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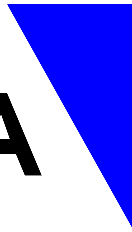

european
federation of
hereditary ataxias

Newsletter No. 9
SPECIAL EDITION
March 1996

FA GENE FOUND!

THE MAIN FACTS

- **The Friedreich's ataxia gene is located at 9q13, band 13 of the long arm of chromosome 9.**
- **96% of FA patients have the same mutation, a trinucleotide expansion, on both chromosomes.**
- **The other patients have a trinucleotide expansion on one chromosome and a point mutation on the other chromosome.**
- **The trinucleotide expansion mutation is the repetion of hundreds of trinucleotides GAA in a row. The number of repetition varies from patient to patient (the normal sequence has 7 to 22 GAA in a row)**
- **The expansion mutation is likely to reduce the amount of protein synthesized from the mutated gene.**
- **The Friedreich's ataxia gene codes for a new protein, frataxin, that doesn't look like anything known before. (So there is no single glimpse on its function.)**
- **Frataxin is a fairly small protein that might have a very basic and ancient function since there is a frataxin-like molecule in probably every animal or plant (known for yeast and worm).**

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STATEMENT BY EURO-ATAXIA'S PRESIDENT

All of us in EURO-ATAXIA were tremendously excited to receive the news that Masssimo Pandolfo and Michel Koenig had finally succeeded in isolating the Friedreich's ataxia gene. This particular search has been one of the most difficult in the field of genetic research into the hereditary ataxias. To examine a recessive disorder, like Friedreich's ataxia, one needs relatively large pedigrees from which a maximum number of people are willing to participate. It is a great merit of all researchers that they were able to motivate enough people (affected people and their relatives likewise) to cooperate in this search. The identification of the gene is of course only the first step in the search for a cure for Friedreich's ataxia. We all know it can, and probably will, take years of hard work to reach this goal. EURO-ATAXIA would like to thank and congratulate not only Massimo Pandolfo and Michel Koenig, but indeed all the researchers and their teams who put so much time and effort working towards the isolation of the Friedreich's ataxia gene over the years, and who showed as well such an exemplary behaviour in international cooperation.

Manfred Van den Kerchove, MD, President

EDITORIAL

This is a special edition of *Euro-Ataxia* to mark a special occasion: the discovery of the Friedreich's ataxia gene.

The discovery of the Friedreich's ataxia gene represents years of hard and patient work by many ataxia research groups throughout Europe and the USA. Leading the search were the groups of Dr Michel Koenig (Strasbourg, France) and Dr Massimo Pandolfo (now in Houston, Texas, USA). Groups based in Naples, Italy and Valencia, Spain were also closely involved.

For us in EURO-ATAXIA this is marvellous news, the 'holy grail' almost of ataxia research, and one that we are keen to share with our readers. And not only can we report the discovery of the Friedreich's ataxia gene itself, the protein the gene codes for – frataxin – has also been discovered. This will open a whole new chapter in research into Friedreich's ataxia, as the purely genetic approach will be joined, and possibly in time supplanted by, a renewed biochemical investigation into frataxin and its role within the body's nervous system.

This edition of *Euro-Ataxia* is therefore entirely taken up with analysis of the discovery itself and of the consequences of that discovery, both immediate and long-term. We hope that our readership whose interest is in other ataxias will not begrudge us this one opportunity to pat ourselves on the back or otherwise congratulate ourselves.

Since it was founded in 1989 one of the principal aims of EURO-ATAXIA has been the creation of an information 'interface' between scientists, neurologists and ataxic people themselves, most usually, though not always, organised in National Ataxia Groups. Our goal has been to disseminate new information on ataxia to the European and indeed world-wide ataxic community as quickly and accurately as possible, and to ensure that everybody, everywhere within that community is kept fully informed of the news as it breaks.

Finally thanks to the long list of people who have helped with this special issue. To Diane Dondershine and Lincoln Richman of the American Association for the Advancement of Science for their kind permission allowing us to print an extract of the original article from *Science* magazine. To Michel Koenig, Sue Chamberlain, Sandro Banfi and Ewout Brunt for taking the time and trouble to explain the significance of the scientific findings and what they will mean to us ataxic people in our daily lives.

FRIEDREICH'S ATAXIA: AUTOSOMAL RECESSIVE DISEASE CAUSED BY AN INTRONIC GAA TRIPLET REPEAT EXPANSION

[Excerpted with permission from *Science*, Vol. 271, pp. 1423-1426, 8 March 1996. Campuzano,V., Montermini, L., et al., Friedreich's Ataxia: Autosomal Recessive Disease Caused by an Intronic GAA Triplet Repeat Expansion.
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The mutated gene in FRDA has been mapped to chromosome 9q13-q21.1. We recently narrowed the FRDA candidate region to a 150 kb segment flanked by the ZO-2 gene (distal) and the marker F8101 (proximal). Previously proposed candidate genes are excluded: the X104/CSFA1/Z0-2 gene on the basis of absence of deleterious mutation in patients, and the STM7 and PRKACG genes because they lie in entirety on the centromeric side of F8101.

Potential exons were identified in the FRDA critical region by direct complementary DNA (cDNA) selection, exon amplification, and computer prediction from random sequences. One exon, called d26, was identified independently by the last two approaches. Nested primers based on the d26 sequence, when used in a rapid amplification of cDNA 5' end (5'-RACE) experiment on a heart cDNA template, yielded two independent but overlapping products. Sequence from these clones matched another amplified exon and an expressed sequence tag (EST) from a human liver plus spleen cDNA library. This gene, called *X25*, apparently had alternate transcripts, because the sequences at the 3' end of the EST and RACE products were different. The gene structure of *X25* was resolved by obtaining intronic sequences flanking the identified exons, by inverse polymerase chain reaction (PCR), and by the direct sequencing of cosmids. Five exons (1 to 5a, where exon 5a corresponds to the 3' end of the EST) were found to be spread over 40 kb. They contain an open reading frame (ORF) encoding a 210 amino-acid protein, which we named frataxin. An alternative exon (5b), corresponding to d26, was localized at about 40 kb from exon 5a in the telomeric direction. Exon 5b also has an in-frame stop codon, so that the alternative transcript encodes a shorter, 171 aminoacid protein, whose 11 COOH-terminal residues differ from the main isoform. We further investigated the 3' end of the transcript encoding the alternative form by 3' RACE, and showed that, depending on the alternate usage of the 3' donor splice site in exon 5b, either a transcript ending with this exon, or a longer transcript including an additional non-coding exon 6 could be generated.

A polyadanylated [Poly A+] Northern (RNA) blot of different human tissues revealed highest expression of *X25* in heart, intermediate levels in liver, skeletal muscle, and pancreas, and minimal in other tissues, including whole brain. A 1.3 kb major transcript was identified, in agreement with the predicted size of an exon 5a-containing mRNA. Fainter bands of 1.05, 2.0, 2.8, and 7.3 kb were also detected. A Northern blot of total RNA from selected parts of the central nervous system (CNS) revealed high expression of the 1.3 kb transcript in the spinal cord, with less expression in cerebellum, and very little in cerebral cortex (not shown). Overall, expression of *X25* appeared to be highest in the primary sites of degeneration in FRDA, both within and outside the CNS. To investigate the nature of the larger transcripts, we screened a fetal brain cDNA library with the EST clone (exons 2 through 5a). Among nine positive clones, four ware isolated whose sequence extended beyond the limits of the previously identified *X25* mRNAs. Sequence analysis of these clones indicated that they originated from a related gene, differing from *X25* at several positions, and with stop codons in the sequence corresponding to *X25* exon 1. The *X25* related gene was excluded from the critical FRDA region, and at least one intronless copy exists in the genome, as indicated by Southern (DNA) blot and PCR analysis.

A BLASTN DNA database search with the *X25* DNA sequence and a BLASTP search with the translated sequence did not reveal any significant match. However, a TBLASTN search in which the protein sequence was compared to the six-frame translation of the DNA databases, yielded highly significant matches with an ORF contained in a *Caenorhabditis elegans* cosmid (BLAST probability = 7.6 x 10-13), and with a *Saccharomyces cerevisiae* EST (BLAST probability = 2.0 x 10-10). In both cases, the closest

match involved a 27-amino acid segment of the protein (positions 141-167) encoded in exons 4 and 5a, showing 25 out of 27 and 22 out of 27 amino-acid identity with the C. *elegans* and S. *cerevisiae* sequences, respectively, and 65% identity at the DNA level. Secondary structure predictions for the *X25*-encoded protein suggested an a-helical structure for the NH_2-terminal 30 amino acids and the regions between residues 90-110 and 185-195, with possible interspersed b-sheet regions around residues 125-145 and 175-180. No transmembrane domain was identified. The 22 NH_2-terminal amino acids might form a cleavable signal peptide.

We amplified all six coding exons of *X25* with flanking primers, and screened them for mutations in 184 FRDA patients. Three point mutations that introduce changes in the *X25* gene product were identified. The first change, in a French family with two affected sibs, consisted of a T - G transversion in exon 3 that changed a leucine codon (TTA) into a stop codon (TGA) (L106X). The second case, in a Spanish family with one affected member, was an A - G transition that disrupted the acceptor splice site at the end of the third intron, changing the invariant AG into a GG. Finally, a change from isoleucine to phenylalanine (I154F) was found in exon 4 in five patients from three Southern Italian families. This conservative change of an hydrophobic aminoacid affects an invariant position within the highly conserved domain shared between human, worm and yeast. In all three cases, affected individuals were heterozygous for the point mutation. The I154F mutation was also found in 1 out of 417 chromosomes from 210 control individuals from the same Southern Italian population, which is compatible with the possibility that this is a disease-causing mutation.

Southern blot analysis did not reveal any difference between FRDA patients and normal controls when DNAs digested with Msp I, Taq I, or Bst XI were hybridized with an *X25* cDNA probe, thereby excluding major rearrangements. However hybridization of Eco RI-digested DNAs from FRDA patients revealed that the fragment containing exon 1 was on average 2.5 kb larger than in normal control individuals, with no detectable normal band. FRDA carriers were heterozygous for an enlarged and a normal sized fragment. The size of the enlarged fragment was clearly variable, even among FRDA carriers who were related. The enlarged region was further localized to a 5.2 kb Eco RI-Not I fragment within the first intron of *X25*, which was subcloned from a cosmid and sequenced.

We designed oligonucleotide primers to amplify this fragment using a long-range PCR technique, and confirmed its increase in size in FRDA patients. Cosmid sequence analysis revealed a (GAA)9 repeat apparently derived from a poly(A) expansion of the canonical A_5TACA_6 sequence linking the two halves of an Alu repeat. The (GAA)9 repeat is located 1.4 kb downstream from exon 1, and restriction analysis of long-range PCR fragments from FRDA patients located the abnormal size increase within 100 bp from this triplet repeat. Digestion of the same fragments with Mbo II, whose recognition site is GAAGA, suppressed size difference between patients and controls, indicating that the GAA repeat may be involved. Direct sequencing proved that the mutation consists of an almost pure GAA repeat expansion. PCR primers were then designed to evaluate the presence and size of the GAA expanded repeat in FRDA patients, and any variability of the repeat in normal individuals.

Seventy-nine unrelated FRDA patients with typical disease, including five known to carry *X25* point mutations, were tested for the GAA expansion by Southern analysis, PCR, or both. The patients previously known to carry point mutations were all heterozygous for the expansion. Segregation analysis within families indicated that the point mutation and the GAA expansion had different parental origin, demonstrating that the point mutations, including the conservative missense mutation I154F, are disease causing. Homozygosity for expanded alleles was demonstrated in 71 of the 74 patients without previously detected *X25* point mutations, and hoterozygosity in three. Overall, according to these data, the GAA expansion accounted for about 98 % of the FRDA chromosomes.

The sizes of the enlarged alleles were found to vary between 200 and more than 900 GAA units, with most alleles containing 700 to 800 repeats. Instability of expanded repeats during parent-offspring transmission was clearly demonstrated, both directly by analysis of parent-offspring pairs, and indirectly by the detection of two distinct alleles in affected children of consanguineous parents, who are expected to be homozygous by descent at the FRDA locus. PCR products corresponding to expanded repeats appeared as slightly blurred bands, suggesting the occurrence of only a limited degree of somatic mosaicism for different size repeats due to mitotic instability, at least in lymphocyte DNA. Seventy-seven normal individuals who ware tested by Southern analysis were homozygous for a normal allele. PCR analysis of additional 98 normal controls also did not show any

expansion, and revealed that the GAA repeat is polymorphic, its length varying from 7 to 22 units. Smaller alleles were more prevalent.

GAA repeats, up to 30-40 units, are common in many organisms and are sometimes polymorphic, as in the 3' untranslated region of the rat polymeric immunoglobulin (Ig) receptor; they have not previously been associated with disease. A recently proposed theoretical model suggested that ability to form a hairpin structure is crucial for the susceptibility of trinucleotide repeats to give rise to large expansions. According to this model, CAG/CTG or CGG/CCG repeats were predicted to be expansion prone, while the GAA/CCT repeat had lowest propensity to expand, making the FRDA expansion an unexpected finding. A striking linkage disequilibrium between FRDA and a polymorphism in a newly identified exon of the ZO-2 gene (about 120 kb telomeric to the expanded triplet repeat) in French and Spanish families suggests a single origin for the FRDA expansion, but it is also compatible with a multistep or recurrent expansion on an allele at risk.

The fact that FRDA is autosomal recessive makes the natural history of the mutation at the population level strikingly different from any other known disease due to trinucleotide expansions. In fragile X and myotonic dystrophy, where expansions of comparable size occur in non-coding sequences, carriers have severe early-onset disease and a strong reproductive disadvantage. Large expansions in these diseases are newly formed from unstable alleles of intermediate sizes, resulting in the phenomenon of anticipation. In FRDA large expanded alleles are transmitted by asymptomatic carriers, and new expansion events in heterozygotes would go undetected at the phenotypic level. The absence of negative selection against heterozygotes plays the key role in maintaining the frequency of large FRDA expanded alleles as high as 1 per 250 chromosomes, at least one order of magnitude higher than any other characterized trinucleotide expansion. Conversely, deletions of CTG repeats in myotonic dystrophy with reversion to normal size alleles have been observed. In our sample of FRDA families, large expanded alleles were present in all tested asymptomatic carriers, and, despite their size instability, neither new expansions deriving from an intermediate allele, nor reversions to normality were detected. Although we cannot exclude the occasional occurrence of such events in the general population, given the large number of heterozygous individuals, it appears that their frequency is low enough not to introduce detectable distortions in the pattern of FRDA inheritance, particularly inconsistencies in linkage results.

FRDA patients appear to have shown either undetectable or extremely low mRNA levels when compared to carriers and unrelated controls. This observation suggests that either an abnormality in RNA processing, or an interference with the transcription machinery, occur as a consequence of the intronic GAA expansion. Patients with deleterious point mutations affecting *X25* clearly demonstrate that no other gene in the region, which could in principle be affected by a GAA expansion, is involved in the causation of FRDA. The restricted expression of *X25* in the sites of degeneration or malfunction distinguishes FRDA from the dominant ataxias and from ataxia telangiectasia, where expression of the causative gene is ubiquitous. A severely reduced *X25* mature mRNA is expected to result in a similarly low level of frataxin. Reduced frataxin in spinal cord, heart and pancreas is the likely primary cause of neuronal degeneration, cardiomyopathy and increased risk of diabetes. Functional studies on frataxin are likely to be facilitated by its evolutionary conservation, and will hopefully generate new therapeutic possibilities.

THE APPLICATIONS

The discovery of the Friedreich's ataxia gene will have profound implications for **diagnosis**, **testing** and possible **treatment** of Friedreich's ataxia. We shall deal with each of these in turn.

DIAGNOSIS

It will give neurologists and clinicians a fast and accurate diagnostic tool, based on a single blood sample. Normal delay between presentation and diagnosis will be cut to days – which may have important consequences for future family planning (see below). Most importantly, however, the discovery will give certainty to people whose diagnosis is or has previously been questionable. Current diagnosis of Friedreich's ataxia is based on the skill of the Neurologist in weighing up the individual symptoms presented to him/her within a clinical setting. Now, these skills will be augmented by a speedy and definitive test. Also in this context we may recall that research into Friedreich's ataxia was once undermined because of the inclusion of samples from people who had been *misdiagnosed* as having

Friedreich's ataxia. Thus scientists too will benefit from a general 'cleaning-up' operation which will guarantee sample reliability.

TESTING

The speed, accuracy and reliability of new testing procedures should have important consequences for pre-natal testing and genetic counselling. It is as well, however, not to overstate this. Only a minority of Friedreich's ataxia families will be in a position to take advantage of pre-natal testing. That's partly because Friedreich's ataxia is a *recessive* disorder, so the first warning of its presence within a particular family is when a child-member first develops symptoms. But also, as age of onset for Friedreich's ataxia averages at 10 years the family may already be complete before anybody's aware the condition's present. Only universal screening for Friedreich's ataxia at birth would make a big difference overall. Whilst that's now theoretically possible it's not a realistic scenario (because of cost). Maybe, in the next century when the entire Human genome has been fully sequenced and a new generation of supercomputers have been developed to handle the logistics of the exercise, it may indeed become possible to make genetic profiles off all new-born babies which would immediately pick up abnormal conditions such as Friedreich's ataxia. But for now this is in the realm of science fiction. Therefore to summarise: as far as **pre-natal** testing is concerned, discovery of the Friedreich's ataxia gene will simplify procedures and improve accuracy for testing for those families who are already in a position to avail of it.

Presymptomatic testing for Friedreich's ataxia has always invited controversy. Clinicians are especially reluctant to do it for children at the behest of parents as there is a potential conflict of interest here. The scenario is this: once one child has been diagnosed as having Friedreich's ataxia, parents immediately want the rest of the family tested 'to see who else has it'. But presymptomatic testing may serve no real purpose other than to satisfy the parents wish to know. The children are by definition in no position to make their wishes known – this is the problem. Under European Law the rights of the child are paramount – even against its own parents. Geneticists often find themselves being caught up in this dilemma. In this case the ease and accuracy of new testing procedures for Friedreich's ataxia will in all probability increase pressure on geneticists to carry out presymptomatic testing. As an ethical 'hot-potato' the argument over presymptomatic testing looks set to get hotter.

Perhaps though the greatest advance in new testing procedures is that it will now be possible to test *anyone* for Friedreich's ataxia carrier status as well as Friedreich's ataxia victim status. Again, although in theory any individual can walk in off the street to be tested, in practice it will be people who are not related by blood to a Friedreich's ataxia family but are planning to be, who will reap most benefit. For example if a Friedreich's ataxia victim or carrier plans to found a family then his/her prospective partner can be tested. Of course the risk that the intended partner is him/herself a carrier is still relatively low about 1 in 120 – but it will now be possible to give a definite yes or no. It will add certainty to the equation and also, should a positive result be obtained, give adequate forewarning of the necessity for future pre-natal testing and genetic counselling.

TREATMENT

Unquestionably however most people – certainly most people with Friedreich's ataxia – will be focusing on whether or not an effective treatment is in the pipeline and, if so, what sort of time scale are we looking at before this happens? Scientists are notoriously cagey about giving definite yes/no answers to anything, so perhaps the best way to get to grips with this question is by outlining just what the scientists who made the discovery have found. The Friedreich's ataxia gene codes for a new protein, frataxin, that doesn't looks like anything known before. There is no single glimpse on its function either inside or outside of the Central Nervous System as yet – which is the direction future research will take. However frataxin is a fairly small protein that might have a very basic and ancient function – which seems to raise at least the possibility of its early replication?

Future research on Friedreich's ataxia will utilise biochemical as well as genetic approaches. It will be very important to study in depth the biochemical properties of this novel protein to understand its role in the central nervous system both in normal and in pathological conditions. For this purpose, it will be essential to generate an animal model for Friedreich's ataxia. 'Knock-out' mice – with mutations in both copies of the Friedreich's ataxia gene – will be bred for this purpose. Any therapeutic application of the discovery will be in the long term however. There is just so much more to find out – such as the mechanisms through which mutations of the Friedreich's ataxia gene lead to the disease – in order to design an effective therapy for this disorder. At present the only realistic answer to the question of

when? is ***not yet, not yet*** ... But undoubtedly, yes, we've just taken a quantum leap towards that goal.

Michael Morgan
(with additional help from *Michel Koenig* and *Sandro Banfi*)

THE GREAT FRIEDREICH'S ATAXIA GENE HUNT

The search for the cause of Friedreich's ataxia was a truly remarkable piece of genetic detective work, joining together teams of scientists from all over Europe and the USA. This was a major feat of scientific collaboration linking UK, French, Italian, Spanish and American research groups. Everybody played a part in tightening the noose. At the end four groups of scientists were involved in the actual discovery. In lead position were those of Dr Michel Koenig (Strasbourg, France) and Dr Massimo Pandolfo (now in Houston, Texas, USA), while groups based in Naples, Italy and Valencia, Spain also participated.
In 1988 the gene for Friedreich's ataxia was mapped to the long arm of chromosome 9 (9q13-q21.1). But this area containes millions of base-pairs – the individual rungs of the DNA ladder. Now the hunt began in earnest. By 1993 the search area had been narrowed to just one million base-pairs. This was further reduced to 300,000 base-pairs in 1994 and to 150,000 in 1995. Still the end, when it came, was unexpected. After initial investigation failed to find anything promising on it, a new candidate gene, X25, was about to be 'shelved' – geneticists parlance for binned – when a subsidiary experiment showed conclusively hat this was indeed the Friedreich's ataxia gene. Almost accidentally the 'holy grail' of ataxia research had been delivered, it seemed. Head of the laboratory, Dr Massimo Pandolfo, recalls: "But for this chance finding, we could have been stumbling around this region for another five or more years!"

The gene was initially identified by Massimo Pandolfo in April 1995. Pieces of potential coding sequences had however been identified in Strasbourg several months beforehand and had been passed to Pandolfo in Texas at the beginning of 1995. Michel Koenig continues: "We then identified the first point mutation and we were very enthusiastic at that time. Only for a short while, since we then failed to identify the majority (98%) of mutations for awhile. We even thought that this one wasn't the gene yet and we started to look for another gene in the tiny bit of genome that wasn't excluded yet (that was in July). Only in November and after a lot of elucidation's and false reasoning, the group of Massimo stepped on what looked like a rearranged fragment in intron 1 of patients. We and Massimo identified that the rearranged fragment was in fact a GAA trinucleotide repeat expansion by the beginning/mid December. At that time we realised we reached the long sought goal and we were all very happy and relieved. The first version of the paper was sent to Science just before Christmas."
Within the gene a basic division can be made between coding and non-coding sections, known as exons and introns. Exons are like islands of solid land, whithin the gene. The intervening stretches of DNA are called introns where nothing much seems to happen most of the time (which is why they're often referred to as 'junk DNA'). In Friedreich's ataxia there is a massive increase in the number of trinucleotide repeats – the repetition of the single genetic message GAA – within one of the first introns of the gene (1.4kb downstream from exon 1 of the gene to be exact).
Normal people, or rather people unaffected by Friedreich's ataxia, have a small number of trinucleotide repeats too – but only within a range of 7-22. People with Friedreich's ataxia, however, have a massive expansion – within a range of 200-900. The resulting expansion of the intron prevents a normal translation of the exons into protein. (The scientific name for this, I think, is 'steric hindrance'.) X25 is thus inhibited from fully carrying out its function of arranging the production of a particular protein, in this case a new, hitherto unknown protein now named Frataxin. To state it baldly, the evidence points to Friedreich's ataxia being caused by a lack of Frataxin reaching the spinal cord, heart and pancreas in the body.
Reaction from other scientists has been one of astonishment. "Concerning the reaction of other scientists that were told of the discovery," writes Michel Koenig, "they were all amazed, as we were, that the vast majority of patients have a trinucleotide expansion mutation, moreover of an unusual type. This is a scientific novelty that breaks a certain number of preconceived ideas:

- trinucleotide expansions are only in dominant or X-linked diseases;
- trinucleotide expansions are only of CTG/CAG or CGG/CCG sequences;
- trinucleotide expansions are only in parts corresponding to mature RNA."

It looks as though the discovery of FA might lead to a rewriting of scientific textbooks!

Michael Morgan

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