Newsletter
der
Deutschen Gesellschaft für Neurogenetik

July, 1999
DGNG News No. 10

Society News

To date, the DGNG has almost 170 members, of those 30 % are human geneticists, 26 % neurologists, 13 % neuropathologists and neuroanatomists, 7 % psychiatrists, 6 % neurobiologists, 5 % neuropediatricians, 3 % neurosurgeons, 2 % are industry-affiliated and the speciality of 8 % is unknown.

6th Workshop Neurogenetics in Germany, 5th Annual Meeting of the DGNG

The 6th workshop Neurogenetics in Germany and 5th Annual Meeting of the DGNG will be held in Bonn from September 16 to 18, 1999. The organizers of the meeting are O. Steinlein, P. Propping, and T. Klockgether.

Scientific program

Ion channel diseases
- Sodium channels
- Potassium channels
- Calcium channels
- Acetylcholine receptors

Neurodegenerative disorders
- Friedreich ataxia
- Dystonia
- Alzheimer disease
- Parkinson disease
- Amyotrophic lateral sclerosis
- Spinal muscular atrophy

Invited confirmed speakers:

O. Bandmann (Marburg), *D. Bertrand* (Geneva), *T. Siddique* (Chicago), *E. Hol* (Amsterdam), *T.J. Jentsch* (Hamburg), *F. Lehmann-Horn* (Ulm), *R.A. Ophoff* (Leiden), *M. Polymeropoulos* (Gaithersburg), *B. Wirth* (Bonn), *H. Puccio* (Strasburg).

Deadline for the submission of abstracts: July 1, 1999

Workshop language: English

Abstracts: Deadline for the submission of abstracts: July 1, 1999. Abstracts must be submitted in English. They may not exceed 2000 characters including title, authors, affiliation, and text. Abstracts should be submitted on disk (PC 3.5'') in MS-Word or ASCII format. They will be published in the 'Medizinische Genetik' 1999 and will be posted on this web-site. Free oral communications will be selected from submitted abstracts. Abstract forms and instructions may be downloaded.

Submission: Registered participants only. Abstract mailing address: Ortrud Steinlein, M.D., Rheinische Friedrich-Wilhelms-Universität, Institute of Human Genetics Wilhelmstr. 31, D-53111 Bonn

Registration fees:
DGNG members: DM 80.-
Non-members: DM 120.-
Students (with student I.D.): free

Workshop account: Bank transfers to the workshop account are preferred (bank account 1065773, BLZ 38050000, Sparkasse Bonn). Fees may be paid on site either with cash or Eurocheques. Please, note that we are not able to handle credit cards.

Oral presentations: Free oral communications will be selected from submitted abstracts. The time allotted to each presentation will be 15 min.

Poster session: There will be a poster session during the meeting; posters will be exhibited from Friday morning to the end of the workshop on Saturday. Poster size: 90 cm wide x 100 cm high.

The year 2000 meeting of the DGNG **(7th workshop Neurogenetics in Germany and 6th annual meeting)** will be held in Dresden from September 14 to September 16. It will be organized by Prof. Dr. Heinz Reichmann, Dr. Janet Schmiedel and Dr. Peter Seibel. For further information visit the homepage at http://www.fnz.med.tu-dresden.de/dgng/.

Research News

A QTL in 6p influences various components of dyslexia. Dyslexia is a specific language-based disorder. It is characterized by "difficulty learning to read and spell, despite adequate intelligence and educational opportunity and in the absence of sensory and neurological impairment". (Lyon, 1995; Smith et al., 1996). The reading process can be divided into several components such as word recognition (WR), orthographic coding (OC), phonological decoding (PD), and phoneme awareness (PA). Earlier linkage studies have suggested the existence of several quantitative trait loci (QTLs) in the genome that might influence different components of the reading process (Grigorenko et al., 1997). The previously mapped loci included one in 6p that was thought to be specific for PA. Now two research groups (Gayan et al., 1999; Fisher et al., 1999) demonstrate that the QTL in 6p influences several different components of dyslexia. Performing sib pair analysis with polymorphic markers from 6p they fine mapped the QTL to a region of 5 cM. While their analyses demonstrate that the QTL influences the major components of reading, they also show that it may differentially influence different measures of reading. Thus the QTL appears to account for 60% of the variance of OC and for about 20% of PD and phoneme deletion.

1. Lyon GR (1995) Toward a definition of dyslexia. Ann Dyslexia 45: 3-27
2. Smith SD, Gilger JW, Pennington BF (1996) Dyslexia and other specific learning disorders. In: Rimoin DL, Connor JM, Pyeriitz RE (eds) Principles and practice of medical genetics, Churchill Livingston, New York, pp 1767-1789
3. Grigorenko EL, Wood FB, Meyer MS, Hart LA, Speed WC, Shuster A, Pauls DL (1997) Susceptibility loci for distinct components of developmental dyslexia on chromosomes 6 and 15. Am. J Hum. Genet. 60: 27-39
4. Gayan J, Smith SD, Cherny SS, Cardon LR, Fulker DW, Brower AM, Olson RK, Pennington BF, DeFries JC (1999) Quantitative-trait locus for specific language and reading deficits on chromosome 6p. Am. J. Hum. Genet. 64: 157-164.
5. Fisher SE, Marlow AJ, Lamb J, Maestrini E, Williams DF, Richardson AJ, Weeks DE, Stein JF, Monaco AP (1999) A quantitative-trait locus on chromosome 6p influences different aspects of developmental dyslexia. Am. J Hum Genet 64: 146-156

The ever expanding family of autosomal dominant spino-cerebellar ataxias. Spinocerebellar ataxias (SCAs) or autosomal dominant cerebellar ataxias (ADCAs) are a clinically and genetically heterogeneous group of disorders. Based on neuropathological findings they are referred to as olivopontocerebellar atrophies (OPCAs). Clinically, three groups can be distinguished: ADCA I,

characterized by ophthalmoplegia in addition to pyramidal and extrapyramidal symptoms, ADCA II with associated retinopathy, and ADCA III with no associated signs. There is, however, considerable overlap between these three groups. The disease gene has been identified in 5 ADCAs, i.e. SCA1 on chromosome 6p23, SCA2 on 12q24, SCA3/MJD on 14q24.3-q31, SCA6 on 19p13, and SCA7 on 3p21.1-p12. In all cases a CAG trinucleotide repeat expansion causes malfunction of the gene. With the potential exception of SCA6 the mutation results in a "gain of gene function" in SCAs (see also DGNG News 9). Two additional loci have been assigned, i.e. SCA4 to 16q22.1 and SCA5 to 11p11-q11.

In contrast to the CAG repeat expansions in most autosomal dominant SCAs, Laura Ranum's group now describes a CTG expansion in the 3'-UTR of a novel transcript which has not yet been cloned in full length (Koob et al., 1999). However, cloning of this gene is another proof of feasibility of the RAPID cloning technique (Koob et al., 1998). Although SCA8, which has been mapped to chromosome 13q21, has several features unique to SCAs, the repeat size of the expanded alleles (107-127 CTGs) is more comparable to that known for adult-onset myotonic dystrophy (DM). Furthermore, similar to DM, expanded alleles are commonly transmitted through the mother and longer repeat expansions are observed exclusively during maternal meiosis. Therefore, the dominant inheritance pattern of SCA8 is complicated, showing reduced penetrance with an extreme maternal penetrance bias. Although a detailed clinical description has not been provided, SCA8 patients present with dysathria, nystagmus, limb and gait ataxia, limb spasticity and diminished perception of vibration. Consistent with the clinical findings, cerebellar atrophy has been demonstrated by MRI. Given the different molecular basis of SCA8 and CAG/polyglutamine disorders different neuropathological findings are expected. In particular, intranuclear inclusion bodies might be absent in SCA8.

SCA8, SCA4, and SCA5 appear to be rather rare forms of SCA and there are additional forms in which the gene defect has not been identified. The recent report of Zu et al. (1999) has further decreased the number of SCAs with an unknown chromosomal location. Performing a whole genome scan in a large Mexican-American family, the authors were able to assign the disease locus, referred to as SCA10 to a 15 cM interval on chromosome 22q13. The phenotype of this family resembles that of ADCAIII. Patients of this pedigree present with truncal and gait ataxia, dysarthria, and nystagmus. Twenty percent of the patients suffer from seizures (Grewal et al., 1998). This new disorder was referred to as SCA10 since another, to date unmapped locus, is implicated in yet another form of autosomal dominant SCA.

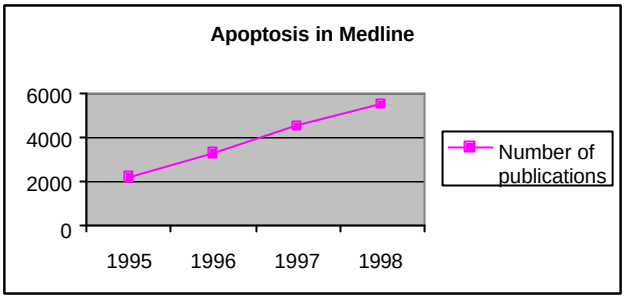
1. Koob MD, Moseley ML, Schut LJ, Benzow KA, Bird TD, Day JW, Ranum LPW (1999) An untranslated CTG expansion causes a novel form of spinocerebellar ataxia (SCA8). Nature Genet 21: 379-384

2. Koob MD, Benzow KA, Bird TD, Day JW, Moeseley ML, Ranum LPW (1998) Rapid cloning of expanded trinucleotide repeat sequences from genomic DNA. Nature Genet 18: 72-75

3. Zu L, Figueroa, KP, Grewal R, Pulst SM (1999) Mapping of a new autosomal dominant spinocerebellar ataxia to chromosome 22. Am J Hum Genet 64: 594-599

4. Grewal RP, Tayag E, Figueroa KP, Zu L, Durazo A, Nunez C, Pulst SM (1998) Clinical and genetic analysis of a distinct autosomal dominant spinocerebellar ataxia. Neurology 51: 1423-1426.

Apoptosis and Mitochondria. Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be genetically programmed. Research in this area is evolving at an enormous rate. Recently, the role of mitochondria has become a focus of interest within this field and is now developing at an even higher speed (Fig. 1). Nearly all physiological cell deaths in animals proceed by the process of apoptosis, during which the dying cells vanish without a trace, silently cleared without any accompanying inflammatory response (1). The apoptotic process can be divided into essentially three phases: an induction phase, the nature of which depends on the specific death-inducing signals, an effector phase, during which the cell becomes committed to die, and a degradation phase, during which cells acquire the morphological and biochemical features of end-stage apoptosis (2). Two alternative concepts have emerged regarding what actually kills a cell undergoing apoptosis. Whereas some authors believe that a cascade of caspases, which represent cysteine proteases that cleave certain proteins at aspartic acid residues, represents the key mechanism of execution, other authors have suggested that opening of the mitochondrial "megachannel" marks the point of no return of the cell-death process (2). It has been shown that mitochondrial cytochrome c release in apoptosis occurs upstream of DEVD-specific caspase activation (3) (DEVD stands for Asp-Glu-Val-Asp). Thus, mitochondria appear to play a key role in the regulation of apoptosis. Susin and colleagues have now identified a mitochondrial apoptosis-



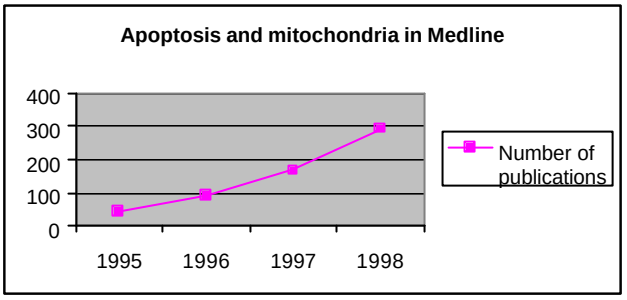


Fig. 1: Occurrence of "apoptosis" and "mitochondria, mitochondrion, mitochondrial", respectively, in the Medline database (June 1999)

inducing factor, AIF, which is sufficient to induce apoptosis of isolated nuclei. This factor is a flavoprotein of relative molecular mass 57 000 and shares homology with the bacterial oxidoreductases. It is normally confined to mitochondria but translocates to the nucleus when apoptosis is induced (4). Overexpression of Bcl-2, which controls the opening of mitochondrial permeability transition pores ("megachannel"), prevents the release of AIF from mitochondria. The authors concluded that AIF provides a new molecular link between mitochondrial membrane permeabilization and nuclear apoptosis and that the caspases and AIF are probably engaged in complementary cooperative or redundant apoptotic pathways.

1. Green DR (1998) Apoptotic pathways: The roads to ruin. Cell 94:695-698
2. Green D, Kroemer G (1998) The central executioners of apoptosis: caspases or mitochondria? Trends Cell Biol 8:267-271
3. Bossy-Wetzel E, Newmeyer DD, Green DR (1998) Mitochondrial cytochrome c release in apoptosis occurs upstream of DEVD-specific caspase activation and independently of mitochondrial transmembrane depolarization. EMBO Journal 17:37-49
4. Susin SA, Lorenzo HK, Zamzami N, Marzo I, Snow BE, Brothers GM, Mangion J, Jacotot E, Costantini P, Loeffler M, Larochette N, Goodlett DR, Aebersold R, Siderovski DP, Penninger JM, Kroemer G (1999) Molecular characterization of mitochondrial apoptosis-inducing factor. Nature 397:441-446

We are looking forward to seeing you in Bonn.

Sincerely yours,

Ulrich Müller
Olaf Riess
Manuel B. Graeber