Clinical Management Guidelines for Friedreich Ataxia

Chapter 12. Friedreich ataxia due to compound heterozygosity

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12. Friedreich ataxia due to compound heterozygosity

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This chapter, describes Friedreich ataxia due to compound heterozygosity, which is found in about 4% of individuals with Friedreich ataxia. The various mutations, insertions and deletions that can be found in one *FXN* allele (along with a GAA expansion on the other allele) are described as well as implications for management. In formulating best practice for management of individuals with Friedreich ataxia due to compound heterozygosity, the author was tasked with answering the question:

What is the best management for individuals with Friedreich ataxia due to compound heterozygosity for a *FXN* intron 1 GAA expansion and point mutation/insertion/deletion?

12.1 Overview of mutations other than the FXN intron 1 GAA expansion

While approximately 96% of Friedreich ataxia (FRDA) is due to homozygosity for *FXN* intron 1 GAA expansions, about 4% is due to compound heterozygosity for a GAA expansion on one *FXN* allele and a point mutation, small insertion and/or deletion or large deletion on the other (1, 2). Here, this latter group will be called "*FXN* compound heterozygosity".

A large study compared the phenotype associated with compound heterozygosity in 111 individuals with FRDA with clinical features of 131 individuals with homozygous GAA repeat expansions (3). Mutations were examined using structural modelling, stability analyses and systematic literature review. Based on this, the *FXN* compound heterozygosity group was divided into three groups: (i) null mutation (no frataxin produced); (ii) moderate/strong impact on FXN function; (iii) minimal impact on FXN function. The group with a null mutation had a significantly earlier average age of onset and were more likely to have diabetes mellitus than people homozygous for a GAA expansion (3). However, individuals homozygous for a GAA expansion were more likely to have cardiomyopathy than those in the three compound heterozygosity groups (3).

The phenotype of individuals with *FXN* compound heterozygosity is very variable in part due to the non-GAA repeat mutation. For some, the phenotype is indistinguishable from "classical" FRDA due to homozygosity for GAA expansions and the management issues are identical. Other point mutations or deletions can lead to a milder, more severe or somewhat different phenotype to typical FRDA and this may mean that there are different management issues. Drawing conclusions about the impact of non-GAA repeat mutations is difficult because:

(i) only one or few individuals with the mutation are reported and where there is more than one individual reported with the mutation, they are often from the same family.

(ii) there is limited or no clinical data available for many of the mutations.

(iii) the size of the expanded *FXN* GAA repeat on the other allele is likely to be important in the phenotype.

The only mutation that is relatively common for which sufficient clinical data is available to make specific comment about phenotype is p.Gly130Val. The following characteristics are associated with p.Gly130Val:

(i) Lower limb spasticity is more prominent than in typical FRDA.

(ii) Upper limbs are affected to a far lesser extent than lower limbs.

(iii) Cardiomyopathy is less commonly seen than in typical FRDA.

(iv) Dysarthria is not reported.

Three siblings from a family where there is parental consanguinity have homozygosity for p.Arg165Cys, making them the first individuals to be reported with bi-allelic point mutations and no GAA expansion (4). They presented with a phenotype akin to Charcot Marie Tooth disease with optic atrophy resulting in diminished vision and dysarthria. One of the sibs was reported to have a normal echocardiogram.

12.2 Management for individuals with compound heterozygosity

For individuals with *FXN* compound heterozygosity where the phenotype is the same as typical FRDA due to homozygosity for intron 1 GAA repeat expansions, the management guidelines in this document should be followed. The main atypical phenotype seen in *FXN* compound heterozygosity is "spastic ataxia" where there is marked lower limb spasticity. Here the management is directed at treatment of spasticity (see Chapter 3.4). It cannot be assumed that other features of typical FRDA are not present and therefore monitoring for other features should be done, such as regular monitoring for cardiomyopathy (see Chapter 4.2) and diabetes mellitus (see Chapter 10.1).

Best practice statements

If a person compound heterozygous for a *FXN* GAA expansion and a point mutation/deletion has a similar phenotype to those with Friedreich ataxia due to homozygosity for GAA expansions, they should be managed as per the guidelines in this document.
If spastic ataxia is the predominant phenotype, then the main management issue is that of spasticity and the guidelines for management of spasticity should be followed.
It should never be assumed that other features of typical Friedreich ataxia (e.g., cardiomyopathy, diabetes) will not be present in individuals with compound heterozygosity; therefore, monitoring for these should take place.

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