Soluble receptors for tumor necrosis factor-α (TNF-R p55 and TNF-R p75) in familial combined hyperlipidemia

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Abstract

We investigated the potential role of the 75 kD receptor for tumor necrosis factor-α (TNF-α) (TNFRSF1B, located on chromosome 1 band p36.2) as a modifier gene in familial combined hyperlipidemia (FCH), based on previous linkage and association data. Age-corrected values for the soluble (s) extracellular domain of TNF-R p75 were lower in 156 well-characterized hyperlipidemic (HL) FCH relatives than in 168 normolipidemic (NL) relatives (P < 0.01). Plasma concentrations of the soluble domain of the 55 kD receptor (sTNF-R p55, the other TNF-α receptor) did not differ between HL and NL relatives. In conditional logistic regression analysis, plasma sTNF-R p75 concentration was the only non-lipid variable that contributed significantly to prediction of affected FCH status (regression coefficient = −0.413, P = 0.01). The present findings have potentially important diagnostic and therapeutic implications in FCH. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Insulin resistance; Tnf-sr55; Tnf-sr75; TNFRSF1B; Disorders; Genetic; Regression analysis

1. Introduction

Familial combined hyperlipidemia (FCH) is a common genetic dyslipidemia, with major and modifier genes. FCH is characterized by premature coronary heart disease (CHD) and different plasma lipid phenotypes among first degree relatives. The prevalence of FCH in the general population is 1–2% and FCH is estimated to cause 10–20% of premature CHD [1]. Metabolic disturbances in FCH include overproduction of very low density lipoproteins (VLDL), increased free fatty acid (FFA) fluxes, and insulin resistance (reviewed in [2]). The current concept is that FCH is a complex genetic disorder. In addition to already published genetic linkage found in FCH kindred [3,4], we observed suggestive linkage of FCH (presence of disease) with a polymorphic marker (D1S1597) on chromosome 1 (LOD = 1.0, [3]). This chromosomal region, 1p36.2, is different from the previously reported locus 1q21-23 [4]. In this region, TNFRSF1B (tumor necrosis factor superfamily member 1B) is an important positional candidate gene for FCH taking into account the role of TNF-α and the TNF-receptors in lipoprotein metabolism and insulin resistance. Moreover, no other plausible candidate genes are present in this region.

Since FCH is a genetic lipid disorder with insulin resistance [3,5,6] and visceral obesity [7], we have focused on the TNF-α/TNF-receptor pathway to test the biological relevance of TNFRSF1B as a potential modifier gene in FCH. Indeed, marker D1S1597 showed significant linkage in sib-pair analysis with plasma concentrations of the soluble product of TNFRSF1B (i.e. sTNF-R p75), but not sTNF-R p55. Moreover, further analysis revealed significant linkage of FCH with a polymorphic CA repeat in intron 4 of the TNFRSF1B gene as well [8].

The physiological roles of both receptors for TNF-α, i.e. TNF-R p55 and TNF-R p75, are not yet fully understood. The ligand-binding, extracellular portions
of these two receptors are quite similar. The intracellular domains, however, activate different pathways for intracellular signal transduction. It is therefore plausible that the two TNF-receptors have different physiological functions in vivo (reviewed in [9]). TNF-R p55 (55 kD, the soluble product of TNFRSF1A, also known as TNF-R type 1, and located on chromosome 12 band p13) is involved in processes such as inflammation and apoptosis [10]. The in vivo functions of the TNF-R p75 (75 kD, also known as TNF-R type 2, and located on chromosome 1 band p36.2) are less well-defined but include local inflammatory responses [11].

Upon expression on the cell surface, both TNF-receptors can be shed by action of a metalloproteinase resulting in the release of soluble portions of the ligand-binding domains into the circulation [12]. Shedding of TNF-receptors appears to be a relatively specific process that can be regulated independently for TNF-R p55 or TNF-R p75 [13]. Circulating soluble TNF-receptors may have various functions. They may be involved in inactivation of TNF-\( \alpha \), but may also play a role in stabilization of TNF-\( \alpha \). Increased shedding of TNF-R p75 and sTNF-R p55, probably as a response to neutralize increasing concentrations of TNF-\( \alpha \), has been associated with a large variety of inflammatory diseases.

Relations between TNF-\( \alpha \) and insulin resistance, or between TNF-\( \alpha \) and lipoprotein metabolism, are of particular interest in FCH. Obese subjects have elevated plasma levels of sTNF-R and in adipocytes of obese individuals, elevated production of TNF-\( \alpha \) has been documented [14]. Also, TNF-\( \alpha \) reduces cellular insulin sensitivity [15,16] and a polymorphism in the promoter of the TNF-\( \alpha \) gene (\(-308 \) G to A) which leads to increased gene transcription and thus to higher TNF-\( \alpha \) levels, has been associated with insulin resistance as well [17]. FCH has been associated with insulin resistance [5,6] and multiple events in lipoprotein production and metabolism are under control of insulin. An important characteristic of FCH is overproduction of hepatic apoB containing lipoproteins (VLDL). Insulin is involved in the intracellular assembly of VLDL [18] and also affects the supply of substrate for VLDL synthesis, via regulation of the FFA flux from adipose tissue to the liver [19]. In adipocytes, insulin resistance leads to increased activity of hormone sensitive lipase (HSL) and thus to the higher concentrations of FFA in the circulation [20]. Direct effects of TNF-\( \alpha \) on several metabolic processes involved in lipoprotein metabolism have been documented as well. It reduces the amount of lipoprotein lipase (LPL) on the endothelial wall [21] and induces de novo fatty acid synthesis in both adipocytes and hepatocytes [22,23]. TNF-\( \alpha \) also induces manganese super oxide dismutase (MnSOD) [24] and reduces lecitin cholesterol acyl transferase (LCAT) [25], genes located on the chromosomal loci that show linkage with FCH in our study population [26]. The general thought in the current literature is that increased activity of the TNF-\( \alpha \)/TNF-receptor axis leads to insulin resistance and, as a consequence, possibly to lipid abnormalities. It is the TNF-R p75, rather than TNF-R p55, which is frequently implicated in development of insulin resistance in obesity in man [27,28]. It is not clear whether these effects are caused by paracrine TNF-\( \alpha \) effects or may be related to genetic susceptibility, for instance in TNFRSF1B.

Based upon these data, and the linkage of FCH with markers in and nearby the TNFRSF1B gene, we investigated the potential role of TNF-R p75 as a modifier gene contributing to expression of FCH.

2. Methods

2.1. Study population

In 462 members of FCH families who had been studied in the framework of genetic studies on hyperlipidemia [7,29], we have determined plasma concentrations of the two soluble receptors for TNF-\( \alpha \), soluble (s)TNF-R p55 and sTNF-R p75. The subjects descended from 32 kindred and included hyperlipidemic (HL; \( n = 159 \)) and normolipidemic (NL; \( n = 168 \)) relatives as well as their spouses (\( n = 135 \)). The group of HL FCH relatives consisted of the index patients as well as their HL relatives. Characteristics of the present study groups are given in Table 1. Phenotypes measured included fasting plasma concentrations of apolipoprotein (apo) A-I, apo B, apo C-III, cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides (TG), HDL-TG, glucose, free (non-esterified) fatty acids (FFA), glycerol, insulin, as well as waist-to-hip ratio (WHR) and body mass index (BMI) [29].

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Main characteristics of the study population*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HL</td>
</tr>
<tr>
<td>( N ) (male/female)</td>
<td>84/72</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 ± 15</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 3.4</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>3.11 ± 0.35</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>1.33 ± 0.29</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>7.07 ± 1.88</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.13 ± 0.33</td>
</tr>
<tr>
<td>HDL-TG (mmol/l)</td>
<td>0.33 ± 0.09</td>
</tr>
</tbody>
</table>

* Data are expressed as mean ± S.D. To convert mmol/l to mg/dl multiply with 38.5 for cholesterol and with 88.8 for TG.
2.2. Plasma concentrations of sTNF-R p55, sTNF-R p75, and TNF-α

Plasma concentrations of sTNF-R p55 and sTNF-R p75 were determined using sandwich ELISA procedures exactly as published [30]. Soluble receptor concentrations may reflect plasma concentrations of TNF-α. We therefore measured plasma TNF-α concentrations in 80 individuals, i.e. the ten individuals with the highest and with the lowest values of sTNF-R p75, as well as in ten randomly selected individuals from the male and female HL relatives, NL relatives and spouse groups. These preliminary determinations of TNF-α concentrations in this study group, using an ELISA for TNF-α as described in [31], did not reveal any difference between sub-populations. Plasma TNF-α concentrations were in the normal range: the values varied between undetectable (n = 44, < 5 pg/ml) and 50 pg/ml. Two individuals had very high TNF-α concentrations (ng/ml range). There were no indications that very high or very low sTNF-Rp75 concentrations coincided with high and low TNF-α concentrations, respectively (data not shown).

2.3. Data analyses

All statistical analyses were performed using the SPSS package version 7.0 (SPSS, Chicago, IL, USA).

2.3.1. Linear regression

We performed backward linear regression for variance in sTNF-R p55 and sTNF-R p75. Plasma variables added in the equation as independent variables were, apoA-I; apoC-III; glucose; HDL-cholesterol; HDL-TG; log insulin; FFA; glycerol; and sTNF-R p55 or sTNF-R p75 (depending on which of both was the dependent variable). Non-plasma trait variables added were, age; BMI; gender; waist; and WHR. We controlled for disease (FCH) status (HL relative, NL relative, or spouse) by including dummy variables in the analyses. We have chosen not to include apoB, cholesterol and TG in the independent variable list since these data are used to define the variable ‘FCH status’. The best equation was selected by using backward elimination analysis (dummy variables were kept in the equation regardless of the significance of their β).

2.3.2. Conditional logistic regression

A standard logistic regression procedure for FCH could not be used in the analysis of our data, because family relations exist between the subjects in our study population. A conditional logistic regression (Cox’s regression survival analysis) was therefore used to analyze the data. These analyses are non-parametric with respect to time of survival but parametric in terms of the covariates. Cases were stratified for family descent (family number), survival was 1 for HL relatives (= FCH patients) and 2 for NL relatives and spouses. We have performed conditional logistic regression with HL relatives versus either NL relatives or spouses. Variables that had a significance level < 0.2 in univariate analyses were entered into a saturated model and sequentially eliminated until all remaining variables had a significance level P < 0.05.

3. Results

3.1. Study population

In Table 1 the main phenotypic characteristics of the study population are summarized. As expected, TG, apoB and cholesterol were higher, and HDL-cholesterol was lower in HL relatives than in NL relatives and spouses. BMI of HL relatives was slightly higher than that of NL relatives and spouses. The NL group was younger than the HL relatives and spouses.

3.2. STNF-receptors in FCH

Unadjusted plasma sTNF-R p55 concentrations and sTNF-R p75 concentrations, as well as their ratios are given in Table 2. The ratio of sTNF-R p75/sTNF-R p55 was higher in spouses than in HL relatives (P < 0.012, ANOVA). There was no effect of gender, but the data revealed a strong age-dependence of both sTNF-R p55 and sTNF-R p75 (best fitted with a cubic equation; Fig. 1). sTNF-R p75 and sTNF-R p55 were corrected for age in linear regression analysis. The age-corrected plasma sTNF-R p75 concentrations in HL relatives were significantly lower than in NL relatives (difference of 0.14 ng/ml, P < 0.01) and borderline significantly lower than in spouses (difference of 0.10 ng/ml, P = 0.056). Plasma sTNF-R p75 levels did not differ between spouses and NL relatives (difference of 0.04 ng/ml, P = 0.46). Age-corrected plasma sTNF-R p55 concentrations were similar in the three groups.
3.3. Contribution of lipid variables to variation in plasma concentrations of the sTNF-R

To identify parameters in our set of data that contribute to variation in plasma concentrations of sTNF-R p55 and sTNF-R p75, linear regression analysis was used. Concentrations of both types of soluble TNF-receptors were positively correlated in plasma (Pearson’s correlation coefficient \((R) = 0.50\) in HL relatives, \(P < 0.001\); \(R = 0.40\) in NL relatives, \(P < 0.001\); and \(R = 0.63\) in spouses, \(P < 0.001\)). This strong association was also reflected by the large contribution of these variables to each other in the regression models (Table 3A and B). However, several differences were of interest.

**Soluble TNF-R p55 (Table 3A):** Of all plasma and non-plasma variables tested, the single additional variable (besides the before-mentioned sTNF-R p75) that had a significant contribution to sTNF-R p55 was BMI. The affected FCH status (HL or NL) of the individuals did not contribute to variance of sTNF-R p55.

**Soluble TNF-R p75 (Table 3B):** Although sTNF-R p55 was indeed the most important contributor to sTNF-R p75, a substantial part (10%) of TNF-R p75 variance was also accounted for by FCH-related variables. Age was a significant positive contributor to variance in sTNF-R p75, as was HDL-TG. HDL-cholesterol and HL status on the other hand were significant negative contributors.

3.4. Plasma concentration of sTNF-R p75 as predictors of HL FCH status

With conditional logistic regression analysis we have identified factors that contribute to the hyperlipidaemia in our FCH families. We have corrected for the effect of family relations by stratifying the individuals by family identification codes. We have compared HL and NL relatives (Table 4A), as well as HL relatives and spouses (Table 4B). The negative estimated coefficient for sTNF-R p75 (Table 4B) reveals that the risk of being a HL subject increased significantly with decreasing sTNF-R p75 levels \((P = 0.01)\). The odds ratio of 0.66 for sTNF-R p75 means that a 1 ng/ml lower plasma concentration of sTNF-R p75 gives a 1.54 times higher risk of being HL FCH relative. Conversely, a higher sTNF-R p75 confers a lower risk on expressing FCH. Log TG, non-HDL-cholesterol and sTNF-R p75 plasma concentrations were the independent variables that predicted the FCH affected status versus spouses. Notably, log TG was the most powerful discriminating variable, followed by non-HDL-cholesterol, to identify affected FCH individuals relative to their unaffected relatives (odds ratio = 4.3, Table 4A), or spouses (odds ratio = 3.3, Table 4B).

4. Discussion

In the present study, we have focused on the potential role of TNFRSF1B in the development of hyperlipidaemia in FCH. Our data show that HL FCH relatives had lower plasma sTNF-R p75 concentrations than NL relatives and spouses. Moreover, the conditional logistic regression analysis confirmed that a low plasma sTNF-R p75 level increased the risk of expressing FCH. When the FCH diagnostic variables (non-HDL-
Our data probably reflect the fact that HDL-cholesterol was negatively associated with sTNF-R p75 (Table 3B). This result was unexpected, since low concentrations of HDL-cholesterol are a common characteristic of FCH and conditional logistic analysis) indicate that expression of disease in FCH is associated with lower plasma levels of sTNF-R p75. This association of FCH with low plasma sTNF-R p75 concentrations was initially a surprising finding. The rationale behind the present study, however, was suggestive linkage between FCH and gene for TNFRSF1B. The present approach therefore focused on responsiveness of FCH patients to TNF-α through its receptor (TNF-R p75), and not on production of this cytokine.

TNF-α receptors exist either as membrane-bound or as soluble forms. Membrane-bound TNF-receptors become inactive upon shedding their TNF-α binding domains as sTNF-R p55 or sTNF-R p75. Shedding of TNF-α receptors is an enzymatic process that is regulated by metalloproteases. A well-known inducer of receptor shedding is TNF-α in the circulation [32].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta (B)</th>
<th>95% CI</th>
<th>S.E. B</th>
<th>Std B</th>
<th>P</th>
<th>Partial $R^2$</th>
<th>$R^2$</th>
</tr>
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<tbody>
<tr>
<td>Intercept</td>
<td>0.281</td>
<td>0.157</td>
<td>n.s.</td>
<td></td>
<td>&lt; 0.001</td>
<td>0.299</td>
<td></td>
</tr>
<tr>
<td>STNF-R P75</td>
<td>0.328</td>
<td>0.261–0.395</td>
<td>0.034</td>
<td>0.460</td>
<td>&lt; 0.001</td>
<td>0.278</td>
<td></td>
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<tr>
<td>BMI</td>
<td>0.013</td>
<td>0.004–0.022</td>
<td>0.004</td>
<td>0.130</td>
<td>&lt; 0.003</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td>0.025</td>
<td></td>
<td>0.038</td>
<td>0.018</td>
<td>n.s.</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>0.032</td>
<td></td>
<td>0.036</td>
<td>0.042</td>
<td>n.s.</td>
<td>0.001</td>
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<tr>
<td>Age$^2$</td>
<td>$8.6 \times 10^{-5}$</td>
<td>0.000</td>
<td>0.393</td>
<td>n.s.</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>$-6.5 \times 10^{-5}$</td>
<td>0.005</td>
<td>$-0.309$</td>
<td>n.s.</td>
<td>0.000</td>
<td></td>
<td></td>
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<tr>
<td>Intercept</td>
<td>1.443</td>
<td>1.048–1.837</td>
<td>0.201</td>
<td></td>
<td>&lt; 0.001</td>
<td>0.412</td>
<td></td>
</tr>
<tr>
<td>STNF-R P55</td>
<td>0.563</td>
<td>0.450–0.676</td>
<td>0.057</td>
<td>0.400</td>
<td>&lt; 0.001</td>
<td>0.282</td>
<td></td>
</tr>
<tr>
<td>Age$^2$</td>
<td>$2.8 \times 10^{-4}$</td>
<td>1.4 $\times 10^{-4}$–4.1 $\times 10^{-4}$</td>
<td>0.000</td>
<td>0.905</td>
<td>&lt; 0.001</td>
<td>0.068</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>$-0.018$</td>
<td>$-0.030$ to $-0.005$</td>
<td>0.007</td>
<td>$-0.601$</td>
<td>&lt; 0.010</td>
<td>0.020</td>
<td></td>
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<tr>
<td>HDL-cholesterol</td>
<td>$-0.244$</td>
<td>$-0.358$ to $-0.129$</td>
<td>0.058</td>
<td>$-0.165$</td>
<td>&lt; 0.001</td>
<td>0.017</td>
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<tr>
<td>HDL-TG</td>
<td>0.511</td>
<td>0.053–0.969</td>
<td>0.233</td>
<td>0.088</td>
<td>&lt; 0.025</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>$-0.156$</td>
<td>$-0.248$ to $-0.064$</td>
<td>0.047</td>
<td>$-0.156$</td>
<td>= 0.001</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td>$2.7 \times 10^{-2}$</td>
<td>0.050</td>
<td>0.540</td>
<td>n.s.</td>
<td>0.000</td>
<td></td>
<td></td>
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</table>

* Results of a backward stepwise regression analysis with sTNF-R p55 (panel A) or sTNF-R p75 (panel B) as dependent variables. Variables included in the saturated model were, apoA-I, apoC-III, glucose, HDL-cholesterol, HDL-TG, log insulin, FFA, glycerol, and sTNF-R p55 or sTNF-R p75 (depending on which was the dependent variable), age, BMI, gender, waist, and WHR. Affected FCH status (HL relative, NL relative, or spouse) was included as dummy variable. Dummy variables and age were kept in the equation at all times. Those variables that accounted for a significant variation in the dependent variable (italic) and the dummy variables are shown. Confidence intervals (CI) of the significant coefficients ($P < 0.05$) are indicated. B, unstandardized regression coefficient ($\beta$); S.E. B, standard error of B; std B, standardized B; n.s., not significant; 95% CI, 95% confidence interval.
Soluble receptors may function as scavengers for free TNF-α in plasma or, alternatively, may be involved in maintaining a plasma pool of TNF-α for rapid TNF-α response following a trigger. Pellegrini et al. [33] have shown that decreased shedding of TNF-R p75 may be more related to the development of disease than elevated secretion of TNF-α. Shedding of the receptor correlated in their study with disease severity, implying that the response of cells to TNF-α was regulated by the number of remaining functional receptors on the cell surface; this number will be greater if shedding is reduced.

It is likely that efficiency of receptor shedding can be affected by intrinsic properties of the receptor. For instance, functional DNA polymorphisms leading to changes in the cleavage site of a TNF-α receptor could result in biologic variation in receptor shedding. Reduced shedding can affect (e.g. increase) the actual number of functional receptors that will remain on the cell surface, and thus affect the response of the cell to TNF-α. Physiological consequences of reduced shedding are relatively low plasma concentrations of sTNF-R p75, as seen in FCH relatives, with on the other hand relatively high levels of unshed, functionally intact TNF-R p75 remaining on the cell surface, providing a potentially greater responsiveness to TNF-α at physiological levels. Hypersensitivity to TNF-α could lead to reduced insulin sensitivity [15,27,28,34], increased lipolysis in adipocytes [20] and increased FFA levels [20]. Such a mechanism provides a good explanation for the present data.

Alternatively, low plasma concentrations of sTNF-R p75 in FCH can be explained by mutations in the intracellular part of the receptor that cause moderate increases in signaling activity of the receptor. Cells would then be hyperresponsive to circulating TNF-α, even at physiological levels. Hypersensitivity can be counteracted by the cells via down-regulation of TNFRSF1B expression. If such a regulatory mechanism would be inadequate than the result would include a lower than normal expression of TNF-R p75 on the cell surface and therefore lower levels of shed sTNF-R p75, but still a higher than normal responsiveness of the cells to circulating TNF-α, through the hyperactive TNF-R p75 on the cells.

One ‘genetic mechanism’ that can lead to reduced shedding of TNF-R p75 is a mutation in or nearby the site of the receptor where cleavage by the metalloprotease occurs. This possibility is currently under investigation in our laboratory. We have started these investigations with a mutation screening of exon 6 TNFRSF1B in a subgroup of our original study population (n = 131). Exon 6 contains (part of) the receptor protein domain that is cleaved by the metalloprotease, yielding soluble TNF-R p75 [35]. Two polymorphisms were identified in TNFRSF1B exon 6. One common polymorphism (T to G; Met196 to Asp) is present in 45% of all analyzed subjects. This polymorphism apparently underlies the conflicting data on the published TNFRSF1B sequence [36,37]. One novel, rare polymorphism was also identified (G to A; Glu232 to Lys, present in 5% of all subjects). Preliminary analyses did not reveal differences in frequency distribution of the mutated alleles between HL relatives, NL relatives, and spouses in this sub-population. These preliminary data on variations in exon 6 of TNFRSF1B do not directly support the possibility that receptor shedding is the predominant mechanism in FCH. However, to fully understand the contribution of TNFRSF1B to the expression of FCH, we need to complete the mutation screening of this gene and also perform association analyses. These approaches are currently undertaken in our laboratory.

In summary, we propose that TNFRSF1B is actively involved in expression of FCH as a modifier gene. The underlying mechanism that is involved has not yet been

Table 4
sTNF-R p75 as predictor of HL FCH status

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E. B</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) HL relatives versus NL relatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log TG</td>
<td>1.455</td>
<td>0.435</td>
<td>4.283</td>
<td>1.827–10.037</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL-cholesterol</td>
<td>0.297</td>
<td>0.072</td>
<td>1.346</td>
<td>1.170–1.549</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(B) HL relatives versus spouses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log TG</td>
<td>1.210</td>
<td>0.416</td>
<td>3.352</td>
<td>1.483–7.579</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Non-HDL-cholesterol</td>
<td>0.186</td>
<td>0.098</td>
<td>1.204</td>
<td>1.053–1.377</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>sTNF-R p75</td>
<td>-0.413</td>
<td>0.161</td>
<td>0.662</td>
<td>0.483–0.907</td>
<td>= 0.01</td>
</tr>
</tbody>
</table>

* Conditional logistic regression survival analysis with the diagnostic variables for FCH status included in the equation, i.e. logTG, apoB, and non-HDL-cholesterol, respectively. All variables with an individual B of P<0.2 were entered in the model (i.e. apo C-III, sTNF-R p75, BMI, the ratio cholesterol/HDL-cholesterol, glucose, HDL-cholesterol, HDL-TG, waist, apo B, log TG and non-HDL-cholesterol). Method is backward Wald. Variables were eliminated until all remaining variables were significant. Gender, age and age² did not contribute significantly to the saturated model. All variables were corrected for family code. B, Cox’s regression coefficient (β); S.E. B, standard error of B; non-HDL-cholesterol, (total cholesterol in plasma)—(HDL-cholesterol); 95% CI, 95% confidence interval; OR, odds ratio.
elucidated, but it leads to a FCH phenotype with low levels of sTNF-R p75 protein and, possibly, hyperresponsiveness to TNF-α. We hypothesize that functional mutations in TNFRSF1B contribute to the phenotype of low plasma sTNF-R p75 concentrations and concomitant alterations in the cell-surface concentration of this TNF-α receptor. This would result in increased sensitivity of the TNF-α/TNF-R p75 pathway and makes FCH patients hyperresponders to TNF-α in the circulation. Hyperresponsiveness to TNF-α can partly explain why FCH patients are extremely sensitive to moderate increases in their fat mass (which synthesizes TNF-α) and are prone to develop insulin resistance even when only mildly obese. Implication of the TNF-α/TNF-R p75 pathway in the expression of FCH may have potential diagnostic and therapeutic implications.

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References


