

## REVIEW PAPER

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## Genetic Forms of the Cardiometabolic Syndrome: What Can They Tell the Clinician?

Over the past 5 years, the cardiometabolic syndrome (CMS), defined as the clustering of multiple metabolic abnormalities that together increase cardiovascular disease (CVD) risk, has attracted considerable interest and debate. Researchers and clinicians have gauged its validity and potential to identify individuals at risk for diabetes and/or CVD.<sup>1,2</sup> Whatever definition or phenotype is used, the etiology of the CMS is complex and is determined by the interplay between genetic and environmental factors that affect the development of obesity, insulin resistance, and inflammation. The CMS appears to have a component of genetic susceptibility, as evidenced by clustering of the syndrome in families, although typically without the presence of a defined genetic mutation or polymorphism.

A strategy that has earlier been successfully applied to understand a complex risk phenotype was to thoroughly study individuals with a defined molecular lesion (often a rare single-gene disorder) who displayed elements of a common phenotype. For instance, study of patients with the rare genetic dyslipoproteinemia familial hypercholesterolemia yielded new understanding of the pathogenesis of elevated plasma low-density lipoprotein cholesterol (LDL-C). This knowledge was rapidly translated toward the development of statin drugs to lower LDL cholesterol and to prevent future atherosclerosis—not just in patients with familial hypercholesterolemia, but in all individuals at risk for CVD with elevated LDL cholesterol. Following this example, many investigators have begun to actively search for other rare monogenic disorders that might lead to new understandings of more prevalent phenotypes, including the CMS.

### Does the Cardiometabolic Syndrome Exist as a Distinct Entity?

A primary concern when searching for

A well-worn medical aphorism states that “when you hear hoof beats, think of a horse and not a zebra.” When applying this principle to the cardiometabolic syndrome (CMS), the horse would be represented by the prevalent CMS phenotype that affects approximately 30% of individuals in Westernized societies, while the zebra is represented by very rare conditions—such as lipodystrophy syndromes—that share some features with the more prevalent CMS. For instance, familial partial lipodystrophy types 2 and 3 result from heterozygous mutations in LMNA, encoding nuclear lamin A/C, and in PPAR $\gamma$ , encoding peroxisome proliferator-activated receptor (PPAR)- $\gamma$ , respectively. Patients with either subtype of partial lipodystrophy exhibit an increased ratio of central to peripheral fat stores, dysglycemia, dyslipidemia, and hypertension, with predisposition for developing insulin-resistant diabetes and atherosclerosis end points. Sometimes, however, the zebra serves as a model that can help us understand the horse, so that the rare partial lipodystrophies might offer some insight into pathogenesis and treatment of the more prevalent CMS. (JCMS. 2007;2:45–48) ©2007 Le Jacq

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genetic subtypes of any so-called syndrome is whether or not the syndrome actually exists. A recent provocative article argued that the CMS, or its doppelganger *metabolic syndrome* (MetS) was not a true medical syndrome, because it: (1) had no unifying pathology; (2) did not confer a CVD risk that was greater than the sum of its parts; (3) lacked an unambiguous definition; and (4) was not proven to alter intervention and treatment decisions.<sup>2</sup>

Nonetheless, the word *syndrome* is derived from the Greek roots *syn* and *dromos* that jointly mean “running together.”<sup>3</sup> Following the literal definition, the CMS/MetS can rightfully be designated a syndrome because its constituent elements, such as hypertriglyceridemia, depressed high-density lipoprotein

cholesterol (HDL-C), elevated blood pressure, elevated plasma glucose, and abdominal obesity “run together” more often than predicted by chance alone.<sup>1</sup> Whether the defining elements constitute an actual disease state is a different issue, but strictly speaking these elements define both a syndrome and a clinical phenotype. Many phenotypes studied by human geneticists are defined by cut points imposed on continuous quantitative traits; the CMS/MetS merely incorporates several quantitative traits simultaneously. Furthermore, the CMS/MetS has a unifying or cornerstone anthropometric pathology, namely increased visceral or central obesity.<sup>1</sup> The CMS/MetS concept is at minimum a convenient way for clinicians to research and follow the complex metabolic disturbances





including new selective agonists for PPAR- $\alpha$ ,  $\gamma$ , and  $\delta$ ; dual ligands for PPAR- $\alpha$  and  $\gamma$ ; and target gene-selective PPAR receptor modulators that might selectively affect adipose differentiation.<sup>25</sup> Also, some of the new classes of drugs for management of dyslipidemia might be appropriate for management of hypertriglyceridemia, prophylaxis of pancreatitis, and secondary prevention of CVD in FPLD.<sup>26</sup> Finally, medications once thought to be specific for 1 enzyme or 1 target pathway, such as TZDs, statins, or ACEIs, could exert as beneficial effects by targeting multiple metabolic risk factors, and these treatments could benefit several CMS/MetS components simultaneously.

### Implications of FPLD for the CMS/MetS

FPLD2 and FPLD3 resulting from mutations in *LMNA* or *PPARG*, respectively,

among all lipodystrophies, are an appropriate model of the more prevalent CMS/MetS, because these genetic syndromes: (1) are characterized by relatively gradual fat redistribution to central depots rather than outright global fat loss from birth; (2) are progressive, evolving relatively slowly by defined stages over years; and (3) recapitulate most of the clinical and biochemical attributes of the more prevalent CMS/MetS, including increased visceral fat stores, dysglycemia, dyslipidemia, hypertension, and predisposition to diabetes and CVD. Treatments that prove to be successful in modulating the natural metabolic history of FPLD might also prove to be useful in the treatment of these CMS/MetS. We also note that in patients who receive highly active antiretroviral therapy in acquired immune deficiency syndrome, the

CMS/MetS is steadily growing in clinical importance,<sup>27</sup> and insights regarding pathogenesis and treatment from FPLD patients might also prove to be relevant for this condition.

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