

The tale of the Watanabe rabbit

SCIENTIFIC NAME

Oryctolagus cuniculus

TAXONOMY

PHYLUM: Chordata

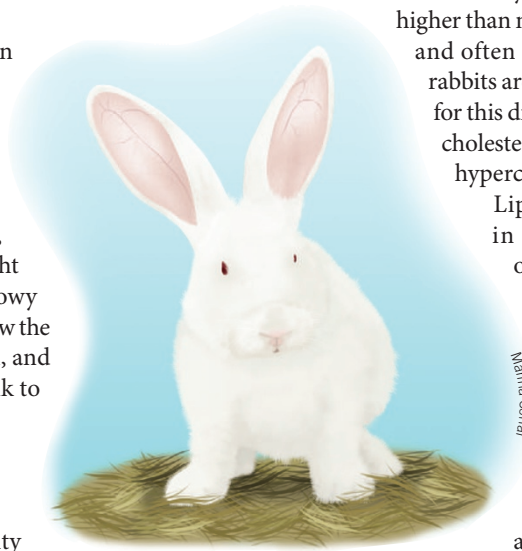
CLASS: Mammalia

ORDER: Lagomorpha

FAMILY: Leporidae

Physical description

The Watanabe rabbit is an inbred strain developed from the New Zealand White breed commonly found in laboratories. New Zealand Whites are relatively large rabbits: adult males can weigh 8–10 lb and females up to 12 lb. They have muscular bodies, large hind feet, thick fur and long ears that stand straight up. Because of albinism, their fur is snowy white. The shorter hairs on their ears allow the pale pink of their skin to show through, and their eyes range in color from light pink to deep ruby red.



Martina Corral

Strain development and characteristics

Dr. Yoshio Watanabe of Kobe University (Japan) first identified spontaneous hyperlipidemia in a male rabbit in 1973 (ref. 1) and confirmed that it was the result of an inherited recessive mutation. Through selective breeding over the next 7 years, he established the Watanabe heritable hyperlipidemic (WHHL) strain from that mutant rabbit, describing the strain in *Atherosclerosis* in 1980 (ref. 2). He maintained the strain and provided rabbits to collaborators worldwide until his retirement in 1990. Dr. Watanabe passed away in 2008 at the age of 81 years, but his contributions to our understanding of lipoprotein metabolism and atherosclerosis endure.

Watanabe rabbits have a rare genetic defect—a deficiency of low-density lipoprotein receptor expression—that predisposes them to hypercholesterolemia and hyperlipidemia¹. As a result, they develop vascular lesions, atherosclerotic disease and sometimes heart attacks. Total cholesterol levels may be eight to fourteen times higher in Watanabe rabbits than in normal rabbits².

Research résumé

After the strain was introduced to the biomedical community, many researchers studying lipoprotein metabolism, hypercholesterolemia, atherosclerosis and related diseases requested Watanabe rabbits to be used in their experiments. Working with Watanabe rabbits, Goldstein and Brown clarified the mechanisms of lipoprotein metabolism *in vivo* and were awarded the Nobel Prize in 1985 (ref. 1). Watanabe rabbits were also important models for the development and testing of statins as inhibitors of cholesterol biosynthesis¹.

The heritable hyperlipidemia found in Watanabe rabbits mirrors the fatal human condition familial hypercholesterolemia, which is characterized by blood cholesterol levels three to seven times higher than normal. Affected children suffer heart attacks and often die before reaching their teens. Watanabe rabbits are used in efforts to develop better treatments for this disease, including methods of removing excess cholesterol from the blood of children suffering from hypercholesterolemia^{3,4}.

Lipoprotein metabolism and atherosclerosis in Watanabe rabbits mimic clinical signs observed in human coronary and peripheral artery disease. A new strain of rabbit that is prone to myocardial infarction was derived from the Watanabe rabbit and is being used in translational research on cardiovascular diseases⁵. Furthermore, it was recently reported that rabbits of this myocardial infarction-prone strain that had accumulation of visceral fat can serve as appropriate models for metabolic syndrome⁶.

1. Shiomi, M. & Ito, T. The Watanabe heritable hyperlipidemic (WHHL) rabbit, its characteristics and history of development: A tribute to the late Dr. Yoshio Watanabe. *Atherosclerosis* **207**, 1–7 (2009).
2. Watanabe, Y. Serial inbreeding of rabbits with hereditary hyperlipidemia (WHHL-rabbit). *Atherosclerosis* **36**, 261–268 (1980).
3. Okura, H. *et al.* Transplantation of human adipose tissue-derived multilineage progenitor cells reduces serum cholesterol in hyperlipidemic Watanabe rabbits. *Tissue Eng. Part C Methods* **17**, 145–154 (2011).
4. Saga, A. *et al.* HMG-CoA reductase inhibitor augments the serum total cholesterol-lowering effect of human adipose tissue-derived multilineage progenitor cells in hyperlipidemic homozygous Watanabe rabbits. *Biochem. Biophys. Res. Commun.* **412**, 50–54 (2011).
5. Kobayashi, T., Ito, T. & Shiomi, M. Roles of the WHHL rabbit in translational research on hypercholesterolemia and cardiovascular diseases. *J. Biomed. Biotechnol.* **2011**, 406473 (2011).
6. Shiomi, M., Kobayashi, T., Kuniyoshi, N., Yamada, S. & Ito, T. Myocardial infarction-prone watanabe heritable hyperlipidemic rabbits with mesenteric fat accumulation are a novel animal model for metabolic syndrome. *Pathobiology* **79**, 329–338 (2012).