

EURO-ATAXIA

EUROPEAN FEDERATION OF HEREDITARY ATAXIAS

EDITORIAL

The fifth AGM of EURO-ATAXIA was recently held in Naples between 25 and 26 September. We have a new president, Dr. Alessandro Filla from University Federico II in Naples. Dr. Filla expressed his enthusiasm for the work of EURO-ATAXIA.

Full details of the recent breakthroughs in genetics, as announced at the international workshop at Capri, were presented. We also print the original American report of the discovery of the SCA1 gene, from *Generations*, the official publication of the National Ataxia Foundation. Other research reports are included: from Strasbourg, from London. A review of the Capri workshop is presented by Manfred Van de Kerchove and Dagmar Kroebel.

EURO-ATAXIA is also keen to promote the interests of ataxic people as well as that of the research community. It was agreed that EURO-ATAXIA should attempt to bring together medical, health and welfare personnel, dealing with the ataxia's on a daily basis, in a single European conference, details of which will follow later.

During the meeting there was much discussion on the booklet we are producing on ataxia's. Many articles have already been received. Many more have been promised. There is still a long way to go of course, but definite progress has been made.

Next year's AGM will be held in München between September 30 and October 2, to be organised by the German DHAG.

SCA1 GENE FOUND

The news that American researchers have located and cloned SCA1 is indeed exciting. We reprint the lead article from *Generations* announcing the discovery.

The first gene for ataxia has been found by researchers at the University of Minnesota and Baylor College of Medicine, with the help of the families who participated in the study! Finding the first ataxia gene is a major breakthrough. For the first time ever, we know what causes at least one form of ataxia. While finding the gene doesn't mean we have a cure, it is the first major step toward that goal. Now we can concentrate on how the ataxia gene makes people sick and focus our efforts on stopping that process!

People with the chromosome 6 form of dominant ataxia (SCA1) have too many copies of a genetic 'word', CAG, within the DNA encoding the SCA1 ataxia gene. Normally there are between 19 and 36 copies of CAG located in a small section of the SCA1 gene. In people with the disease, however, there are anywhere from 43 to 81 copies of CAG that are repeated. This

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CONTENTS

Editorial	1
SCA1 gene found	1
The Capri workshop	2
Call for bookreviews	3
Bookreview	3
International research report	4
Research report from Strasbourg ...	6
Spain	7
Global Ataxia Penpals	7
Calendar	7
EURO-ATAXIA: members & contacts .	8

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increase in the number of CAGs somehow interferes with the gene's normal function, causing illness. We do not yet understand why extra copies of CAG in the SCA1 gene cause ataxia but now that we have identified the cause of the disease we can perform experiments specifically to answer that question.

Within the past two years, scientists have found that four other genetic diseases involve increasing numbers of what geneticists call 'trinucleotide repeats' (or strings of repeats of three of the four letters of the genetic code). For one disease, the genetic 'word' repeated is 'CGG' and for the other three diseases, including Myotonic Dystrophy and Huntington Disease, the repeated word is CAG, the same 'word' found in the chromosome 6 ataxia gene. The remarkable presence of expanded trinucleotide repeats in each of these diseases leads us to believe that trinucleotide repeats may cause other neurological and neuromuscular diseases, including other forms of ataxia not involving the chromosome 6 gene. Thus, results of research on each disease may help those with the other ataxias.

In general, the longer the CAG repeat, the earlier the age of onset of the disease. At this time, however, we cannot accurately predict when an individual will get the disease based on the number of repeats he or she may have. The longest strings of 'CAG' have been found among the juvenile-onset cases.

The size of the CAG repeat can vary from generation to generation. It is the variability in the length of CAGs that likely explains much of the differing symptoms and severity of the disease even within a single kindred.

(...) We are just beginning to learn where the SCA1 gene is 'on' or actively working. So far we know that the SCA1 gene is 'on' in the brain and muscle and to a lesser extent in the blood and other parts of the body. We hope to understand soon why certain parts of the brain, such as the cerebellum, are damaged when the SCA1 gene contains too many 'CAGs'.

The ataxias are a complex group of diseases. Most often there is no known family history of ataxia in individuals with the disease. Among the cases of ataxia in which multiple family members are affected by the same disease, there are recessive forms in which two bad copies of a gene must be present for someone to get the disease, and dominant forms in which only a single bad copy will cause illness. So far, four different ataxia genes have been mapped, one of which has now been cloned. The cloning and identification of the first ataxia gene is a big breakthrough. It will greatly increase our understanding of ataxia because for the first time ever we know what causes one form of the disease. Finding the SCA1 gene will give us important clues about

what to look for in our search for other ataxia genes. Identifying the SCA1 gene is (...) a terrific start, but we can't stop until we find a cure(s), for this debilitating group of diseases.

Dr. Laura P.W. Ranum

THE CAPRI WORKSHOP

Scientists from all over the world came to Capri in Italy to participate in an International Workshop on the Molecular Genetics of Friedreich's and Dominant Ataxias. The meeting was held between 20 - 22 June 1993. Our President, Manfred Van den Kerchove, and Secretary, Dagmar Kroebe, attended the meeting throughout, and this is their report.

First of all, some news. A team of American geneticists have tracked down the gene of spinocerebellar ataxia type 1 (SCA 1), already known to be located on chromosome 6. A Japanese laboratory discovered that the 'Machado-Joseph' gene is linked to chromosome 14. Machado-Joseph's disease is a dominant type of ataxia, presumably originating from Portuguese navigators. The Strasbourg group have established that recessive vitamin E-dependent ataxia is transmitted via chromosome 8. This form of ataxia may mimic Friedreich's disease, and it follows that measurement of serum vitamin E concentration become standard procedure when faced with a recessive ataxia.

The search for the Friedreich's ataxia gene continues: an arduous task, as this gene is probably located close to the centromere of chromosome 9. The centromeric region of a chromosome is notorious for its lack of accessibility.

An interesting paper dealt with late onset Friedreich's ataxia (LOFA), i.e., commencing after the age of 25, and clinically indistinguishable from 'classical' Friedreich's. It was thus proposed that age of onset no longer be regarded as a diagnostic criterion.

The meeting in Capri was the second of its kind. The first was organised by Dr. Sue Chamberlain in Ising in the Chiemsee near Munich. What is the purpose of these meetings? Up until some years ago, many groups worked more or less on their own. It now appears possible to establish and expand contacts, and to exchange information.

Although primarily dedicated to molecular genetics, this workshop succeeded in 'linking-up' with clinical aspects, even suggesting, and rightly so, that neurologists examine and re-examine their patients more closely. Clinical examination is and will remain

the cornerstone of successful medicine, and it is not likely that molecular science is about to put neurologists and GPs 'out of business'. We presume that a person, presenting what is perceived as a wrong functioning of in casu the motor system, will seek the medical attention of an 'ordinary' doctor first, who can then refer the client to a more specialised unit if necessary.

The ethical and social implications inevitably generated by the ever increasing, often cluttered, amount of genetic information constitute material about which we should all reflect on, and this is an area where EURO-ATAXIA should play an important role, i.e., acting as a go-between at the service of scientists, clinicians and ataxic people's organisations. They will all have to sit round the table together and reflect upon how to cope, for example, with often distressing predictions. With this in mind we suggest that, at the next convention, a session be reserved for this issue.

In the relative absence of immediate therapeutic avenues, the problem of ante-natal, or pre-clinical, diagnosis becomes a delicate one, not least when one takes into account the unpredictability of clinical expression of the same disease in a given family. This is only one of the reasons why it is of paramount importance that patients, and possibly family members, see their neurologist on a regular basis. Even if this at first sight does not seem very useful, the long-term result will be an improved understanding of the evolution of a clinical picture. This holds especially true in the extremely complex and often confusing domain of hereditary ataxias.

M. Van den Kerchove, M.D. *Dagmar Kroebel*
President Secretary

CALL FOR BOOKREVIEWS

It's an indication of the impact of the new genetics that many new books on all aspects of genetic science, technology and applications are making their way into the high-street bookstore. These books are aimed at both the informed lay reader as well as the specialist, and are now being published at an increasing rate. EURO-ATAXIA policy is to review new material on genetics/ataxia. Indeed the current issue of EURO-ATAXIA contains one such, a UK publication, Tom Wilkie, *Perilous knowledge*. However if any of our specialised readers come across a book on genetics/ataxia which they think should be brought before a wider audience, just send the Editor the details and he'll try and get them a review copy from the publisher. All he asks in return is a 500 word

review (in English!) for EURO-ATAXIA.

NB: this could be a way for students, say, to get their hands on a new genetics/ataxia book free

BOOKREVIEW

Whether or not you enthuse over The Human Genome Project (and it must be said it has as many detractors as enthusiasts within the international scientific community) there is one group of people for whom there is no dispute as to the validity of the new genetics: those suffering from the effects of the 4,000 or so single gene disorders. These may be simple, even trifling, errors in individual genetic coding systems but result in appalling disabilities at the physiological level. Of these the ataxias are a mere handful. The infant science of molecular genetics is fast uncovering the identity of the genes that cause many of these - including ataxia genes (as we report elsewhere in EURO-ATAXIA). Progress is accelerating at a terrific pace, with new advances being made every few months. Yet, for that very reason, it behoves those of us with a direct interest in the application of the new genetic technology to at least make an attempt at understanding the background science involved. Likewise, it behoves the scientists themselves to stand back from the biotechnological 'cutting edge' in the laboratory to reflect on the moral, social and political consequences of their work. For both readers, Tom Wilkie's, *Perilous Knowledge: The Human Genome Project And Its Implications*, will be an ideal introduction. The first chapters deal with the intricacies of modern genetics. Most will probably know about general issues in genetics, such as the 'double-helix' structure of DNA, but Wilkie moves beyond this to more detailed topics such as recombination, DNA/RNA, genetic mapping techniques and the use of restriction enzymes.

Later chapters move on to consider the ethical and moral dilemmas raised by The Human Genome Project, largely through a discussion of the social and political framework within which the new genetics will emerge. Existing inequalities (of race, class, wealth, etc.) may become even more pronounced with the development of the new genetic technology. For example, the commonest single gene disorder in the world today is sickle-cell anaemia - which affects only black people of African descent. Will the new genetics be developed to treat poor people in the third world or for cosmetic uses in the affluent first world?

Genetic advances are in danger of being hyped out of all recognition (creating spiralling expectations among people suffering from single gene disorders in

particular), so Wilkie pays close attention to the applications side of the new technology. For example, the results of genetic screening programmes have been mixed so far. In the USA, screening for sickle-cell anaemia among Black Americans in the 1970s was something of a disaster, though that for thalassaemia among Cypriots was more effective. Also, gene therapy may have been 'oversold' as practical medicine, for the technical difficulties involved in it remain enormous - possibly insurmountable.

Wilkie points to the need for realism in any discussion of the new genetics. Genes are not the 'essential particles' of existence, but simply a convenient way for our bodies to obtain proteins, he reminds us. This may be a timely warning, particularly for those of us suffering from single-gene disorders like ataxia where hype and hope are combining to fuel unrealistic expectations.

Michael Morgan

Tom Wilkie, *Perilous Knowledge: The Human Genome Project And Its Implications*, is published in the U.K. by Faber & Faber, Ltd.

INTERNATIONAL RESEARCH REPORT

Funding of research in the UK by the Ataxia Group is part of a worldwide effort. Sharing of information by the different centres is immensely valuable in speeding up the process of research and increasing scientific interest. Both competition and co-operation have their parts to play!

The International Workshop on the Molecular Genetics of Friedreich's and Dominant ataxias was held on 20 - 22 June 1993 in Italy. Funding was obtained from the local universities and institutes, the EEC, EURO-ATAXIA and from the British, Italian, Spanish and Canadian patient groups.

Even before the meeting took place, it promised to be extremely valuable, bringing together more than 70 eminent clinicians and scientists from all over the world, including representatives from Japan, India and Russia. The number of registrants at this meeting reflects the vast increase in research being carried out to identify the underlying genetic defects for both Friedreich's and dominant forms of ataxia. However, none of the participants could be prepared for the privilege of witnessing the announcement of data which would mark major milestones in the history of research into this group of neurodegenerative disorders within the course of just 48 hours!

The meeting opened with a review of current progress towards identifying the gene causing Friedreich's

ataxia and was co-chaired by Dr Susan Chamberlain of St Mary's Hospital Medical School, London. Data was presented by groups from London, Strasbourg, Milan, Naples, Montreal and Nicosia. Sadly, none of the researchers could report the isolation and characterisation of the defect giving rise to this disorder.

The 'candidate' gene (X11) reported last year by the Strasbourg group has now been eliminated from further study on the basis of a recombination event detected in an inbred Tunisian family. However, a consensus was agreed as to the direction in which we must progress in order to 'capture' the FRDA gene. In this respect, a new marker was announced by Dr Koenig from Strasbourg; the analysis of this locus in the recombinant families should facilitate the positioning of the FRDA gene. As explained in the St Mary's research report (see Annual Report & Accounts 1993), the main problem lies in the location of this gene very close to the centromere of chromosome 9 and the difficulties in generating a marker which determines the minimum region in which the gene resides.

However, the research groups agreed to work together more closely, distributing new markers and sharing data, in order to progress more rapidly towards the isolation of the gene. In particular, it was proposed that a database be set up containing the results of the analysis of all families studied through the international collaboration.

Molecular genetic analysis is also helping to clarify some of the diagnostic problems surrounding these disorders. An age of onset under 20 years was previously considered essential for the diagnosis of Friedreich's ataxia. Dr Klockgether (Tübingen) and Dr Filla (Naples) presented data relating to late onset Friedreich's ataxia (LOFA) where onset occurs after the age of 25 years. The ataxia in these families also results from mutation in the chromosome 9 locus, presumably in a region which is less important to the construction of the protein product, and hence, the disease course is milder. Consequently, age of onset will no longer be regarded as a distinguishing clinical criteria for diagnosis.

In contrast to the molecular genetic approach currently being followed by most of the groups, Dr Schapira (Royal Free, London) and funded by Ataxia, has been studying protein abnormalities in the dorsal root ganglia of Friedreich's ataxia patients; the dorsal root ganglia are thought to be the first region affected by the loss of nerve cells. He presented data relating the consistent loss of a specific protein from ganglia removed from patients and reported that the identification of this protein was currently under way (see Research Report RF1).

The afternoon session was co-chaired by Professor

Anita Harding of the Institute of Neurology and a Trustee of the Ataxia Group.

Perhaps the most interesting presentation in this session was given by Dr Koenig, who reported the mapping of the genetic defect giving rise to a selective vitamin E deficiency associated with ataxia to chromosome 8. Although not directly relevant to Friedreich's ataxia (a vitamin E deficiency in FRDA having already been eliminated by Professor Harding), much discussion ensued concerning the clinical differences between these two disorders which had previously seemed clinically indistinguishable. Although vitamin E deficiency is even less common than Friedreich's ataxia, it was suggested that biochemical investigation would be prudent in all newly diagnosed cases, in view of the potential benefits from dietary supplementation. The effect of correcting the vitamin E deficiency has yet to be fully assessed, but looks promising in terms of slowing or arresting the progression of the ataxia in these few specific cases.

The second day of the meeting, devoted to the molecular analysis of dominant ataxia, proved to be the highlight. Over the past few years, it has been established that dominant ataxia can be caused by mutation in at least two different genes and parallel studies to those being carried out for Friedreich's ataxia has been initiated in a number of centres in order to identify the underlying biochemical abnormalities. In the course of one hour, the audience was presented with data relating to the mapping of two of these genes to chromosomes 12 (Chamberlain, London in association with Auburger, Düsseldorf) and 14 (Tsuji, Niigata, Japan) and more importantly, the identification of the mutation causing the form of dominant ataxia (spinal cerebellar ataxia 1) to chromosome 6. The papers reporting this data will appear together in the July 1 issue of *Nature Genetics* celebrating the progress made in the investigation of these disorders.

Doctors Zoghbi (Houston) and Orr (Minneapolis) reported their finding of an error in the genetic code in a very small region of chromosome 6 corresponding to the gene causing spinal cerebellar ataxia 1. This gene has not been described before, and consequently, its normal function remains to be ascertained. However, it would seem that in patients with the form of dominant ataxia mapping to chromosome 6, the alteration in the genetic code results in the expansion or contraction of the region which renders it unstable. As a consequence, the protein encoded by this sequence is altered in some way - either not being produced at the correct concentration or the correct conformation to facilitate the normal functioning of the nerve cell.

This finding will have major consequences for the

ataxia research field, and ultimately, the patients. This is the first 'ataxia' gene to be identified and it is envisaged that considerable effort will be devoted to the investigation of the normal function of the disease gene in the first instance and the subsequent development of a mouse model for the disorder in the immediate future. The production of a mouse model will allow clinicians and scientists to monitor the earliest changes leading to the premature death of the nerve cells and, hopefully, provide insight into mechanisms by which the neurodegeneration can be arrested. The model will, therefore, also provide a basis for the testing of future therapies.

From the preliminary data, it would also seem that the gene causing this form of ataxia is active in all tissues. This is especially promising in terms of future therapy, as it may not be necessary to develop techniques which facilitate the delivery of corrective genes directly to the nervous system. Because the dominant ataxias are clinically very similar, it has been speculated that the different forms may arise from mutation in several related genes, possibly members of a gene family. Therefore, the identification of one ataxia gene may facilitate the rapid isolation of other members of the family, including the Friedreich's ataxia gene, on the basis of the similarities in their respective genetic codes.

What are the immediate implications of these discoveries for families with dominant ataxia?

For any family requesting genetic counselling, the first objective is to establish which of the three known loci is responsible for the disorder in the family in question. For the genes on chromosomes 12 and 14, the accuracy of counselling will improve as closer markers are developed, but will still rely on the analysis of the entire family. For the chromosome 6 locus where the gene and the mutation mechanism has been identified, the availability of families with multiply affected living individuals will no longer be necessary for analysis. Once the parameters of the mutation have been fully established, the analysis of single surviving affected individuals for mutation in this gene will be possible.

Prenatal diagnosis will certainly be available to those families in which this gene is implicated. However, one issue which will have to be faced by the individual families, probably as a consequence of a request for prenatal diagnosis, is the question of presymptomatic diagnosis - diagnosing a family member before the earliest symptoms of the ataxia are apparent. This will, of course, raise many ethical issues which patients and their families will need to address in the immediate future. However, counselling will only be given to families who have received comprehensive information relating to the implications of these in-

vestigations from their genetic counsellors or neurologists.

Susan Chamberlain

RESEARCH REPORT FROM STRASBOURG

Friedreich's ataxia

Although the Friedreich's ataxia gene still withholds its secrets, significant advances have been made in the last year to track it down. The main problem is to locate the gene with respect to the two markers shown to be the closest to the Friedreich's ataxia gene. There were three possibilities: that the disease gene lay between the two markers, that it lay 'below' them (distal on the chromosome), or 'above' them (centromeric on the chromosome).

Because the two markers are so close to the Friedreich's ataxia gene, families which could indicate which of the three possibilities is the correct one are extremely rare (the markers are close to the disease gene in genetic distances which still represent impressive DNA length). Only collaboration between all the groups working on the genetics of Friedreich's ataxia allowed us to identify six such families. As stressed in EURO-ATAXIA 3 by Dr. Susan Chamberlain, the problem in interpreting the results is that some or all of the six families may have a disorder clinically indistinguishable from Friedreich's ataxia, but caused by a mutation within another gene, possibly located on another chromosome. Recent advances allowed us to sort out this issue in some cases. It seems that one of the six families has a disease caused by a gene elsewhere in the genome but this possibility can be safely ruled out now for two other families and is pending for the last three. The advances were due to new markers isolated by our group here in Strasbourg, that of Massimo Pandolfo in Milan, and as part of the systematic marker mapping effort undertaken at the Généthon, funded by the Association Française contre les Myopathies (AFM).

The two critical families that clearly have chromosome 9q13-q21 Friedreich's ataxia indicated that the Friedreich's ataxia gene is not distal from the two initial markers analysed. As well, one of the two families studied indicates that the Friedreich's ataxia gene is not located between these two markers and is not in a 200,000 base pair segment centromeric to these markers. It is a relief to exclude the Friedreich's ataxia gene from all these segments (amounting altogether to 500,000 base pairs) as this spares us having to search through them for the cause of the disease. The excluded segment contains a cerebellum expressed gene that we identified recently and which

we have also excluded by independent means.

The next question is, how far is the Friedreich's ataxia gene from our most centromeric marker? There is no definite answer to this for now. We hope that the small genetic distance between the markers and the Friedreich's ataxia gene indicates that it is in the next 500,000 base pairs rather than further away. There is however no real basis to convert genetic distance into base pair distance in this part of the genome. Only isolation of new markers in this direction, which is in progress in our lab, will allow us to bracket down the Friedreich's ataxia gene. However, the present genetic picture is precise enough for the time being to justify a parallel search of genes in the appropriate segment and we have already identified two of them. The limiting step, as pointed out by Dr. Susan Chamberlain, is that the characterisation of any new gene may represent the efforts of several researchers over a 6-12 month period. Our strong hope is that the Friedreich's ataxia gene will be the first gene identified rather than the last.

Ataxia associated with vitamin E deficiency

During the analysis of Friedreich's ataxia families with markers from chromosome 9, we identified a few families for whom it became clear that the disease gene lay elsewhere in the genome. This was because either the families were large enough to exclude the Friedreich's ataxia gene by genetic analysis or because the diagnosis was wrong in two cases (these families not among the six mentioned above). Those families were identified in collaboration with the groups of Mongi Ben Hamida in Tunis, Lefkos Middleton in Cyprus and Massimo Pandolfo in Milan.

The surprise came when, by retrospective analysis, all patients turned out to suffer from severe and isolated vitamin E deficiency and that in the large families the condition was indistinguishable from Friedreich's ataxia. Albeit ataxia with vitamin E deficiency had already been described in rare cases, this was the first demonstration that the Friedreich's ataxia phenotype could be associated with autosomal recessive vitamin E deficiency. This entity is however very rare and represents no more than one per cent of all the Friedreich's ataxia families in Europe, but much more in Tunisia.

In cases with isolated vitamin E deficiency, patients may benefit from long term supplementation with α -tocopherol (vitamin E) before irreversible neurodegenerative damage has taken place. It is thus important to diagnose this form of ataxia early, and a systematic test of vitamin E levels, at least in one proband in each recessive ataxia family, might be recommended, especially for families for which the disease does not segregate with the 9q13-q21 markers. Con-

versely, it is known that supplementation with α -tocopherol is inefficient in Friedreich's ataxia linked to chromosome 9. However the two diseases may still be due to different genes involved in the same pathological process. For example, Friedreich's ataxia might be due to a protein that becomes insensitive to vitamin E when mutated. Cloning of the two genes should shed light on these hypotheses. Towards this goal we have determined the chromosomal assignment of the gene locus for ataxia associated with vitamin E deficiency. We have used a strategy that takes advantage of the rarity of the disease - the high rate of consanguinity frequently found in rare autosomal recessive diseases. Without this information genetic linkage analysis would have been much more difficult given the small number of families that we have. The consanguinity information allowed us to narrow down the gene locus within a relatively small genetic interval on chromosome 8, thanks also to the dense marker map developed at Généthon (AFM). The analysis of vitamin E deficiency ataxia should benefit from the experience gained with Friedreich's ataxia and from the impressive development of new genetic and DNA tools. The rarity of vitamin E deficiency ataxia should not be considered a barrier to the identification of the defective gene.

Michel Koenig

Laboratoire de Génétique Moléculaire du CNRS et de l'INSERM, Faculté de Médecine de Strasbourg, August 1993

SPAIN

Santander, in Cantabria, was the setting for the 9th Spanish Congress of Neurology, held between 26 - 28 May. The conference was dedicated to three topics: the clinical and genetic aspects of hereditary ataxias and paraplegias, alteraciones neurológicas inducidas por fármacos (*the editor doesn't know any Spanish beyond ¡hola! and mañana, so readers can translate this bit themselves!*) and the molecular pathology of the nervous system. The President of the Organising Committee, José Berciano Blancco, opened the conference, the main part of which took place in the University Hospital, 'Marqués de Valdecilla'. This was appropriate, he added, as 'Marqués de Valdecilla' was the main site for most clinical work in Cantabria. The ubiquitous poster presentations were also held during the conference, taking place in three one hour sessions staggered over the weekend.

GLOBAL ATAXIA PENPALS

GAP-Global Ataxia Penpals is a new scheme aiming to establish an international network of personal communication between ataxic people. The main medium of communication will be English, I think, but whether this is an essential requirement is something that can best be discussed with the organiser. For further information, please contact:

GAP-Global Ataxia Penpals

Lynda Bonnor

14 Kenilworth Gardens

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Essex SS6 9HS

UNITED KINGDOM

CALENDAR

In the USA, the National Ataxia Foundation will be holding its 1994 Annual Membership Meeting - *Its Up To Us* - over the weekend of February 25 - 27 in San Diego, California. With the recent breakthrough in ataxia research announced by the Americans it promises to be an exciting meeting.

For more details contact NAF head office or local representatives:

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The Genetic Interest Group in the UK are holding another in their excellent series of 'Interface' meetings on Friday 17 November 1993. Entitled, *A Home, A Job And A Pension*, the day-long meeting will consist of individual talks and discussions on employment and related social issues. Starting time is 9.30 am in the NCVO Conference Centre, Regents Wharf, London.

Registration, booking details are available from:

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