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Puppy bred to have muscular dystrophy saved by surprise mutation

Dog study provides potential pathway to new treatments for the disease.

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12 November 2015

CEGH-CEL/University of São Paulo

Ringo, a golden retriever, avoided muscular dystrophy despite being bred with a faulty gene.

Ringo, a golden retriever born in 2003 in a Brazilian kennel, was never expected to live long. Researchers bred him and his littermates to inherit a gene mutation that causes severe muscular dystrophy. They hoped that the puppies would provide insight into Duchenne muscular dystrophy (DMD), an untreatable and ultimately fatal human disease caused by inactivation of the same gene.

But Ringo's muscles didn't waste away like his littermates', and researchers have now determined why: he was born with another mutation that seems to have protected him from the disease, according to a paper published in *Cell*[1]. Scientists hope that by studying Ringo's mutation — which has never before been linked to muscular dystrophy — they can find new treatments for the disease.

As many as 1 in 3,500 boys inherit mutations that produce a broken version of a protein called dystrophin, causing DMD. (The disease appears in boys because the *dystrophin* gene sits on the X chromosome, so girls must inherit two copies of the mutated gene to develop DMD.) The protein helps to hold muscle fibres together, and its absence disrupts the regenerative cycle that rebuilds muscle tissue. Eventually, fat and connective tissue replace muscle, and people with DMD often become reliant on a wheelchair before their teens. Few survive past their thirties.

Special cases

Some golden retriever females carry dystrophin mutations that cause a similar disease when passed onto male puppies. Dog breeders can prevent this through genetic screening. But Mayana Zatz, a geneticist at the University of São Paulo in Brazil, and her colleagues set out to breed puppies with the mutation to model the human disease.

DNA testing confirmed that Ringo had inherited the *dystrophin* mutation, but he showed none of the severe symptoms. Ringo's case flummoxed Zatz and her team, so she decided to follow his life closely in her laboratory's kennel. "We treat the dogs here like children," Zatz says. "They are very well kept, they have a place to run, they have sun, and air conditioning when it's hot."

Ringo proved something of a troublemaker. "When people would leave the door open he would run and mate," Zatz says. In total,

Ringo sired 49 puppies with four different females — “from natural intercourse”, she and colleagues note in one paper[2]. One of his puppies, Suflair, also never developed full muscular dystrophy, despite inheriting a faulty *dystrophin* gene.

“These were two very unusual dogs, the father and the son, so we decided to map what gene might be the modifier,” says Louis Kunkel, a geneticist at Boston Children's Hospital in Massachusetts, who first identified the gene and protein responsible for DMD in the 1980s[3]. Kunkel became involved with Ringo and Suflair when a former graduate student in Zatz’s lab, Natassia Viera, did a postdoc in his lab.

Rescue gene

The team compared the genomes of Ringo and Suflair with those of other golden retrievers with muscular dystrophy and identified a mutation in a development gene, *Jagged1*, that distinguished the father and son from 31 severely affected dogs in the same colony. The muscles of Ringo and his son harboured higher levels of the Jagged1 protein compared with affected dogs. When the researchers mimicked this trait in zebrafish lacking dystrophin, it also protected the fish from muscle tearing and other symptoms of muscular dystrophy.

Kunkel says that the team does not yet know how higher levels of Jagged1 protect the dogs from muscular dystrophy. The protein is a player in a pathway with a role in many aspects of biology, including muscle development and regeneration. Perhaps, says Kunkel, Ringo and Suflair’s *Jagged1* mutation compensates for the muscle regeneration problems caused by a lack of dystrophin. They are now looking for drugs that produce higher levels of Jagged1 in mice and zebrafish. But Kunkel cautions that it will be difficult to mimic the dogs' exact biology with a drug.

Elizabeth McNally, a geneticist at Northwestern University Feinberg School of Medicine in Chicago, Illinois, thinks that mutations that counteract muscular dystrophy could point to new treatments — not only for DMD, but also for other causes of muscle atrophy including old age. “I love that it came out of the dog model,” she says.

Ringo died last year aged 11, within the normal lifespan for a golden retriever. Nearly 10 years old, Suflair is now showing his age too. “Suflair can walk but he can’t jump anymore,” Zatz says. “But he’s an old dog.”

Nature | doi:10.1038/nature.2015.18784

References

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