Genetic analysis of total cholesterol and triglycerides in a pedigree of St. Thomas rabbits

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Abstract A pedigree consisting of 103 New Zealand White hyperlipidemic and normal rabbits was used in a genetic analysis of total cholesterol and triglyceride levels to test for Mendelian control of hyperlipidemia. The founder male of this pedigree was identified through hypercholesterolemia and evidence suggested vertical transmission of a hypercholesterolemic phenotype in this pedigree, although a combined hyperlipidemia phenotype (elevated cholesterol and triglycerides) also occurred in many descendents of the original founders. Segregation analysis of quantitative measures of total cholesterol and triglycerides in this pedigree was employed to test hypotheses about Mendelian control in the presence of substantial inbreeding. A simple Mendelian model was the best explanation for triglycerides in these animals. This best fitting model was essentially co-dominant with genotypic specific variances, where the heterozygote was hypertriglyceridemic and the mutant homozygote showed even more extreme values. The observed distribution of total cholesterol was also compatible with a mixture of distinct genotypic distributions, but there was evidence of non-Mendelian transmission in this pedigree. The observed hypertriglyceridemia in these animals may reflect an abnormality of very low density lipoprotein metabolism described previously. Further studies will be required to elucidate the genetic control of hypercholesterolemia and the associated combined hyperlipidemia in these rabbits.—**Beaty, T. H., P. O. Kwiterovich, A. Laville, and B. Lewis.** Genetic analysis of total cholesterol and triglycerides in a pedigree of St. Thomas rabbits. *J. Lipid Res.* 1989. **30:** 387–394.

Supplementary key words hypertriglyceridemia • combined hyperlipidemia • hypercholesterolemia • pedigree analysis • rabbits

A pronounced hypercholesterolemia in chow-fed New Zealand White rabbits has been described by Laville and co-workers at St. Thomas' Hospital in London (1). This hypercholesterolemia phenotype is transmitted vertically, and affected descendants of a single founder male show hypercholesterolemia alone, hypertriglyceridemia alone, or a combined hyperlipidemia phenotype. The combined hyperlipidemia phenotype is accompanied by elevations in very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low density lipoprotein (LDL) cholesterol levels.

Kinetic studies with ^{131}I- and ^{125}I-labeled rabbit lipoproteins indicated that there was a marked increase in the production rates of VLDL-apoB and LDL-apoB in affected rabbits (1). This inherited metabolic disorder does not appear to be associated with an abnormality in the LDL (apoB or apoE) receptor, and therefore this St. Thomas strain of New Zealand White rabbits appears distinct from Watanabe heritable hyperlipidemic (WHHL) rabbits who carry a genetic defect in the LDL receptor (2–4).

The St. Thomas strain of rabbits develops atherosclerotic lesions, particularly in the descending thoracic aorta, when fed standard chow (5). Thus, these rabbits are also distinct from those with another disorder in which pronounced hyperlipidemia and atherosclerotic arterial lesions develop in response to cholesterol feeding (called hyper-responders) (6).

The hyperlipidemia in this St. Thomas rabbit has some clinical and metabolic features in common with familial combined hyperlipidemia (FCH), a recognized hyperlipidemic syndrome in humans. FCH was originally described as a Mendelian dominant disorder that can be manifest as hypercholesterolemia alone, hypertriglyceridemia, or both in affected members of families of patients with premature coronary artery disease (CAD) (7). Increased hepatic synthesis of apolipoprotein B and VLDL-B and LDL-B also occurs in FCH (8, 9), suggesting some similarities in the metabolic basis for the hyperlipidemic phenotype seen in the St. Thomas strain.

Abbreviations: LDL, low density lipoproteins; IDL, intermediate density lipoproteins; VLDL, very low density lipoproteins; WHHL, Watanabe heritable hyperlipidemia; FCH, familial combined hyperlipidemia; FH, familial hypercholesterolemia; CAD, coronary artery disease; PAP, pedigree analysis package; LRT, likelihood ratio test; AIC, Akaike's information criterion.

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In this report, we present a genetic analysis of the quantitative levels of plasma total cholesterol and triglyceride designed to test specific models of inheritance for a single pedigree of these St. Thomas rabbits. The pedigree containing 103 individuals shown in **Fig. 1** has a high level of inbreeding which must be considered in the genetic analysis. A series of models of inheritance were fit to these data, including a simple polygenic model, a Mendelian single locus model with homogeneous variances about each genotypic mean, models in which genotypic specific means and variances were estimated, and mixed models with both Mendelian and polygenic components.

METHODS

Pedigree

The pedigree shown in Fig. 1 resulted from successive breedings of a male New Zealand White rabbit with two female non-litter mates from this same strain. The founder male had marked hypercholesterolemia but normal triglyceride levels, while both females had cholesterol and triglycerides within the normal range. Backcross matings with two daughters from the resulting half-sibships were carried out, descendants were mated with one another and with other rabbits from this same strain. There is a substantial level of inbreeding in this pedigree, and inbreeding coefficients were calculated for each member of the pedigree using a program provided by Boyce (10). Under the assumption that the founders of this pedigree were themselves not inbred, the mean inbreeding coefficient was 0.1208 for the 103 members of this pedigree. Inbreeding coefficients ranged from 0.0 to 0.375, as shown in Fig. 1. The highest values occurred in offspring of full sibs from a father-daughter mating, i.e., individuals 42–46 and 56–58 in Fig. 1.

Individual rabbits were sampled at the age of 2 months after an overnight fast of 16 hr. At this age, the rabbits were 1 month post-weaning and on a standard diet. Total cholesterol and triglyceride levels were measured by enzymatic methods as described previously (1). **Table 1** lists the means, standard error of the mean, variances, and coefficients of skewness and kurtosis for both total cholesterol and triglycerides in these animals.

Segregation analysis

In addition to the calculation of kinship coefficients, segregation analysis was carried out on this pedigree comparing a series of models of inheritance for total cholesterol and triglycerides separately using the Pedigree Analysis Package (PAP) (11). This program allows the calculation of joint genotypic probabilities for sets of individuals which must be considered simultaneously in an inbred pedigree such as this.

The models of inheritance included a sporadic model where every individual was assumed to have the same genotype; Mendelian single locus models with distinct genotypic means and a common variance estimated; Mendelian single locus models with both genotypic specific means and vari-

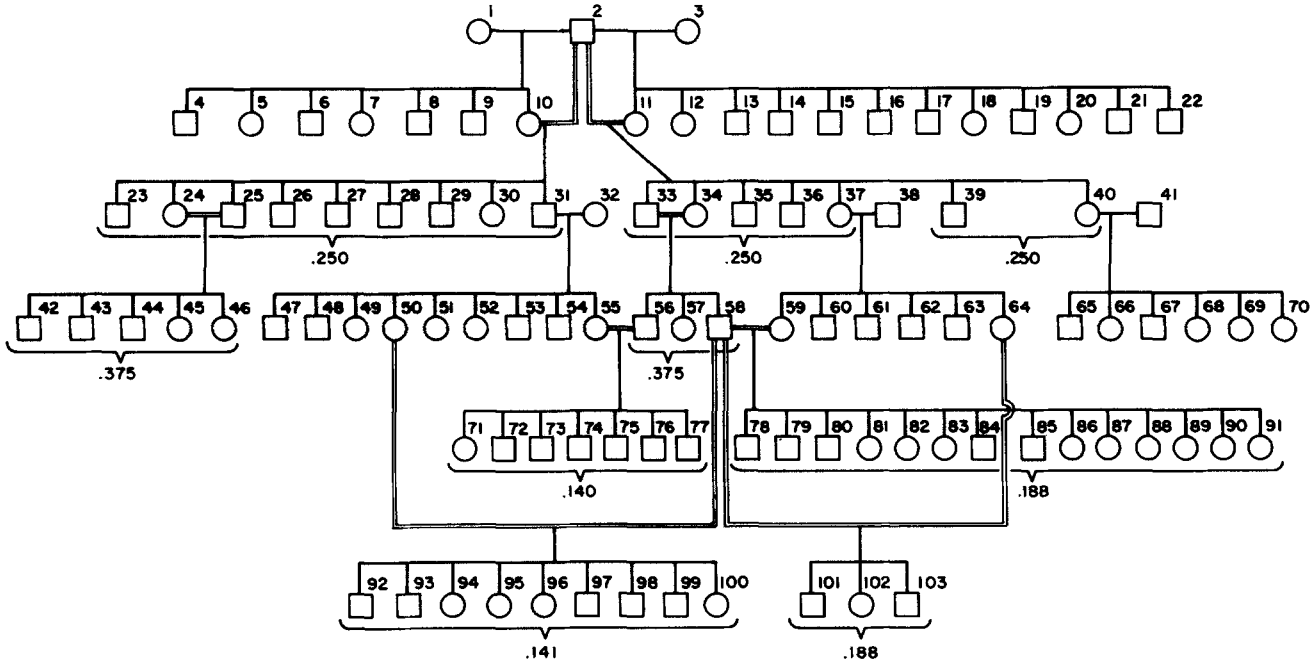

Fig. 1. Pedigree of 103 St. Thomas rabbits showing inbreeding coefficients for inbred individuals.

TABLE 1. Descriptive statistics for total cholesterol and triglycerides in 103 St. Thomas rabbits

	N	Mean ± SEM	Variance	Skewness	Kurtosis
		mmol/l			
Total cholesterol	103	5.952 ± 0.314	10.164	0.86[a]	0.26
Triglyceride	103	1.655 ± 0.118	1.438	2.04[a]	5.88[a]

[a]Significantly different from expectation under normal distribution.

ances but strict Mendelian transmission between parent and offspring; polygenic models where correlations between relatives were assumed to result from the additive effects of many independent genetic factors; mixed Mendelian models where both Mendelian and polygenic factors were considered simultaneously; and arbitrary models of inheritance where the segregation parameters were estimated directly.

Usually when doing segregation analysis, tests of hypotheses about the underlying parameters (either frequency, penetrance, or transmission parameters) rely on the likelihood ratio test (LRT) which is computed as minus twice the difference between the ln-likelihood for a reduced model (i.e., a model with a given parameter constrained to some value) and that for a complete model (i.e., a model with that parameter estimated from the data), i.e.,

$$\text{LRT} = -2\{\ln L \text{ (reduced model)} - \ln L \text{ (complete model)}\}.$$

This LRT approximates a chi-square distribution with degrees of freedom equal to the difference in the number of parameters in the complete and reduced models, as the sample size gets larger. Here our sample consists of a single pedigree, however, so the usual LRT should not be viewed directly as a chi-square statistic. Nonetheless, the magnitude of the improvement in the ln-likelihood function of one model compared to another model in a hierarchical series still serves as an indication of its overall fit to the data. Since the LRT is only appropriate for strictly hierarchical models (i.e., the 'reduced' model must be a subset of the 'complete' model) and since not all genetic models are hierarchical, Akaike's information criterion (AIC) was examined for each model to guide in the selection of the most parsimonious model among non-hierarchical models (12, 13). This test statistic is also based on the ln-likelihood (i.e., AIC = $-2 \ln L + 2$ (number of parameters)), and models with smaller AIC values are considered more parsimonious, i.e., they give a better fit with fewer parameters.

RESULTS

The results of segregation analysis of total cholesterol are shown in **Table 2** which lists parameter estimates and their standard errors for allele frequency ($\hat{p}$); up to three genotypic means ($\hat{\mu}_1$, $\hat{\mu}_2$, $\hat{\mu}_3$) and the corresponding standard deviations about these means ($\hat{\sigma}_1$, $\hat{\sigma}_2$, and $\hat{\sigma}_3$); the proportion of variance attributable to a shared polygenic component ($\hat{H}p$); and the probability of a heterozygote (genotype 2) transmitting a specific allele to an offspring (τ_2). Note that some of these parameters are constrained to certain values in some models. For example, a Mendelian recessive model implies $\mu_1 = \mu_2$ and $\tau_2 = 0.5$. Also shown in Table 2 are the -2ln-likelihood values and Akaike's information criterion for each model which are used to compare the various models.

From this table, it is clear that the Mendelian models were favored over either a sporadic model (i.e., model 1 where a common mean and variance were estimated but every individual was assumed to be independent) or a simple polygenic model (i.e., model 2 where all correlation among individuals was assumed to be due to additive genetic factors). Among the Mendelian models (models 3–6), the more general model with three distinct genotypic means and three distinct standard deviations was better than either a recessive model where two genotypes were constrained to have the same mean and the same variance (model 5), or a Mendelian model with a single variance common to all genotypes (model 3). Mixed Mendelian models (7 and 8 in Table 2) were also examined. The recessive mixed model (model 7) was not better than the recessive Mendelian models with genotypic specific variances. Furthermore, the estimated correlation or heritability under a recessive mixed model was quite small (6.5%) for this pedigree. Boundary problems were encountered when fitting codominant mixed model (model 8), invalidating further comparison using either the LRT or Akaike's criterion. Note that under these mixed models, as currently defined, the correlation among relatives is computed assuming a homogeneous variance across all genotypes, so it was not possible to estimate genotypic specific variances and the residual heritability.

The best fitting Mendelian model appeared to be the one with three distinct genotypes and three genotype specific variances (model 6), i.e., a codominant model where both the heterozygote and homozygote would be considered hypercholesterolemic, but the mutant homozygote has both a greater mean and variance. Further tests for the transmission of this hypothetical Mendelian gene were carried out by estimating the segregation parameter representing the transmission between a heterozygote parent and an offspring, along with the parameters of both the Mendelian and mixed models. A strict Mendelian model dictates that this segregation parameter, termed τ_2 by Elston and Stewart (14), be equal to 0.5. The estimated value of τ_2 was considerably below this value for both models allowing genotypic specific variances (models 12 and 13 in Table 2). For example, an LRT statistic comparing the best fitting Mendelian model (model 6) to a more general alternative (model 13) was 4.49 (= 496.34 − 491.85) and would lead to reject-

TABLE 2. Segregation analysis of total cholesterol on 103 New Zealand white rabbits

Model	Number of parameters	Parameter Estimates										
		$\hat{P}$	$\hat{\mu}_1$	$\hat{\mu}_2$	$\hat{\mu}_3$	$\hat{\sigma}_1$	$\hat{\sigma}_2$	$\hat{\sigma}_3$	$\hat{H}_p$	$\hat{\tau}_2$	−2lnL	AIC
Non-Mendelian												
1. Sporadic	2	(1.0)	5.952 ± 0.309	(= μ_1)	(= μ_1)	3.173 ± 0.220	(= σ_1)	(= σ_1)	(0)	(0.5)	529.55	533.55
2. Polygenic	3	(1.0)	4.392 ± 0.994	(= μ_1)	(= μ_1)	3.203 ± 0.243	(= σ_1)	(= σ_1)	0.242 ± 0.156	(0.5)	525.28	531.28
Mendelian												
3. Recessive, 1 variance	4	0.791 ± 0.131	4.997 ± 0.270	(= μ_1)	11.260 ± 0.746	2.235 ± 0.185	(= σ_1)	(= σ_1)	(0)	(0.5)	513.98	521.98
4. Codominant, 1 variance	5	0.807 ± 0.123	4.623 ± 0.546	5.272 ± 0.436	11.305 ± 0.750	2.229 ± 0.186	(= σ_1)	(= σ_1)	(0)	(0.5)	513.36	523.36
5. Recessive, 2 variances	5	0.654 ± 0.177	4.567 ± 0.281	(= μ_1)	8.323 ± 0.929	1.896 ± 0.191	(= σ_1)	3.499 ± 0.441	(0)	(0.5)	506.56	516.56
6. Codominant, 3 variances	7	0.740 ± 0.129	1.621 ± 0.235	4.942 ± 0.273	8.077 ± 0.702	0.482 ± 0.151	1.767 ± 0.189	3.642 ± 0.437	(0)	(0.5)	496.34	510.34
Mixed												
7. Recessive, mixed	5	0.973 ± 0.044	3.957 ± 0.613	(= μ_1)	9.965 ± 1.076	2.292 ± 0.175	(= σ_1)	(= σ_1)	0.060 ± 0.034	(0.5)	509.72	519.72
8. Codominant, mixed[a]	6	0.999[a]	2.872	4.877	10.053	2.070	(= σ_1)	(= σ_1)	0.017	(0.5)	492.89[b]	
General												
9. Recessive, mixed[a]	6	0.984	2.599	(= μ_1)	6.824	2.463	(= σ_1)	(= σ_1)	0.078	0.250[a]	502.33[b]	
10. Recessive, 1 variance	5	0.799 ± 0.129	4.972 ± 0.275	(= μ_1)	11.160 ± 0.773	2.227 ± 0.185	(= σ_1)	(= σ_1)	(0)	0.469 ± 0.081	513.84	523.84
11. Codominant, 1 variance	6	0.812 ± 0.121	4.562 ± 0.573	5.233 ± 0.421	11.172 ± 0.785	2.216 ± 0.187	(= σ_1)	(= σ_1)	(0)	0.463 ± 0.077	513.14	525.14
12. Recessive, 2 variances	6	0.784 ± 0.146	4.628 ± 0.266	(= μ_1)	8.462 ± 0.883	1.934 ± 0.190	(= σ_1)	3.525 ± 0.473	(0)	0.327 ± 0.130	505.62	517.62
13. Codominant, 3 variances	8	0.822 ± 0.116	1.912 ± 0.319	5.135 ± 0.309	7.766 ± 0.806	0.581 ± 0.175	1.765 ± 0.194	3.609 ± 0.407	(0)	0.247 ± 0.106	491.85	507.85

[a]Estimator at boundary.
[b]Not at true maximum.

ing the Mendelian hypothesis when simply viewed as a chi-square statistic. Looking at Akaike's criterion also showed the more general model to have a slightly smaller value. Thus, these two test statistics do raise the possibility of non-Mendelian control of cholesterol levels in this pedigree. Furthermore, both of these models (6 and 13) predicted a grand mean that was slightly lower than that of the sample itself, raising the possibility that models with three distinct means and variances cannot adequately explain these data.

The results of a similar analysis on triglyceride levels are shown in **Table 3**. Again, there was a strong familial correlation in triglycerides as evidenced by the high estimated heritability (56.2%) obtained under a simple polygenic model, but the Mendelian models (models 3–6) overall provided better explanations for these data. There was significant heteroscedascity (differences in variances) among the genotypes, however, and the best Mendelian model included three distinct genotypes, each with a different variance. Mixed Mendelian models (models 7 and 8) were also examined, but they had lower ln-likelihoods and involved very modest heritabilities beyond that due to the major gene. When the transmission parameter τ_2 was added to the model, there was no evidence of nonMendelian inheritance for this putative hypertriglyceridemia allele. The most parsimonious model for triglycerides in this pedigree was, therefore, a Mendelian codominant mechanism with mild hypertriglyceridemia in the heterozygote and severe hypertriglyceridemia in the mutant homozygote.

A number of nongenetic models were also examined which hypothesize mixtures of distinct distributions but with equal transmission probabilites from parent to child. These so-called 'equal τ' models often resulted in maximization problems, but in no case did they appear to be better fitting than the Mendelian models used here.

Testing for co-segregation

Even though the evidence of Mendelian control of total cholesterol was ambiguous, it is logical to ask whether the two best fitting Mendelian models could give any evidence of independent control of triglycerides and total cholesterol.

TABLE 3. Segregation analysis of triglycerides on 103 New Zealand white rabbits

Model	Number of parameters	Parameter Estimates									−2lnL	AIC
		$\hat{P}$	$\hat{\mu}_1$	$\hat{\mu}_2$	$\hat{\mu}_3$	$\hat{\sigma}_1$	$\hat{\sigma}_2$	$\hat{\sigma}_3$	$\hat{H}_p$	$\hat{\tau}_2$		
Non-Mendelian												
1. Sporadic	2	(1.0)	1.655 ± 0.117	(= μ_1)	(= μ_1)	1.193 ± 0.083	(= σ_1)	(= σ_1)	(0)	(0.5)	131.66	135.66
2. Polygenic	3	(1.0)	1.335 ± 0.451	(= μ_1)	(= μ_1)	1.258 ± 0.116	(= σ_1)	(= σ_1)	0.562 ± 0.191	(0.5)	119.30	125.30
Mendelian												
3. Recessive, 1 variance	4	0.765 ± 0.142	1.330 ± 0.101	(= μ_1)	4.128 ± 0.324	0.787 ± 0.082	(= σ_1)	(= σ_1)	(0)	(0.5)	99.68	103.68
4. Codominant, 1 variance	5	0.769 ± 0.139	1.151 ± 0.170	1.430 ± 0.133	4.132 ± 0.295	0.760 ± 0.064	(= σ_1)	(= σ_1)	(0)	(0.5)	102.78	112.78
5. Recessive, 2 variances	5	0.634 ± 0.200	1.235 ± 0.164	(= μ_1)	3.002 ± 0.673	0.601 ± 0.167	(= σ_1)	1.390 ± 0.196	(0)	(0.5)	82.77	92.77
6. Codominant, 3 variances	7	0.797 ± 0.128	0.827 ± 0.052	1.513 ± 0.113	3.385 ± 0.458	0.201 ± 0.040	0.662 ± 0.075	1.527 ± 0.280	(0)	(0.5)	59.93	73.93
Mixed												
7. Recessive, mixed	5	0.823 ± 0.160	1.246 ± 0.164	(= μ_1)	4.014 ± 0.354	0.787 ± 0.078	(= σ_1)	(= σ_1)	0.036 ± 0.069	(0.5)	103.59	113.59
8. Codominant, mixed[a]	6	0.999[a]	0.553	1.275	3.610	0.746	(= σ_1)	(= σ_1)	0.114	(0.5)	94.21[b]	
General												
9. Recessive, mixed	6	0.775 ± 0.177	1.277 ± 0.162	(= μ_1)	4.077 ± 0.334	0.773 ± 0.067	(= σ_1)	(= σ_1)	0.019 ± 0.066	0.577 ± 0.075	102.68	114.68
10. Recessive, 1 variance	5	0.738 ± 0.155	1.321 ± 0.891	(= μ_1)	4.133 ± 0.285	0.771 ± 0.066	(= σ_1)	(= σ_1)	(0)	0.584 ± 0.071	102.76	112.76
11. Codominant, 1 variance	6	0.747 ± 0.148	1.132 ± 0.149	1.477 ± 0.145	4.180 ± 0.274	0.748 ± 0.060	(= σ_1)	(= σ_1)	(0)	0.600 ± 0.067	100.82	112.82
12. Recessive, 2 variances	6	0.682 ± 0.161	1.134 ± 0.077	(= μ_1)	2.877 ± 0.387	0.496 ± 0.061	(= σ_1)	1.435 ± 0.197	(0)	0.507 ± 0.080	79.85	91.85
13. Codominant, 3 variances	8	0.792 ± 0.132	0.831 ± 0.052	1.538 ± 0.130	3.468 ± 0.508	0.207 ± 0.044	0.665 ± 0.077	1.516 ± 0.290	(0)	0.528 ± 0.067	59.76	75.76

[a]Estimator at boundary.
[b]Not at true maximum.

To do this, we looked for evidence of possible co-segregation or linkage between these two putative loci. Linked genes will co-segregate within a family and evidence of complete linkage could mean that there were either two loci located physically near one another (i.e., true linkage) or that a single locus controlled both cholesterol and triglycerides (i.e., pleiotropic expression of a single locus). On the other hand, any evidence of recombination would exclude this latter possibility.

The high degree of inbreeding present in this pedigree makes it impossible to directly evaluate a two-locus model, since the number of genotypic combinations for individuals in the pedigree who must be considered jointly was too large. Therefore, to address the question of linkage, we computed the probability of each individual's having each of the three genotypes at the hypothetical cholesterol locus and the apparent hypertriglyceridemia locus, separately, using the respective best fitting Mendelian models. For example the best fitting model for triglycerides was a Mendelian codominant with genotype specific variances (model 6 in Table 3) where the most common homozygote (genotype T_1T_1) had a phenotypic mean of 0.83 mmol, the heterozygous T_1T_2 genotype had a phenotypic mean of 1.51, and the mutant homozygote had a mean of 3.39 mmol (genotype T_2T_2). The best fitting model for total cholesterol was also a Mendelian codominant with three distinct variances (model 6 in Table 2) with an estimated mean of 1.62 mmol for genotype C_1C_1, 4.94 for genotype C_1C_2, and 8.08 for C_2C_2 homozygotes.

Using these two models, the probabilities of each genotype at the hypothetical Mendelian loci were computed for each member of the pedigree and the entire pedigree was examined for evidence of independent segregation. There were three matings in the pedigree informative for linkage under these models (between individuals 2 and 10, 58 and 59, and 58 and 64), each involving a phase known double heterozygote female ($C_1C_2T_1T_2$ in coupling) and a male homozygous at the cholesterol locus and heterozygous at

the hypertriglyceridemia locus ($C_2C_2T_1T_2$). The probability of these genotypic assignments was over 98% for all parents in these three matings, although the probabilities of genotypic assignments in offspring ranged well below this. Looking at the predicted genotypes of the 26 offspring of these matings showed 4 apparent recombinants, 10 apparent nonrecombinants, and 12 noninformative offspring. The full sib mating between individuals 24 and 25 represented a similar mating ($C_2C_2T_1T_2$ male by $C_1C_2T_1T_2$ female) but phase was not known, so it was not possible to identify recombinant offspring. Overall, this analysis of the best fitting Mendelian models suggests triglycerides and total cholesterol are not under control of a single genetic mechanism.

DISCUSSION

While there are many familial forms of hyperlipidemia, some of which appear to be Mendelian, it is not a simple task to identify genetic mechanisms from human data due to small family sizes and the influence of covariates such as age, sex, etc. Animal models for hyperlipidemia are extremely useful in identifying genetic mechanisms since controlled matings can be made and large sibship or litter sizes are often available. However, the level of inbreeding present in matings among standard laboratory animals can create its own problems for segregation analysis. For relatively simple models of inheritance (single locus models), it is possible to consider explicitly the observed inbreeding using available programs for pedigree analysis. More complex models (e.g., two-locus models with 10 or more genotypes) remain computationally intractable for highly inbred pedigrees such as the one used here.

It must always be remembered, however, that analysis of small groups of laboratory animals necessarily limits the inferences that can be made. The goal of this type of genetic analysis is to identify possible Mendelian models underlying a phenotypic distribution, and then use them to predict outcomes of further matings or experiments. All estimates of proportions of variation attributable to polygentic variation (i.e., the heritability) or variation due to the Mendelian locus itself lose relevance when drawn from a single inbred pedigree such as this. For example, heritability is defined as the proportion of total phenotypic variation attributable to variation in independently segregating genes, each contributing equally to the observed phenotype. However, in the presence of inbreeding, the apparent polygenic component is inflated by the average inbreeding coefficient (which was 0.12 in this particular pedigree) (15). Since this computed level of inbreeding assumes (falsely) that the founders were themselves noninbred, it is extremely hazardous to estimate from this analysis how much of the total variation in cholesterol or triglycerides is due to additive genetic factors. Similarly, it is extremely difficult to estimate how much of the total variation in New Zealand white rabbits is due the apparent hypertriglyceridemia locus found in this pedigree of St. Thomas rabbits, because this is a function of both the genotypic means and the allele frequency. With only six founders in this pedigree, any estimate of allele frequency must be viewed with caution. Nonetheless, this segregation analysis remains extremely useful for identifying possible Mendelian models and then predicting genotypes for individual animals. Even if there is no meaningful population of reference when analyzing a single pedigree such as this, it is still possible to make inferences about biological systems and then go on to design further tests and experiments.

Hypertriglyceridemia in this pedigree of St. Thomas rabbits seems to be under clear Mendelian control with codominant expression of the mutant allele and substantial heteroscedasticity (differences in variances) among the three genotypes at this locus. **Fig. 2** shows the observed distribution of triglycerides and the hypothetical underlying genotypic distributions derived from model 6 in Table 3. Such genotypic specific variance are biologically reasonable in that a mutant allele could well affect both the mean and the variance in a complex physiological trait such as triglycerides. Indeed, Moll et al. (16) have shown that both the mean and variance of cholesterol in the LDL fraction differ between heterozygotes for the familial hypercholesterolemia (FH) gene and homozygous normal individuals. In this analysis of a large human pedigree, Moll et al. (16) found there was an additional difference in the effect of age on LDL cholesterol levels between these two genotypes.

Often log transformations are used for traits that show significant skewness (as do triglycerides), since it is possible for skewness alone to spuriously lead to inferring the presence of a Mendelian mechanism (17). A series of models similar to that shown in Table 3 was examined on ln-triglycerides (with rescaling) in this pedigree, and again strong evidence for a Mendelian component was seen (the LRT was 9.82 for the null hypothesis of no Mendelian component). However, transformation had three major effects on the inferences drawn from this analysis. First, the heteroscedasticity among genotypic distributions was no longer statistically significant. Second, it was no longer possible to distinguish between the means of the normal homozygote and the heterozygote. This is to be expected since ln-transformation compresses the phenotypic scale considerably. Last, after ln-transformation there was some residual correlation over and above that due to the Mendelian component, representing some 6% of the total variation in ln-triglycerides. From this analysis of transformed triglycerides, however, it was still possible to compute genotypic probabilities for each animal in the pedigree under the best fitting model and compare genotypic assignments. Aside from the expected difficulty in distinguishing between T_1T_1 and T_1T_2 genotypes using ln-triglycerides, there was near complete agreement in identifying animals homozygous for

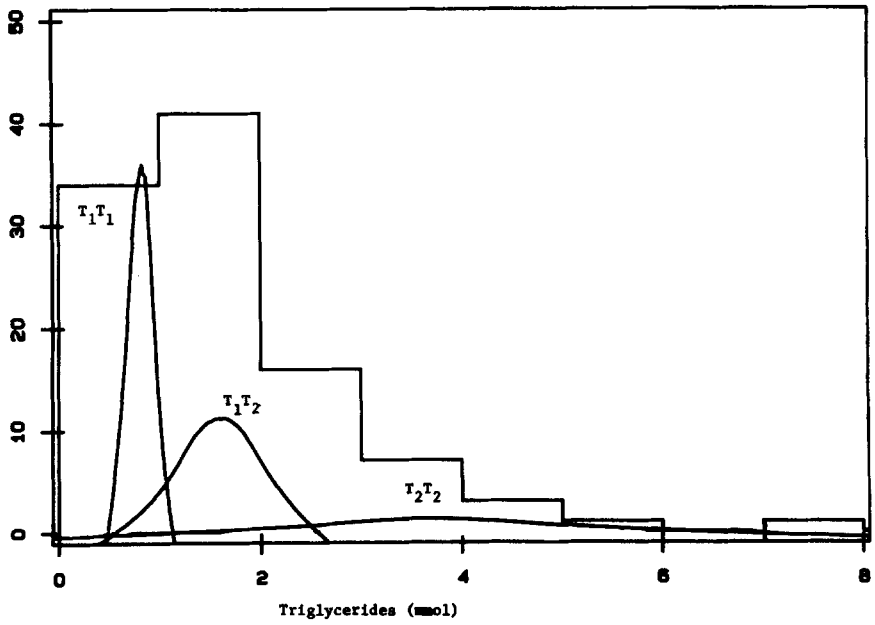

Fig. 2. Frequency distribution of observed triglycerides in a 103 member pedigree. The hypothetical genotypic distributions for the three genotypes at the hypertriglyceridemia locus from the best fitting Mendelian model (model 6 in Table 3) are also shown.

the mutant hypertriglyceridemia allele (e.g., all individuals identified as being T_2T_2 with probability of 70% or greater under model 6 in Table 3 also had a 70% or greater probability of being homozygous for the rare hypertriglyceridemia allele under the best fitting model obtained from the analysis of ln-transformed triglycerides).

While the distribution of total cholesterol in these St. Thomas rabbits was compatible with a Mendalian codominant model, the overall fit of the best model to the total distribution was not as good as obtained with the analysis of triglycerides. There was some evidence of nonMendelian transmission which may, in part, be due to sampling variation, since there were only six matings involving an apparent heterozygote in this single pedigree (although 50 offspring were produced). However, it is difficult to rigorously interpret either test statistic (the LRT or Akaike's criterion) for the null hypothesis that $\tau_2 = 0.5$ using a single pedigree. Further work to better define this putative hypercholesterolemia locus and its relationship to the more cleanly segregating hypertriglyceridemia locus is obviously needed.

Rabbits homozygous for this apparent hypertriglyceridemia locus in this pedigree have some clinical and metabolic features similar to those seen in patients with familial combined hyperlipidemia (7). Patients with FCH may have hypercholesterolemia, hypertriglyceridemia, or both and the patient's lipid profile may change over time. However, the delayed expression of hyperlipidemia often seen in humans with FCH does not appear to occur in these St. Thomas rabbits that display the abnormality at an early age. Further biochemical and genetic studies will be necessary to determine whether the hyperlipidemia in these St. Thomas rabbits can serve as a model for human FCH.

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