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Polymorphisms of inflammatory genes and the metabolic syndrome and its phenotypes: can dietary fatty acids modulate the risks?

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The metabolic syndrome (MetS) is a common multi-component disorder resulting from genetic and environmental components[(1)]. Low-grade inflammation also plays a role in the pathogenesis of the MetS and polymorphisms of several pro-inflammatory genes have been associated with type 2 diabetes and other phenotypes of the MetS[(2)]. Dietary fat is an important environmental factor that can modify the risk of the MetS[(3)]. However, limited data exist that indicate that an individual's genetic background interacts with their dietary fat exposure, affecting their risk of the MetS. The aim of the LIPGENE prospective case–control study was to examine the interaction between polymorphisms implicated in the pathogenesis of the MetS with biomarkers of habitual dietary fat composition. The LIPGENE cohort consists of 1754 matched case and control subjects. Plasma fatty acid composition (14: 0–22: 6*n*-3) was determined as a biomarker of habitual dietary fat intake.

In the current study associations between polymorphisms of inflammatory-related genes (complement component C3 (C3), IL-6, lymphotoxin α (LTA), signal transducer and activator of transcription factor 3 (STAT3), TNFα and transforming growth factor β (TGFβ)) on the risk of having the MetS and its components (fasting hyperglycaemia, HOMA (an index of insulin resistance), abdominal obesity, high blood pressure, high TAG and low HDL) were investigated. Significant associations were found between two C3 single-nucleotide polymorphisms (SNP) and the MetS (C3 rs11569562, $P=0.01$; C3 rs2250656, $P=0.02$). Several SNP from C3, IL-6, STAT3 and TNFα were also associated with phenotypes of the MetS including: high TAG (C3 rs11569562, $P=0.02$); high systolic blood pressure (SBP; C3 rs1047286, $P=0.006$; C3 rs344550, $P=0.049$); high diastolic blood pressure (C3 rs7257062, $P=0.02$); high HOMA (C3 rs2230204, $P=0.033$; IL-6 rs1800795, $P=0.008$; IL-6 rs1800797, $P=0.005$; IL-6 rs2069832, $P=0.04$); fasting hyperglycaemia (TNFα rs1799724, $P=0.004$); abdominal obesity (STAT3 rs1053005, $P=0.01$; STAT3 rs744166, $P=0.007$; STAT3 rs8069645, $P=0.002$). Further examination of whether these polymorphisms interact with plasma fatty acids to modulate individuals' MetS susceptibility revealed a significant interaction between C3 rs1047286 and plasma SFA levels on SBP (Table).

Table. OR for the prevalence of high SBP across C3 rs1047286 genotypes stratified by plasma SFA

	GG (*n* 1107)		AG (*n* 509)		AA (*n* 65)	*P* for genotype effect	*P* for interaction
SFA (mol/100 mol)	OR	95% CI	OR	95% CI	OR		
<32	1.27	0.30, 5.44	3.49	0.78, 15.7	1	0.0027	0.0492
>32	3.66	0.49, 27.6	3.32	0.42, 26.3	1	0.4512	
	GG (*n* 1107)		AG + AA (*n* 574)				
<32	0.42	0.24, 0.73	1			0.0024	0.0179
>32	1.25	0.59, 2.64	1			0.5583	

Among subjects in the lowest 50th percentile of plasma SFA GG homozygotes have a lower risk of high SBP than AG and AA, particularly comparing A allele carriers *v*. non-carriers ($P=0.0024$). However, in the highest 50th percentile of plasma SFA the apparent protective effect of the GG homozygotes is lost with a 3-fold increased risk of having high SBP. In conclusion, the study reports significant associations between inflammatory gene SNP and the MetS and its components. Furthermore, the data suggest that high dietary SFA modulates the risk of high SBP, with levels of plasma SFA above the median significantly increasing the risk of high SBP.

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