

Kullo Lab Assertion Criteria 2015

LDLR Sequence Linked to EHR

Variants in *LDLR* (OMIM 606945) were classified using variant assertion concepts and principles adopted by the 2015 ACMG guidelines for the interpretation of sequence variants [PMID: 25741868].

Primary indication for testing: research

Incidental findings in *LDLR* were annotated based on scoring criteria encompassing extensive electronic health record (EHR) review including assessment of demographic data, low-density lipoprotein cholesterol (LDL-C) level and ascertaining Dutch Lipid Clinic Network (DLCN) criteria for FH, comprising lipid levels, presence of personal or family history of premature atherosclerotic cardiovascular disease and hypercholesterolemia, arcus cornealis and xanthomas. Structured EHR data were mined for the highest LDL-C levels. Family history was defined as occurrence of ASCVD before age 55 in men and 65 years in women.

The EHR review was supplemented by:

(i) review of variant-level data, such as variant frequency, variant repositories, *in-silico* pathogenicity scores, and

(ii) review of primary literature for the reported variants in the context of FH; dbSNP and dbVar were queried for *LDLR* variants and PubMed and Google Scholar searched using the following search terms: rsID and cDNA position for each variant, familial hypercholesterolemia, secondary, and incidental findings.

DNA variation databases included NCBI-ClinVar, NHLBI-EVS, and *LDLR*-LOVD.

For each rare variant the likelihood of altered LDL receptor protein activity was determined by PolyPhen2 and SIFT.

The putative impact of the variant was assessed dichotomously as high and low impact using a conservation GERP score threshold of 2.95.

EHR-derived race and ethnicity data were used to calculate differences in variant frequency.

Each component of the framework was assigned 1 point and a total score was calculated for each variant. Variants scoring 6 points were defined as likely pathogenic.

Web Resources:

NCBI ClinVar database, <http://www.ncbi.nlm.nih.gov/clinvar>

LDLR Leiden Open Variation, LOVD; versions 1.1.0 build 12, 2.0 build 36, and 3.0 build 13;
http://www.ucl.ac.uk/ldlr/LOVDv.1.1.0/index.php?select_db=LDLR

<http://www.ucl.ac.uk/ldlr>, https://grenada.lumc.nl/LOVD2/UCL-Heart/home.php?select_db=LDLR

http://databases.lovd.nl/whole_genome/genes/LDLR

NHLBI Exome Variant Server, EVS; <http://evs.gs.washington.edu/EVS/>

PolyPhen-2, <http://genetics.bwh.harvard.edu/pph2>

SIFT, <http://sift.jcvi.org>