Two Major Loci Control Variation in $\beta$-Lipoprotein Cholesterol and Response to Dietary Fat and Cholesterol in Baboons


Abstract—We explored the genetic control of cholesterolemic responses to dietary cholesterol and fat in 575 pedigreed baboons. We measured cholesterol in $\beta$-lipoproteins (low density lipoprotein cholesterol [LDLC]) in blood drawn from baboons while they were consuming a baseline (low in cholesterol and fat) diet, a high–saturated fat (lard) diet, and a high-cholesterol, high–saturated fat diet. In addition to baseline levels (LDLC$_{\text{base}}$), we analyzed two variables for diet response: LDLC$_{\text{RF}}$, which represents the LDLC response to increasing dietary fat (ie, high-fat diet minus baseline), and LDLC$_{\text{RC}}$, which represents the LDLC response to increasing dietary cholesterol level (ie, high-cholesterol, high-fat diet minus high-fat diet). Heritabilities ($h^2$) of the 3 traits were 0.59 for LDLC$_{\text{base}}$, 0.14 for LDLC$_{\text{RF}}$, and 0.59 for LDLC$_{\text{RC}}$. In addition, LDLC$_{\text{base}}$ and LDLC$_{\text{RC}}$ had a significant genetic correlation (ie, $\rho_G=0.54$), suggesting that 1 or more genes exert pleiotropic effects on the 2 traits. Segregation analyses detected a single major locus that accounted for nearly all genetic variation in LDLC$_{\text{RC}}$ and some genetic variation in LDLC$_{\text{base}}$ and LDLC$_{\text{RF}}$ and confirmed the presence of a different major locus that influences LDLC$_{\text{base}}$ alone. Preliminary linkage analyses indicated that neither locus was linked to the LDL receptor gene, a likely candidate locus for LDLC. Detection of these major loci with large effects on the LDLC response to dietary cholesterol in a nonhuman primate offers hope of detecting and ultimately identifying similar loci that determine LDLC variation in human populations. (Arterioscler Thromb Vasc Biol. 1998;18:1061-1068.)

Key Words: LDL • diet • genetics • baboons

The role of plasma LDLC in predicting risk of coronary heart disease is well established,1 and dietary fat and cholesterol are recognized as the major environmental determinants of LDLC concentration.2 However, cholesterolemic responses to dietary lipids vary among individuals, in both humans and experimental animals, and much recent effort has been devoted to explaining this variability by physiological and, ultimately, genetic mechanisms.3

We began to search for genes controlling responsiveness to dietary lipids in baboons having high and low plasma cholesterol and lipoprotein levels after a 7-week challenge diet enriched in saturated fat and cholesterol. Both the basal and challenge levels of LDL and HDL were highly heritable.4 Subsequent studies focused on detecting and identifying the responsible genes by molecular5– 8 and statistical9–11 genetic strategies. A previous study suggested that the response to dietary cholesterol and to dietary saturated fat might be controlled by separate genes in baboons.12 In the present study, we subjected baboons to a dietary challenge protocol that enabled us to analyze the separate responses to dietary cholesterol and saturated fat.

Methods

Animals

Baboons (Papio hamadryas sensu lato13,14) were maintained at the Southwest Foundation for Biomedical Research, a facility certified by the American Association for the Accreditation of Laboratory Animal Care, under conditions approved by the institutional animal care and use committee.

We studied the effects of dietary fat and cholesterol in 575 pedigreed baboons, primarily olive (P h anubis) and yellow (P h cynocephalus), and their hybrids. Of these baboons, 47 (8%) had been reared in the nursery on artificial human infant formula,10,15 which has been shown to have a significant effect on cholesterol and apoAI concentrations.10,15 Average age (in years) of the baboons at the outset of the experiment was 9.0 (SD, 6.8; range, 2.2 to 28.5).

The pedigreed baboons represented the genetic diversity of 187 founders not known to be related. There were 209 males and 366 females in 28 sire families, with a total of 191 dams and their offspring. These families provided a large number of pairwise relationships for genetic analyses, including 1129 first-degree, 6090 second-degree, 2114 third-degree, and 633 fourth-degree relative pairs.
**Selected Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>LDL_{base}</td>
<td>baseline LDL</td>
</tr>
<tr>
<td>LDL_{rats}</td>
<td>LDL response to dietary cholesterol</td>
</tr>
<tr>
<td>LDL_{RF}</td>
<td>LDL response to dietary fat</td>
</tr>
<tr>
<td>LDLR</td>
<td>LDL receptor gene</td>
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</table>

**Diet Protocol**

All baboons were subjected to the same 4-step diet challenge protocol as follows: (1) Animals were fed a baseline monkey diet (Wayne Teklad), low in fat (~4% of calories) and cholesterol (0.03 mg/kcal), for at least 2 months before the baseline blood sample was drawn. (2) They were then fed a diet high in saturated fat (40% of calories from lard) and cholesterol (1.7 mg/kcal) for 7 weeks before the high-cholesterol, high-fat–diet blood sample was drawn. (3) They were then fed the baseline diet again for 7 weeks to provide a “washout” period between challenge diets. (4) After the washout, the animals were fed a high fat–only diet (40% of calories from lard, 0.03 mg cholesterol per kcal) for 7 weeks before the high fat–diet blood sample was taken. We previously reported results of a pilot study with 60 animals, which indicated that LDL levels had returned to the initial baseline levels by the end of the baseline diet washout period.

For each of the diet treatments, blood samples were drawn from the femoral vein after baboons were fasted overnight and immobilized with ketamine (10 mg/kg). The blood was allowed to clot and body weight (in kilograms) was recorded.

**Measurements of LDL C**

Cholesterol concentrations were measured enzymatically with a reagent supplied by Boehringer Mannheim Diagnostics and a Ciba-Corning Express Plus clinical chemistry analyzer. Cholesterol in HDL was determined in the supernatant after precipitation of lipoproteins (LDL) were estimated as the difference between total serum and HDL cholesterol levels. Cholesterol in baboon apoB-containing lipoproteins resides primarily in LDL particles; other relatively minor contributors of cholesterol to this LDL value include VLDL, IDL, and Lp(a).

We used univariate quantitative genetic analysis to calculate genetic correlations (\(r_{\text{G}}\)) among the LDL phenotypes and to estimate the magnitude of pleiotropic effects of underling genes. Large genetic correlations between traits imply that the same genes influence both traits. Hypotheses regarding the extent of pleiotropic effects (ie, \(r_{\text{E}}=0\) for no pleiotropy or \(r_{\text{E}}=1.0\) for complete pleiotropy) were evaluated using likelihood ratio tests. The total phenotypic correlation \(r_{\text{PT}}\) was estimated as \(r_{\text{PT}}=\sqrt{h_1^2 \cdot h_2^2 \cdot \rho_G + (1-h_1^2) \cdot (1-h_2^2) \cdot \rho_E}\), where \(h_1^2\) and \(h_2^2\) are heritabilities for traits 1 and 2, respectively, and \(\rho_E\) is the environmental correlation.

**Segregation Analyses**

We used multivariate quantitative genetic analysis to calculate genetic correlations \(r_{\text{G}}\) among the LDL/C phenotypes and to estimate the magnitude of pleiotropic effects of underlying genes. We tested against the most general model several classes of submodels, including a single-distribution (polygenic) model, a multiple-distribution (environmental) model, and a mendelian model (transmission probabilities, \(T\), fixed at their mendelian expectations: \(T_p=1\), \(T_a=0.5\), and \(T_e=0\)). Each submodel was compared with the unrestricted general model by using likelihood ratio test statistics obtained as twice the difference between the natural-log likelihoods of the 2 models. These test statistics approximate a \(\chi^2\) distribution with degrees of freedom equal to the difference in the numbers of parameters between the 2 models. The best model is one that has the fewest estimated parameters and is not significantly worse than the most general model.

We have developed automated methods that search the likelihood surface for various models of inheritance. This approach enables us...
to find with high probability all maxima on the likelihood surface and to select the global maximum. In addition, simulation studies 28,29 have shown that local maxima could contain information regarding additional loci affecting a trait.

**Major Locus Pleiotropy**

We employed bivariate segregation analysis 10 to determine whether the major gene for 1 trait had any effect on phenotypic variation for a second trait. In brief, this model considers the effect of a single trait locus on 2 traits simultaneously. The hypothesis is that the major gene influences a second trait was tested by comparing the likelihood of a model in which genotypic means were estimated for both phenotypes (unrestricted model) to a model in which genotypic means were estimated for the first trait and a single mean was estimated for the second trait (restricted model). Major gene pleiotropy is indicated if the likelihood of the former model is significantly higher than that of the latter.

To further evaluate the pleiotropic actions of both genes simultaneously and to estimate the proportions of phenotypic variance explained by each locus on each trait, we also performed a 2-locus, bivariate segregation analysis. 10 In this model, the effects of 2 loci were estimated on each of 2 traits simultaneously. Under this more general framework, we tested several models, including the following: (1) 1 locus affects both traits, (2) 2 loci are present and 1 locus explains the covariance (ie, \( \rho_k^2 = 0.29 \)) in the 2 traits.

**Univariate Quantitative Genetic Analyses**

Table 1 gives the parameter estimates for each of the traits resulting from univariate quantitative genetic analyses. We tested for the effects of sex, age, and the square of age in males and females; weight; nursery rearing; and subspecies admixture; only those covariates giving a P value < 0.10 were retained in the final model for each trait. Two potential covariates found in other studies, breast fed versus formula fed 10,12 and subspecies admixture, 13 did not satisfy the requirement and were not retained in subsequent models for any of the traits.

**Bivariate Quantitative Genetic Analyses**

There was a positive phenotypic correlation between LDLC base and LDLC RF (Table 2). This phenotypic correlation was caused by a strong genetic correlation (\( \rho_k = 0.54 \)), which explained 29% of the covariance (ie, \( \rho_k^2 = 0.29 \)) in the 2 traits. The phenotypic correlations of LDLC RF with LDLC base and with LDLC RC were small or negative due to strong negative environmental correlations.

**Segregation Analysis of LDLC Response to Dietary Cholesterol**

Segregation analysis (Table 3) indicated that a major gene, herein labeled the R locus, affected LDLC response to dietary cholesterol (ie, LDLC RC ). The single-distribution polygenic model was strongly rejected when compared with the multiple-distribution unrestricted general model (\( P < 0.00001 \)). Likewise, a multiple-distribution model that allowed for polygenic effects (the environmental model) was also rejected (\( P < 0.000001 \)). The multiple-distribution model in which the underlying distributions reflected genotypes (the mendelian model) described the data as well as the unrestricted model (\( P = 0.58 \)). Estimates of the transmission parameters in the unrestricted model (1, 0.43, and 0.12) are similar to those expected under mendelian transmission (1, 1/2, and 0, respectively). Furthermore, the residual heritability for the mendelian model was low (\( h^2 = 0.15 \pm 0.09 \)), suggesting that genetic variation at the R locus accounted for most of the genetic control of LDLC RC . Figure 2 presents a frequency histogram for LDLC RC together with the 3 underlying distri-

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**Table 1. Trait Means (\( \mu \)), SDs, Heritabilities (\( h^2 \)), and Covariate Effects (\( \beta \)) in Univariate Quantitative Genetic Analyses of 575 Baboons**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LDLC base</th>
<th>LDLC RF</th>
<th>In LDLC RC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu ), mmol/L</td>
<td>0.91 ± 0.07</td>
<td>0.35 ± 0.03</td>
<td>1.77 ± 0.01</td>
</tr>
<tr>
<td>SD</td>
<td>0.41 ± 0.01</td>
<td>0.43 ± 0.01</td>
<td>0.16 ± 0.01</td>
</tr>
<tr>
<td>( h^2 )</td>
<td>0.59 ± 0.07</td>
<td>0.14 ± 0.06</td>
<td>0.59 ± 0.08</td>
</tr>
<tr>
<td>( \beta_{sex} )</td>
<td>0.24 ± 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta_{age-females} )</td>
<td>−0.03 ± 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta_{age-males} )</td>
<td>0.003 ± 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta_{sex-age-males} )</td>
<td>0.002 ± 0.0003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta_{weight, kg} )</td>
<td>−0.005 ± 0.003</td>
<td>−0.004 ± 0.001</td>
<td></td>
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</table>

*Only those covariates giving a P < 0.10 were estimated.

**Table 2. Total Phenotypic (\( \rho_p \)), Genetic (\( \rho_g \)), and Environmental (\( \rho_e \)) Correlations for Pairs of Traits Subjected to Bivariate Quantitative Genetic Analyses**

<table>
<thead>
<tr>
<th>Trait Pairs</th>
<th>n</th>
<th>( \rho_p )</th>
<th>( \rho_g )</th>
<th>( \rho_e )</th>
<th>( P )</th>
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</thead>
<tbody>
<tr>
<td>LDLC base</td>
<td>572</td>
<td>−0.21</td>
<td>0.49 ± 0.24</td>
<td>(0.025)</td>
<td>−0.54 ± 0.07</td>
<td>(&lt;0.00001)</td>
</tr>
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<td>LDLC RF</td>
<td>571</td>
<td>0.26</td>
<td>0.54 ± 0.11</td>
<td>(0.0001)</td>
<td>−0.11 ± 0.11</td>
<td>(0.30)</td>
</tr>
<tr>
<td>In LDLC RC</td>
<td>570</td>
<td>0.05</td>
<td>0.69 ± 0.39</td>
<td>(0.033)</td>
<td>−0.34 ± 0.08</td>
<td>(0.001)</td>
</tr>
</tbody>
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<td>(0.001)</td>
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</table>
butions for each of the major gene genotypes as estimated from segregation analysis.

Analysis of Pleiotropic Effects

Previously, we detected a major gene for LDLC Base, herein termed the B locus, by using a different set of baboons.11 We wished to determine whether the R gene for LDLC RC concentrations was the same as the B gene previously detected for LDLC Base. First, we performed segregation analysis to confirm the presence of a major gene affecting LDLC Base in this group of animals and to estimate the major gene parameters. The environmental and polygenic models were rejected (data not shown), but not the mendelian model, and the parameter estimates were similar to those previously reported.11

Next, we conducted a 1-locus, bivariate segregation analysis to test the hypothesis that the B locus for LDLC Base exerts pleiotropic effects on LDLC RC. Because the R locus for LDLC RC explains virtually all of the genetic variation in the trait, results of this analysis would indicate whether only one major gene exerts pleiotropic effects on both LDLC Base and LDLC RC. Table 4 presents the results of this analysis. The B locus for LDLC Base does not explain a significant proportion of variation in LDLC RC (P = 0.37). We also tested for significant pleiotropic effects of the LDLC RC major locus (R) on LDLC Base. The R locus for LDLC RC accounted for a small but significant proportion of variation in LDLC Base (P = 0.0003) (Table 4). In addition, allowing for major locus pleiotropy on the 2 traits reduces the residual heritability for LDLC Base (from 0.59 to 0.45) as well as the residual genetic correlation (from 0.42 ± 0.29 to 0.09 ± 0.30).

On the basis of these results, we tested by 2-locus, bivariate segregation analyses whether only 1 locus was affecting both traits, 2 loci were affecting both traits, or there was some intermediate effect (Table 5). In comparison with the general model (No. 1) in which both loci affect both traits, the 1-locus models (No. 5 and 6), in which 1 of the loci (either B or R) affects both traits, were strongly rejected. Likewise, the 2-locus model (No. 4), in which the B locus affects only LDLC Base and the R locus affects only LDLC RC, was rejected. However, the model (No. 2) in which the B locus affects LDLC Base only but the R locus affects both LDLC Base and LDLC RC was not significantly different from the most general model. This model was the one suggested by the results of the 1-locus, bivariate analyses. Furthermore, by comparing the best 2-locus, bivariate model, in which recombination was estimated to a model in which recombination was fixed at ½, we found no evidence for linkage between the B and R loci (P = 0.21, results not shown). Using the best 2-locus, bivariate model, we estimated the mean genotypic effects on LDLC Base for the 9 possible genotype combinations of the two loci. On average, bbrr individuals had a 2.3-fold higher LDLC than did BBRR individuals (Table 6).

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**Figure 2.** Frequency histogram for LDLC RC with distributions representing the 3 LDLC RC major locus genotypes RR, Rr, and rr. LDLC RC concentrations were logarithmically transformed (after adding 5 mmol/L) before segregation analysis.
Although the heritability of LDLC RF was low ($h^2 = 0.14$), we also tested whether the $B$ or $R$ locus had pleiotropic effects on LDLC RF. We found no strong consistent effects of the $B$ locus on LDLC RF (data not shown), but we did find a significant ($P < 0.004$) pleiotropic effect of the $R$ locus on LDLC RF (Table 4). The $R$ locus accounted for much of the additive genetic variance in LDLC RF, as evidenced by the decrease in the estimated residual heritability from $0.12 \pm 0.05$ to $0.03 \pm 0.05$ (Table 2, no major gene was included) to $-0.34 \pm 0.67$ (when the $R$ locus was included). This result implies that much of the genetic correlation between the 2 traits was attributable to the $R$ major gene.

### Components of Variance for 3 LDLC Traits

For each trait we estimated the proportion of total phenotypic variance attributable to various factors (Table 7). For the trait LDLC<sub>Base</sub>, the major gene for LDLC<sub>Base</sub> ($B$ locus) accounted for $'27\%$ of total phenotypic variance. Because this gene behaves as a dominant-recessive locus, some of its effects are not detected as additive (ie, not included in the heritability estimate). Approximately $3\%$ of total phenotypic variance is accounted for by the major locus for LDLC<sub>RC</sub> (the $R$ locus), which exerts a pleiotropic effect on LDLC<sub>Base</sub>. Residual polygenic effects account for $'38\%$ of total phenotypic variance, covariates explained $'22\%$ (residual error) was not explained by the model for LDLC<sub>Base</sub>.

### Table 4. Single-Locus, Bivariate Segregation Analyses to Test for Pleiotropic Effects of the Major Loci for LDLC<sub>Base</sub> and LDLC<sub>RC</sub>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trait = LDLC&lt;sub&gt;Base&lt;/sub&gt;</th>
<th>Trait = LDLC&lt;sub&gt;RC&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_n$</td>
<td>0.74</td>
<td>0.73</td>
</tr>
<tr>
<td>$f_r$</td>
<td>0.73</td>
<td>0.73</td>
</tr>
<tr>
<td>$h^2$</td>
<td>0.67</td>
<td>0.67</td>
</tr>
</tbody>
</table>

### Table 5. Results of 2-Locus, Bivariate Segregation Analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>$f_n^*$</th>
<th>$f_r^*$</th>
<th>LDLC&lt;sub&gt;Base&lt;/sub&gt;</th>
<th>LDLC&lt;sub&gt;RC&lt;/sub&gt;</th>
<th>$df$</th>
<th>$\chi^2$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Two-locus (general)</td>
<td>0.72</td>
<td>0.84</td>
<td>Yes</td>
<td>Yes</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2. Two-locus</td>
<td>0.72</td>
<td>0.87</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
<td>2.6</td>
<td>0.28</td>
</tr>
<tr>
<td>3. Two-locus</td>
<td>0.74</td>
<td>0.85</td>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
<td>10.9</td>
<td>0.004</td>
</tr>
<tr>
<td>4. Two-locus</td>
<td>0.74</td>
<td>0.88</td>
<td>Yes</td>
<td>No</td>
<td>4</td>
<td>12.7</td>
<td>0.013</td>
</tr>
<tr>
<td>5. One-locus</td>
<td>0.74</td>
<td>(1)</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>48.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6. One-locus</td>
<td>(1)</td>
<td>0.86</td>
<td>No</td>
<td>No</td>
<td>4</td>
<td>95.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*$F$requencies of the $B$ and $R$ alleles were estimated or fixed (in parentheses) in each model.
TABLE 6. Genotype Means for LDLC base (in mmol/L)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>LDLC base Genotype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BB</td>
<td>Bb</td>
</tr>
<tr>
<td>RR</td>
<td>0.86</td>
<td>0.88</td>
</tr>
<tr>
<td>Rr</td>
<td>1.03</td>
<td>1.05</td>
</tr>
<tr>
<td>rr</td>
<td>1.10</td>
<td>1.12</td>
</tr>
<tr>
<td>Marginals</td>
<td>0.98</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Approximately 47% of total phenotypic variation in LDL-C was explained by effects of the R locus. After inclusion of the major locus effects, only a small portion (4% of total phenotypic variation) of residual variation was due to the additive effects of genes; covariates explained 7% of the total phenotypic variance, and ≈42% was unexplained in the model for LDL-C.

Only ≈9% of the phenotypic variation in LDL-C could be explained by genes: the R locus accounted for 6% and residual polygenes accounted for the remaining 3%. Ninety-one percent of total phenotypic variation in LDL-C was not accounted for in the model.

Discussion

Summary of the Results

The LDL-C response to dietary cholesterol was strongly heritable (h^2=0.59), whereas response to dietary fat was only weakly heritable (h^2=0.14). A major gene (R locus) explained about half the phenotypic variation in LDL-C. In addition, the R locus exerted pleiotropic effects on 2 other related traits: R explained ≈3% of the variation in LDL-C and ≈6% of the phenotypic variation (and almost all of the additive genetic variation) in LDL-C. The previously described major gene (B locus) for LDL-C, however, explained variation in LDL-C only and in neither of the response variables. Thus, we have evidence for 2 separate major loci that regulate LDL-C levels.

Nature of the Major Locus for Cholesterol Responsiveness

The magnitude of the effect of the R locus on responsiveness is similar to that of the 7α-hydroxylase mutation in the cholesterol-resistant rabbit and the unidentified genetic variant responsible for the JAX rabbit. The effect is much greater than the differences among inbred and recombinant strains of mice and among swine with apoB variants. Physiological mechanisms associated with dietary responsiveness have been studied extensively in squirrel monkeys, African green monkeys, rhesus monkeys, and baboons, but no single gene affecting responsiveness to dietary cholesterol has been identified in any nonhuman primate. Given the close phyllogenetic relatedness of baboon and human species and their similarity in the physiological processes of lipoprotein metabolism, this major locus for response to dietary cholesterol may also exist in humans. Discovery of such a gene in humans would be valuable in identifying diet-susceptible people or, potentially, suggesting new strategies for developing drugs targeted to control plasma LDL-C.

We do not yet know the identity of the major locus that controls response to dietary cholesterol in baboons. An obvious candidate is the LDLR, which is regulated by intracellular cholesterol levels. In a previous study, we found a polymorphic site in intron 17 of baboon LDLR that was associated with serum LDL and apoB levels on both the basal and high-cholesterol, high–saturated fat diets.

We tested for linkage of this LDLR polymorphism with the R locus in these baboon families. However, we found no evidence of linkage (log of the odds score was −0.9; D.L.R. et al, unpublished observations, 1997) and conclude that the major gene for response to dietary cholesterol is not LDLR.

Other earlier studies that focused on high and low LDL-C–responding baboons showed that high responders had increased cholesterol absorption, apoB production, and conversion of VLDL to LDL. High responders also had lower plasma levels of 27-hydroxycholesterol and lower hepatic levels of sterol 27-hydroxylase protein and activity. These latter observations suggest that a locus affecting bile acid metabolism may be a candidate for the LDL-C major gene.

Relationship of LDL-C Response to Fat and to Cholesterol

The major locus affecting response to dietary cholesterol also affects responsiveness to dietary saturated fat under the conditions of this study and accounts for most of the genetic correlation between the traits, as well as most of the heritability for each of the 2 traits. Thus, the data suggest that the product of the R locus, which affects both diet response and baseline levels of LDL-C, is central to LDL metabolism.

A much greater interindividually variability has been observed in the response of baboons to dietary cholesterol compared with the response to saturated fat, and the same observation was made in this study. Dietary cholesterol has dominated most animal model studies of diet-induced hyperlipidemia, whereas its role in human hyperlipidemia is considered small relative to that of saturated fatty acids. A possible explanation for the differences in responsiveness to dietary cholesterol among animal species (including humans) is greater interspecies variation in the frequencies of alleles for genes affecting cholesterol response compared with those affecting fat response. That is, animals of all species show a
consistent response to dietary fat, whereas the proportion of animals responding to dietary cholesterol varies considerably across species. This explanation suggests that, although lower in frequency, polymorphisms associated predominantly with responsiveness to dietary cholesterol may also exist in human populations.

**Genetic Control of LDL**

The previously described 1 major locus for LDL was confirmed in this study of a different group of baboons. This B locus influences more than a quarter of the variation in LDL, but exerts no detectable effects on the response to dietary components. The identity of this locus is also unknown, although our preliminary results suggest that, like the R locus discussed above, this locus is not linked to the candidate locus LDLR (log of the odds score was ≈0.7). D.L.R. et al, unpublished observations, 1997). There remains substantial genetic variation in LDL (e.g., ~38% of LDL-C) that is not accounted for by either the R or the B locus. Included in this set of genes is the effect of variation at the LDLR locus, which explains ~6% of total phenotypic variation in this trait.6 Thus, in this study, we have detected the actions of at least 2 different loci that exert substantial effects on LDL variation and that may also play important roles in LDL variation in humans.

**Acknowledgments**

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