THE MOLECULAR BASIS OF FRIEDREICH ATAXIA

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Friedreich ataxia (FRDA) is the most common of the early-onset hereditary ataxias in Indo-European and North African populations. The disease was first described in 1863 by Nicholaus Friedreich, Professor of Medicine in Heidelberg. Friedreich’s papers reported the essential clinical and pathological features of the disease, a “degenerative atrophy of the posterior columns of the spinal cord” leading to progressive ataxia, sensory loss and muscle weakness, often associated with scoliosis, foot deformity and heart disease. However, the subsequent description of atypical cases and of clinically similar diseases clouded classification for many years. Diagnostic criteria were established in the late 1970s, after a renewed interest in the disease prompted several rigorous clinical studies. The Québec Collaborative Group described the typical features of the disease in well-established cases. Harding modified some of the Québec Collaborative Group diagnostic criteria to include cases at an early stage of the disease. According to Harding, essential clinical features include:

i) autosomal recessive inheritance,
ii) onset before 25 years of age,
iii) progressive limb and gait ataxia,
iv) absent tendon reflexes in the legs,
v) electrophysiologic evidence of axonal sensory neuropathy, followed within five years of onset by: dysarthria, areflexia at all four limbs, distal loss of position and vibration sense, extensor plantar responses and pyramidal weakness of the legs.

The associated neuropathology is characterized by atrophy of the sensory pathways, with early loss of large neurons in the dorsal root ganglia (DRG), sensory axonal neuropathy, and degeneration of the posterior columns of the spinal cord. The cerebellum shows atrophy of the deep dentate nucleus, but its cortex is relatively preserved.
The identification of the FRDA gene and of its most common mutation, the unstable hyperexpansion of a GAA triplet repeat sequence (TRS), has allowed to re-evaluate these issues on the basis of the results of molecular testing. While the above criteria certainly identify the typical cases of FRDA, it is now clear that the disease shows a remarkable clinical variability, sometimes even within the same sibship, a rather uncommon finding for recessive disorders. Variability involves age of onset, rate of progression, severity and extent of disease involvement. Cardiomyopathy, kyphoscoliosis, pes cavus, optic atrophy, hearing loss and diabetes mellitus only occur in some patients. Atypical cases with an overall FRDA-like phenotype but missing some of the essential diagnostic features can be identified. These include late-onset Friedreich ataxia (LOFA), which develops after the age of 25, sometimes as late as the sixth decade, and Friedreich ataxia with retained tendon reflexes (FARR). The molecular basis for such a variability is still uncertain. Germ-line and somatic instability of the GAA TRS certainly plays a role, but additional genetic and environmental factors are clearly involved.