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Friedreich's ataxia

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CONTENTS

Abstract

Friedreich's ataxia (FRDA) is the most common cause of early-onset ataxia in the Western world. It is caused by lack of the mitochondrial protein frataxin. Frataxin deficiency leads to impaired iron–sulfur cluster biogenesis, resulting in respiratory chain defects and increased oxidative stress. Idebenone is a short-chain analogue of coenzyme Q with antioxidant properties. Several open-label and two controlled trials demonstrated positive effects for idebenone on cardiac hypertrophy associated with FRDA, especially in adolescent patients, but neurological outcome may be improved as well with higher doses. Currently, a phase III trial is ongoing to determine the most efficient dose and to establish idebenone as the first drug licensed for FRDA. Greater understanding of the pathogenic processes underlying FRDA will enable the development of additional strategies for the treatment of FRDA, including iron chelation using deferiprone and upregulation of frataxin levels using recombinant human erythropoietin or histone deacetylase (HDAC) inhibitors. Early diagnosis and treatment appear mandatory to maximize beneficial effects irrespective of which compound turns out to be most efficient in FRDA in the future.

Introduction

History

Friedreich's ataxia (FRDA) has been known for almost 150 years, since the early description of the German physician Nicolaus Friedreich in Heidelberg (1). He observed patients suffering from ataxia and weakness starting around puberty, with progressive worsening over time and substantial loss of proprioception. In his autopsy studies, Friedreich found severe degeneration and atrophy of the dorsal columns, with some extension to the lateral columns of the spinal cord as the pathoanatomical equivalent of neurological deficits. In his description, Friedreich already recognized the multisystemic character of the disorder, including cardiac symptoms, and pointed out the hereditary nature of the disease bearing his name.

Epidemiology

FRDA is thought to be the most frequent type of autosomal recessive ataxia in Western countries, whereas it is almost absent in Japan, China and southern Africa (2, 3). The incidence is estimated to be 1:30,000-1:50,000 in Europe, with some gradient from the north (few cases in Scandinavia) to the south (Italy). The carrier frequency has been determined to be 1:60-1:100 in central Europe (4, 5) and 1:500 in Finland (3).

Genetics

FRDA was mapped to chromosome 9 in 1988 (6). When the groups of Koenig and Pandolfo cloned the responsible *FXN* gene in 1996, this was a major breakthrough in FRDA research (7). The most frequent mutation (98%) turned out to be located in a noncoding region of the *FXN* gene and comprised the expansion of a GAA trinucleotide repeat stretch in the first intron. Whereas normal alleles have 6-34 GAA repeats, this number is expanded to 66 or even 1,700 GAAs in FRDA alleles (4); 96% of FRDA patients are homozygous for GAA repeat expansions, and the remaining 4% of patients carry a GAA expansion on one allele and a point mutation in the *FXN* gene on the other allele. No patients with point mutations on both alleles have been described.

Patients with point mutations in the *C*-terminal part of the *FXA* gene tend to have severe disease with rapid progression, whereas patients with *N*-terminal point mutations may have an atypical course. For example, the G130V mutation is associated with early onset but only mild ataxia, prominent pyramidal tract involvement and rather slow disease progression (8, 9).

As stated in more detail in the section on "Pathomechanism", the repeat expansion leads to reduced levels of the *FXN* gene product frataxin, with larger expansions resulting in smaller amounts of residual frataxin. Due to this mechanism, the number of GAA repeats on the smaller allele influences the age of onset and severity of the disease. Patients with less than 500 GAA repeats tend to have later onset, slower progression and milder disease than patients with larger expansions. However, correlations are limited, *e.g.,* because of somatic mosaicism, and do not allow a reliable prediction of the individual prognosis from the respective repeat length for a specific FRDA patient.

Pathomechanism

FRDA is a mitochondrial disease. The *FXN* gene product frataxin is a nuclear coded protein of 210 amino acids that is localized in the inner mitochondrial matrix (10). The repeat expansion interferes with transcription of the *FXN* gene in a length-dependent manner that results in reduced levels of frataxin (11). Expanded GAA·TCC stretches are prone to non-B-DNA structures by forming abnormal "sticky" DNA structures, such as triplexes of persistent DNA·RNA hybrids containing two purine GAA strands and one pyrimidine TTC strand (12).

Although the precise function of frataxin is still uncertain, it clearly has a role in iron–sulfur (Fe/S) cluster biogenesis. Fe/S clusters are essential for the synthesis of respiratory chain complexes I, II and III and aconitase. In accordance with this view, cardiomyocytes and skeletal muscle of FRDA patients show reduced activity of complexes I, II and III (13, 14). Yeast lacking the frataxin homologue *Yfh1* show, besides impaired respiratory chain function, increased levels of mitochondrial iron and are highly sensitive to oxidative stress (15). Frataxin-deficient mice have severely impaired respiratory chain function, but iron accumulation occurs clearly secondary to impaired oxidative phosphorylation (16). Similarly, iron accumulation has been observed in cardiac tissue and fibroblasts of FRDA patients and has been postulated in the dentate nucleus based on magnetic resonance imaging (MRI) studies (17), but could not be proven in a recent neuropathological approach (18).

The role of oxidative stress in the pathophysiology of human disease is unclear. Whereas one study found increased levels of the oxidative stress marker 8-hydroxy-2'-deoxyguanosine (8-OH-2'dG) in the urine of FRDA patients (19), this could not be reproduced in a more recent study (20).

Phenotype

The phenotype of FRDA largely reflects mitochondrial disease, including sensory axonal neuropathy, afferent ataxia, pyramidal damage, cardiomyopathy and diabetes. Ptosis, optic atrophy and hearing loss are additional although less frequent signs of FRDA in accordance with mitochondriopathy.

Harding defined the classical clinical diagnostic criteria of FRDA (21) as follows:

- Early onset (before 25 years of age)
- Progressive gait ataxia
- Loss of tendon reflexes
- Sensory axonal neuropathy
- Extensor plantar response
- Dysarthria that may develop late in the disease

These criteria turned out to be highly specific, since in almost all patients with these characteristics FRDA was confirmed in genetic tests (22). However, the Harding criteria lack sensitivity. About 20% of FRDA patients have a normal plantar response, preserved reflexes or late onset up to 60 years of age or more (23, 24). According to our experience, FRDA should be suspected in idiopathic or recessive ataxia if no gross cerebellar atrophy is seen on MRI and ataxia has an afferent component with clear worsening of gait or stance when eyes are closed. Additionally, reduced sensory nerve action potentials of sural nerves and repolarization abnormalities on electrocardiography are typical findings in FRDA.

Cardiomyopathy in FRDA is supposed to be of hypertrophic type. Cardiac hypertrophy may be more pronounced in children than in adults. In a recent study using cardiac MRI as a precise measure of cardiac left ventricular volume, hypertrophy was present in only 30% of adult FRDA patients (25). Long-term data on the development of cardiac mass over time are rare, but the few observations available suggest a decrease rather than an increase of left ventricular mass and interventricular septum thickness during the spontaneous course of the disease (25, 26). However, cardiac function rather than cardiac hypertrophy appears to be the adequate measure in terms of disability and disease progression. Results from ongoing prospective studies of ejection fraction and cardiac strain (27) are awaited.

Diabetes is present in about 18% of FRDA patients but has rarely been studied systematically. From our experience, the response to oral antidiabetics is poor and insulin therapy is required soon after diagnosis of diabetes, indicating insufficient insulin secretion rather than insulin resistance as underlying diabetes in FRDA. Diabetes in FRDA is thought to be caused by impaired energy metabolism in insular cells of the pancreas, but ATP-dependent insulin oscillations were normal in FRDA patients (28).

Pharmacological treatment

Increasing insight into the pathophysiological mechanisms and initial therapeutic trials in animal models and humans have brought treatment for FRDA patients into reach. However, some shortcomings hamper interventional trials. Data on the progression of FRDA in the natural course of the disease are mandatory for power calculations of upcoming studies. Very few longitudinal studies in representative cohorts have been published

(26). Additionally, results from recent studies tend to be confounded by the use of antioxidants and other supplements (29). Some natural history data can be expected from the placebo arms of ongoing studies, such as the MICONOS trial with idebenone.

Furthermore, ideal outcome measures remain to be identified. Motor performance assessed by ataxia rating scales is widely used but validity and sensitivity to change are critical and require large cohorts and a long study duration (30, 31). If cardiac hypertrophy is used in the future as an outcome measure despite the aforementioned methodological limitations, assessment by MRI is recommended as the most accurate measure of cardiac anatomy (25). Nonmotor problems like fatigue and psychosocial conflicts are frequently present but widely ignored, and quality of life has been systematically assessed in FRDA only very recently (32). Biomarkers indicating disease activity and pharmacological response would be of great help in establishing effective therapy. In FRDA, oxidative stress markers like 8-OH-2'dG or malondialdehyde have been investigated, so far with inconsistent results (19, 20, 33). Despite such problems, trials with several compounds that potentially address the pathogenic processes in FRDA at different levels have been started recently and are summarized on the Friedreich's Ataxia Reasearch Alliance website (http://www.curefa.org/docs/research_pipeline.pdf).

Antioxidants

Frataxin deficiency makes cells highly sensitive to oxidants (34). Normally, only a few electrons leak from the respiratory chain, but this leakage increases if the respiratory chain becomes defective, as in FRDA. Leaking electrons generate superoxide (O_2^-), which is catalyzed by the mitochondrial superoxide dismutase SOD2 to the oxidant hydrogen peroxide (H_2O_2). This establishes a vicious circle with reduced Fe/S cluster synthesis resulting in impaired respiratory chain complexes I, II and III, which leads to increased leakage of electrons and subsequently enhances the generation of oxidants, which add further damage to the respiratory chain. Antioxidants and coenzyme Q may help to prevent this vicious circle by detoxifying radicals and reducing the leakage of electrons from the respiratory chain.

Idebenone

Idebenone is a synthetic short-chain analogue of coenzyme Q_{10} (Fig. 1) that is thought to cross the blood–brain barrier more readily than coenzyme Q_{10} due to better lipid solubility. It is a potent antioxidant and electron carrier (35). Since the first report on the potency of idebenone in protecting cardiac muscle from oxidative stress (36), several small studies have been performed in FRDA patients, with conflicting results (Table I). One of the few controlled trials found a reduction in left ventricular mass of about 5% after 12 months of treatment with idebenone (5 mg/kg/day) in patients selected for cardiac hypertrophy at baseline (37). A long-term open-label follow-up study over up to 5 years in 104 FRDA patients, 88 of whom were treated with idebenone, found a decrease in cardiac hypertrophy on treatment, but no improvement in cardiac function. Interestingly, the decrease in left ventricular mass was even more pronounced in the untreated group, questioning the pharmacological effect of idebenone on cardiomyopathy in FRDA (26). This study found a slowly progressive deterioration of the neurological condition even with long-term idebenone treatment. Apart from one small, uncontrolled study in young ambulatory patients (38), no effect on neurological symptoms has been reported with a dose of 5 mg/kg/day idebenone.

Recently, a trial examining the safety and feasibility of higher doses of idebenone in young FRDA patients (9-17

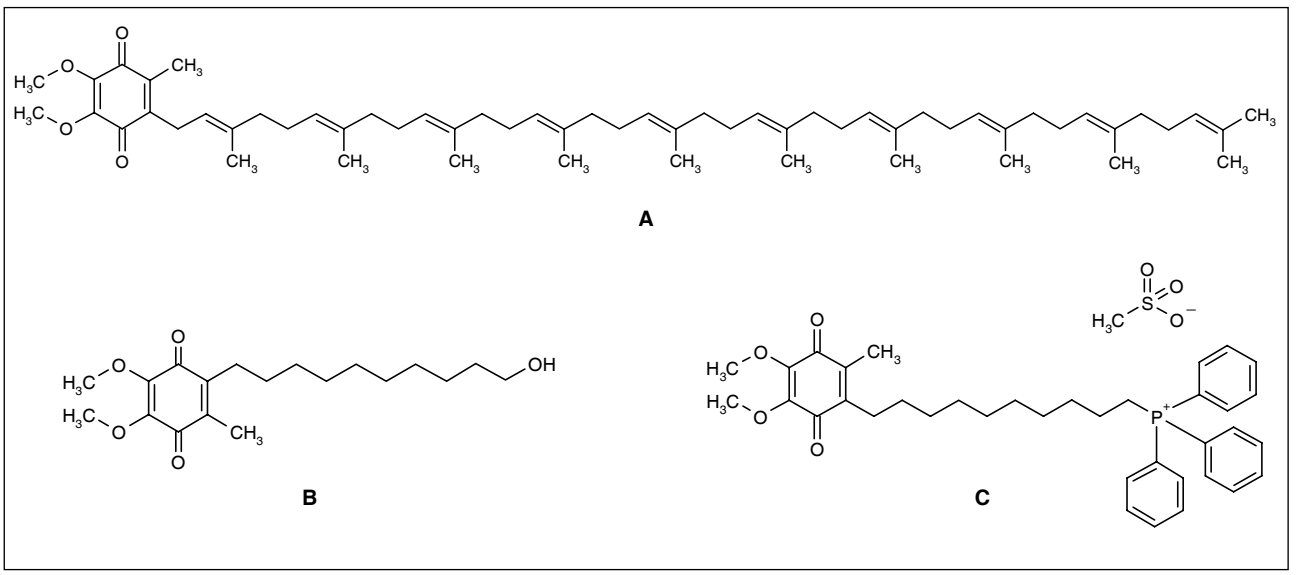

Fig. 1. Structures of coenzyme Q_{10} (**A**), idebenone (**B**) and mitoQ (**C**).

Table I: Idebenone trials in Friedreich's ataxia.

Daily dose	No. of patients	Age (years)	Study period (months)	Trial design: controlled/ blinded	Effect on LV mass	Effect on ataxia	Comments (Ref.)
5 mg/kg	3	11-21	4-9	–/–	+	–	Only patients with cardiac hypertrophy (36)
360 mg	9	19-54	1.5	+/+	–	–	No effect on energy metabolism in ^{31}P-MRS (56)
5 mg/kg	38	4-22	6	–/–	+	–	Shortening fraction improved in 5 of 6 patients (57, 58)
5 mg/kg	9	11-19	12	–/–	–	+	Oculomotor disorder improved (38)
5 mg/kg	29	20-31	12	+	+	–	Exclusion of patients with normal IVS (37)
5 mg/kg	8	8-27	12	–/–	+	–	(27)
5 mg/kg	104	13-74	6-84	+/–	+	–	No comparison to untreated group (26)
4-50 mg/kg	48	9-17	6	+/+	?	+	Dose-dependent improvement in ICARS (20)
5-20 mg/kg	24	8-46	36-60	–/–	–	?	Stabilized neurological function in pediatric patients (59)

LV, left ventricular; MRS, magnetic resonance spectroscopy; IVS, interventricular septal thickness; ICARS, International Cooperative Ataxia Rating Scale.

years of age) reported indications of a dose-dependent response, as assessed by the International Cooperative Ataxia Rating Scale (ICARS). When wheelchair-dependent patients were excluded, a significant improvement was observed in the subgroup taking the highest dose (30-50 mg/kg/day) (20).

Idebenone was originally developed by Takeda for the treatment of Alzheimer's disease and stroke. This provided extensive data on safety and tolerability in the elderly and patients with multiple morbidities (39). A recent open-label phase IA dose-escalating trial investigated the tolerability of single doses of idebenone up to 75 mg/kg. No dose-limiting toxicity was found in adults, adolescents and children suffering from FRDA. In a second phase IB study, 14 of 15 subjects tolerated 60 mg/kg/day idebenone for 1 month with at most mild adverse events, mainly of gastrointestinal origin (40). On the basis of these results, a double-blind, placebo-controlled phase II trial was initiated with idebenone at doses of 4-50 mg/kg/day. In general, side effects in the idebenone groups did not differ in frequency from placebo. However, 1 patient in the high-dose group (45 mg/kg/day) developed neutropenia that resolved after discontinuation of idebenone (20). Since neutropenia has been observed in 10 individuals of approximately 8 million treated patients in Japan, it may be a very rare but serious side effect of idebenone that requires careful monitoring, especially in high-dose studies.

Idebenone has a reasonable bioavailability. After oral application, plasma levels increase in proportion to the drug dose up to 55 mg/kg/day (40). Higher doses do not further increase plasma levels. Idebenone is considered to have a substantial first-pass effect by conjugation to a pharmacologically ineffective form. Despite this fact, only applications up to three times a day have been studied. Apart from studying different doses of idebenone, it may be interesting to develop new formulations, including slow-release products.

Idebenone is licensed in Italy and Portugal for cognitive disorders. In other countries it is available via international pharmacy. Whereas costs for the treatment of FRDA are covered by the French and Swiss health systems, it is only exceptionally accepted by health insurance in other countries. Currently, a placebo-controlled trial with three different doses of idebenone up to 2250 mg/day is ongoing in FRDA in several European countries, including Germany, the U.K., France, Belgium and The Netherlands. Additionally, a phase III placebo-controlled trial is being performed in the U.S. testing two idebenone doses (450/900 mg/day and 1350/2250 mg/day for patients of below/above 45 kg body weight) in patients 8-17 years of age over a period of 6 months. Apart from FRDA, trials are being performed in Duchenne muscular dystrophy and Leber's hereditary optic atrophy. Facial creams containing 0.5% or 1.0% idebenone have been shown to be effective in reducing fine lines/ wrinkles and improving skin hydration and skin dryness (41). Recently, the E.U. accepted the marketing authorization application of Santhera/Takeda for the treatment of FRDA.

Coenzyme Q_{10} + vitamin E

Vitamin E deficiency largely resembles clinical features of FRDA. Because of its antioxidant potency and lipid solubility, vitamin E is an interesting molecule for the treatment of FRDA. High doses of vitamin E (2100 U/day) have been studied in a fixed combination with coenzyme Q_{10} (400 mg/day) over 4 years with encouraging results on cardiac ATP synthesis, as measured by phosphorus magnetic resonance spectroscopy. A slower progression of neurological deficits compared to historical controls has been claimed, but the lack of an appropriate control group hampers reliable conclusions from this study (42).

MitoQ

To improve the efficacy of antioxidant therapy, new compounds have been designed to specifically target mitochondria as the primary compartment of pathology in FRDA. MitoQ (mitoquinone) is a derivative of ubiquinone that has been coupled to a triphenylphosphonium cation (Fig. 1). This lipophilic cation easily permeates lipid membranes and accumulates within mitochondria by exploiting the mitochondrial membrane potential (43). In fibroblasts of FRDA patients, mitoQ was several hundred-fold more potent than idebenone in the prevention of damage from oxidative stress (44). The disadvantage of this molecule is that the phosphonium group hampers its interaction with the respiratory chain, *e.g.*, the ability to reduce complex III. The first trials of mitoQ in FRDA patients are awaited in the near future.

L-Carnitine supplementation

L-Carnitine is transformed to acetyl-L-carnitine by carnitine acyltransferase (45). It may thereby exert additional neuroprotective effects by inducing heme oxygenase 1 (HO-1), heat shock protein 70 (HSP70) and superoxide dismutase 2 (SOD2) (46). Additionally L-carnitine supplementation may ameliorate carnitine deficiency arising secondary to impaired respiratory chain function in FRDA (47). In a double-blind, placebo-controlled, crossover trial, L-carnitine had a positive but not significant effect on ATP synthesis, as assessed by phosphorus magnetic resonance spectroscopy in skeletal muscle (48, 49).

Iron chelation

Excess mitochondrial iron is seen in frataxin-deficient yeast, as well as fibroblasts, heart and liver of patients suffering from FRDA. In a mouse model, intramitochondrial iron accumulated only after breakdown of respiratory chain function, suggesting that iron is a biomarker of disease progression rather than the cause of cardiac pathology in FRDA (50).

1. Deferiprone

Deferiprone is a membrane-permeant iron chelator suitable for reducing the levels of intracellular labile iron without depleting transferrin-bound iron from plasma (51). Since deferiprone crosses the blood–brain barrier, it appears to be a promising candidate for the therapy of FRDA.

An open-label phase I/II trial in 13 young FRDA patients (aged 14-23 years) investigated 20 or 30 mg/kg/day of deferiprone in two administrations over 6 months. One patient developed agranulocytosis that resolved after cessation of deferiprone. Three patients were withdrawn because of musculoskeletal pain, dizziness or Guillain-Barré syndrome. MRI was assessed as a surrogate marker of iron concentration using a multigradient T2* echo sequence and found normalization of MRI signals in the dentate nucleus of FRDA patients. Additionally, ICARS improved in this open-label study by Δ –7.3 ± 1.1% in the 9 patients who finished the study (51). A double-blind, placebo-controlled trial has commenced in Italy, Belgium, France and the U.K. testing daily doses of 20, 40 or 60 mg/kg deferiprone for 6 months, with the primary objective of demonstrating safety and tolerability of deferiprone in FRDA and evaluating efficacy as assessed by the 9-Hole Peg Test, Timed 25-Foot Walk, Low-Contrast Letter Acuity (LCLA) test, ICARS and the Friedreich Ataxia Rating Scale (FARS). An extension of this study to Canada and the inclusion of centers in the U.S. in a phase III trial are intended in the near future.

Increasing frataxin levels

Whereas antioxidants and iron chelators only treat secondary effects of frataxin deficiency, various compounds have been found to increase concentrations of frataxin, including cisplatin, 3-nitropropionic acid, sodium butyrate, erythropoietin and histone deacetylase (HDAC) inhibitors.

1. Erythropoietin

Beside its main function in the stimulation of bone marrow erythrocyte proliferation, erythropoietin has broad neuroprotective and cardioprotective capabilities which are probably mediated by widely expressed erythropoietin receptors (52). Recently, recombinant human erythropoietin was found to increase frataxin expression in lymphocytes and cardiomyocytes *in vitro* (53) and *in vivo* (54). In an open-label pilot study, 12 FRDA patients were treated with 5000 U s.c. recombinant human erythropoietin 3 times a week for 8 weeks. Frataxin levels were raised by 27% in lymphocytes compared to individual baseline levels. Additionally, oxidative stress markers were reduced (54). Hematocrit increased from 0.45 to 0.53 in males, whereas it remained stable in female patients. This study supports the concept of increasing frataxin, although further controlled trials addressing long-term effects on ataxia, cardiomyopathy and diabetes as major manifestations of FRDA are needed to prove the beneficial effect of erythropoietin in FRDA. Additionally, modified erythropoietin analogues such as CEPO (carbamylated erythropoietin), which lack hematological effects, may be better tolerated and are candidates for long-term treatment.

2. HDAC inhibitors

A different approach aims to raise frataxin expression by reversing heterochromatin formation. Aberrant acetylation and trimethylation of histone proteins were found with expanded *FXN* alleles, suggesting that gene silencing in FRDA is associated with hypoacetylation of histones H3 and H4. By screening a series of HDAC inhibitors in lymphocyte culture, compounds have been identified that increase histone acetylation and relieve repression of expanded *FXN* alleles. These HDAC inhibitors have been shown to increase both mRNA lev-

els of *FXN* and protein levels of frataxin in cultured lymphocytes of FRDA patients (55).

Symptomatic treatment

The prospect of new therapies for FRDA in the near future should not lead us to ignore already available symptomatic treatment options. Regular monitoring of FRDA patients for cardiomyopathy, cardiac arrhythmia and diabetes is mandatory for early treatment. Physiotherapy is still the backbone of treatment in Friedreich's ataxia. In most patients, a combination of training of gait, stance and coordinated movements, as well as ergotherapy for activities of daily living and speech therapy, including swallowing training, is indicated. Surgery for scoliosis and pes cavus requires special experience with these problems in neurodegenerative diseases, including problems of wound healing and triggering of dysesthesia and spinal automatism. Low doses of antispastics may be especially helpful during the night and spasmolytics may ameliorate urinary urgency.

Early diagnosis and treatment

In light of potential new therapeutic options, early diagnosis in FRDA is mandatory. Considerable delay in the diagnosis of FRDA is likely to occur, especially if the disease presents with an atypical phenotype (see above). Genetic tests are almost ubiquitously available and offer a simple and cost-effective tool for reliable diagnosis. Early diagnosis and treatment are most likely to maximize the beneficial effect of therapies irrespective of which compound will turn out to be the most effective for FRDA in the future. One of the truly inspiring aspects of FRDA research is the intense international collaborative efforts that are being utilized.

References

1. Friedreich, N. *Über degenerative Atrophie der spinalen Hinterstränge*. Arch Path Anat 1863, 391-419; 433-59.

2. Labuda, M., Labuda, D., Miranda, C. et al. *Unique origin and specific ethnic distribution of the Friedreich ataxia GAA expansion*. Neurology 2000, 54(12): 2322-4.

3. Juvonen, V., Kulmala, S.M., Ignatius, J., Penttinen, M., Savontaus, M.L. *Dissecting the epidemiology of a trinucleotide repeat disease - Example of FRDA in Finland*. Hum Genet 2002, 110(1): 36-40.

4. Epplen, C., Epplen, J.T., Frank, G., Miterski, B., Santos, E.J., Schols, L. *Differential stability of the (GAA)n tract in the Friedreich ataxia (STM7) gene*. Hum Genet 1997, 99(6): 834-6.

5. Cossee, M., Schmitt, M., Campuzano, V. et al. *Evolution of the Friedreich's ataxia trinucleotide repeat expansion: Founder effect and premutations.* Proc Natl Acad Sci USA 1997, 94(14): 7452-7.

6. Chamberlain, S., Shaw, J., Rowland, A. et al. *Mapping of mutation causing Friedreich's ataxia to human chromosome 9.* Nature 1988, 334(6179): 248-50.

7. Campuzano, V., Montermini, L., Molto, M.D. et al. *Friedreich's ataxia: Autosomal recessive disease caused by an intronic GAA triplet repeat expansion.* Science 1996, 271(5254): 1423-7.

8. Gates, P.C., Paris, D., Forrest, S.M., Williamson, R., Gardner, R.J. *Friedreich's ataxia presenting as adult-onset spastic paraparesis*. Neurogenetics 1998, 1(4): 297-9.

9. Cossee, M., Durr, A., Schmitt, M. et al. *Friedreich's ataxia: Point mutations and clinical presentation of compound heterozygotes.* Ann Neurol 1999, 45(2): 200-6.

10. Campuzano, V., Montermini, L., Lutz, Y. et al. *Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes*. Hum Mol Genet 1997, 6(11): 1771-80.

11. Grabczyk, E., Usdin, K. *The GAA*TTC triplet repeat expanded in Friedreich's ataxia impedes transcription elongation by T7 RNA polymerase in a length and supercoil dependent manner.* Nucleic Acids Res 2000, 28(14): 2815-22.

12. Wells, R.D. *DNA triplexes and Friedreich ataxia.* FASEB J 2008, 22(6): 1625-34.

13. Rotig, A., De Lonlay, P., Chreiten, D. et al. *Aconitase and mitochondrial iron-sulfur protein deficiency in Friedreich's ataxia.* Nat Genet 1997, 17(2): 215-7.

14. Lodi, R., Cooper, J.M., Bradley, J.L. et al. *Deficit of in vivo mitochondrial ATP production in patients with Friedreich ataxia.* Proc Natl Acad Sci USA 1999, 96(20): 11492-5.

15. Babcock, M., de Silva, D., Oaks, R. et al. *Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin*. Science 1997, 276(5319): 1709-12.

16. Puccio, H., Simon, D., Cossée, M. *Mouse models for Friedreich ataxia exhibit cardiomyopathy, sensory nerve defect and Fe-S enzyme deficiency followed by intramitochondrial iron deposits.* Nat Genet 2001, 27(2): 181-6.

17. Waldvogel, D., van Gelderen, P., Hallett, M. *Increased iron in the dentate nucleus of patients with Friedrich's ataxia*. Ann Neurol 1999, 46(1): 123-5.

18. Koeppen, A.H., Michael, S.C., Knutson, M.D. et al. *The dentate nucleus in Friedreich's ataxia: The role of iron-responsive proteins.* Acta Neuropathol 2007, 114(2): 163-73.

19. Schulz, J.B., Dehmer, T., Schöls, L. et al. *Oxidative stress in patients with Friedreich ataxia*. Neurology 2000, 55(11): 1719-21.

20. Di Prospero, N.A., Baker, A., Jeffries, N., Fischbeck, K.H. *Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: A randomised, placebo-controlled trial.* Lancet Neurol 2007, 6(10): 878-86.

21. Harding, A.E. *Friedreich's ataxia: A clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features.* Brain 1981, 104(3): 589-620.

22. Schöls, L., Amoiridis, G., Przuntek, H., Frank, G., Epplen, J.T., Epplen, C. *Friedreich's ataxia. Revision of the phenotype according to molecular genetics.* Brain 1997, 120(Pt. 12): 2131-40.

23. McDaniel, D.O., Keats, B., Vedanarayanan, V.V., Subramony, S.H. *Sequence variation in GAA repeat expansions may cause differential phenotype display in Friedreich's ataxia.* Mov Disord 2001, 16(6): 1153-8.

24. Galimanis, A., Glutz, L., Spiegel, R., Burgunder, J.M., Kaelin-Lang, A. *Very-late-onset Friedreich ataxia with disturbing head tremor and without spinal atrophy-A case report.* Mov Disord 2008, 23(7): 1058-9.

25. Meyer, C., Schmid, G., Gorlitz, S. et al. *Cardiomyopathy in Friedreich's ataxia - Assessment by cardiac MRI.* Mov Disord 2007, 22(11): 1615-22.

26. Ribai, P., Pousset, F., Tanguy, M.L. et al. *Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up*. Arch Neurol 2007, 64(4): 558-64.

27. Buyse, G., Mertens, L., Di Salvo, G. et al. *Idebenone treatment in Friedreich's ataxia: Neurological, cardiac, and biochemical monitoring.* Neurology 2003, 60(10): 1679-81.

28. Meyer, C., Carlqvist, H., Vorgerd, M., Schols, L., Ostenson, C.G., Ristow, M. *Regular insulin secretory oscillations despite impaired ATP synthesis in Friedreich ataxia patients.* Horm Metab Res 2006, 38(10): 683-7.

29. Myers, L., Farmer, J.M., Wilson, R.B. et al. *Antioxidant use in Friedreich ataxia.* J Neuro Sci 2008, 267(1-2): 174-6.

30. Fahey, M.C., Corben, L., Collins, V., Churchyard, A.J., Delatycki, M.B. *How is disease progress in Friedreich's ataxia best measured? A study of four rating scales*. J Neurol Neurosurg Psychiatry 2007, 78(4): 411-3.

31. Fahey, M.C., Corben, L.A., Collins, V., Churchyard, A.J., Delatycki, M.B. *The 25-foot walk velocity accurately measures real world ambulation in Friedreich ataxia*. Neurology 2007, 68(9): 705-6.

32. Wilson, C.L., Fahey, M.C., Corben, L.A. et al. *Quality of life in Friedreich ataxia: What clinical, social and demographic factors are important?* Eur J Neurol 2007, 14(9): 1040-7.

33. Emond, M., Lepage, G., Vanasse, M., Pandolfo, M. *Increased levels of plasma malondialdehyde in Friedreich ataxia*. Neurology 2000, 55(11): 1752-3.

34. Wong, A., Yang, J., Cavadini, P. et al. *The Friedreich's ataxia mutation confers cellular sensitivity to oxidant stress which is rescued by chelators of iron and calcium and inhibitors of apoptosis.* Hum Mol Genet 1999, 8(3): 425-30.

35. Gillis, J.C., Benefield, P., McTavish, D. *Idebenone. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in age-related cognitive disorders.* Drugs Aging 1994, 5(2): 133-52.

36. Rustin, P., von Kleist-Retzow, J.C., Chantrel-Groussard, K., Sidi, D., Munnich, A., Rotig, A. *Effect of idebenone on cardiomyopathy in Friedreich's ataxia: A preliminary study*. Lancet 1999, 354(9177): 477-9.

37. Mariotti, C., Solari, A., Torta, D., Marano, L., Fiorentini, C., Di Donato, S. *Idebenone treatment in Friedreich patients: One-year-long randomized placebo-controlled trial.* Neurology 2003, 60(10): 1676-9.

38. Artuch, R., Aracil, A., Mas, A. et al. *Friedreich's ataxia: Idebenone treatment in early stage patients*. Neuropediatrics 2002, 33(4): 190-3.

39. Thal, L.J., Grundman, M., Berg, J. et al. *Idebenone treatment fails to slow cognitive decline in Alzheimer's disease.* Neurology 2003, 61(11): 1498-502.

40. Di Prospero, N.A., Sumner, C.J., Penzak, S.R., Ravina, B., Fischbeck, K.H., Taylor, J.P. *Safety, tolerability, and pharmacokinetics of high-dose idebenone in patients with Friedreich ataxia.* Arch Neurol 2007, 64(6): 803-8.

41. McDaniel, D., Neudecker, B., Dinardo, J., Lewis, J. 2nd, Maibach, H. *Clinical efficacy assessment in photodamaged skin of 0.5% and 1.0% idebenone.* J Cosmet Dermatol 2005, 4(3): 167-73.

42. Hart, P.E., Lodi, R., Rajagopalan, B. et al. *Antioxidant treatment of patients with Friedreich ataxia: Four-year follow-up.* Arch Neurol 2005, 62(4): 621-6.

43. Murphy, M.P., Smith, R.A. *Drug delivery to mitochondria: The key to mitochondrial medicine.* Adv Drug Deliv Rev 2000, 41(2): 235-50.

44. Jauslin, M.L., Meier, T., Smith, R.A., Murphy, M.P. *Mitochondria-targeted antioxidants protect Friedreich ataxia fibroblasts from endogenous oxidative stress more effectively than untargeted antioxidants*. FASEB J 2003, 17(13): 1972-4.

45. Bieber, L.L., Emaus, R., Valkner, K., Farrell, S. *Possible functions of short-chain and medium-chain carnitine acyltransferases*. Fed Proc 1982, 41(12): 2858-62.

46. Calabrese, V., Colombrita, C., Sultana, R. et al. *Redox modulation of heat shock protein expression by acetylcarnitine in aging brain: Relationship to antioxidant status and mitochondrial function.* Antioxid Redox Signal 2006, 8(3-4): 404-16.

47. Infante, J.P., Huszagh, V.A. *Secondary carnitine deficiency and impaired docosahexaenoic (22:6n-3) acid synthesis: A common denominator in the pathophysiology of diseases of oxidative phosphorylation and beta-oxidation.* FEBS Lett 2000, 468(1): 1-5.

48. Schols, L., Zange, J., Abele, M. et al. *L-Carnitine and creatine in Friedreich's ataxia. A randomized, placebo-controlled crossover trial.* J Neural Transm 2005, 112(6): 789-96.

49. Sorbi, S., Forleo, P., Fani, C., Piacentini, S. *Double-blind, crossover, placebo-controlled clinical trial with L-acetylcarnitine in patients with degenerative cerebellar ataxia.* Clin Neuropharmacol 2000, 23(2): 114-8.

50. Seznec, H., Simon, D., Monassier, L., Criqui-Filipe, P., Gansmuller, A., Rustin, P. *Idebenone delays the onset of cardiac functional alteration without correction of Fe-S enzymes deficit in a mouse model for Friedreich ataxia*. Hum Mol Genet 2004, 13(10): 1017-24.

51. Boddaert, N., Le Quan Sang, K.H., Rotig, A. et al. *Selective iron chelation in Friedreich ataxia: Biologic and clinical implications.* Blood 2007, 110(1): 401-8.

52. Bogoyevitch, M.A. *An update on the cardiac effects of erythropoietin cardioprotection by erythropoietin and the lessons learnt from studies in neuroprotection.* Cardiovasc Res 2004, 63(2): 208-16.

53. Sturm, B., Stupphann, D., Kaun, C. et al. *Recombinant human erythropoietin: Effects on frataxin expression in vitro*. Eur J Clin Invest 2005, 35(11): 711-7.

54. Boesch, S., Sturm, B., Hering, S., Goldenberg, H., Poewe, W., Scheiber-Mojdehkar, B. *Friedreich's ataxia: Clinical pilot trial with recombinant human erythropoietin.* Ann Neurol 2007, 62(5): 521-4.

55. Herman, D., Jenssen, K., Burnett, R., Soragni, E., Perlman, S.L., Gottesfeld, J.M. *Histone deacetylase inhibitors reverse gene silencing in Friedreich's ataxia*. Nat Chem Biol 2006, 2(10): 551-8.

56. Schols, L., Vorgerd, M., Schillings, M., Skipka, G., Zange, J. *Idebenone in patients with Friedreich ataxia.* Neurosci Lett 2001, 306(3): 169-72.

57. Hausse, A.O., Aggoun, Y., Bonnet, D. et al. *Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia.* Heart 2002, 87(4): 346-9.

58. Rustin, P., Rotig, A., Munnich, A., Sidi, D. *Heart hypertrophy and function are improved by idebenone in Friedreich's ataxia.* Free Radical Res 2002, 36(4): 467-9.

59. Pineda, M., Arpa, J., Montero, R. et al. *Idebenone treatment in paediatric and adult patients with Friedreich ataxia: Long-term follow-up.* Eur J Paediatr Neurol 2008, Epub ahead of print.