Newsletter
der
Deutschen Gesellschaft für Neurogenetik

January, 2003
DGNG News No. 17

Society News

Neurogenetics in Ulm

The 9th workshop on Neurogenetics in Germany, the 8th Annual Meeting of the German Society of Neurogenetics took place in Ulm from December 5 to December 7. The conference was organized by Professors Bernhard Landwehrmeyer and Walther Vogel and was of highest scientific standard. The symposium focussed on basic principles of research relevant to neurogenetics (mechanisms of neurodegeneration and neuronal dysfunction, model systems, multifactorial traits). In addition, there were sessions on epilepsy, motor neuron disorders, and neurogenetics of tumors of the CNS and PNS.

The first session centred on epilepsies. R. Nabbout-Tarantino (Paris) reviewed generalized epilepsy with febrile seizures plus (GEFS+) and related syndromes. GEFS+ starts with febrile seizures up to age 6 that are followed (with some overlap) by afebrile seizures including absence, myoclonic, partial, and generalized seizures. Prevalence of GEFS+ is 2-7%. Mutations causing GEFS+ have been found in *SCN1A,B* (chromosomes 2q, 19q) coding for voltage gated sodium channel proteins and in *GABRG* (chromosome 5q) coding for the γ2 subunit of the GABA receptor. Furthermore, she reported on a locus on chromosome 6q (*FEB5*) that was discovered by her own group and is implicated in simple febrile seizures with good prognosis. Y. Weber (Ulm) presented her findings on assignment of a new locus in GEFS+ to chromosome 4 (p14) and H. Lerche (Ulm) summarized his findings on Na+ currents in human embryonic kidney cells transfected with wild-type and mutated ion channel genes.

Talks by U. Hartl, P. Nicotera, and M. Coleman dealt with mechanisms of neurodegeneration and neuronal dysfunction. U. Hartl (Martinsried) reported on possible mechanisms of neurotoxicity in CAG repeat expansion disorders such as Huntington disease (HD). The expansion codes for long poly Q (glutamine) chains within the encoded polypeptides, e.g. Huntingtin in HD. Intracellular poly Q aggregates that form in these disorders can trap transcription factors that contain small poly Q stretches. Hartl demonstrated this for the TATA binding protein (TBP) in two strains of yeast. One strain expressed exon 1 of the human Huntingtin gene containing normal range $(CAG)_{20}$, the other pathologically expanded $(CAG)_{100}$. A growth defect occurred in the 100 Q Huntingtin strain if the yeast TBP that does not contain a poly Q stretch was replaced by human TBP containing a poly Q chain. The 20 Q Huntingtin strain, however, was not affected. The growth defect could be rescued by heat shock protein (Hsp) 40 and 70 chaperones by inhibition of TBP trapping in the aggregates. This points to possible new therapies. Hartl´s group already succeeded in suppressing

huntingtin protein aggregation by inducing overexpression of Hsp40/70 in a mammalian cell system. P. Nicotera (Leicester) reviewed mechanisms of cell death, specifically of apoptosis (organized cell death, dependent on caspase activity) and necrosis (caspase independent). He stressed the requirement of ATP for apoptosis to occur. Brain ischaemia results in necrosis at the location of injury due to rapidly falling ATP levels. ATP depletion precludes caspase activation and switches execution of cell death towards necrosis. In the periphery (penumbra) of the injury, however, both necrosis and apoptosis occur due to presence of ATP. He also reviewed experimental use of caspase inhibitors as potential medications in animal stroke models. M. Coleman (Köln) reported on survival of axons in injury and disease. He is studying the C57Bl/Wld(S) mouse carrying a dominant mutation that dramatically delays Wallerian degeneration of neurons after injury. The mutation is caused by fusion of the two genes coding for ubiquitin fusion degradation protein 2 (Ube4b) and for nicotinamide mononucleotide adenyl-transferase (Nmnat). The resulting chimeric protein Ube4b/Nmnat causes delay in axon degeneration. He is now studying how the chimeric protein delays axon degeneration and pointed out that neither wild-type Nmnat nor Ube4b alone is sufficient to do so.

K.-F. Fischbach, M. Driscoll, and R. Dahm gave introductions to the use of animal models in the neurosciences. K.-F. Fischbach (Freiburg) is studying drosophila as a model system. His presentation covered membrane recognition processes in visual systems and muscle development. He demonstrated that an overlapping set of cell adhesion molecules such as Kirre and IrreC-rst (both members the immunoglobulin superfamily) are involved in both processes. M. Driscoll (Rutgers University, New Jersey) talked about cell death in Cenorhabditis elegans. She showed that mec4 (d) results in the specific death of 6 neurons. Mec4 encodes a Na^{+} ion channel subunit and the mutation gives rise to a blocked open channel. The effect can be suppressed by calreticulin, a Ca^{++} binding ER protein. Neuronal cell death can also be induced by excitotoxic glutamate. This effect can be antagonized by dantrolene, which blocks ER Ca^{++} release. R. Dahm (Tübingen) explained the usefulness of the zebra fish in the neurosciences giving aspects of eye development and the role of FGF8 in brain development as examples.

Multifactorial traits were discussed by K. Goddard, J.E. Swartz, and G. Assum. D. Goddard (Case Western, Cleveland, Ohio) presented a model including covariates for the analysis of complex traits. She studies the genetics of late-onset Alzheimer disease (AD) using ApoE status, age at onset, and current age as covariates to account for sample heterogeneity. Her analysis confirmed known loci on chromosomes 6, 10, 19 (ApoE), and 21 (APP) but did not find evidence of a locus on chromosome 12 (one or more loci on this chromosome have been reported by several groups). In addition, she detected a locus on chromosome 20. Previously, an association of a polymorphism in cystatin C (located on chromosome 20) with AD had been reported in one study but was not confirmed in three additional studies. Further investigations are required to find out whether there is an association of cystatin C and a subset of AD patients as Goddard´s studies suggest. J.E. Swartz (GlaxoSmithKline, Cambridge) discussed the use of single nucleotide polymorphisms (SNPs) in pharmacogenetics. She reported that approximately 200,000 SNPs which are spaced at 15 kb intervals on average might suffice to tailor individual drug therapy. In

addition, she talked about individual gene association studies to find evidence of efficacy or adverse effects of given drugs in patients. Currently, the latter approach appears to be most promising in individual drug treatment. Finally, G. Assum (Ulm) gave an overview of the pattern of linkage disequilibrium within the human genome.

V. Ramesh, D.H. Evans, and T. Wiederhold represented aspects of the genetics of tumor formation in CNS and PNS. V. Ramesh (Boston) discussed tuberous sclerosis and the pathophysiological role of hamartin (TSC1, chromosome 9q34) and tuberin (TSC2, chromosome 16p13) in the disease. She showed that TSC1 and TSC2 do not strictly act as tumor suppressor genes since loss of heterozygosity at the respective loci is not found in all lesions, particularly not in the brain. She demonstrated association of hamartin and tuberin and informed about the identification of hamartin/tuberin associated poly-peptides. She speculated that this protein complex plays an important role in neuronal development. D.H. Evans (Manchester) reported on clinical and molecular features of neurofibromatosis 2 (NF2) in his vast patient collection. He pointed out that 28% of patients with de novo mutations in the NF2 gene are mosaics for the mutation, i.e. the mutation occurred during postzygotic development. The interaction of merlin, the product of the NF2 gene, with other proteins such as actin, ezrin, moesin, and radixin, was discussed by T. Wiederhold (Boston).

Motoneuron disorders were another major topic of the meeting. C. Shaw (London) discussed the clinical picture of amyotrophic lateral sclerosis (ALS) and reviewed genetic heterogeneity of the disorder. To date, four loci have been mapped in autosomal dominant forms. A gene on chromosome 21 codes for Cu/Zn superoxide dismutase 1 (SOD1), and mutations in this gene are observed in about 20% of autosomal dominant cases. The exact mechanism of disease development in mutSOD1 patients is not yet known. Significantly, however, ubiquitin inclusion bodies are found in neurons from mutSOD1 patients and ubiquitin/SOD1 aggregates are found in mutSOD1 transgenic mice. A locus implicated in juvenile-onset ALS was assigned to chromosome 9q, other loci were mapped to chromosome 18q and 16q. Some of the patients of the two pedigrees allowing for locus assignment to chromosome 16 had frontotemporal dementia in addition to ALS. The gene mutated in one autosomal recessive variant of ALS has been assigned to 2q33 and been identified; it encodes ALSIN. Disease onset of this form is < 20 years and the phenotype can include spastic paraplegia and tetraplegia. Another autosomal recessive form has been assigned to chromosome 15. Carmeliet (Leuven) presented animal models suggesting that reduced activity (approx. 75% of normal) of vascular endothelial growth factor (VEGF) can produce a motoneuron disorder phenotype in mice. He provided data showing a direct effect of VEGF on neuronal cells. H.X. Deng (Chicago) reviewed the identification of ALSIN and reported that ALSIN is not part of the aggregates found in mutSOD1 transgenic mice.

Additional presentations included a report by L. Schöls (Bochum) convincingly demonstrating that patients with hereditary spastic paraplegia caused by mutations in SPG4 can be clinically distinguished from non - SPG4 cases by abnormal nerve conduction and/or motor evoked potentials that are found in the latter only. A report by A. Zimprich (Munich) showed that sequencing of the known genes in a region

of 2p implicated in Parkinson disease has not revealed a mutation in patients yet.

10th Workshop Neurogenetics in Germany, 9th Annual meeting of the DGNG

The 9th Annual Meeting of the DGNG (10th Workshop Neurogenetics in Germany) will be held in Tübingen from September 25 – 27, 2003. The conference will be organized by Professors O. Rieß, T. Gasser, and J.B. Schulz

Research News

HSP27 facilitates survival of injured adult neurons. Heat shock proteins are important in protecting cells against stress-induced damage. In the nervous system, upregulation and phosphorylation of heat-shock 27-KD protein 1 (HSP27) plays a pivotal role in the survival of injured motor and sensory neurons from adult but not from newborn rats (Benn et al., 2002). While injury of neurons from newborn rats causes cell death by apoptosis, neurons from adult animals frequently survive injury. Benn et al. demonstrated that a different response of HSP27 expression explains the different fate of injured neurons in adults vs newborns. In a first set of experiments the authors showed that HSP27 levels increase rapidly in both motor and sensory neurons from adult rats after axonal damage. In contrast, no such increase is found in most neurons from newborns. (In newborns, an increase of HSP27 levels was detected in a few injured motor neurons only). A second set of experiments established the causative role of HSP27 in neuronal survival. Overexpression of human HSP27 in newborn rats before nerve injury resulted in the survival of a large number of motor neurons. Conversely, inhibition of expression of HSP27 in adult neuronal cultures and in adult rats after nerve injury greatly reduced neuronal survival and resulted in apoptosis of sensory neurons. HSP27 can only exert its protective function if phosphorylated. Transfer of a non-phosphorylatable mutant does not prevent neuronal death. HSP27 appears to interfere with the activity of caspase 3 which mediates one of the final steps of the apoptosis cascade. The authors speculate that it might become possible to treat neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) by drug-induced upregulation of HSP27. This notion is not supported by the recent finding of upregulation of HSP27 in transgenic models of ALS, i.e. transgenic mice that overexpress human mutant SOD1 (Vleminckx et al., 2002).

Benn SC, Perrelet D, Kato AC, Scholz J, Decosterd I, Mannion RJ, Bakowska JC, Woolf CJ: Hsp27 upregulation and phosphorylation is required for injured sensory and motor neuron survival. *Neuron* 36: 45-56 (2002).

Vleminckx V, Van Damme P, Goffin K, Delye H, Van Den Bosch L, Robberecht W: Upregulation of Hsp27 in a transgenic model of ALS. *J Neuropathol Exp Neurol* 61: 968-74 (2002)

Neurotrypsin mutation in autosomal recessive mental retardation (MR). 2% to 3 % of the population are mentally impaired with an intelligence quotient of <70. Of those about 0.3% are severely incapacitated with IQs <50. Known underlying causes of MR include teratogens, chromosomal anomalies, disorders of brain development, and metabolic diseases. In most cases, however, mental dysfunction occurs in persons with apparently normal brain development and in the absence of other clinical features (non-syndromic MR). To date mutations have been detected in about 10 different genes in X-chromosomal

recessive non-syndromic MR. The identification of autosomal genes has proved more difficult mainly due to the absence of large pedigrees. Now, Molinari et al. (2002) describe the discovery of mutations in an autosomal gene in a family with autosomal recessive MR. The family was consanguineous and came from Eastern Algeria. Of 8 children 4 (three girls and one boy) were severely mentally retarded with IQs <50. A whole genome scan identified a region of shared homozygosity on chromosome 4 (4q24-q25). Applying haplotype analysis they further delineated the critical interval to about 14 Mb. This interval includes about 29 genes. One of these genes, neurotrypsin (PRSS12) was a good candidate due to its function as a brain serine protease, possibly involved in synapse development and neural plasticity (Wolfer et al., 2001). The authors established the intron – exon structure of the gene in silico (13 exons and 12 introns) and sequenced each exon, including intron-exon boundaries in affected and unaffected members of the family. They identified a 4 bp deletion in exon 7 of the gene which was absent in unaffected controls. This mutation results in truncation of the polypeptide and thus renders neurotrypsin defunct. The deletion was homozygous in the affected siblings and heterozygous in the parents. Studying additional MR cases from Eastern Algeria, Molinari et al. identified the same deletion in another severely mentally retarded person that was not obviously related to the original family. This finding argues for either remote relation or for a founder effect. Investigation of neurotrypsin gene expression by in situ hybridization in fetal human brain showed that expression started at 44 days of embryonic life. At 15 weeks of development PRSS12 was highly expressed in the cortical plate, the hippocampus, and the tegmental nuclei of the brain stem. Neurotrypsin was also detected in the intermediate zone of the cerbral mantle which contains late migrating neurons from which some intermediate neurons derive. The authors stress the important role of interneurons in the establishment of neuronal connections and cognitive function. Electron microscopy demonstrated that neurotrypsin is present in the presynaptic membrane. The data suggest that the physiological role of neurotrypsin might be the coordination and regulation of synaptic development and function.

Molinari F, Rio M, Meskenaite V, Encha-Razavi F, Augé J, Bacq D, Briault S, Vekemans M, Munnich A, Attié-Bitach T, Sonderegger P, Colleaux L: Truncating neurotrypsin mutation in autosomal recessive nonsyndromic mental retardation. *Science* 298: 1779-1781 (2002)

Wolfer DP, Lang R, Cinelli P, Madani R, Sonderegger P: Multiple roles of neurotrypsin in tissue morphogenesis and nervous system development suggested by the mRNA expression pattern. *Mol Cell Neurosci* 18: 407-33 (2001)

With the best wishes for a successful New Year

Sincerely yours,

Ulrich Müller

Olaf Riess

Bernhard Landwehrmeyer

Protokoll der Mitgliederversammlung 2002

anlässlich der 8. Jahrestageung der

Deutschen Gesellschaft für Neurogenetik

Ort: Ulm

Datum: 05.12.2002

Beginn: 17:00 Uhr

Ende: 17:30 Uhr

Anzahl der Teilnehmer: 9-14

Der stellvertretende Vorsitzende, Prof. Riess, fehlt entschuldigt

TOP 1 Das Protokoll der letzten Sitzung wird verabschiedet (9 Ja, 0 Nein, 0 Enthaltungen)

TOP 2 Professor Müller dankt den Professoren Landwehrmeyer, W. Vogel und deren Mitarbeitern für die Ausrichtung der Tagung.

Die nächste Tagung wird in Tübingen (verantwortlich Prof. Riess) stattfinden. Die Vorbereitungen für dieses Treffen laufen bereits.

TOP 3 Professor Müller appelliert an die Mitglieder der Gesellschaft, Beiträge für den *Newsletter* zu verfassen

TOP 4 Als Kassenprüfer haben sich diesmal Prof. Landwehrmeyer (Ulm) und Dr. Holzmann (Rostock) zur Verfügung gestellt.

Frau Dr.Köhler informiert über Einnahmen/Ausgaben im Zeitraum 15.10.2002-30.09.2002. Die finanzielle Situation der Gesellschaft ist weiterhin gut und stabil. Die Differenz von 5 Cent zwischen errechnetem und tatsächlichem Guthaben ist auf die Währungsumstellung von DM auf € zurückzuführen.

Die Kassenprüfer erklären nach Kontrolle aller relevanten Unterlagen, dass der Kassenbericht richtig ist.

Prof. Müller stellt den Antrag auf Entlastung der Kassiererin. Dem wird mit 9 Ja Stimmen und 1 Enthaltung zugestimmt.

TOP 5 Als Jury für die diesjährigen Posterpreise werden Dr. Lerche (Ulm) und Dr. Joos (Gießen) vorgeschlagen und eingesetzt. Es sollen wieder die drei besten Poster gleichrangig prämiert werden. Die Preisträger sollen am Samstag bekannt gegeben werden und ihre Urkunden erhalten. Die Preise werden wieder die Erstattung der Kosten für die Anreise zur nächsten Tagung (Tübingen), für die Tagungsgebühr sowie für die Unterkunft (bis 50€/Nacht) beinhalten.

TOP 6 Prof. Müller gibt bekannt, dass anlässlich der nächsten Tagung der Präsident und der/die Kassierer/in neu gewählt werden sollen.

Gemäß dem interdisziplinären Charakter der Gesellschaft sollte angestrebt werden, den Vorstand entsprechend zu besetzen.

Prof. Müller erläutert kurz die Aufgaben des Präsidenten. Dazu gehören die Herausgabe des Newsletters, bei der Prof. Müller auch in Zukunft bereit ist, als Editor zu fungieren. Die Herausgabe

könnte dann weiterhin über sein Sekretariat erfolgen. Eine weitere wichtige Aufgabe ist die Öffentlichkeitsarbeit.

Zur Frage nach der professionellen Zusammensetzung der Gesellschaft wird erklärt, dass u.a. Humangenetiker, Neuropathologen, Neurologen, Psychiater und Biologen als Mitglieder registriert sind.

Prof. Müller erläuert, dass sich Neuzugänge und Ausscheidungen, die bisher nur aus Altersgründen erfolgt sind, aus der Gesellschaft in etwa die Waage halten.

Prof. Landwehrmeyer schlägt vor, die Vorträge dieser Tagung nach dem üblichen Review-Verfahren in *Neurogenetics* zu veröffentlichen. Dem stimmt Prof. Müller zu.

Der Ort für die übernächste Tagung soll im Verlauf dieses Meetings eruiert und am Samstag bekannt gegeben werden. Die Tagung wird 2004 in Rostock stattfinden.

Dr. A. Köhler
(Vertreterin des Schriftführers)

Prof. Dr. U. Müller
(Präsident)