

**MALD analysis of plasma Lp(a)
concentration and the apo(a) gene
in kidney failure patients**

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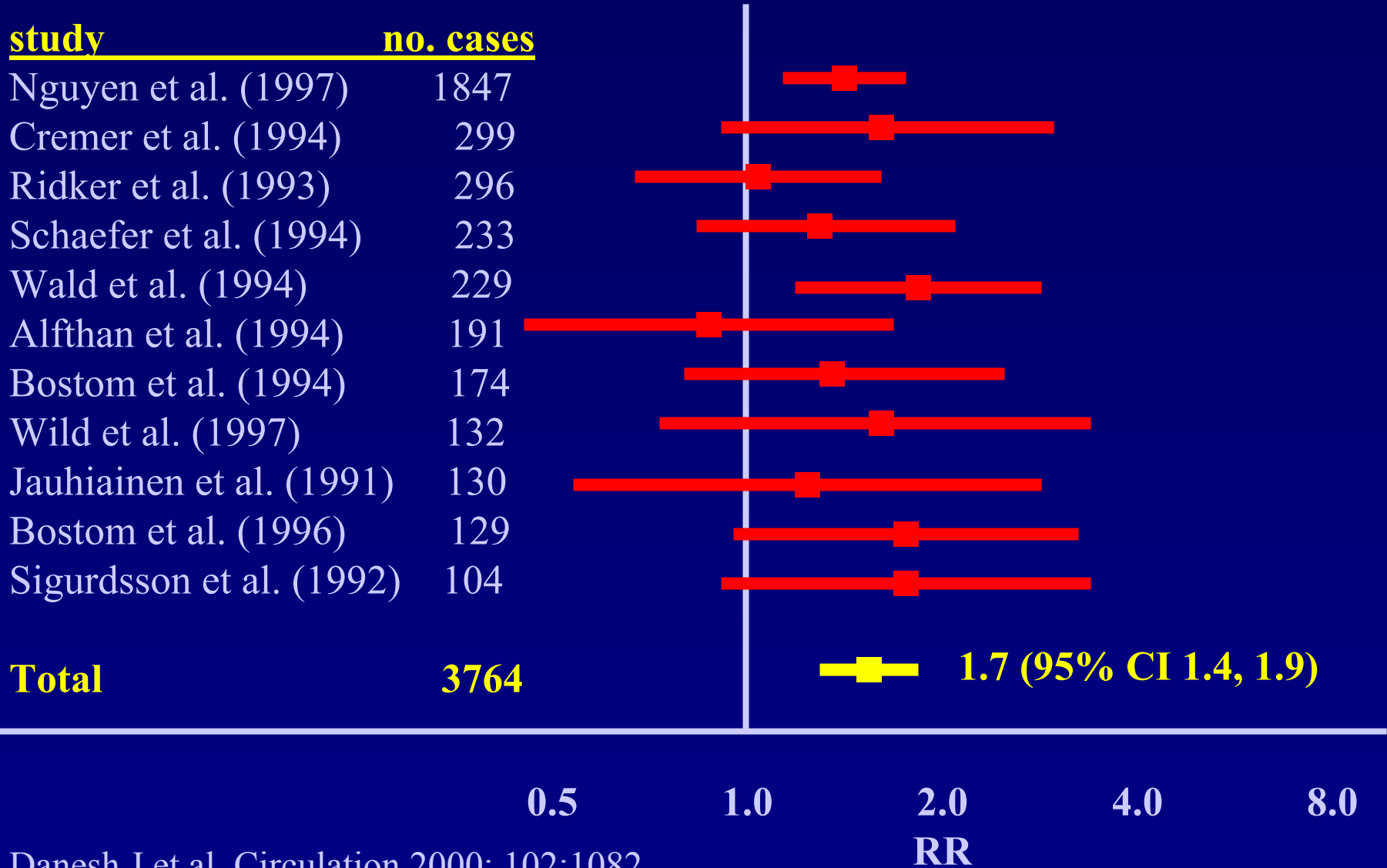
CHOICE Cohort Study

- Impact of dialysis management on outcomes and cost of care
- New dialysis patients enrolled 1995-1998
- Specimen bank: 262 AA and 569 EA
 - Lp(a), apo(a) isoforms
 - DNA

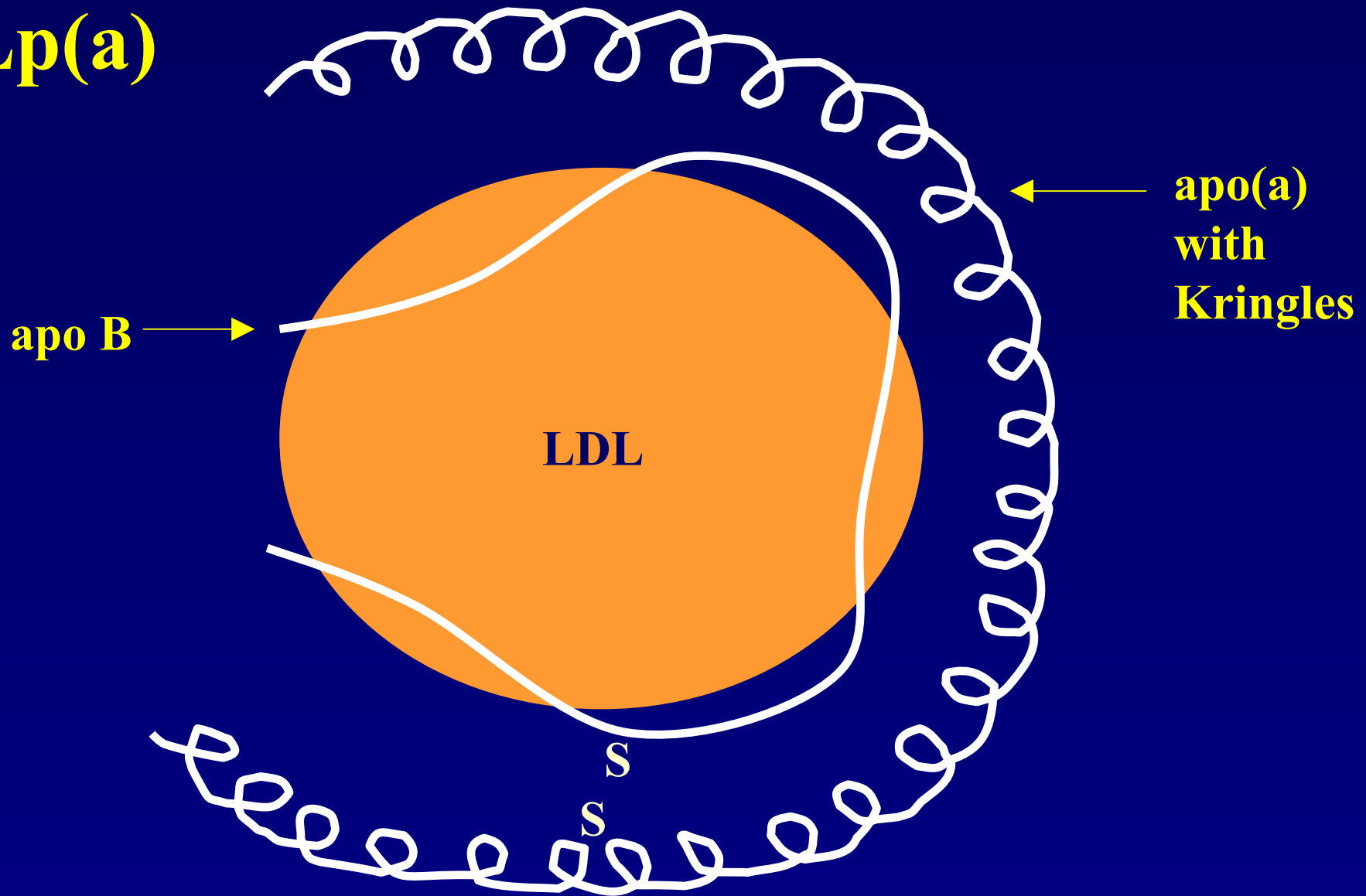
CHOICE baseline characteristics

Characteristic	Value (n=876)
Age (mean)	57.3
Race (%)	
EA	65
AA	30
Sex (% male)	53
Cause of RF (%)	
Diabetes	48
Hypertension	17
Other	35
Modality (% HD)	80
Prevalent CAD (%)	42

Meta-analysis of prospective studies of Lp(a) and CHD in the general population: highest versus lowest tertile

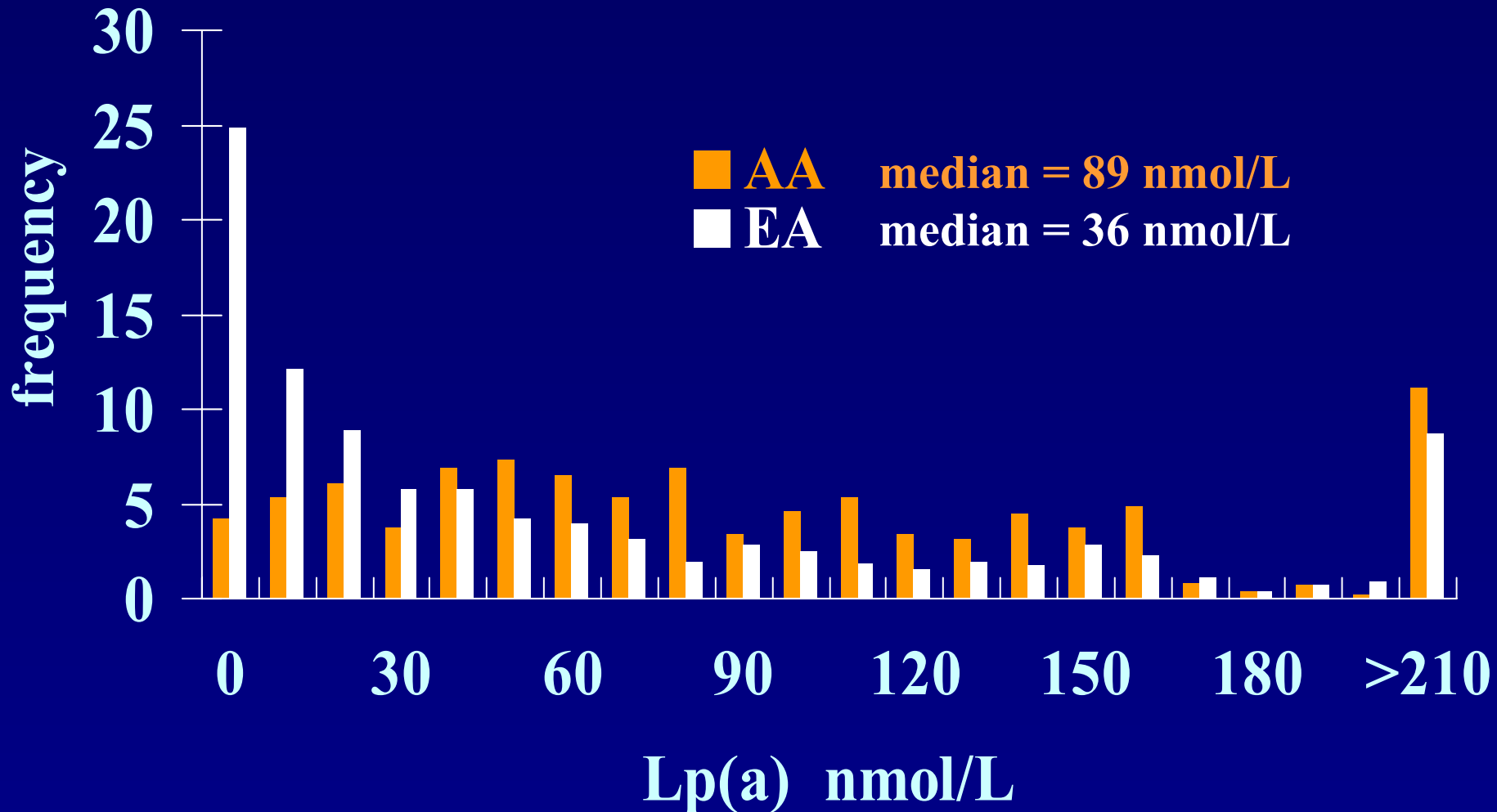


Lp(a)

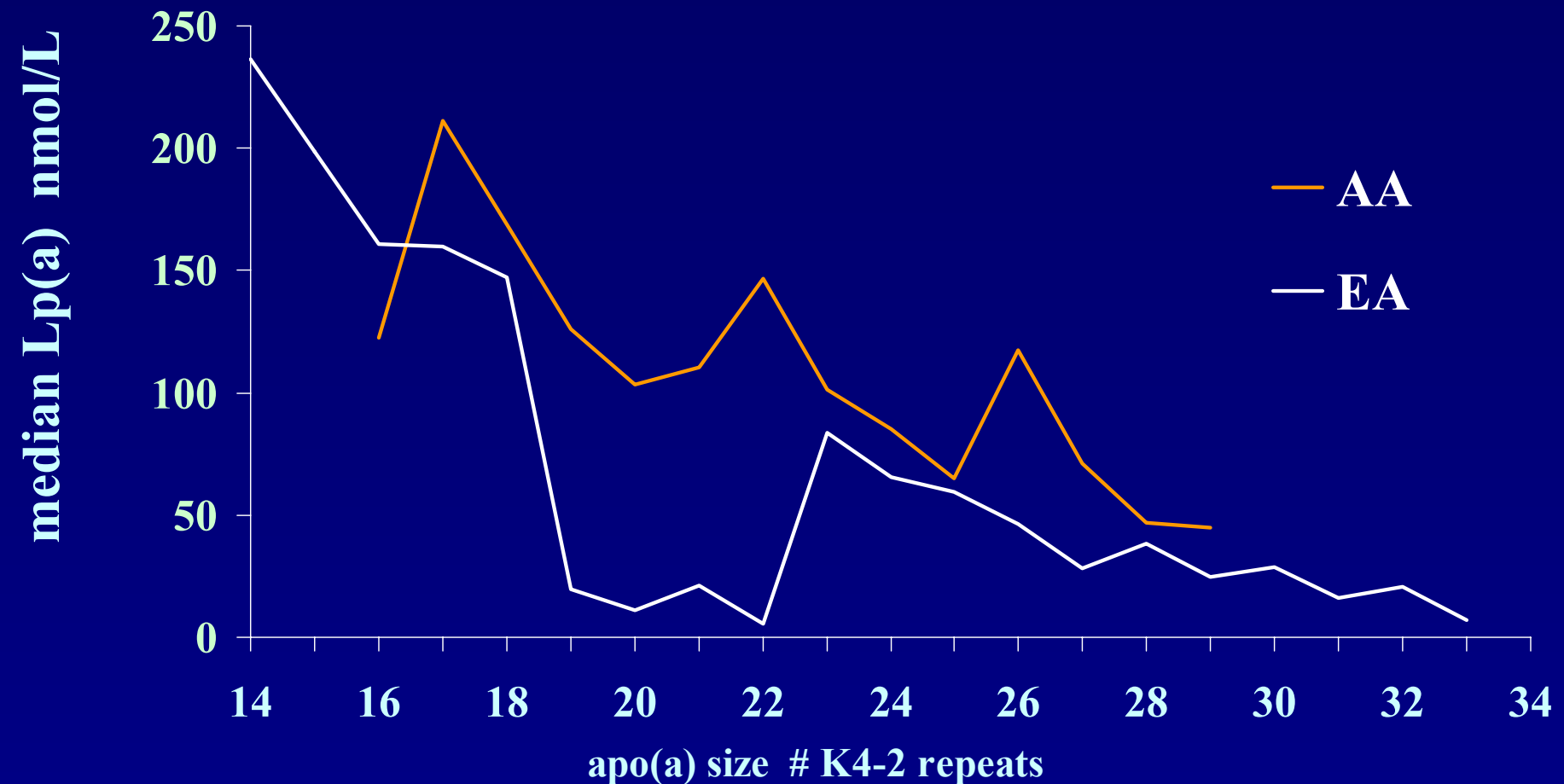


Adapted from Utermann G, Science 1989; 246:904

Lp(a) distribution in the CHOICE cohort (n=249 AA, 535 EA)

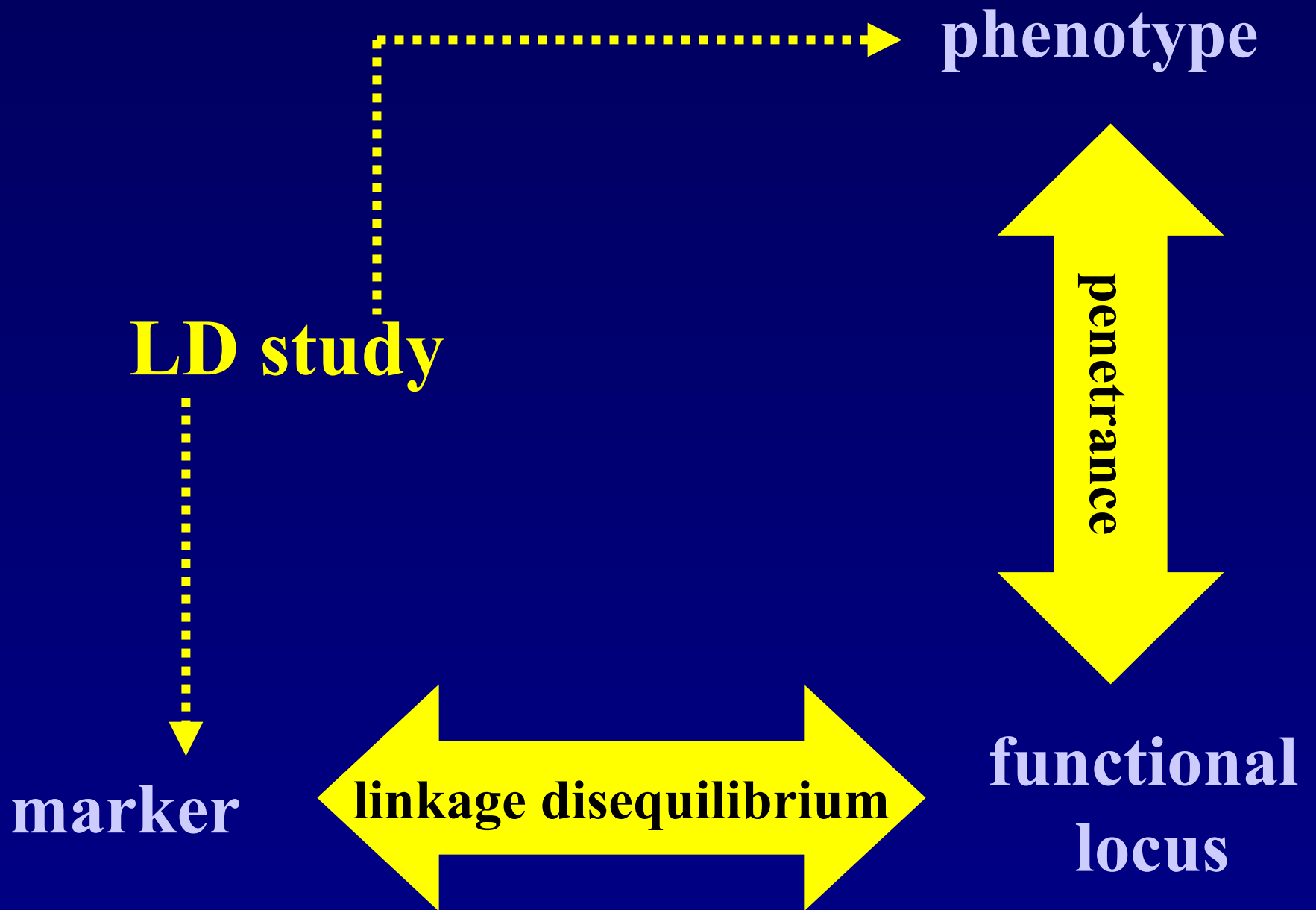


Median Lp(a) concentration and size of predominant isoform (n=249 AA, 535 EA)



Genetic control of Lp(a) concentration

Population	Lp(a) variance explained by apo(a)	
	size (#studies)	other seq. (#studies)
EA	43% (7) CHOICE: 37%	48% (3)
AA	53% (1) CHOICE: 40%	25% (1)



Populations with more LD

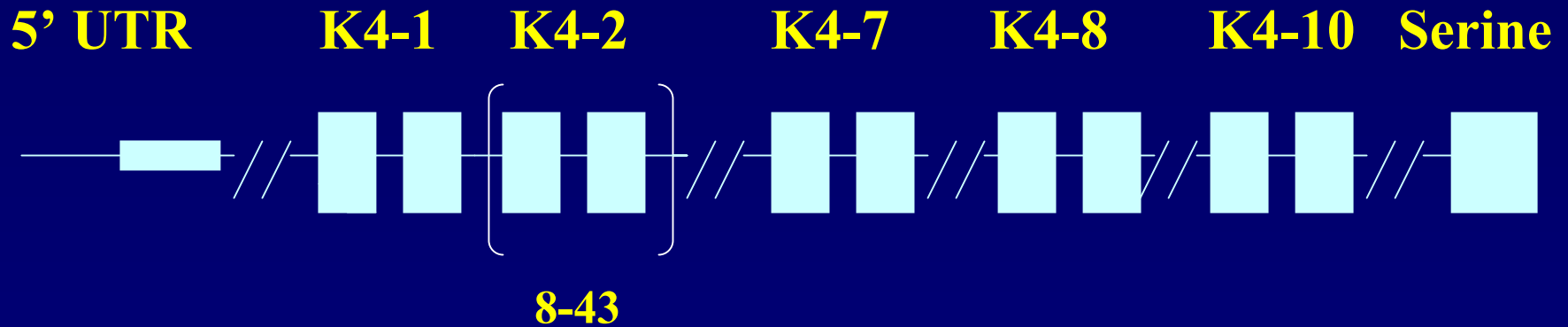
- Isolated populations (founder effects)
- Unexpanded populations (genetic drift)
- Admixed populations

Admixture Linkage Disequilibrium

If sequences linked to apo(a) explain the ethnic difference in Lp(a), then we expect:

- **Marker - Lp(a) association in AA:**
 - genotypes more common in AA: Lp(a) \uparrow in AA
 - genotypes more common in EA: Lp(a) \downarrow in AA
- **No such association in EA**

apolipoprotein(a) locus



6q26-27

-10 cM

15 cM

D6S1633

D6S419

D6S1655

D6S437

D6S1581

PNRP

D6S305

D6S1550

D6S1579

D6S264

D6S1719

MALD analysis

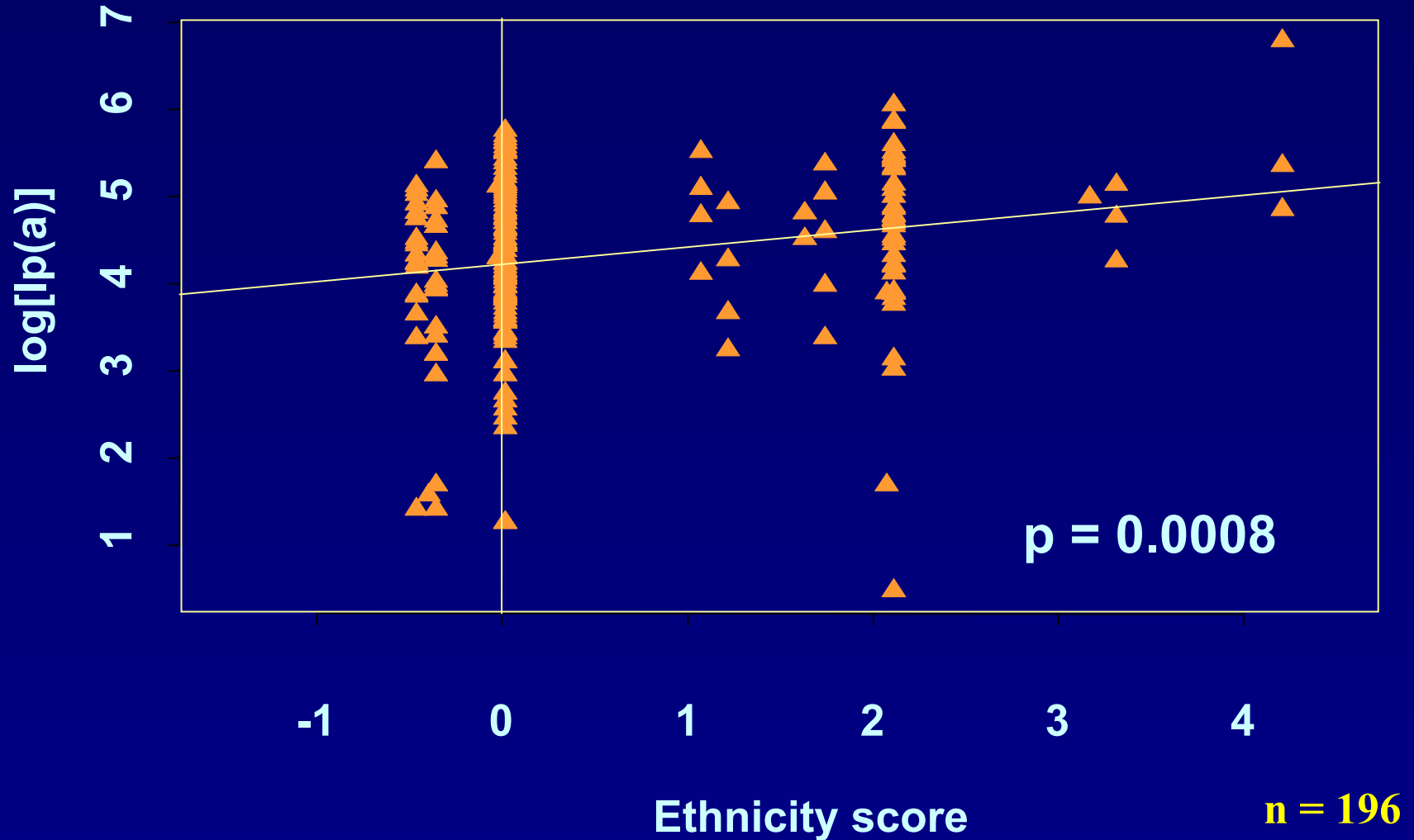
“ Ethnicity score” for individual with genotype $x,y =$

$$\log \left[\frac{AAx * AAy}{EAx * EAy} \right]$$

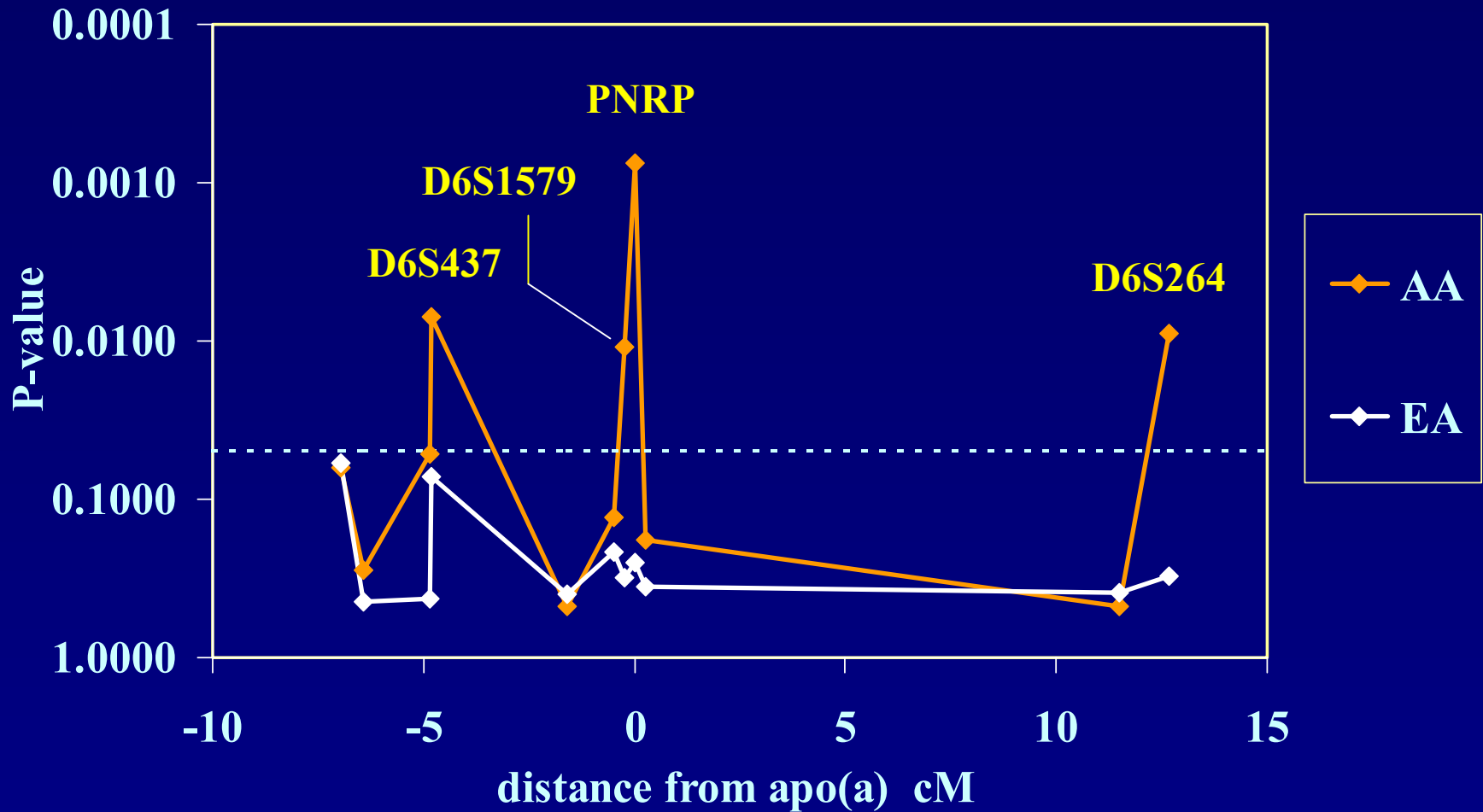
$$= \{ \log(AAx) - \log(EAx) \}$$

$$+ \{ \log(AAy) - \log(EAy) \}$$

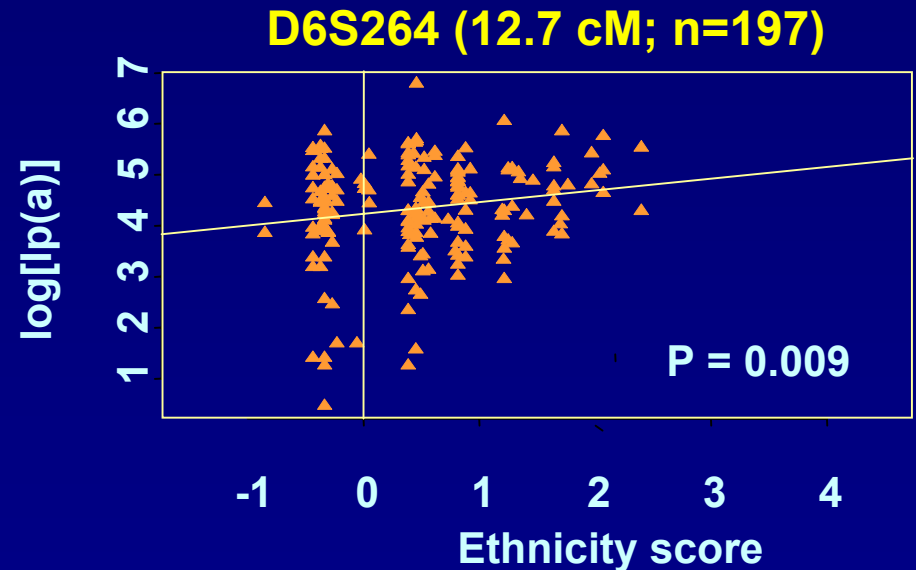
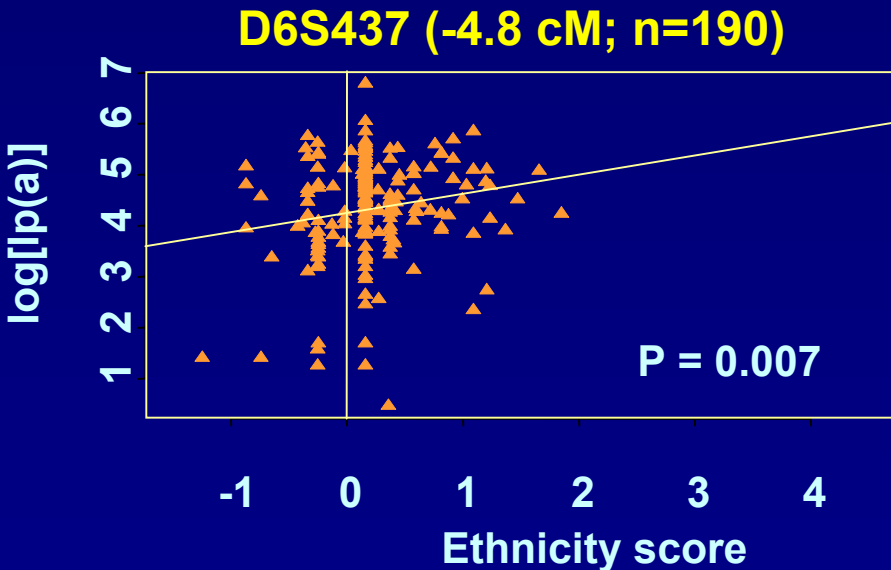
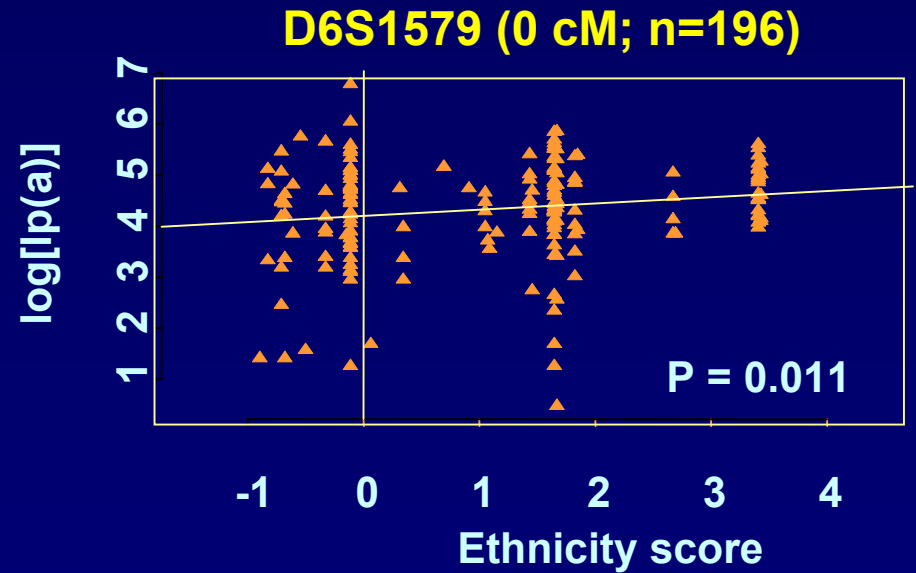
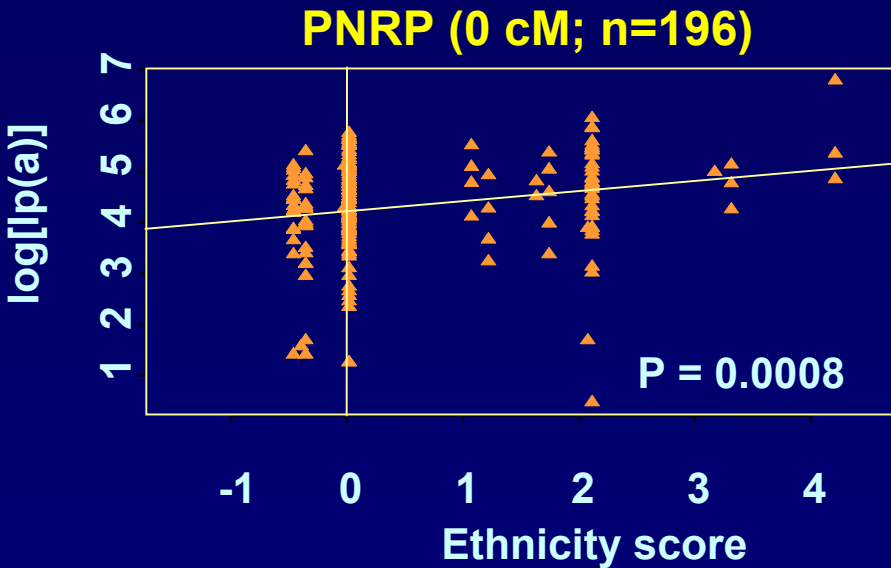
African-Americans: PNRP



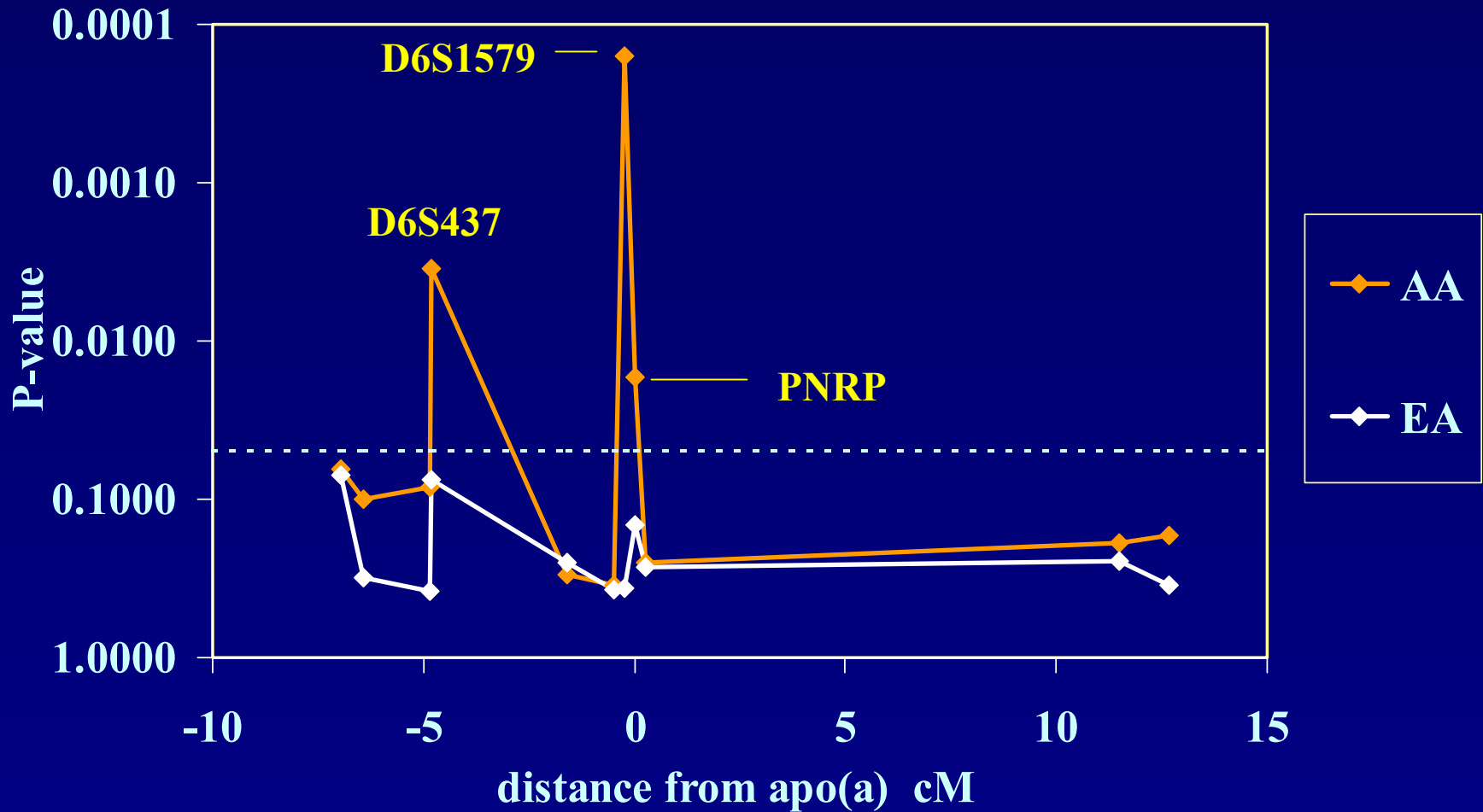
MALD analysis of apo(a)



AA loci with $p < 0.05$



MALD analysis of apo(a): adjusted for apo(a) size



On-going research

- MALD study: multilocus analysis
- Type 15 reported SNPs in apo(a)
 - Lp(a) concentration
 - ASCVD incidence (med. 3.5 yrs. FU)
- Screen apo(a) enhancers DHII and DHIII

Acknowledgements

JHU:

Josef Coresh MD PhD

Terri Beaty PhD

Michael Klag MD MPH

LGD:

Michael W. Smith PhD

Stephen J. O'Brien PhD

Melissa Levasseur

Marianne Subleski

Ann Truelove

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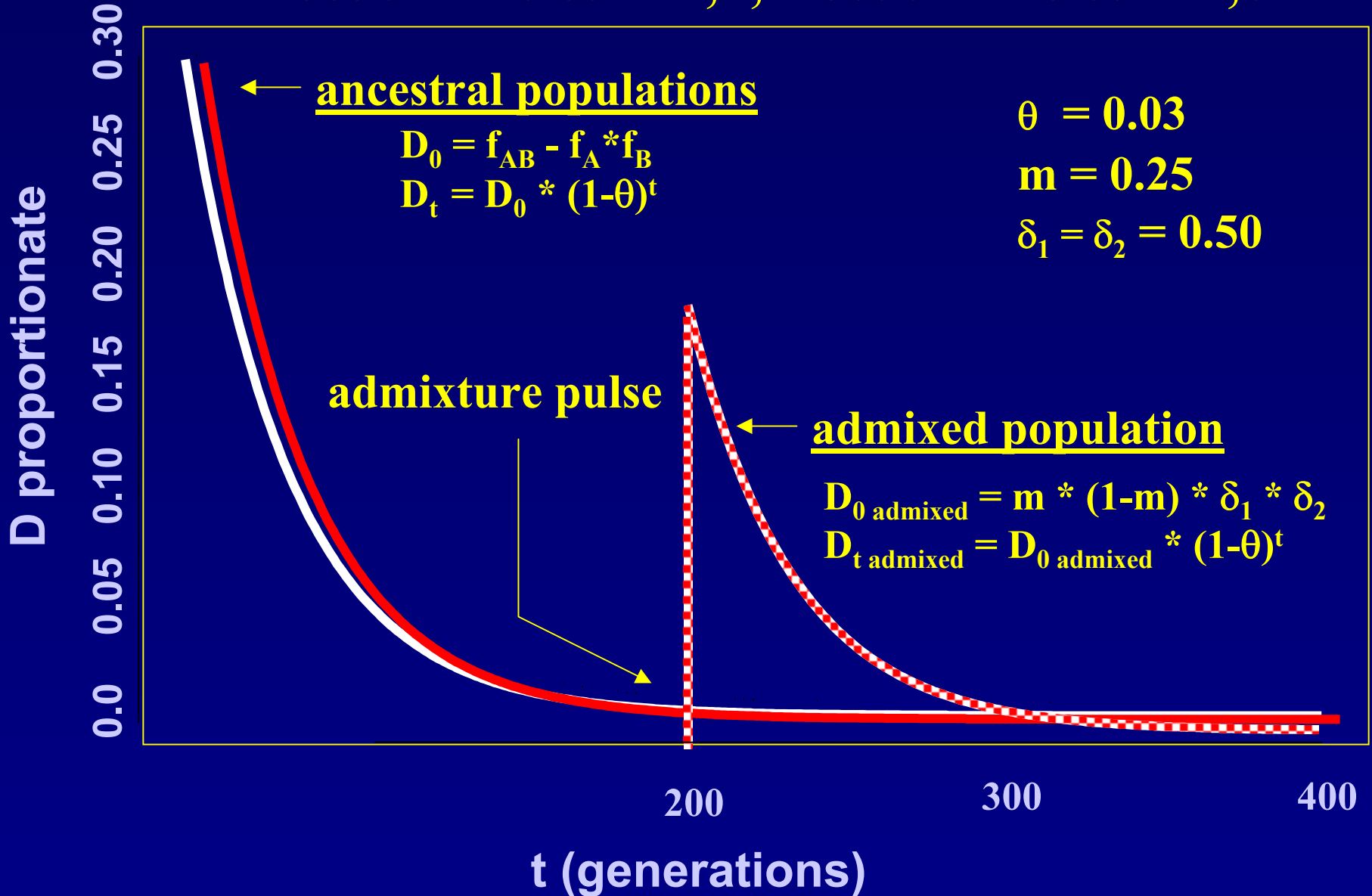
Nancy Fink MPH Klemens Meyer MD

Andrew Levey MD Haya Rubin MD PhD

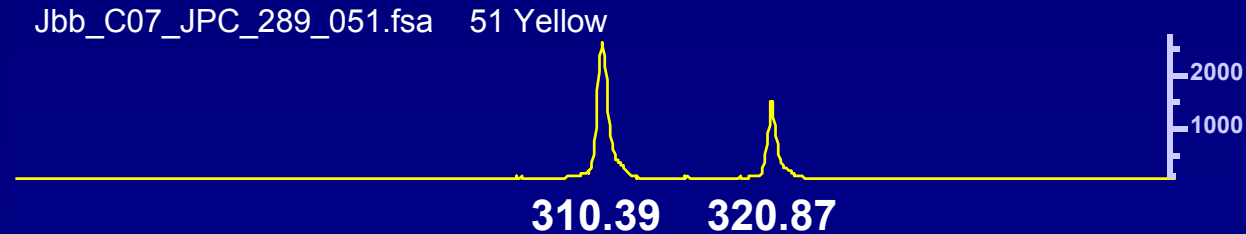
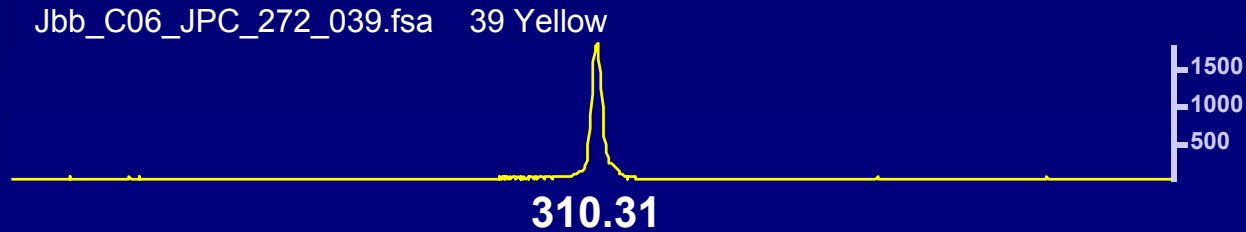
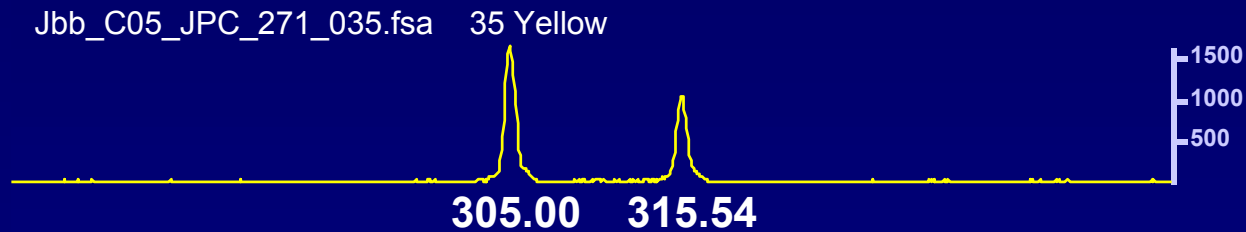
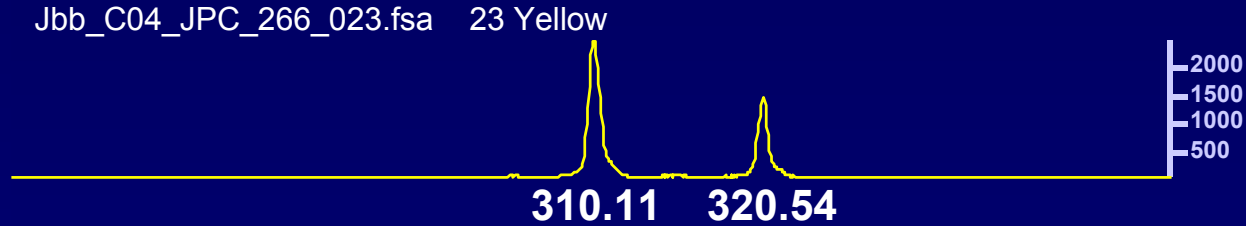
Nathan Levin MD Albert Wu MD MSPH

END

Disequilibrium decay for 2 bi-allelic loci: Locus 1 alleles = A,a; Locus 2 alleles = B,b



GENOTYPER plots: PNRP



Two-step analysis

Step 1:

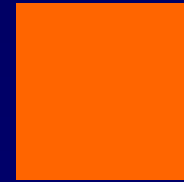
Estimate effect of each marker allele on Lp(a) level (codominant model)

Step 2:

Measure association between allele effect on Lp(a) level and allelic delta, AA freq. - EA freq.

Two-step analysis

higher $L_p(a)$



$$f_{AA} > f_{EA}$$



Locus 1
Allele 2



$$f_{EA} > f_{AA}$$

avg.
 $L_p(a)$



Locus 1
Allele 1



Locus 1
Allele 3



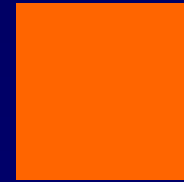
Locus 1
Allele 4

lower $L_p(a)$

Two-step analysis

higher $L_p(a)$

$$f_{AA} > f_{EA}$$



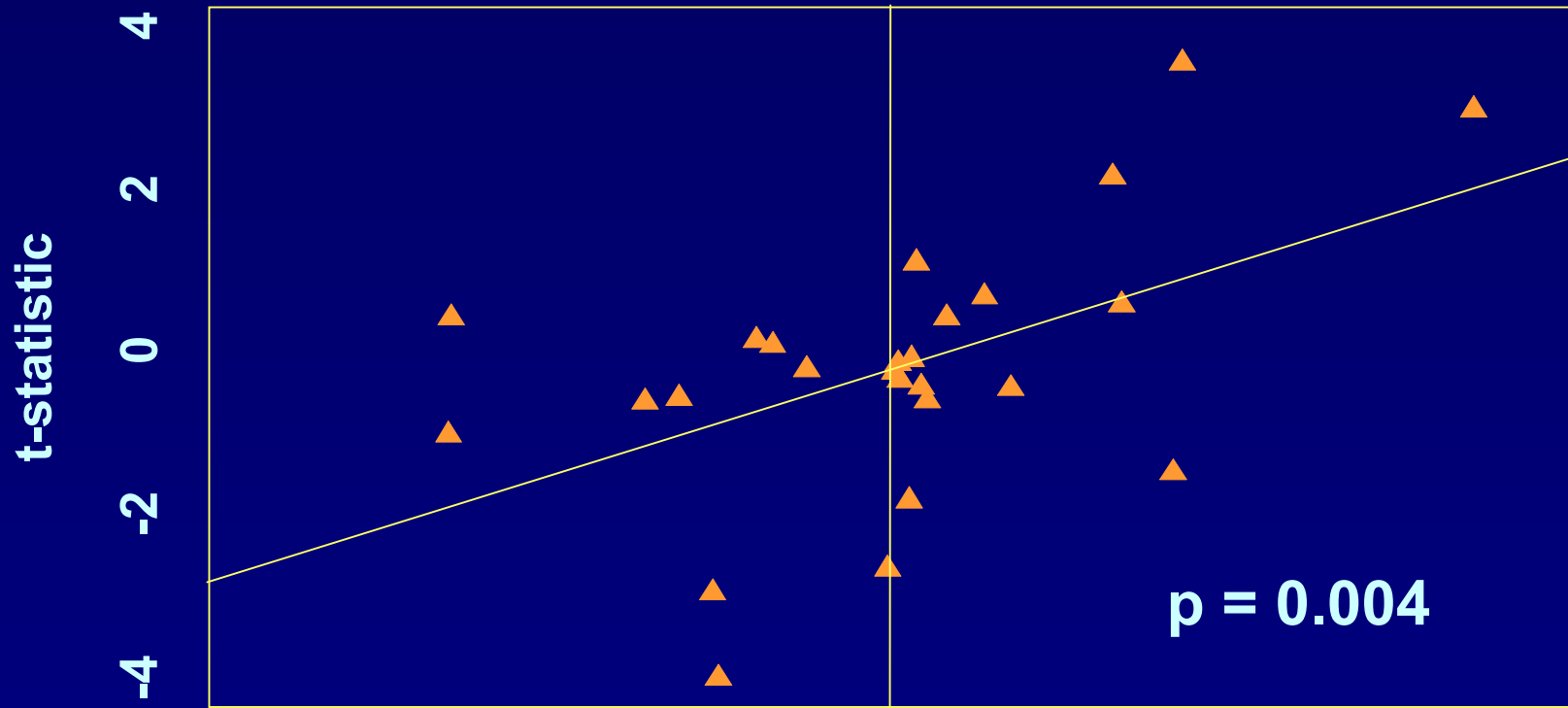
$$f_{EA} > f_{AA}$$

avg.
 $L_p(a)$



lower $L_p(a)$

African-Americans: 0 cM

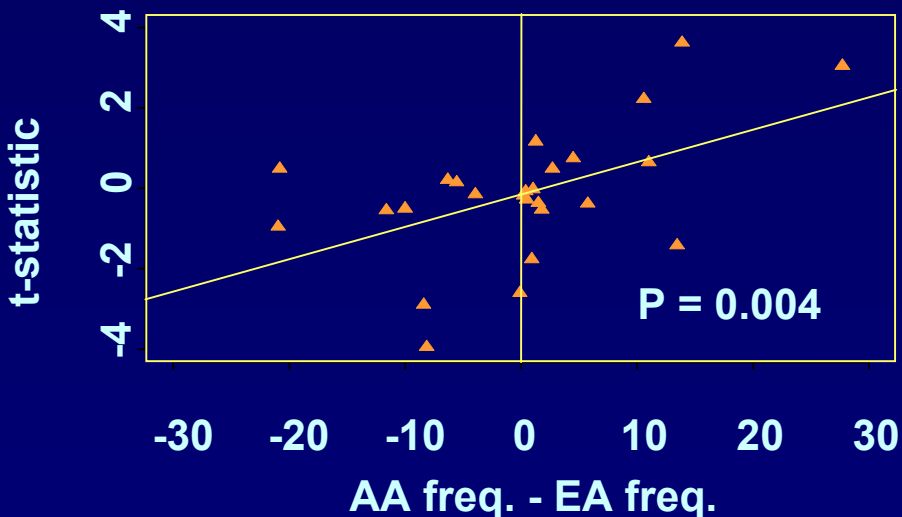


AA freq. - EA freq.

25 alleles at 3 loci

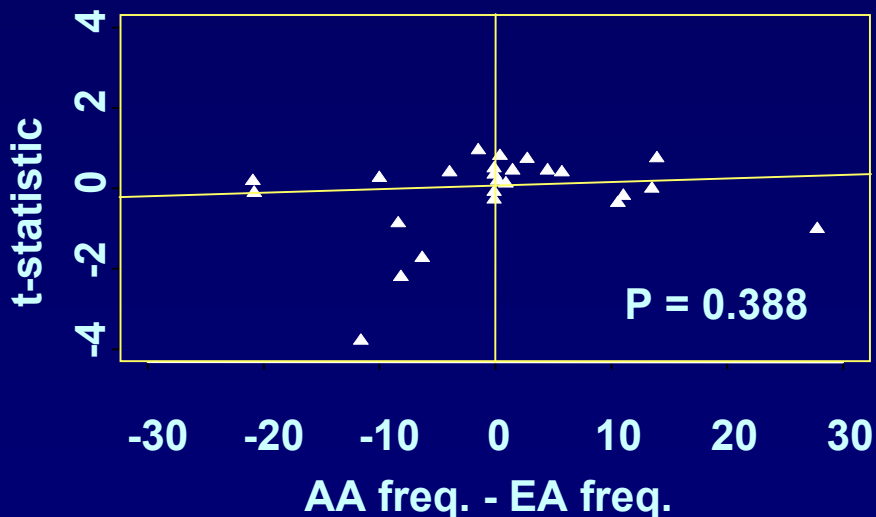
AA alleles

0 cM (25 alleles at 3 loci)

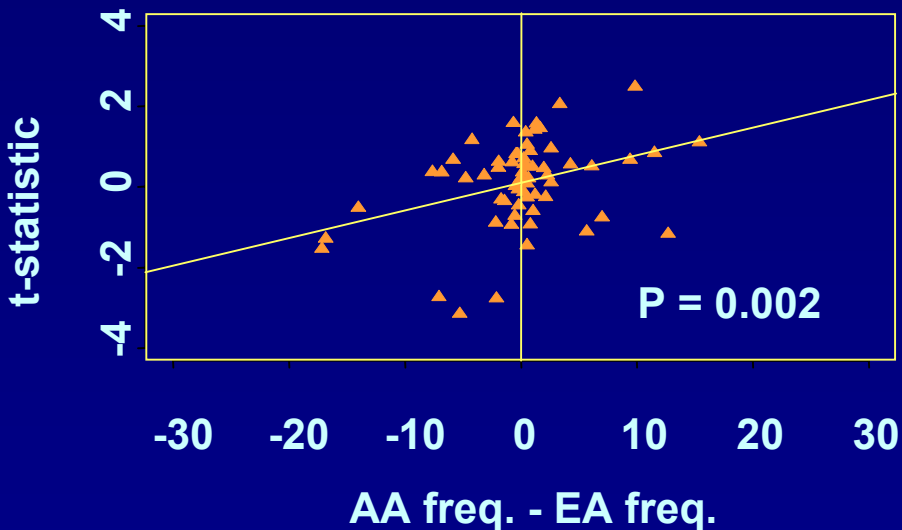


EA alleles

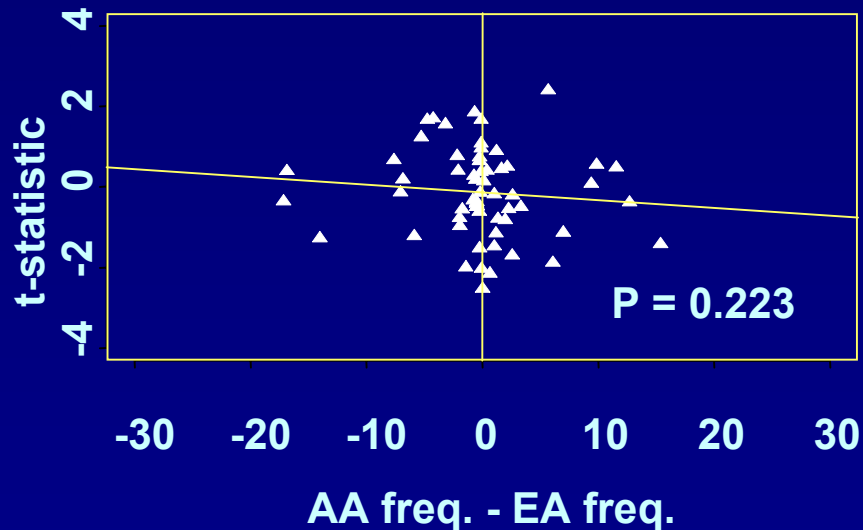
0 cM (25 alleles at 3 loci)



-1.6 to -4.8 cM (61 alleles at 4 loci)



-1.6 to -4.8 cM (59 alleles at 4 loci)



Epidemiologic and functional studies of Lp(a) level and apo(a) polymorphisms

location	pop	freq	epi assoc	funct signif
PNRP	EA	0(<8), .7(8), .3(>8)	3/3	0/3
	A	.1(<8), .7(8), .2(>8)	0/1	equal expr
+93 C/T	EA	.87, .13	0/2	2/2
	A	.91, .09	1/1	T early ATG
+121 G/A	EA	.84, .16	1/1	1/1 A expr ↑ 50%
KIV-8 intron +1 G/A	EA	.94, .06	1/1	1/1
	A	1.00, 0.00	--	splice defect → null

Epidemiologic and functional studies of CVD and apo(a) polymorphisms

location	pop	freq	epi assoc	funct signif
KIV-8 thr ¹² /pro	EA	.82, .18	1/1	1/1 pro fibrin binding ↓ 75%
KIV-10 met ⁶⁶ /thr	EA	.30, .70	0/2	0/2 equal fibrin binding
KIV-10 trp ⁷² /arg	EA	.98, .02	--	3/4 arg fibrin binding ↓, aortic Lp(a) ↓ 35% mice

