



### EDITORIAL

Michael Morgan

Special editions of *Euro-Ataxia* are becoming more frequent than normal ones it seems. Just over a year has gone by since ataxia researchers finally succeeded in isolating and cloning the Friedreich's ataxia gene. This in itself was a major leap forward but it has now been overshadowed by this year's news – initial studies of frataxin, the protein coded by the FA gene – reveals findings which may point the way to an understanding of the biochemical cause of FA and even raises the possibility of treatment within the not too distant future.

The news that lack of frataxin may be linked to an accumulation of iron in the mitochondria was first revealed at the Montreal Symposium on Inherited Ataxias at the end of May, and made generally available to the ataxic public – or that section of it with access to the Internet – in mid-June in a separate cyber-article written by Fraser Goodmurphy, in conjunction with Dr. Massimo Pandolfo.

*Euro-Ataxia* prints both these articles inside. We also include an up to the minute report on the latest developments in 'FA and Iron' research by Dr. Michel Koenig, which takes into account the as yet unpublished findings of a further three projects.

As might have been expected the news has electrified the ataxia world, both the scientific research teams and the wider ataxic community. Reaction has generated a tremendous upsurge of interest among ataxians, not all of it well-informed, and this has prompted the NAF in the USA to issue two further articles stressing caution and patience in the interpretation of findings. We print both inside. These are not meant to be negative; rather to temper hope and to urge restraint at this critical juncture. For, as Massimo Pandolfo points out, we need to 'do this right'. In Europe this means that all National Groups should try to promote research within their own countries, by fund-raising or by lobbying. We recommend that all 'National' clinical, scientific researchers, etc., get in direct contact with the Global Committee set up at Montreal, so that effort isn't duplicated and every shot is made to count.

This is such an amazing turn of events as to warrant a separate issue devoted specifically to FA. But other Ataxias have not been ignored either: The Montreal Symposium reports progress there too.

Finally a great words of thanks to everybody who helped put this edition of *Euro-Ataxia* together in such a short space of time. Much of this issue is reliant on articles emanating from North America. It's a long list of people to thank, including Fraser Goodmurphy and Dr. Massimo Pandolfo from Canada; Drs. Subramony and Martha Nance, and Arnie Gruetzmacher of the NAF in the US; and of course Dr. Michel Koenig of France.

We conclude this issue with introductions of two EURO-ATAXIA board-members, Dagmar Kroebe, driving force and secretary-general, and Evelina Raveggi, representative from AISA in Italy.

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# FRIEDREICH'S ATAXIA MAY BE DUE TO MITOCHONDRIAL IRON OVERLOAD

Michel Koenig (IGBMC, Strasbourg–Illkirch, France)

with parts from the press releases written by Marcia Vital (NINDS-NIH) and Fraser J. Goodmurphy (Internaf).

Just over one year after the discovery of the Friedreich's ataxia gene, new results shed light on the likely mechanism involved in this disease. The discovery of the Friedreich's ataxia gene already had an important impact on diagnosis and understanding of the clinical variability of the disease. At the same time, the discovery raised new questions. The protein made from the gene – christened frataxin – was novel and of unknown function. Five recent papers have started to answer this issue. Three of them (Babcock et al. 97, Koutnikova et al. 97 and Campuzano et al. 97) demonstrate that frataxin is located in small structures of the living cells, called mitochondria, which produce, among other things, the universal fuel (called ATP) used by all cells to meet their energy needs. The papers of Koutnikova et al. and Campuzano et al. also demonstrate that the Friedreich's ataxia gene codes for frataxin alone and does not include the neighbouring gene, STM7, that codes for a phosphatidyl inositol phosphate kinase (Carvajal et al. 95). Hence the claim that Friedreich's ataxia is due to a phosphatidyl inositol phosphate kinase deficiency (Carvajal et al. 96) is incorrect.

Four of the five papers (Babcock et al. 97, Koutnikova et al. 97, Wilson et al. 97 and Foury et al. 97) make use of a simple organism model, the baker's yeast, to unravel frataxin function. Yeast also has frataxin and the structure of the human and yeast frataxins are similar enough to hypothesise that they also have a similar function. Indeed, yeast frataxin is also located in the mitochondria (Babcock et al. 97). The three groups have therefore inactivated the yeast gene, mimicking in a way the inactivation of the frataxin gene in patients. Unlike humans, yeast can live without mitochondria when grown on certain media. When the yeast frataxin mutants were forced to use their mitochondria, they became rapidly seriously sick, failed to produce energy and lost their mitochondria. In particular, the mutants became more sensitive to oxidative compounds, such as hydrogen peroxide, known to be toxic by-products of the mitochondria generated during the process of energy production (Babcock et al. 97 and Foury et al. 97). These two studies also identified a specific iron overload in the mitochondria of the mutant yeast (and not elsewhere within the yeast cells) at a level about 10 fold above normal. The extra iron in the mitochondria is the obvious cause of higher sensitivity to oxidative com-

pounds, since iron is a well known catalyst (rusty iron is well known to all) of the production of so-called free radicals from such compounds. One of the produced free radicals, the hydroxyl radical (OH<sup>•</sup>) is known to be particularly damageable to cell structures and to mitochondria in particular.

We have shown that human frataxin is localised at mitochondrial membranes (Campuzano et al. 1997). Taken together with the yeast iron results, it suggests that frataxin is a modulator of iron import or export in or out from the mitochondria.

"I'm cautiously optimistic about the finding," says Massimo Pandolfo, M.D. "Further research may give us clues to understanding the pathogenesis of this disease and lead to treatments." "We now have a window into the cell," says Giovanna Spinella, M.D., a medical officer at the NINDS. "We went from having no understanding of the function of this gene to having a working model for what might be going on in humans."

The organs affected in Friedreich's ataxia, heart been one of them, are indeed very rich in mitochondria. In a detailed study of frataxin expression in mouse, Koutnikova et al. (1997) show that frataxin is more expressed in these tissues than in others. Though frataxin is moderately expressed in the spinal cord, it is highly expressed in the dorsal root ganglia ñ known to be the primary site of neuronal degeneration in Friedreich's ataxia. The dorsal root ganglia is the location of the cell bodies of the neurons whose axons (neurologic wires) run in the sensitive nerves and in the posterior columns of the spinal cord (these structures are heavily affected in Friedreich's ataxia patients). Further evidence for a connection between Friedreich's ataxia and iron overload exists in post-mortem studies of patients' hearts that show an unnaturally high level of iron (Lamarche et al. 1994). Researchers, however, have yet to find evidence of iron accumulation or oxidative damage in brain or spinal cord tissue. Other tissues known to be rich in mitochondria also show a high expression of frataxin, such as liver, pancreas, brown fat (present in new-borns) and stomach (Koutnikova et al. 97). With the exception of pancreas, these tissues are not known to be affected in Friedreich's ataxia. Several explanations might account for the differences between sites of expression and sites of pathology (luckily less widespread):

- this might reflect a difference between mouse and

man (studies were done in mouse);

- tissues that are affected are made of nondividing cells and therefore cannot regenerate;
- human (and mouse cells) have developed sophisticated means to cope with free radicals, even in the absence of frataxin, in most but not all cells. Iron accumulation will probably not appear as clear and dramatic in patient's cells than in yeast, which do not have as many free radical scavenger enzymes as higher organisms, and the difference may account for the very slow progression of the disease in man.

Despite his optimism, Dr. Kaplan who is the senior author of the Babcock study, advises against jumping to conclusions. Future research into Friedreich's ataxia may lead to some intervention therapies, he says, but scientists must first confirm the theory of iron overload in the human disease. Dr. Kaplan states that scientists need to conduct further research before they can generally apply yeast function to human disease. Still, he says, the finding is a step in the right direction. "No one suspected previously that this lethal neurological disease resulted from mitochondrial iron overload," says David Badman, Ph.D., director of hematology research at the National (US) Institute of Diabetes and Digestive and Kidney Diseases. "This is a clear example of how essential fundamental research is to improving treatments for specific diseases."

Dr. Pandolfo says that there may be some hope for treatment with iron chelators, substances that remove excess iron from cells, and antioxidants, like vitamin E, which break down or remove toxins from cells. However Dr. Pandolfo stresses caution and patience to those tempted to try untested remedies. He says that even though the symptoms of patients suffering from vitamin E deficiency resemble the symptoms in Friedreich's ataxia, studies involving vitamin E therapy for Friedreich's ataxia patients have shown limited success. On an optimistic note, he says that scientists may find a significantly therapeutic combination of iron chelators and antioxidant drugs for Friedreich's ataxia patients in the future. "The idea of this kind of treatment is just at the embryonic stage at this point," says Dr. Pandolfo. "We still need to work out the system before we can recommend any kind of treatment." The availability of mutant mice having inactivated frataxin genes should facilitate and speed up the validation of the iron theory and the testing of new therapeutic protocols and combinations. Such mutations are under construction in our laboratory (M. Koenig). Although they are more sophisticated to create than yeast mutants, they should be available within a year. It is important to note that, owing to the very unique nature of the major Friedreich's ataxia mutation (an intronic trinucleotide expansion), frataxin is reduced but probably not totally absent in patients. This fea-

ture might need to be reproduced in the mutant mouse, in order to be viable.

At the recent First International Symposium on Inherited Ataxias held in Montreal, Doctor Pandolfo took the names of over 20 Neurologists and Geneticists from Canada, the United States, England, Italy, Spain, France, Germany, Australia, and Russia who are interested in investigating the possibilities of treating this accumulation with iron chelators and antioxidants. This global committee needs to meet a number of critical aims before rushing into Clinical Trials: development of a working model of Friedreich's ataxia in mice, development of a safe and effective iron chelator, selection of an appropriate antioxidant, and development of meaningful measurements of effects. According to Doctor Pandolfo, the committee wants to "do this right". They urge you to refrain from asking your Doctor for any sort of iron chelator, and they advise you not to attempt to completely eliminate iron from your diet because iron deprivation directly causes a number of other disorders which are just as serious as Friedreich's ataxia.

Fraser J. Goodmurphy wrote to INTERNAF: "We have all been waiting a long time for this news. Encouraging results may be published sooner than you might expect. In the meantime, because FRDA research is not well supported, you may want to consider helping fund this project by donating your time or money to one of the organizations which fund Ataxia research in your country. Speaking as someone who has been coping with FRDA for 20 years, I believe that we all have a valid reason to be optimistic about the possibility of a viable treatment becoming available in the near future."

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## FRIEDREICH'S ATAXIA: FRATAXIN AND IRON ACCUMULATION IN THE MITOCHONDRIA

Fraser J. Goodmurphy (London, Canada)

Massimo Pandolfo (Centre de Recherche Louis-Charles Simard, Montreal, Canada)

In the 8 March 1996 issue of *Science*, Doctor Massimo Pandolfo and his colleagues in Houston, Texas and around the world announced that they had cloned the gene responsible for Friedreich's Ataxia (FRDA), a recessively inherited neurodegenerative disorder characterized by a wide range of symptoms including cardiac, muscular-skeletal, and metabolic complications.

Its cause has remained a mystery and has been untreatable since it was first identified by Nicholas Friedreich, a Professor of Medicine in Heidelberg, Germany, over 120 years ago. Since relocating to Montreal, Canada, Doctor Pandolfo and a number of laboratories in Canada, the United States, France, Italy, and Belgium have clarified how lack of *Frataxin* – the protein expressed by the FRDA gene X25 – appears to cause FRDA and how this cause *might* eventually be treated. Although the connection between the role of Frataxin and the cause of FRDA is based on *theory* and *observation* at the moment, it may eventually lead to a clinical trial. *No* drugs are currently available to safely and effectively treat or cure the cause of this disorder but this research remains a significant breakthrough. It offers us a new and valid reason to hope that a treatment to halt or slow the progression of FRDA might be on the horizon.

During the past year, laboratories around the world have observed that Frataxin is apparently a mitochondrial protein, concentrated in the tiny structures inside cells which convert food into energy. When Doctor Jerry Kaplan and his colleagues at the University of Utah 'knocked out' a gene in Baker's Yeast (Yeast Frataxin Homologue 1, YFH1) which is genetically similar to X25, iron accumulates in the mitochondria causing mitochondrial dysfunction, possibly by catalyzing the production of free radicals; by 'chemically helping' the formation of unstable molecules which destroy nerves and organs. These observations, which appear in the Friday 13 June 1997 issue of *Science* in an article co-authored by Doctor Pandolfo, suggest

that the process of iron accumulation in the mitochondria could be studied within FRDA cells grown in a test tube, and if the accumulation appears to cause the degeneration characteristic of FRDA, the efficacy of iron chelators – drugs which remove iron from cells – could be evaluated for protecting these cells. If the relationship proves to be valid and reliable, an investigation of the therapeutic benefits of iron chelating drugs alone or in combination with antioxidants such as Vitamin E among individuals who have been diagnosed with FRDA may be considered.

While this news is very exciting, a number of caveats about the hypothesis itself and the method in which it ought to be tested need to be addressed before it can be applied, especially among humans. Obviously, our cells are infinitely more complicated than Yeast cells. Because we cannot live without functional mitochondria and because our cells contain a varying amount of them, unlike yeast, the connection between iron accumulation and the degeneration characteristic of FRDA may not be as straightforward as it first appears. Furthermore, as all of us who have been diagnosed with FRDA express some amount of residual Frataxin no matter how much our DNA differs from the norm, observations drawn from Yeast cells may not be entirely compatible with the processes that cause FRDA in humans. A number of laboratories around the world are diligently working on developing a 'transgenic' model of FRDA in mice in order to study how Frataxin functions in organisms that are closer to humans but none of them have published results to date.

Although a published result indicates that a single individual has been successfully treated for Aceruloplasminemia, an autosomal-recessive neurodegenerative disorder characterized by iron overload in the Central Nervous System, with an iron chelator, the particular drug has a number of drawbacks. It is very expensive, it is not overly effective in children, and occasionally it has some toxic side effects. Furthermore, it is not administered orally, but injected or infused by a small pump. An oral medication is currently in Clinical Trials in Canada and Europe but evidence of its safety and effectiveness in chelating iron – eliminating it from iron-overloaded cells – remains inconclusive. The problem of measuring the extent of iron overload and free radical damage among

those of us with FRDA is equally complicated. Minerals cannot be easily visualized by non-invasive investigative techniques such as Magnetic Resonance Imaging (MRI), which actually images structures according to their difference in water content. Similarly, free radical production and damage are impossible to quantify in living organisms at the moment. Procedures may be developed, however, to increase the sensitivity of MRI to iron, and experiments aimed at extending free radical assessment beyond tissue samples and cultured cells to those of us with FRDA are currently underway.

These latter concerns need to be addressed because the severity and symptoms of FRDA vary so much. Before anyone who has been diagnosed with FRDA can be treated with an iron chelator or an antioxidant, we need to confirm beyond a reasonable doubt that iron accumulation in the mitochondria is indeed the primary cause of the progression of FRDA, and that this kind of treatment is safe and effective. A number of circumstances however, warrant optimism. Another Neurologist at the University of Sherbrooke in Quebec observed iron accumulation in the mitochondria of the heart cells among those of us with FRDA almost 20 years ago. Up to this year, the cause of the accumulation remained a mystery – until genetic science advanced far enough to reveal that the protein expressed by X25 appears to cause the iron accumulation which seems to produce FRDA. At the recent First International Symposium on Inherited Ataxias held in Montreal, Doctor Pandolfo took the names of over 20 Neurologists and Geneticists from Canada, the United States, England, Italy, Spain, France, Germany, Australia, and Russia who are interested in investigating the possibilities of treating this accumulation with iron chelators and antioxidants.

This global committee needs to meet a number of critical aims before rushing into Clinical Trials: development of a working model of FRDA in mice, development of a safe and effective iron chelator, selection of an appropriate antioxidant, and development of meaningful measurements of effects. According to Doctor Pandolfo, the committee wants to “do this right”. They urge you to refrain from asking your Doctor for any sort of iron chelator, and they advise you not to attempt to completely eliminate iron from your diet because iron deprivation directly causes a number of other disorders which are just as serious as FRDA. We have all been waiting a long time for this news. Encouraging results may be published sooner than you might expect. In the meantime, because FRDA research is not well supported, you may want to consider helping fund this project by donating your time or money to one of the organizations which fund

Ataxia research in your country. Speaking as someone who has been coping with FRDA for 20 years, I believe that we all have a valid reason to be optimistic about the possibility of a viable treatment becoming available in the near future.

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## **OUR COMMON ANCESTRY: The origin of the Friedreich's ataxia GAA repeat expansion**

*Michel Koenig (IGBMC, Strasbourg-Illkirch)*

Genetic studies on the origin of the Friedreich ataxia major mutation (the GAA trinucleotide repeat expansion mutation) have revealed that over 95% of patients of ‘Caucasian’ ancestry (including the Europeans and most populations of the Arabic countries) received the mutations from a single ancestor who lived tens of thousand of years ago (Cossée et al. 1997). The study revealed that the common ancestor (called the founder) did not pass an expansion mutation to his descendants but a frataxin GAA repeat longer (presumably around 18 GAA) than the GAA repeat prevailing at that time (presumably around 9 GAA). However, the longer GAA repeat happened to be more instable (as this is usually the case for simple nucleotide repeats) and gave rise to GAA repeat expansions (disease causing) by successive enlargement over centuries, even millennia. One of the last steps of enlargement (which appeared to be quite spectacular) has even been seen in a very small number of Friedreich ataxia families, with one of the parental repeats (from 34 to 65 GAA) being much smaller than the one found in the affected child (from 350 to 650 GAA). (Cossée et al. 1997, Epplen et al. 1997, Montermini et al. 1997) The smallest known disease causing expansion is about 110 GAA, found in patients with very late onset Friedreich ataxia (after 40 years). (Cossée et al. 1997)

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# INTERNATIONAL SYMPOSIUM ON INHERITED ATAXIAS

Montreal, May 29 – June 1, 1997

Summary by Martha Nance, MD, National Ataxia Foundation

Over 100 ataxia researchers, clinical specialists, and neurology trainees met in Montreal, Canada, from May 29 – June 1, 1997, for an International Symposium on Inherited Ataxias. The main sponsors for the meeting which was chaired by Dr. Massimo Pandolfo, were Hoechst Marion Roussel and Teva Marion Partners Canada. NAF and a number of other organizations were also sponsors. The meeting was truly international and packed with information, including 80 presentations by researchers from 15 countries, about research performed in 27 different countries! The audience was updated on the clinical and genetic features of 11 different forms of hereditary ataxia. I will try to summarize the major points of the meeting below, in three sections: the dominant ataxias, Friedreich's ataxia, and other. I apologize for the length of this "summary" – it was a very busy meeting!

## I. Dominant Ataxias

### a. SCA1, SCA2, SCA3

**Clinical update:** SCA1, SCA2, and SCA3 are all forms of what the late Dr. Anita Harding termed, "adult-onset cerebellar ataxia type 1 (ADCA1)". All presenters emphasized that while certain neurologic symptoms are more or less frequent in one disease or another, even an experienced ataxia specialist cannot reliably tell whether an individual patient has SCA1, SCA2, or SCA3 just by examining the patient. All three conditions are characterized by adult-onset ataxia. Brisk reflexes are common in SCA1. Slow eye movements are a core feature of SCA2 and some families have dementia, muscle cramps, and facial myokymia (muscle twitches in facial muscles). Dystonia and spasticity are more common in SCA3, and vestibular dysfunction with nystagmus may be more common in this disorder. MRI scans may show more prominent cerebellar and brainstem atrophy in patients with SCA2 than in SCA3 patients.

**Frequency:** The relative frequency of these disorders is clearly different in different parts of the world. Together, SCA1, SCA2, SCA3, and SCA6 (see below) account for about 40-80% of dominant hereditary ataxia families. Researchers from the US, Britain, Japan, Germany, Russia, South Africa, India, Cuba, Portugal, and Spain each presented data about how many patients have which disorder. It seems that SCA1 is far more common in Russia and South Africa, SCA1 and 2 are more common in Britain, SCA2 is more common in Germany, and SCA3 is more common in Japan and Germany. SCA2 is responsible for almost all dominant ataxia in India and Cuba, and SCA3 in Portugal. The great melting pot of the United States seems to have a mixture of diseases, with SCA1 being the least common.

**Genetics:** All three diseases are caused by expansions of CAG repeat sequences within their respective genes. The three diseases share several features which are becoming well-known, because they are common to most CAG repeat diseases. There is a correlation between the age that symptoms begin and

repeat number, with larger repeat numbers being associated with earlier onset. Abnormally expanded CAG repeat sequences are unstable when they are passed to the next generation; they tend to expand further, so that the child has a higher repeat number than the parent, although decreases in repeat numbers are possible. The tendency to expansion seems to be more prominent when the abnormal gene comes from an affected father. Finally, there is mild instability of repeat numbers in body tissues, with the cerebellum tending to have slightly fewer repeats than other tissues. What is a normal repeat number, and what is an abnormal repeat number, are a little different for each disease.

**Biology:** Several presentations concerned the mechanisms that lead to trinucleotide repeat expansions. Although there are no definite answers, it seems that DNA sequences with a large number of CAG repeats twist into a shape that makes it easier for the enzymes that copy DNA to make mistakes (which might lead to a larger number of CAG repeats in the next generation). This is a new area of research which will attract scientists studying DNA repair and DNA replication to studying problems that involve ataxia genes.

**Protein:** The enlarged SCA1 and SCA3 proteins appear to be located in the nucleus of the cell, or in the mitochondria; further work in this area will help us understand how the enlarged proteins cause symptoms.

**SCA1 Mouse:** An update about the "SCA1 mouse" was given. An abnormal SCA1 gene has successfully been put into a strain of mice, who develop progressive ataxia shortly after birth. These mice are being used by a number of research groups to study how the abnormal gene is expressed in the cell, what the earliest changes in the brain are, and a number of other questions.

### b. SCA4

SCA4 seems to be very rare. The unique clinical feature of SCA4 is a sensory axonal neuropathy (in addition to ataxia). The average onset is about age 40, and

the progression is slow. The gene is located on chromosome 16, but it has not been identified yet.

#### c. SCA5

SCA5 was described in a large kindred descended from relatives of Abraham Lincoln. This appears to be a slowly progressive disease that includes only ataxia as a symptom. The gene is located on chromosome 11, but it has not been identified yet.

#### d. SCA6

The gene responsible for SCA6 was identified in late 1996, and a number of presentations discussed this new disorder.

**Clinical features:** In most families, this is a late onset (>50 years), slowly progressive, pure cerebellar disorder (according to Dr. Harding's classification, this would be "ADCA type 3", or what some older physicians would call "Holmes ataxia". Occasional families have earlier onset; individuals in these families may have additional neurologic symptoms (abnormal eye movements, for example). SCA6 is responsible for about 15% of dominant ataxia in most series.

**Genetics:** This is another "CAG repeat" disease, but it is different from the CAG repeat diseases in several ways. The abnormal, expanded repeat range begins at about 20 repeats, and expanded repeats do not appear to be unstable. Other mutations in the SCA6 gene are known, and cause one of two other neurologic diseases: episodic ataxia type 2, and familial hemiplegic migraine. The SCA6 gene codes for a protein called CACNL1A4, the alpha 1A voltage-dependent calcium channel.

#### e. SCA7

SCA7 is the only known form of ADCA type 2, ataxia with retinal degeneration. The onset in this ataxia tends to be earlier than for the other ataxias, often in the teens or twenties. The gene is located on chromosome 3, but it has not been identified yet.

## II. Friedreich's Ataxia

Dr. Pandolfo led the research team that discovered the FA gene, and it is not surprising that almost a third of the presentations were about FA. The most exciting news of the meeting was about FA (Biology section, below).

**Clinical update:** Now that gene tests can determine who really has an abnormal FA gene and who doesn't, the clinical definition of FA has been redefined a little bit. In the past, two main variations from "classical FA" were named FARR (Friedreich's ataxia with retained reflexes), and LOFA (late-onset Friedreich's ataxia); it was unclear if these were genetically the same as FA or not. They are, most of the time. The "core findings" of FA are still progressive ataxia, dysarthria, absent reflexes in the legs, decreased vibra-

tion and position sensation in the legs, and "positive Babinski signs". Some presenters believed that other less common symptoms, such as cardiomyopathy, diabetes, scoliosis, optic atrophy, and hearing loss, were more likely to occur in patients with larger repeat numbers (see below); others felt that these symptoms related more to how long an individual had had FA. Symptoms that were uncommon in patients who have genetically proven FA include mental retardation, dystonia or chorea, onset before age 4, and the presence of cerebellar atrophy on brain imaging tests early in the disease.

**Genetics:** FA is caused by expansions of a GAA repeat sequence within a gene called the frataxin gene. Most normal individuals have fewer than 12 GAA repeats, but about 17% of normal people have slightly higher repeat numbers, up to about 34 repeats. A very small number of people have been found to have repeat numbers between 34 and 100. People with FA have two abnormal frataxin genes, usually with both genes showing expansions of 100-1700 GAA repeats. Combining the results of ten presentations on this subject, it appears that about 5% of people with FA have only one gene with an expanded repeat. Some of these people have been proven to have a mutation somewhere else in the frataxin gene which does not have an expanded repeat. These individuals do not appear to be different from FA patients with two expanded repeat-containing genes. The presentation together suggest that about 6% of patients with "classical FA" and 16% of patients with ataxic disorders which are not so "classical", do not have GAA repeat expansions in either frataxin gene. Whether these people have some other mutation in both of their frataxin genes, or another disease which looks very similar to FA clinically but is caused by a different gene, is entirely unknown. As for the CAG repeat diseases, there appears to be a relationship between the size of the GAA repeat and the age of symptom onset, with large repeats more common in individuals with earlier onset. Unlike the CAG repeat diseases, however, GAA repeat numbers are often smaller in affected children than in their parents who carry the abnormal genes.

**Caution:** A few unusual families with atypical or confusing gene test results were reported, which pointed out strongly that even leading researchers in the field do not yet understand fully the meaning of or implications of GAA repeat expansions in FA. For those who are having or have had a gene test for FA, this leads to an important point: we will learn much more over the next 1 – 2 years about the significance of repeat numbers in FA. Most of the work presented has not yet been published (and is therefore not widely known, and certainly not widely accepted). It is important for anyone who has already had, or plans to have, a gene test (for any kind of ataxia, really) to remain in contact with a physician, ataxia specialist, genetic

counselor, or NAF, and to ask every so often, so that any changes in the meaning of the gene test can be explained.

**BiologY:** This was the most exciting section of the meeting. An enormous amount of work has been accomplished in the last year to understand what the frataxin protein does, where it is found in the cell, and so on. Some clear leads were reported. Frataxin protein is normally present in the tissues (spinal cord, heart), and appears to be located in or near the mitochondria of the cells. The levels of frataxin in the blood cells, muscle, spinal cord, and brain, are much lower in FA patients than in normals, and the level seems to correlate with the size of the smaller GAA repeat expansion.

Yeast cells contain a protein that is very similar to frataxin, called YFH1 (yeast frataxin homologue). This protein is located in the mitochondria, and is important in regulating the transport of iron out of mitochondria. Yeast cells deficient in YFH1 accumulate iron in their mitochondria, which then do not function properly, and the yeast cells die. There is some very old research, long-forgotten, which suggested that iron accumulates in the heart cells of FA patients. If this work can be reconfirmed using more modern techniques, if iron can be demonstrated in other affected tissues of FA patients, if frataxin can be shown to prevent accumulation of iron in yeast cells deficient in YFH1, and if iron accumulation can be shown to have anything to do with causing the symptoms of FA (as opposed to being a secondary effect of the disease), this could lead to promising avenues for further research and treatment of FA. Mitochondria, the “energy storehouses” of cells, have been studied for decades, and much is known about them. Not only that, drugs called “chelators” have been used in other diseases that cause iron accumulation in cells. If chelators can prevent iron accumulation or cell damage or death in FA cells cultured in the laboratory, this would be a promising treatment to try in people with FA.

**CAUTION:** A word of caution is important. People are not yeast cells; they are much more complicated. What happens in the yeast may not relate directly to humans; sometimes what scientists predict or hope for turns out to be far from what they find. In addition, even if iron accumulation is important in FA, it is not difficult to imagine ways that treatment with chelator could actually be harmful (sometimes lowering the amount of a material in the blood sends a signal to the cell to protect itself by keeping more of that material in the cell, so the net result is a higher level in the cell, even though the amount in the blood has been lowered). If the “ifs” of the last paragraph are answered as we hope, ataxia specialists will work quickly to form well-designed clinical trials, to make

sure that any drugs tried are safe, tolerated, given in appropriate doses, and proven effective. It is not appropriate right now for people affected with FA to request or demand chelators from their physicians; too many questions are unanswered. Work is moving rapidly in this area, and it is best to help the research teams get real answers to their questions.

### III. Other Topics

#### a. Ataxia with Vitamin E Deficiency (AVED)

AVED is a recessive, child or young adult onset ataxia which is clinically indistinguishable from FA in a single patient. The gene is located on chromosome 8, and encodes the alpha-tocopherol transfer protein. Patients with this condition can be diagnosed because they have Vitamin E deficiency, and presumably can be treated with Vitamin E to overcome this deficiency. This disease has been studied most in Tunisia, where it seems to be more common than elsewhere.

#### b. Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

Patients with this disease have ataxia, spasticity, dysarthria, a non-progressive sensory axonal-demyelinating neuropathy, and an unusual appearance of the optic fundus. The gene has been localized to chromosome 13, but has not been identified yet. Some researchers think that this condition is not restricted to the French Canadian population, but is not recognized or diagnosed properly in other populations.

#### c. X-linked Non-Progressive Cerebellar Hypoplasia

This was described in a group of families from Russia. Patients with this disease are all male, and are noted, within the first two years, to have delayed motor development, abnormal eye movements, and spasticity. There is no mental retardation, and no progression of symptoms. MRI scans show that the cerebellum is small. The gene is located on X chromosome, but it has not been identified yet.

#### d. Sporadic Ataxias

Some patients with sporadic ataxia (without a family history of ataxia) appear to have “gluten sensitivity”, a problem usually associated with gastrointestinal symptoms such as diarrhea and malabsorption. It appears that some patients have neurologic symptoms, including ataxia, without gastrointestinal symptoms. This condition could be identified by a blood test for “antigliadin antibodies”, but this test is not readily available. The effects of treatment on neurologic symptoms were not discussed.

Occasional patients (less than 5%, perhaps less than 1%) with “sporadic ataxia” have been shown to have mutations in the SCA2 gene, the SCA6 gene, or the FA gene. Whether a particular patient wishes to have

tests for SCA1, 2, 3, 6, FA, antigliadin antibodies, Vitamin E, or anything else probably depends on the exact set of symptoms, family issues (would there be any children at risk), and whether any specific treatment would be available. Each patient should discuss these issues with his physician.

#### **e. Treatment Trials**

Two current trials of buspirone in the treatment of ataxia were presented, but both are ongoing and do not have completed results available.

## **NAF STATEMENT ABOUT IRON AND FRIEDREICH'S ATAXIA**

*Dr. Martha Nance, Board of Directors, National Ataxia Foundation*

**Having had many inquiries regarding the research on iron & FA and what the patient should do, NAF would like to offer their position and suggestions.**

A recent scientific report has raised the possibility that accumulation of iron inside cells has something to do with the symptoms of Friedreich's ataxia. Because of this report, many patients and families affected by Friedreich's ataxia are asking whether they should take iron supplements, change to diets low in iron, or take pills or shots to lower their iron levels.

NAF warns those with FA NOT to change their diets, take supplements or iron-lowering treatments. Anyone who despite this warning considers making changes anyway should do so ONLY after consulting with his or her physician. There are a number of reasons for this warning.

1. The scientific report that has caused the excitement was a study of yeast cells, which showed that the yeast protein that most closely resembles the frataxin protein appears to be important in helping to pump excess iron out of the cell's "furnace", or mitochondria. It is not known whether this is the only function of this protein. It is not known whether the human frataxin protein also has anything to do with removing iron from the mitochondria.

2. Although iron is known to accumulate in the heart cells of people with FA, it is not known whether this has anything to do with causing the symptoms of FA, or whether it is an effect of FA. (as an example, although it may seem like having a runny nose always happens when you have a cold, so you might think that a runny nose causes the cold, it is really the other way around – having the cold causes the runny nose).

#### **f. Committees**

Two committees were formed among members of the World Federation of Neurology: a Nomenclature Committee, to agree on and define standard terms or names for all the different kinds of ataxia, so that neurologists throughout the world can be encouraged to use the same name for the same disease (wouldn't that be nice!); and a Genetic Testing Committee, to write guidelines about predictive and prenatal genetic testing for the hereditary ataxias that can be made known to neurologists around the world.

Iron accumulation in the cells is known to occur in many neurodegenerative diseases as an effect of the disease.

3. Finally, even if accumulation of iron in the mitochondria has something to do with FA, it is not known whether changes in the amount of iron in the diet will help or whether that would make matters worse (as an example, although you think of salt as something that dries you out and makes you thirsty, sometimes when you are really dehydrated from heat and exercise, what you really should be drinking is not plain water, but something like Gatorade, which contains – you guessed it – salt!) The body works in funny ways, and sometimes taking in less of a material in the diet sends a signal to the cells to work even harder to store the material inside the cells. Other times, taking less of a material in the diet IS the right thing to do.

4. Iron is an important mineral in our bodies. It is present in the red blood cells, and helps to make our bones strong. It is particularly important for growing children to take in adequate amounts of iron. Without adequate iron, people can develop anemia, which causes fatigue, poor exercise tolerance, and sometimes a lower resistance to infections. One should not deliberately try to take too much or too little iron without the advice of a physician.

The research community is as excited as you are about this possible advance in the understanding of FA, and that work is quickly being done to determine whether and how this should change the treatment of FA. NAF plans to increase its support of FA research, to answer these exciting questions as quickly as possible.

**MEDLINE is now free available on the World Wide Web:**

**<http://www.ncbi.nlm.nih.gov/PubMed/>**

## ISSUES REGARDING DRUG TRIALS IN FRIEDREICH'S ATAXIA

*S.H. Subramony, MD, Research Director, National Ataxia Foundation*

**With all of the news and excitement regarding the recent discoveries, NAF asked Dr. Subramony for some of his thoughts and ideas.**

All the exciting new findings regarding the frataxin gene and protein have raised hopes that rational therapy for FA may become possible. The clinicians and research groups are as excited about this as the patients and the families. A sense of urgency pervades us all and a lot of work is going on already with such aims in mind. Nevertheless, this optimism should be tempered with caution.

Many questions remain unanswered. While there is circumstantial evidence, derived from work in yeast cells regarding the functions of frataxin, direct proof of such activity in human tissue is still lacking. We do not know if there is excess iron in patients with FA. We do not know if removing iron will benefit patients. We do not know what potential deleterious effects may result from such treatment, if any. Proteins tend to have more than one function and there may be other functional effects of frataxin deficiency. Findings applicable to tiny organisms, such as yeast, may not be directly applicable to complex mammalian organisms such as human beings.

The major idea has been the use of chelating agents that remove iron from the body. The only medication that is currently available cannot be given orally. This drug has many potential side effects, including possible deleterious effects on bone growth and toxicity to the retina and peripheral nerves, tissues that are already affected by FA. Therefore, indiscriminate use of such medication may be fraught with considerable danger. In addition, such 'open' (not subjected to formal randomized study) use may never show whether the medication is working or not. There are several reasons for this. Even if the drug works, it may simply slow down the progression of the disease and may not reverse the process. The major variability in the progression of this disease in different patients may make it difficult to tell whether the drug is working or not unless careful observations are made. FA has a slower progression rate than many other illnesses (for example, ALS) and it may take a long time to tell if a treatment works or not. The drug may be effective but to a modest degree and, unless the right observations are made, we may miss this effect. However, it is important not to miss such a finding because it will tell us that we are on the right track.

I have simply listed some but not all of the issues that cloud the issue of drug trials in FA. Clinicians and research workers should not lose sight of the sense of urgency that pervades patients and families. The current dilemma is how to reconcile this sense of urgency, to treat everyone with a possible effective drug, against the possibility of using ineffective drugs or one that is too toxic. Proper studies must be done and close observations made to not miss the effects of potential drugs.

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## DAGMAR KROEBEL

**A couple of months ago Dagmar addressed a meeting of AISA in Genoa (Italy). We reproduce her address here, so you all can get to now her a little bit better.**

Ladies and Gentlemen, dear Friends.

First of all I want to say to you that I am honoured to speak in front of you. My English is far from being perfect, and if you do not understand what I say, do not hesitate to ask.

The title of my communication is: How I live with an hereditary disease, in my case with a dominant hereditary ataxia. What is ataxia? Look at me and you have a little idea of this disease.

A dominant hereditary disease is a disease where one of the parents is affected and transmit it to 50% of their children. My parents had three daughters and two of them have the disease, my oldest sister showed the first signs of the disease when she was 28 years of age, in my case it started between one and two years, therefore even before the first neurological signs could be seen on my mother. Only when I was 8, the disease began to be visible on my mother and she was diagnosed having a dominant hereditary ataxia. On my side I discovered since my early childhood that I had to make efforts to learn special movements. And what I learned once was slowly 'forgotten' by my body.

This didn't frighten me, because I never compared myself to others. I lived in my own world. I was able to do what I wanted and nobody had the power to make me realise that I was not normal.

My sisters, as all children, were afraid about my difference. They didn't know how to live with it and they tried to ignore me.

My parents told me later that most of my teachers had difficulties in accepting my difference. They thought that every physical disability was always accompanied by mental disability. I felt this attitude too, but I never understood their problems. I changed schools often. Only in one school, where teachers followed the anthroposophic philosophy, I was entirely accepted

with my differences.

Later at University, no one had difficulties to accept me and my difference. I was physically different, but this was my problem. I had to organise my life to be able to live with the other students.

Since almost a year, I know precisely the form of dominant ataxia I have: SCA 2, also named the Cuban form. 'My' disease has now a name. I am always surprised when somebody tells to me "You look happy, you must have accepted the disease." One can only accept a situation if one has a choice. And I had no choice. I hope that I will never accept the disease.

I chose to live with this disease. Sometimes you have to beat the lazybones in you, sometimes you have to struggle against the desire to move. Life gets never boring. The situations change all the time and I can never trust my body. Living with ataxia is not a disaster. It brought in my life another dimension.

I will relate to you an old story: the bishops decided one day that even the Presbyterians had to know to write, so Tom Smith had to leave the job he liked above all at St. Mary's. He went back to town and heard of an announcement for a job in a grocer's shop. He was successful in his job and one day he took over the shop. He opened a second and third shop and got rich. One day he saw his banker. The banker tried to convince him, to transfer his money to another account. For this he had only to sign a paper. The grocer told that he didn't know to write and the surprised banker kept on asking him "Oh! How important would you be now, if you had known how to write." "Let me tell it to you," the grocer said, "I would be Presbyterian at St. Mary's now."

I do not know what might have become of me, if I did not have the ataxia. But without ataxia I would have never met you, and this would have been a pity.

I will tell you three stories of my daily life. The first story begins in 1968. We lived in the south of Brussels. The traffic police took always care of me because as they said (and they were right) I was a public menace. Then in 1973 I was knocked down by a car, going myself on a bike. As the policemen told me later, they were not at all astonished that they had to gather me together on a road. I had to go to court to claim my innocence in this accident and I won this action. The local traffic policemen never gave to anybody their opinion they had about me.

The second story took place in 1975 on a nice and sunny day. As every week I went out by car with friends. I do not remember why, but my friends left their wheelchairs on my parking place. The city was full of gendarmes because a demonstration of students was expected. Suddenly a car in front of me stopped at

a red light which was impossible to see in the sun. I stopped my car in time but the tram behind me had not enough space, my car had now no trunk. I left the car and the gendarmes helped my friends to do the same. Then the car burned. Now I had qualified people to witness the accident and it did not occur to anybody to state that I was a disabled driver. 2 months later I got from the tramway company the estimated value of my car and some indemnity.

My third story is not an example for good practice between disabled and able-bodied. For a problem with my back I went to a local physiotherapist. I explained to him what he had to know about neurological diseases, ataxia and about dominant heredity. Then he asked me: "Why did your parents than have children?" I retook the prescription and I left his office.

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## EVELINA RAVEGGI

**Evelina Raveggi, the representative from AISA in Italy, has been a board-member from the first moment on, and is – in a certain way – the 'mother' of EURO-ATAXIA.**

Dear friends,

My name is Evelina Raveggi. I'm a member of EURO-ATAXIA. I represent Italy. My experience with ataxia began 19 years ago; since 6 years I'm in a wheelchair. My ataxia started when I was 43. It was a bad stroke. I had to overcome tremendous difficulties. I had to change my life, but with time I learned how to live altogether.

I'm president of AISA (Italian Association for Ataxia Syndromes) for the region of Toscana. My aim is to help those who need it by putting my experiences at their disposal.

In 1995 I felt a nodule in my breast. And here is, again, a new serious illness, cancer. All took place in a hurry: operation, chemotherapy, the problems that come with this disease. But now it's bygone, everything is right.

I have always tried to confront life like a normal person, but to live with two illness with different pathologies, often means 'no'. And that is difficult, the secret is to overcome the 'no'.

Luckily my husband Wais is always beside me. For him I'm still the Evelina he met. For me that is important. Even if I complain of his character, he reassures me and everything is okay.

We need courage because life is a challenge. Struggle gives meaning to life. Life is a gift and we have to live it with our heart.

Thank you friends,

Evelina

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