

Currently, there is no FDA-approved treatment for FRDA. Antioxidants and iron chelation have not been overly effective, and, despite treatment, patients typically experience progressive loss of motor control and die, cardiomyopathy being the primary cause of death.

Protein replacement therapy is a well-established approach to metabolic diseases, such as diabetes, lysosomal storage disorders and hemophilia. Work in patient-derived cellular and animal models has demonstrated that replacement of functional FXN can correct or improve the FRDA disease phenotype. However, there is a need in the art for a reliable and efficient assay to measure clinical response and effectiveness of FXN replacement.

SUMMARY

In one example, the present disclosure is based, at least in part, on providing a set of markers, also referred to herein as FXN-sensitive genomic markers (or FSGMs), whose respective levels are positively or negatively correlated to frataxin (FXN) levels in a cell.

In some examples, the FSGMs of the present disclosure are contrarily regulated by FXN gene ablation followed by FXN protein replacement. Thus, said FSGMs of the present disclosure are both associated with FXN deficiency in a subject conversely associated with FXN replacement. The FSGMs disclosed herein were found to be sensitive to FXN and are considered markers of FXN replacement.

Therefore, these FSGMs can be used to determine, evaluate, and/or monitor the effectiveness of FXN replacement therapy in a subject, as described herein. In some examples, the effectiveness of FXN replacement therapy in a subject can be determined, evaluated, and/or monitored based on the analysis of one or more FSGM expression profiles before and after administration or initiation of FXN replacement therapy in the subject. Based on the results of the FSGM expression profile analysis, adjustments can be made to the FXN replacement therapy in a subject to, *e.g.*, initiate, increase, decrease or cease FXN replacement therapy in the subject.

Provided in the present disclosure is a method for evaluating FXN replacement therapy by determining an expression profile (a “baseline FXN(-) profile”) for one or more FSGMs in a sample from an FXN deficient patient prior to treatment with an FXN replacement therapy; determining an expression profile (a “FXN replacement profile”) for the one or more FSGMs in a sample from an FXN-deficient patient subsequent to treatment with an FXN replacement therapy; comparing the baseline FXN(-) profile and the FXN replacement profile, and using the comparison to determine effectiveness of the FXN replacement therapy.

In an example of the disclosure, determining an FXN expression profile for the FSGMs comprises determining an FXN feature vector of values indicative of expression of the FXN-sensitive genomic markers. FXN feature vectors may reflect the FXN expression profile status of the sample, whether the sample is from an FXN healthy subject, from an FXN deficient patient, or from an FXN deficient patient following FXN replacement therapy.

In one aspect, the present disclosure provides a method for evaluating effectiveness of frataxin (FXN) replacement therapy, the method comprising: (a) determining an FXN replacement expression profile for one or more FXN-sensitive genomic markers (FSGMs) in a sample from an FXN deficient subject following treatment with FXN replacement therapy; (b) comparing the subject FXN replacement expression profile with a baseline FXN(-) expression profile; and (c) using the comparison to determine effectiveness of the FXN replacement therapy; wherein the one or more FSGMs comprise one or more markers selected from BTG2, EGR1, PTGS2 and CTSS. In another example, the present disclosure provides a method for evaluating effectiveness of frataxin (FXN) replacement therapy, the method comprising (a) determining an FXN replacement expression profile for one or more FSGMs in a sample from an FXN deficient patient following treatment with FXN replacement therapy; (b) comparing the patient FXN replacement expression profile with a baseline FXN(-) expression profile; and (c) using the comparison to determine effectiveness of the FXN replacement therapy; wherein the one or more FSGMs are any one or more markers defined in Table 2, Table 4 and/or Figure 3.

In one example, the method further comprises determining a baseline FXN(-) expression profile for one or more FXN-sensitive genomic markers (FSGMs) in a sample from a patient exhibiting FXN deficiency prior to FXN replacement therapy.

In one example, the one or more FSGMs comprise at least one or any combination of more than one of a mitochondrial gene, a EGR-family gene, insulin-like gene, ribosome depletion response gene, mitochondrial energy production gene, proteasome regulation gene, ribosomal function gene, respiratory chain gene, cardiac muscle development gene, macromolecule catabolism gene, a translational initiation gene, mitochondrial components gene, oxidative phosphorylation gene, negative regulation of macromolecule metabolic process gene, or regulation of apoptotic process gene.

In another example, the one or more FSGMs comprise a gene encoding a secreted protein or a secreted protein, *e.g.*, a secreted protein defined in Table 2. In one example, the one or more FSGMs comprise one or more of CYR61, ADAMTS1, ASPN, FAM177A, IGF1, LOX, NRTN, SERPINE1, STC1, and THBS1. In another example, the one or more FSGMs comprise CYR61.

In another example, the one or more FSGMs comprise one or more of NR4A1, PTP4A1, ATF3, BTG2, EGR1, EGR2, EGR3, CYR61, and ABCE1.

In another example, the one or more FSGMs comprise one or more of EGR1, EGR2, EGR3 and IGF1.

In another example, the one or more FSGMs comprise one or more of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO3, MT-ATP6, MT-ATP8, and CYCS.

In another example, the one or more FSGMs comprise one or more of OPS2, VBP1, PSMA3, SLIRP, CUL2, DCUN1D1, UBE2D3, ZNRF1, RNF2, and LAMP2.

In another example, the one or more FSGMs comprise one or more of RPS15A, EIF1AX, RPL24, RPL32, RPL26, RPL10, RPL39, RPL38, RPS27L, and ABCE1.

In another example, the one or more FSGMs comprise one or more of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO3, and CYCS.

In another example, the one or more FSGMs comprise one or more of NR4A1, EGR1, EGR3, ADAMTS1, THBS1, SERPINE1, IGF1, PTGS2, and CYR61.

In another example, the one or more FSGMs comprise one or more of PSMA3, CUL2, UBE2D3, ZNRF1, RPS15A, RPL24, RPL32, RPL26, RPL10, RPL39, and RPL38.

In another example, the one or more FSGMs comprise one or more of ABCE1, RPS15A, EIF1AX, RPL24, RPL32, RPL26, RPL10, RPL39, and RPL38.

In another example, the one or more FSGMs comprise one or more of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO3, MT-ATP6, MT-ATP8, CYCS, TMEM-126A, MAOA, and ABCE1.

In another example, the one or more FSGMs comprise one or more of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO3, MT-ATP6, and MT-ATP8.

In another example, the one or more FSGMs comprise one or more of ABCE1, RPL26, RPL38, RPL10, RPL32, RPS15A, RPL24, RPL39, SLIRP, COPS2, DCUN1D1, RNF2, EGR1, BTG2, ATF3, PTGS2, IGF1, SERPINE1, and THBS1.

In another example, the one or more FSGMs comprise one or more of RPL26, THBS1, SERPINE1, IGF1, PTGS2, RPL10, RPS27L, CYCS, ATF3, BTG2, EGR1, EGR3, and CYR61.

In one example, the one or more FSGMs are upregulated following treatment with FXN replacement therapy.

In one example, the one or more FSGMs that are upregulated following treatment with FXN replacement therapy are mt-RNR1, mt-RNR2, ADNP, AI480526, C230034O21RIK, CCDC85B, CCDC85C, CTCFL, NRTN, PDE4A, PHF1, RPL37RT, SLC26A10, SNORD17, SUV420H2, WNK2, YAM1 or ZNRF1.

In one example, the one or more FSGMs are downregulated following treatment with FXN replacement therapy.

In one example, the one or more FSGMs that are downregulated following treatment with FXN replacement therapy are CYR61, mt-ATP6, mt-ATP8, mt-CO2, mt-CO3, mt-ND1, mt-ND2, mt-ND3 and mt-ND4, EGR1, EGR2, EGR3, IGF1, LAMP2, or SLIRP.

In another example, determining an FXN expression profile for FSGMs comprises determining an FXN feature vector of values indicative of expression of the FSGMs. In one example, the method comprises using the comparison to determine effectiveness of the FXN replacement therapy comprising determining first and second FXN feature vectors for the patient FXN replacement expression profile and the baseline FXN(-) expression profile respectively and determining a distance between the feature vectors.

In one example, determining the distance between the feature vectors comprises determining a scalar product of the first and second feature vectors.

In one example, the method further comprises determining a third feature vector for a normal FXN expression profile for the FSGMs for a healthy subject.

In one example, the method further comprises determining a distance between the second and third feature vectors.

In one example, the method further comprises determining a distance between the first and third feature vectors, and normalizing the distance between the first and third feature vectors to the distance between the second and third feature vectors.

In one example, the method further comprises using the normalized distance to determine effectiveness of the FXN replacement therapy.

In one example, the expression profile is determined by any one of sequencing, hybridization or amplification of the sample RNA.

In one example, the expression profile is determined by HPLC/UV-Vis spectroscopy, enzymatic analysis, mass spectrometry, NMR, immunoassay, ELISA, or any combination thereof.

In another example, the methods of the disclosure further comprise modifying treatment with the FXN replacement therapy when the FXN replacement therapy is indicated as being ineffective.

In one example, the patient is suffering from Freidrich's Ataxia (FRDA).

In one example, the method further comprises obtaining a biological sample from a patient exhibiting FXN deficiency.

In another aspect, the present disclosure refers to a method of detecting one or more frataxin-sensitive genomic markers (FSGMs) in a biological sample from a FXN-deficient subject by contacting the biological sample, or a portion thereof, with one or more detection reagents specific for detection of one or more FSGMs, wherein the one or more FSGM comprises one or more FSGMs selected from Table 2, Table 4 and/or Figure 3.

In one example, the present disclosure provides a composition for determining the expression profile of FSGMs, the composition comprising reagents for the detection of at least one or more FSGMs described in Table 2, Table 4 and/or Figure 3.

In another aspect, the present disclosure refers to the use of an FXN replacement therapy in the manufacture of a medicament for treating of a mitochondrial disease, wherein the use comprises: determining an FXN expression profile in a sample obtained from an FXN-deficient subject for one or more FXN-sensitive genomic markers (FSGMs), comparing the FXN expression profile of the sample with at least one other expression profile selected from a group consisting of normal FXN expression profile for one or more FSGMs, baseline FXN(-) expression profile for one or more FSGMs, and an FXN replacement expression profile for one or more FSGMs, classifying the sample FXN expression profile as corresponding to a normal FXN expression profile, baseline FXN(-) expression profile or an FXN replacement expression profile, wherein treating comprises initiating, increasing or decreasing the dosage of FXN replacement therapy based on the classification of the sample FXN expression profile. In another

example, the present disclosure provides a method for treatment of a mitochondrial disease, the method comprising providing a sample from a subject suffering from FXN deficiency, determining an FXN expression profile in the sample for one or more FXN-sensitive genomic markers (FSGMs), comparing the FXN expression profile of the sample with at least one other expression profile selected from the group consisting of normal FXN expression profile for one or more FSGMs, baseline FXN(-) expression profile for one or more FSGMs, and an FXN replacement expression profile for one or more FSGMs, classifying the sample FXN expression profile as corresponding to a normal FXN expression profile, baseline FXN(-) expression profile or an FXN replacement expression profile, and initiating, increasing or decreasing the dosage of FXN replacement therapy to be administered to the subject based on the classification of the sample FXN expression profile.

In another example, the present disclosure provides a method for treatment of a mitochondrial disease, the method comprising determining expression of one or more FXN-sensitive genomic markers (FSGMs) in a sample from a suffering from FXN deficiency, wherein the one or more FSGMs are any one or more markers defined in Table 2, Table 4 and/or Figure 3, and initiating, increasing or decreasing the dosage of an FXN replacement therapy to be administered to the subject based on the expression of the one or more FSGMs.

In one example, the method comprises providing or obtaining a sample from a subject suffering from FXN deficiency.

In one example, the mitochondrial disease is Friedrich's Ataxia (FRDA).

In another example, the one or more FSGMs comprise a secreted protein, *e.g.*, a secreted protein defined in Table 2. In one example, the one or more FSGMs comprise one or more of CYR61, ADAMTS1, ASPN, FAM177A, IGF1, LOX, NRTN, SERPINE1, STC1, and THBS1. In another example, the one or more FSGMs comprise CYR61.

In one example, the one or more FSGMs comprise one or more of NR4A1, PTP4A1, ATF3, BTG2, EGR1, EGR2, EGR3, CYR61, and ABCE1.

In another example, the one or more FSGMs comprise one or more of EGR1, EGR2, EGR3 and IGF1.

In another example, the one or more FSGMs comprise one or more of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO3, MT-ATP6, MT-ATP8, and CYCS.

In another example, the one or more FSGMs comprise one or more of OPS2, VBP1, PSMA3, SLIRP, CUL2, DCUN1D1, UBE2D3, ZNRF1, RNF2, and LAMP2.

In another example, the one or more FSGMs comprise one or more of RPS15A, EIF1AX, RPL24, RPL32, RPL26, RPL10, RPL39, RPL38, RPS27L, and ABCE1.

In another example, the one or more FSGMs comprise one or more of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO3, and CYCS.

In another example, the one or more FSGMs comprise one or more of NR4A1, EGR1, EGR3, ADAMTS1, THBS1, SERPINE1, IGF1, PTGS2, and CYR61.

In another example, the one or more FSGMs comprise one or more of PSMA3, CUL2, UBE2D3, ZNRF1, RPS15A, RPL24, RPL32, RPL26, RPL10, RPL39, and RPL38.

In another example, the one or more FSGMs comprise one or more of ABCE1, RPS15A, EIF1AX, RPL24, RPL32, RPL26, RPL10, RPL39, and RPL38.

In another example, the one or more FSGMs comprise one or more of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO3, MT-ATP6, MT-ATP8, CYCS, TMEM-126A, MAOA, and ABCE1.

In another example, the one or more FSGMs comprise one or more of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO3, MT-ATP6, and MT-ATP8.

In another example, the one or more FSGMs comprise one or more of ABCE1, RPL26, RPL38, RPL10, RPL32, RPS15A, RPL24, RPL39, SLIRP, COPS2, DCUN1D1, RNF2, EGR1, BTG2, ATF3, PTGS2, IGF1, SERPINE1, and THBS1.

In another example, the one or more FSGMs comprise one or more of RPL26, THBS1, SERPINE1, IGF1, PTGS2, RPL10, RPS27L, CYCS, ATF3, BTG2, EGR1, EGR3, and CYR61.

In another aspect, the present disclosure refers to a kit for detecting one or more frataxin-sensitive genomic markers (FSGMs) in a biological sample from an FXN-deficient subject or a subject being treated for FXN deficiency, comprising one or more reagents for measuring the level of the one or more FSGMs in the biological sample obtained from the subject, wherein the one or more FSGMs comprise one or more markers selected from BTG2, EGR1, CTSS and PTGS2, and a set of instructions for measuring the level of the FSGMs. In another example, the present disclosure provides a kit for detecting one or more frataxin-sensitive genomic marker (FSGM) in a biological sample from a subject exhibiting frataxin (FXN) deficiency or being treated for FXN deficiency, comprising one or more reagents for measuring the level of the one or more FSGM in the biological sample from the subject, wherein the one or more FSGM comprises one or more FSGMs selected from Table 2, Table 4 and/or Figure 3, and a set of instructions for measuring the level of the FSGM.

In one example, the reagent is an antibody that binds to the one or more frataxin-sensitive genomic marker (FSGM) or an oligonucleotide that is complementary to the corresponding mRNA of the one or more FSGM.

In one example, the one or more FSGMs comprise a secreted protein, *e.g.*, a secreted protein defined in Table 2. In one example, the one or more FSGMs comprise one or more of CYR61, ADAMTS1, ASPN, FAM177A, IGF1, LOX, NRTN, SERPINE1, STC1, and THBS1. In another example, the one or more FSGMs comprise CYR61.

In another aspect, the present disclosure refers to a panel for use in a method of monitoring or evaluating the efficacy of frataxin (FXN) replacement therapy, the panel comprising one or more detection reagents, wherein each detection reagent is specific for the detection of one or more frataxin-

sensitive genomic markers (FSGMs), wherein the one or more FSGMs comprise one or more markers selected from BTG2, EGR1, CTSS and PTGS2. In another example, the present disclosure provides a panel for use in a method of monitoring or evaluating the efficacy of frataxin (FXN) replacement therapy, the panel comprising one or more detection reagents, wherein each detection reagent is specific for the detection of one or more frataxin-sensitive genomic marker (FSGM), wherein the one or more FSGM comprises one or more markers selected from Table 2, Table 4 and/or Figure 3.

In one example, the frataxin-sensitive genomic marker (FSGM) comprises at least two or more FSGMs.

In one example, the one or more FSGMs comprise a secreted protein, *e.g.*, a secreted protein defined in Table 2. In one example, the one or more FSGMs comprise one or more of CYR61, ADAMTS1, ASPN, FAM177A, IGF1, LOX, NRTN, SERPINE1, STC1, and THBS1. In another example, the one or more FSGMs comprise CYR61.

In yet another aspect, the present disclosure refers to a kit comprising the panel as disclosed herein and a set of instructions for obtaining information relating to frataxin (FXN) replacement therapy based on a level of the one or more frataxin-sensitive genomic markers (FSGMs). In another example, the present disclosure provides a kit comprising a panel of the disclosure and a set of instructions for obtaining information relating to frataxin (FXN) replacement therapy based on a level of the one or more frataxin-sensitive genomic markers (FSGMs).

In another example, the present disclosure provides a method of detecting one or more frataxin-sensitive genomic markers (FSGMs) in a biological sample from a patient suffering from a frataxin (FXN) deficiency, optionally wherein the patient is being treated with a FXN replacement therapy, by contacting the biological sample, or a portion thereof, with one or more detection reagents specific for detection of one or more FSGMs, wherein the one or more FSGMs comprises one or more FSGMs selected from Table 2, Table 4 and/or Figure 3. In one example, the sample is contacted with one or more detection reagents specific for detection of one or more FSGMs. In another example, a portion of the sample, such as an isolated or purified nucleic acid, or protein, can be contacted with one or more detection reagents specific for detection of one or more FSGMs.

In one example, the one or more FSGMs comprise a secreted protein, *e.g.*, a secreted protein defined in Table 2. In one example, the one or more FSGMs comprise one or more of CYR61, ADAMTS1, ASPN, FAM177A, IGF1, LOX, NRTN, SERPINE1, STC1, and THBS1. In another example, the one or more FSGMs comprise CYR61.

In the discussion, unless otherwise stated, adjectives such as “substantially” and “about” modifying a condition or relationship characteristic of a feature or features of an example of the disclosure, are understood to mean that the condition or characteristic is defined to within tolerances that are acceptable for operation of the example for an application for which it is intended. Unless otherwise indicated, the word “or” in the description and claims is considered to be the inclusive “or” (having the

meaning of and/or) rather than the exclusive or, and indicates at least one of, or any combination of items it conjoins.

This Summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This Summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

BRIEF DESCRIPTION OF FIGURES

Non-limiting examples of embodiments of the disclosure are described below with reference to figures attached hereto that are listed following this paragraph. Identical features that appear in more than one figure are generally labeled with a same label in all the figures in which they appear.

Figure 1 shows clusters generated by string analysis of predicted interactions of protein products of 85 FXN-sensitive genomic markers (FSGMs) from Table 2, in accordance with an embodiment of the disclosure.

Figure 2 is a photo of a representative Western blot showing FXN levels in normal dermal fibroblasts (Norm_#23971) and FDRA patient-derived fibroblasts (FA_#03816 and FA_#68).

Figure 3 is a graph showing a baseline FXN (-) expression profile in FDRA-derived fibroblasts FA-GM03816, FA-GM04078, FA-4654 and FA-4675 treated with vehicle and compared to normal fibroblast control N-GM07522 and N-GM23971, in accordance with an embodiment of the disclosure.

Figure 4A is a graph showing gene expression analysis in FRDA patient-derived fibroblasts, illustrating that EGR1, EGR2, EGR3, and IGF1 are overall upregulated in the FRDA patient-derived fibroblasts compared to normal fibroblasts. Figure 4B is a graph showing the effect of the FXN fusion protein described in Example 1 on the expression of hFXN, EGR1, EGR2, EGR3, and IGF1 in FDRA-derived fibroblasts FA-68, compared to vehicle-treated cells, in accordance with an embodiment of the disclosure.

CLAIMS

1. A method for evaluating effectiveness of frataxin (FXN) replacement therapy, the method comprising:
 - (a) determining an FXN replacement expression profile for one or more FXN-sensitive genomic markers (FSGMs) in a sample from an FXN deficient subject following treatment with FXN replacement therapy;
 - (b) comparing the subject FXN replacement expression profile with a baseline FXN(-) expression profile; and
 - (c) using the comparison to determine effectiveness of the FXN replacement therapy;wherein the one or more FSGMs comprise one or more markers selected from BTG2, EGR1, PTGS2 and CTSS.
2. The method according to claim 1, further comprising determining a baseline FXN(-) expression profile for the one or more FXN-sensitive genomic markers (FSGMs) in a sample from the FXN deficient subject prior to FXN replacement therapy.
3. The method of claim 1, wherein the one or more FSGMs further comprise any one or more markers defined in Table 2, Table 4 and/or Figure 3.
4. The method of claim 1, wherein the one or more FSGMs comprise one or more of BTG2 and EGR1.
5. The method according to claim 1, wherein the one or more FSGMs are modulated following treatment with FXN replacement therapy.
6. The method according to any of the preceding claims, wherein determining an FXN expression profile for FSGMs comprises determining an FXN feature vector of values indicative of expression of the FSGMs.
7. The method according to claim 6, wherein using the comparison to determine effectiveness of the FXN replacement therapy comprises determining first and second FXN feature vectors for the subject FXN replacement expression profile and the baseline FXN(-) expression profile respectively and determining a distance between the feature vectors.

8. The method according to claim 7, wherein determining the distance between the feature vectors comprises determining a scalar product of the first and second feature vectors.
9. The method according to any one of claims 7 or 8, further comprising determining a third feature vector for a normal FXN expression profile for the FSGMs for a healthy subject.
10. The method according to claim 9, further comprising determining a distance between the second and third feature vectors.
11. The method according to claim 10, further comprising determining a distance between the first and third feature vectors, and normalizing the distance between the first and third feature vectors to the distance between the second and third feature vectors.
12. The method according to claim 11, further comprising using the normalized distance to determine effectiveness of the FXN replacement therapy.
13. The method according to claim 1, wherein the expression profile is determined by any one of sequencing, hybridization or amplification of the sample RNA.
14. The method according to claim 1, wherein the expression profile is determined by HPLC/UV-Vis spectroscopy, enzymatic analysis, mass spectrometry, NMR, immunoassay, ELISA, or any combination thereof.
15. The method according to claim 1, further comprising that the treatment with the FXN replacement therapy is to be modified when the FXN replacement therapy is indicated as being ineffective.
16. The method according to claim 1, wherein the subject is suffering from Freidrich's Ataxia (FRDA).
17. The method according to claim 1, further comprising obtaining a biological sample from the FXN deficient subject.

18. The method of claim 1, wherein the FXN replacement therapy comprises treatment with CTI-1601.
19. A method of detecting one or more frataxin-sensitive genomic markers (FSGMs) in a biological sample from a FXN-deficient subject by contacting the biological sample, or a portion thereof, with one or more detection reagents specific for detection of one or more FSGMs, wherein the one or more FSGM comprises one or more FSGMs selected from Table 2, Table 4 and/or Figure 3.
20. The method of claim 19, wherein the subject is being treated with a FXN replacement therapy.
21. The method of claim 19, wherein the FXN replacement therapy comprises treatment with an FXN fusion protein.
22. The method of claim 19, wherein the FXN replacement therapy comprises treatment with CTI-1601.
23. Use of an FXN replacement therapy in the manufacture of a medicament for treating of a mitochondrial disease, wherein the use comprises:
- determining an FXN expression profile in a sample obtained from an FXN-deficient subject for one or more FXN-sensitive genomic markers (FSGMs),
 - comparing the FXN expression profile of the sample with at least one other expression profile selected from a group consisting of normal FXN expression profile for one or more FSGMs, baseline FXN(-) expression profile for one or more FSGMs, and an FXN replacement expression profile for one or more FSGMs,
 - classifying the sample FXN expression profile as corresponding to a normal FXN expression profile, baseline FXN(-) expression profile or an FXN replacement expression profile, wherein treating comprises
 - initiating, increasing or decreasing the dosage of FXN replacement therapy based on the classification of the sample FXN expression profile.
24. The use of claim 23, wherein the mitochondrial disease is Friedrich's Ataxis (FRDA).

25. The use of claim 23, wherein the one or more FSGMs further comprise any one or more markers defined in Table 2, Table 4 and/or Figure 3.

26. A kit for detecting one or more frataxin-sensitive genomic markers (FSGMs) in a biological sample from an FXN-deficient subject or a subject being treated for FXN deficiency, comprising one or more reagents for measuring the level of the one or more FSGMs in the biological sample obtained from the subject, wherein the one or more FSGMs comprise one or more markers selected from BTG2, EGR1, CTSS and PTGS2, and a set of instructions for measuring the level of the FSGMs.

27. The kit of claim 26, wherein the reagent is an antibody that binds to the one or more frataxin-sensitive genomic markers (FSGMs) or an oligonucleotide that is complementary to the corresponding mRNA of the one or more FSGMs.

28. A panel for use in a method of monitoring or evaluating the efficacy of frataxin (FXN) replacement therapy, the panel comprising one or more detection reagents, wherein each detection reagent is specific for the detection of one or more frataxin-sensitive genomic markers (FSGMs), wherein the one or more FSGMs comprise one or more markers selected from BTG2, EGR1, CTSS and PTGS2.

29. A kit comprising the panel of claim 28 and a set of instructions for obtaining information relating to frataxin (FXN) replacement therapy based on a level of the one or more frataxin-sensitive genomic markers (FSGMs).