Objectives PURPOSE: Our purpose is to identify the causal gene and its mechanism for familial coronary artery disease in Chinese Han Population.

Methods We recruited a large Chinese Han family with coronary artery diseases (CAD), which was ascertained through a proband, who was diagnosed as myocardial infarction at age of 42. The affected family had three generations consisting of 16 patients and non-affected first-order relatives. In order to seek for the genetic causes for CAD in this family, we sequenced all exons and intron-exon boundaries of LRP6, low density lipoprotein receptor-related protein 6, in which one mutation (R611C) was found to cause familial CAD in an Iranian population.

Results A heterozygous variant in exon 6 of LRP6 was identified to be segregated with CAD phenotypes in this family. The variant, causing a substitution of histidine to lysine (Y418H), was located in an evolutionarily conserved domain YWTD (Tyr-Trp-Thr-Asp) and was not found in 500 unrelated healthy individuals. These suggested that Y418H was a novel mutation in LRP6 for CAD. Functional characterisation demonstrated that, unlike the known mutation (R611C) of LRP6, Y418H did not impair cellular LDL clearance significantly. However, it impaired the proliferation, migration, and survival of endothelial cells. Additionally, we found that Y418H weakened signalling pathway of WNT by impairing the function of LRP6 as a Wnt's co-receptor. To assess the contribution of LRP6 to CAD, we screened LRP6 in additional 40 probands and didn't find any mutations, suggesting that LRP6 may not be a major gene involved in the pathogenesis of CAD.

Conclusions Taken together, we identified a novel mutation in LRP6 gene causing familial CAD in Han Chinese population and revealed a new mechanism underlying familial CAD.

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**A NOVEL MUTATION IN YWTD DOMAIN OF LRP6
IMPAIRS ENDOTHELIAL CELL FUNCTION AND LEAD TO
FAMILIAL CORONARY ARTERY DISEASE**

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