A loss-of-function mutation in *LIMA1* decreases intestinal cholesterol absorption and prevents cardiovascular disease

Supported by the National Natural Science Foundation of China, a collaborative study by the laboratories of Dr. Song BaoLiang (宋保亮) from Wuhan University and Dr. Ma YiTong (马依彤) from the First Affiliated Hospital of Xinjiang Medical University demonstrates that a rare frameshift mutation in the *LIMA1* gene promotes low plasma low-density lipoprotein cholesterol (LDL-C) and decreases intestinal cholesterol absorption. This work was recently published in *Science* (2018, 360(6393): 1087—1092).

Cholesterol is an essential component of eukaryotic membranes and the precursor to many biological active molecules. It can be synthesized *de novo* and obtained from the diet. However, too much low-density lipoprotein-cholesterol (LDL-C) in the plasma is a major risk factor for coronary heart disease and stroke. The genetic factors affecting LDL-C have not been fully characterized.

To search for LDL-C-associated mutations, the teams led by Dr. Song and Dr. Ma conducted a cardiovascular risk survey in Xinjiang Uygur Autonomous Region of China and found a Chinese Kazakh family with inherited low levels of LDL-C and reduced cholesterol absorption. Whole-exome sequencing and genome-wide linkage analysis revealed that the *LIMA1*-K306fs variant was associated with lower plasma LDL-C of this family. The *LIMA1* gene (also known as *EPLIN* or *SREBP3*) has not been linked to lipid metabolism prior to the study, and the *LIMA1*-K306fs mutation has not been reported in any published databases. In mice, LIMA1 was highly expressed by the brush border membrane of the small intestine. Ablation of *LIMA1* in the small intestine impaired dietary cholesterol absorption and ameliorated diet-induced hypercholesterolemia. At the mechanistic level, LIMA1 interacted with Niemann-Pick C1-like 1 (NPC1L1) and myosin Vb. NPC1L1 is a key protein that shuttles between the plasma membrane (PM) and the endocytic recycling compartment to mediate intestinal cholesterol absorption, and the molecular pathway of NPC1L1-dependent cholesterol uptake has been systematically characterized by Dr. Song and colleagues in the past few years. The formation of NPC1L1-LIMA1-Myosin Vb ternary complex regulated NPC1L1 transportation to the PM and consequently cholesterol absorption through the small intestine. These findings reveal the cholesterol regulatory mechanism in humans and suggest that pharmacological targeting through the LIMA1 pathway may serve as a new strategy to treat hypercholesterolemia.

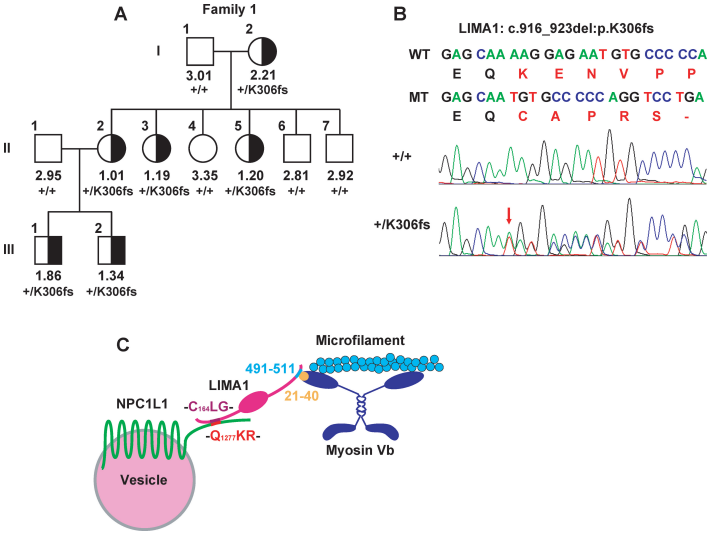

Figure LIMA1 regulates intestinal cholesterol absorption by anchoring NPC1L1 to myosin Vb. A: Pedigree of the Kazakh family with lower levels of plasma LDL-C; B, identification of the LIMA1 mutation in low LDL-C members; C, Schematic model of NPC1L1-LIMA1-myosin Vb interaction.