



Unintended Effects of Genetic Manipulation

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Genetically Manipulating Rabbits to Increase Meat Production Caused Enlarged Tongues and Severe Health Problems

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Genetically engineering rabbits to try to increase meat production did increase their birthweight and muscularity, but it also caused a high incidence of the animals growing enlarged tongues and suffering “severe health problems, including stillbirth and early stage death,” in experiments led by a China-U.S. research team.

The researchers used the popular new CRISPR-Cas 9 method in their study, which was conducted in part to try to evaluate the safety of genetically engineering the suppression or inactivation of myostatin, a protein that limits the development of muscle tissue. There is interest among breeders in “knocking out” genetic material associated with the production of myostatin as a new way to produce more meat from livestock animals, since meat is mostly animals’ muscle tissue.

Some animals are born with a natural mutation associated with inactivating myostatin or reducing its quantity, and such animals do develop more muscle than normal. But the overall biological functions of myostatin have not been thoroughly studied. The researchers, as they explain in the 2016 report of their experiments in the journal *Scientific Reports*, were trying to evaluate how well using CRISPR-Cas 9 to interrupt myostatin would work as intended here and whether that method would cause off-target effects, in terms of changing genes they were not intending to manipulate. But they also wanted to know if achieving the intended gene change at the precise site they targeted would itself have harmful, unintended effects for animals’ health.

From 315 genetically modified embryos inserted into 27 surrogate mother rabbits, 34 rabbits were eventually delivered. Of the 34, 14 were “unexpectedly” born with enlarged tongues, including five rabbits that were stillborn. Moreover, eight more rabbits died during the early infant stage, either because of weakness or because their health was so poor that researchers decided to euthanize them. In comparison, only one in a control group of 42 young rabbits was stillborn. And only one was stillborn out of the eight infant rabbits that were subjected to the CRISPR-Cas 9 method as embryos but that did not show that the intended genetic change had taken place.

Previous research using CRISPR-Cas 9 to try to “knock out” the genetic material associated with myostatin in pigs had also shown that some of the animals were born with enlarged tongues, the researchers noted. They concluded, from their genomic analyses, that the “huge tongue phenomenon” in their own study was clearly caused by their success in genetically targeting the production and action of myostatin.

The research team’s members were from the Nanjing Agricultural University in China, the

Stanford University School of Medicine, and Akeagan, a California biotechnology company. They also reported that their analyses indicate that “mutations could be transmitted to the next generation through the germline” in rabbits and goats, which they had also studied and were presenting results about in their 2016 *Scientific Reports* paper. They found no evidence in the rabbits of changes in parts of the genome that they were not trying to change, and so concluded that there were “no detectable off-target effects” of their manipulations.

“For the first time,” they added, “we presented direct evidence that Mstn KO [myostatin knock-out] caused abnormalities in gene edited animals, which suggested that Mstn KO may not be an ideal way to improve the muscle mass in rabbits, and also in animals, such as pigs and goats.”

This particular feat of genetic engineering “is a powerful tool to improve domestic animal breeding and meat production,” the researchers concluded. But since it may cause the same severe health problems in other species, its safety “must be studied further before applied to animal reproduction processes.”

Sources

Guo, Rihong Guo, Yongjie Wan, Dan Xu et al (2016). “Generation and Evaluation of Myostatin Knock-out Rabbits and Goats Using CRISPR/Cas9 System,” *Scientific Reports* vol. 6, Article number: 29855 (July 15). <https://www.nature.com/articles/srep29855>

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