highly significant, it's just too good to pass up."

The researchers shared these results with colleagues at the National Institute of Mental Health, who are sequencing the gene in people with OCD.

Meanwhile, Dodman says his work on Bull Terriers will be useful for autism research. He's found that males in this breed that chase their tails can also exhibit autism-like behaviors, including aggression, seizures and something he calls "trancing".

"They fixate on something, and the stare cannot be broken. It's like they're off in some kind of dream world," he says. "The parallels with autism are striking." His group is performing a similar SNP analysis of this breed.

Despite dogs' value as models for certain behaviors, not everyone is optimistic that they will prove useful for studying autism.

Psychiatric phenotypes in dogs are tricky to measure because it's impossible to assess whether the animals have obsessive thoughts or frequent anxiety, notes Arnold, who is collaborating with Finnish researchers to study repetitive behaviors in Bull Terriers. "You can't ask dogs what they're thinking, so many symptoms of OCD are just inaccessible," he says. "Autism would be even more

challenging."

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