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MOVEMENT DISORDERS

Genetic and epigenetic factors determine the clinical course in Friedreich ataxia

Friedreich ataxia (FRDA) is an autosomal recessive disorder caused by a GAA repeat expansion in the frataxin gene (*FXN*). Changes in DNA methylation around the GAA expansion combine with the gene mutation to alter clinical parameters of the disease, according to a recent case–control study.

Kyle Bryant, a patient with Friedreich ataxia who was involved in the study. Courtesy of the Friedreich Ataxia Research Alliance, USA.

FRDA is the most common inherited ataxia, and no disease-modifying treatments are available. The size of the repeat expansion was known to account for some—but not all—of the variability in age of onset, and evidence suggested a role for epigenetic modification of *FXN*. "This evidence begged the questions: how does epigenetic dysregulation affect clinical outcome, and can these relationships be used in clinical research and practice?" says Marguerite Evans-Galea, who was the lead investigator of the study.

The study involved 136 patients with FRDA from two cohorts, one in Australia and one in the USA, who provided samples of blood and/or buccal cells for analysis. The researchers measured DNA methylation around the site of the triplet expansion. They found significant hypermethylation at a specific CpG dinucleotide upstream of the expansion in FRDA compared with controls, and this change correlated with reduced *FXN* mRNA levels. By contrast, downstream of the expansion, DNA methylation was decreased in FRDA compared with controls, and showed an inverse correlation with age of onset. Profiling of epigenetic modifications could, therefore, be used as an early biomarker of FRDA and might assist in predicting the clinical course of this highly variable disorder.

Evans-Galea *et al.* also showed that *FXN* expression was inversely correlated with disease severity, as measured on the Friedreich Ataxia Rating Scale, providing a key link between genetic, epigenetic and clinical features of the disease.

"Our study highlights the potential importance of novel therapies that could modify DNA methylation and increase expression of the affected *FXN* gene," says Evans-Galea. An epigenetic modifier, RG2833, is a histone deacetylase inhibitor that is entering clinical trials for FRDA.

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Original article Evans-Galea, M. V. *et al. FXN* methylation predicts expression and clinical outcome in Friedreich ataxia. *Ann. Neurol.* doi:10.1002/ana.22671