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EDITORIAL

A call for considering biochemical concepts in clinical genetics research

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The field of *Clinical Genetics* describes the spectra of the symptoms and of the associated genomic variants for inherited disorders. These two domains are at the extremes of the chain of disease-linked abnormalities: the mutation as the ultimate cause on the one end and the phenotypic manifestation as the ultimate consequence at the other. There are, however, a number of additional in-between areas that may be altered in a disease-specific manner. These not only include structural units at the subcellular, cellular, and tissue level, but also the transcriptome, the proteome, and the metabolome. Conceptually linking these levels to *Clinical Genetics* will not only entail a better understanding of inherited disorders, but also facilitate the discovery of corresponding biomarkers.

The ideal biomarker, especially for a genetic condition, fulfills the following criteria: (i) be reliably quantifiable, (ii) be present in an easily accessible clinical sample, (iii) elucidate the molecular pathogenesis of the disease, (iv) reflect disease burden, and (v) enable monitoring of therapeutic measures (1). In this respect, the metabolome may be regarded a particularly promising type of disease link. It is highly complex, but made up of discrete, measurable entities. These metabolites are present throughout the human body, including in blood, are stabilized by sampling on dried blood spots, and can easily be determined using mass spectrometry (2).

Recent findings in the field of metabolic biomarkers are highly promising. One example is the recessive lysosomal storage disorder Gaucher disease. This multi-system metabolic condition usually manifests as bone pain, anemia, and organomegaly. The primary genetic defect is in the *GBA* gene, which codes for the enzyme glucocerebrosidase (3). Lyso-Gb1, an alternative degradation product of glucocerebroside, was initially reported to be increased in the blood of Gaucher patients in a highly specific manner (4). Subsequent studies revealed that, in addition, its levels accurately reflect the extent as well as the duration of therapeutic intervention by enzyme replacement therapy (5). Lyso-Gb1 in Gaucher disease can, thus, be considered a true metabolic biomarker success story.

While observing metabolic changes in inherited metabolic disorders may not be surprising, there is evidence for a more general impact of the genome on the metabolome (6). Indeed, even genetically determined neurodegenerative changes may be reflected by the alterations in the levels of certain blood metabolites (7). We, therefore, urge clinical geneticists to not only focus on symptoms and mutations, but to also consider options for metabolic analyses during patient compilation and sample collection as well as during design and publication of research projects. As already reflected by its name, the *Journal of Biochemical and Clinical Genetics* intends to provide a widely visible platform for pertinent efforts.

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