

A quantitative trait locus  
determining dietary  
macronutrient intakes is located  
on human chromosome 2p22

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## ABSTRACT

Obesity is generally accompanied by increased food intake. The major genes influencing variation in dietary macronutrient intakes in a population have not been identified. We conducted a genome-wide scan using data derived from food frequency questionnaires in 816 Mexican Americans from The San Antonio Family Heart Study. Household effect was simultaneously estimated in a variance component model using SOLAR. All of the dietary intake measures (total calories, total proteins, total fat, saturated fat, mono-unsaturated fat, poly-unsaturated fat, carbohydrates, sucrose) were moderately heritable. Household effect was insignificant except on total calories and sucrose. Suggestive evidence of linkage with saturated fat intake was shown on chromosome 2p22 near marker D2S1346 (59cM) with a LOD of 2.62. Intakes of total calories, total fat, total protein, and monounsaturated fat were also linked to the same marker with LOD scores over 2. We previously reported a significant linkage signal on chromosome 2p22 near marker D2S1788 (55cM) with leptin levels and fat mass in this population. Using leptin or fat mass as a covariate, multipoint LOD scores for saturated fat dropped to 1.27 and 1.90, respectively, suggesting that this region on chromosome 2p might contribute to both saturated fat intake and body adiposity. This chromosomal region contains several candidate genes, especially proopiomelanocortin (*POMC*). However, two (C→T) polymorphisms in exon 3 of the *POMC* did not show any association with saturated fat intake. These results strengthen the proposal that 2p22 might harbor genes influencing a variety of obesity-related phenotypes including variation in macronutrient intake, although *POMC* might not be the responsible gene.

# Background

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- Increased food intake relative to energy expenditure is the major contributor to the development of obesity.
- The regulation of dietary behavior is complex, and includes environmental, biological, psychological, and genetic factors.
- The genes influencing the variation in the amounts of macronutrient intake (fats, carbohydrates, and proteins), which can predispose a general population to a risk of obesity and obesity-related diseases, have not been identified.

# Method

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- We analyzed nutrient intake of Mexican Americans of the San Antonio Family Heart Study (SAFHS).
- Nutrient intake was estimated using standardized questionnaires adjusted for low-income Mexican Americans in San Antonio, Texas.

# Method

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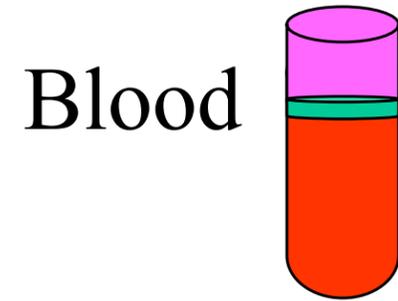
A total of 102 food items were included in the questionnaire, accounting for 80-85% of the macronutrient consumption of this population: total calories, total protein, total fat, and total carbohydrate. The daily intake of these food components were derived using the nutrient table of the US Department of Agriculture.

# Method

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- A total of 1431 subjects of 42 extended Mexican American families were recruited in the San Antonio Family Heart Study (SAFHS).
- Families were ascertained through a randomly chosen proband (without regard to any existing disease) from a listing of residences in a low-income area of San Antonio, Texas.

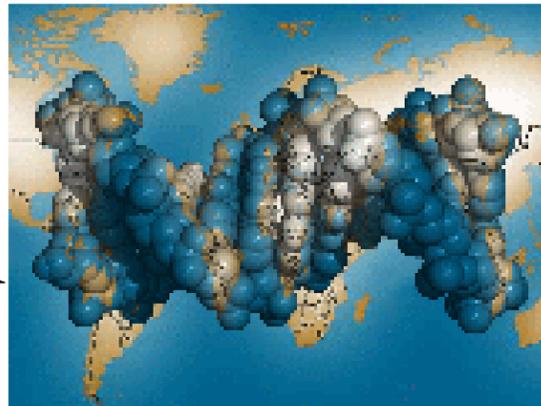
# Methods - Genotyping



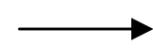
Lymphocytes →



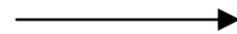
DNA



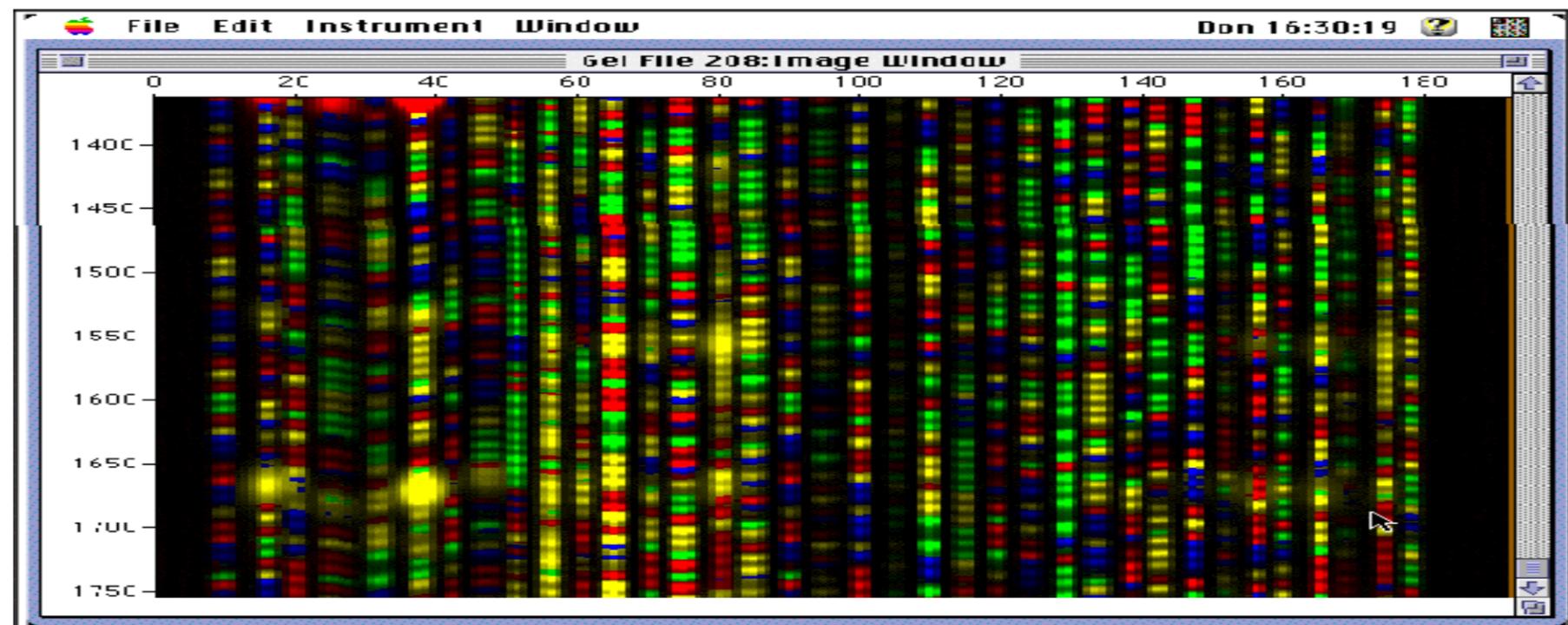
(endonuclease)



PCR ( with fluorescently labeled primers)



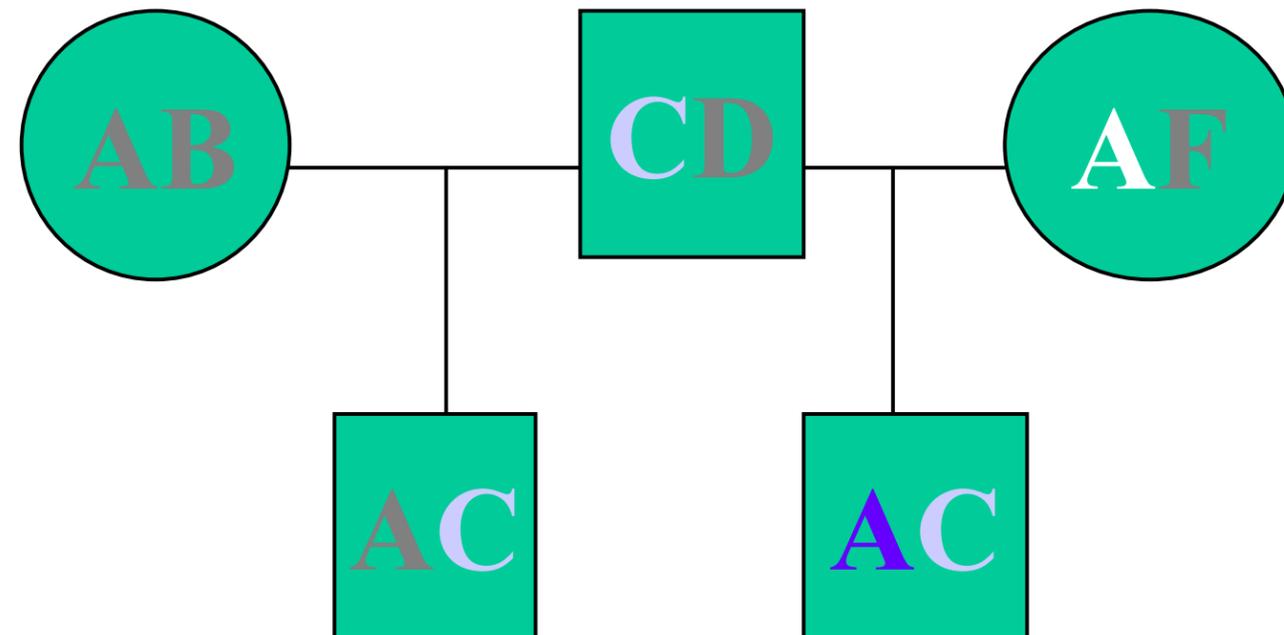
DNA sequencer



# Genome-wide Scan

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- IBD (Identical By Descent)



**C:** IBD sharing -- linkage

**A:** IBS (Identical By State) -- population level association

# Quantitative Genetic Analyses: The variance component approach

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$$\sigma_p^2 = \sigma_g^2 + \sigma_{ho}^2 + \sigma_e^2$$

$$*h^2 = \sigma_g^2 / \sigma_p^2$$

$$**c^2 = \sigma_{ho}^2 / \sigma_p^2$$

\*: heritability

\*\* : household effect

# Quantitative Genetic Analyses: The variance component approach

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## Model:

$$\mathbf{\Omega} = \sum_{i=1}^n \hat{\Pi}_i \sigma_{qi}^2 + 2\mathbf{\Phi} \sigma_a^2 + \mathbf{I} \sigma_e^2 + \mathbf{H} \sigma_{ho}^2$$

$\mathbf{\Omega}$ : covariance;  $\hat{\Pi}_i$ : IBD estimate matrix at marker  $i$ ;  $\sigma_{qi}^2$ : additive genetic variance QTL $_i$ ;  
 $\mathbf{\Phi}$ : kinship matrix;  $\sigma_a^2$ : residual additive genetic variance;  $\mathbf{I}$ : identity matrix;  $\sigma_e^2$ : environmental variance;  $\mathbf{H}$ : household matrix;  $\sigma_{ho}^2$ : household variance.

# Quantitative Genetic Analyses: The variance component approach

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- Hypothesis testing:  $\sigma^2_{qi} = 0$ ;  $\sigma^2_{ho} = 0$
- LOD score =  $\log_{10}(\text{likelihood Ha})$   
-  $\log_{10}(\text{likelihood Ho})$
- Criteria for linkage: LOD score > 3.0
- Suggestive linkage: LOD score > 2.0

# Association Study

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- To investigate the association between dietary saturated fat intake and polymorphisms in *POMC*:

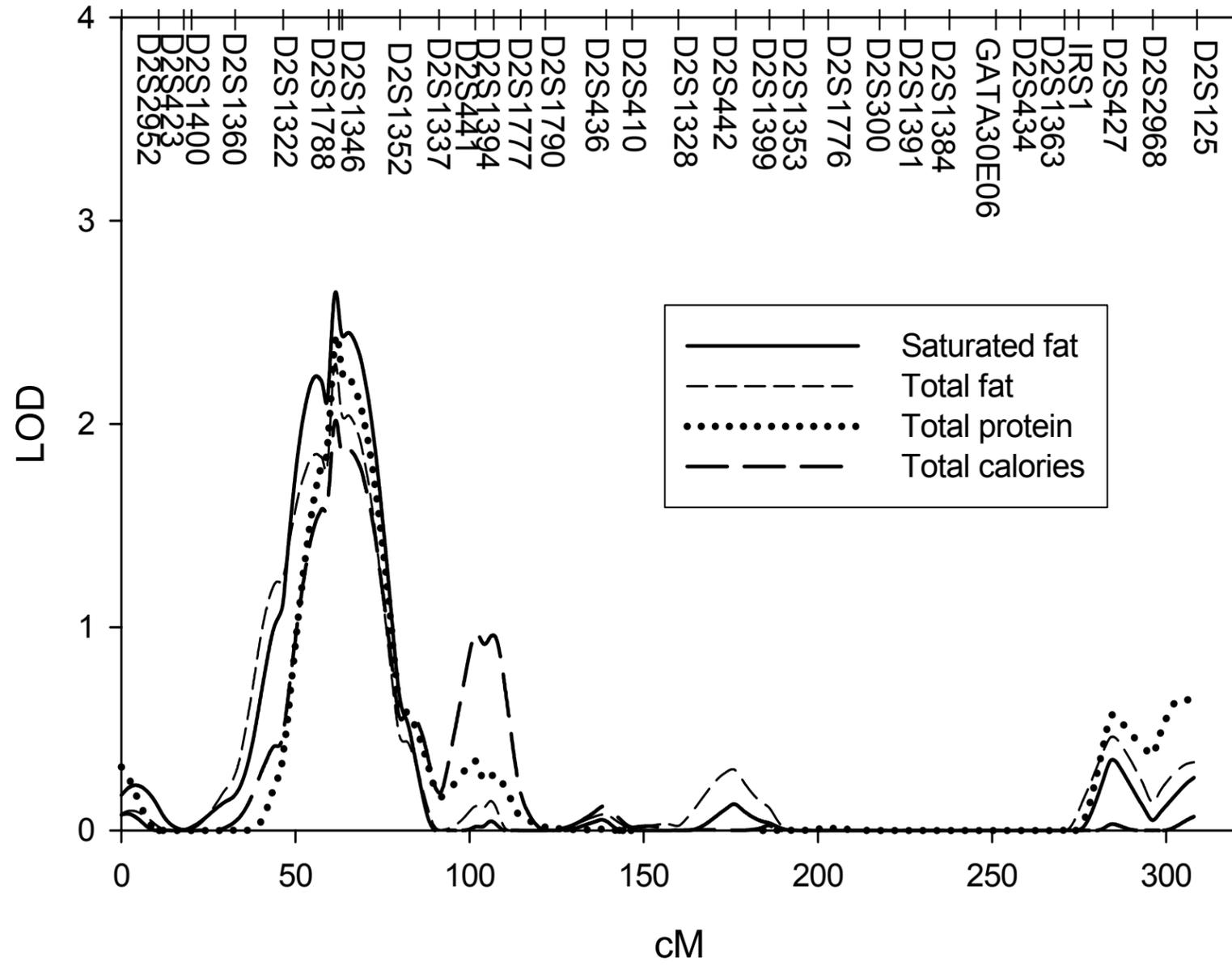
A model where the main effects of a polymorphism were estimated using a maximum likelihood method was compared to a null model where the main effects were constrained to zero.

Table 1. The characteristics of the dietary intakes, leptin and fat mass in Mexican Americans

Trait	Mean	
	Male (n=491)	Female(n=736)
Age	38.7 ± 17.3	39.4 ± 16.3
Total Calories (kcal)	3301 ± 1613	2762 ± 1277
Total Proteins(g)	122.2 ± 62.5	105.7 ± 48.9
Total Fats(g)	116.0 ± 62.7	97.1 ± 51.3
Saturated fat(g)	42.9 ± 22.9	36.2 ± 19.5
Mono-unsaturated fat(g)	49.5 ± 27.8	40.9 ± 22.5
Poly-unsaturated fat(g)	18.5 ± 10.7	16.7 ± 8.7
Total Carbohydrates(g)	406.7 ± 205.6	355.2 ± 169.5
Total sucrose(g)	86.3 ± 64.2	76.4 ± 52.3
% from protein	15.1 ± 2.8	15.6 ± 2.9
% from fat	31.5 ± 5.1	31.3 ± 5.1
% from carbohydrate	49.3 ± 7.6	51.5 ± 7.3
Leptin (ng/mL) <sup>a</sup>	4.9 ± 4.5	14.3 ± 7.6
Fat mass (lb) <sup>b</sup>	40.8 ± 26.2 <sup>c</sup>	59.8 ± 26.6
<sup>a</sup> : male/female=373/546		
<sup>b</sup> : male/female=455/712		

Table 2. Heritability analyses and genome scan results on dietary intakes in Mexican Americans							
Trait	H <sup>2</sup>	p-value <sup>a</sup>	C <sup>2</sup>	p-value <sup>b</sup>	LOD <sup>c</sup>	Kurtosis	Skewness
Calories	0.17 ± 0.06	0.0001	0.12 ± 0.07	0.04	2	0.15	0.15
Proteins	0.14 ± 0.06	0.001	0.03 ± 0.06	0.3	2.22	0.75	0.17
Fats	0.19 ± 0.06	0.00006	0.04 ± 0.07	0.3	2.09	0.58	0.06
Saturated fat	0.20 ± 0.07	0.0008	0.05 ± 0.07	0.2	<b>2.62</b>	0.63	-0.04
Mono-unsaturated fat	0.21 ± 0.06	0.00003	0.03 ± 0.07	0.3	2.05	0.64	0.06
Poly-unsaturated fat	0.09 ± 0.05	0.03	0.11 ± 0.08	0.07	1	0.54	0.15
Carbohydrates	0.17 ± 0.06	0.0002	0.11 ± 0.07	0.06	0.73*	-0.07	0.04
Sucrose	0.16 ± 0.06	0.0009	0.16 ± 0.08	0.02	0**	0.08	-0.14
a: p-value for H <sup>2</sup> (heritability)							
b: p-value for C <sup>2</sup> (household)							
c: maxLOD was found at chromosome 2 near marker D2S1346.							
*: maxLOD=0.95 was found at chromosome 2 near marker D2S1394.							
**: maxLOD= 1.60 was found at chromosome 2 near marker D2S1394							

# Chromosome 2



# Summary

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- To our knowledge, this is the first genome wide scan using dietary intake derived from food frequency questionnaires.
- Detected significant heritabilities in macronutrient consumption after accounting for shared household environment.
- Showed suggestive linkage of total calories, total fat, total protein, saturated fat, monounsaturated fat, and polyunsaturated fat intake to chromosome 2p near marker D2S1346.

# Summary

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- Two (C→T) polymorphisms in exon 3 of the *POMC* did not show any association with saturated fat intake.

# Conclusions

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- The same genetic marker was identified in multipoint linkage analysis using serum leptin levels and fat mass in this Mexican American population (Comuzzie et al., 1997).
- Combined with previous findings in this region, our study suggests that chromosome 2p22 may contain QTLs related to dietary intake and obesity-related phenotypes.

# Acknowledgement

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This study was supported by grants P01 HL45522 from the National Heart, Lung, and Blood Institute and MH59490 from the National Institute of Health.