Newsletter
der
Deutschen Gesellschaft für Neurogenetik

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DGNG News No. 7

Society News

Neurogenetics in Bochum

The 4th Workshop Neurogenetics in Germany and 3rd meeting of the German Society of Neurogenetics was held in Bochum (Organizers: J.T. Epplen and O. Riess) from October 2-4, 1997. As in previous years, the program was quite attractive and most contributions were of the highest quality. The relatively small format of the conference (there were approximately 100 participants) facilitated in-depth discussions of the various research topics. The meeting focussed on trinucleotide repeat disorders and multiple sclerosis. In addition, various current topics such as nerve regeneration, Charcot-Marie-Tooth disease, dystonias, CADASIL syndrome, and animal models were covered. The abstracts of this conference have been published in the journal "Medizinische Genetik" as have the abstracts of the previous meeting.

This has now been the fourth exciting Neurogenetics workshop since 1994. The success of these conferences is due to various factors. All meetings have been truly interdisciplinary representing as many and diverse fields as there are scientific backgrounds in the DGNG. As a result, formerly inapparent interfaces between disciplines have become evident. The motivation of most attendees was way above average. Issues complicating the conferences of many professional societies such as finances and politics were not dealt with during the main meeting. Finally, presentation and discussion of the "hottest" topics in this rapidly developing field explains the exceptionally high "novelty score" of all the neurogenetics conferences. There is good reason to expect more exciting meetings in the future.

5th Workshop Neurogenetics in Germany, 4th Annual Meeting of the DGNG

The 1998 meeting of the society will be held in Freiburg/i.Br. from October 22 to October 24, 1998 and will be organized by Dr. G. B. Landwehrmeyer, Prof. R. Korinthenberg, Prof. C. H. Luecking, Dr. D. Morris-Rosenthal, and Prof. U. Wolf.

Hungarian Society of Neurogenetics, List of representatives

Following is a list of representatives of the **Hungarian Society of Neurogenetics** (see Newsletter No. 6):

<table>
<tr><td colspan="2">Prof. Ferenc Mechler
(President)
Institute of Neurology
Med. Univ. of Debrecen
Debrecen</td></tr>
<tr><td>Dr. Maria Judit Molnar
Secretary
Institute of Neurology
Med. Univ. of Debrecen
Debrecen</td><td>Dr. Rita Horvath
Treasurer
Dept. of Neurology
Jahn Ferenc Hospital
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<tr><td>Dr. Agnes Hercegfalvi
Public Relations
Dept. of Neurology
Children’s Hosp. Heim Pal
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<tr><td>Dr. Katalin Jakab
Courses, Continuing Education
Neurological Clinic
Szentgyorgyi Albert Univ.
Szeged</td><td>Dr. Ferenc Garzuly
Conferences
County Hospital
Szombathely
Szombathely</td></tr>
</table>

The Hungarian Society has started with 40 members.

Institutes performing neurogenetic testing in Germany and neighboring countries

We have been approached by a number of individuals requesting this information. In reply to this request, we would like to refer to a recent listing published in Med. Genetik 9 (1997) 505-523 (see also Newsletter 2 of the DGNG). In addition, we ask all institutes interested in being mentioned on the home page of the DGNG to provide us with their URL.

Research News

Huntingtin and the nucleus. Some of the discoveries in neurogenetics are real surprises. This is true for the finding of intranuclear inclusions in nerve cells undergoing degeneration in Huntington disease (HD), the best-known example of a dominantly-inherited neurodegenerative disorder. For many years, the disease has been studied but conventional morphology has failed to detect the changes now reported in two recent papers (1, 2). Using transgenic mice expressing an NH_2-terminal mutant huntingtin fragment with 115 to 156 glutamine repeats, Davies and co-workers found that intraneuronal nuclear inclusions reactive to NH_2-terminal antiserum to huntingtin developed in the brain. These neuronal intranuclear inclusions contained the proteins huntingtin and ubiquitin and developed prior to the expression of a neurological phenotype (1). Subsequently, an NH_2-terminal fragment of mutant huntingtin was localised to neuronal intranuclear inclusions and dystrophic neurites in human HD cortex and striatum. Importantly, polyglutamine length influenced the extent of huntingtin accumulation in these structures. As in the transgenic mice, ubiquitin was found in the huntingtin aggregates suggesting that abnormal huntingtin is targeted for proteolysis but resistant to removal (2). As a result of these studies, therapeutic intervention may be envisioned that aims at the inhibition of aggregation of mutant huntingtin or increasing the efficiency of its ubiquitin-dependent degradation.

References

1. Davies SW, Turmaine M, Cozens BA, Difiglia M, Sharp AH, Ross CA, Scherzinger E, Wanker EE (1997) Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 90:537-548

2. DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP, Aronin N (1997) Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science 277:1990-1993

CAG expansion in SCA7. SCA7 is an autosomal dominant cerebellar ataxia (ADCA) associated with progressive macular dystrophy. Anticipation is a well established feature of SCA7. The RED (repeat-expansion detection) technique has implicated a CAG expansion as the underlying cause of the disorder (1). The disease gene in 3p12-p12 has now been isolated (2). YACs from the critical region were subcloned into bacteriophage vector Lambda DASH II. The phage library was screened with a $(CAG)_{10}$ oligonucleotide probe and positive clones were sequenced. One clone contained two putative exons and an uninterrupted CAG repeat within one of these exons. Primers flanking the repeat were constructed and a CAG expansion was found in SCA7 patients. Expansion of the repeat varies greatly in SCA7 and ranges from 38 to 130 CAG trinucleotides in patients as compared to 7-17 in controls. A small fragment of 107 bp located in the predicted open reading frame (ORF) of the gene was used to screen a cDNA library and several cDNAs were isolated. Sequence analysis of overlapping cDNAs established a 3,969 bp consensus sequence that contained a 2,727 bp open reading frame (ORF), flanked by a 513 bp 5' - and by a 729 bp 3' - untranslated region (UTR). The CAG repeat is transcribed and close to the start codon ATG,

probably within exon 1 of the gene. As in other SCAs with CAG expansions (SCA1,2,3,6), the gene is ubiquitously expressed. It was detected in great abundance in heart, placenta, skeletal muscle, and pancreas. Expression was less in brain, lung, liver, and kidney. The function of the gene is presently unknown. Based on findings in other CAG repeat expansion disorders one can speculate that the expanded polyglutamine stretch of the gene product causes aberrant protein-protein interactions in the nervous system.

1. Lindblad K, Savontaus M-L, Stevanin G, Holmberg M, Digre K, Zander C, Ehrsson H, David G, Benomar A, Nikoskelainen E, Trottier Y, Holmgrem G, Ptacek LJ, Anttinen A, Brice A, Schalling M: An expanded CAG repeat sequence in spinocerebellar ataxia type 7. Genome Res. 6:965-971 (1996)

2. David G, Abbas N, Stevanin G, Dürr, A, Yvert G, Cancel G, Weber C, Imbert G, Saudou F, Antoniou E, Drabkin H, Gemmill R, Giunti P, Benomar A, wood N, Ruberg M, Agid Y, Mandel JL, Brice A: Cloning of the SCA7 gene reveals a highly unstable CAG repeat expansion. Nature Genet 17: 65-70 (1997).

Alpha-synuclein gene mutations in families with Parkinson Disease. PD is inherited as an autosomal dominant trait in rare cases. A disease locus in autosomal dominant PD has recently been assigned to the long arm of chromosome 4 (4q21-q23) in a large family (reviewed in Newsletter 6). Using additional polymorphic markers, Polymeropoulos et al. (1) have narrowed down the critical interval in this family to a region of approximately 6cM flanked by markers D4S2372 and D4S2986 (1). The authors constructed a yeast artificial chromosome (YAC) contig of this region. Testing for potential candidate genes, they found the gene coding for alpha-synuclein, previously assigned to 4q21.3-q22 (2), to map to this contig. Alpha-synuclein is a presynaptic protein and thus a possible candidate for the disease gene. The gene was sequenced and a mutation was found in exon 4 in patients of this family but not in controls. The mutation detected is a G-A transition at nucleic acid position 209 and results in an Ala to Thr substitution at amino acid position 53. This mutation was not found in any of the 157 controls tested. The same mutation, however, was found in affected members from three addtional PD families. Although the substitution is not conserved in rodents, these findings support the notion that the mutation causes disease and is not a neutral polymorphism. There are three homologues of alpha-synuclein in the rat. One of these, SYN1, exhibits 95 % homology to the human alpha-synuclein protein. Interestingly, SYN1 is expressed in all those areas of the brain in which Lewy bodies are found in PD patients. These areas include olfactory bulb and tract, hippocampus, dentate gyrus, habenula, amygdala, piriform cortex, granular layer of the cerebellum, substantia nigra, nucleus caudatus, putamen, and dorsal raphe. This is also consistent with a functional role of alpha-synuclein in the etiology of PD. Furthermore, synuclein has been localized to Lewy bodies in post-mortem brain tissue (3). It is unlikely, however, that alpha-synuclein mutations play a role in the etiology of the majority of sporadic and familial cases. In fact, alpha synuclein mutations probably occur in a small proportion of familial cases only and are restricted to autosomal dominant, highly penetrant forms with an early disease onset.

1. Polymeropoulos MH, Lavendan C, Leroy E, Die SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL: Mutation in the α-synuclein gene identified in families with Parkinson's disease. Science 276: 2045-2047 (1997).

2. Chen X, de Silva RHA, Pettenati MJ, Rao PN, St. George-Hyslop P, Roses AD, Xia Y, Horsburgh K, Uéda K, Saitoh T: The human NACP/α-synuclein

gene: chromosome assignment to 4q21.3-q22 and *TaqI* RFLP analysis. Genomics 26: 425-427 (1997).

3. Spillantini MG, Schmidt ML, Lee VMY, Trojanowski JQ, Jakes R, Goedert M: Alpha-synuclein in lewy bodies. Nature 388: 839-840 (1997).

An ATP-binding protein gene is mutated in autosomal dominant, early onset dystonia.
Primary dystonias are a genetically and clinically heterogeneous group of movement disorders. The disease locus, DYT-1, implicated in early onset autosomal dominant torsion dystonia was assigned to the distal long arm of chromosme 9 in 1989. Now the hunt for DYT-1 has come to an end and the disease gene has been identified. Ozelius et al. (1) constructed an integrated physical (a cosmid contig) and transcript map of the critical region in 9q34 that is flanked by loci D9S2161 and D9S63. In this region four transcripts were identified by exon trapping and cDNAs (DQ1-DQ4) were isolated. Mutation analysis of the four cDNAs revealed numerous neutral nucleotide changes (polymorphisms) and a trinucleotide deletion (GAG) in DQ2 that was confined to patients. Studying a large sample of patients of various ethnic backgrounds the GAG deletion was the only mutation detected. Haplotype analysis revealed that this mutation had arisen more than once in torsion dystonia. DQ2 has an open reading frame of 998 bp which is predicted to code for a polypeptide of 332 amino acids. The gene is alternatively spliced. Northern analysis revealed two ubiquitously expressed transcripts of 1.8kb and 2.2kb and an additional low abundance transcript of 5 kb that was detected in fetal brain, lung, and kidney and in adult brain, heart, and pancreas. The gene product has homology with an ATP-binding protein and is evolutionarily highly conserved. Its role in the pathology of dystonia, however, is presently not understood.

1. Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, deLeon D, Brin MF, Raymond D, Corey DP, Fahn S, Risch NJ, Buckler AJ, Gusella JF, Breakefield XO: The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nature Genet 17: 40-48 (1997)

With the best wishes for a successful NEW YEAR!

Sincerely yours,

Ulrich Müller
Olaf Riess
Manuel B. Graeber

Announcements

Alzheimer Disease Research Group, Hamburg

The Alzheimer Disease Research Group at the University of Hamburg (Speaker: R.M. Nitsch) is an integrated and interdisciplinary consortium of basic and clinical research departments. The group is funded by the DFG, and it is located at the Center for Molecular Neurobiology (ZMNH), the University Hospital Eppendorf (UKE) and the Max Planck Society at DESY in Hamburg. The scientific program includes memory clinic-based diagnostic studies, treatment trials, as well as molecular, functional, and structural and pathophysiological analyses of genes and gene products involved in the pathogenesis of Alzheimer disease. In particular the presenilins, amyloid precursor protein, and its derivatives, apolipoprotetin E and tau are studied.

As part of the genetic research project, early onset and familial cases with Alzheimer disease are systematically collected in order to determine the clinical significance of single major genes in the etiology of the disease. Therefore, tests have been established for a DNA sequence-based mutation search in the presenilin genes *PS1* and *PS2* and *APP* (amyloid precursor protein gene). Additional genes will be included in the future. The tests are

available for diagnostic and differential diagnostic purposes, and will be added to the inventory „Molekulargenetische Diagnostik in Deutschland und den Nachbarländern“ in issue 3/1997 of the Journal *Medizinische Genetik*. For further information contact Dr. med. U. Finckh or Prof. Dr. med. A. Gal, Universitäts-Krankenhaus Eppendorf, Institut für Humangenetik, Butenfeld 42, 22529 Hamburg, Tel.: 040 4717 2120, FAX.: 040 4717 5138; email: finckh@plexus.uke.uni-hamburg.de.

Discounts for society members

Personal Subscription to Neurogenetics

At the last membership assembly in Bochum (see attached protocol) the “Vorstand” of the DGNG was asked to inquire about a special Neurogenetics subscription rate for DGNG members. In reply, Springer Publishers offer a personal subscription of Neurogenetics for DM 390,- which is approximately 34 % off the regular price. These subscriptions are available directly from the publisher (subscriptions@springer.de).

Personal Subscription to Current Biology, and current opinion in Neurobiology

The publishers of *Current Biology* offer DGNG members a 20 % discount in 1998. The pricing and ordering details are as follows:

Current Opinion in Neurobiology 1998, volume 8

Full personal rate: #125, DGNG member rate: #100, discount is 20 %

Current Biology, 1998 volume 8

Full personal rate: #120, DGNG member rate: #96, discount is: 20 %

All prices include postage and are for personal subscriptions only. Personal subscriptions must be paid for by personal cheques or credit card. Orders should be forwarded to: Current Biology Ltd., c/o Turpin Distribution Services Ltd, Blackhorse Road, Letchworth, Hertfordshire, SG6 1HN, UK, Tel: + 44 1462 672555, Fax: + 44 1462 480947, email: turpin@rsc.org. In order to take advantage of these discounts members MUST quote reference 'DGNG' when placing their order.

Discount for Cyrillic for Windows

Cherwell Scientific is offering a 20 % discount to DGNG members on Cyrillic 2.1, the Windows program for pedigree drawing and genetic data management. This new version of Cyrillic includes a tool for calculating the risk of familial cancers and other complex diseases. With this discount, Cyrillic is available for DM 899,-- (a saving of over DM 225,-- off the list price of DM 1.125,--). Please quote reference "MCYNGS18" to take advantage of this special offer, which lasts until 28 February 1998. Please contact Cherwell Scientific Publishing, c/o CHEM Research GmbH, Hamburger Allee 26-28, D-60486 Frankfurt. Tel: 069-970841-11, Fax: 069-970841-41, e-mail: cyrillic.d@cherwell.com, URL: http://www.cherwell.com