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Twin Studies of Coronary Heart Disease and Its Risk Factors

Kare Berg
Institute of Medical Genetics, University of Oslo, and Department of Medical Genetics, City of Oslo

Abstract. The ongoing comprehensive study of the updated population-based Norwegian Twin Panel (like-sexed twin pairs born since 1915) has already given results of interest to the research on coronary heart disease and its risk factors. Significantly more dizygotic (DZ) than monozygotic (MZ) pairs are discordant for death between 40 and 60 years of age. Presumably, several of the cases must have been coronary heart disease deaths. In pairs where both members are alive, concordance rate for coronary heart disease before the age of 60 years is significantly higher in MZ than in DZ pairs. Concordance rate for reported hypertension is significantly higher in MZ than in DZ pairs. These findings are compatible with a significant genetic effect on premature death, coronary heart disease and hypertension.

There is a strong genetic effect on serum level of apoB, apoA-I and apoA-II, a weaker effect on cholesterol level and a doubtful effect on triglyceride level. Genes belonging to several normal genetic polymorphisms may participate in the control of environmentally/dietary caused variability in lipid and lipoprotein parameters. The study of MZ twins that was conducted to detect these effects holds considerable promise for the detection of gene control of many kinds of quantitative parameters. Further work with this twin panel may provide more definite answers to several questions raised during the present investigation. Application of more sophisticated models for twin family analysis on several normal and pathological traits may be very informative. Also, this updated Norwegian Twin Panel should in the long run make it possible to estimate the predictive value for the second member of a twin pair of having a twin contracting coronary heart disease (or any other reasonably frequent disease) by a given age. Finally, the subsample that is subjected to extensive laboratory analyses will provide useful data for genetic linkage

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analyses since in many cases, offspring of two members of a MZ pair can effectively be considered as one single (more informative) sibship.

Key Words: **Coronary heart disease, Hypertension, Cholesterol, Triglycerides, Lipoproteins, Twin panel**

INTRODUCTION

It is becoming widely realized that genetic factors play a role in a significant proportion of coronary heart disease (CHD) cases. Present knowledge in this area originates from many studies of various designs (for review see Berg [3]). Nevertheless, important questions still remain. For example, there is a need to study the exact nature of genetic effects, their interaction, and the interaction between genetic factors and environmental/dietary factors.

Twin studies have yielded significant information concerning the importance of genetic factors in the etiology of coronary heart disease, particularly when the disease occurs at a relatively young age. Twin studies have also yielded information concerning genetic effects on risk factors for CHD, and they have made possible a new approach to the study of permissive or restrictive effects of marker genes on environmentally/dietary caused variability in lipid and lipoprotein parameters.

In this review of twin studies of coronary heart disease and its risk factors, results of an ongoing study of Norwegian twin pairs will be presented. The review reflects the status of the Norwegian twin study concerning coronary heart disease and its risk factors, as of June, 1983.

THE NORWEGIAN TWIN PANEL

Two previously established, manual twin registers and census data have made it possible to established a population-based register comprising all like-sexed twin pairs born in Norway between 1915 and 1960, whose addresses could be traced in central population files. All pre-existing registry information on these twins has been updated and computerized. In the following, this updated, computer-based register of Norwegian twins born since 1915 will be referred to as the Norwegian Twin Panel. The census data are believed to be very accurate from 1946 and onwards, and information on every multiple birth in Norway since 1946 has been available to us.

We have been able to trace 16,230 pairs of like-sexed twins born in the period 1915 through 1960. Out of these, 3,262 pairs were excluded because both twins had died, or one twin had died prior to the age of 20 years. Another 216 pairs were excluded because they had (relatively recently) been included in other studies.

Thus, 12,752 pairs were available for the questionnaire study and more than 25,000 first questionnaires were sent to them. Responses were received from 11,175 pairs to this first questionnaire, a zygosity questionnaire which predicted zygosity correctly in more than 97% of the pairs [5]. More than 18,000 extensive health questionnaires were sent to those who in the response to the first questionnaire had indicated that they were prepared to participate in the extensive main study. As of today, the extensive health questionnaire has been completed by at least one member of 8,516 pairs. Thus, the basis for our twin studies on coronary heart disease and its risk factors now comprise more than 8,500 like-sexed twin pairs.

ZYGOSITY IN PAIRS WHERE BOTH MEMBERS ARE ALIVE AS COMPARED TO PAIRS WHERE ONE MEMBER HAS DIED AFTER THE AGE OF 20 YEARS

Approximately 40% are MZ of the pairs where both members are alive as opposed to only 33.5% of pairs where one member is alive and the other has died in the age period 20-65 years.

Since existing data suggest that genetic factors are particularly important in the etiology of coronary heart disease when such disease occurs at a relatively young age [2,3] it was of interest to study separately those pairs where one member had died within the age of 60 years. Death from coronary heart disease is relatively rare prior to the age of 40 years, and the pairs in which one member had died in the age period from 40 to 60 years were analysed separately in order to have the highest possible proportion of early coronary deaths in the death discordant twin pairs. The result was that only 28% of twin pairs where one twin had died in this group were MZ (as opposed to the previously mentioned frequency of 40% of pairs where both members are alive).

Since it is reasonable to assume that coronary heart disease accounted for a number of the deaths in this age bracket, the data provide, albeit indirect, evidence that genetic factors are of importance for CHD in the 40-60 years age period.

CORONARY HEART DISEASE IN MZ AND DZ TWIN PAIRS

Our health questionnaire comprised questions aimed at detecting CHD in the twins and their families. For the purpose of the present analyses, CHD was considered to be present if there was a "yes" response to the angina pectoris and/or myocardial infarction question in the questionnaire. Due to the study design, hospital confirmed diagnoses are not yet available on death discordant pairs. Hence, the direct information on coronary heart disease and hypertension is for the time being exclusively from pairs where both members are alive.

For the time being, we know of 157 pairs in which at least one member has coronary heart disease, and of 22 pairs where both members are affected. Out of these pairs, 14 were MZ and 8 DZ. The difference does not reach statistical significance.

In Table 1, only affected pairs that are 60 years old or younger are considered. Among the 17 pairs where both members are affected with coronary heart disease, 12 are MZ. The difference is highly significant. The finding permits the conclusion that there is a significant difference between MZ and DZ pairs with respect to concordance for CHD, and the difference is compatible with a significant genetic influence on CHD prior to the age of 60 years.

Although the concordance rate for CHD is higher in MZ than in DZ pairs, the concordance rate in MZ twins is considerably lower than it was at a previous count [1]. It should be noted that at the time of the previous count the greater part of the available data was from twins born relatively shortly after 1915. Therefore, a significant proportion of the pairs in which the first twin had become affected prior to the age of 60 had had at least a five-year observation period for the second, unaffected twin, by the time the pairs were scored as discordant.

At the present count, it was noteworthy that in many of the pairs where one member only is affected, the first disease manifestation had occurred only a short while prior to filling in the health questionnaire. One may expect an increase in concordance rate, when a reasonable stretch of time has elapsed after the disease became manifest in the first twin. At this transitory stage of the study, the observed rates of concordance and discordance, respectively, may indeed be quite misleading.

HYPERTENSION IN MZ AND DZ TWINS

Table 2 shows the zygosity in 705 pairs in which at least one member had reported hypertension. The difference in zygosity between pairs where both members were affected and pairs where only one member was affected is highly significant, and the concordance rate for reported hypertension is 0.34 in MZ and 0.09 in DZ pairs, compatible with a significant effect of genes on blood pressure elevation. As in the case of coronary heart disease, it is plausible that the concordance rate may change with longer observation time of pairs that are discordant at present.

GENETIC INFLUENCE ON LIPID LEVELS

We have previously reported [1-3] on our twin studies on genetic influence on level of serum lipid and lipoprotein parameters. Table 3 gives the best estimate of heritability for cholesterol, fasting triglycerides, apoB, apoA-I and apoA-II level, based on the previous studies. The estimate of heritability for cholesterol level, 0.34, suggests an effect of genes, but also of environment and diet on total serum cholesterol, the estimate (c^2) of the total effect of common environment being 0.18. It is possible that the heritability of cholesterol is higher than indicated here, since it would be 0.52 if only the 76 pairs of fasting MZ pairs were considered (taking the intraclass correlation coefficient for MZ pairs as the heritability estimate).

The surprisingly high heritability estimate for fasting triglycerides must be interpreted with extreme caution because in male pairs the heritability estimate was zero. This fact, together with previously known data, suggests that heritability of fasting triglyceride level may in fact be very low.

The heritability estimate for the main apoprotein in low density lipoprotein (LDL) apoB, surprisingly came out as high as 0.66 when only fasting same-sexed twin pairs were considered. The greater part of cholesterol in fasting serum resides in LDL. The difference from the result obtained in the analysis of total serum cholesterol suggests that genetic effects may become blurred when lipid analysis is used instead of measurement of particles actually containing apoB. The data set forms another piece of evidence that the level of atherogenic LDL is under strong genetic influence in the general population.

The heritability estimate for apoA-I is from MZ twins alone. Mean squares obtained from analysis of variance also were fitted to simple models specifying genetic and environmental variance components, using the method of iterative weighted least squares. Heritability could be estimated as the ratio between the genetic variance component and total variance. The heritability estimate based on such analyses and a model of additive genetic variance, dominance variance, and random environmental variance form the basis for the heritability estimate for apoA-II.

Further studies are needed to arrive at a more complete answer to the questions

Table 1 - Coronary Heart Disease (Angina Pectoris and/or Myocardial Infarction) in Norwegian Same-Sexed Twin Pairs (Both Members alive) 60 Years Old of Younger (Data as of June 1983)

Category	No. of twin pairs		
	MZ	DZ	Total
Both members affected	12	5	17
One member affected	29	56	85
Total	41	61	102

$\chi^2 = 6.4;\ 0.01 < P < 0.02$

Table 2 - Hypertension in Norwegian Same-Sexed Twin Pairs (Both Members Alive) Born 1915-1960 (Data as of June 1983)

Category	No. of twin pairs		
	MZ	DZ	Total
Both members affected	91	40	131
One member affected	177	397	574
Total	268	437	705

$\chi^2 = 65;\ P < 0.0001$

Table 3 - Best Estimates of Heritability of Serum Lipid and Lipoprotein Levels, from Studies of 98 MZ and 100 DZ Same-Sexed Norwegian Twin Pairs

Parameter	h^2
Cholesterol	0.34
Triglycerides (fasting)	0.40*
ApoB level	0.66**
ApoA-I level	0.53
ApoA-II level	0.69

* $h^2 = 0$ for male pairs

** Lower in males than in females

Table 4 - Intrapair Difference in Fibroblast ^{125}I-LDL Association and Degradation (as ng ^{125}I-LDL/mg Cell Protein/4.5 hr) in MZ and DZ pairs. Data from Magnus et al [7]

Twin Category	No. of pairs	^{125}I-LDL Association	^{125}I-LDL Degradation
MZ	14	160	200
DZ	21	310	310
Significance of Difference*		P = 0.031	P = 0.048

* Wilcoxon-Mann-Whitney test

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concerning heritability of lipid and lipoprotein parameters. Studies on twin families are expected to yield important results in this connection.

GENETIC CONTROL OF LDL CELL MEMBRANE RECEPTOR ACTIVITY IN HEALTHY PEOPLE

The problem of possible genetic control of LDL cell membrane receptor activity in the general population is difficult to approach because of the considerable experimental variation in LDL receptor activity assays. In an attempt to overcome this problem, an experiment was designed by our group in which cell strains from a number of like-sexed twin pairs were examined in duplicate in one experiment. The resulting data which have been published by Magnus et al [7] are summarized in Table 4.

The intrapair difference was larger in DZ than in MZ pairs for the association as well as the degradation parameter. Both differences were significant according to the Wilcoxon-Mann-Whitney test. We concluded from this study that LDL cell membrane receptor activity may be strongly influenced by genetic factors even in people who do not have a gene for autosomal dominant hypercholesterolemia. The relevance, if any, of this finding to CHD in the general population needs to be clarified.

INFLUENCE OF MARKER GENOTYPES ON ENVIRONMENTALLY CAUSED VARIABILITY IN LIPID AND LIPOPROTEIN PARAMETERS

Since any difference between two MZ twins must be caused by environmental or nutritional factors, a possible "restrictive" or "permissive" effect of a given gene on the variability could be detected by comparing MZ pairs possessing the gene with pairs lacking it. If a gene were found to be associated with a low level of intrapair difference, it could be considered to have a restrictive effect with respect to environmentally or dietary caused variation.

This new approach, which has been reported by Magnus and his coworkers from our group [6], is obviously of interest far beyond parameters associated with atherosclerotic disease. Any quantitative parameter correlated with a given disease that exhibits evidence for genetic predisposition could be examined. Suffice it to mention uric acid and plasma insulin, or insulin and glucose response to a glucose load.

In the first study where this method was applied [6], 97 MZ pairs were analysed with respect to ten genetic marker systems and serum total cholesterol level. Significant findings were made with respect to the MNSs blood group system and suggestive findings were made with respect to the Kidd blood group system.

The within-pair difference was much smaller in MZ pairs possessing the M allele than in MZ pairs lacking it, the difference being significant at the 0.001 level. There was no significant difference in mean level of cholesterol or in total variance between MZ pairs with or without the M allele.

Although the general usefulness of the method was considered far more interesting than the finding concerning total serum cholesterol, we cautiously concluded that the M allele in the MNSs blood group system may have a restrictive effect on environmentally caused variation in serum cholesterol. There was an obvious need for further studies. Fabsitz et al [4] have reported an insignificant trend in the same direction and Martin et al [8] have made findings that support our conclusion, employing more sophisticated sta-

Table 5 - Mean Within-Pair Difference (Δ) in Fasting Serum Triglyceride Level in MZ Twins Grouped According to Phenotype in the Rhesus System (Z Scores of ln Transformed Values)

Genotype	No. of pairs	Δ
rr	5	1.04
R_1r	32	0.68
R_1R_1	16	0.75
R_2r	13	1.28
R_1R_2	9	0.89
R_0r	1	0.08
R_2R_2	1	2.99
Total	77	0.86

F = 2.80; P = 0.017

Table 6 - Mean Within-Pair Difference (Δ) in Serum ApoA-I Level in MZ Twins Grouped According to Phenotype in the Rhesus System (Z Scores of ln Transformed Values)

Genotype	No. of pairs	Δ
rr	8	0.54
R_1r	36	0.62
R_1R_1	20	0.71
R_2r	16	0.70
R_1R_2	15	1.21
R_0r	1	1.05
R_2R_2	1	0.12
Total	97	0.73

F = 2.23; P = 0.047

Table 7 - Mean Within-Pair Difference (Δ) in Fasting Serum Triglyceride Level in MZ Twins Grouped According to ADA Genotype (Z Scores of ln Transformed Values)

ADA genotype	No. of pairs	Δ
1 - 1	69	0.78
2 - 1	8	1.62
Total	77	0.86

F = 9.51; P = 0.003

Table 8 - Mean Within-Pair Difference (Δ) in Serum ApoA-I Level in MZ Twins Grouped According to ADA Genotype (Z Scores of ln Transformed Values)

ADA genotype	No. of pairs	Δ
1 - 1	89	0.77
2 - 1	8	0.32
Total	97	0.73

F = 4.12; P = 0.045

Table 9 - Mean Within-Pair Difference (Δ) in Serum ApoA-II Level in MZ Twins Grouped According to AcP Type (Z Scores of ln Transformed Values)

AcP type	No. of pairs	Δ
A	12	0.89
B	29	0.59
AB	44	0.58
AC	4	0.14
BC	7	0.35
Total	96	0.58

F = 2.60; P = 0.030

Table 10 - Mean Within-Pair Difference (Δ) in Serum ApoA-II Level in MZ Twins Grouped According to MNSs Genotype (Z Scores of ln Transformed Values)

Genotype	No. of pairs	Δ
MNss	22	0.31
MNSs	21	0.60
MNSS	4	0.87
MMss	9	0.72
MMSs	18	0.73
MMSS	2	1.41
NNss	13	0.69
NNSs	8	0.47
Total	97	0.60

F = 2.16; P = 0.045

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tistics. Despite the lack of significance of the data of Fabsitz et al [4], it seems intriguing that three different studies have all shown the same trend, and significantly so in two of them. Thus, the possibility remains that the M gene may have a restrictive effect on environmentally or dietary caused variation in total serum cholesterol.

The suggested effect of genes belonging to the Kidd blood group system is likely to have been a chance event since the two additional studies mentioned failed to detect this effect.

In our data, we found no evidence for an effect of genes belonging to either the MNSs or the Kidd system on variation in fasting serum triglycerides.

POSSIBLE MARKER GENE CONTROL OF TRIGLYCERIDE AND apoA-I VARIABILITY

We have recently conducted analyses of possible marker gene effects on intrapair variation in MZ twins with respect to triglycerides, apoB, apoA-I and apoA-II. For these analyses, z score of ln transformed values were used for the lipid and lipoprotein parameters. Table 5 shows the results concerning triglycerides and the Rhesus blood group system. Fasting triglycerides in our sample of 77 MZ twin pairs exhibited differences between genotypes with respect to intrapair variation. Although the numbers are small, the difference between R_1r and R_2r is statistically significant, suggesting a restrictive effect of R_1 and a permissive effect of R_2.

There is a negative correlation between serum triglycerides and high density lipoprotein (HDL). Table 6 shows the intrapair differences in the main apoprotein of high density lipoprotein, apoA-I, according to Rhesus type. Rhesus genotypes differ with respect to intrapair difference, each one of the first four phenotypes in the table being significantly lower than the fifth genotype. Because of the small numbers, the data must be interpreted with great caution. Nevertheless, there was a significant difference between pairs who have and those who lack the E antigen in the Rhesus system, those lacking this component having the smaller within-pair difference (suggesting that E has a "permissive" effect).

One more marker system, the adenosine deaminase (ADA) polymorphism, may possibly influence within-pair difference in triglycerides and apoA-I. Table 7 shows the data for fasting serum triglycerides and the ADA polymorphism. The difference between the two genotypes observed in our twin series in within-pair difference is highly significant.

Table 8 shows data on apoA-I level and the ADA polymorphism. The difference between the two genotypes observed is statistically significant.

If the findings in the Rhesus system and the ADA polymorphism reflect gene effects on fasting triglycerides and apoA-I, at least two different genetic systems, each affecting triglyceride level as well as apoA-I level, would have to be involved, since the Rhesus locus is on chromosome 1 and the ADA locus is on chromosome 20.

GENETIC MARKERS AND VARIATION IN apoA-II LEVEL

The second apoprotein typical of HDL, apoA-II, also exhibited variation in mean within-pair difference in a way compatible with an influence of marker genes. Table 9 shows the intrapair difference in various genotypes in the acid phosphatase polymorphism. The variation is statistically significant and the data could be interpreted as the result of a

Table 11 - Mean Within-Pair Difference (Δ) in Serum ApoA-II Level in MZ Twins, According to Presence or Absence of Genes in the MNSs Blood Group System (Z Scores of ln Transformed Values)

Gene	Δ for pairs with gene (n)	Δ for pairs without gene (n)	P
M	0.60 (76)	0.60 (21)	ns
N	0.52 (68)	0.78 (29)	0.037
S	0.68 (53)	0.50 (44)	ns
s	0.57 (91)	1.05 (6)	0.035

Table 12 - Lipid and Lipoprotein Parameters in Individuals Belonging to a Norwegian Twin Series, According to Lp Phenotype (Z Scores of ln Transformed Values)

Phenotype	Parameter	No. of persons	Mean
Lp (a+)	Colesterol	47	0.139
Lp (a−)	Cholesterol	180	− 0.058
Lp (a+)	Triglycerides*	33	0.349**
Lp (a−)	Triglycerides*	147	− 0.088**
Lp (a+)	ApoA-I level	46	0.276**
Lp (a−)	ApoA-I level	179	− 0.081**
Lp (a+)	ApoA-II level	46	0.164
Lp (a−)	ApoA-II level	179	− 0.050
Lp (a+)	ApoB level	46	0.111
Lp (a−)	ApoB level	177	− 0.014

* Fasting
** $0.02 < P < 0.05$

Table 13 - Mean Within-Pair Difference (Δ) in Various Lipid or Lipoprotein Parameters, in MZ Twin Pairs Grouped According to Lp Phenotype (Z Scores of ln Transformed Values)

Phenotype	Parameter	No. of pairs	Δ
Lp (a+)	Cholesterol	73	0.816
Lp (a−)	Cholesterol	19	0.723
Lp (a+)	Triglycerides	56	1.001
Lp (a−)	Triglycerides	16	0.797
Lp (a+)	ApoA-I level	73	0.609
Lp (a−)	ApoA-I level	19	0.799
Lp (a+)	ApoA-II level	73	0.702
Lp (a−)	ApoA-II level	19	0.561
Lp (a+)	ApoB level	72	0.684
Lp (a−)	ApoB level	19	0.550

restrictive effect of the C allele on environmentally or dietary caused apoA-II variation.

Table 10 shows mean within-pair difference in serum apoA-II level in MZ twins grouped according to the MNSs genotype. The variation between genotypes is statistically significant. In Table 11, within-pair difference in serum apoA-II level is analysed with respect to presence or absence of each of the genetic factors M, N, S, s. At face value, the data seem to suggest a restrictive effect on environmentally caused apoA-II variation of N and s. In both cases the finding is of borderline significance.

If the findings concerning apoA-II level were to reflect marker gene effects on apoA-II variability, two different genetic systems would have to be invoked as the explanation, since the locus for acid phosphatase variation is on chromosome 2 whereas the MNSs locus is on chromosome 4.

MEAN WITHIN-PAIR DIFFERENCES IN LIPID OR LIPOPROTEIN LEVELS, AND THE LP AND AG POLYMORPHISMS

In this study, the samples were also analysed with respect to the lipoprotein polymorphisms Lp and Ag (for review, see ref. 3). It is known from other studies that the Lp phenotype has a small effect on total serum cholesterol and apoB level and also in the present series there was a suggested difference in cholesterol and apoB level in the expected direction (Table 12). These differences were not significant. However, significant differences were found with respect to ApoA-I and triglyceride levels. This result must be interpreted with great caution since triglycerides have not been significantly associated with Lp phenotype in other series examined by us.

Table 13 shows mean within-pair difference in various lipid or lipoprotein parameters in MZ twin pairs grouped according to Lp phenotype. In no case did Lp phenotype yield a significant difference, but the series is relatively small and some of the observed differences should be checked in a more extensive twin series.

In previous studies, a significant association was found in middle aged and older population groups between Ag(x) phenotype and cholesterol as well as triglyceride level, the higher level of both lipids being found in Ag(x–) persons (for review, see ref. 3). Also in this series there was a trend in the expected direction, but the differences were not statistically significant (Table 14).

Table 15 shows mean within-pair difference in various lipid or lipoprotein parameters in MZ twin pairs grouped according to Ag phenotype. There is a significant difference between Ag(x+) and Ag(x–) pairs with respect to fasting triglyceride level. At face value, this would suggest that presence of the Ag^x gene has a permissive effect on triglyceride variation. As mentioned, other studies have shown a significantly higher triglyceride level in Ag(x–) than in Ag(x+) persons and the present data could indicate that less triglyceride variability in response to environmental or dietary factors, is possible in Ag(x–) than in Ag(x+) individuals. Thus, it may appear that Ag(x–) persons are assigned a higher triglyceride level than Ag(x+) persons and have only limited possibilities to react to environmental or dietary stimuli by changing their triglyceride level. The relevance, if any, of this finding to familial clustering of people with moderately increased triglyceride level remains to be elucidated.

Table 14 - Lipid and Lipoprotein Parameters in Individuals Belonging to a Norwegian Twin Series, According to Ag Phenotype (Z Scores of ln Transformed Values)

Phenotype	Parameter	No. of persons	Mean
Ag (x+)	Cholesterol	105	− 0.132
Ag (x−)	Cholesterol	132	0.106
Ag (x+)	Triglycerides*	83	− 0.042
Ag (x−)	Triglycerides*	106	0.032
Ag (x+)	ApoA-I level	104	0.082
Ag (x−)	ApoA-I level	131	− 0.066
Ag (x+)	ApoA-II level	104	0.027
Ag (x−)	ApoA-II level	131	− 0.021
Ag (x+)	ApoB level	104	− 0.054
Ag (x−)	ApoB level	130	0.042

* Fasting

Table 15 - Mean Within-Pair Difference (Δ) in Various Lipid or Lipoprotein Parameters, in MZ Twin Pairs Grouped According to Ag Phenotype (Z Scores of ln Transformed Values)

Phenotype	Parameter	No. of pairs	Δ
Ag (x+)	Cholesterol	46	0.680
Ag (x−)	Cholesterol	51	0.764
Ag (x+)	Triglycerides	38	1.047*
Ag (x−)	Triglycerides	39	0.685*
Ag (x+)	ApoA-I level	46	0.657
Ag (x−)	ApoA-I level	51	0.803
Ag (x+)	ApoA-II level	46	0.648
Ag (x−)	ApoA-II level	51	0.554
Ag (x+)	ApoB level	46	0.577
Ag (x−)	ApoB level	50	0.574

* P = 0.040

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ON THE SIGNIFICANCE OF APPARENT MARKER GENE INFLUENCES ON LIPID AND LIPOPROTEIN VARIABILITY

The analyses (including those reported previously) comprised 17 loci and 5 lipid or lipoprotein parameters (total serum cholesterol concentration, apoA-I level, apoA-II level, apoB level, fasting triglyceride level). Thus, analysis of variance was conducted 85 times and outcome significant at the 5% level would therefore be expected to result from chance alone in approximately 4 cases (or in 1 case at the 1% level of significance). The significant test results reported here (a total of 7) together with the previously reported results [1] concerning the MNSs and Kidd systems in relation to cholesterol, bring the total number of significant results to 9. In addition, the analysis of variance came out significant also for the PGM1 system with respect to cholesterol. The total number (10) of significant test results is thus higher than expected by chance alone. In addition, significant results of single factor analyses were obtained in 4 marker systems, but they are for the time being disregarded since the variance analysis that included all genotypes did not yield a significant result.

At this stage, the result of the variance analysis concerning the PGM1 and cholesterol is not presented, because the intrapair difference in cholesterol was lower in heterozygotes than in both types of homozygotes. Thus, they could not reflect a restrictive effect of one gene and a permissive effect of its allele. It should be emphazised, however, that one homozygous category consisted of only two twin pairs and there is therefore a need to explore this problem further.

It seems plausible that some of the variance analyses that yielded a significant result reflect true biological phenomena. The previously reported effect of genes in the MNSs system on cholesterol variability exhibited the highest level of significance. Of the results that are reported here for the first time, the apparent effect on genes belonging to the Rh and ADA systems on fasting triglyceride level, together with the apparent effect of genes in the acid phosphatase polymorphism on apoA-II variability, seem to be of particular interest.

Despite the possibility that at least some of the significant results reflect true biological phenomena, it must be emphasized that the reported findings must be interpreted with great caution. It is possible that most, if not all, of the findings are chance events. We consider the present results merely as early suggestions of potentially interesting biological effects. Their importance lies in the tentative hypotheses one may base on them, with the aim to seek confirmation or rejection in more extensive series.

Because of the limited size of the present series, important relationships may have been overlooked. Some of the non-significant differences observed could well turn out to be significant in very large series.

There are alternative ways to do the computations which follow from the fundamental idea that marker gene effects on quantitative parameters can be detected by the study of within-pair differences in MZ twin pairs possessing, versus those lacking, the marker gene in question. Martin et al [8] have made several useful suggestions in this connection and also estimated the size of twin series needed for more conclusive studies.

If the analyses that yielded significant results did in all cases reflect a true marker gene effect on environmentally or dietary caused variation in the parameters studied, loci participating in the control of lipid and lipoprotein variability would seem to be present on chromosomes 1, 2, 4 and 20. In addition, the LDL cell membrane receptor locus is on chromosome 19.

The present approach to the study of gene-environment interaction is likely to become very useful, as a great number of restriction fragment length polymorphisms in DNA become available for study. We are, for example, studying linkage relationships of chromosome 19 loci, with a DNA probe for the C3 locus, developed by Dr. Fey. Additional chromosome 19 probes will be of great interest since at least two loci (the locus for familial hypercholesterolemia with xanthomatosis and the apoE locus) involved in lipoprotein metabolism or structure is on that chromosome (Berg et al in preparation). The relationships suggested by the present study may be further examined by DNA probes detecting restriction fragment lenght polymorphisms on chromosomes 1, 2, 4 and 20.

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Correspondence: Professor Kare Berg, M.D., Institute of Medical Genetics, University of Oslo, P.O. Box 1036, Blindern, 0315 Oslo 3, Norway.