HMGCR Variation, Statins, and You

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Overview

- Background
  - HMGCR, cholesterol synthesis, and statins
  - LDL vs. HDL
- LDL metabolism
- SNP/Splicing variation in HMGCR
- Sample genetic tests
Cholesterol 101

The Good, The Bad, and The Ugly
The metabolism of LDL-cholesterol in relation to the role of HMGCR

- HMGCR normally converts HMG-CoA into mevalonate
- Promotes intracellular cholesterol synthesis
- Statins are competitive inhibitors of HMGCR
3 SNPs indicating H7 haplotype

NCBI-Entrez:
Effect of Splice/SNP variation in HMGCR on LDL cholesterol

- Chasmin, et al. 2004. on pravastatin
  - SNP12 of the HMG-CoA reductase gene can be found on chromosome 5 at position 74726928 (Human genome July 2003 UCSC version hg16, based on build 34, NCBI) by a match to the sequence
    - AAAAAAATTTTT[AT]AAATCTTTATATTA
  - SNP29, chr 5 at position 74739571
    - TTTTCCAAACTCTTT[TG]GTCATATCAGCCTAA.
So what drug is most effective based on your genetics?

- Current literature/data is lacking
  - Efficacy vs. side effects between statins
  - Single statin "attenuation" from variation
  - Sample often not stratified

- Future directions
  - Study encompassing a variety of ethnicities and people with different risk factors/levels (high LDL, familial hypercholesterolemia, etc)
  - HMGCR, cytochrome P450 (CYP), solute carrier organic anion transporter (SLCO1B1), Apolipoprotein E (APO-E) gene, etc.
  - Test multiple drugs in the study
    - Check for significant correlations with strength of statin

- Disclaimer
References


• Lara M, Mangravite; Marisa Wong Medina; Jinrui Cui; Sheila Pressman; Joshua D. Smith; Mark J. Rieder; Xuqing Guo; Deborah A. Nickerson, Jerome I. Rotter; Ronald M. Krauss. Combined Influence of LDLR and HMGCR Sequence Variation on Lipid-Lowering Response to Simvastatin. Arteriosclerosis, Thrombosis, and Vascular Biology. 2010;30:1485-1492


Thank you for listening!