A High-Throughput Assay for Frataxin Allows for Newborn Screening, Diagnosis, and Treatment Monitoring of Friedreich Ataxia

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Friedreich ataxia (FA or FRDA) is an autosomal recessive neurodegenerative disorder caused by mutations in the frataxin (FXN) gene located on chromosome 9q. Discovery of the genetic cause of FA has led to an understanding of the clinical and basic science aspects of the disorder and has implications for therapeutic discoveries (1, 2). For example, a mutant mouse has been developed, allowing a model for treatment evaluation (3). However, as clinical trials have developed for this disorder, it has become apparent that although genetic testing is necessary for confirmation of the diagnosis, the current DNA-based testing is not suitable for population screening, nor can it help monitor potential treatments, leaving clinical researchers searching for a suitable biomarker.

In this issue of Clinical Chemistry, Oglesbee et al. (4) present new methodology that can be used in newborn screening, leading to an earlier diagnosis, and therefore a chance for therapeutic intervention, even before the development of symptoms. In addition, this technology allows for therapeutic monitoring, a necessity for clinical trials. The development of an improved technology for rapid, high-throughput diagnosis allows the possibility of newborn screening for FA. Early diagnosis can certainly allow for earlier treatments in the presymptomatic phase of this progressive disorder, which will be much more likely to result in clinical improvements and better prognosis.

FA was first described in the 1860s by German physician Nicholas Friedreich as a “degenerative atrophy of the posterior columns of the spinal cord” (5). At a prevalence of 1:50 000 in European populations, it is the most frequent form of hereditary ataxia, although it is rare in sub-Saharan Africans and not yet seen in the Far East (6). Genetic testing of the expansion mutations provides a diagnosis of FA; before this, clinical criteria were used as established by Geoffroy et al. (7) and Harding (8), but these clinical criteria would have excluded 25% of people who were found to have genetic mutations (9).

The symptoms of FA typically begin in childhood or adolescence, but may appear in adulthood (10). The first notable symptom is ataxia, or a gait imbalance, and limb incoordination. The ataxia is followed by a neuropathy that causes loss of deep tendon reflexes as well as loss of position and vibration sensation. Cardiac symptoms such as cardiomyopathy or an arrhythmia are common and can lead to early death. Scoliosis, or curvature of the spine, is typical and can be severe enough to require surgical intervention. Loss of speech from dysarthria (difficulty talking), hearing loss, and vision loss can occur. FA is progressive and symptoms of weakness and exercise intolerance progress over 10–20 years after onset, leaving most affected people wheelchair bound. Other manifestations can include diabetes mellitus, movement disorders such as chorea, and restless legs syndrome.

Although the gene was not discovered until 1996, recognition that FA is an autosomal recessive disorder occurred in 1976 (11). FA is now known to be an autosomal recessive trinucleotide repeat disorder, with the most common mutation being an expanded GAA triplet repeat in intron 1 on both alleles of FXN. Whereas unaffected individuals can have 5–30 GAA repeats, people affected by FA have 70–1000 repeats (12). Thus, there is an intermediate zone in which the individual may have a higher number of repeats than normal, but it remains unclear whether the person is a carrier or will exhibit later-onset disease. The mutations lead to decreased production of the protein frataxin, localized in the mitochondria. The loss of frataxin is hypothesized to disrupt iron–sulfur clusters and iron homeostasis, increasing toxic free iron and reactive oxygen species. Free oxygen radicals are thought to cause the cellular damage in target organs such as the heart and central nervous system. Emerging treatments are focused on either antioxidant therapy such as idebenone, reducing the toxic free iron, or increasing frataxin concentrations through other gene or drug delivery systems.

The ability to measure frataxin, the reduced gene product of FXN, in a high-throughput immunoassay will provide not only the ability to perform population
screening and presymptomatic diagnosis, but also a biomarker to be used to measure disease progression or response to clinical trials. It also helps to distinguish those patients that may have an expansion on a single allele from asymptomatic to late-onset presentation of disease, as the authors have demonstrated in a case example (4). The discovery of this basic science technology shows the promise of a clinically relevant application and will no doubt be used as an outcome measure in future clinical trials of FA as well as implemented in newborn screening. The ability to measure and use frataxin concentrations as a biomarker gives hope that a treatment will be found for this progressive, neurodegenerative disease.

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