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ARTICLE

Genetic control of lipoprotein(a) concentrations is different in Africans and Caucasians

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Lipoprotein(a) (Lp(a)) represents a quantitative trait in human plasma associated with atherothrombotic disease. Large variation in the distribution of Lp(a) concentrations exists across populations which is at present unexplained. Sib-pair linkage analysis has suggested that the *apo(a)* gene on chromosome 6q27 is the major determinant of Lp(a) levels in Caucasians. We have here dissected the genetic architecture of the Lp(a) trait in Africans (Khoi San, South African Blacks) and Caucasians (Austrians) by family/sib-pair analysis. Heritability estimates ranged from h^2 = 51% in Blacks, h^2 = 61% in Khoi San, to h^2 = 71% in Caucasians. Analysis by a variance components model also demonstrated that the proportion of the total phenotypic variance explained by genetic factors is smaller in Africans (65%) than in Caucasians (74%). Importantly the sib-pair analysis clearly identified the *apo(a)* gene as the major locus in Caucasians which explained the total genetic variance. In the African samples the *apo(a)* gene accounted for only half the genetic variance. Together with previous results from population studies our data indicate that genetic control of Lp(a) levels seems to be distinctly different between Africans and Caucasians. In the former genetic factors distinct from the apo(a) locus and also non-genetic factors may play a major role.

Keywords: lipoprotein(a); apolipoprotein(a); family analysis; sibpair analysis; heritability; quantitative genetic trait; Caucasians; Africans

Introduction

Lipoprotein(a) (Lp(a)) is an unusual quantitative genetic trait in humans with over 1000-fold concentration differences among individuals and marked differences across populations.[1,2] High plasma levels of Lp(a) are a major susceptibility factor for atherothrombotic disease (coronary heart disease, stroke) in Caucasians and Asians.[3–6] Understanding the genetic control of Lp(a) levels may therefore have practical implications. Whether Lp(a) is also a risk factor in Blacks is at present controversial.[7,8]

Lp(a) is a complex assembled from low density lipoprotein (LDL) and the plasminogen-related apolipoprotein(a). Like plasminogen apo(a) contains a 5' signal sequence, a 3' protease domain and so-called Kringle domains.[9] Ten different types of Kringle IV domains are present in apo(a), one of which (type K IV-

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2) exists in variable numbers in individual alleles (K IV variable number of repeats = K IV VNTR). Twin, family and sib-pair analysis in Caucasians have suggested that the large variability in Lp(a) plasma concentrations is highly heritable with h^2 estimates in the order of 93–99%[10–12] and almost entirely determined by the apo(a) locus on chromosome 6q27.[13,14] Three studies have concluded that this locus explains > 90% of the phenotypic variability in Lp(a) plasma concentration in Caucasians.[11,12,15] An inverse correlation of K IV repeat number with Lp(a) levels exists in all populations analysed so far. The K IV VNTR alone explains 30–70% of the variability in Lp(a) levels across populations depending on the population and the type of analysis.[16–18] There are, however, notable differences in the Lp(a) plasma concentrations as well as in the relation of the K IV VNTR and other intragenic variation to Lp(a) levels across ethnic groups.[19] Lp(a) concentrations are about two to threefold higher in African and American Blacks than in Caucasians. This is neither explained by differences in K IV VNTR frequencies among populations[16,17,20] nor by known differences in other polymorphisms and at present remains unexplained. The extent to which Lp(a) levels are genetically determined in Africans is also unknown. Recently a study of African Americans showed that 78% of the variability is due to polymorphisms at or close to the apo(a) locus[21] but data on African Blacks or other aboriginal African populations are still lacking. Several observations might suggest that the control of Lp(a) levels in Africans could be in part different in nature from that in Caucasians. The association of the K IV VNTR with Lp(a) levels is considerably weaker in Blacks than in Caucasians or Asians[16,18] and explains significantly less of the phenotypic variability in Lp(a) concentrations. Lp(a) concentrations associated with K IV VNTR alleles of identical size are also different between ethnic groups.[16] A pentanucleotide repeat polymorphism at –1.4 kb in the 5' region of the *apo(a)* gene is associated with Lp(a) levels in Caucasians but not in Africans[19] and a C/T polymorphism at +93 affects Lp(a) in Africans but not in Caucasians.[22] In the present study we have used a family and sib-pair approach to analyse to what extent Lp(a) levels are genetically determined in Africans (South African Blacks and Khoi San) and whether there is any contribution of the apo(a) locus beyond the effect of the K IV VNTR in the African populations. We further have reanalysed our previously published Caucasian families[12] using the same methodology as for the Africans in order to see whether or not differences exist among these major human groups.

Materials and Methods

Subjects

EDTA blood was drawn from apparently healthy family members stemming from three populations (Caucasians from Austria, Khoi San and Blacks from South Africa). The Austrian samples (51 families, constituting 63 nuclear families, 221 individuals) have been described previously.[12] The Khoi San sample consisted of 25 nuclear families with 112 individuals which were collected in an area of the Northern Cape Province, called Schmidtsdrift.[23] Samples from 67 Black families including 270 individuals were obtained from the North-West Province of South Africa. All the Black families belonged to the Tswana people and lived in a rural environment. An aliquot (1 ml) of the African specimen was centrifuged to obtain plasma and both, blood and plasma were immediately frozen at –20°C. All the samples were shipped on dry ice to Innsbruck for further analysis.

Lp(a) Concentration

A sandwich type ELISA[24] was used to determine the Lp(a) plasma levels. Care was taken that plasma specimen of members from the same family were all thawed on the same day and analysed on the same ELISA plate.

Apo(a) Genotyping

The number of K IV repeats in the apo(a) allele were determined using pulsed field gel electrophoresis/Southern blotting exactly as described.[12,16] The number of TTTTA repeats in the 5' flanking region (Pentanucleotide repeat polymorphism–PNRP) was determined by a PCR-based technique.[19] The apo(a) alleles leading to a Met or Thr in K IV type 10 (codon 4168 in the apo(a) cDNA[9]) were analysed as published previously.[25]

Statistical Methods

Allele frequencies of the three polymorphisms in the apo(a) gene were estimated by allele counting in unrelated individuals from the three populations. Where two populations were pooled for the analysis, the allele frequencies were also estimated from the combined sample. The distribution of Lp(a) concentration was highly skewed in these data. This is a known phenomenon for Lp(a) concentrations. Thus Lp(a) levels were natural-log-transformed (ln) prior to analysis. A square-root transformation was found not to be justified as indicated by classical regression diagnostics.

Two different strategies were applied to identify the interindividual variability for Lp(a) concentrations due to genetic components and due to the apo(a) locus in particular: midparent–offspring regression and a variance components approach. Midparent–offspring regression allowed the estimation of the heritability from the slope coefficient of the linear regression of mean ln Lp(a) of offspring on mean ln Lp(a) of the parents.[26] Here the natural-log-transformation was necessary to make the regression valid. The heritability h^2 measured by this approach is the contribution of the overall additive genetic variance to the phenotypic variance. To account for the different sibship sizes in the families offspring

means were weighted with a factor containing the intra-class correlation coefficient *t*.[26] The intra-class correlation coefficient *t* has been calculated by a random effects analysis of variance.[27] Since families were a random sample from the population it was appropriate to consider the effect of belonging to the same family as a random effect of this population.

To make also use of the available genetic information on the apo(a) K IV VNTR a components of variance approach was additionally applied to the nuclear family data. We used the method described by Amos.[28] Here the model for the *k*th family is represented by

$$y_{ik} = \mu + X_{ik}\beta + g_k + G_k + \varepsilon_k,$$

where y_{ik} is the observed vector of ln Lp(a) concentrations for the *i*th individual of family *k*, μ is the overall mean, X_{ik} is a vector of additionally observable covariates, G_k is a random polygenic and g_k the unobservable major gene effect for the *k*th family. Further we assume $G_k \sim (0, \sigma^2_G R_k)$ and $g_k \sim (0, \sigma^2_a \Pi_k)$. Thus, the variance–covariance matrix conditional on the identity by descent (IBD) sharing of relative pairs is partitioned as

$$\mathrm{Cov}(Y_i, Y_j|\pi_{ij}) = \begin{cases} \sigma^2_a + \sigma^2_G + \sigma^2_e \text{ if } i = j \\ \pi_{ij}\sigma^2_a + R_{ij}\sigma^2_G \text{ if } i \neq j \end{cases}$$

The expression π_{ij} is the estimated proportion of alleles IBD at the marker locus for the *i,j*th pair, R_{ij} is the kinship coefficient between relative pairs. In general the term σ^2_a represents the additive genetic variance due to a linked major locus, σ^2_G is the variance due to unlinked genetic factors or polygenes and σ^2_e represents the residual variance. Therefore, $\sigma^2_a + \sigma^2_G + \sigma^2_e$ will be denoted by σ^2_P and describes the total phenotypic variance. Further we assumed for this analysis that there is no dominance component of genetic variance, no genetic–environment interaction and a recombination fraction of $\theta = 0$. These assumptions are reasonable since it has been extensively demonstrated that the apo(a) locus is a candidate gene region for our trait of interest and, as stated,[28] a dominance component is generally negligible. Consequently σ^2_a represents the genetic variability due to a completely linked major locus, namely the apo(a) gene. Heritabilities were estimated from the ratio of σ^2_a/σ^2_P (narrow sense) and from the ratio of $(\sigma^2_a + \sigma^2_G)/\sigma^2_P$ (broad sense), respectively. The latter value of the heritability is comparable to the h^2 from the midparent–offspring regression.

A quasi-likelihood method was applied to estimate the variance components and with it the heritabilities. In simulation studies[29] this approach yielded better results than the usual Haseman-Elston method[30] in almost all circumstances, particularly when there was strong non-normality in the error structure, as in our dataset. Therefore the Haseman-Elston method was not considered here. Another advantage of the employed method was the possibility to incorporate additional covariates (eg age and sex) simultaneously. Estimates for the proportion of alleles IBD were obtained from the SIBPAL program of SAGE.[31] Simultaneous 95% confidence intervals for all ratios were calculated according to Fieller's theorem.[32]

Results

Lp(a) plasma levels and apo(a) genotype (number of K IV repeats in both apo(a) alleles) were determined in all family members from three populations (Khoi San and Blacks from South Africa and Caucasians from Austria). The distribution of the K-IV alleles in the three populations is shown in Figure 1 (only the parents were considered for this presentation). In the statistical analysis only those families and individuals were included in which the offspring apo(a) K IV VNTR matched the paternal K IV VNTR. In the African samples a large proportion of families/individuals had to be excluded due to non-paternity and also non-maternity. Tswana people have a different comprehension of 'family' compared with Caucasians. In addition to the genetic children the 'family' may include also children of one of the parents by another partner, or who have been adopted. Other apo(a) intragenic markers were used to confirm paternity for the remaining children. Mean age and sex ratio in the three population samples used for the analysis are given separately for parents and children in Table 1.

Midparent–Offspring Analysis

Heritability of Lp(a) Concentrations in Africans For estimating the heritability of Lp(a) concentrations by midparent–offspring regression analysis 55 Black South African nuclear families with a total of 105 children, and 22 Khoi-San nuclear families including 44 children, were available. In all families IBD status at the apo(a) locus was determined by the analysis of the K IV VNTR using PFGE/genomic blotting. Other intragenic polymorphisms (1.4 kb PNRP, K IV-10 M/T, C/T polymorphism in the 5' region[33]) were also analysed when the K IV polymorphism alone was not informative (data not shown). Lp(a) concentrations were determined in all individuals by ELISA. A basic description of Lp(a) levels and their distribution in the families is given in Table 1. In a first step regression analysis was performed using untransformed Lp(a) values (data not shown). Validation of the regression analysis using the residuals demonstrated that the requirements for linear regression are not fulfilled by the untransformed values. Therefore the heritabilities calculated on the basis of untransformed Lp(a) values cannot be used. Since the distribution of Lp(a) concentrations is skewed in the populations (Table 1) a transformation of Lp(a) values to natural log (ln) values appeared necessary and appropriate before the further analysis. After transformation the

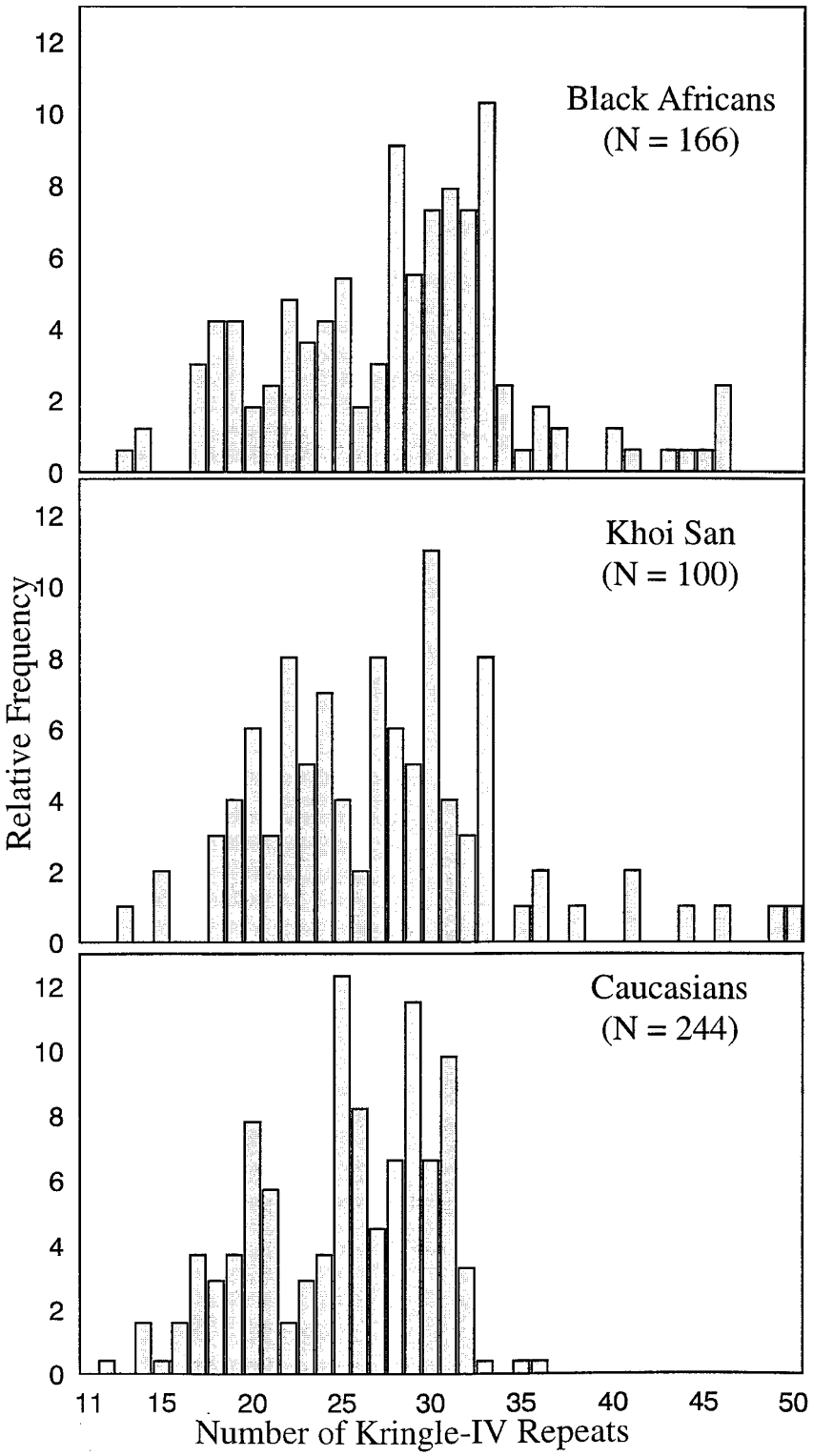

Figure 1 *Bar graphs showing the distribution of apo(a) K-IV alleles in the three study populations (only the parents were included). A* χ^2 *analysis shows that the distribution is significantly (*$P < 0.001$*) different between the three populations. The African population samples have higher frequencies of large and very large apo(a) alleles.*

distribution of ln Lp(a) concentrations was close to normal. The subsequent analysis demonstrated that the transformed data yielded better and more consistent results than untransformed values or square root Lp(a) transformed data (not shown). The calculated heritabilities are shown in Table 2. To adjust for differences in the number of children in families we next performed a weighted regression analysis.[27] The intraclass correlation coefficient *t* was calculated by random effect ANOVA. Thereby the heritability (h^2) of Lp(a) was estimated to be h^2 = 51% (SD 12%) in the Black South Africans and h^2 = 61% (SD 21%) in the Khoi San. Results of the h^2 analysis are shown in Table 2.

Heritability of Lp(a) Concentrations in Caucasians Using the same procedures we reanalysed our data set of 63 families from Tyrol (Austria). This resulted in a heritability estimate of 71% (SD 21%) by the weighted analysis of the ln transformed Lp(a) (Table 2).

Table 1 Lp(a) plasma levels in family samples of three populations

Population	*Austrians*	*Blacks*	*Khoi San*
Families (*n*)	63	55	22
Individuals (*n*)	221	216	89
Parents			
age (mean)	54.9	41.5	39.7
male/female	1/1	1/1	1/1
Lp(a) median (mg/dl)	10.0	13.9	33.0
IQD[a]	28.3	17.9	31.2
skewness	1.40	4.16	0.30
Offspring			
age (mean)	30.7	10.7	9.4
male/female	0.98/1	1.36/1	0.72/1
Lp(a) median (mg/dl)	8.45	10.2	23.2
IQD[a]	22.4	12.8	36.1
skewness	1.97	2.61	0.56

[a]IQD inter quartile distance = difference between the 75th and 25th quantile.

Sib Pair Analysis

For the next analysis we used a variance components model in combination with a quasi-likelihood estimation procedure.[28,29] This type of analysis was preferred over the classical Haseman-Elston (H-E) method because of the non-normal distribution of the residuals. All calculations were based on ln Lp(a) concentrations. The model allows for the estimation of σ_a^2 which is the variance linked to the apo(a) locus, σ_G^2 which is the variance contributed by a polygenic component and σ_E^2 which is the residual non-genetic variance. $(\sigma_a^2 + \sigma_G^2)/\sigma_P^2$ then defines the total genetic variance as a proportion of the total phenotypic variance as σ_a^2/σ_P^2 defines the fraction of explained phenotypic variance due to the apo(a) locus. Results are presented in Table 3.

Caucasians For our analysis we used different subsets of the Austrian families which included A) all nuclear families, B) all independent nuclear families to guarantee model assumptions and C) all independent nuclear families with typed parents. In the Black Africans and Khoi San only one type of these family sets was represented, ie all were independent nuclear families with parents typed for apo(a) alleles. In this case results are considered most reliable since they are not affected by estimates of allele frequencies for the apo(a) locus.

In the Austrian family sample results were very consistent across the different subsets. Independent of the family subset analysed 71% to 74% of the total phenotypic variance was explained by variation linked to the apo(a) gene locus. Notably the total genetic variance ($\sigma_a^2 + \sigma_G^2$) and the apo(a) linked genetic variance (σ_a^2) were identical in the different subsets. Thus there was no evidence for a polygenic component.

Table 2 Heritability of ln Lp(a) in three populations based on midparent–offspring regression analysis

Population	*Austrians*	*Blacks*	*Khoi San*	*pooled Africans*
unweighted regression				
h^2	0.65	0.65	0.52	0.73
SD (h^2)	0.20	0.13	0.22	0.11
weighted regression[a]				
t	0.43	0.13	0.12	0.20
h^2	0.71	0.51	0.61	0.65
SD (h^2)	0.21	0.12	0.21	0.10

[a]weighted regression was performed according to Falconer and MacKay, p179[26]; *t*: intraclass correlation coefficient estimated by random effects ANOVA; h^2: heritability; SD: standard deviation.

Rather the residual variability can be due to non-genetic/environmental factors.

The Caucasian sample included three families accounting for almost half of the sib pairs. Repeating the analysis without these families resulted in a lower but not significant estimate (49%) of the apo(a) linked variance which likely reflects fluctuation due to smaller sample size. The total genetic variance remained almost unchanged (67%).

Africans In both African samples, the South African Blacks and the Khoi San, approximately 64% (Table 3) of the phenotypic variability in ln Lp(a) levels was attributable to genetic factors (major gene and/or polygenes). The genetic component however, could not be identified. Though the analysis indicates that 33% (Blacks) and 34% (Khoi San) of the phenotypic variability in Lp(a) concentrations is explained by variation linked to the major locus apo(a) this is not significant (Table 3). Likewise the polygenic component (σ^2_G) was not significant. We therefore in a next step pooled the African families. Because of the differences we had detected between the two populations (Table 1) we introduced 'population' as a covariate into the analysis. Again the data revealed that a large fraction (74%) of the phenotypic variance is explained by genetic factors but the identity of the genetic component remained unclear despite the increased sample size. Although the point estimate proposes that about half the genetic variance is explained by the apo(a) locus, these data alone cannot exclude the alternative hypothesis that the apo(a) locus explains all the genetic variance or none of it.

Discussion

Lp(a) levels represent one of the most intriguing quantitative traits in humans the analysis of which has posed several challenges. As a risk factor for coronary heart disease, peripheral vascular disease, and stroke Lp(a) has also attracted much medical attention.

Previous studies have identified the *apo(a)* gene as a major locus controlling Lp(a) plasma concentrations and demonstrated an inverse correlation of transcribed and translated repeats in the *apo(a)* gene (*KIV VNTR*) with Lp(a) plasma concentrations. This relationship exists in every population studied so far. Molecular biology studies have demonstrated that the effect of the *KIV VNTR* on Lp(a) levels is direct and causal and exists also in non-human primates.[34] Hence this seems to be a basic mechanism underlying the genetic variation in Lp(a) concentrations in all human ethnic groups. Despite this similarity there exist also significant differences between human populations. Several studies have documented significantly higher average Lp(a) levels in Black populations as compared to Caucasians,[20,35–37] but the underlying mechanism(s) remained unclear. Differences in the frequency distribution of K IV VNTR alleles certainly do not explain Lp(a) level differences among populations.[16–18,20] As a correlary it has been measured that K IV VNTR allele associated Lp(a) concentrations are different in various

Table 3 Heritability of ln Lp(a) in three populations based on sib pair analysis using a variance component model

Population	*Subset*	*Families/sib-pairs*	σ^2_a/σ^2_P	$(\sigma^2_a/\sigma^2_G)/\sigma^2_P$	P-*value* (σ^2_A=0)
Austrians	A	63/256	74% [40%; 100%]	74% [42%; 100%]	<0.00001
	B	51/233	73% [36%; 100%]	73% [40%; 100%]	<0.00001
	C	27/154	71% [26%; 100%]	71% [32%; 100%]	0.00031
Blacks	C	55/76	33% [0%; 100%]	65% [35%; 95%]	0.27345
Khoi San	C	22/31	34% [0%; 100%]	63% [0%; 95%]	0.27994
pooled Africans	C	77/107	32% [0%; 97%]	74% [39%; 87%]	0.11259

σ^2_a: variance of additive genetic component due to major gene (apo(a)); σ^2_G: polygenic variance component; σ^2_P: phenotypic variance; 95% confidence intervals are given in brackets below the point estimates; Description of subsets: A: all nuclear families; B: independent nuclear families; C: independent nuclear families with apo(a) genotyping results in parents and children.

populations.[16] Further there exist differences in the strength of the negative association between Lp(a) levels and K IV repeats across populations and the fraction of the phenotypic variance attributed to the apo(a) size polymorphism in genetic epidemiological studies varies from a low of 28% in Sudanese to a high of 70% in Chinese.[18]

This raises the questions whether genetic effects beyond the apo(a) K IV VNTR exist in all populations and if so whether they are the same in different populations. Twin, family and sib pair linkage analysis using genotypic information of the apo(a) locus, which allows estimation of the total genetic contribution to the trait and also specifically the contribution of the apo(a) locus, have only been performed in Caucasians[11,12,15] and very recently in African Americans.[21] The present analysis of African and Caucasian families has yielded some new insights into the genetic control of Lp(a) levels. The most important is that the control of Lp(a) concentrations in Africans and Caucasians appears not to be the same.

The following relevant observations were made:

1) The contribution of genetic factors to Lp(a) concentrations is large in all populations (from about 50% to 70%);

2) In Caucasians this contribution is considerably less than previously estimated;

3) Whereas variation linked to the apo(a) gene explains virtually all the genetic contribution in Caucasians, this is not the case in Africans.

These conclusions are based on two types of analysis which gave remarkably consistent results. First, we calculated the heritability of Lp(a) levels by a weighted midparent–offspring regression. This resulted in heritabilities of h^2 is 71% for Caucasians, 51% for Black Africans, and 61% for Khoi San. Second, we analysed our data by a variance component model which allowed for the quantification of the total genetic variability, the estimation of additive genetic variability linked to the apo(a) locus (σ^2_a), and the variability due to polygenes (σ^2_G) as a fraction of the total phenotypic variability (σ^2_P) in Lp(a) levels. The proportion of the total phenotypic variability explained by undefined genetic variation was 71% in Caucasians, 65% in Blacks and 63% in Khoi San. Hence, both estimates of heritability h^2 and $(\sigma^2_a + \sigma^2_G)/\sigma^2_P$ gave very similar results in Caucasians and Khoi San and were in an acceptable agreement in Blacks.

Several of our data, some of which are at variance with previous results, need comment. The heritability of 71% in Caucasians, which according to our analysis is entirely due to the contribution of the apo(a) locus, is lower than in most previous studies which have estimated h^2 values of > 90% from twin analysis[10,38,39] and correlation among sibs.[11,12] Determination of h^2 by correlation analysis of sib data are generally too high and only yield an upper boundary for the estimate of heritability[26] (p 164). Both, shared environment and dominant genetic variance may increase the estimate in such analysis. Thus the h^2 estimate of 92%[12] was probably too high. Twin studies in general also result in an overestimation of heritability[26] (p 171). The estimate of 71% which we have obtained here also appears more realistic than the higher reported values in view of independent lines of evidence. Longitudinal studies suggest that individual variation in Lp(a) levels with time is larger than generally considered (unpublished 1998). Furthermore, diet[40,41] and hormones[42–44] may have a considerable impact on Lp(a) concentrations. We do not, however, ignore that the value of 71% estimated here is a point estimate with all previous published estimates lying within the range of its 95% confidence interval. Nevertheless, all previous point estimates were higher.[10–12,38,39]

The contribution of the apo(a) locus to Lp(a) level variability in Caucasians is also much less, being about 70% in the present analysis as opposed to > 90% in three previous studies.[11,12,15] Obviously the contribution to the phenotypic variability in Lp(a) levels of the apo(a) locus alone cannot be larger than the total genetic contribution. Boerwinkle *et al*[11] have calculated that > 91% of the variance in Lp(a) levels is explained by the apo(a) locus using a weighted Haseman-Elston (H-E) method. This method was not appropriate for our data set (see Amos[28]). Sibships with more than five sibs were present in the Tyrolean families. Whereas simulations by Amos *et al*[29] demonstrated that up to five sibs per family there is no apparent effect on the H-E analysis, data on sibships with > 5 are lacking. The most serious problem, which may arise if the H-E method is applied, is that the distribution of the residuals may significantly deviate from a normal distribution, eg towards a χ^2 distribution. For that case Amos *et al*[29] demonstrated that the H-E estimator is distorted and there exists a considerable loss of power. Therefore we preferred the method proposed by Amos *et al*.[28,29] Further, this method has the advantage of introducing covariates and using also the phenotypic

information of the parents. In addition to the covariate 'population' in the pooled data set we introduced sex and age as independent factors because of the detected differences between the populations. As in previous studies no influence of age and sex was found, and also the estimated heritability did not differ significantly.

We have nevertheless performed an H-E analysis of the Tyrolean family sample to compare our results with those of Boerwinkle *et al*.[11] According to this analysis 80% of the total phenotypic variability in our sample is explained by variation linked to the apo(a) locus. This value dropped to 66% when ln Lp(a) was used.

Together our data indicate that in Caucasians about 70% of the variability in Lp(a) levels is genetically determined and that the genetic component is entirely explained by the major locus apo(a). This should not be misinterpreted to mean that other genes and/or environmental factors may not have a significant impact on Lp(a) concentrations in certain subsets of the population. Examples for non-genetic effects are kidney failure[45] and for genetic effects disorders of lipoprotein metabolism including Abetalipoproteinaemia, familial LCAT deficiency, and familial defective apolipoprotein B.[46–48] The present analysis describes the situation in apparently healthy families/individuals.

We did not obtain unequivocal evidence that the *apo(a)* gene is a major locus for Lp(a) levels in Africans, unlike Caucasians. This finding is in obvious contrast to the results of Mooser *et al*[21] who concluded that the *apo(a)* gene is the major determinant of Lp(a) level variation in African Americans. Employing the standard H-E method[30] they detected that 78% of the variance in their sample are explained by the apo(a) locus. We have reanalysed their data using the variance components model. This did not change the result. Thus the discrepancy between their and our data is not explained by methodological differences. Rather it may have resulted from the different populations analysed. African Americans show admixture of Caucasian and other genes.[49,50] It should, however, be pointed out that also in the African Americans the contribution of the apo(a) locus to Lp(a) level variance was lower (78%) than in the respective Caucasian American sample ($> 90\%$).

The present analysis alone provides neither definitive data on the type nor the number of genes contributing to the heritability of Lp(a) in Africans. Overall the heritability was lower in Blacks than in Caucasians. Though our present data do not formally exclude the possibility that none of the genetic variance in Lp(a) levels in Africans is explained by the apo(a) locus this is excluded by population genetic studies[16,18] and cell culture experiments.[51] Large population studies based on apo(a) genotyping have shown that variation in the number of Kringle IV repeats in the *apo(a)* gene explains about 38% of the total phenotypic variance in Blacks and Khoi San.[16] In the present study 34% of the phenotypic variance was attributable to the apo(a) locus. This implies that also in Africans (Blacks, Khoi San) the KIV VNTR almost entirely explains the contribution of the apo(a) locus to the phenotypic variance in Lp(a) levels.

Moreover, this strongly suggests that the residual genetic contribution may be through variation in (an)other gene(s). We find it rather unlikely that the differences between Africans and Caucasians identified here are caused by differences in the number, size, and structure of analysed families (see Table 1). Thus other explanations are required. One might be the presence of environmental factors in African populations as recently proposed.[52] Another could be the existence of (a) transacting factor(s) in Africans. This has also been suggested by Mooser *et al*[21] for African Americans. It will be a challenge for the future to identify this/those gene(s) which presumably are responsible for the high Lp(a) in Africans. This may give further insight into the genetic regulation of Lp(a) concentrations and possibly may provide clues towards the development of drugs with the potential to reduce the concentrations of this risk factor for atherothrombotic disease.

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