A Major Gene Effect on Fasting Insulin and Insulin Sensitivity in Familial Combined Hyperlipidemia

Jussi Pihlajamäki,1 Melissa Austin,2 Karen Edwards,2 and Markku Laakso1

From the 1Department of Medicine, University of Kuopio, Kuopio, Finland; and the 2Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Washington.

Address correspondence and reprint requests to Jussi Pihlajamäki, MD, Department of Medicine, University of Kuopio, 70210 Kuopio, Finland. E-mail: pihlajam@uku.fi.

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apoB, apolipoprotein B; FCHL, familial combined hyperlipidemia; WBGU, whole-body glucose uptake.

The most common inherited dyslipidemia, familial combined hyperlipidemia (FCHL), is associated with insulin resistance. Whether insulin sensitivity in these families is inherited is not known. Therefore, we investigated the inheritance of insulin sensitivity in 352 nondiabetic family members from 37 families with FCHL, 105 of whom had undergone testing using the hyperinsulinemic-euglycemic clamp technique for the measurement of insulin sensitivity. First, complex segregation analysis of fasting insulin levels (both unadjusted and age-, age2-, and BMI-adjusted) was used for modeling of the variance in fasting insulin levels. In these analyses, Mendelian codominant inheritance (P = 0.320 for unadjusted and P = 0.295 for adjusted insulin values) was not rejected over the most general model and fit the data significantly better than the sporadic model (P < 0.001). Polygenic and environmental models were rejected (P < 0.001). The Mendelian codominant model explained 44 and 45% of the variance in unadjusted and adjusted fasting insulin levels, respectively. The proposed genotypes of this locus, based on segregation analysis, were associated with directly measured insulin sensitivity in 105 FCHL family members who underwent the hyperinsulinemic-euglycemic clamp (P < 0.001). These results provide evidence for a major gene regulating insulin sensitivity in FCHL families. Possible pleiotropic effects of this insulin sensitivity locus on dyslipidemias in FCHL remain to be elucidated.

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However, several loci identified in genome-wide random searches have been proposed to modify lipid levels (16–18).

Insulin resistance, defined as insulin’s impaired ability to exert its normal function (19), can be quantified directly with the hyperinsulinemic-euglycemic clamp (20). In Pima Indians, insulin sensitivity measured by this technique has been reported to be distributed as a mixture of three normal distributions. This suggests that a major codominant gene may determine insulin sensitivity (21). Because the clamp study is difficult to perform in large families with several generations, fasting insulin level has been used as a surrogate of insulin action (22). Using segregation analysis in families randomly ascertained (23) or through siblings with type 2 diabetes (24), major genes have been proposed to determine fasting and postglucose insulin levels. These segregation analyses suggested a presence of a common allelic variation explaining ~30% of the variance in insulin levels.

The inheritance of insulin levels or insulin resistance has not been studied previously in FCHL families. Therefore, we investigated the inheritance of fasting insulin levels in 37 FCHL kindreds with 352 nondiabetic family members using complex segregation analysis. Furthermore, we investigated whether the proposed fasting insulin locus determines insulin sensitivity in 105 FCHL family members who underwent the hyperinsulinemic-euglycemic clamp.

RESEARCH DESIGN AND METHODS

All participants in this study were Finnish. The Finnish population is genetically relatively homogeneous, originating mainly from southern (European) and eastern (Asian) immigration 2,000 years ago (25,26).

FCHL family members. Twenty-five of the probands with FCHL were selected from the myocardial infarction survivor family study carried out at our department (27). Selection of the probands and criteria for FCHL have been described previously in detail (7). Briefly, cutoff points for lipids were 7.7 mmol/l for total cholesterol and 2.4 mmol/l for triglycerides in women and 2.2 mmol/l for total triglycerides in women and 2.4 mmol/l in men. These cutoff points were based on the lipid values of the control population, which consisted of 250 people (161 males and 89 females) of the same myocardial infarction survivor family study from which FCHL families were identified. The cutoff points for abnormal lipids were defined as 80th percentile for total cholesterol and 90th percentile for total triglycerides. The 80th percentile for total cholesterol was used because of high cholesterol level among participants living in eastern Finland. After adjustment for age with linear regression analysis, the values for the median age (55 years) of this population were used as cutoff points for abnormal lipids. To meet the criteria for FCHL, each family had to have at least three affected members with different types of dyslipidemias and at least one affected family member in two different generations. Combined hyperlipidemia had to be present in the family but not necessarily in the proband. In addition, 12 FCHL probands and their families were identified from the Coronary Angiography Register of the Kuopio University Hospital according to the previously mentioned lipid criteria. None of the study participants had tendon xanthomas or defects in the LDL receptor gene, which explain ~90%
of all cases of familial hypercholesterolemia in this area (28). Nineteen participants with type 2 diabetes according to the World Health Organization criteria (29) and three participants with very high fasting insulin values over 300 pmol/l were excluded from the study to avoid extreme skewness of the insulin distribution. Altogether, 37 families with FCHL and their 352 family members (37 probands, 82 siblings of the probands, 46 children of the probands, 128 second-degree relatives, and 58 spouses) met the criteria and were included in this study (Table 1). All included FCHL family members had a normal glucose tolerance; normal liver, kidney, and thyroid function tests; no history of excessive alcohol intake; and no severe chronic disease.

Subset of FCHL family members for metabolic studies. All family members with dyslipidemia and a random sample of relatives without dyslipidemia were invited for the hyperinsulinemic-euglycemic clamp, after exclusion of participants who were ≥50 years of age and those with severe chronic disease (8,9). This resulted in a sample of 105 family members, including 50 relatives without dyslipidemia (29 men, 21 women), 19 with hypercholesterolemia (14 men, 5 women), 22 with hypertriglyceridemia (16 men, 6 women), and 14 with combined hyperlipidemia (8 men, 6 women).

Informed consent was obtained from all participants after the purpose and potential risks of the study were explained to them. The protocol was approved by the Ethics Committee of the University of Kuopio and was in accordance with the Helsinki Declaration.

Determination of insulin sensitivity. The degree of insulin sensitivity was evaluated with the hyperinsulinemic-euglycemic clamp technique (20). After baseline blood drawing, a priming dose of insulin (Actrapid 100 IU/ml; Novo Nordisk, Gentofte, Denmark) was administered during the initial 10 min to raise plasma insulin concentration quickly to the desired level, where it was maintained by a continuous insulin infusion of 480 pmol/m² per min. Under these study conditions, hepatic glucose production is completely suppressed in nondiabetic participants (30) and in FCHL patients (4). Blood glucose was clamped at 5.0 mmol/l for the next 180 min by the infusion of 20% glucose at varying rates according to blood glucose measurements performed at 5-min intervals. The mean rates of glucose infusion during the last hour of the clamp were used to calculate the rates of insulin-stimulated whole-body glucose uptake (WBGU).

Analytical methods. Plasma glucose levels in the fasting state and after an oral glucose load as well as blood glucose levels during the euglycemic clamp were measured by the glucose oxidase method (2300 Stat Plus; Yellow Springs Instrument, Yellow Springs, OH). For the determination of plasma insulin, blood was collected in EDTA-containing tubes, and after centrifugation the plasma was stored at −20°C until the analysis. Plasma insulin concentration was determined by a commercial double-antibody solid-phase radioimmunoassay (Phadeseph Insulin RIA 100; Pharmacia Diagnostics AB, Uppsala, Sweden). Cholesterol and triglyceride levels from whole serum and lipoprotein fractions were assayed by automated enzymatic methods (Boehringer-Mannheim, Mannheim, Germany). ApoB levels were determined by a commercial immunoturbidimetric method (Kone Instruments, Espoo, Finland).

Statistical analysis. All basic calculations were done with the SPSS/Win programs (version 7.5; SPSS, Chicago). Because of the skewed distribution of insulin levels, they were logarithmically transformed to achieve a distribution not significantly different from normal (for log-transformed fasting insulin, \( P = 0.196 \), Kolmogorov-Smirnov test) before statistical analysis. Bivariate Pearson correlations were calculated between log-transformed fasting and 2-h postglucose insulin values and the rates of WBGU. Fasting insulin had a stronger negative correlation (\( r = −0.617 \)) with the rates of WBGU than 2-h postglucose insulin (\( r = −0.485 \)) and therefore was used in segregation analysis.

Segregation analysis of fasting insulin levels. To investigate the genetic and environmental influences on fasting insulin levels in the FCHL families, we evaluated a series of class D regressive models using the REGC program (S.A.G.E., version 2.2, Cleveland, OH) (31). These models assume that the variation among individuals for a quantitative trait is the result of a major gene effect and a residual variation caused by both additional familial correlations and individual variance. Additional familial correlations may reflect both polygenic effects and unmeasured common environmental effects. Based on a maximum likelihood method in the most general model, all parameters are estimated. Eleven parameters are considered. First, the frequency of a single factor assuming two alleles A and B (i.e., an allelic variation in a major gene) following Hardy-Weinberg equilibrium was estimated. The mean insulin value associated with each of the possible three genotypes \( \mu AA \), \( \mu AB \), and \( \mu BB \) was estimated assuming equal variance \( \sigma^2 \) among all genotypes. In the most general model, Mendelian inheritance was not assumed and the probabilities of transmission \( +AA \), \( +AB \), and \( +BB \) also were estimated. Finally, the correlation of the remaining variance between spouse, parent-offspring, and sib-sib pairs was calculated.

Thereafter, seven restricted models were compared with the general model. First, a model assuming a Mendelian inheritance in which transmission probabilities were fixed to 1, 0.5, and 0 was considered (eight parameters estimated). Second, a polygenic model in which familial correlation was allowed but \( \mu AA = \mu AB = \mu BB \) were fixed and therefore no genotype-effect was allowed (five parameters estimated). Third, an environmental model in which transmission was fixed similar in all genotypes indicating a nongenetic effect (nine parameters estimated). Fourth, the model was a sporadic model in which no type-effect, transmission, and additional correlation were allowed (two parameters estimated). Fifth, in the pure codominant model, the Mendelian model was restricted further by fixing additional familial correlations to 0 (five parameters estimated). Finally, two submodels of codominant model in which either recessive (\( \mu AA = \mu AB \) or dominant (\( \mu AB = \mu BB \) were considered (four parameters estimated). In the second segregation analysis, the effect of age, \( \text{age}^2 \), BMI, and sex also was included in the model. Restricted models were compared with the most general model by using the likelihood ratio test in which the difference in −2ln(Likelihood) of the submodels follows \( \chi^2 \) distribution with degree of freedom equal to difference in the number of estimated parameters in each model. No correction for ascertainment was used. Family trees are available on request to interested readers (contact J.P.).

The effect of the fasting insulin locus on insulin resistance was investigated by comparing insulin sensitivity in participants with assigned genotypes AA, AB, and BB for the proposed fasting insulin locus identified by segregation analysis. Genotype was assigned when the likelihood of a genotype was higher than 0.2 in a given family member. When no genotype had a likelihood higher than 0.2, that family member was excluded from this portion of the analysis. Then, mean values of insulin-stimulated rates of WBGU were compared in 105 available family members according to this assigned genotype using analysis of variance with contrasts to estimate the effect of individual genotypes.
TABLE 2
Segregation analysis of logarithmically transformed insulin values (backtransformed values shown) in Finnish FCHL families

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>(\mu_{\text{AA}})</th>
<th>(\mu_{\text{AB}})</th>
<th>(\mu_{\text{BB}})</th>
<th>(\tau_{\text{AA}})</th>
<th>(\tau_{\text{BB}})</th>
<th>(\sigma^2)</th>
<th>(r_{sp})</th>
<th>(r_{po})</th>
<th>(r_{so})</th>
<th>(-2\ln(L))</th>
<th>(\chi^2) (df)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>0.73</td>
<td>45.6</td>
<td>82.5</td>
<td>184.3</td>
<td>0.95</td>
<td>0.65</td>
<td>0.42</td>
<td>0.098</td>
<td>0.35</td>
<td>-0.11</td>
<td>0.07</td>
<td>454.2</td>
<td>...</td>
</tr>
<tr>
<td>Mendelian</td>
<td>0.75</td>
<td>46.6</td>
<td>76.9</td>
<td>166.7</td>
<td>(1)</td>
<td>(0.5)</td>
<td>(0)</td>
<td>0.120</td>
<td>0.31</td>
<td>-0.14</td>
<td>0.06</td>
<td>457.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Polygenic</td>
<td>(1)</td>
<td>61.7</td>
<td>=(\mu_{\text{AA}})</td>
<td>=(\mu_{\text{AA}})</td>
<td>(1)</td>
<td>(0.5)</td>
<td>(0)</td>
<td>0.238</td>
<td>0.15</td>
<td>0.10</td>
<td>0.14</td>
<td>482.7</td>
<td>28.7</td>
</tr>
<tr>
<td>Environmental</td>
<td>0.71</td>
<td>61.1</td>
<td>51.5</td>
<td>188.0</td>
<td>=(\mu_{\text{AA}}) =(\mu_{\text{AA}})</td>
<td>(1)</td>
<td>(0.5)</td>
<td>0.245</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>502.6</td>
<td>48.4</td>
</tr>
<tr>
<td>Sporadic</td>
<td>(1)</td>
<td>61.1</td>
<td>=(\mu_{\text{AA}}) =(\mu_{\text{AA}})</td>
<td>(1)</td>
<td>(0.5)</td>
<td>(0)</td>
<td>0.135</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>463.3</td>
<td>9.1</td>
<td>(6)</td>
</tr>
<tr>
<td>Codominant</td>
<td>0.74</td>
<td>47.5</td>
<td>71.0</td>
<td>155.4</td>
<td>(1)</td>
<td>(0.5)</td>
<td>(0)</td>
<td>0.158</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>469.3</td>
<td>15.1</td>
</tr>
<tr>
<td>Dominant</td>
<td>0.38</td>
<td>122.1</td>
<td>54.1</td>
<td>=(\mu_{\text{AB}})</td>
<td>(1)</td>
<td>(0.5)</td>
<td>(0)</td>
<td>0.158</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>469.3</td>
<td>15.1</td>
</tr>
<tr>
<td>Recessive</td>
<td>0.62</td>
<td>54.1</td>
<td>=(\mu_{\text{AA}}) 122.1</td>
<td>(1)</td>
<td>(0.5)</td>
<td>(0)</td>
<td>0.158</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>469.3</td>
<td>15.1</td>
<td>(7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fasting insulin (pmol/l)</th>
<th>adjusted for age, age^2, and BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>0.87</td>
</tr>
<tr>
<td>Mendelian</td>
<td>0.78</td>
</tr>
<tr>
<td>Polygenic</td>
<td>(1)</td>
</tr>
<tr>
<td>Environmental</td>
<td>0.93</td>
</tr>
<tr>
<td>Sporadic</td>
<td>(1)</td>
</tr>
<tr>
<td>Codominant</td>
<td>0.78</td>
</tr>
<tr>
<td>Dominant</td>
<td>0.17</td>
</tr>
<tr>
<td>Recessive</td>
<td>0.83</td>
</tr>
</tbody>
</table>

P, frequency of the A allele; \(\mu_{\text{AA}}, \mu_{\text{AB}}, \mu_{\text{BB}}\), means for each ouisiotype; \(\tau_{\text{AA}}, \tau_{\text{BB}}\), transmission probabilities for each ouisiotype; \(\sigma^2\), residual variance; \(r_{sp}\), correlation between spouses; \(r_{po}\), correlation between parents and offspring; \(r_{so}\), correlation between siblings; \(-2\ln(L)\), -2 times natural logarithm of the likelihood of each model; \(\chi^2\), difference in \(-2\ln(L)\) compared with the general model (in parentheses is the difference in estimated parameters, which is equal to degree of freedom). Values fixed before analysis in each model are in parentheses.

RESULTS
Characteristics of the FCHL probands and family members. Characteristics of 37 FCHL probands and all 352 FCHL family members, including the probands and subset of FCHL family members who underwent metabolic studies, are shown in Table 1.

Segregation analysis of fasting insulin levels. In univariate segregation analysis based on unadjusted fasting insulin levels (after logarithmic transformation), the Mendelian codominant inheritance model (model 2) could not be rejected over the most general model (model 1, \(P = 0.320\)), whereas pure polygenic, environmental, and sporadic models were rejected (models 3, 4, and 5, all \(P < 0.001\); Table 2). The Mendelian codominant inheritance model with additional familial correlation did not differ from models with dominant or recessive inheritance (\(P = 0.087\), models not shown). The Mendelian codominant model with familial correlation restricted to 0 also was accepted (model 6, \(P = 0.105\)). However, restriction of Mendelian model to either dominant or recessive inheritance (models 7 and 8) led to the rejection of these models (\(P = 0.035\)). Thus, Mendelian codominant model provided the best fit to the family data and suggested a major gene effect on fasting insulin levels with a B allele frequency of 0.26 (associated with higher insulin levels) and genotypic means of insulin 47.5 for the genotype AA, 71.0 for AB, and 155.4 pmol/l for BB. The difference in the variance of insulin levels explained by the Mendelian and sporadic model was 0.245 - 0.135 = 0.110, suggesting that 44% (0.110/0.245) of the variance in fasting insulin was explained by this locus. These values corresponded well with the observed distribution of fasting insulin levels in these families (Fig. 1).

Inclusion of covariates (age, age^2, and BMI) into the segregation models improved the fit of all models with the data (\(P < 0.001\)) but did not change the main results of analysis (Table 2). In all models, the regression coefficients were similar: 0.0004 for age^2, -0.037 for age, and 0.061 for BMI. Sex-dependent models did not fit the data better than respective sex-independent models (data not shown). Similar to the analysis of unadjusted insulin values, Mendelian codominant model could not be rejected (model 2, \(P = 0.295\)) and the pure codominant model without additional familial correlations (model 6, \(P = 0.412\)) was the best-fitting model. Also in this analysis, polygenic, environmental, sporadic models (models 3–5) and dominant (model 7) and recessive (model 8) submodels of the codominant

![Fig. 1. Distribution of unadjusted fasting insulin levels in 352 FCHL family members. Vertical lines indicate mean values for genotypes AA, AB, and BB based on segregation analysis.](image)
model were rejected (all \( P < 0.001 \)). The segregation analysis of adjusted insulin levels suggested a major gene effect on fasting insulin levels with the B allele frequency of 0.22 and adjusted (to mean age and BMI shown in Table 1) genotypic means of insulin 52.0 for the genotype AA, 76.2 for AB, and 132.3 pmol/l for BB. In this case, the difference in residual variance between Mendelian and the sporadic models was 0.141 − 0.077 = 0.064, suggesting that 45% (0.064/0.141) of the variance in fasting insulin was explained by this locus, compared with 44% shown above based on the segregation analysis of unadjusted insulin values.

**The effect of proposed insulin locus on insulin resistance.** To investigate the effect of the proposed insulin locus on insulin resistance, we calculated the likelihoods of the genotypes AA, AB, and BB for each individual who underwent the hyperinsulinemic clamp for the estimation of insulin sensitivity. When genotypes based on the segregation analysis of fasting insulin levels were used, 90 of the 105 family members had genotype probabilities of 0.6 or higher. Of these, 48 had genotype AA, 36 had genotype AB, and six had genotype BB. The rates of WBGU differed among participants with these assigned genotypes \((P < 0.001\), analysis of variance over the three genotypes; Fig. 2). Both participants with the AB genotype \((P = 0.015)\) and participants with the BB genotype \((P = 0.032)\) had lower rates of WBGU than participants with the AA genotype. Similarly, when 85 participants were assigned genotype on the basis of the segregation analysis, including covariates, participants with the genotype AA had higher rates of WBGU than participants with the genotype AB \((n = 66\) and \(n = 19; P = 0.010; \text{Fig. 2})\).

**DISCUSSION**

In FCHL, earlier studies indicated the presence of major genes for triglycerides \((2,10)\), apoB \((11–13)\), and small, dense LDL \((14,15)\), suggesting an oligenic background for this disease. This study demonstrates that fasting insulin levels also are determined by a major gene locus in these families. Because this proposed locus also was associated with directly measured insulin sensitivity in these families, we infer that insulin sensitivity, which is an essential characteristic of FCHL \((4–8)\), also is at least partly genetically determined in these families.

Impaired insulin action, i.e., insulin resistance, has been acknowledged as a central part of the metabolic syndrome, which is an important risk factor for cardiovascular diseases \((19,32)\). Because patients with FCHL have several components of the metabolic syndrome, e.g., hypertriglyceridemia \((2,3)\), postprandial lipemia \((33)\), high prevalence of small, dense LDL particles \((14,34,35)\), low HDL cholesterol levels \((36,37)\), and central obesity \((38)\), it is not surprising that these patients also have hyperinsulinemia \((33,37)\) as a result of insulin resistance \((4–6)\). Our earlier studies suggested that insulin resistance also is present in young relatives of FCHL patients who are at risk to develop FCHL. Therefore, we hypothesized that a gene defect in insulin action may be important in FCHL \((7)\).

The segregation analysis of fasting insulin levels in this study suggests that a major gene may explain up to 40% of the variance in fasting insulin levels in nondiabetic members of FCHL families. This may be an upper estimate because families were ascertained via dyslipidemic (hyperinsulinemic) family members. However, the finding is not surprising because similar results have been obtained in nondiabetic members of families with or without type 2 diabetes \((23,24)\). In all of these studies, diabetic patients have been excluded because in diabetic patients, a major genetic effect on insulin levels is likely to be overruled by the insulin-elevating effect of various glucose levels. We used fasting insulin level as a surrogate for directly measured insulin sensitivity because direct measurement of insulin sensitivity is not feasible in families with several generations. We are confident that our results suggest that also insulin sensitivity is inherited in FCHL families for two reasons. First, fasting insulin has a correlation of \(-0.60\) to \(-0.70\) with directly measured insulin sensitivity \((22)\), which was also the case in this study. Second, the proposed genotypes of the assumed fasting insulin locus were associated with directly measured insulin sensitivity.
Only a few genes that determine insulin sensitivity in humans are known. Uncommon mutations in the insulin gene and in the insulin receptor gene can cause insulin resistance (39) and mutations in the peroxisome proliferator–activated receptor-γ gene are known to impair insulin sensitivity (40–42). However, our previous results show that the peroxisome proliferator–activated receptor-γ variants are not the cause of insulin resistance in Finnish FCHL families (43). We also have excluded many other genes as major determinants of insulin sensitivity in FCHL, e.g., the genes encoding fatty acid binding protein 2 (44), β3-adrenergic receptor and uncoupling protein 1 (45), angiotensinogen-converting enzyme, and apolipoprotein E (unpublished findings). The hepatic lipase gene recently was proposed to play a role in FCHL (46,47), and we have suggested that the promoter variants in that gene also may regulate insulin sensitivity in FCHL families (48). However, the estimates of the impact of these genes may be biased because the currently unknown major genes in FCHL families may have a confounding effect on the results. Therefore, the search for major genes in FCHL is essential.

Because of the known association between high serum triglycerides and insulin resistance both in the general population (49) and in FCHL families (6,8), the novel loci that have been linked to FCHL (17,18), especially with serum triglycerides in FCHL families (50,51), also are promising with respect to insulin resistance. In fact, genes may have a pleiotropic effect on several lipoprotein traits and insulin sensitivity, and therefore the search for novel FCHL genes may be more effective if combined phenotypes are used (52).

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