

# Genetic approaches to the metabolic syndrome

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**The term "metabolic syndrome" (MetS) was proposed by the World Health Organization and has been accepted by other international medical authorities. The main components of this syndrome are: central obesity, hyperglycemia, hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol levels, and hypertension.<sup>1</sup> Insulin resistance seems to be the pathophysiological basis for these components. Prothrombotic and proinflammatory states, fatty liver disease, ovarian polycystosis, and other conditions could also be included in this category. Several synonyms have also been suggested for MetS: "syndrome X," "the deadly quartet," "insulin resistance syndrome," "cardiometabolic syndrome," and others. MetS is dramatically increasing in the contemporary world and represents a major health problem. It is determined by a combination of genetic and environmental factors; included in the latter is an essential part played by the so-called "modern negative lifestyle."<sup>2,3</sup>**

Family and twin studies have revealed a heritable contribution to the key components of MetS. In fact, the genetics of these different components is complex and varies in spectrum from monogenic and syndromic forms, usually rare, to the most common polygenic and multifactorial forms, including some with mitochondrial defects.<sup>3</sup>

Taking into consideration MetS as a whole, there are some important aspects of genetic research to present. First, we have to mention animal models, as their use has a number of advantages. Among these models are the Dahl salt-sensitive/resistant rat, the spontaneously hypertensive rat, the Zucker diabetic fatty rat, the KKAY mouse, and ob, db, tubby, agouti, and fatty acid translocase (FAT) mice.

There is also a new rodent model of MetS named the Wistar Ottawa Karlsburg W (WOKW) rat. Animal investigations have discovered a large number of candidate genes with biologic and pathologic relevance.<sup>2</sup>

Second, genome-wide scans have identified strong links between certain chromosomal regions and MetS. Interesting data have been reported in relation to chromosomes 1, 2, 3, 6, 7, 9, 10, 12, 14, 15, and 19.<sup>2-4</sup> However, the chromosomal regions indicated by genomic scans are relatively large and the difficulty is in knowing how to identify disease genes and their etiologic variants.<sup>3</sup>

Third, candidate gene studies have involved several groups of genes, such as:

- Genes affecting insulin sensitivity (ie, those for PPAR $\gamma$ , insulin receptor substrates, CAPN10, and others);
- Genes affecting lipid metabolism (ie, those for CD36, 11 $\beta$ -HSD I, and others);
- Genes regulating free fatty acid metabolism (ie, those for adiponectin,  $\beta$ -adrenergic receptor, and others);
- Genes producing monogenic obesity (ie, those for leptin and others);
- Genes related to inflammation (ie, those for TNF $\alpha$ , CRP, and others).<sup>2</sup>

The human nuclear receptor superfamily comprises 48 ligand-inducible transcription factors that respond to a variety of stimuli. PPAR $\gamma$  is the third member of a subdivision within the superfamily, the other two members being PPAR $\alpha$  and PPAR $\delta$

(also called  $\beta$ ).<sup>5-7</sup> The PPAR $\gamma$  gene maps to 3p25 (chromosome 3, short arm, band 25). PPAR $\gamma$  controls many different genes involved in lipid and glucose metabolism.<sup>2</sup> Multiple putative endogenous activators have been described for PPAR $\gamma$ , including fatty acids, eicosanoids, and derivatives of oxidized low-density lipoprotein (LDL).<sup>8</sup> In a short period of time, PPAR $\gamma$  evolved from a simple regulator of adipogenesis to a key therapeutic target in modern pathology (obesity, insulin resistance, MetS).<sup>5</sup>

Other candidate genes (ie, those for adiponectin, CD36, and the  $\beta$ -receptor) could also have an important role in the pathogenesis of MetS, as has been suggested by many authors.<sup>2,3,9</sup>

**The exploration of the genetics of MetS will certainly develop further in the future, due to the important preventive and therapeutic perspectives it offers.**

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