NEWS

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EMBARGOED UNTIL 8/25/07 8:00 AM PT

GOLD MINE OF GENE DISCOVERY YIELDS "GOOD CHOLESTEROL" GENE - work to be presented at the 57th ASHG Annual Meeting

San Diego – October 25 --Using a powerful new approach they term a "gold mine of gene discovery," researchers at the Southwest Foundation for Biomedical Research (SFBR) and collaborating institutions have identified a novel gene *(VNN1)* that appears to play a significant role in determining levels of HDL-cholesterol (HDL-C), the so-called "good" cholesterol molecule. Low levels of HDL-C are known to be associated with increased risk of cardiovascular disease (CVD), whereas high levels are thought to be protective.

The researchers have also identified five genes that are causally downstream of *VNN1* and thus may constitute members of a biochemical pathway related to cholesterol metabolism. Elucidation of this possible pathway might prove useful in identifying new targets for clinical interventions to reduce CVD risk. The discovery also has implications for obesity and obesity-related complications.

"Reduced levels of the good cholesterol HDL are a hallmark of the new world syndrome known as metabolic syndrome," said Ahmed Kissebah, M.D., Ph.D., professor of medicine and pediatrics and director of the TOPS Center for Obesity and Metabolic Research at the Medical College of Wisconsin. Dr. Kissebah is one of the authors of the research report. "This is a cluster of features commonly associated with truncal obesity and is genetically passed through families. Now we can understand why this syndrome is strongly associated with CVD. The good news is that these findings should pave the way for a new generation of therapies that could overcome the health complications of obesity and this syndrome."

VNN1 (for vanin-1 or vascular non-inflammatory molecule 1) codes for the enzyme pantetheinase which produces cysteamine, a potent antioxidant that prevents lipid peroxidation. Therefore, *VNN1* is a reasonable candidate gene for affecting HDL-C concentration.

This association of *VNN1* with HDL-C levels serves as proof of principle for an exciting new gene discovery approach that focuses on what are called "cis-regulated" genes in a whole transcriptome analysis. The approach is highly statistic dependent and key to success was use of the SFBR's AT&T Genomics Computing Center, which is said to be the academic world's largest parallel computing cluster dedicated to human genetic research. Use of the center's powerful cluster of 3,000 processors allowed scientists to analyze vast amounts of complex genetic data at record speed.

Cis-regulated genes are ones for which variations in the levels of mRNA and protein product from the genes are determined largely by sequence variations within or very near the gene itself, often in the promoter regions of these genes. By focusing on cis-regulated genes in studies of disease associations, researchers can reduce the number of genes that they need to sift through (from the ~25,000 total in humans to approximately 1,000 to 2,000) and also immediately home in on the region of the gene that is likely responsible for variation (namely, the promoter region).

“We basically just zeroed in on the low-hanging fruit,” said John Blangero, Ph.D., senior author of the report and director of the SFBR's AT&T Genomics Computing Center. “Instead of looking at all of the genes, we focused on the ones that strongly control their own outputs, and of those genes, we then looked at the ones that correlate with disease risks. This approach narrows down the field of genes to target very quickly."

"While this has been done before on a very limited scale, the sheer power of our AT&T Genomics Computing Center, plus multiple generations of genetic data we have accumulated in the San Antonio Family Heart Study, allowed us to apply this method to a much larger number of study samples. No one has ever applied this method on an epidemiological scale before.”

“The ability to pinpoint the cis-regulated genes not only speeds up the discovery process, but means that you immediately have a good target for drugs to treat those diseases that they influence.”

“This research method has tremendous potential to accelerate the development of pharmaceutical therapies to target the genetic causes of a whole range of diseases that affect people worldwide,” said Greg Collier, CEO of ChemGenex, one of the collaborating institutions.

Using their cis-regulated-gene-focused, whole transcriptome analysis, the researchers showed that increased levels of *VNN1* mRNA transcript are significantly associated with increased levels of HDL-C. Increased levels of *VNN1* transcripts were also found to be significantly associated with levels of triglycerides, ApoA1, and ApoA2, and with LDL (low-density lipoprotein) peak diameter. All of these parameters are associated with risk of CVD and the *VNN1* levels were directly associated with the levels (high or low) associated with reduced CVD risk.

The *VNN1* gene and its effects were identified in a large-scale transcriptional profiling analysis of 1,240 individuals enrolled in the San Antonio Family Heart Study.
This is a multigeneration study evaluating the risk of heart disease in Mexican-Americans.

“The transcriptional profiling was originally performed to identify normal variation in a rare monogenic disorder (cystinosis) that we are studying,” says Joanne Curran, Ph.D., the first author of the report and an assistant scientist at the SFBR. “The results however are now proving useful for many aspects of human biology including common diseases."

The reported analysis was designed to identify cis-acting genes that correlated with HDL-C levels. Because of the cis-effects, the researchers resequenced 2 kb of the *VNN1* promoter region in 96 founders (those at the top of the family pedigrees) and identified five variants (SNPs) highly correlated with *VNN1* expression. Two of these SNPs showed significant correlation with HDL-C levels, and one showed evidence of a functional role, namely transcription factor binding.

The authors also looked for genes causally downstream of *VNN1* by testing for the trans effects of *VNN1* promoter variations. Trans effects are ones in which a gene's effects are exerted on genes on different chromosomes. This approach revealed associations with several lipid metabolism/CVD genes, including LPL (lipoprotein lipase), LCAT (lecithin cholesterol acyltransferase), LRP3 (lipoprotein receptor-related protein 3), ACAT2 (acetyl-coenzyme A acetyltransferase 2), and IL-10 (interleukin-10).

They conclude that *VNN1* is likely to play a significant role in determining HDL-C levels and that cis-regulated-gene-focused transcriptional profiling is a valuable method of identifying genes reflecting causal relationships with complex phenotypes.

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In addition to the SFBR, ChemGenex, and the Medical College of Wisconsin, collaborating institutions included the International Diabetes Institute and the University of Western Australia.

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