

# Association of candidate gene polymorphisms with metabolic syndrome and inflammation

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## Background and objectives:

Metabolic syndrome is a clustering of phenotypes (central adiposity, glucose intolerance, hypertension, and dyslipidemia) thought to be induced by insulin resistance. According to the Third National Health and Nutrition Examination Survey (NHANES III) and various other studies, the prevalence of metabolic syndrome varies by ethnicity but ranges between 16-25%. This prevalence is steadily increasing worldwide. The public health impact of the syndrome is considerable, since associated morbidities include obesity, type 2 diabetes, atherosclerotic cardiovascular disease, and diseases of the liver and gallbladder. Inflammation is associated with metabolic syndrome, as indicated by an increase in circulating levels of proinflammatory cytokines.

Our objectives were: 1) to identify candidate gene polymorphisms associated with both metabolic syndrome and inflammation, and 2) to analyze these polymorphisms in the NHANES III cohort for significant associations with metabolic syndrome.

## Methods:

The study population consisted of participants from NHANES III, a cross-sectional, nationally-representative sample of the U.S. population. Twenty-three polymorphisms within the *IL10*, *TNF*, *CRP*, *TGFβ1*, *SERPINE1*, *CCR2*, *IL1β*, *TLR4*, and *VDR* genes were analyzed based on their proposed biological involvement in metabolic syndrome physiology. The Adult Treatment Panel III (ATP III) criteria were used to identify metabolic syndrome cases from ~7000 NHANES III individuals collected from 1991-1994. We analyzed data using logistic regression stratified by race/ethnicity, and included three models with analyses run for both dominant and additive modes of inheritance.

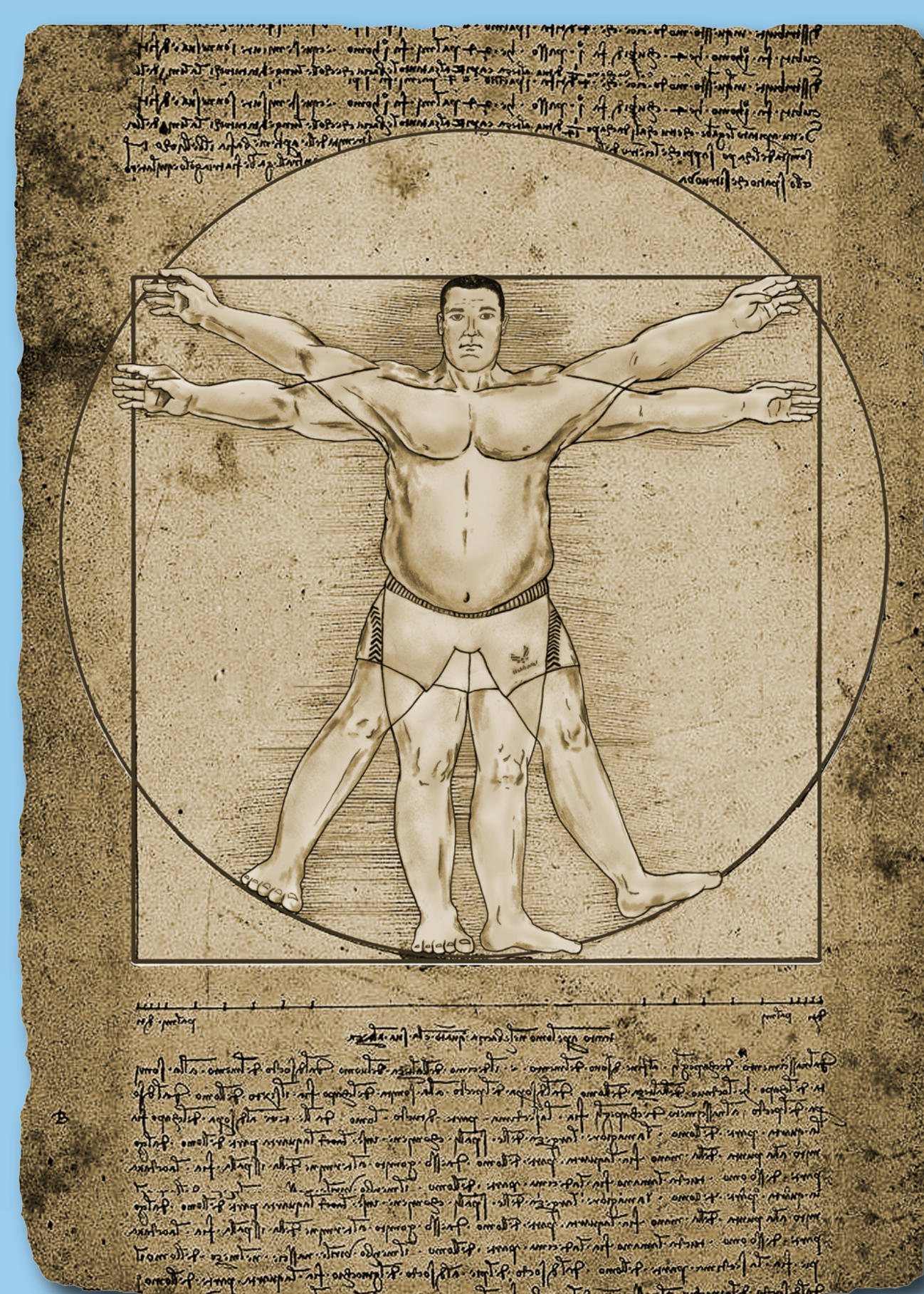


Illustration by Sammie W. King

## Results:

- The significance of the associations between the polymorphisms and metabolic syndrome differed markedly between the three race/ethnicity subpopulations (Tables 1 & 2).
- *IL10* (rs180896) was significantly associated with increased prevalence in crude analysis in non-Hispanic whites (dominant) and with a borderline decreased association in Mexican Americans (additive).
- *TNF* (rs361525) was significantly associated with decreased prevalence of metabolic syndrome in non-Hispanic whites for all three models for both modes of inheritance.
- *CRP* (rs1417938) was significantly associated with decreased prevalence in non-Hispanic blacks in both adjusted models for both inheritance modes, and in the crude model under the dominant mode of inheritance.
- *TGFβ1* (rs1800468) was significantly associated with decreased prevalence of metabolic syndrome in non-Hispanic blacks for all models and both inheritance modes.
- *SERPINE1* (rs1799762) was significant for an increased prevalence in Mexican-Americans for the crude additive model.

## Discussion/Conclusion:

- Our results indicate an association between polymorphisms in *TNF*, *CRP*, *TGFβ1*, *IL10* and *SERPINE1* and metabolic syndrome in at least one race/ethnicity subgroup in a representative sample of the U.S. population.
- Racial/ethnic groups differ from each other by genotype frequencies, as well as by environmental, social and behavioral factors. Differences in associations by race/ethnicity may reflect unmeasured gene-environment interactions.
- Understanding how these interactions affect the inflammatory pathway in different subpopulations may enhance development and implementation of public health interventions for those with increased disease susceptibility.

Table 1: Dominant Model Odds Ratios

Predictor	Level	Model 1*		Model 2†		Model 3‡	
		OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
<b>Non-Hispanic Whites</b>							
rs1800896 ( <i>IL10</i> )	GG/GA vs. AA	<b>1.38 (1.03-1.87)</b>	<b>0.025</b>	1.31 (0.96-1.78)	0.070	1.32 (0.97-1.80)	0.064
rs361525 ( <i>TNF</i> )	AA/AG vs. GG	<b>0.46 (0.27-0.81)</b>	<b>0.005</b>	<b>0.43 (0.23-0.78)</b>	<b>0.004</b>	<b>0.33 (0.19-0.58)</b>	<b>0.0001</b>
rs1417938 ( <i>CRP</i> )	TT/TA vs. AA	1.03 (0.64-1.65)	0.906	0.97 (0.55-1.69)	0.896	0.95 (0.49-1.84)	0.866
rs1800468 ( <i>TGFβ1</i> )	AA/AG vs. GG	1.43 (0.86-2.39)	0.146	1.53 (0.86-2.71)	0.125	1.21 (0.74-2.00)	0.421
rs1799762 ( <i>SERPINE1</i> )	4G4G/4G5G vs. 5G5G	0.98 (0.66-1.47)	0.927	0.95 (0.60-1.50)	0.816	0.85 (0.50-1.43)	0.518
<b>Non-Hispanic Blacks</b>							
rs1800896 ( <i>IL10</i> )	GG/GA vs. AA	1.29 (0.84-1.98)	0.215	1.36 (0.90-2.04)	0.120	1.23 (0.80-1.89)	0.311
rs361525 ( <i>TNF</i> )	AA/AG vs. GG	1.16 (0.70-1.93)	0.543	1.42 (0.76-2.64)	0.250	1.65 (0.76-3.55)	0.181
rs1417938 ( <i>CRP</i> )	TT/TA vs. AA	<b>0.64 (0.40-1.02)</b>	<b>0.047</b>	<b>0.54 (0.32-0.91)</b>	<b>0.015</b>	<b>0.60 (0.37-0.96)</b>	<b>0.026</b>
rs1800468 ( <i>TGFβ1</i> )	AA/AG vs. GG	<b>0.46 (0.28-0.76)</b>	<b>0.002</b>	<b>0.46 (0.26-0.81)</b>	<b>0.005</b>	<b>0.47 (0.28-0.81)</b>	<b>0.004</b>
rs1799762 ( <i>SERPINE1</i> )	4G4G/4G5G vs. 5G5G	0.67 (0.44-1.03)	0.053	0.66 (0.42-1.03)	0.055	0.70 (0.43-1.13)	0.123
<b>Mexican Americans</b>							
rs1800896 ( <i>IL10</i> )	GG/GA vs. AA	0.66 (0.40-1.09)	0.086	0.72 (0.41-1.25)	0.2175	0.64 (0.36-1.16)	0.1211
rs361525 ( <i>TNF</i> )	AA/AG vs. GG	1.01 (0.62-1.67)	0.951	1.06 (0.59-1.91)	0.8237	0.89 (0.41-1.93)	0.7463
rs1417938 ( <i>CRP</i> )	TT/TA vs. AA	1.01 (0.67-1.51)	0.977	1.06 (0.66-1.69)	0.8110	0.99 (0.64-1.51)	0.9456
rs1800468 ( <i>TGFβ1</i> )	AA/AG vs. GG	0.94 (0.44-1.99)	0.860	0.88 (0.40-1.95)	0.7461	1.07 (0.50-2.27)	0.8549
rs1799762 ( <i>SERPINE1</i> )	AA/AG vs. GG	1.32 (0.96-1.81)	0.072	1.14 (0.72-1.80)	0.5581	1.09 (0.65-1.81)	0.7374

\*Crude odds ratio

†Adjusted for age and sex

‡Adjusted for age, sex, serum CRP levels, alcohol consumption, smoking, caloric intake, and carbohydrate intake

Table 2: Additive Model Odds Ratios

Predictor	Model 1*		Model 2†		Model 3‡	
	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
<b>Non-Hispanic Whites</b>						
rs1800896 ( <i>IL10</i> )	1.14 (0.89-1.45)	0.281	1.12 (0.88-1.44)	0.328	1.11 (0.89-1.39)	0.312
rs361525 ( <i>TNF</i> )	<b>0.55 (0.30-1.01)</b>	<b>0.043</b>	<b>0.52 (0.27-1.03)</b>	<b>0.049</b>	<b>0.36 (0.20-0.65)</b>	<b>0.0003</b>
rs1417938 ( <i>CRP</i> )	1.12 (0.78-1.60)	0.525	1.07 (0.70-1.64)	0.747	1.06 (0.63-1.77)	0.819
rs1800468 ( <i>TGFβ1</i> )	1.37 (0.83-2.27)	0.195	1.46 (0.84-2.55)	0.154	1.18 (0.73-1.92)	0.477
rs1799762 ( <i>SERPINE1</i> )	0.91 (0.74-1.13)	0.386	0.88 (0.69-1.11)	0.252	0.81 (0.63-1.04)	0.078
<b>Non-Hispanic Blacks</b>						
rs1800896 ( <i>IL10</i> )	1.16 (0.85-1.58)	0.328	1.17 (0.86-1.58)	0.297	1.08 (0.79-1.49)	0.599
rs361525 ( <i>TNF</i> )	1.12 (0.68-1.84)	0.630	1.34 (0.72-2.47)	0.328	1.52 (0.74-3.14)	0.230
rs1417938 ( <i>CRP</i> )	<b>0.67 (0.43-1.05)</b>	<b>0.068</b>	<b>0.57 (0.35-0.93)</b>	<b>0.017</b>	<b>0.59 (0.39-0.90)</b>	<b>0.011</b>
rs1800468 ( <i>TGFβ1</i> )	<b>0.46 (0.29-0.75)</b>	<b>0.001</b>	<b>0.46 (0.26-0.80)</b>	<b>0.004</b>	<b>0.47 (0.28-0.80)</b>	<b>0.003</b>
rs1799762 ( <i>SERPINE1</i> )	0.73 (0.49-1.08)	0.099	0.71 (0.48-1.05)	0.069	0.73 (0.48-1.10)	0.109
<b>Mexican Americans</b>						
rs1800896 ( <i>IL10</i> )	<b>0.69 (0.47-1.01)</b>	<b>0.044</b>	0.72 (0.47-1.10)	0.108	0.67 (0.44-1.03)	0.054
rs361525 ( <i>TNF</i> )	1.08 (0.69-1.68)	0.731	1.11 (0.67-1.84)	0.673	0.93 (0.47-1.83)	0.830
rs1417938 ( <i>CRP</i> )	1.01 (0.74-1.36)	0.966	1.01 (0.72-1.42)	0.949	0.97 (0.71-1.32)	0.821
rs1800468 ( <i>TGFβ1</i> )	0.92 (0.45-1.91)	0.821	0.87 (0.40-1.88)	0.715	1.05 (0.51-2.19)	0.880
rs1799762 ( <i>SERPINE1</i> )	<b>1.30 (1.08-1.56)</b>	<b>0.003</b>	1.17 (0.94-1.46)	0.137	1.14 (0.89-1.48)	0.275

\*Crude odds ratio

†Adjusted for age and sex

‡Adjusted for age, sex, serum CRP levels, alcohol consumption, smoking, caloric intake, and carbohydrate intake

