

The swinging pendulum of biomarkers in mitochondrial disease

The role of FGF21

Hannah E. Steele, MRCP
Rita Horvath, MD, PhD
Robert W. Taylor, PhD,
FRCPath

Correspondence to
Dr. Horvath:
rita.horvath@ncl.ac.uk

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Mitochondrial diseases are clinically and genetically heterogeneous metabolic disorders that often present a substantial diagnostic challenge even for experienced clinicians.¹ Although diagnostic clues are sought using widely available clinical chemistry tests (e.g., elevated serum lactate, pyruvate, or creatine kinase levels), patients are frequently subjected to invasive investigations including a muscle biopsy. Even then, a definitive diagnosis may not be forthcoming and consequently the identification of non-invasive diagnostic biomarkers has the potential to streamline the diagnostic process for both clinicians and patients.

Over the last 5 years, increased levels of fibroblast growth factor 21 (FGF21)—a circulating hormone-like cytokine involved in the regulation of lipid metabolism and starvation response—has emerged as a diagnostic biomarker for mitochondrial muscle disease. First identified in a mouse model of mitochondrial myopathy, the findings were subsequently confirmed by Suomalainen et al.² in a heterogeneous mitochondrial myopathy patient population showing that serum FGF21 (S-FGF21) levels correlated with disease severity and increased with disease progression. However, the known influence of obesity, diabetes, and liver disease on S-FGF21 levels—the latter two representing common comorbidities in many mitochondrial diseases—remained a key issue preventing immediate translation to clinical practice, even after the demonstration that S-FGF21 levels were not affected by body mass index, diabetes, triglyceride, or lipid state in another mitochondrial patient cohort.³ In parallel, serum growth differentiation factor 15 (S-GDF15)—a cytokine regulated by p53 and oxidative stress—also materialized as a potential diagnostic biomarker.^{4,5} Comparison between the two was inevitable, and because S-GDF15 showed enhanced diagnostic sensitivity and higher specificity, it appeared to have an advantage over S-FGF21.⁶

Thereafter, an assessment of the prognostic value of both biomarkers was undertaken in a genetically uniform adult cohort carrying the m.3243A>G *MT-TL1* mutation with variable tissue

involvement.^{7,8} While S-GDF15 correlated moderately with both myocardial strain, determined by echocardiogram, and disease severity—in keeping with previous work⁶—neither S-FGF21 nor S-GDF15 levels correlated with disease progression over 2 years despite objectively worsening clinical symptoms. Consequently, despite the initial anticipation surrounding both biomarkers, a consensus on how to best utilize them was lacking. The report published in this issue of *Neurology*® by Lehtonen et al.⁹ is therefore timely, because it provides clarity as to how both biomarkers can be applied in clinical practice.

The authors examine whether S-FGF21 and S-GDF15 levels—measured using commercially available ELISA kits—are influenced by the specific underlying mitochondrial respiratory chain (RC) deficiency. In addition, they assess levels in disorders without a proven mitochondrial etiology, but with clinical features common to patients with mitochondrial disease including inherited and acquired myopathies, cardiomyopathy, liver disease, and sarcopenia. Of note, both S-FGF21 and S-GDF15 are elevated in subgroups of mitochondrial disease due to abnormal mitochondrial translation, or in mitochondrial DNA (mtDNA) maintenance disorders, with mitochondrial translation defects in pediatric patients demonstrating particular increases. In contrast, no correlation is observed between S-FGF21 and RC deficiency due to mutations in RC structural components or assembly factors. Reported sensitivities of S-FGF21 and S-GDF15 are 67.3% vs 76%, respectively, which is broadly in keeping with previous work.^{6,10} Given that the sensitivities of serum lactate, pyruvate, lactate/pyruvate ratio, and creatine kinase range between 31.3% and 75%, this represents a vast improvement on existing diagnostic markers.² However, Lehtonen and colleagues demonstrate that S-GDF15 is elevated in a broad range of nonmitochondrial conditions (see figure 1E).

Despite some limitations, particularly low subject numbers in one of the patient groups, the work is strengthened by the inclusion of data from 6 representative mouse models of mitochondrial disease.

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From the Wellcome Trust Centre for Mitochondrial Research, Institute of Genetic Medicine (H.E.S., R.H.) and Institute of Neuroscience (R.W.T.), Newcastle University, Newcastle upon Tyne; and John Walton Muscular Dystrophy Research Centre (H.E.S., R.H.), Institute of Genetic Medicine, Newcastle University, Central Parkway, Newcastle upon Tyne, UK.

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Specifically, the authors replicate their reported observation of FGF21 induction in muscle-manifesting multiple RC enzyme deficiency caused by mtDNA deletions, but not in knockout models involving either RC subunit (*NDUFS4*) or RC assembly (*SURF1*) genes, and thereby establish that S-FGF21 is likely to derive from muscle, not liver. In addition, it is notable that some nonmitochondrial disease controls show increased S-FGF21 and S-GDF15 levels on a par with patients with mitochondrial disease (figure 1D; table 3), indicating that results in patients will continue to require expert clinical interpretation.

Moreover, this report also suggests that despite converging on a final common pathway, the notion of an overarching biomarker for “mitochondrial disorders” may be oversimplistic. While the utility of S-FGF21 and S-GDF15 in combination requires further assessment, both have improved diagnostic capabilities over existing biomarkers and as such should be incorporated into updated diagnostic algorithms for mitochondrial disease, particularly before a muscle biopsy and as a guide to the interpretation of diagnostic next-generation sequencing datasets. Evolving mitochondrial patient cohorts around the world will facilitate the longitudinal study of S-FGF21 and S-GDF15 levels in a broader range of mitochondrial translational and maintenance disorders to determine their value in both natural history and prognostic settings. It is crucial that S-FGF21 and S-GDF15 be carefully assessed as possible outcome measures in therapeutic trials for mitochondrial diseases and, on the basis of this study, this would be particularly salient where the underlying genetic defect leads to a disorder of mitochondrial translation or mtDNA maintenance.

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