

Genome-Wide Linkage Analysis of Lipids in the HyperGEN Study: An Investigation of the Effects of Lipid-Lowering Medications

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Abstract

The blood lipid levels are often distorted by the use of anti-hyperlipidemic medications. To investigate this medication effect, a genome scan of lipids was performed in HyperGEN Study after a systematic adjustment of medication effect on lipid levels with an empirical method. Published clinical trials were reviewed for two major groups of lipid-lowering medications separately by ethnicity as mono-therapy, including HMG-CoA reductase inhibitors and fibric acid derivatives. The effects of HMG-CoA reductase inhibitors were corrected in whites by 20.0%, 27.3%, 5.7%, and 12.4% for CHR (total cholesterol), LDL (low density lipoprotein) cholesterol, HDL (high density lipoprotein) cholesterol, and TG (triglycerides), respectively. The same effects were adjusted in blacks except using 2.7% for HDL cholesterol. For fibric acid derivatives, 13.2% was used to obtain the adjusted CHR in whites, 12.5% for LDL cholesterol, 13.2% for HDL cholesterol, and 37.5% for TG, while the lipid measurements in blacks were adjusted by the following corresponding percentages: 7.5%, 4.1%, 9.2%, and 32.0%. Multipoint variance components linkage analyses was carried out for lipid measurements and their corrected values with 1869 pairs of siblings from 1208 white nuclear families and 1840 sibling pairs from 1774 black families. A total of 391 polymorphic markers were used. The standard errors of heritabilities of different lipid phenotypes by race all dropped after medication adjustment. The pattern of LOD score peaks were also changed by the medication adjustment, such as the LOD score of the peak for HDL cholesterol in blacks centered at 76 cM on chromosome 9q22.1 increased from 1.87 to 2.81, and the peak with LOD score of 3.22 for triglycerides in blacks on chromosome 11q24.3 dropped to 2.87. There are four more regions revealing promising LOD scores (LOD score ≥ 1.75) after medication adjustment: chromosome 5q23.3 for HDL cholesterol and chromosome 9p22.1 for TG in whites, chromosome 5q35 for LDL cholesterol and chromosome 21q21.3 for HDL cholesterol in blacks. The medication adjustment using this empirical method improved signal-to-noise ratio and can be employed in genetic and other studies, in which a more precise estimation of the phenotype is required.