



EDITORIAL

Michael Morgan

To say that the 1999 AGM at Westende was perhaps not the best thing we in Euro-Ataxia have done in the ten years of our existence sounds a bit of an understatement. More than anything else this attracted a lot of internal dissension and criticism. So, inside, the inevitable post-mortem.

One paper that stood out was that given by J.J. Cassiman, of Leuven, who stressed the need for a grand alliance between scientists, patients groups and the pharmaceutical industry at EU level. The reality was however that the pharmaceutical companies who partly-sponsored the conference insisted on a purely scientific agenda. As an example of 'The Grand Alliance' in action this was not entirely reassuring – because the sponsors insisted on a scientific agenda alone, we in Euro-Ataxia felt we were losing control of 'our' AGM in having the agenda dictated by outside influences. Or so I think inside.

In Euro-Ataxia 17 Peter Bayliss wrote about voice recognition programs, especially those coming from Dragon Systems – which many ataxians seem to rate highly. DragonDictate is a so called discrete voice recognition program where each word has to be logged in separately. NaturallySpeaking however is a program for continuous speech, which means that it is made for the recognition of entire sentences spoken at a normal or natural speed. Inside Carolien Koopmans gives her appraisal of both systems.

Sex is a perennially fascinating subject for us ataxic people – just as it is for everybody else too. Tarja Ketola was until recent resident neuropsychologist at the Masku centre for people with neuromuscular impairments in Finland. Recently she made a presentation on *Sex and Ataxia* at the Finnish ataxia groups' annual meeting in August 1999. It's a very good and sympathetic analysis, certainly deserving a much wider readership through Euro-Ataxia.

Fully accessible aeroplanes do not as yet exist, anywhere. A plane with a wider entrance, the possibility to fold the first seats against the wall, and rails on the floor of domestic planes for locking the wheelchair on-board, is alas only a dream. But these musings and others struck Päivi Mustonen recently as she flew between Oulu and Helsinki and inside she shares her thoughts...

Dr. Gert Jan van Ommen is professor in anthropogenetics at Leyden University and president of the Human Genome Organisation. But he's also something of a gene-sceptic who holds that a human being will never be an 'open book'.

The 2000 Annual General Meeting will be held from 29 September - 1 October at Valjeviken in the South of Sweden.

Finally, in case you hadn't noticed, it's now 2000 plus *. So, from all the editorial cyber-board at Euro-Ataxia may I wish everybody a happy new year, new century and new millennium!

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WESTENDE 1*Michael Morgan*

One of the more interesting papers presented to the Westende conference was given by J.J. Cassiman, of the University of Leuven, Belgium. Entitled, Impact Of The Commission Projects On The Future Medicine And Public Perception Of Research, the paper stressed the need for a broad alliance between scientists, patients groups and the pharmaceutical industry in order to further our shared aims for treatments and in particular how best we can co-operate to pursue these aims at EU level. Whilst I am totally in agreement with this argument may I say that the reality of such co-operation as practised at the Westende conference was not entirely reassuring. Although the pharmaceutical industry – well a number of companies really – sponsored the event alright, they then insisted that the agenda should reflect their own concerns, which meant in this case a purely scientific agenda. This was not so much co-operation as coercion – using your financial muscle to essentially dictate the content of the conference. The Westende conference was supposedly under the control of Euro-Ataxia, yet because the sponsors insisted on a scientific agenda alone, we in Euro-Ataxia felt we were losing control in having our agenda dictated by outside influences.

Now, to the pharmaceutical companies involved this could seem like an entirely legitimate course of action – “Whoever pays the piper names the tune”. But if our aim is to create a broad alliance between our different groups this sort of behaviour could seem to be short-sighted. Rather than winning friends, it alienates and creates resentment.

It was altogether a different story a few years ago when pharmaceutical companies invited groups of disabled people to come to Strasbourg to help lobby for the Gene Patenting directive then coming before the European Parliament. Lavish hospitality, free drinks and dinners, were proffered to all disabled groups and individuals involved and the directive was duly passed. Of course using disabled people in this way is a well-known PR trick, hoping to ride interest on the back of sentimentality – after all, who can resist the image of a kid in a wheelchair? But the most irritating thing about this kind of basically marketing strategy is that it's a short-term approach. It's certainly not in the best long-term interest of building a broad alliance – a much better strategy would be to fund patient's conference's without attempting to dictate the agenda. It would win more friends for the pharmaceutical industry for a start and surely build more trust and confidence between all our different party's. This would be a much more effective way of building that broad alliance which we all want to see.

WESTENDE 2*Michael Morgan*

The Westende conference attracted a lot of internal dissension and criticism and was, in retrospect, perhaps not the best thing we in Euro-Ataxia have done in the ten years of our existence. But then it's easy to be wise after the event. Yes some of the criticism was indeed valid, but much wasn't. Organisationally the conference fell into two parts. The basic organisation was excellent and well thought-out: The location of the conference at Zon en Zee, the accommodation therein and transport to/from Zaventem Airport. All these things were well-organised, reflecting a lot of hard work from the conference organisers, in particular Dagmar Kroebel. Dagmar had to make some difficult choices and indeed compromises to get the conference going in the first place, and it's a tribute to her professionalism that we were able to hold an AGM anywhere this year.

Unfortunately problems which could not have really been foreseen emerged to make our stay in Zon en Zee uncomfortable and not really up to the mark. Renovation work at Zon en Zee put us in a small room difficult to access for many of the delegates. Added to which the restaurant and bar presented a wall of noise – which made things very difficult for those of us with hearing problems.

But these in themselves were only irritants. The main criticism tended to focus on the structure of the conference, and in particular the way in which the agenda seemed to be skewed towards scientific perspectives. No paper was presented which even attempted to address problems in living with Ataxia – supposedly such an important feature of any Euro-Ataxia conference. The general rule is that both scientific issues and living issues should be addressed, and in that way a balanced agenda be maintained. This didn't happen and in turn allowed a vagueish feeling to emerge that



Michael Morgan & Carolien Koopmans at Westende

somewhere along the line we ataxic people had lost control of 'our' conference to the scientists.

Not that there was anything wrong with the scientific papers presented – indeed they illuminated many areas for many of the scientists present and gave us non-medical people a good insight into the Cerebellar Ataxias. However the conference fell far short of its stated aim of bringing scientists and ataxic people together. There was in fact little interaction between the two groups, a separation illustrated by the fact of the scientists sitting on the right hand side of the room and the ataxic people sitting on the left. This was not so much a informed get together as two groups just thrown together in the same room. But then again this was nobody's fault as such, for intimacy can't be achieved in a single day.

An evaluation of the Westende conference was carried out by the Finnish group. Interestingly, this reported dissension with parts of the conference but not in the whole thing. Many thought the day's proceedings too scientific, many others reported satisfaction at the level of scientific input; many complained that the conference time was too rushed and overloaded, others wanted to see another session built in to explain scientific matters in a more accessible layman's vocabulary. Overall therefore, it seems the jury remains out on the Westende conference. Hopefully lessons will be learnt and taken account of for the conference in Sweden.



Coffee break at Westende, the Finnish delegation

NATURALLYSPEAKING

Carolien Koopmans

Finally! A Dutch program for voice recognition! Made by Dragon Systems, the same company that made DragonDictate. In the previous newsletter Peter Bayliss wrote a praising article about DragonDictate and according to some contributions on Internaf many ataxians seem to appreciate DragonDictate extremely. And knowing how relaxed I work with the old English VoiceType (a program of IBM made in 1989 in co-



Some delegates outside the 'restaurant'

operation with Dragon Systems), I can understand their enthusiasm.

NaturallySpeaking differs from DragonDictate in that it is a program for continuous speech, which means that it is made for the recognition of entire sentences spoken at a normal or natural speed. VoiceType and DragonDictate are so called discrete voice recognition programs: you have to pause after every word. What would NaturallySpeaking do with the pauses I take between two words? We only could find out by trying.

So I bought NaturallySpeaking and just tried. In practice NaturallySpeaking accepted my word for word dictation. (By dictating word for word you don't make full use of the enormous capacities of the program for the recognition of continuous speech, that are mainly based on statistics. That's a pity, but not a cause for worrying.) But somehow I seem to hold on to my words too long. Especially the short words - and they are used a lot in Dutch - I don't pronounce quickly enough. The program expects me to speak more than one word at once, so it takes my slurring sometimes for the beginning of a new word. However, the mistake is easily corrected (only by saying 2 commands).

Before I explain any further I have to tell about the speech files, that are an essential part of every voice recognition program. In voice recognition programs a file is made of everything you dictate together with the way the program interprets what you say. That file is called your speech file. That speech file is the basis on which the program interprets what you say to the computer. When you start the voice recognition program the speech file is automatically loaded into the memory of the computer. After every session you are asked if you want to save the new speech file. If you answer "yes" the program adds the commands and words you just spoke to the already existing speech file. So the speech file gets larger after each session. And the program recognizes your voice better every time you use it. That's why they call a voice recognition program a 'self-learning' system.

NaturallySpeaking's recognition of the voice is fantastic! A good illustration of this is the letter 'r'. I don't

pronounce the 'r' with a beautiful rolling sound but more like a Dutch 'g', a guttural sound or a sound that seems to come out of the throat. That Dutch 'g' (or 'ch') is a sound which foreigners can't pronounce. At first NaturallySpeaking didn't accept a single word of mine with a 'r' in it. I had to correct all those words by spelling them letter for letter. But after a while the program got used to my strange way of pronouncing the 'r' and even accepted new words with a 'r' and put them on the screen correctly from the first time onward.

Voice recognition is really a perfect invention for ataxians. And because of the continuous training of your speech, your voice tends to be kept in a better condition than without.

TAKE CARE OF YOURSELF AND YOUR RELATIONSHIP

Tarja Ketola with Minna Kaitaniemi.

Tarja Ketola was until recent resident neuropsychologist at the Masku rehabilitation centre in Finland. Recently she made a presentation on *Sex and Ataxia* at the Finnish ataxia groups' annual meeting in August 1999. It's very good and deserves a wider readership in Euro-Ataxia we feel.

An illness is not the end of good sex, assures neuropsychologist Tarja Ketola. Your sex life will change, it's true, but you decide in which direction. The right attitude and activity will lead to a new kind of enjoyment in the bedroom.

Tarja Ketola admits that ataxia is not unproblematic as regards a person's sexuality. The condition does not directly affect sexual desire or interest, but it may have indirect impacts. Especially in the early stage of the illness and when other changes occur, negative feelings easily surface.

"An illness in the family arouses very strong feelings both in the affected person and in his or her partner. There are feelings of distress, worry, anger, disappointment, sadness, anxiety, helplessness, dependency and depression. Often there are problems with self-esteem, feelings of worthlessness, performance pressures, guilt, jealousy, gratitude, pity, bitterness and so on. A whole range of feelings which have been found to reduce sexual desire."

When the relationship runs into crisis, the partners have to cooperate to fix things. "You can always seek external help, but the best first aid is to sit down at the kitchen table to discuss the situation. Both partners have to face the facts and think about what to do next."

When the couple shares these thoughts, the underlying hurtful feelings are eventually encountered. This will make it easier to start finding solutions to the

problems.

It requires work to improve a relationship, but it's worth it. "If you don't do anything about it, the issue tends to get worse, like most unpleasant things in life. If we want to enjoy life and couplehood, we'll have to be active," Ketola reminds us.

Household chores and self-esteem

Ataxia often changes practical things in life, and household chores are redistributed in the family.

"It doesn't matter who does what, as long as things get done. But it's worthwhile discussing these matters, as we identify surprisingly many things in the household with our own identity as a man or woman," says Ketola.

In addition to practical issues, it's important to consider how we feel about the new division of labour at home. Manhood or womanhood does not really depend on who changes the tyres or sews a button.

"Our self-esteem is most vulnerable in those areas which relate to our manhood or womanhood. This is precisely why it's important to pay attention to changes in simple household chores, so that we don't let small everyday issues ruin our life," Ketola stresses.

It is through our self-esteem that changes in everyday matters may affect things in bed, so it's not a waste of time to think things through.

Change for the better

Bodily changes affect our sexual habits, and this is as it should be in the course of our lives. The changes brought by an illness, however, are often such that we haven't necessarily wanted or expected them. This is why there is a common belief that they'll interfere with our sex life.

Tarja Ketola does not share this view. "I'm not at all convinced that changes will make things worse. They do pose challenges and force us to change our old habits. On the other hand, change contains the possibility to enjoy a kind of richness which would never have come about had we stuck to our routines. In other words, a change may always be a change for the better."

"It all depends on how we relate to the change. The more open we keep our eyes and the more willing we are to experiment, the more positive can the change be," Ketola explains and continues: "Physical changes do not necessarily mean reduced quality or diminished pleasure. They mean a different kind of pleasure."

Practical hints

"Ataxia affects mobility, and this is why we should openly discuss undesirable forms of movements," Tarja Ketola recommends. "As a couple, you should search for forms of caresses which feel good to both partners. You should try different positions and think how they affect the control of movements."

As a tip, Ketola points out that pillows are helpful

aids. "When you want to have good sex, you should have 20 to 30 pillows that you place in the right angles." Pillows are also useful when physical strength is diminished, because they provide support and reduce the need for physical strength. "Also, don't forget your mouth and tongue. Long hair can also be used to caress your partner," Ketola reminds us.

Different sensations are an important part of our sexuality. Some illnesses affect sight, which is often a more erotically stimulating sense for men than women. Male sexuality is more visual than female. "If your sight is affected, you can ask your partner to describe certain things that you would enjoy seeing. A mental picture still exists in the mind, so it's a good idea to use some imagination."

Ataxia causes fatigue, because daily tasks require more effort than before. This should also be taken into account in sexual matters. "There's no point having sex when you're exhausted. The best time for sex is when physical strength is at its peak. I recommend mornings and other times when both partners feel physically strong."

Caring for one's personal hygiene is also part of sexuality, and illness does not affect this fact. However, one may need help in this, and it may be a difficult thing to ask.

According to Ketola, Finns don't easily ask their assistant to help them with their make-up or hair styling, even though these things may be very important to the person. Ketola points out that taking care of one's personal hygiene and physical appearance is just as important as, for instance, meals. "I recommend that you start seeing beautification as your right and ask for it when you need it," Ketola stresses.

FLYING WITH WHEELCHAIRS

Päivi Mustonen

On a recent flight from Oulu to Helsinki I got talking to another wheelchair user on the plane. I told my friend that when I was booking my flight to Belgium, I was asked whether I would like to sit in my own wheelchair. In a moment, my friend envisioned a wider entrance to the aeroplane, the possibility to fold the first seats against the wall, and rails on the floor of domestic planes for locking the wheelchair onboard. Alas the fully accessible aeroplane has not yet arrived, and wheelchair users remain forced to leave their chair in the cargo hold. Maybe this is why Finnair grants discounts to the disabled? Instead of new plane's they trade mobility and comfort for wheelchair user's for discounts.

Every piece of luggage left in a plane's cargo hold is automatically covered by the air companies insurance, so you don't have to take out an extra insurance for a wheelchair when actually flying. However on the

ground it's different. For example if I had broken my wheelchair in *Zon en Zee* I could only claim if I had taken out an additional travel insurance policy - just as in Finland where I have taken out the same kind of insurance for my wheelchair as little girls and boys have for their motorbikes. This insurance is valid in all EU countries.

The biggest worry of the attendants of Scandinavian airlines was whether the battery of my wheelchair was "dry or wet". The question struck my mouth wide open. Try to imagine a dry light substance that conducts electrical power. A "wet" battery is a bit more understandable. In the old days batteries were filled with distilled water. Nowadays they are filled with a gel that does not leak even if the battery is set upside down. SAS was informed in advance of the type of wheelchair battery I was bringing.

And when a disabled person requires an assistant, this person is not allowed any discount. In addition to his or her own discount ticket, the disabled person has to pay a full-price ticket for the assistant. In my view, carriers should improve flight comfort and charge all passengers the same price, but if the disabled person needs an assistant, it is unfair for him or her to be charged twice. The personal assistant has to do his or her job no matter where the assisted person happens to be. It has been suggested to Finnair that it should adopt the practice followed by railway companies, a number of municipalities and sports organisations: a free ticket for the personal assistant.

A HUMAN BEING WILL NEVER BE AN 'OPEN BOOK'

Rietje Krijnen

Dr. Gert Jan van Ommen is professor in anthropogenetics at Leyden University (Netherlands) and president of the Human Genome Organisation (HUGO), the world-wide co-operative project to map the entire human genome or all the human genes.

Van Ommen tells that in the beginning HUGO focused almost entirely on DNA. No or little attention was paid to the ethical dimension of DNA research. But the ethical aspect is an integral part of the problem. It is a part of his job to co-ordinate the different points of view that exist in the world.

The human genome has the interest of a lot of people. That is not in the latter part due to the fact that the mapping of the genes is happening at such a rapid speed. Recently a landmark has been reached. Chromosome 22, the smallest of the 23 pairs of chromosomes in every cell in the human body, has been mapped completely.

In contrast with what might be expected Van Ommen isn't overwhelmed over the complete mapping of the first human chromosome. He almost shrugs his shoulders. "I have no specific knowledge about chromosome 22," says Van Ommen. "It is obvious that the mapping of chromosome 22 is an important landmark for me and my colleagues. Now we know more about some deformity syndromes, about the origin of some forms of cancer and heart failures. But a human being will never be an open book." Seeing the astonished expression on the face of the interviewer, he quickly continues: "I am not stating that HUGO has no value. On the contrary. We now know a lot more than we did before. We now know where and how certain genes are located and how they function. In the past we only knew that a certain gene had to exist but didn't know the location and form of it. But if the entire human genome is mapped there's still a long way to go. To know more about heredity, families in more than one generation have to be researched. Furthermore, we have to know how the concerned human beings live and what they eat. There are so many factors that influence the way people are." Van Ommen illustrates his remark with the following example. Among the native Americans in the south-west of the USA there is a lot of 'morbid obesity': about 68% of the native Americans is extremely fat. This can be caused by a hereditary disorder but the cause can't be located in the genes in a direct way. It appears that these people having lived for millennia on a vegetarian diet of plant roots aren't physically adapted to the hamburger culture. That inadequacy of the digestive system is expressed by obesity. Other population groups don't develop that in such a serious form.

"There are some general characteristics in the genetic material," explains Van Ommen, "but to predict if and when people get a certain disease and to what extent and how the disease will develop, much more has to be known. Correlations have to be found. And some of the aspects can never be analysed." He refers to the hereditary muscular dystrophy of Duchenne and Becker. One person has a mild form and in the other person the disease is much more progressive. It is known that in the case of Duchenne the protein dystrophin is not made by the body of the person who has the disorder. In some patients a fraction of that protein is still being produced in some muscle groups and then the dystrophy is called Becker dystrophy. This disease is far less progressive. What is the cause of such differences? The scientists don't know. Muscular dystrophy appears to have physically a greater impact on dogs than it has on cats or mice. What can be learned by this? Maybe it means that because the body is smaller and the muscle groups are more developed the animals tend to have less trouble and get less ill. Some pieces of the jig-saw puzzle of life are known. But before all effects are analysed many years will have passed.

"Sometimes it frightens people to know that all hereditary diseases are now visible," says Van Ommen. "But one has to realise that this insight brings only restricted power. Maybe we will find a therapy for hereditary diseases. But there are so many other diseases which have a hereditary component that we don't know yet." Van Ommen himself is a good example. He is deaf on one side. Not since birth but since he was very young. When he was a little child they gave him a certain drug when he was ill. And by consuming that antibiotic he became one-sided deaf. "I had a latent hereditary disorder which is inherited through the female line. To become deaf it is necessary to get a certain antibiotic; they didn't know at the time but that is exactly what happened to me," he says.

Hearing problems have always been his special interest. After visiting a rock concert he wrote an article about loud music and the damage it could do to the hearing. Following the publication of that article Van Ommen was offered a job on the side as a rock critic. So in the sixties he was engaged in circles quite different from the scientific for part of the time. He visited rock concerts regularly. Through this job he met with people like The Who and Frank Zappa, and saw Jim Morrison of The Doors tumble off the stage. That is quite another world than the world of science. The world of science is a highly rational world. "As president of HUGO it's my task to keep the communication between the scientists going. Some of the scientists may be totally concentrated on their work in the laboratory and don't care about the rest of the world, but in reality it is the external world that matters. The human being and his surroundings, that is what matters. And that is what makes my job so interesting."

[Reprinted from *Contact*, magazine of the Dutch VSN, december 1999; adapted and translated by Carolien Koopmans.]

MEDICINE TRIALS

Ewout Brunt

The best way to establish if a medicine is really working is conducting a *randomised, controlled, double blind* trial. *Randomised* means the patients are *at random* divided into groups which are to be compared. *Controlled* means this comparison is made between the medicine to be tested and a not working medicine (placebo) and/or an other known medicine. *Double blind* means neither the patient nor the doctor knows which treatment the patient gets.

With this kind of trials you have to be very well aware of the desired result after a certain period. The size of both groups is established according to the desired result. This is a question of statistics. If the desired result is only small, you need larger groups. Finally the result of a trial is expressed as a certain degree of reliability, i.e. the chance the effect is real or coincidental.

There are different phases in medicine trials. Often a open trial is held before a double blind randomised trial to establish dose and side effects of the medicine. Until now we only have results of the open trial with *idebenone* in France from dr. Rustin. In this open trial in a small group of patients the results show a positive effect of idebenone on the heart tissue of FA patients with cardiomyopathy. The group of dr. Rustin is very convinced of these results. But as I explained above, this trial does not meet with the criteria for a scientific proof.

In England the group of dr. Shapira is conducting a well established trial with Q10 and Vitamin E, and within NAF in the United States preparations are being made for a scientific trial with idebenone.

Treatment with these medicines has to be considered as experimental until we have a convincing scientific proof of their effects.

1999 UPDATE ON DOMINANT ATAXIAS

Ewout Brunt

Since the previous AGM in Turku, both the genetic diagnosis of SCA, and the research on the mechanism of neuronal cell death in SCA's and related disorders have seen impressive progress. This short review is meant to summarize these new developments.

New SCA's

In last year's update on dominant ataxia's, I could name 8 genetically identified types, SCA1-7 and DRPLA. Since then, 4 additional SCA's have been genetically identified: SCA8, SCA10, SCA11 and SCA12 (see table 1). A funny thing seems to be going on with SCA9, which is still missing. Rumours go that this number has been reserved for a non-SCA1-7 family, as was the case with SCA6 at the time of publication of SCA7.

SCA8, a number first used for an early onset recessive type of ataxia (IOSCA), has now been reassigned to an ADCA I type of ataxia. SCA8 was first reported by the group of researchers from Minneapolis in 1998, who localized the gene on chromosome 13q21, and found an unstable CTG expansion mutation in this gene. Normally with a length below 37, most affected people have an expansion between 105 and 130 copies. This CTG expansion is contained in an untranslated part of the gene, meaning that it is copied – transcribed - by messenger RNA, but is not translated from messenger RNA into the protein, the gene product. So the trinucleotide repeat expansion in SCA8 differs from the CAG repeat expansion in SCA1, 3, 6 and 7 in two ways: the type (nucleotide sequence) and absent translation into the gene's product. Also, something special is going on with this unstable, untranslated CTG expansion. A further expansion frequently occurs in maternal transmission, while a contraction often occurs in paternal transmission. As a result of this, unaffected mothers with an asymptomatic expansion under 90 may have affected children with an expansion of for example 120, and on the other hand, affected fathers may have healthy children. The frequent expansion in maternal transmission also explains the uncommon pattern of dominant inheritance, with apparent maternal penetrance bias, the large majority of affected people having an affected mother. A second special characteristic of SCA8 is that very large expansions, beyond 250 repeats, do not cause ataxia. (These very large 'safe' expansions probably prevent the transcription of DNA by messenger RNA.) But then, in paternal transmission such a very large expansion may again contract and give the situation of affected children of an unaffected father. As a consequence of all this, genetic diagnosis in SCA8 is not as straight forward as in other SCA's. Although relatively rare with a prevalence of < 1:100.000, SCA8 has by now been recognized in many countries. Of the clinical signs ataxia stands

SCA	MIM	chr.	repeat
SCA1	164400	chr 6p22-23	CAG
SCA2	183090	chr 12q23-24	CAG
SCA3/MJD	109150	chr 14q32.1	CAG
SCA4	600223	chr 16q24-ter	?
SCA5	600224	chr 11c	?
SCA6	183086	chr 19p13	CAG
SCA7	164500	chr 3p14-21	CAG
SCA8	603680	chr 13q21	CTG
SCA10	603516	chr 22q13-ter	?
SCA11	(n.a.)	chr 15q14-21.3	?
SCA12	604326	chr 5q31-33	CAG
DRPLA	125370	chr 12p	CAG
EA1	160120	chr 12p	(KCNA1 mutation)
EA2	601011	chr 19p13	(CACNA1A mutation)

Table 1. Genetically identified dominantly inherited ataxia's, comparing SCA numbers, Mendelian Inheritance in Man (MIM) numbers, the chromosomal localization of the gene, and the mutation.

out, with some spasticity and reduced vibration sense variably present. The age at onset shows a wide range from below 20 to beyond 60 years and is correlated to the length of the repeat expansion. The progression is relatively slow.

The genetic localization of SCA10 was reported in early 1999 by researchers from Los Angeles and from Houston, who had studied two different families of Mexican-Spanish descent. The gene itself has not been identified, but has been localized to chromosome 22q13-qter. SCA10 differs from other known SCA's in the combination of ataxia with epilepsy, a combination however, which does also occur in DRPLA. Epileptic attacks occur in 20-65% of affected people with SCA10, and may also be the first manifestation. Clinical manifestations become manifest between 20 and 50 years, and the occurrence of anticipation suggests that the causative mutation may again be a dynamic trinucleotide expansion.

In autumn 1999 SCA11 was reported in a single large family from the south of England. In this family, a gene causing a relative pure (ADCA III type) cerebellar ataxia, could be localized to chromosome 15q14-21.3. The gene itself has not yet been identified, but it is already apparent that the mutation is not a large CAG repeat, as is also suggested by the absence of anticipation in this family. In addition to cerebellar ataxia, some loss of muscle strength and deep sensation may develop. SCA10 compares largely to SCA6, and although it starts obviously earlier than SCA6 with an average age at onset of approximately 25 years, progression is notably slow, with no affected family members being wheelchair bound. MR imaging of the brain in affected members shows isolated cerebellar atrophy.

Almost simultaneously with SCA11, SCA12 was reported in a large family of German descent by researchers from Baltimore, in collaboration with German and other North American centres. The causative gene was localized to chromosome 5q31-33, and the mutation was found to be another unstable CAG repeat expansion in a known gene. Normally below 28 copies, in affected people the length of this CAG repeat is between 66 and 78 copies, with moderate instability in generational transmission. SCA12 is noteworthy for two reasons; the mechanism by which the CAG expansion causes cellular dysfunction, and its clinical manifestations. The expanded CAG repeat is localized in what is called the gene's promoter region, that is the region, which is involved in starting the gene's transcription. As with SCA8, this expanded trinucleotide repeat is not translated into the gene protein product, which in fact is normal in SCA12. The mutation in the promoter region seems to cause the production of an excessive amount of this protein. This protein is known to play a steering role for an enzyme, PP2A,

which is involved in processes of ageing and death of certain brain cells. Much unlike other SCA's, the first clinical manifestation of this disorder usually is not ataxia, but (action) tremor of hands and head. The age at onset ranges between 8 and 55 years. Over years ataxia develops and becomes prominent, but in addition, paucity of movements, dystonia, hyperreflexia and weakness of eye muscles may develop, and elderly patients with advanced disease sometimes become demented. On MRI, cerebellar cortical atrophy is found.

Progress in understanding pathogenesis

Last year I mentioned the MJD/SCA3 fruit fly model and the finding of inclusion bodies found in neuronal nuclei. Transgenic mouse models for the dominant ataxia's now include SCA1, SCA2, SCA3, SCA7 and DRPLA. Nuclear inclusion bodies, which also occur in DRPLA, Huntington's disease and SBMA (Spinobulbar-muscular atrophy), are present in SCA1, SCA3 and SCA7. In SCA2 and SCA6, inclusion bodies are present not within the nucleus, but in the cell's cytoplasm. All of these aggregates consist of parts of the abnormal protein, and in the case of intra-nuclear aggregates different cellular protein degrading enzymes are also found. The current understanding is that the abnormal protein has an abnormal shape – folding – which may cause abnormal interaction with other proteins, and prevents its normal degradation. The answer to the question why only certain brain regions are affected, while the abnormal proteins are widely expressed, may be related to interaction with specific proteins in these cells. In SCA1 cells, prevention of the abnormal protein to enter the nucleus prevents cell death, while inhibition of aggregation promotes cell death, and promotion of aggregation reduces cell death. So there is now evidence that it is not these aggregates themselves, but (parts of) the unaggregated abnormal protein, which cause harm to the cell, and that formation of aggregates may even reflect a defensive handling of these difficult to degrade proteins.

In summary, the genetic identification of dominant ataxia's has leaped forward again. Different molecular mechanisms, which cause inherited ataxia are now recognized. In addition to the formation of abnormal proteins from a translated CAG repeat expansion (SCA1, 2, 3, 7 and DRPLA), and a mutation causing a dysfunction of a calcium channel, also abnormal DNA transcription (SCA8) and enhanced production of a normal protein (SCA12) appear to be involved in the pathogenesis of dominant ataxia. For the SCA's with translated expanded CAG repeats resulting in proteins with a polyglutamine stretch, perhaps not the neuronal intra-nuclear aggregates themselves but rather the unaggregated (truncated) abnormal proteins cause the cell damage.

Many reasons to hope for a future possible treatment, but meanwhile let's not forget to enjoy life as it comes.

2000 ANNUAL GENERAL MEETING, 29 SEPTEMBER – 1 OCTOBER IN VALJEVIKEN, SWEDEN

The 2000 Annual General Meeting will be organised by the Swedish Neurologiskt Handikappades Riksförbund (NHR) in their Rehabilitation Centre Valjeviken in Sölvesborg in the South East of Sweden.

We 'borrowed' some pictures of Valjeviken's website and reproduce them here, so you can have a first impression.



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