

# A genome scan for linkage with aortic root diameter (ARD) in the HyperGEN study.

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# What is the HyperGEN Study?

- Hypertension Genetic Epidemiology Network (HyperGEN)
- One of four networks of the NHLBI Family Blood Pressure Program (FBPP)
- A family study designed to identify the genetic contributions to hypertension
- 2407 hypertensive individuals (1262 African-Americans and 1145 whites) from 917 sibships (Williams et al, 2000)
- Includes five field centers:
  - Birmingham, AL
  - Forsyth County, NC
  - Minneapolis, MN
  - Salt Lake City, UT
  - Framingham, MA

# Why is aortic root diameter important?

- The aortic root is located at the base of the ascending aorta, which carries oxygenated blood from the left ventricle of the heart to the systemic circuit.
- Aortic root dilation (increased aortic root diameter) has been shown to be associated with hypertension. (Kim et al, 1996)
- Aortic root dilation can lead to aortic regurgitation (diastolic blood flow from aorta into left ventricle), which can lead to left ventricular hypertrophy and heart failure. (Dujardin et al, 1999)
- Other complications of aortic root dilation: aortic aneurysm and dissection.

# Might genes influence ARD?

- Dilation of the aortic root is commonly found in Marfan syndrome, an autosomal dominant disorder involving the fibrillin-1 gene on chromosome 15.
- It has previously been shown that the inter-individual variation in ARD is highly heritable, particularly in African Americans. (Pezeshkian et al, 2000)
- A major locus for familial (dominant inheritance) thoracic aortic aneurysms and dissections maps to 5q13-14, with 9 of 15 of families identified demonstrating evidence of linkage to this locus. (Guo D et al, 2001)

## Study Hypothesis:

Aortic root diameter is a trait influenced by many factors. It is likely that there are genes influencing this trait. This study seeks to identify previously uncharacterized region(s) on the genome that are linked to variation in the aortic root diameter in hypertensive African Americans and Whites.

# Study Population

- 1129 African American siblings with phenotypic and genotypic data from 504 sibships.
- 883 White siblings with phenotypic and genotypic data from 374 sibships.
- At least 2 siblings in a sibship were diagnosed with hypertension before age 60 years.
- Hypertension: systolic blood pressure = or > than 140 mmHg and/or diastolic blood pressure = or > than 90 mmHg at two separate visits, or under current treatment for hypertension.
- Age range: 23-85
- 62% female, 38% male

# Study Population cont.

## Sibship Structures

### African Americans

| # sibs/sibship | # sibships | Total |
|----------------|------------|-------|
| 2              | 410        | 820   |
| 3              | 69         | 207   |
| 4              | 23         | 92    |
| 5              | 2          | 10    |
| 6              | 0          | 0     |
| 7              | 0          | 0     |

Total=1129

### Whites

| # sibs/sibship | # sibships | Total |
|----------------|------------|-------|
| 2              | 282        | 564   |
| 3              | 65         | 195   |
| 4              | 18         | 72    |
| 5              | 4          | 20    |
| 6              | 3          | 18    |
| 7              | 2          | 14    |

Total=883

# Study Population cont.

## Description of Study Participants with ARD data and genotypic data

|            | A.A. Women | A.A. Men   | WhiteWomen | White Men  |
|------------|------------|------------|------------|------------|
| N=         | 766        | 363        | 474        | 409        |
| ARD(cm)    | 3.21(0.32) | 3.62(0.37) | 3.32(0.33) | 3.75(0.36) |
| Age(yrs)   | 51.2(11.0) | 51.8(10.3) | 59.9(9.0)  | 61.0(8.3)  |
| Weight(kg) | 90.0(23.0) | 93.0(20.9) | 80.6(20.0) | 93.0(16.1) |
| Height(m)  | 1.63(0.06) | 1.76(0.07) | 1.62(0.06) | 1.76(0.06) |
| SBP(mmHg)  | 133(22)    | 135(22)    | 128(21)    | 129(19)    |
| DBP(mmHg)  | 74(11)     | 80(12)     | 67(10)     | 75(10)     |

Mean(StDev)

# Data Collection

- Aortic root measurements taken at the sinuses of Valsalva with two-dimensional echocardiography.
- ARD expressed as a continuous variable.
- Echocardiography performed on subset of HyperGEN participants. Goal: detect genes influencing left ventricular hypertrophy.
- Genotyping of short tandem repeat polymorphisms (STRPs) by the NHLBI Mammalian Genotyping Service in Marshfield, WI. (Broman et al 1998)
- 367 polymorphic markers, an average of 9.2 cM apart, from Cooperative Human Linkage Center screening set 8

# Data Analysis

- Standardized residual values for ARD were created using a linear regression model, adjusting for age, age<sup>2</sup> and field center within sex and race specific models using SAS version 6.12. This is the minimally adjusted model.
- Height, weight, systolic blood pressure and diastolic blood pressure were also included in fully adjusted model.
- Exclusions: 1 A.A. and 1 White individual due to extreme phenotypic values ( $\pm 4$  S.D. from the mean) in minimally adjusted model. 1 A.A. and 2 Whites in fully adjusted model.
- Skewness:
  - A.A. 0.29 in min. adj, 0.38 in full adj.
  - Whites 0.45 in min. adj, 0.42 in full adj.
- Kurtosis:
  - A.A. 0.24 in min. adj, 0.33 in full adj.
  - Whites 0.73 in min. adj, 0.97 in full adj.

# Data Analysis cont.

- Multipoint linkage analysis was performed on the standardized residual values using the variance components method in GENEHUNTER version 2.0.
- This approach looks for evidence of QTLs influencing variation in the trait to be analyzed.
- To do so, it calculates maximum likelihood values for:
  - the mean trait value separately for each sex
  - additive variance components for the QTL
  - additive variance components for other, unlinked loci
  - environmental variance component.
- This maximum likelihood model is then compared to one in which the QTL variance components are constrained to zero.
- The likelihood ratio of the two models is used to calculate a LOD score to test the significance of the QTL effects, which can be compared to a chi-squared distribution. (Pratt et al, 2000)

# Results

- The proportion of the variation of ARD explained by the minimally adjusted model, expressed as the  $r^2$  value: 0.045-0.060 in the four sex/race specific groups. In the fully adjusted model,  $r^2$  values: 0.11-0.15 in the four groups.
- $h^2 = (\text{additive genotypic variance} / \text{total phenotypic variance})$ 
  - 0.63 for A.A. / min. adj.
  - 0.62 for A.A. / full adj.
  - 0.41 for Whites / min. adj.
  - 0.30 for Whites / full adj.

# Results cont.

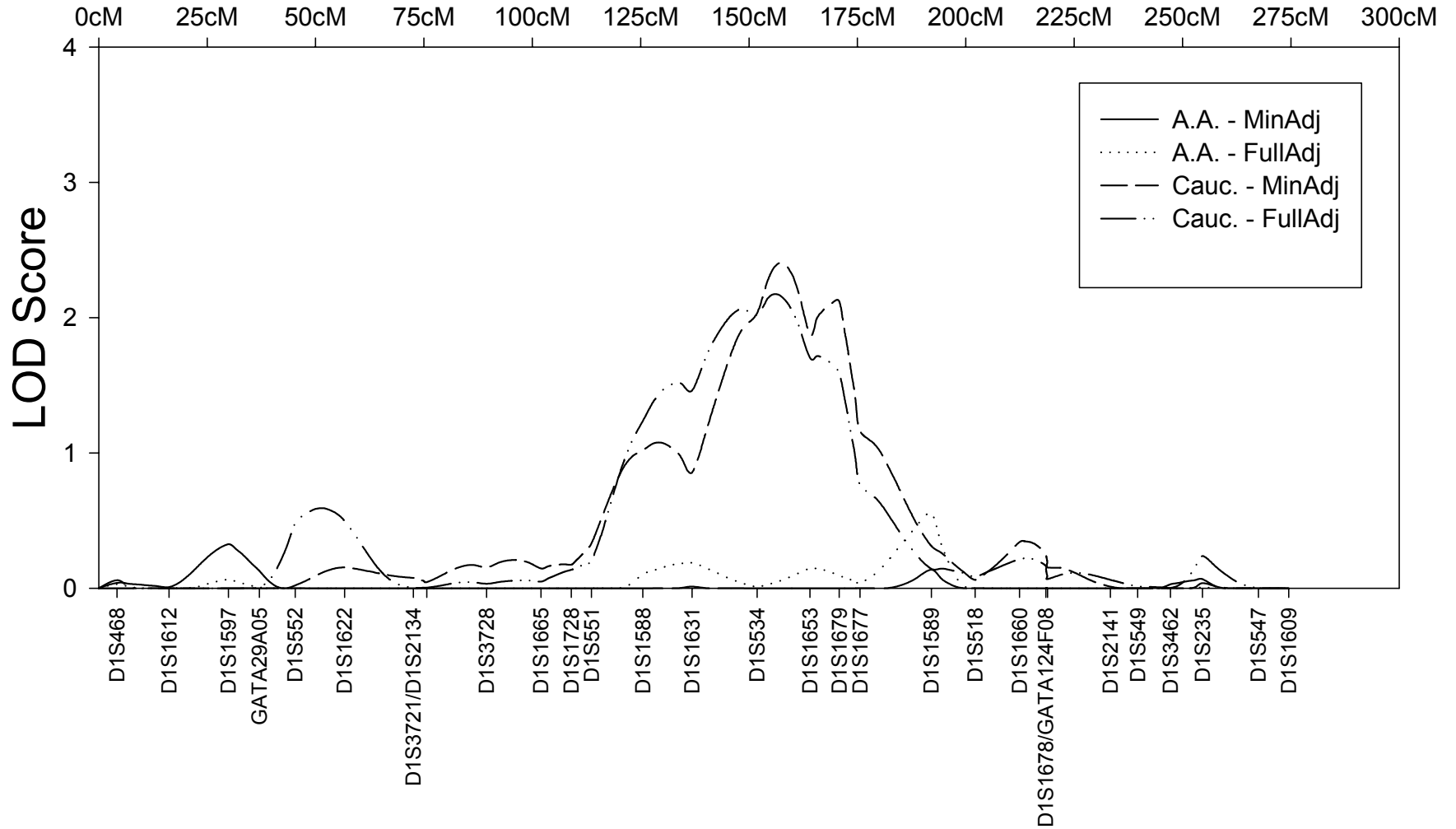
## Best Evidence for Linkage

- **African Americans**
  - Minimally Adjusted:
    - LOD score = 2.07, Chromosome 5, 85.25 cM from p-terminus (marker D5S1501)
  - Fully Adjusted:
    - LOD score = 1.22, same location
- **Whites**
  - Minimally Adjusted:
    - LOD score = 2.40, chromosome 1, 156.76 cM from p-terminus (marker D1S534)
  - Fully Adjusted:
    - LOD score = 2.17, same location

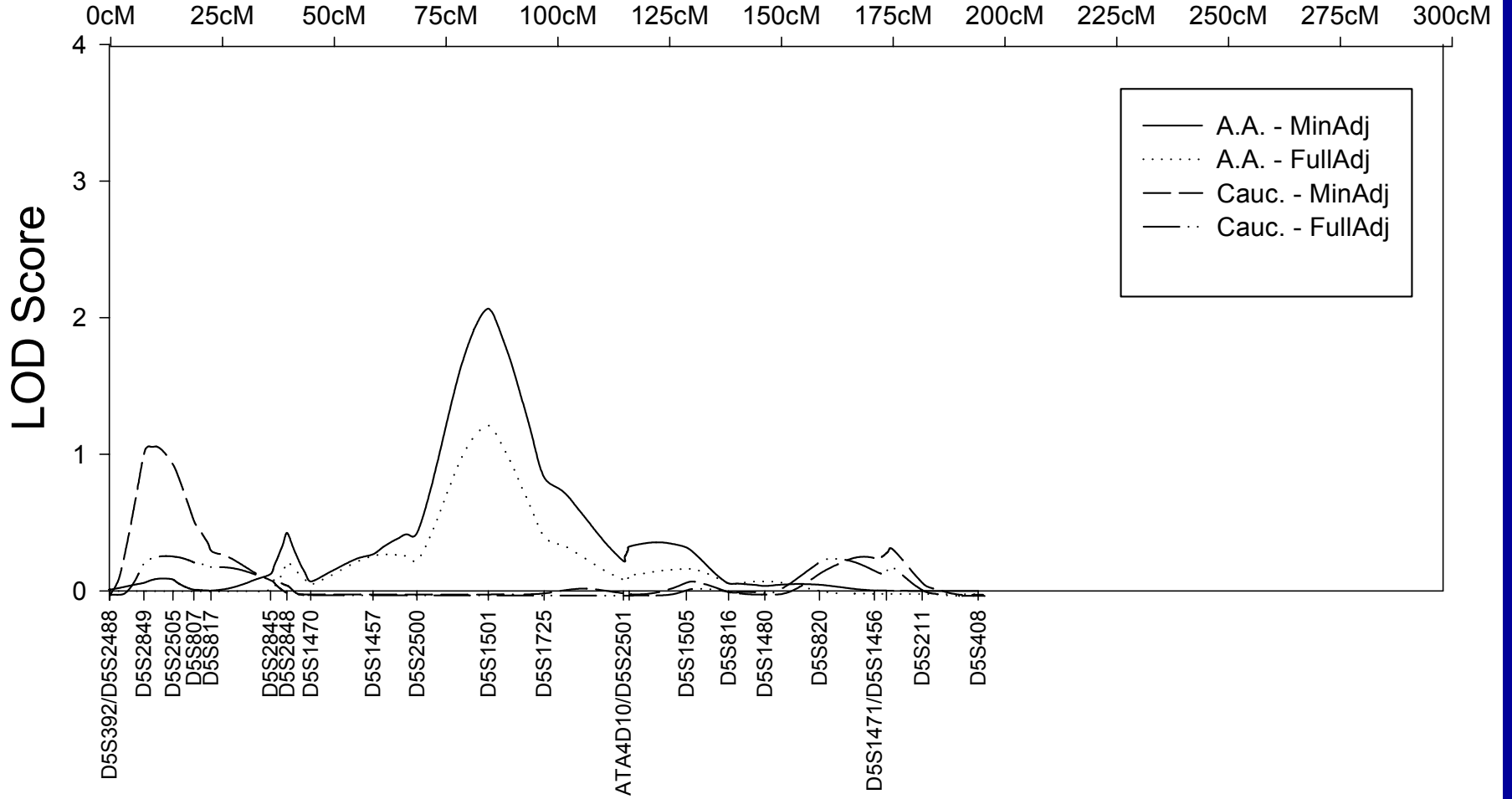
Significant evidence for linkage: LOD score = 3.6 (Lander and Kruglyak, 1995)

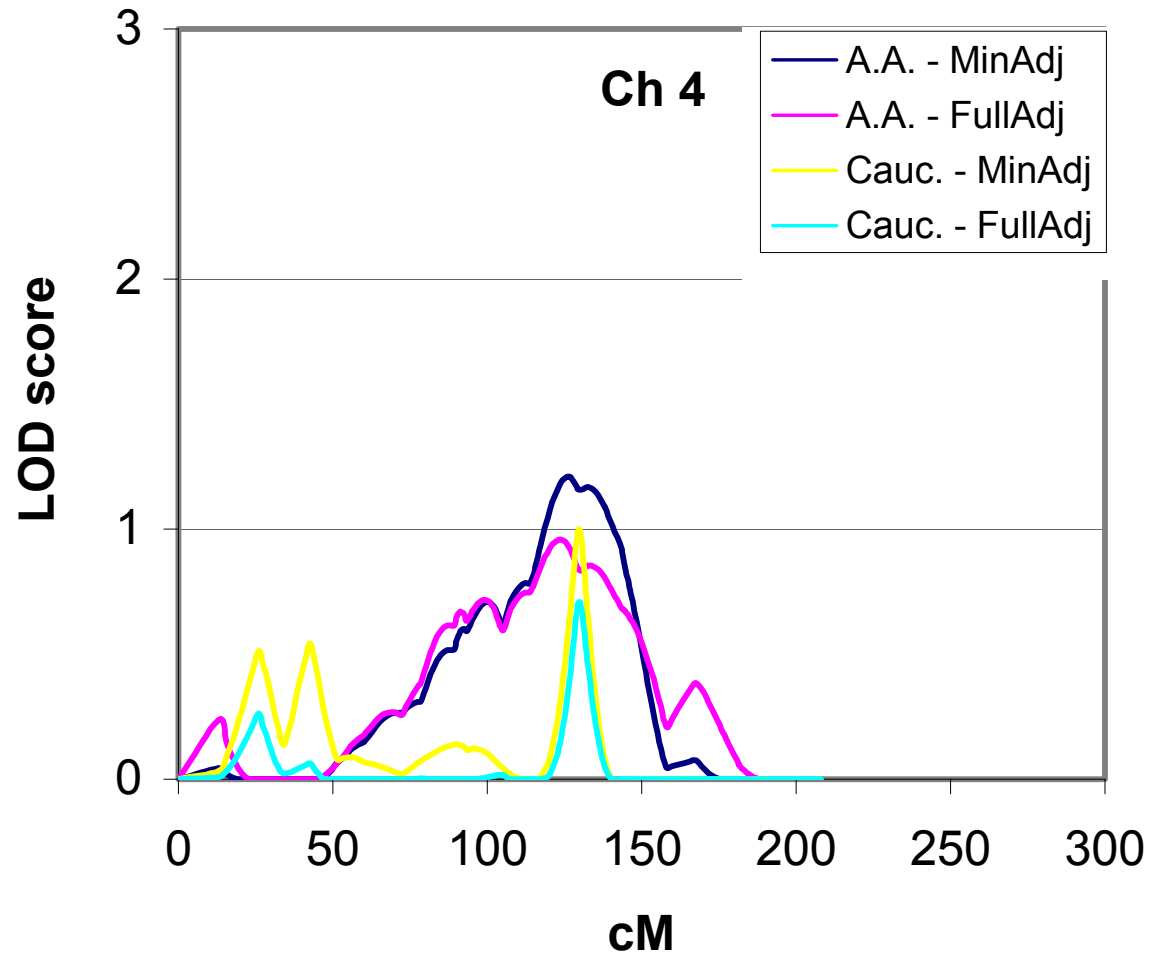
Suggestive evidence for linkage: LOD score = 2.0 (Morton, 1998)

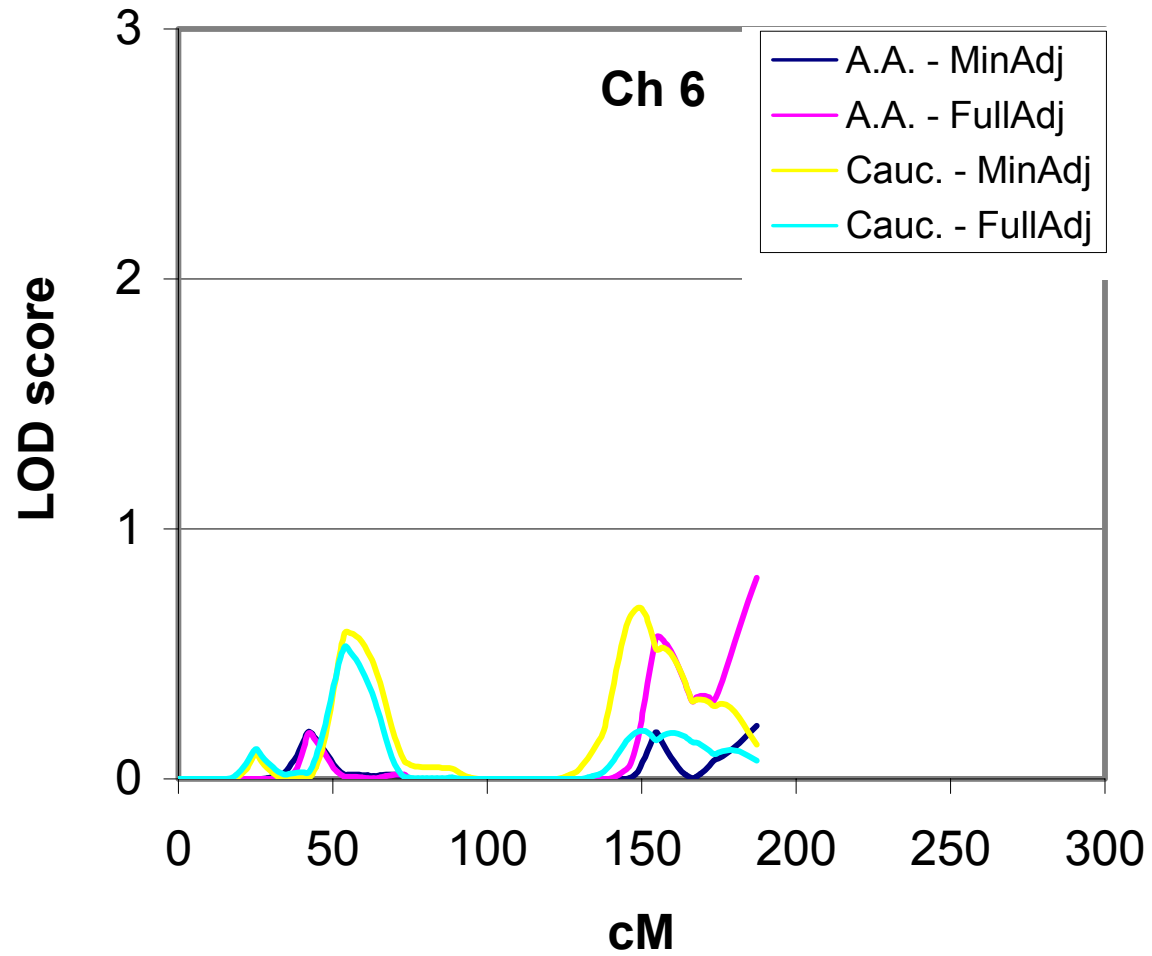
# Chromosome 1

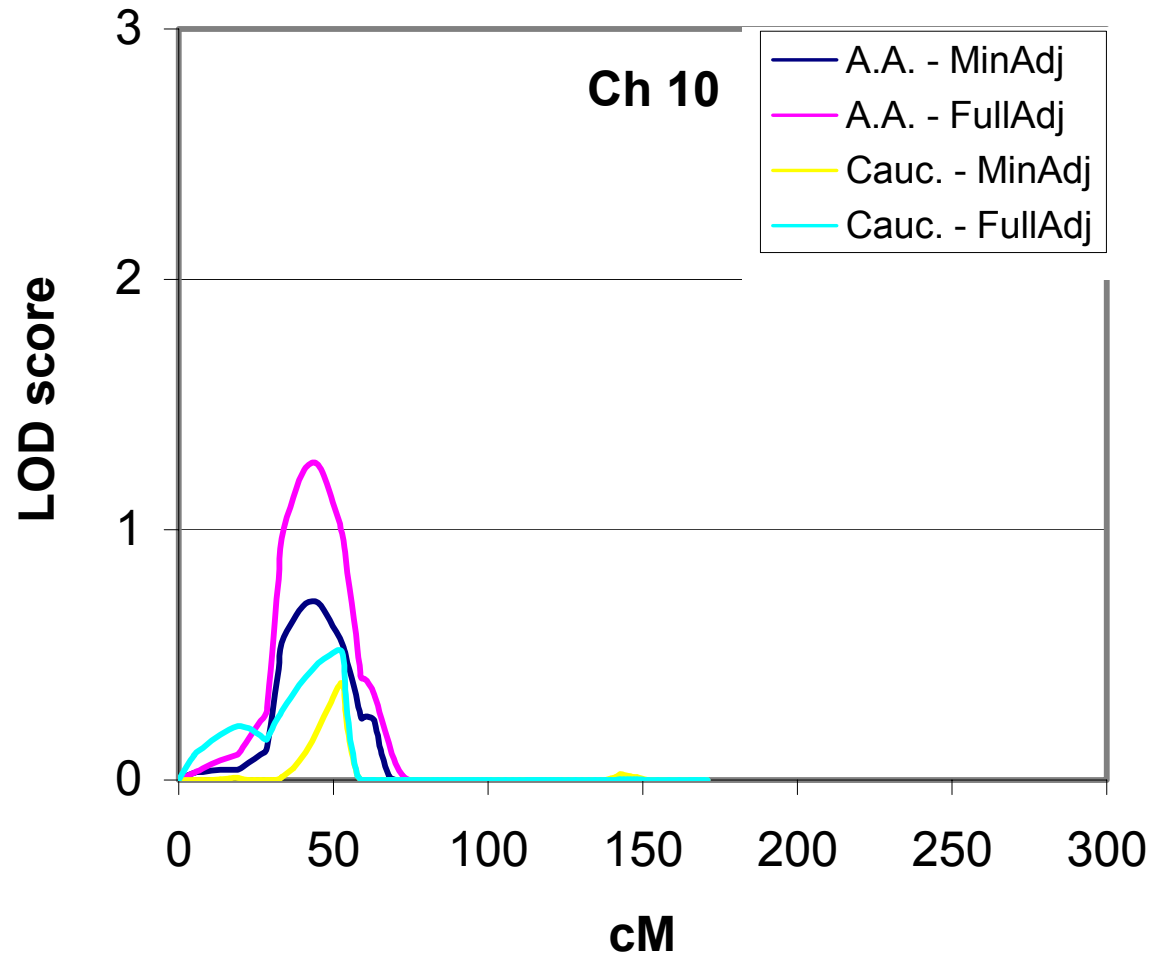


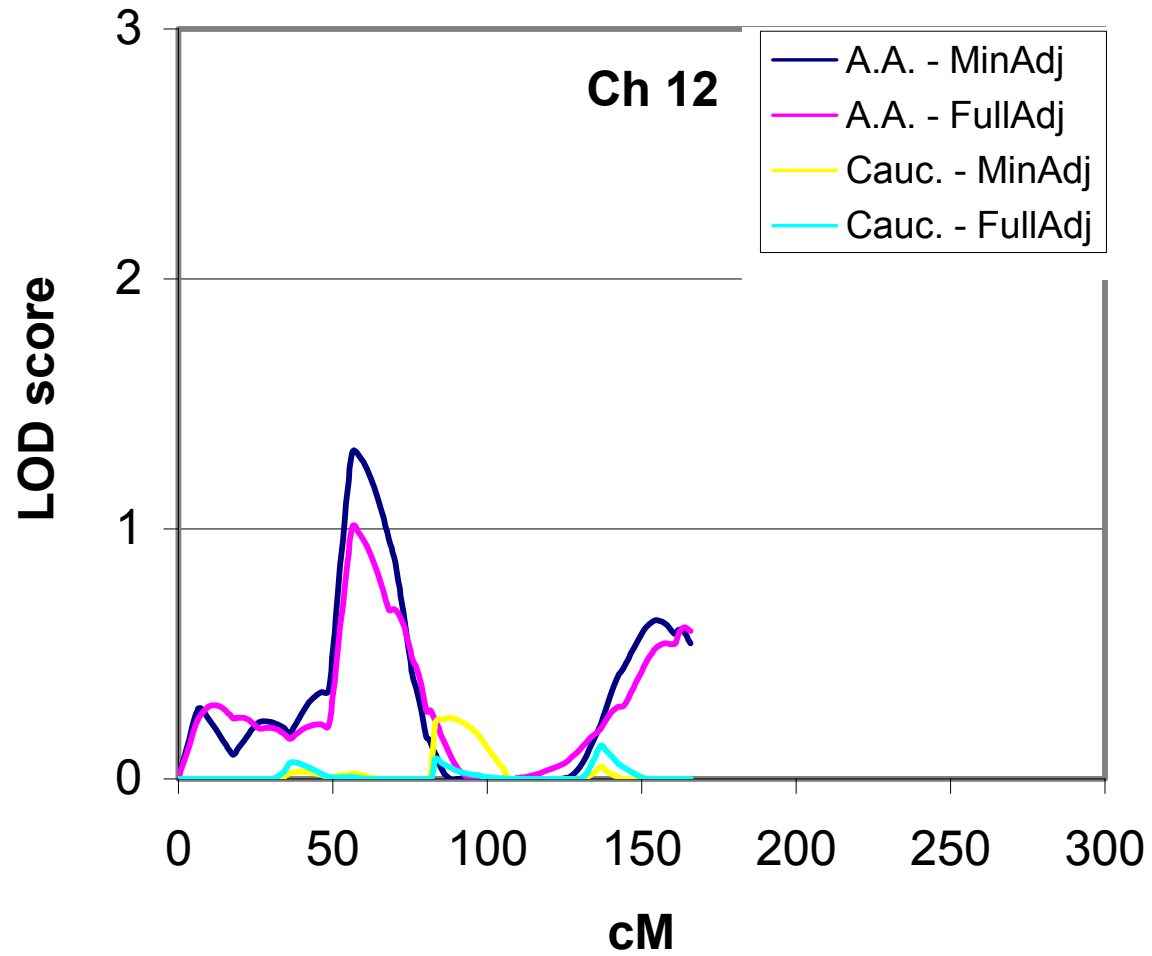
# Chromosome 5











## Previously characterized genes in the regions of the peak LOD scores

- A search of electronic databases yielded no obvious candidates in the immediate region.
- Dermatopontin gene (DPT) at 190 cM on chromosome 1. Dermatopontin is an extracellular matrix protein assumed to play an important role in cell-matrix interactions and assembly. (35 cM from peak in Whites)
- Fibrillin-2 gene (FBN2) at 135 cM on chromosome 5 – mutations cause congenital contractural arachnodactyly (CCA). CCA patients occasionally have aortic root dilations similar to those seen in Marfan syndrome. (50 cM from peak in A.A.s)

# Limitations

- Family structures include sibships only – variance components method more powerful when larger, more complex family structures are used. (Williams 1999)
- Generalizability – all subjects from hypertensive sibships, difficult to say whether these findings apply to a normotensive population.
- Measurement error - are measurements precise enough to detect small differences? Are there systematic differences in measurement error between groups?

## Conclusion:

Two genetic regions show suggestive evidence for linkage to the aortic root diameter in hypertensive African Americans and Whites:

In African Americans the maximum LOD score of 2.07 is found on chromosome 5 at 85.25 cM in the model adjusted for age, age<sup>2</sup> and center. This is in the same region as the linkage found in the Guo study on aortic aneurysms and dissection.

In Whites the maximum LOD score of 2.40 is found on chromosome 1 at 156.76 cM in the model adjusted for age, age<sup>2</sup> and center.