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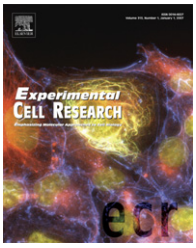

Review Article

# Phenomics and lamins: From disease to therapy

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ABSTRACT

Systematic correlation of phenotype with genotype is a key goal of the emerging field of phenomics, which is expected to help define complex diseases. Careful evaluation of phenotype–genotype associations in monogenic disorders, such as laminopathies, might provide new hypotheses to be tested with molecular and cellular studies and might also suggest potential new intervention strategies. For instance, evaluation of the clinical features of carriers of mutant *LMNA* in kindreds with familial partial lipodystrophy suggests rational, staged intervention using established pharmaceutical agents to prevent cardiovascular complications not just for patients with lipodystrophy but by extension for patients with the common metabolic syndrome. Careful non-invasive imaging shows phenotypic differences between partial lipodystrophy due to mutant *LMNA* and not due to mutant *LMNA*. Furthermore, hierarchical cluster analysis detects systematic relationships between organ involvement in laminopathies and mutation position in the *LMNA* genomic sequence. However, sometimes the same *LMNA* mutation can underlie markedly different clinical phenotypes; cellular and molecular experiments can help to explain the mechanistic basis for such differences. Finally, promising novel treatment modalities for laminopathies, such as farnesyl transferase inhibition and gene-based therapies, might help not only to illuminate mechanisms that link genotype to phenotype, but also to provide hope for patients suffering with laminopathies, since these treatments are designed to modulate key early or proximal steps in the pathogenesis of these disorders.



## Contents



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## Introduction

Modern genomic tools are revolutionising the prediction, prevention and treatment of human diseases. However, non-quantitative, non-specific, insensitive phenotypes are weak links in the discovery chain. The critical importance of well-characterised phenotypes – observable structures and functions arising from the effects of molecules, cells, tissues and organs – was underscored by the introduction of the concept of "phenomics" [1–4]. Phenomics can be defined as integrated multidisciplinary research to understand the complex consequences of genomic variation through systematic evaluation and cataloguing of standardized phenotypes [3,5]. Sensitive phenomic tools can reveal previously unseen phenotypic markers, also called "early" or "intermediate" phenotypes. Herein, we present examples of phenomics applied to define laminopathies at the levels of pathogenesis and potential clinical intervention. Specifically, we will discuss: (1) phenomic assessment of the stages of partial lipodystrophy and how this both suggests staged interventions using existing treatments and serves as a potential model for the common "metabolic syndrome" (MetS); (2) phenomic differences between familial partial lipodystrophy (FPLD) subtypes caused by *LMNA* mutations and not caused by *LMNA* mutations; (3) how phenotypic analogy between genetic and acquired partial lipodystrophy led to discovery of mutations in the re-annotated *LMNB2* gene; (4) phenomic–genomic analysis showing a non-random relationship between *LMNA* mutations and clinical phenotypes; (5) phenotypic heterogeneity among some patients with identical genomic mutations; (6) mechanistic insights into phenomic–genomic relationships from cellular and molecular investigations; and (7) the role of novel therapies – such as farnesyl transferase inhibition and gene-based approaches – in further elucidating phenotype–genotype relationships in laminopathies, which for the purpose of this review will refer to diseases caused by mutations in genes encoding lamins (*LMNA*, *LMNB1* and *LMNB2*) and also genes encoding lamin-associated proteins of the inner nuclear membrane, although we will focus on *LMNA*-associated diseases. Our review begins with lipodystrophies, which serve as monogenic models for the common MetS.

## The common metabolic syndrome (MetS)

The constellation of disturbed carbohydrate and insulin metabolism, with central obesity, dyslipidemia (elevated triglycerides [TG] with depressed HDL cholesterol), hypertension, and type 2 DM (T2DM) is called the "metabolic syndrome" (MetS) or "insulin resistance syndrome" [6]. MetS affects ~30% of North Americans and results from the interaction of environmental factors, such as caloric excess and physical inactivity, with largely unknown genetic susceptibility factors [5,6]. Altered serum concentrations of inflammatory markers are a recognized part of MetS [7–9]. The World Health Organization [10], the National Cholesterol Education Program [11] and the International Diabetes Federation [12] have proposed clinical definitions for MetS. Despite debate as to whether MetS is a discrete phenotype, the MetS concept has been useful for clinical and research applications [5]. Genetic studies have revealed novel etiologies for MetS [5]. Some molecularly characterized monogenic forms, such as the lipodystrophies, have provided important insights for understanding common MetS.

## Lipodystrophies: monogenic models of MetS

Lipodystrophy refers to rare conditions that are characterized by fat loss in some anatomical sites, with fat accumulation in non-dystrophic sites, and unusual sites such as liver and muscle. Increased fatty acid flux through plasma and liver is associated with development of dyslipidemia, insulin resistance and atherosclerosis. Lipodystrophies can be either inherited or acquired, and either partial or generalized. Some molecularly defined types of partial lipodystrophy include: familial partial lipodystrophy type 2 (FPLD2; MIM 151660) caused by mutations in *LMNA* [13–15] and type 3 (FPLD3; MIM 604367) caused by mutations in *PPARG* [16], and acquired partial lipodystrophy (APL, "Barraquer–Simons syndrome" MIM 608709) caused in some cases by mutations in *LMNB2* [17]. These partial lipodystrophies each display features of common MetS, including dysglycemia, dyslipidemia (elevated TG and depressed HDL cholesterol), hypertension and central obesity. Although the expression of MetS in rare monogenic syndromes could simply be secondary to fat redistribution, the causative gene products might produce insulin resistance directly, and thus might illuminate new causative mechanisms for insulin resistance in such common disorders as T2DM and obesity.

## Metabolic evolution of Dunnigan-type familial partial lipodystrophy type 2 (FPLD2)

Dunnigan and Kobberling independently described patients who were normal at birth but later lost subcutaneous fat from extremities and the gluteal region, resulting in prominent,