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ASHG 2008: Six New Loci Associated With Serum Lipid Levels

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November 18, 2008 (Philadelphia, Pennsylvania) — An international genomewide association study has identified 6 genetic loci associated with serum lipid levels in European populations. This brings to 22 the total number of genomic regions affecting serum lipid levels, a major risk factor in cardiovascular disease. The study, presented here at the American Society of Human Genetics 58th Annual Meeting, is part of the ENGAGE Consortium, an extensive research project funded by the European Union.

Presenter Samuli Ripatti, PhD, from the Karolinska Institute, Solna, Stockholm, Sweden, and the University of Helsinki, Finland, reported that the study combined genomewide association data from 16 European cohorts of nonselected population-based samples. A total of 22,562 samples were collected. "We also extended the definition of Europe a bit to be inclusive," he added, noting that there were 424 samples from Australia.

The threshold for genomewide significance was $<5 \times 10^{-8}$. Analysis for loci associated with total cholesterol levels found 3 loci not previously identified in genomewide association studies: *TMEM57* ($P = 5.4 \times 10^{-10}$), *ABCG5* ($P = 1.5 \times 10^{-11}$), and *FADS3/FADS2* ($P = 1.5 \times 10^{-10}$), on chromosomes 1, 2, and 11 respectively. An additional locus on chromosome 7 was associated with low-density lipoprotein (LDL) cholesterol levels (*DNAH11*; $P = 6.1 \times 10^{-9}$), and 2 additional loci were associated with serum high-density lipoprotein (HDL) cholesterol levels: the *CTCF-PRMT8* region ($P = 8.3 \times 10^{-16}$) on chromosome 16 and the *MADD-FOLH1* region ($P = 6 \times 10^{-11}$) on chromosome 11. The large HDL-related region on chromosome 11 merits further functional studies.

The 22 genomic regions associated with serum lipid levels account for as much as 5.6% of the variation in serum lipid levels at the population level. Three of these loci have differential effects in men and women. "The females, in total, have more than 2 times the effect size than the males," said Dr. Ripatti in his presentation.

Senior author Cornelia M. van Duijn, PhD, head of the Genetic Epidemiology Unit, Erasmus University Medical Center, Rotterdam, the Netherlands, commented to *Medscape Pathology & Lab Medicine* by email: "Although we know a lot about the difference in the blood distribution of lipids between men and women, in particular concerning HDL and triglycerides, we know very little about differences in the *impact* of genes in humans. The reason is statistical," said Dr. van Duijn.

"To show differences between subgroups (in this case, men vs women), we needed roughly 4 times the sample size than that needed to discover the gene.... With 20,000 to 30,000, we are beginning to find genes with small effects. We need to study more than 100,000 persons to find genes that act only in men or women," Dr. van Duijn observed. "We are trying to achieve this number by merging consortia into a large one: global lipids."

To calculate genetic-risk scores, the investigators not only looked at the risk alleles per person, but also weighted risk alleles by their effect sizes, as estimated in the complement cohorts. They calculated genetic risk for subjects in the Rotterdam study, a large longitudinal study, focused on subjects older than 55 years.

Dr. van Duijn added: "If you are interested in the effect of lipids [over a] lifetime, you do not want to study a young population, in which there will be many persons who still have not developed pathology yet, but who will in the future.... In women in particular, the lipid levels change drastically after menopause (±50 years). This is one of the 'forgotten' side effects. We tend

to think of osteoporosis as the major problem, but lipids change as dramatically postmenopausally. In the Rotterdam study, we can be fairly sure that we can see the lipid problems."

The investigators looked at the predictive power of the genetic-risk scores for future cases of hypercholesterolemia, intima-media thickness, and coronary heart disease. "The bottom line," said Dr. Ripatti, "was when we looked separately at the risk scores based on the HDL genes, the LDL genes, and the total-cholesterol genes. One of the findings was that the total-cholesterol genes had the most predictive power for all of these." Total-cholesterol scores were significantly associated with risk for hypercholesterolemia ($P < .001$), intima-media thickness ($P = .001$), and coronary heart disease ($P = .042$).

Medscape Pathology & Lab Medicine also spoke with comoderator Ruth McPherson, MD, PhD, FRCPC, director of the Lipid Clinic, Lipid Research Laboratory, University of Ottawa Heart Institute, in Ontario. "We're now having the opportunity to go beyond SNPs [single-nucleotide polymorphisms] that confer effects on [coronary heart disease] risk factors, like proteins that are associated with risk, to actually look at SNPs that may have gender-specificity," Dr. McPherson said.

"We've known in genetics for many years, in many areas, that genetic variants may interact with other factors...so that should be pointed out as something that we have to do in the consortiums that are sharing their data from various genomewide association studies," said Dr. McPherson. "We're now able to look at things like gender effects and effects of other lifestyle factors, looking at gene-environment interactions. And I think that's going to be pretty exciting."

Dr. Ripatti, Dr. van Duijn, and Dr. McPherson have disclosed no relevant financial relationships.

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