Role of Insulin Resistance in Familial Combined Hyperlipidemia

M.J. Veerkamp, J. de Graaf, A.F.H. Stalenhoef

Objective—Insulin resistance is associated with increased triglyceride levels, low high-density lipoprotein cholesterol, small dense low-density lipoprotein (LDL), and increased apolipoprotein B (apoB) levels, all characteristics of familial combined hyperlipidemia (FCH). Therefore, we explored the role of insulin resistance in FCH lipid phenotype expression.

Methods and Results—FCH was defined by traditional diagnostic criteria including plasma total cholesterol or triglyceride levels >90th percentile. Insulin resistance was assessed by the Homeostasis Model Assessment (HOMA) index. In total, 132 subjects with FCH, 350 normolipidemic relatives, and 81 spouses who referenced as controls were studied. FCH subjects were significantly more insulin resistant compared with controls and normolipidemic relatives (HOMA index 2.9 [95% CI, 2.6 to 3.2], 2.2 [95% CI, 2.0 to 2.5], and 2.0 [95% CI, 1.9 to 2.2], respectively), even after correction for sex, age, and body mass index (BMI). The degree of insulin resistance was associated with the lipid phenotype expression, and a change in insulin-resistant state was associated with a change in lipid phenotype expression over 5 years. For any level of insulin resistance and degree of obesity, FCH subjects had increased levels of apoB and more small dense LDL compared with controls.

Conclusion—Insulin resistance is a characteristic feature of FCH, which is not fully explained by their increased BMI and is associated with (change in) lipid phenotype expression. Furthermore, our results support the concept of genetic origin of high apoB and small dense LDL in FCH, which is modulated by insulin resistance and obesity. (Arterioscler Thromb Vasc Biol. 2005;25:1026-1031.)

Key Words: apolipoprotein B ■ familial combined hyperlipidemia ■ insulin resistance ■ obesity ■ small dense low-density lipoproteins
Subjects and Methods

Study Population
We recently performed a large study in FCH families (n=667 individuals), including a 5-year follow-up period (1994 to 1999), to investigate the metabolic and genetic aspects of FCH.4 For the current study, we included all subjects with FCH, normolipidemic (NL) relatives, and spouses of whom glucose and insulin levels were available in 1999, resulting in a study population of 132 FCH subjects, 350 NL relatives, and 81 spouses who referenced as controls. The relatives and spouses were ascertained through probands recruited from our outpatient clinic. The probands exhibiting a combined hyperlipidemia (combined HPL), with plasma total cholesterol (TC) and TG concentrations above the 90th percentile, were adjusted for age and gender, as obtained from the Prospective Cardiovascular Munster (PROCAM) study.19 These values were confirmed by repeated measurement on a lipid-lowering diet and without lipid-lowering drugs. At least 1 first-degree relative of the proband had a multiple-type hyperlipidemia with elevated levels of plasma TC and/or TG. Furthermore, at least the proband or 1 of the first-degree relatives should have premature cardiovascular disease at <60 years of age. All probands were tested for an underlying cause of hyperlipidemia (ie, diabetes mellitus, hypothyroidism, and hepatic or renal impairment). The presence of 1 of these causes excluded the proband and his/her family from further analysis. None of the probands in these families were homozygous for the apoE2 allele, and none of them or their first-degree relatives had tendon xanthomas. The relatives were classified as affected FCH when plasma TC and/or TG levels exceeded the 90th percentile based on the PROCAM study.19 These percentiles are age and gender adjusted. The probands and affected FCH relatives were defined as FCH subjects in the manuscript. NL relatives were defined by TC and TG levels <90th percentile, and the spouses were referenced as controls. All individuals were white and >12 years of age. All subjects filled out a questionnaire about their previous medical history, especially cardiovascular status. Body mass index (BMI), waist/hip ratio (WHR), and blood pressure were determined in all subjects. After a withdrawal of 4 weeks of lipid-lowering medication and an overnight fast, venous blood was drawn by venipuncture. Among the 132 FCH subjects, data of lipids and glucose/insulin levels were also available in 1994 in 76 subjects (58%). Fifty-five of these patients were affected with FCH in 1994 and 1999 (72%) based on K>90th percentile adjusted for age and gender. These subjects were included in the follow-up to study the interdependence of change in insulin resistance in time on lipid phenotype expression. Among the 350 NL relatives, data of lipids and glucose/insulin levels were also available in 1994 in 180 subjects (51%). A total of 156 of the 180 subjects (87%) were NL relatives in 1994 and 1999 and were also included in the follow-up study. Twenty-one of the 76 affected subjects (28%) in 1994 showed a NL lipid profile in 1999, and 24 of the 180 NL subjects (13%) in 1994 were affected with FCH in 1999. The study protocol was approved by the ethical committee of the University Medical Center in Nijmegen.

Plasma Lipid, Lipoprotein, and Apolipoprotein Analysis
Plasma TC and TG concentrations were determined by enzymatic, commercially available reagents (Boehringer-Mannheim, catalog 237574; and Sera Pak, Miles, catalog 6639; respectively). Total plasma apoB concentrations were determined by immunonephelometry as described recently in detail.4,20 LDL Subfraction Profile Analysis
LDL subfractions were separated by single-spin density gradient ultracentrifugation.24 Each individual LDL subfraction profile was defined by a continuous variable K, as described in detail previously.22,23 A negative value (K<0) reflected a more dense LDL subfraction profile, and a positive K value (K>0), a more buoyant profile.

Glucose, Insulin, and Insulin Resistance Analysis
Glucose concentrations were measured in duplicate using the oxidation method (Beckman Glucose Analyser2; Beckman). Plasma insulin concentrations were determined using a double-antibody method with an interassay variability of 6%. Insulin resistance was assessed by the Homeostasis Model Assessment (HOMA) index and calculated using the formula HOMA index=fasting serum insulin (mU/L)×fasting plasma glucose (mmol/L)/22.5.25

Statistical Analysis
Descriptive values were expressed as mean (95% CI) or absolute numbers with percentages. TG, HOMA index, insulin, and glucose were logarithmically transformed to obtain normal distributions before statistical analysis. Differences in characteristics between subjects with FCH, controls, and NL relatives were tested by generalized estimating equations because of possible correlated values within families. Correlations between HOMA index and variables were analyzed using Spearman correlation coefficients. The 90th percentile of HOMA index, apoB concentration, and K value were based on the group of controls. Multiple linear regression test was used to select the variables that contributed independently to HOMA index. P values <0.05 were considered statistically significant. All analyses were computed using STATA 8.0 software.

Results
In total, 563 subjects, including 132 subjects with FCH, 350 NL relatives, and 81 controls, were included in the study. Table 1 shows the anthropometric and biochemical variables. The ratio of women to men was not significantly different between the groups. The mean age of the group of subjects with FCH was significantly lower compared with controls and significantly higher compared with the NL relatives. The BMI was significantly higher in the FCH group compared with the control group and NL relatives. By definition, the FCH group had significantly higher plasma TC and TG concentrations compared with controls and NL relatives. In addition, subjects with FCH had a more atherosclerotic lipid and lipoprotein profile, as reflected by increased LDL cholesterol (LDL-C), decreased HDL cholesterol (HDL-C), increased apoB concentrations, and a smaller dense LDL subfraction profile, as reflected by a more negative value of parameter K compared with the control group and NL relatives. The differences between the control group and NL relatives are indicated in Table 1.

FCH and Insulin Resistance
Subjects with FCH were more insulin resistant, as assessed by the HOMA index, which was significantly higher in FCH subjects compared with the NL relatives and group of controls (Table 2), with a mean difference of 0.9 (95% CI, 0.79 to 0.92) between FCH subjects and controls. Even after adjustment for age, sex, and BMI, subjects with FCH were still significantly more insulin resistant, with a mean difference in HOMA index of 0.9 (95% CI, 0.83 to 0.95). Controls and NL relatives did not differ in HOMA index. A significantly higher number of FCH subjects (18%) had a HOMA index >90th percentile compared with 6% in the group of NL relatives (Table 2). The glucose concentration was not significantly different between the FCH group and control group, whereas the subjects with FCH had significantly higher insulin levels compared with both other groups. HOMA index was not statistically different between males and females in the 3 different groups (data not shown).
We evaluated the effect of different variables on insulin resistance. The degree of insulin resistance (HOMA index) had significant correlations with BMI \((R=0.48; P<0.001)\), WHR \((R=0.30; P=0.001)\), systolic blood pressure \((R=0.23; P=0.009)\), diastolic blood pressure \((R=0.25; P=0.004)\), HDL-C \((R=-0.18; P=0.039)\), and K value \((R=-0.21; P=0.18)\) evaluated in the FCH group \((n=132)\). As shown in Table 2, the higher HOMA index in FCH patients is the result of the relatively higher levels of insulin compared with the glucose levels. Therefore, almost similar correlations for fasting insulin levels with the different parameters were found as for HOMA index (data not shown). With the linear regression model using HOMA index as the dependent variable and sex, age, BMI, WHR, systolic and diastolic blood pressure, TC, TG, HDL-C, apoB, and small dense LDL as the independent variables, only BMI proved to contribute independently to the degree of insulin resistance. BMI explained 23% of the variance in HOMA index. Similar results were found for the control group and the group of NL relatives (data not shown).

### Lipid Phenotype and Insulin Resistance in FCH

Of the 132 FCH subjects, 86 subjects were affected based on the presence of isolated hypertriglyceridemia (hyperTG; TG >90th percentile according to PROCAM\(^{19}\)), 24 subjects based on the presence of combined HLP (TC and TG >90th percentile), and 22 subjects based on isolated hypercholesterolemia (hyperTC; TC >90th percentile). Lipid and lipoprotein profiles are given in Table 3. The FCH subjects affected based on hyperTG or combined HLP have a significantly higher BMI, TC, TG, apoB level, and more small dense LDL compared with controls. The HOMA index of FCH subjects who presented with hyperTG or combined HLP was significantly higher compared with controls even after correction for BMI. FCH subjects with combined HLP have higher TC, TG, and apoB levels and more small dense LDL compared with hyperTG subjects, but they do not differ in BMI or HOMA index. The FCH subjects affected based on hyperTC have higher TC, TG, and apoB levels compared with controls. Strikingly, although all affected FCH subjects had higher

### Table 1. Anthropometric and Biochemical Parameters in Subjects With FCH Compared With Controls and NL Relatives

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FCH (n=132)</th>
<th>Controls (n=81)</th>
<th>NL Relatives (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % male</td>
<td>58 (44%)</td>
<td>39 (48%)</td>
<td>168 (48%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>46.4 (43.6–49.2)*†</td>
<td>52.4 (46.9–56.0)‡</td>
<td>38.4 (36.5–40.3)</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>27.7 (27.0–28.4)*†</td>
<td>26.5 (25.6–27.3)‡</td>
<td>24.2 (23.7–24.7)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.88 (0.86–0.89)†</td>
<td>0.86 (0.84–0.87)‡</td>
<td>0.93 (0.83–0.84)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>6.3 (6.1–6.5)††</td>
<td>5.2 (4.9–5.4)‡‡</td>
<td>5.0 (4.8–5.1)</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>2.8 (2.6–3.0)††</td>
<td>1.1 (1.0–1.2)‡‡</td>
<td>1.1 (1.0–1.1)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>4.0 (3.8–4.2)††</td>
<td>3.5 (3.2–3.7)‡‡</td>
<td>3.3 (3.2–3.4)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.95 (0.90–1.00)†</td>
<td>1.29 (1.22–1.35)‡</td>
<td>1.22 (1.18–1.26)</td>
</tr>
<tr>
<td>ApoB, mg/L</td>
<td>1328 (1285–1370)†</td>
<td>993 (939–1047)‡</td>
<td>981 (954–1008)</td>
</tr>
<tr>
<td>K value</td>
<td>−0.26 (−0.31–0.22)†</td>
<td>0.07 (0.02–0.12)‡</td>
<td>0.04 (0.01–0.07)</td>
</tr>
</tbody>
</table>

**Values are estimated mean (95% CI) and absolute numbers (%) for sex distribution. FCH indicates familial combined hyperlipidemia; NL, normolipidemic relatives; BMI, body mass index; WHR, waist hip ratio; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; apoB, apolipoprotein B; K value<0, reflecting small dense LDL.**

*\(P<0.05\) FCH compared with controls; †\(P<0.05\) FCH compared with NL relatives; ‡\(P<0.05\) controls compared with NL relatives, \(P<0.05\) = statistical significance.

### Table 2. Degree of Insulin Resistance (HOMA Index) in Subjects With FCH Compared With Controls and NL Relatives

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FCH (n=132)</th>
<th>Controls (n=81)</th>
<th>NL Relatives (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA index</td>
<td>2.9 (2.6–3.2)††</td>
<td>2.2 (2.0–2.5)‡‡</td>
<td>2.0 (1.9–2.2)</td>
</tr>
<tr>
<td>HOMA index &gt;90th percentile</td>
<td>24 (18%)††</td>
<td>8 (10%)‡‡</td>
<td>22 (6%)</td>
</tr>
<tr>
<td>Insulin, mU/L</td>
<td>12.5 (11.4–13.7)††</td>
<td>9.7 (8.6–10.8)‡‡</td>
<td>9.2 (8.6–9.8)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.2 (5.1–5.3)*‡</td>
<td>5.2 (5.0–5.3)‡‡</td>
<td>4.9 (4.9–5.0)</td>
</tr>
</tbody>
</table>

**Values are estimated mean (95% CI) and absolute numbers (%) for HOMA index >90th percentile (4.3). FCH indicates familial combined hyperlipidemia; NL, normolipidemic relatives; HOMA, homeostasis model assessment for insulin resistance defined by fasting plasma insulin×fasting plasma glucose/22.5.**

*\(P<0.05\) FCH compared with controls; †\(P<0.05\) FCH compared with NL relatives; ‡\(P<0.05\) controls compared with NL relatives, \(P<0.05\) = statistical significance.
apoB, TC, and TG levels compared with controls, subjects with FCH based on hyperTC did not show a small dense LDL subfraction profile and were not insulin resistant.

**Lipid Phenotype and Insulin Resistance Over a 5-Year Period**

To evaluate the interdependence of insulin resistance on change in lipid phenotype expression, we studied 55 subjects who were affected FCH in 1994 and 1999, including 156 subjects who were NL in 1994 and 1999 (Table 4). Among the NL subjects, the HOMA index and BMI increased significantly over 5 years, with a correlation between ΔBMI and ΔHOMA index of \( R=0.24 \) and \( P=0.001 \). Also among all FCH subjects, an increase in BMI over 5 years was associated with an increase in HOMA index \( (R=0.47; P<0.001) \). Seven subjects were affected with FCH based on hyperTC in 1994 and 1999. BMI increased in 5 years, but this increase did not reach statistical significance. HOMA index did not change over this period. In 1994 and 1999, BMI and HOMA index were higher among these FCH subjects are significantly higher compared with NL subjects. Eight subjects were affected FCH in 1994 based on hyperTC and in 1999 based on combined HLP or hyperTG. Their BMI and HOMA index increased significantly over the 5-year period. In 1994 and 1999, BMI and HOMA index were higher compared with the NL subjects; however, the HOMA index in 1994 did not reach statistical significance. Among the 39 subjects who remained affected with FCH based on hyperTG or combined HLP, BMI showed a trend of increase, and the HOMA index increased significantly. Again, BMI and HOMA index among these FCH subjects are significantly higher compared with the NL group. There was only 1 subject who changed from hyperTG to hyperTC; the HOMA index of this individual decreased from 1.96 in 1994 to 0.43 in 1999, whereas the BMI increased slightly from 24.0 to 24.1 kg/m².

**Can Insulin Resistance or Obesity Explain the Elevated ApoB Levels and High Occurrence of Small Dense LDL in FCH?**

Scatter plots were generated to explore the relationship between insulin resistance, obesity and apoB levels, and

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**TABLE 3. Anthropometric and Biochemical Parameters of FCH Subjects With Different Lipid Phenotypes Compared With Controls**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>n</th>
<th>HyperTG</th>
<th>Combined HLP</th>
<th>HyperTC</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td>46.7</td>
<td>48.7</td>
<td>42.0</td>
<td>52.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td>28.1</td>
<td>27.8</td>
<td>26.7</td>
<td>26.3</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td></td>
<td>5.7</td>
<td>7.8</td>
<td>7.2</td>
<td>5.2</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td></td>
<td>2.9</td>
<td>3.8</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>ApoB, mg/L</td>
<td></td>
<td>1205</td>
<td>1629</td>
<td>1505</td>
<td>999</td>
</tr>
<tr>
<td>K value</td>
<td></td>
<td>3.0</td>
<td>3.3</td>
<td>2.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Values are mean (95% CI). FCH indicates familial combined hyperlipidemia; BMI, body mass index; TC, total cholesterol; TG, triglyceride; apoB, apolipoprotein B; K value: <0, reflecting small dense LDL; HOMA, homeostasis model assessment for insulin resistance defined by fasting plasma insulin×fasting plasma glucose/22.5; hyperTC, FCH subjects based on TC > 90th percentile; hyperTG, FCH subjects based on TG > 90th percentile; combined HLP, FCH subjects based on TC and TG > 90th percentile.

**TABLE 4. Insulin Resistance (HOMA index) and Obesity (BMI) in FCH Subjects Stratified by Different Lipid Phenotype Expression Compared With NL Relatives in 1994 and 1999**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>n</th>
<th>HyperTG-HyperTC</th>
<th>HyperTG or combined HLP</th>
<th>HyperTC or combined HLP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOMA index</strong></td>
<td></td>
<td>2.6 (1.7–4.1)†</td>
<td>2.6 (2.1–3.3)§</td>
<td>2.6 (2.1–3.3)§</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>27.6 (25.3–39.9)‡</td>
<td>27.0 (23.6–30.4)‡</td>
<td>26.7 (23.5–28.0)§</td>
</tr>
</tbody>
</table>

Values are mean (95% CI). hyperTG indicates FCH based on hypercholesterolemia; hyperTG, FCH based on hypertriglyceridemia.

**TABLE 5. Values of Insulin Resistance (HOMA index) and Obesity (BMI) in FCH Subjects Stratified by Different Lipid Phenotype Expression Compared With NL Relatives in 1994 and 1999**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>n</th>
<th>HyperTG-HyperTC</th>
<th>HyperTG or combined HLP</th>
<th>HyperTC or combined HLP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOMA index</strong></td>
<td></td>
<td>2.6 (1.7–4.1)†</td>
<td>2.6 (2.1–3.3)§</td>
<td>2.6 (2.1–3.3)§</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>27.6 (25.3–39.9)‡</td>
<td>27.0 (23.6–30.4)‡</td>
<td>26.7 (23.5–28.0)§</td>
</tr>
</tbody>
</table>
These studies were performed in a small number of subjects. In the present study, we included a large population of 563 subjects, including 132 FCH subjects, 81 controls, and 350 NL relatives. Therefore, the level of insulin resistance was determined by HOMA index. The accuracy and precision of the HOMA index as a measure of insulin resistance has been determined in literature by comparison with euglycemic and hyperglycemic clamps and the intravenous glucose tolerance test. In this large population, we confirm that FCH subjects are more insulin resistant compared with controls. Pathophysiologically, this could be related to the higher BMI in FCH subjects. However, we show that even after correction for BMI, FCH subjects are more insulin resistant compared with NL relatives and controls. So our results suggest that a genetic component influences the degree of insulin resistance in FCH besides the traditional environmental influences such as BMI. Indeed, recently, a major gene effect on insulin resistance in FCH has been suggested. 

FCH is characterized by multiple lipoprotein phenotype expression; in 1 affected family, subjects may present with hyperTC, hyperTG or combined HLP. We demonstrate that insulin resistance is associated with lipid phenotype expression because FCH subjects based on hyperTG or combined HLP, were more insulin resistant compared with FCH subjects based on hyperTC. This was also shown previously by Pihlajamaki et al and Vakkila et al. This could be related to the increased BMI frequently reported in hyperTG subjects; however, even after correction for BMI, subjects with hyperTG or combined HLP were more insulin resistant compared with FCH subjects based on hyperTC. Thus, the degree of insulin resistance appears to be related to lipid phenotype expression.

The main feature of FCH is the variability in lipid phenotype expression within an individual in time. We showed recently that 43% of the FCH patients had a change in lipid phenotype expression after 5 years. If the effect of these intraindividual changes in lipid phenotype expression in time is related to change in insulin resistance, it has not been addressed in literature. Twenty-four of the 55 FCH subjects (44%) in this study show an intraindividual change in lipid phenotype expression over the period of 5 years. Independent of lipid phenotype expression is an increase in BMI in time associated with an increase in insulin resistance ($R=0.47$; $P<0.001$). The subjects who were NL in 1994 and 1999 show a similar increase in HOMA index and BMI as the subjects who were affected based on hyperTG or combined HLP in 1994 and 1999; however, a switch in lipid phenotype from isolated hyperTC to hyperTG or combined HLP is associated with a much larger increase in BMI and HOMA index.

Most strikingly, our data show that FCH defined by the traditional criteria (TC and/or TG levels >90th percentile) potentially comprise a heterogeneous group; subjects defined as FCH by the presence of hyperTG or combined HLP are characterized by the presence of small dense LDL and insulin resistance, whereas the FCH subjects based on hyperTC do not show these major characteristics of FCH. It appears that subjects with hyperTC comprise a distinct group within FCH. However, the definition used for these patients (isolated TC and a family member with combined high TC/TG) could be incorrect because maybe the family member had the same high TC disorder but also high TG for 1 of many possible reasons. These results...
suggest that several metabolic pathways may contribute to the lipid phenotype expression in FCH.

The diagnostic criteria for FCH have been debated in literature. We and others have recently shown that apoB and small dense LDL are important potential new diagnostic characteristics. Insulin resistance and obesity are also associated with increased levels of apoB and the presence of small dense LDL. Therefore, we explored whether insulin resistance or obesity can explain the increased apoB levels or high occurrence of small dense LDL in FCH.

Purnell et al examined this question for only apoB in a population of 11 FCH subjects. In our large cohort of 132 FCH, subjects we confirmed that most FCH subjects had increased apoB levels for any level of insulin resistance (HOMA index) or BMI compared with controls. In addition, we show that FCH subjects also have more small dense LDL for any level of insulin resistance (HOMA index) or BMI compared with controls. So obesity or insulin resistance do not fully account for the elevated levels of apoB but also not for the high prevalence of small dense LDL in FCH. These results support the physiological concept of separate but additive genetic determinants in the etiology of the FCH lipid phenotype with modulation by BMI and insulin resistance. We reported previously that in our FCH families, a major gene influences apoB levels and small dense LDL; however, the gene has not been found yet. Recently, Pajukanta et al published interesting data about association between FCH and upstream transcription factor 1 (USF1). USF1 encodes a transcription factor known to regulate several genes of glucose and lipid metabolism.

References
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