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A PLEIOTROPIC QTL ON 2p INFLUENCES SERUM LP-PLA₂ ACTIVITY AND LDL CHOLESTEROL CONCENTRATION IN A BABOON MODEL FOR THE GENETICS OF ATHEROSCLEROSIS RISK FACTORS

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Abstract

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂), the major portion of which is bound to low-density lipoprotein, is an independent biomarker of cardiovascular disease risk. To search for common genetic determinants of variation in both Lp-PLA₂ activity and LDL cholesterol (LDL-C) concentration, we assayed these substances in serum from 679 pedigreed baboons. Using a maximum likelihood-based variance components approach, we detected significant evidence for a QTL affecting Lp-PLA₂ activity (LOD=2.79, genome-wide P=0.039) and suggestive evidence for a QTL affecting LDL-C levels (LOD=2.16) at the same location on the baboon ortholog of human chromosome 2p. Because we also found a significant genetic correlation between the two traits ($\rho_G=0.50$, $p<0.00001$), we conducted bivariate linkage analyses of Lp-PLA₂ activity and LDL-C concentration. These bivariate analyses improved the evidence (LOD=3.19, genome-wide P=0.015) for a QTL at the same location on 2p, corresponding to the human cytogenetic region 2p24.3–p23.2. The QTL-specific correlation between the traits ($\rho_Q=0.62$) was significantly different from both zero and 1 ($P[\rho_Q=0]=0.047$; $P[\rho_Q=1]=0.022$), rejecting the hypothesis of co-incident linkage and consistent with incomplete pleiotropy at this locus. We conclude that polymorphisms at the QTL described in this study exert some genetic effects that are shared between Lp-PLA₂ activity and LDL-C concentration.

Keywords

Lp-PLA₂; LDL cholesterol; genome scan; bivariate; pleiotropy; baboon

1. Introduction

Lp-PLA₂, or lipoprotein-associated phospholipase A₂, is increasingly implicated as a reliable biomarker of cardiovascular disease that is independent of other biomarkers of inflammation [1]. The major portion of circulating Lp-PLA₂ is bound to low-density lipoprotein (LDL)

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particles [2], and the amino acid residues that determine this binding have been identified and described [3]. Consistent with evidence showing that Lp-PLA₂ is responsible for over 95% of LDL-associated phospholipase activity [4], positive correlations between Lp-PLA₂ activity and LDL-C concentration have been described both in normolipidemic [5] and in hypercholesterolemic individuals [5,6].

While variation in both Lp-PLA₂ activity and LDL-C concentration is known to be influenced by genes, the latter has been the subject of more extensive genetic analysis. In studies of humans and animals, genes have been shown to account for a moderate proportion of the variance – 36% to 59% – in LDL-C levels [7,8]. Published genome scans have mapped quantitative trait loci (QTLs) affecting LDL-C concentration in humans to multiple chromosomal regions that harbor candidate genes affecting the regulation of LDL metabolism, processing and transport [7,9,10]. A number of these findings in humans correspond well with those reported in studies of mice [11] and non-human primates [12].

In contrast, comparatively little is known about the genetics of quantitative variation in Lp-PLA₂ activity. Only two studies report heritability estimates for this trait in humans: one, a study of 240 individuals from 60 nuclear families from Dallas, Texas [5], and the other, a study of 1,341 Mexican Americans from 42 extended pedigrees from San Antonio, Texas [13]. Both studies found that approximately 60% of the variance in Lp-PLA₂ activity is due to the additive effects of genes. The latter study [13] also reported significant evidence for a QTL on chromosome 1q when accounting for interaction with adiposity.

In the present study, we hypothesized that some of the well-documented biological correlation between Lp-PLA₂ activity and LDL-C concentration is due to pleiotropy, or the shared effects of the same gene or genes. To test this hypothesis, we conducted analyses to detect, characterize, and localize to specific chromosomal regions the effects of genes contributing pleiotropically to variation in both phenotypes in pedigreed baboons, a model species with documented utility for studies of the genetics of lipoproteins and other risk factors for cardiovascular disease [8,14,15].

2. Methods

2.1. Subject Description

We obtained data for this study from a sample of 679 pedigreed baboons (*Papio hamadryas*) comprising 440 females and 239 males maintained at the Southwest National Primate Research Center (SNPRC), located at the Southwest Foundation for Biomedical Research in San Antonio, Texas. The age of baboons in this sample ranged from 2–29 years, corresponding approximately to a human developmental age range of 6–85 years. All animals are housed outdoors in social groups and are maintained on a low-cholesterol, low-fat commercial monkey diet (7% fat from plant oils, 0.02 mg/g cholesterol) to which they have *ad libitum* access. Animal care personnel and staff veterinarians provided routine and emergency health care to all animals in accordance with the Guide for the Care and Use of Laboratory Animals. The SFBR facility is certified by the Association for Assessment and Accreditation of Laboratory Animal Care International, and all procedures were approved by the Institutional Animal Care and Use Committee.

For the purposes of this study, these baboons were organized into 11 distinct pedigrees, yielding a diverse array of relative pair classes: 671 parent-offspring; 598 sibling; 73 grandparent-grandchild; 96 avuncular; 6,732 half-sibling; 1,794 half-avuncular; 6 first cousin; 47 half-first cousin; 5 half-first cousin, once removed; 27 half-sibling and first cousin; 633 half-sibling and half first cousin; 7 half-sibling and half avuncular, and 37 double half-avuncular. These 11

baboon pedigrees may be viewed at the SNPRC website:
<http://www.snprc.org/baboon/map/BPPpedigrees/bppeds.htm>.

2.2. Phenotyping

Lp-PLA₂ activity and LDL-C concentration were assayed in serum samples, obtained as part of a large, ongoing study of the effects of diet and genotype on variation in atherosclerosis risk factors. Blood samples were drawn in the morning from a femoral vein of animals on basal diet following an overnight fast (prior to blood collection, sedatives were administered to ensure relaxation). Serum samples were separated from whole blood by low-speed centrifugation and stored in individual, single-use aliquots at -80°C , protected from oxidation and desiccation [16].

Serum Lp-PLA₂ enzyme activity was measured at 30°C using a kit provided by Cayman Chemical Company (Ann Arbor, MI). Hydrolysis of the substrate, 2-thio platelet-activating factor, produced a free thiol which was quantified using 5,5'-dithio-bis-(2-nitrobenzoic acid). The reaction was monitored at 405 nm using a BioTek ELx808 microplate reader running in kinetic data acquisition mode. Rates were calculated from at least 15 minutes of readings in the linear phase and converted to nmol/min/mL plasma using an extinction coefficient value of 13.6/mM-cm. Each sample was run in duplicate, and the average coefficient of variation was 1.7% (n=2,542). The across-plate coefficient of variation, based on a control sample run on each plate, was 4.3% (n=59).

Cholesterol concentrations were measured enzymatically [17] with a reagent supplied by Boehringer Mannheim Diagnostics and using a Ciba-Corning Express Plus clinical chemistry analyzer. Cholesterol carried by HDL was estimated following precipitation of apoB-containing lipoproteins with heparin-Mn²⁺ as described [18] and LDL cholesterol was calculated as the difference between total and HDL cholesterol. Ninety percent (90%) of non-HDL cholesterol on basal diet is associated with particles in the LDL size range [15]; for convenience, we refer to it as LDL-C. Average between-assay coefficients of variation for these determinations were 2.2% and 4.6% for total and HDL cholesterol, respectively.

2.3. Baboon Genotyping and Whole Genome Linkage Map

Statistical genetic analyses of these two traits took advantage of a baboon whole genome linkage map based on genotype data at nearly 300 microsatellite marker loci (mean inter-marker interval=8.9 cM) from 984 pedigreed baboons in these same 11 extended pedigrees. The physical locations in the human genome for nearly all marker loci in the baboon map are known, thus facilitating the identification of likely orthologous chromosomal regions in the two species. Construction of the current baboon linkage map is described in detail elsewhere [19], and additional information can be found at the SNPRC website:
<http://www.snprc.org/baboon/genome/index.html>.

2.4. Statistical Genetic Methods

Accounting for random and measured environmental contributions to the phenotypic variance can improve power to detect genetic effects. Prior to all analyses, we used likelihood ratio tests to screen each of the following variables for significant mean effects on Lp-PLA₂ and LDL-C levels: age, sex, age², age*sex, and age²*sex. After regressing out the mean effects of all nominally significant ($P \leq 0.10$) covariates, we applied an inverse Gaussian transformation to the residuals to correct for departures from multivariate normality that might inflate evidence for linkage. All polygenic and linkage analyses were conducted using these normalized residual data.

2.4.1 Univariate Analyses—All statistical genetic analyses were conducted using a maximum likelihood-based variance decomposition approach implemented in the computer package SOLAR (Sequential Oligogenic Linkage Analysis Routines [20]). We used this approach to partition the phenotypic variance in a trait (σ_P^2) into components corresponding to additive genetic effects (σ_G^2), estimated as a function of relatedness among pedigreed baboons, and environmental effects (σ_E^2). We define residual heritability (h^2) as the proportion of residual phenotypic variance unexplained by covariates that can be attributed to additive genetic effects

$$h^2 = \frac{\sigma_G^2}{\sigma_P^2}.$$

To identify regions of the baboon genome harboring QTLs affecting either Lp-PLA₂ activity or LDL-C concentration, we used an extension to this variance decomposition method to conduct univariate multipoint linkage analyses for each phenotype. In these analyses, we modeled the phenotypic covariance among relatives as the sum of the additive genetic covariance attributable to a specified marker locus, the additive genetic covariance due to the effects of other loci, and the variance due to unmeasured environmental factors.

We estimated probabilities of identity-by-descent (IBD) among relatives at marker loci in the baboon linkage map using Markov Chain Monte Carlo routines implemented in the computer package Loki [21]. We tested linkage hypotheses at 1 cM intervals along each chromosome using likelihood ratio tests, and converted the resulting likelihood ratio statistic to the LOD score of classic linkage analysis [22].

To control for the genome-wide false positive rate, we calculated genome-wide P-values for each LOD score using a method suggested by Feingold et al. [23] that takes into account pedigree complexity and the finite marker density of the linkage map. Accordingly, our threshold for significant evidence of linkage was LOD=2.69, and for suggestive evidence of linkage was LOD=1.46.

Because variation in LDL-C concentration is known to be influenced by multiple genes and we expect variation in Lp-PLA₂ activity to be determined in a similar manner, we performed sequential multipoint whole genome linkage screens to facilitate detection of multiple QTLs for each trait [20]. That is, after a first genome screen detected a putative QTL, we repeated the linkage screen using a model that accounted for the effect(s) of the previously detected, significant QTL(s). This was done sequentially until a genome screen failed to detect a QTL for which there was at least suggestive evidence at the genome-wide level.

2.4.2 Multivariate Analyses—To determine the extent to which phenotypic variation in serum Lp-PLA₂ activity and LDL-C concentration may be affected by shared genes and shared non-genetic factors, we conducted bivariate analyses in which both traits are considered simultaneously. In comparison to the univariate polygenic model, the bivariate polygenic model additionally estimates the additive genetic and environmental correlations between both traits. The genetic correlation (ρ_G) is an estimate of pleiotropy between the two traits, and ρ_G^2 thus estimates the portion of the additive genetic variance in each trait due to shared genetic effects. The random environmental correlation (ρ_E) is an estimate of the shared effects of non-additive genetic factors and unmeasured environmental variables. Using these estimates, we calculated the phenotypic correlation between the trait pair as

$\rho_P = \rho_G \sqrt{h_1^2} \sqrt{h_2^2} + \rho_E \sqrt{1 - h_1^2} \sqrt{1 - h_2^2}$ [24]. We assessed the significance of ρ_G and ρ_E by means of likelihood ratio tests comparing the likelihoods of models in which the correlation

was estimated to those in which it was constrained to zero (rejection of $\rho_G=0$ indicates pleiotropy) or to 1 (failure to reject $|\rho_G|=1$ indicates complete pleiotropy).

To search for pleiotropic QTLs affecting phenotypic variation in both Lp-PLA₂ activity and LDL-C concentration, we conducted bivariate multipoint linkage analyses, limiting these analyses to chromosomes exhibiting at least suggestive evidence for QTLs in the univariate screens. To facilitate comparison with univariate linkage results, we adjusted bivariate LOD scores to be equivalent to univariate LOD scores in terms of degrees of freedom [25].

An additional parameter estimated in the bivariate linkage model is ρ_Q , the additive genetic correlation between the traits due to the effects of the QTL. In a bivariate linkage analysis, QTLs may be found that appear to influence phenotypic variation in both traits. To distinguish the event where two traits may each be independently influenced by closely linked genes (“co-incident linkage”) from QTL pleiotropy, we conducted a likelihood ratio test of the hypothesis $\rho_Q=0$. In accordance with Almasy et al. [26], failure to reject this hypothesis supports the co-incident linkage of two QTLs over pleiotropic effects at the same locus.

3. Results

3.1. A Priori Analysis of APOB concentration

Given that “LDL-C” refers to all the apoB-containing lipoproteins in the LDL size interval in baboons, we conducted initial analyses to confirm that our focus on LDL-C concentration did not ignore genetic information contained in measures of apoB. Like LDL-C concentration, a significant proportion of the variance in apoB concentration in these baboons was due to the additive effects of genes ($h^2=0.48$). Further, the additive genetic correlation between these two traits was not significantly different from 1 ($\rho_G=0.97$, $P[\rho_G=1]=0.20$), indicating that all, or nearly all, the additive genetic variance in LDL-C and apoB concentrations measured in this study is due to the effects of the same gene or genes.

3.2. Univariate Analyses: Genetic effects on Lp-PLA₂ activity and LDL-C levels

Maximum likelihood estimates of heritability, mean covariate effects, and the proportion of total phenotypic variation due to significant covariates for both Lp-PLA₂ activity and LDL-C concentration are provided in Table 1. The proportion of phenotypic variance due to significant age and sex terms was moderate for both traits, accounting for approximately 29% of the phenotypic variance in Lp-PLA₂ activity and 18% for LDL-C concentration. The additive effects of genes accounted for statistically significant and similar proportions of the residual phenotypic variance in the two traits: $h^2=0.67$ for Lp-PLA₂ activity and $h^2=0.63$ for LDL-C concentration. When considered on a scale describing total phenotypic variance, the additive effects of genes were responsible for approximately half the variation in each trait (i.e., 48% for Lp-PLA₂ and 52% for LDL-C).

Univariate multipoint linkage analysis for Lp-PLA₂ (Table 2) revealed significant evidence in the first genome scan for a QTL located at position 26 cM from the pter-most marker locus on baboon chromosome 13 (PHA13, LOD=2.79, genome-wide $P=0.0394$). A second genome scan, conditioned on the significant QTL found on PHA13, found suggestive evidence for a second QTL on PHA20 (LOD=2.03, results not shown). Estimates of heritability specific to the QTLs found on PHA13 and PHA20 are 0.13 and 0.11, respectively. When we consider these QTL-specific heritabilities as a proportion of the total residual heritability in Lp-PLA₂ activity, each QTL accounts for approximately 19% and 16% of the total additive genetic effect on variation in Lp-PLA₂ activity, respectively (h^2_Q/h^2).

Univariate linkage analysis for LDL-C concentration (Table 2) also revealed suggestive evidence for a QTL at the same region on PHA13 (26 cM, LOD=2.16) as that for Lp-PLA₂. Estimated heritability specific to this QTL was 0.16, and accounts for approximately 25% of the total additive genetic effect on LDL-C concentration.

3.3. Multivariate Analyses: Pleiotropy between Lp-PLA₂ activity and LDL-C levels

Because the detected QTLs for both traits mapped to PHA13, we conducted bivariate analyses to further characterize the gene(s) responsible. The results of the bivariate polygenic analysis for Lp-PLA₂ activity and LDL-C concentration are summarized in Table 3. The estimated additive genetic correlation between Lp-PLA₂ and LDL-C concentration was 0.50 ($P[\rho_G=0] < 0.00001$), indicating that both traits are influenced by shared additive genetic effects and that an estimated 25% of the additive genetic variance in each of the two traits is due to the effects of the same gene or genes. The hypothesis of complete pleiotropy between these two traits, $\rho_G=1$, was rejected ($P < 0.000001$). The genetic effects common to both traits account for approximately 17% and 16% of the residual phenotypic variance in Lp-PLA₂ activity and LDL-C concentration, respectively. The magnitude of these shared genetic effects accounted for much of the residual phenotypic variance shared between Lp-PLA₂ activity and LDL-C concentration (i.e., $\rho_p^2 = 0.22$).

Results from bivariate multipoint linkage analysis of Lp-PLA₂ activity and LDL-C concentration for PHA13 are summarized in Table 4, and Figure 1 presents the multipoint LOD plots on PHA13 for each trait from the univariate analyses, and for both traits from the bivariate analysis. While the maximum LOD score in all analyses was obtained at 26 cM from the ptermost marker on this chromosome, the evidence for a QTL influencing variation in the Lp-PLA₂/LDL-C bivariate phenotype was improved over that obtained in the analyses of individual traits (LOD=3.19, genome-wide $P=0.0148$).

We defined a support interval surrounding the bivariate QTL as the interval bounded by the locations on the baboon genetic map at which the LOD score was 1-LOD unit lower than the peak LOD score ("1-LOD drop" method). We then used the markers flanking this support interval to ascertain a likely orthologous region of interest in the human genome. Thus, the region likely to harbor the bivariate QTL is a 16 Mb interval mapping to HSA2p24.3-p23.2, a region narrower than either region identified in the same manner by the univariate linkage analyses (results not shown).

The estimated additive genetic correlation between Lp-PLA₂ activity and LDL-C concentration at this QTL was significantly greater than zero ($\rho_Q=0.62$; $P[\rho_Q=0]=0.0465$), rejecting the hypothesis of co-incident linkage (no shared genetic effects) and consistent with the hypothesis that this QTL exerts pleiotropic effects on both traits. However, the hypothesis of complete QTL pleiotropy between both traits was also rejected ($P[\rho_Q=1]=0.0217$). These results indicate the existence at this QTL of incomplete, or partial pleiotropic effects on variation in both traits.

3.4. A Posteriori Analysis of APOB RFLP Polymorphism

Prominent among identified genes mapping to the region of HSA2p24.3-p23.2 is *APOB*, the structural locus for the apoB isoform associated primarily with circulating LDL-C. We took advantage of *APOB* genotype data previously collected for a small subset of these animals [27] to test for a possible effect of this locus on the two phenotypes in this study. We performed a measured genotype analysis [28] in which we included additive and dominance effects of PvuII restriction fragment length polymorphisms in *APOB* as covariates in our genetic models for LDL-C concentration and Lp-PLA₂ activity. Results of these analyses provided marginal support for additive effects of this polymorphism on Lp-PLA₂ activity ($P=0.07$, $n=323$) and

significant support for dominance effects of the same polymorphism on LDL-C concentration ($P=0.04$, $n=315$).

4. Discussion

Genes contribute substantively to the variance in both Lp-PLA₂ activity and LDL-C concentration in pedigreed baboons, accounting for approximately one-half of the total phenotypic variation in each trait. Our estimates of residual heritability are consistent with previous findings from different researchers also describing the substantial effect of genes on Lp-PLA₂ [5,13] and LDL-C concentration [7,8].

The magnitude of the genetic contributions to phenotypic variation in both Lp-PLA₂ activity and LDL-C concentration facilitated the detection of a QTL for each trait, both of which mapped to a location on PHA13 that corresponds to HSA2p24.3-p23.2. Both QTLs appear to account for only a moderate proportion of the individual additive genetic variation in each trait. Thus, it is likely that other QTLs (undetected in this analysis) also affect phenotypic variation in each trait, a conclusion consistent with a complex genetic architecture for both traits.

Localization of QTLs at the same genetic location for both Lp-PLA₂ activity and LDL-C concentration is not sufficient to support the conclusion that the same gene(s) at this QTL are exerting pleiotropic effects on the two traits, as the cytogenetic interval implicated at the QTL may contain many hundreds of genes. Rather, finding a moderate but statistically significant QTL-associated genetic correlation between the traits leads us to propose that the same gene(s) exert a measurable, pleiotropic influence on coordinated changes in phenotypic variation in Lp-PLA₂ activity and LDL-C concentration reported by others in previous studies of these two traits [5,6]. Although previous studies of Lp-PLA₂ activity and LDL-C concentration in humans have reported correlations between both phenotypes, this is the first study to demonstrate a genetic basis for this phenotypic correlation.

Consistent with our experience in the analysis of complex traits [29], because a substantial proportion of the shared genetic variance between the two traits was attributable to the QTL, our bivariate analyses of Lp-PLA₂ activity and LDL-C levels increased both our confidence in localization of a QTL and substantially narrowed its support interval in the baboon genome, and the orthologous region of interest on human chromosome 2p. However, pleiotropic effects on variation in Lp-PLA₂ activity and LDL-C concentration at this QTL, though considerable, are not complete (i.e., the correlation between the traits due to the QTL is less than one). This is consistent with sharing by Lp-PLA₂ activity and LDL-C levels of the effects of some, but not all, genetic effects at the QTL. Incomplete QTL-specific pleiotropy between Lp-PLA₂ activity and LDL-C levels could be explained by genes or regulatory elements with variably correlated effects on the two traits. Such a set of functional elements may be part of a metabolic or regulatory pathway shared by the two phenotypes, e.g., *cis*-acting transcription elements such as promoters or enhancers, or *trans*-acting phenomena, such as factors affecting transcription initiation or regulation.

APOB, a positional candidate gene from the human chromosomal region implicated by our linkage analyses, codes for the apoB100 isoform, known to be involved in molecular cascades affecting risk of atherosclerosis. ApoB100 plays a critical role in the binding of Lp-PLA₂ to the LDL particle [3], and is the defining protein of LDLs. Genome screen using data from human populations have localized QTLs to adjacent regions of HSA2p for apoB [10,30], total cholesterol [10,31], and familial combined hyperlipidemia [10,30,32]. Additionally, Austin et al. [33] reported *APOB* effects on multiple lipoprotein traits comprising an atherogenic phenotype: peak particle diameter of LDL, triglycerides, and HDL cholesterol levels. Although not conclusive, the results of our measured genotype analyses in a subset of these pedigreed

baboons lend additional support to *APOB* as a positional candidate gene for the pleiotropic QTL detected in this study. Additional analyses of DNA-level variation in *APOB* and other genes within the support interval for this QTL will be necessary to confirm and expand on our current results.

In summary, we have localized a QTL with pleiotropic effects on phenotypic variation in serum Lp-PLA₂ activity and LDL-C concentration, and provided evidence nominating *APOB* as a positional candidate for this QTL, in a baboon model for studies of the genetics of atherosclerosis risk factors. To the best of our knowledge, this is the first report of a QTL affecting both serum Lp-PLA₂ activity and the concentration of its biological partner, LDL. Because variation in both phenotypes is associated with cardiovascular disease risk in humans, we anticipate that subsequent studies to identify and characterize the genetic variants responsible for this pleiotropic QTL in these pedigreed baboons will have tangible implications for our understanding of the human condition. While genetically and physiologically similar to our own species [34], the non-inbred baboons used in this study belong to pedigrees characterized by relatively greater size and complexity than those in most human family studies. Consequently, the study design, analytical methods, and results from this study can be extrapolated readily to genetic analyses of Lp-PLA₂ activity and LDL-C concentration in humans. While experimental control of environmental contributors to phenotypic variation certainly is greater for captive animals, currently available analytical methodologies can accommodate potential environmental covariates in studies of these traits in humans, particularly when informed by results from a closely related nonhuman primate species.

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Figure 1. Univariate linkage results for Lp-PLA₂ (dashed line) and LDL-C (dotted line), and bivariate linkage results for the combined phenotype Lp-PLA₂/LDL-C (solid line) on PHA13, the baboon ortholog of human chromosome 2p.

Table 1

Univariate polygenic analysis of variation in serum Lp-PLA₂ activity (nmol/min/mL, N=657) and LDL-C concentration (SIU*10, N=670) in pedigreed baboons: Maximum likelihood parameter estimates. Parentheses enclose SEM.

Parameter	Lp-PLA ₂	LDL-C
μ	5.49 (0.14)	6.94 (0.46)
σ	1.18 (0.04)	3.73 (0.12)
h^2 residual*	0.67 (0.08)	0.63 (0.07)
β age	-0.13 (0.01)	-0.37 (0.04)
β sex	0.22 (0.13)	3.20 (0.42)
β age x sex	ns [†]	0.27 (0.05)
β age ²	0.02 (0.00)	0.04 (0.01)
β age ² x sex	-0.01 (0.00)	-0.03 (0.01)
c^2_{age} **	0.29	0.18

* $P < 0.000001$

[†] ns: not significant at $P \leq 0.10$

** Proportion of total phenotypic variance due to significant covariates

Table 2

Significant evidence for QTLs influencing variation in Lp-PLA₂ activity and LDL-C concentration in pedigreed baboons (univariate whole genome linkage screen results).

	Lp-PLA₂	LDL-C
Maximum LOD	2.79	2.16
Genome-wide P	0.0394	ns
Baboon Chromosome (PHA)	13	13
Genetic location (cM from pter-most marker)	26 cM	26 cM
QTL-specific h ²	0.13	0.16
Residual h ² at QTL	0.52	0.46

Table 3

Bivariate polygenic analysis of variation in Lp-PLA₂ activity and LDL-C concentration in pedigreed baboons: Maximum likelihood parameter estimates. Parentheses enclose SEM.

Parameter	Lp-PLA ₂		LDL-C
h^2 residual *	0.66 (0.08)		0.63 (0.07)
ρ_G		0.50 (0.09)	
ρ_E		0.40 (0.11)	
ρ_P		0.47	

* $P < 0.000001$

Table 4

A pleiotropic QTL on baboon chromosome 13 (HSA2p) influencing variation in Lp-PLA₂ activity and LDL-C concentration in pedigreed baboons: Summary of bivariate linkage analysis results.

	Lp-PLA ₂ , LDL-C
LOD	3.19
Genome-wide P	0.0148
Baboon chromosome (PHA)	13
Genetic location (cM from pter-most marker locus)	26
Flanking microsatellite marker loci (pter, qter)	D2S131, D2S146
Human chromosome (HSA)	2p
Corresponding HSA cytogenetic region	p24.3-p23.2
QTL-specific h ² (Lp-PLA ₂ , LDL-C)	0.13, 0.15
ρQ	0.62