Genetic discovery in songbird provides new insights

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New research reveals a genetic quirk in a small species of songbird in addition to its ability to carry a tune. It turns out the zebra finch is a surprisingly healthy bird.

A study published today in the journal *Proceedings of the National Academy of Sciences* reveals that zebra finches and other songbirds have a low-density lipoprotein receptor (LDLR) gene surprisingly different than other vertebrates.

The function of LDLR, which is responsible for cellular uptake of LDL-bound cholesterol, or "bad cholesterol," has been thought to be conserved across vertebrates. OHSU scientists found that in the case of songbirds, key domains for the function of the receptor were lacking.

Mutations like this are a genetic cause of severe high cholesterol and high risk for cardiovascular disease. Surprisingly, this has not resulted in high cholesterol for songbirds; they carry most of their cholesterol in high-density lipoprotein, HDL, or "good cholesterol."

"These songbirds seem to have adapted to the LDLR changes and have developed a healthy cholesterol profile, or ratio of low to high cholesterol ," said senior author Claudio Mello, M.D., Ph.D., professor of behavioral neuroscience in the School of Medicine at Oregon Health & Science University. "It suggests that songbirds may have some sort of protection from cardiovascular disease."

In turn, the discovery could lead to a model to better understand—and ultimately improve treatment—for cardiovascular disease in people.

This unsuspected difference genetic mutation also has implications for viral entry, cellular transport systems and, potentially, gene therapies.

LDLR is also the main receptor for the G protein of vesicular stomatitis virus (VSV G) and are used to pseudotype, by coating, lentiviral vectors for gene manipulation in animals and gene therapy trials in humans. The lack of key functional domains in LDLR explains the low susceptibility of finches to lentiviruses, a family that includes HIV, pseudotyped with VSV-G. Besides the implications for improving gene manipulation tools in finches, this study illustrates the fascinating co-evolution and interplay between viral entry and basic cellular transport systems.

The genetic discovery is part of a broader initiative to generate high quality genome sequences in a large number of animals. It was also part of a three-year initiative funded by the National Science Foundation enabling researchers at OHSU and other institutions to study the genetic makeup of zebra finches, an important model in neurobiology.

More information: Tarciso A. F. Velho el al., "Divergent low-density lipoprotein receptor (LDLR) linked to low VSV-G-dependent viral infectivity and unique serum lipid profile in zebra finches," *PNAS* (2021). www.pnas.org/cgi/doi/10.1073/pnas.2025167118