LDL-C SNP Scorer

Introduction

LDL-C SNP Scorer should be of interest to anyone concerned with the genetics of hypercholesterolemia (herein referred to as hyperLDL-C). Familial hypercholesterolemia (FH) is a relatively prevalent and under-diagnosed Mendelian genetic disorder that is known to be caused by mutations in the *APOB*, *APOE*, *LDLR*, and *PCSK9* genes. It is usually inherited in an autosomal dominant manner, although rare and more severe forms can be inherited in a recessive manner. However, FH due to mutations in these genes, with a prevalence of approximately 1 in 200-500, only accounts for a relatively small proportion of individuals with hyperLDL-C.

HyperLDLC is a very common condition affecting 10-50% of the population. The most frequent cause of hyperLDL-C is multifactorial, that is, due to the combination of lifestyle factors (e.g. diet, exercise, etc) and polygenic factors (i.e. normal genetic variation in genes that each have only a small influence on how the body processes LDL-C).

Molecular genetic testing for hyperLDL-C can include sequencing and dosage analysis of the *APOB*, *APOE*, *LDLR*, LDLRAP1, and *PCSK9* genes, and often also includes genotyping of 12 single nucleotide polymorphisms (SNPs) that are known to influence LDL-C levels. As outlined in the article by Talmud *et al*. (2013), the genotype profile determined by these 12 SNPs generates a 'LDL-C SNP score', which can be used as measure of an individual's polygenic risk for developing hyperLDL-C, with higher scores conferring a higher risk.

LDL-C SNP Scorer allows users to input SNP genotypes for the 12 SNPs that are most predictive of an individual's LDL-C level. Scores are then assigned to each genotype according to the weights as determined by the Global Lipid Genetic Consortium (GLGC) meta-analysis of genome-wide association studies. These scores are as described in the article by Talmud *et al*. (2013). The scores for the *APOE* diplotypes are as described in the article by Bennet *et al*. (2007) (note: the score for the ε2 / ε4 diplotype is incorrect in the Talmud *et al*. article). LDL-C SNP Score sums the scores and then indicates the population decile and risk associated with that score, as described in the Talmud *et al*. (2013) article.

Molecular assays are not usually able to determine the phase of the two *APOE* SNPs in individuals with absolute certainty. However, SNPs rs429358 and rs7412 are in very high linkage disequilibrium (LD; *D'* of ~1), such that the C allele at the former is highly predictive of the C allele at the latter (corresponding to the ε4 haplotype), and the T allele at the latter is highly predictive of the T allele at the former (corresponding to ε2). Based on this LD structure, LDL-C SNP scorer *assumes* that double heterozygote genotypes at these SNPs indicate the ε2 / ε4 diplotype. However, please note that there is a very small possibility that the true diplotype is ε3 / ε3r, where ε3r is the reverse of ε3. A subjective indication of the confidence with which the correct *APOE* diplotype can be assumed is indicated in LDL-C SNP Scorer.

The ε3r haplotype is extremely rare, with only a handful of cases ever described in the literature. Given its rarity, there is currently insufficient data to know what effect this haplotype might have on LDL-C levels. Hence, a score for this haplotype has not yet been determined. Therefore, LDL-C SNP Scorer is unable to calculate a total LDL-C SNP score for any profiles where this haplotype is definitively determined to be present.

How To Use LDL-C SNP Scorer

To use LDL-C SNP Scorer, simply input the detected genotypes for each of the 12 SNPs using the drop-down menus. '*? / ?*' should only be selected in the event that a genotype is unknown. LDL-C SNP Scorer will then calculate the minimum and maximum total scores for the profile.

References

Talmud *et al*. (2013). *Lancet*, 381(9874): 1293-1301. PMID: 23433573.
Bennet *et al*. (2007). *JAMA*, 298(11): 1300-1311. PMID: 17878422.