Evidence of a Polygenic Origin of Extreme High-Density Lipoprotein Cholesterol Levels

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Objective—There are several known monogenic causes of high and low high-density lipoprotein cholesterol (HDL-C) levels, but traditional sequencing studies have had limited success in identifying mutations in the majority of individuals with extreme HDL-C levels. The aim of this study was to assess the power of a targeted high-throughput sequencing strategy to elucidate the genetic basis of extreme HDL-C phenotypes.

Approach and Results—We sequenced 195 genes with either established or implicated roles in lipid and lipoprotein metabolism plus 78 lipid-unrelated genes in patients with HDL-C <1st (n=40) or >99th (n=40) percentile values, and the results were compared with those of 498 individuals representative of the Dutch general population and 95 subjects with normal HDL-C (between 40th and 60th percentile values). The extreme HDL cohort carried more rare nonsynonymous variants in the lipid geneset than both the general population (odds ratio, 1.39; P=0.019) and normal HDL-C (odds ratio, 1.43; P=0.040) cohorts. The prevalence of such variants in the lipid-related and lipid-unrelated genesets was similar in the control groups, indicative of equal mutation rates. In the extreme HDL cohort, however, there was enrichment of rare nonsynonymous variants in the lipid versus the control geneset (odds ratio, 2.23; P<0.0001), and 70% of the lipid-related variants altered conserved nucleotides. The lipid geneset comprised 4 nonsense, 10 splice-site, and 8 coding indel variants, whereas the control geneset contained only 1 such variant. In the lipid geneset, 87% and 28% of the patients carried ≥2 and ≥5 rare variants.

Conclusions—This study suggests that most extreme HDL-C phenotypes have a polygenic origin. (Arterioscler Thromb Vasc Biol. 2013;33:1521-1528.)

Key Words: genetic variation ■ high-density lipoprotein cholesterol ■ lipid metabolism ■ low-density lipoprotein cholesterol ■ polygenic traits ■ triglycerides

There is unequivocal evidence that low levels of plasma high-density lipoprotein cholesterol (HDL-C) are associated with an increased risk of cardiovascular disease.1 This knowledge, combined with evidence from experimental studies that HDL exerts many beneficial effects,2 has fueled the development of drugs to increase HDL-C levels in plasma to reduce cardiovascular disease risk.3 However, recent failures of drugs that target HDL-C levels,4 combined with evidence that HDL might not causally be related to cardiovascular disease,5 underscore the necessity of reevaluating the currently used strategies to intervene in HDL metabolism and a need to develop methods to monitor clinically relevant physiological effects of HDL beyond HDL-C plasma levels.5,7

The strategies that have been developed to raise HDL-C levels find their origin in the unraveling of the molecular origin of extreme HDL-C levels in humans. For example, the finding that loss-of-function cholesteryl ester transfer protein (CETP) mutations are a cause of hyperalphalipoproteinemia8 led to the development of CETP inhibitors. It is noteworthy, however, that the molecular basis of extreme HDL-C phenotypes is poorly understood and that mutations in the main HDL candidate genes (APOA1, lecithin-cholesterol acyltransferase (LCAT), ABCA1, CETP, SCARB1, LIPG, and LIPC) explain extreme HDL-C levels in only a few percent of the individuals studied.9-14

The question addressed by the current study is whether very high or low HDL-C levels are associated with mutations in single genes or in multiple genes. Genome-wide association studies (GWAS) have in this regard shown that common variants with small effect sizes only explain a small proportion of the heritability of plasma lipid levels.15,16
This promotes speculation that (multiple) rare variants with moderate-to-large effect sizes may contribute to the missing heritability. Indeed, several investigators have resequenced individual or small batches of candidate genes and observed a higher number of rare variants in individuals with extreme hypertriglyceridemia.18,19 Recent small-scale studies have also shown that some individuals carry multiple mutations in different genes, with established roles in lipid metabolism in families with apparent Mendelian forms of dyslipidemia.14,20

Since the start of large-scale GWAS in 2008 until to date, the number of candidate genes associated with plasma lipid phenotypes has steadily increased. These studies have underscored that most candidate genes affect multiple lipoprotein traits, and this is especially true for genes affecting HDL and triglyceride (TG) metabolism.16 With this in mind, we set out to assess the burden of rare variants in 195 lipid-associated genes in individuals with HDL-C levels in the range observed in heterozygotes for Mendelian disorders of HDL metabolism.

Materials and Methods

Materials and Methods are available in the online-only Supplement. We studied 40 individuals with very low and 40 with very high HDL-C levels (<1st and >99th percentile for age and gender) from general patient population in the center of the Netherlands. Written informed consent was obtained, and the study protocol was approved by the IRB. Coding sequence and exon-intron boundaries of 195 lipid-related genes (including 97 genes identified through meta-analysis of GWAS data; Table I in the online-only Data Supplement) were sequenced using Agilent SureSelect custom capture library on the Illumina HiSeq 2000 platform. Control cohorts were unrelated individuals representative of the Dutch general population (n=498) sequenced in the Genome of the Netherlands project (GoNL; http://www.nlgenome.com) and a selected subpopulation (n=95) of GoNL cohort with normal HDL-C levels (between 40th and 60th percentile).

Control cohorts were unrelated individuals representative of the Dutch general population (n=498) sequenced in the Genome of the Netherlands project (GoNL; http://www.nlgenome.com) and a selected subpopulation (n=95) of GoNL cohort with normal HDL-C levels (between 40th and 60th percentile).

Results

Characteristics of the Extreme HDL-C Cohort

The characteristics of 40 individuals with HDL-C levels <1st percentile and 40 individuals with HDL-C >99th percentile (for age and sex), as well as representatives of the Dutch general population (Genome of The Netherlands [GoNL] cohort), are shown in Table 1.21 There were no significant differences in mean ages and smoking history between the low and high HDL groups. The low HDL group, however, had statistically significant higher body mass index compared with the high HDL groups (P<0.0001). Compared with the GoNL cohort, the low HDL-C group had >50% lower HDL-C and >90% higher serum TG (both men and women). Conversely, the men in the high HDL-C group had 92% higher HDL-C and 41% lower TG than GoNL individuals. The corresponding values in women were similar, 114% higher HDL-C and 43% lower TG. Although the patients’ referral basis to a physician was not used for inclusion into the current study, the low HDL-C group had higher incidences of diabetes mellitus and cardiovascular disease compared with the high HDL-C group (P<0.001 and P<0.01, respectively).

By design, HDL-C levels in the low HDL-C group were in the range typically observed in heterozygote individuals with deleterious APOA1,22 LCAT,23 and ABCA122 mutations, and such values were accordingly rare in the representative Dutch general population (Figure I in the online-only Data Supplement). Similarly, HDL-C levels in the high HDL group were comparable with those observed in heterozygotes for deleterious CETP,14 SCARB1,23 and GALNT214,24 mutations. We thus anticipated that individuals enrolled in this study would carry mutations in these genes and that their identification would serve as positive control for sensitivity of variant detection. Of note, the lipid profiles of several individuals were close to those observed in patients with homozygote or compound heterozygote mutations in the aforementioned genes (Figure II in the online-only Data Supplement).

Table 1. Demographic, Lipid, and Clinical Characteristics of the Extreme HDL-C and GoNL Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Low HDL</th>
<th>High HDL</th>
<th>GoNL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=25)</td>
<td>Women (n=15)</td>
<td>Men (n=30)</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.6±13.5</td>
<td>68.2±13.9</td>
<td>69.1±11.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.7±3.2</td>
<td>29.6±5.9</td>
<td>23.3±3.3</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>3.74±0.93</td>
<td>4.22±1.13</td>
<td>5.66±0.91</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.58±0.13</td>
<td>0.68±0.16</td>
<td>2.38±0.30</td>
</tr>
<tr>
<td>LDL-C,* mmol/L</td>
<td>3.22±0.20</td>
<td>3.77±0.21</td>
<td>3.44±0.13</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>3.14±4.04</td>
<td>2.76±1.40</td>
<td>0.95±0.42</td>
</tr>
<tr>
<td>Smoker</td>
<td>18</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>CVD</td>
<td>10</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

The lipid profiles were measured after an overnight fast in the central clinical chemistry laboratory of the Academic Medical Center in Amsterdam. Values are represented as mean±SD. BMI indicates body mass index; CVD, cardiovascular disease; GoNL, Genome of the Netherlands; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; and TG, triglyceride.

*When untreated lipid values were not available, estimated baseline LDL-C values were calculated based on the potential of cholesterol-lowering therapy that was used.21
Rare Variants in Lipid Geneset and Lipid-Unrelated Genes

As summarized in Table III in the online-only Data Supplement, we obtained sequences for 99.23% of the targeted region. Throughout the article, rare variants denote nonsynonymous (eg, missense, nonsense, splice-site) variants, with a minor allele frequency of <0.5% in the GoNL sample. Complete annotated lists of rare variants identified in all 80 HDL patients and their frequencies in the Dutch general population, as well as participants of the Exome Sequence Project,25 are presented in Tables IV (lipid geneset) and V (control geneset) in the online-only Data Supplement.

The numbers of rare nonsynonymous variants identified in each of the studied cohorts are shown in Table VI in the online-only Data Supplement. In the extreme HDL-C cohort, for example, we identified 296 rare variants, including 8 coding indels, in the lipid geneset. In Table VII in the online-only Data Supplement, the burden of rare variants per gene is listed. Interestingly, GWAS lipid genes are among genes with the highest burden of rare variants.

Extreme HDL-C Levels Are Associated With a Higher Number of Rare Variants in Lipid-Related Genes

Comparisons between different cohorts or genesets were performed after correcting for the number of individuals studied and the number of nucleotides sequenced in the 2 genesets.

We first compared the frequency of rare variants in the extreme HDL cohort with the 2 control cohorts. The prevalence of rare variants in the lipid geneset was significantly higher in the extreme HDL cohort compared with the normal HDL cohort (odds ratio [OR], 1.43; confidence interval, [CI], 1.02–2.02; P=0.040) and Dutch general population (OR, 1.39; CI, 1.06–1.82; P=0.019; Figure 1A). In a second step, we compared the number of rare variants in the lipid geneset and lipid-unrelated genes, assuming an equal mutation rate in both genesets in control cohorts. Indeed, no differences in frequency of rare variants between the 2 genesets were present in the general population sample (OR, 0.91; CI, 0.81–1.02; P=0.10) and the normal HDL cohort (OR, 1.05; CI, 0.79–1.39; P=0.74; Figure 1B). Furthermore, on comparing the frequency of rare variants in the lipid geneset versus the lipid-unrelated genes in ≈3400 participants of the Exome Sequence Project,25 we found that the frequency of such variants in the lipid geneset was lower, not higher, than the lipid-unrelated geneset (OR, 0.82; CI, 0.80–0.84; P=0.0001; Figure III in the online-only Data Supplement). In marked contrast, the extreme HDL-C cohort carried a significantly higher number of rare variants in the lipid geneset compared with the lipid-unrelated genes (OR, 2.23; CI, 1.58–3.16; P<0.0001; Figure 1B). Thus, collectively, the first and second step analyses indicate that rare variants in lipid-related genes are associated with extreme HDL-C phenotypes.

Rare Variants in Established HDL Genes Are Casually Related to Extreme HDL-C Phenotypes

As anticipated, the 12 well-established HDL genes26 were significantly enriched for rare variants (OR, 2.46; CI, 1.37–4.44; P<0.005; Figure 1C; Table VIII in the online-only Data Supplement): 16 variants in ABCA1, ABCG1, LCAT, CETP, LIPC, and LIPG (Table 2) were identified in 13 individuals. As indicated in Table 2, 4 of these variants were previously shown to be functional,11,27,28 and our analysis of the 2 novel LCAT variants revealed a significant loss of enzymatic activity in plasma of the respective patients (Figure IV in the online-only Data Supplement). These data indicate that rare variants in...
the established HDL genes are casually related to the extreme HDL-C phenotypes in our patient cohort and that, consistent with previous studies,9,11,29 most of the affected individuals did not have a rare variant in a well-established HDL gene.

### Rare Variants in GWAS and Non-HDL Lipid Genes Are Associated With Extreme HDL-C Phenotypes

We next compared the number of rare variants found in the distinct subsets of genes within the lipid dataset (Table I in the online-only Data Supplement) with those in the lipid-unrelated genes (Figure 1C; Table VIII in the online-only Data Supplement). Compared with the lipid-unrelated genes, the extreme HDL cohort exhibited an overrepresentation of rare variants in both the GWAS9 and non-GWAS subsets of lipid genes (OR, 2.09; CI, 1.45–3.01; \( P < 0.0001 \) and OR, 2.40; CI, 1.67–3.46; \( P < 0.0001 \), respectively). We also discriminated between genes assigned to HDL (n=95) and non-HDL (n=100) groupings (Table I in the online-only Data Supplement) and found that both gene sets were significantly enriched for rare variants compared with the lipid-unrelated genes (Figure 2B). When speculating on the functionality of the rare variants identified, it is of note that almost 70% of the missense variants concern nucleotides that are conserved across species (phastCons score >0.5). Potential functionality of the variants in the lipid geneset is further strengthened by the finding that 22 variants (nonsense, splice-site, and coding indel) are predicted to alter the coding capacity of the encoded gene products in a major way (Table 3), whereas only 1 such variant was identified in the lipid-unrelated genes (Table V in the online-only Data Supplement). Combined, these data are suggestive of a polygenic origin for the extreme HDL-C levels in most members of our cohort of patients.

### Eighty-Seven Percent of Patients With Extreme HDL-C Carry ≥2 Rare Variants

Although only 1 individual in the extreme HDL cohort carried no variant in the lipid geneset, 87% of the individuals carried ≥2 rare and 28% of the individuals carried ≥5 such variants (Figure 2B). When speculating on the functionality of the rare variants identified, it is of note that almost 70% of the missense variants concern nucleotides that are conserved across species (phastCons score >0.5). Potential functionality of the variants in the lipid geneset is further strengthened by the finding that 22 variants (nonsense, splice-site, and coding indel) are predicted to alter the coding capacity of the encoded gene products in a major way (Table 3), whereas only 1 such variant was identified in the lipid-unrelated genes (Table V in the online-only Data Supplement). Combined, these data are suggestive of a polygenic origin for the extreme HDL-C levels in most members of our cohort of patients.

### Discussion

Twin studies have shown that plasma HDL-C levels are 50% to 60% heritable.30 Common gene variants have long been anticipated to contribute to this heritability, but GWAS have recently taught us that common variants can currently only explain ≤15% of this heritability.13 This notion has led to the concept of a rare allele model in which multiple rare variants

### Table 2. Rare Nonsynonymous Variants Identified in Genes With an Established24,26 Role in HDL-C Metabolism

<table>
<thead>
<tr>
<th>Chr.</th>
<th>Gene</th>
<th>Transcript ID</th>
<th>Genomic DNA</th>
<th>cDNA*</th>
<th>Cons.</th>
<th>Mutation Type</th>
<th>Protein</th>
<th>Gene List</th>
<th>HDL-C</th>
<th>Carriers</th>
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<tr>
<td>9</td>
<td>ABCA1</td>
<td>NM_005502.3</td>
<td>g.107593832&gt;T</td>
<td>c.1716G&gt;A</td>
<td>1</td>
<td>Splice</td>
<td>ND</td>
<td>HDL, TC†</td>
<td>Low</td>
<td>LM28†</td>
</tr>
<tr>
<td>9</td>
<td>ABCA1</td>
<td>NM_005502.3</td>
<td>g.107581164&gt;C</td>
<td>c.3242G&gt;T</td>
<td>1</td>
<td>Splice/missense</td>
<td>p.Gly1081Val</td>
<td>HDL, TC†</td>
<td>Low</td>
<td>LM26</td>
</tr>
<tr>
<td>9</td>
<td>ABCA1</td>
<td>NM_005502.3</td>
<td>g.107558471&gt;T</td>
<td>c.5245A&gt;G</td>
<td>1</td>
<td>Missense</td>
<td>p.Ile1749Val</td>
<td>HDL, TC†</td>
<td>High</td>
<td>HM67</td>
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<tr>
<td>15</td>
<td>LIPC</td>
<td>NM_000236.2</td>
<td>g.588405868&gt;C</td>
<td>c.866C&gt;T</td>
<td>1</td>
<td>Missense</td>
<td>p.Ser289Phe</td>
<td>HDL, TC, TG†</td>
<td>Low</td>
<td>LF14</td>
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<tr>
<td>15</td>
<td>LIPC</td>
<td>NM_000236.2</td>
<td>g.588557480&gt;C</td>
<td>c.1214C&gt;T</td>
<td>1</td>
<td>Missense</td>
<td>p.Thr405Met</td>
<td>HDL, TC, TG†</td>
<td>High</td>
<td>HM65</td>
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<tr>
<td>15</td>
<td>CETP</td>
<td>NM_000078.2</td>
<td>g.570050156&gt;G</td>
<td>c.597+1G&gt;C</td>
<td>0.99</td>
<td>Splice</td>
<td>ND</td>
<td>HDL, TC, LDL, TG†</td>
<td>High</td>
<td>HM70</td>
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<tr>
<td>16</td>
<td>CETP</td>
<td>NM_000078.2</td>
<td>g.570073640&gt;C</td>
<td>c.872C&gt;A</td>
<td>1</td>
<td>Missense</td>
<td>p.Ala291Asp</td>
<td>HDL, TC, LDL, TG†</td>
<td>High</td>
<td>HM47</td>
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<tr>
<td>16</td>
<td>LCAT</td>
<td>NM_000229.1</td>
<td>g.679741666&gt;A</td>
<td>c.964C&gt;T</td>
<td>0.98</td>
<td>Missense</td>
<td>p.Arg322Cys</td>
<td>HDL†</td>
<td>Low</td>
<td>LM31†</td>
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<tr>
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<td>c.725A&gt;G</td>
<td>1</td>
<td>Missense</td>
<td>p.Lys242Arg</td>
<td>HDL†</td>
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<td>LM22</td>
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<tr>
<td>16</td>
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<td>NM_000229.1</td>
<td>g.679763857&gt;G</td>
<td>c.629A&gt;G</td>
<td>1</td>
<td>Missense</td>
<td>p.His210Arg</td>
<td>HDL†</td>
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<td>LM36</td>
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<td>c.440C&gt;T</td>
<td>0.99</td>
<td>Missense</td>
<td>p.Thr147Ile</td>
<td>HDL†</td>
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<td>LF1</td>
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<tr>
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<td>LIPG</td>
<td>NM_006033.2</td>
<td>g.470917040&gt;C</td>
<td>c.115A&gt;C</td>
<td>0.1</td>
<td>Missense</td>
<td>p.Lys39Gln</td>
<td>HDL, TC†</td>
<td>Low</td>
<td>LM26</td>
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<tr>
<td>18</td>
<td>LIPG</td>
<td>NM_006033.2</td>
<td>g.471099396&gt;A</td>
<td>c.1117G&gt;A</td>
<td>0.84</td>
<td>Missense</td>
<td>p.Glu391Lys</td>
<td>HDL, TC†</td>
<td>High</td>
<td>HM50</td>
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<tr>
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<td>ABCG1</td>
<td>NM_207174.1</td>
<td>g.436401000&gt;G</td>
<td>c.190C&gt;G</td>
<td>0</td>
<td>Missense</td>
<td>p.Arg73Gly</td>
<td>HDL</td>
<td>Low</td>
<td>LM26</td>
</tr>
<tr>
<td>21</td>
<td>ABCG1</td>
<td>NM_016818.2</td>
<td>g.437024236&gt;A</td>
<td>c.628G&gt;A</td>
<td>1</td>
<td>Missense</td>
<td>p.Ala210Thr</td>
<td>HDL</td>
<td>High</td>
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</tr>
<tr>
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<td>c.1072G&gt;A</td>
<td>0.33</td>
<td>Missense</td>
<td>p.Gly358Arg</td>
<td>HDL</td>
<td>High</td>
<td>HM65</td>
</tr>
</tbody>
</table>

*CETP indicates cholesteryl ester transfer protein; Chr., chromosome; Cons., conservation; HDL-C, high-density lipoprotein cholesterol; ND, not determined; TC, total cholesterol; and TG, triglyceride.

†Common variants of gene associated with serum lipids in meta-analysis of genome-wide association studies16 data.

§Deleterious effect of these variants on LCAT activity is shown in Figure IV in the online-only Data Supplement.

¶These individuals carried only 1 variant in 195 lipid-related genes.

As those regulating low-density lipoprotein cholesterol and TG metabolism, may also be causally involved in regulating HDL-C levels.
with moderate-to-large effect on the phenotype play a role in
the heritability of the complex phenotypes.17

When trying to explain very extreme HDL-C levels in
humans, several well-known monogenic origins have to be
considered: loss of APOA1, LCAT, or ABCA1 gene function is
known to cause HDL deficiency,31–33 whereas a loss of CETP
or LIPC causes hyperalphalipoproteinemia.8,34 More recently,
heterozygosity for mutations in LIPG, SCARBI, and GALNT2
was also shown to cause high HDL-C levels.14,23,24,29 However
only few patients with extreme HDL-C levels carry mutations
in any of these genes,9–14 suggesting that deleterious variants
in other, hitherto unsuspected, genes might explain some of
the missing heritability. It is noteworthy, however, that no
major HDL gene has been identified since the discovery of the
ABCA1 in 1999. With this in mind, we set out to unravel the
genetic background of extreme HDL-C levels.

Multiple Rare Variants in Lipid-Related
Genes of the Extreme HDL Cohort

As a first step, we assessed the number of rare variants in 195
lipid-related genes in 80 patients with extreme HDL-C and 2
control cohorts. Comparison revealed significantly more rare
variants in lipid-related genes in the extreme HDL cohort. To
validate this finding, we compared the number of rare vari-
ants in the lipid genaset and a control set of lipid-unrelated
genets. In the control cohorts, we observed no difference in the
frequency of rare variants in the lipid genesets and lipid-unre-
lated genesets after adjustment for the number of nucleotides
sequenced in each of the genesets. This indicates that mutation
rates in each of the 2 genesets were similar in controls.

However, in the extreme HDL cohort, we identified a signifi-
cant >2-fold increase of rare variants in the lipid genaset.

Are the Identified Rare Variants Functional?

In the patients with extreme HDL-C levels, we identified 3
splice-site and 13 missense variants in genes with established
roles in HDL metabolism (Table 2). Specifically, 2 patients
with low HDL-C carried ABCA1 variants within canonical
splice sites of exon–intron boundaries. Both these splice-site
variants involved highly conserved nucleotides (phastCons
score=1). The third splice-site variant was found in CETP in
a patient with high-plasma HDL-C levels and is very likely to be
functional based on previous findings.35 The same is true for
the p.Ala291Asp substitution found in a second patient with
high HDL-C; this variant is not only found at an evolutionary
conserved nucleotide (phastCons score=1) but also resides in
the center of the cholesteryl ester binding tunnel of this lipid
transfer protein.36 We also identified 2 missense variants in
LIPC, both of which were previously detected in families with
hepatic lipase deficiency27,28 and subsequently confirmed to be
deleterious by functional analyses.37 Similarly, we identified 2
LCAT variants, previously shown to be deleterious,11 and show
that the 2 novel LCAT variants found in the current study are
associated with loss of LCAT catalytic activity in the plasma
of the respective patients (Figure IV in the online-only Data
Supplement).

The identification of multiple known and novel functional
mutations in well-established HDL genes in this study under-
scores that our approach to identify molecular causes of very
low or very high HDL-C in this cohort was sound. With this
in mind, it is reasonable to assume that the rare variants iden-
tified in other candidate genes, mainly identified through
GWAS, could also be causally related to the extreme HDL-C
phenotypes, but of course functional studies need to be per-
formed to provide ultimate proof.

A Possible Polygenic Origin of
Extreme HDL-C Levels

After recent insight into the complex background of hypertri-
glyceridemia,39 the current study indicates that this may also
hold true for extreme HDL-C phenotypes. Until recently, we
and others have limited our insight by sequencing 1 or at most
several candidate genes to try to explain extreme HDL-C phe-
notypes. With next-generation sequencing, however, we are
confronted with possible functional variants in an increasing
number of genes. The current study provides interesting
examples, illustrating the complexity of the genetic architec-
ture of extreme HDL-C levels.

Fitting the old concept of a possible monogenic origin
for extremely low HDL-C, we identified a single splice-site
variant in ABCA1 and a functional missense variant in LCAT in
2 patients with low HDL-C levels (Table 2, patient IDs: LM28
and LM31). However, these patients belonged to the small
group of 9 individuals in whom only 1 rare variant was found
in all 195 sequenced lipid-related genes. All other patients
(87%) carried ≥2 rare variants, whereas 28% of the patients carried ≥5 rare variants. Although we have not shown that all of the variants identified are functional, the numbers of gene carriers ≥(87%) carried ≥2 rare variants, whereas 28% of the patients carried ≥5 rare variants. Although we have not shown that all of the variants identified are functional, the numbers of gene carriers ≥2 rare variants, whereas 28% of the patients carried ≥5 rare variants. Although we have not shown that all of the variants identified are functional, the numbers of gene carriers ≥2 rare variants, whereas 28% of the patients carried ≥5 rare variants. Although we have not shown that all of the variants identified are functional, the numbers of gene carriers ≥2 rare variants, whereas 28% of the patients carried ≥5 rare variants. 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readily clarified. For example, 2 splice-site variants in APOC3 most probably gave rise to increased HDL-C in these patients as a direct consequence of enhanced lipoprotein lipase-mediated plasma triglyceride hydrolysis. For other high-impact rare variants (nonsense, splice-site, and coding indel) in PCSK5, PLEC, ABCA8, C5orf35, and CITED5 (Table 3), we are currently investigating how they could have an impact on HDL-C metabolism.

Limitations of the Study
To increase the statistical power of our analyses, we combined individuals at both ends of the plasma HDL-C level distribution, which creates an artificial grouping. Therefore, a similarly designed approach, with considerably larger sample that compares the individual genetic architectures of hypertriglyceridemia and hyperapoHLPemia, is warranted. In our analyses of the extreme HDL cohort, we also elected to study genes associated with lipid metabolism, in general, rather than restricting the focus to only HDL-related entities, given the strong interplay between HDL- and non-HDL-C and triglyceride metabolism. Indeed, we recognize it is often not possible to label lipid genes with unique lipid trait tags and that functional analyses will be required to draw definitive conclusions regarding the mechanisms by which rare variants in the non-HDL genes may contribute to hypertriglyceridemia and hyperapoHLPemia. For most genes studied, there is also limited information on whether a loss- or gain-of-function mutation would increase/decrease HDL-C. Hence, functional studies are required to assess the contribution of each gene and associated variant on HDL metabolism. In some cases, segregation analysis in families of the index patients may also help to resolve whether and how genotypes correlate to the phenotype. However, for individuals with multiple variants (eg, individuals with 12 or 14 rare variants described in this study), resolving genotype-phenotype correlation, if not impossible, will practically be very difficult.

Conclusions
This study shows that extreme HDL-C phenotypes are not necessarily of monogenic origin. The data in fact suggest that multiple rare variants can contribute to the heritability of extreme plasma HDL-C levels. In addition, the data provide support to perform functional studies to elucidate how rare variants in newly proposed candidate genes (mostly from GWAS) exert their effects.

Acknowledgments
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Disclosures
None.

References
A majority of patients with extreme plasma high-density lipoprotein cholesterol levels carry multiple rare variants in lipid-related genes, indicative of a polygenic origin of this phenotype. This study points at possible functional roles of novel lipid-associated genes identified by genome-wide association studies in high-density lipoprotein metabolism. Finally, this study bears significance for investigators striving for the discovery of new major high-density lipoprotein candidate genes.
Evidence of a Polygenic Origin of Extreme High-Density Lipoprotein Cholesterol Levels
Mohammad Mahdi Motazacker, Jorge Peter, Marco Treskes, Carol C. Shoulders, Jan Albert Kuivenhoven and G. Kees Hovingh

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An erratum has been published regarding this article. Please see the attached page for:
http://atvb.ahajournals.org/content/33/8/e128.full.pdf
In the article by Motazacker et al, which appeared in the July 2013 issue of the journal (Arterioscler Thromb Vasc Biol. 2013;33:1521–1528. DOI: 10.1161/ATVBAHA.113.301505), the title should not have indicated that the article was a brief report.

The online version of the article has been corrected and is available at http://atvb.ahajournals.org/content/33/7/1521.full.
Materials and Methods

Study cohorts

**Extreme HDL-cohort**
From 10,000 subjects of a general patient population in the center of The Netherlands, we selected individuals with the most extreme HDL-C levels (40 with HDL-C<1st and 40 with HDL-C>99th for age and gender). We did not use information on the specific referral basis of any of these patients, and none of these patients were participants in our previous studies1,2. All lipid values were measured after an overnight fast in the central clinical chemistry laboratory of the Academic Medical Center in Amsterdam. No prescreening for known monogenic causes of HDL-C phenotypes was performed. Patients were invited to participate and information about medical history was assessed using a questionnaire and included specific information on CVD defined as previous acute myocardial infarction, stroke, coronary artery bypass surgery or percutaneous coronary intervention, CVD risk factors, diabetes, medication use and family history of dyslipidemia and/or CVD. Written informed consent was obtained and the study protocol was approved by the IRB.

**Dutch General Population and Normal HDL-cohort**
In the Genome of the Netherlands project (GoNL; [http://www.nlgenome.com](http://www.nlgenome.com)), genomes of 250 trios (father, mother, and child) were sequenced at the Beijing Genomics Institute (BGI, [http://www.genomics.cn/](http://www.genomics.cn/)). For the current study, data from 498 unrelated parents were used as representative of the Dutch general population. Additionally, a selected subpopulation of GoNL comprising 95 unrelated individuals (47 males and 48 females) with HDL-C levels between 40th and 60th percentile for gender constitute the “normal HDL”-cohort.

Genesets

For the lipid geneset, 195 genes were selected based on established biological relevance to lipid and lipoprotein metabolism and/or significant association of common variants with lipid traits in GWAS (p<5x10^-8) identified through meta-analysis of ~100,000 individuals3. It includes 95 HDL genes (49 GWAS + 46 non-GWAS); 68 triglyceride (TG) genes (34 GWAS + 34 non-GWAS); 56 LDL-C genes (40 GWAS + 16 non-GWAS) and 56 total cholesterol (TC) genes (54 GWAS + 2 non-GWAS). Genes with significant association with multiple lipid traits have been considered in all relevant lipid categories. The complete gene list including lipid-associated categories is shown in Supplemental Table I. Of note, the proposed HDL-C, TG and LDL-C annotation for the sequenced genes are not mutually exclusive due to the inter-relationships between these parameters. ABCA1, ABCG1, APOA1, APOM, ATP5B, CETP, GALNT2, LCAT, LIPC, LIPG, PLTP and SCARB1 were considered established HDL-C genes4,5. Coding sequences and exon-intron boundaries of the lipid geneset encompass 469,032 nucleotides.
The lipid-unrelated geneset comprised 78 genes with potential roles in coagulation, but without known roles in lipid metabolism (Supplemental Table II). Coding exons and exon-intron boundaries in this geneset encompasses 127,466 nucleotides.

**Sequencing and Variant Identification**

In the extreme HDL-cohort, coding sequence and exon-intron boundaries of lipid-associated and lipid-unrelated genesets were sequenced. In the Dutch general population, genome sequencing had been performed as part of the GoNL project. Data from lipid geneset and lipid-unrelated genes of the GoNL cohort were extracted from genome data and were compared to the extreme HDL-cohort. Non-synonymous (missense, nonsense and splice-site) variants with a minor allele frequency (MAF) <0.5% in GoNL are denoted as “rare variants” throughout the manuscript.

**Sequencing experimental pipeline**

For the extreme HDL-cohort, we developed an Agilent SureSelect® Biotinylated custom library to enrich for coding sequences and exon-intron boundaries of lipid and lipid-unrelated genesets, according to the manufacturers’ protocols. In short, genomic DNA was fragmented by AFA (Covaris). The sizes of the DNA fragments (ranging between150 and 200bp) were assessed by gel electrophoresis. Adapters were ligated to both ends of the resulting fragments. Adapter-ligated templates were purified by the Agencourt AMPure SPRI beads and fragments with insert size ~250bp were excised. Extracted DNA was amplified by ligation-mediated PCR (LM-PCR), purified, and hybridized to the SureSelect® Biotinylated RNA Library for enrichment for 24 hrs. Fragments not hybridized to the streptavidin beads were washed out after 24 hours. The magnitude of enrichment was analyzed by the Agilent 2100 Bioanalyzer and upon QC loaded on a HiSeq2000 platform. Each captured library was required to produce an average sequencing depth >50x. Raw image files were processed by Illumina base-calling Software 1.7 for base-calling with default parameters and the sequences of each individual were generated as 90bp paired-end reads.

For sequencing of GoNL project participants ([http://www.nlgenome.com](http://www.nlgenome.com)), the same sequencing protocol was used as for the extreme HDL-cohort, except that no enrichment step was performed and adapter-ligated fragments were selected to have a size of ~500bp. Average sequencing depth was 12x. Insertion/deletion (indel) variant data are not available for GoNL cohort subjects.

**Bioinformatics pipelines**

The following strategy was used to call variants with an error rate of <0.001\(^6\) in the Extreme HDL-cohort:

SOAPaligner/SOAP2 software was used to map sequence reads to the human reference genome - NCBI build37- at UCSC\(^7\). Only mapped sequence reads were used in subsequent analyses. Coverage and depth calculations are based on mapped reads to the target region.

The following parameters were used for analysis:
1. SOAPaligner (v.2.21) was used to align the clean reads to the human reference genome allowing maximum 3 mismatches, the parameters were set as -a -b -D -o -u -p -2 -m -x -s 40 -l 35 -v 3 (http://soap.genomics.org.cn/)

2. SOAPsnp was used to assemble the consensus sequence and call genotypes in target regions. The following parameters were set: -i -d -o -r 0.0005 -e 0.001 -u -L 90 -T -s -2 (http://soap.genomics.org.cn/)

3. Candidate single nucleotide variants were filtered with the following criterion: quality ≥ 50 (thereby an error rate of <0.001), sequencing depth between 4 and 200, estimated copy number <2 and distance between two variants >5.

4. BWA\(^8\) was used to align indels to the human reference genome, the parameters were set as –k 2 –t 4.

5. SAMTOOLS\(^9\) was used to remove duplicates (mdup) and analyze indel using BWA aligned files, parameters were set as view -u -b -s –t.

6. Vcf and Indel files were obtained with GATK\(^10\), the parameters were -- mismatchFraction 0.15 –LOD 3 –maxReadsForRealignment 20000.

Variants with an error rate of <0.001\(^6\) in the extreme HDL-cohort were annotated using ALAMUT® software (Interactive Biosoftware, San Diego, CA, USA).

For the GoNL project, an additional (alternative) bioinformatics pipeline was used to call variants. Each lane of sequence data was aligned to the human reference genome - NCBI build 37 - using BWA\(^8\). Using the Genome Analysis Toolkit\(^10\), duplicate reads were removed, re-alignment performed around known insertions and deletions from the 1000 Genomes Project pilot and base quality scores recalibrated. Lanes were then merged per family and re-alignment was performed around insertions and deletions found in the sequence data and in the 1000 Genomes Phase 1 data (http://www.1000genomes.org/data). SNP discovery and genotyping was done using the GATK Unified Genotyper across all individuals simultaneously. The initial calls were filtered using GATK Variant Quality Score Recalibration (VQSR) and excluded all sites with a Hardy-Weinberg Equilibrium test \(p\)-value below \(10^{-6}\) resulting in 18,822,102 biallelic SNPs called with a corresponding transition/transversion ratio of 2.16. GATK Phase-By-Transmission has been used to compute the most likely genotype for each individual when considering the data for all family members jointly along with expected modes of allele transmission. All analyses using unphased most likely genotypes were performed using this data. For analyses requiring phased data, the raw genotype likelihoods were input to Beagle\(^11\) to infer the haplotypes.

To compensate for the lower average sequence coverage in the GoNL compared to the extreme HDL-cohort (12x vs 50x respectively) and to reduce the chance of including false positive calls, only GoNL variants called by both pipelines were used for further analysis. The 40TB of GoNL sequences were aligned and variant called on the Dutch Target cluster (Target project, http://www.rug.nl/target) and BigGrid using the MOLGENIS compute framework\(^12\). The GoNL variants for all genes in all individuals were annotated with Annovar\(^13\) on the Dutch grid (BiG Grid, http://www.biggrid.nl/) using the e-BioInfra framework\(^14\).
Nonsynonymous (missense, splice-site, nonsense) variants with a frequency of <0.5% in the GoNL cohort were denoted as “rare variants”. Nonsense, splice-site and indel variants identified in extreme HDL-cohort were verified by Sanger sequencing. Nucleotides with a phastCons score >0.5 (UCSC genome browser\(^7\)) were considered conserved between species.

**Statistical analysis**

Differences in characteristics of extreme HDL-cohorts (low and high HDL-cohort) were evaluated using unpaired \(t\)-test (age, BMI and lipid values) or Fischer’s exact test (smoking, diabetes and CVD). For comparison of sequence variants in the lipid geneset and lipid-unrelated genes in each studied cohort (extreme HDL-cohort, normal HDL-cohort, GoNL, or ESP), odds ratios, confidence intervals and \(p\)-values were calculated using Chi-squared test after correction for the number of nucleotides sequenced per genesets/subsets. For comparison of the lipid geneset between the extreme HDL-cohort and control cohorts, odds ratios, confidence intervals and \(p\)-values were calculated using Chi-squared test after correction for the number of individuals included in each cohort.

**References**


## Supplemental Material

### Supplemental Tables

#### Supplemental Table I: Genes in the lipid geneset and related phenotypes associated with each gene.

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<td>NO&lt;sup&gt;16&lt;/sup&gt;</td>
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<td>NPC1</td>
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<td>WWOX</td>
<td>TG</td>
<td>NO&lt;sup&gt;18&lt;/sup&gt;</td>
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<td>ZNF664</td>
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<sup>1</sup>Included on established biological relevance to lipid or lipoprotein metabolism and/or significant association (p<5x10<sup>-8</sup>) of common variants with lipid traits in Genome Wide Association Study (GWAS).

<sup>2</sup>For GWAS genes, the lead trait (i.e. the first named) produced the best p-value among the four traits studied (HDL, TC, LDL, TG) for association with a common allele at the studied gene locus; additional traits listed according to returned p-values.

GWAS data are from meta-analysis of ~100,000 individuals<sup>1</sup>.
## Supplemental Table II: Lipid-unrelated geneset

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<th>KLK3</th>
<th>PF4V1</th>
<th>PROZ</th>
<th>SPP1</th>
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<td>SELE</td>
<td>TFPI</td>
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Supplemental Table III: Targeted capture statistics for the extreme HDL-cohort.

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<th>Target region (bp)</th>
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<td>Average raw data yield (Mb)</td>
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<td>Average reads mapped to target region</td>
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<tr>
<td>Average data mapped to target region (Mb)</td>
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<td><strong>Average mean depth of target region</strong></td>
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<td><strong>Coverage of target region (%)</strong></td>
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<td>Average read length (bp)</td>
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<td>Average rate of nucleotide mismatch (%)</td>
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<td>Average capture specificity (%)</td>
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<tr>
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<td>Average coverage of flanking region (±200bp of target) (%)</td>
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<td>Average fraction of unique mapped bases on or near target</td>
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<tr>
<td>Average mean depth of chrX</td>
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*Includes 5’ and 3’ UTR sequences.
Supplemental Table IV: Variants identified in lipid geneset. Chr.: chromosome, Cons.: conservation score from phastCons, Allele count: number of alleles for each variant found in 80 individuals with extreme HDL-C phenotype; Freq GoNL (%): minor allele frequency (%) in 498 unrelated individuals from the Dutch General population (GoNL project); Freq ESP (%): minor allele frequency (%) in European-Americans included in NHLBI Exome Sequencing Project (Accessed September 2012); Carriers of rare non-synonymous variants are indicated by their HDL-C levels (L: low/H: high) and gender (M: male/F: female) followed by a unique identifier. *Genes with proposed role in lipid metabolism identified by meta-analysis of GWAS data.**Variants also identified in individuals with HDL-C levels between 40-60th percentile values.
### A) Variants identified in individuals with low HDL-C levels

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<th>cDNA</th>
<th>Protein</th>
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<th>Cons.</th>
<th>SIFT</th>
<th>Allele count</th>
<th>Freq. GoNL (%)</th>
<th>Freq. ESP (%)</th>
<th>Carriers</th>
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**Supplemental Table V: Variants identified in coagulation geneset.** Chr.: chromosome, Cons.: conservation score from phastCons, Allele count: number of alleles for each variant found in 80 individuals with extreme HDL-C phenotype; Freq. GoNL (%): minor allele frequency (%) in 498 unrelated individuals from the Dutch General population (GoNL project); Freq. ESP (%): minor allele frequency (%) in European-Americans included in NHLBI Exome Sequencing Project (Accessed September 2012); Carriers are indicated by their HDL-C levels (L: low/H: high) and their gender (M: male/F: female) followed by a unique identifier.

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**Supplemental Table VI: Number of rare non-synonymous variants identified in lipid geneset and lipid-unrelated genes in the extreme HDL-cohort, normal HDL-cohort and Dutch general population cohort (GoNL).** SNV: single nucleotide variants, ND: not determined.

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Supplemental Table VII: Total number of variants identified in individual lipid genes.

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*GWAS data are from meta-analysis of ~100,000 individuals*. 
Supplemental Table VIII: Size of the targeted regions and the number of variants identified in each subgroup of the lipid geneset in extreme HDL-cohort. Odds-ratios and confidence intervals (OR [CI]) and the p-values are calculated for comparison of each subgroup with lipid-unrelated genes after correction for the size of targeted regions.

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<th>Geneset</th>
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<th>OR [CI]</th>
<th>p-value</th>
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<td>469032</td>
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<td>223228</td>
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<td>2.20 [1.53-3.18]</td>
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<td>245804</td>
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<td>2.46 [1.37-4.44]</td>
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Supplemental Figures

Supplemental Figure I: Distribution of plasma lipid and lipoprotein parameters in individuals from the Dutch general population (GoNL).
Supplemental Figure II: Baseline characteristics of the extreme (low and high) HDL-C cohorts. $p<0.0001$ for BMI, HDL and TC and $p<0.0005$ for TG.
Supplemental Figure III: Comparison of the frequency of rare non-synonymous variants in lipid-related geneset and lipid-unrelated genes in ~3400 subjects of European-American ancestry from NHLBI Exome Sequencing Project\textsuperscript{65}. In ESP study, the number of variants in the lipid geneset was significantly lower than in the lipid-unrelated genes.
Supplemental Figure IV: Plasma LCAT activities of patients with novel LCAT mutations. Plasma LCAT activity was measured with a proteoliposome assay as described using pool of plasma from 251 apparently healthy individuals as control. Measurements were performed in duplicate. Values are mean±SD. P-values are calculated using non-parametric t-test.

References


(18) Kocher O, Krieger M. Role of the adaptor protein PDZK1 in controlling the HDL receptor SR-BI. *Curr Opin Lipidol.* 2009;20:236-41


(45) Errera Fl, Canani LH, Yeh E, Kague E, Armelin-Correa LM, Suzuki OT, Tschiedel B, Silva ME, Sertie AL, Passos-Bueno MR. COL18A1 is highly expressed during human adipocyte differentiation and the SNP c.1136C > T in its "frizzled" motif is associated with obesity in diabetes type 2 patients. *An Acad Bras Cienc.* 2008;80:167-77


