

Newsletter der Deutschen Gesellschaft für Neurogenetik

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DGNG News No. 15

Society News

Neurogenetics in Magdeburg

The 8th workshop on Neurogenetics in Germany, the 7th annual meeting of the DGNG took place in Magdeburg from October 25 to October 27, 2001. The highly stimulating conference was organized by Profs. P. Wieacker, E. Gundelfinger, G. Reiser, C-W. Wallesch, and by Drs. D. Montag, S. Vielhaber, S. Jakubiczka, and M. Stumm.

The meeting was opened with a plenary lecture on "Use of stem cells for brain repair" by A. Björklund (Lund, Sweden). Björklund summarized the first successes in the treatment of Parkinson disease (PD) by use of fetal dopamine-secreting (DA) neuronal cells. He showed a video of a female patient with severe Parkinson disease including high-grade bradykinesia before and two years after transplantation of embryonic DA cells. While she was severely handicapped before the operation she is now able to lead an almost normal life. Despite such therapeutic successes several reasons preclude the routine use of embryonic DA cell transplants in the treatment of PD. These include low posttransplantation cell survival (5-10%), shortage of donor tissue (6-8 embryos are required for each transplant), difficulties in standardizing the treatment due to variable quality and viability of cells, and ethical issues. Therefore Björklund favours the use of neuronal stem cells as an alternative. He reported on initial successes in the isolation of neuronal stem cells from

brains of human embryos using EGF and bFGF. Injection of stem cells into the dentate gyrus and SVZa (subventricular zone A) region of immunosuppressed mice and rats resulted in integration of cells in the granular layer of the dentate and in migration of cells from the SVZa region into the olfactory bulb. Some transplanted cells synthesized tyrosine hydroxylase. In general, the cells tended to differentiate into those cell types that are characteristic of the region into which they were grafted. Björklund reported that the percentage of transplanted dopamine secreting cells can be increased by using in vitro predifferentiated cells. Predifferentiation of neuronal stem cells into dopamine-secreting cells can be achieved by culturing the cells in the presence of the differentiation factor sonic hedgehog (SHH), fibroblast growth factor (FGF) 8 and ascorbic acid. However, despite these promising first successes with neuronal stem cells many problems need to be solved before human studies can be initiated. Thus the survival rate of transplanted dopamine secreting cells is poor, their functional capacity is unclear, and we also do not know whether additional cell types such as glia cells are required for their survival.

The Friday sessions focussed on ion channel diseases and transgenic mouse models.

O. Steinlein (Bonn, Germany) gave an overview of her work on monogenic epilepsies. C.M. Becker (Erlangen, Germany) reported on genotype - phenotype correlations in patients with

hypereklesia and mutations in the gene GLRA1 coding for the α 1-subunit of the glycine receptor. The last talk on channelopathies focussed on myotonias and was presented by K. Jurkat-Rott (Ulm, Germany).

Mouse models of neurological and neuromuscular diseases were presented by K. Nave (Göttingen, Germany), U. Suter (Zürich, Switzerland), D. Merry (Philadelphia, USA), and M. Sendtner (Würzburg, Germany).

K. Nave described the analysis of animal models of Pelizaeus-Merzbacher disease. This disorder is caused by mutations in the X-chromosomal gene coding for proteolipid protein (PLP). A naturally occurring model of the human disease is the jimpy mouse. These mice suffer from tremor, paraplegia, and seizures. The major neuropathological finding is death of oligodendrocytes. The molecular pathological mechanism of the disease is impeded transport of PLP to the cell surface. In contrast, PLP knock-out mice are phenotypically indistinguishable from wild-type mice at 3 months of age. They do, however, develop motor abnormalities, clumsiness, ataxia, and paraplegia between 12 and 16 months of life. Unlike the jimpy mouse, they do not develop tremor. Loss of PLP function in the k.o. mice results in unstable myelin and axonal degeneration. Nave then pointed out that proteolipid protein genes encompass a gene family including M6A, M6B, in addition to PLP/DM20. He demonstrated that M6B deficient mice have myelin defects with cortical neurodegeneration, and neuronal apoptosis. The human homologue of this X-chromosomal gene is located in Xp22.1. So far, however, mutations have not been detected in humans.

While Nave focussed on central nervous system defects in myelin disorders, U.

Suter stressed axon-glia interactions in the peripheral nervous system and focussed on PMP22 mutations.

Diane Merry presented transgenic mouse models of spinal and bulbar muscular atrophy (SBMA). In a first series of experiments, she constructed transgenic mice using a full-length construct of the androgen receptor including a CAG expansion comparable in size to those found in patients. These mice did not have any detectable abnormal phenotype. When using a truncated transgene with a large CAG expansion of 112 copies, and a very strong neuronal promoter (PrP promoter or NFL promoter), however, the mice developed hyperactivity, abnormal hindlimb gait, foot claspings, and tremor among other signs. The NFL promoter which is more specific for the affected regions in SBMA such as motor neurons, resulted in a more characteristic phenotype. The trinucleotide expansion in the androgen receptor gene does not appear to interfere with its function. Interestingly, symptoms can be ameliorated by androgen antagonists. Thus she suggested that the common treatment of SBMA patients with androgens (thought to enhance muscle strength) might in fact worsen the symptoms. She discussed the use of androgen antagonists instead.

M. Sendtner's talk on mouse models of spinal muscular atrophy (SMA) concluded the session on model organisms. He reported on the function of the gene product of SMN as part of a spliceosomal complex. Not surprisingly, absence of SMN is not compatible with cellular survival and homozygous inactivation of the SMN gene in mice (unlike humans, mice have only one copy per chromosome) results in preimplantation death.

Additional talks on SMA included the presentation by B. Wirth (Bonn, Germany) on "in vivo modulation of SMN2 alternative splicing as a basis for SMA therapy".

X-linked mental retardation was another major topic of the workshop. H.-H. Ropers (Berlin, Germany) emphasized that 1/600 males is mentally retarded. The only gene that is frequently mutated in X-linked mental retardation is FRAXA. Mutations (usually CGG expansions) cause the "fragile X-syndrome". The latter occurs in 1/6000 males. Thus only 10% of monogenic forms of X-linked mental retardation can be molecularly diagnosed. He then reported the first successes of the European X-linked mental retardation network in the identification of several genes in this common disorder.

F. Laccone (Göttingen, Germany) talked about his experience in the molecular diagnosis of Rett syndrome. Rett syndrome has an incidence of 1/10,000 to 1/22,000 and is the second most common genetic cause of mental retardation in females after Down syndrome. He presented data showing that mutations in the NLS (nuclear localisation signal) region of the disease gene MECP2 (methyl-CpG-binding protein 2) result in a more severe phenotype than mutations in other regions of the gene.

A. Rauch (Erlangen, Germany) spoke about subtelomeric rearrangements in patients with mental retardation. She reported that subtelomeric rearrangements are found in 7.5% of patients with moderate/severe MR. Of these, 50% affect three chromosomes, i.e. chr 1 [del1(p36.3)], chr 2 [del2 (q37.3)] and chr 4 [del 4 (p16.3)]. Each of these rearrangements results in a characteristic phenotype. She also stressed that subtelomeric deletions can be neutral polymorphisms, as found in a family with a 2q deletion. This necessitates testing of affecteds' parents.

The last session addressed clinical and molecular diagnostic aspects of Charcot-Marie-Tooth disease (V. Timmerman,

Antwerpen, Belgium), hereditary spastic paraplegia (A. Brice, Paris, France), and facioscapulohumeral muscular dystrophy (S.M. van der Maarel, Leiden, The Netherlands).

Timmermann reported that 15 genes have been cloned which can be mutated in HMSN, types I - III. He estimates that mutations at as many as 50-100 loci cause peripheral neuropathies. He also stressed significant clinical overlaps between axonal and demyelinating types of HMSN.

Brice gave an overview of his experience with the clinical and molecular analysis of patients with hereditary spastic paraplegia from 344 families. In his patient sample 64% of cases were transmitted as autosomal dominants and 36% as autosomal recessives. The patients included both pure and complex forms. The latter describe cases with spastic paraplegia in association with other neurological findings such as mental retardation, neuropathy, epilepsy, ataxia, amyotrophy, ocular anomalies, etc. In autosomal dominant patients pure forms were more frequent than complex forms (77% vs. 23%). On the other hand, complex forms predominated in autosomal recessive forms (63% complex; 37% pure). Furthermore, the age of disease onset within families varies much more widely in autosomal dominant than in recessive forms. The age of onset is earlier in autosomal recessive (<20 years) than in autosomal dominant cases.

The talk by S.M. Maarel focussed on diagnostic difficulties in the molecular analysis of facioscapulohumeral muscular dystrophy (FSHD) and how these problems can be overcome.

In summary, the meeting addressed many important aspects of neurogenetics relevant to both practicing neurologists and basic scientists. Most talks were followed by in depth discussions.

Recipients of this year's poster awards were K. Langnäse (Institut für Medizinische Neurobiologie, Magdeburg), M. Montag-Sallaz, and C. Seidenbecher (both Leibniz-Institut für Neurobiologie, Magdeburg).

9th Workshop Neurogenetics in Germany, 8th Annual Meeting of the DGNG

The 8th Annual Meeting of the society (9th Workshop on Neurogenetics) will be held in Ulm from September 5 to September 7, 2002. This conference will be organized by Profs. G.B. Landwehrmeyer, A.C. Ludolph, F. Lehmann-Horn, W. Vogel, and Drs. H.Lerche and C.O. Hanemann. Deadline for abstracts is May 31, 2002. <http://www.uni-ulm.de/klinik/neurologie/symposia/neurogen.html>

Research News

Gene defect in myoclonus dystonia (Dystonia 11; alcohol-responsive dystonia; OMIM #159900) identified.

Dystonia 11 (M-D) is characterized by myoclonus and dystonia. Dystonia mainly involves the neck and the upper extremities, sometimes the trunk and bulbar muscles, and least commonly the legs. Myoclonus manifests itself as involuntary lightning jerks (sudden, brief muscular contractions) mainly in the arms and in the axial musculature. The muscle jerks are aggravated by excitement, are drastically ameliorated by intake of alcohol, and disappear during sleep. M-D usually starts within the first and second decade of life, equally affects males and females, and has a relatively benign course compatible with an active life and normal life span. There are no seizures, dementia, or ataxia.

M-D is inherited as an autosomal dominant trait with reduced penetrance and variable expressivity. Zimprich et al. (2001) delineated the disease locus, DYT11, on the long arm of chromosome 7 within a 3.2 Mb interval in 7q21. Searching GenBank, the authors identified 15 genes within this critical interval. They sequenced 10 of these genes in patients and found loss-of-function mutations in the gene coding for ϵ -sarcoglycan (SGCE) in patients from 6 families. SGCE is expressed in many tissues during fetal and adult life, including smooth muscle, Schwann cells of peripheral nerves, and the brain. Within the

brain SGCE appears to be expressed in most if not in all regions.

The finding of mutations in a gene coding for a member of the sarcoglycan family in M-D was quite surprising. Genes coding for the other sarcoglycans, i.e. α , β , γ , and δ , are mainly expressed in muscle, are required for its structural and functional integrity, and – when mutated - cause autosomal recessive limb-girdle muscular dystrophies. The role of ϵ -sarcoglycan in the pathology of M-D is presently not understood. It may be, however, that mutations in SGCE cause subtle changes in the architecture of certain brain cells that result in their abnormal function (Zimprich et al., 2001).

The clinical diagnosis of M-D is not trivial due to its highly variable expressivity. In many cases, only the dramatic response of muscle jerks to alcohol leads to the correct diagnosis. However, the identification of SGCE as the „disease gene“ in most forms of MD now facilitates straightforward diagnosis of the disorder by mutation analysis.

Zimprich A, Grabowski M, Asmus F, Naumann M, Berg D, Bertram M, Scheidtmann K, Kern P, Winkelmann J, Müller-Myhsok B, Riedel L, Bauer M, Müller T, Castro M, Meitinger T, Strom TM, Gasser T. (2001). Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. *Nat. Genet.* **29**, 66-69.

APTX encoding aprataxin is mutated in ataxia-ocular apraxia 1 (AOA1; MIM 208920). [Contributed by Peter Bauer, Institute of Human Genetics, University of Tübingen] Ataxia-ocular apraxia 1 (AOA1) is the most common cause of autosomal recessive ataxia in Japan and is also quite prevalent in Portugal. The clinical features of this adolescence onset disorder include progressive ataxia, absence of tendon reflexes, oculomotor

apraxia, cerebellar atrophy, and hypoalbuminemia. Date et al. (2001) and Moreira et al. (2001) applied a positional cloning approach to the identification of the disease gene in 9p13. By the analysis of candidate genes within a common haplotype they demonstrated that mutations in the gene *APTX* cause AOA1.

APTX codes for aprataxin and is ubiquitously expressed in human tissues. Aprataxin is a novel member of the HIT/Zn finger protein family and is composed of three domains. One shares some homology with the amino terminal domain of polynucleotide kinase 3'-phosphatase (PNKP), one with highly conserved histidine-triad (HIT) polypeptides, and another one with DNA binding zinc finger domains. PNKP is involved in DNA single-strand break repair. Therefore aprataxin via its PNKP homologue domain might be a protein with a function in DNA repair that acts specifically in cerebellar neurons.

The most common mutations found in Japanese and Portuguese patients were c.689insT (V230fs) and c.617C>T (P206L) in exon 5. These mutations are located within highly conserved functional domains of the HIT-motif.

This work establishes “early-onset ataxia with ocular motor apraxia and hypoalbuminemia” as a distinct syndrome. AOA1 has several features overlapping with Friedreich ataxia and is therefore an important differential diagnosis of this disease. Molecular testing now facilitates the unequivocal diagnosis of these two distinct disorders.

Date H, Onodera O, Tanaka H, Iwabuchi K, Uekawa K, Igarashi S, Koike R, Hiroi T, Yuasa T, Awaya Y, Sakai T, Takahashi T, Nagatomo H, Sekijima Y, Kawachi I, Takiyama Y, Nishizawa M, Fukuhara N, Saito K, Sugano S, Tsuji S (2001) Early-onset ataxia with ocular motor apraxia and hypoalbuminemia is caused by mutations in a new HIT superfamily gene. *Nat Genet* **29**, 184-188

Moreira MC, Barbot C, Tachi N, Kozuka N, Uchida E, Gibson T, Mendonca P, Costa M, Barros J,

Yanagisawa T, Watanabe M, Ikeda Y, Aoki M, Nagata T, Coutinho P, Sequeiros J, Koenig M (2001) The gene mutated in ataxia-acular apraxia 1 encodes the new HIT/Zn-finger protein aprataxin. Nat Genet 29, 189-193

With the best wishes for a successful New Year.

Sincerely yours,

Ulrich Müller
Olaf Riess
G. B. Landwehrmeyer

**Protokoll der
Mitgliederversammlung 2001
anlässlich der 7. Jahrestagung der
Deutschen
Gesellschaft für Neurogenetik**

Ort: Magdeburg
Datum: Freitag, 26. Oktober 2001
Beginn: 12:30 Uhr
Ende: 13:15 Uhr

Anzahl Teilnehmer: 14 (13)

Der Schriftführer, Herr Professor Landwehrmeyer, fehlt entschuldigt. Frau Dr. Köhler wird gebeten, das Protokoll der Sitzung zu schreiben.

TOP 1

Herr Professor Müller appelliert an alle Mitglieder sich zu bemühen, neue Mitglieder, auch unter den jüngeren Kolleginnen und Kollegen zu werben. Aktive, engagierte Mitglieder sind Voraussetzung für die Durchführung der jährlichen, bisher hochkarätigen Treffen.

TOP 2

Der 9. Workshop der DGNG wird 2002 in Ulm stattfinden. Herr Professor Landwehrmeyer hat als mögliche Termine 05.-07.09.2002 oder 12.-14.09.2002 vorgeschlagen. Zu diesen Terminen findet zeitgleich keine andere für die Mitglieder relevante größere Tagung statt. Die anwesenden Mitglieder sind einstimmig für den ersten Termin: 05.-07.09.2002. Herr Professor Müller liest aus einer Nachricht von Herrn Professor Landwehrmeyer mögliche Themenschwerpunkte des 9. Workshops vor. Die Wahl der Themen soll im Vorstand besprochen werden, damit eine Redundanz zu früheren Treffen vermieden wird.

Herr Professor Riess weist in diesem Zusammenhang auf ein Treffen der Forschergruppe der DFG „Trinukleotidkrankungen“ hin, die im Mai 2002 in Bonn stattfinden soll. Namhafte Wissenschaftler aus dem In-und Ausland

werden erwartet. Dieses Thema sollte daher für den 9.Workshop nicht gewählt werden.

Informationen zum Treffen dieser Forschergruppe können z.B. bei Herrn Professor Riess erfragt werden, sollen aber auch im nächsten Newsletter erscheinen.

TOP 3

Die Newsletter der DGNG erscheinen seit 2000 (Newsletter 12) in deutscher Übersetzung in „Der Neurologe & Psychiater (DNP)“. Über diese Zeitschrift werden niedergelassene Fachärzte über Aktivitäten und aktuelle Forschungsschwerpunkte informiert. Herr Professor Müller weist darauf hin, dass die Beiträge der zweimal jährlich erscheinenden Newsletter bisher ausschließlich vom Präsidenten und vom Vizepräsidenten bzw. vor dessen Ausscheiden vom ersten Schriftführer der DGNG verfasst wurden. Wünschenswert wären aber Beiträge auch anderer Mitglieder, beispielsweise über eigene Arbeiten oder Zusammenfassungen/Diskussionen von Publikationen, die im Rahmen der Schwerpunkte der Gesellschaft von Interesse sein könnten.

Herr Professor Riess schlägt vor, dass sich im Newsletter z.B. Arbeitsgruppen vorstellen könnten.

TOP 4

Seit letztem Jahr sind wir Mitglied im VdBiol. Herr Professor Müller weist darauf hin, dass über diesen Verein auch Laien (z. B. Lehrer) über die aktuelle Arbeit von Neurologen und Neurogenetikern informiert werden.

TOP 5

Herr Dr. Carsten Holzmann und Herr Thorsten Schmidt, beide Rostock, stellten sich freundlicherweise als Kassenprüfer zur Verfügung. Sie erhielten alle entsprechenden Unterlagen von der Kassiererin zur Kontrolle.

Frau Köhler informierte über Einnahmen/Ausgaben im Zeitraum 01.09.2000 - 15.10.2001. Die finanzielle Situation der Gesellschaft ist gut. Wir verfügten am 15.10.2001 über Guthaben in Höhe von 32.404,62 DM (16.772,74 €).

Es wurde darauf hingewiesen, dass das z. Zt. noch bestehende „Zins&Cash“-Konto abgelöst werden soll durch ein „Aktivsparen“-Konto, das einen besseren Zinsgewinn verspricht.

Die Kassenprüfer erklären, dass der Kassenbericht nachvollziehbar und die angegebenen Zahlen richtig seien.

Herr Professor Müller stellt den Antrag auf Entlastung der Kassiererin. Dem Antrag wird mit 12 Ja-Stimmen und 1 Enthaltung zugestimmt.

TOP 6

In diesem Jahr sollen zum zweitenmal drei Posterpreise vergeben werden. Für die Gewinner werden wieder Reisekosten, Tagungsgebühr und Unterkunft (bis DM 100,--/Nacht) für die nächste Tagung (Ulm) von der Gesellschaft übernommen werden. Die Gewinner werden gebeten, die Kosten vorzulegen und die Quittungen dann bei der Kassiererin der Gesellschaft einzureichen.

Als Juroren zur Beurteilung der Poster 2001 und zur Auswahl der Preisträger werden vom Vorstand eingesetzt: Herr Professor Wieacker, Herr Professor Riess und Herr Professor Sendtner.

Herr Professor Müller schlägt vor, jährlich einen Preis der DGNG an einen verdienten Wissenschaftler zu vergeben. Dieser sollte eine geprägte Goldmedaille plus die Einladung zur Tagung beinhalten, im Wert von 3000 bis 4000 DM. Dieser Vorschlag soll in einem größeren Forum diskutiert werden (Köhler, Wieacker).

Es wird gewünscht, den Posterpreisträgern Urkunden zu überreichen. Herr Professor Riess schlägt vor, dass von seiten der Gesellschaft ein entsprechendes Formular vorbereitet werden soll. Da im letzten Jahr in Dresden spontan von den Veranstaltern sehr schöne Urkunden für die Preisträger gestaltet wurden,

soll nachgefragt werden, ob die Vorlagen noch vorhanden sind und ggf. verwendet werden dürften.

TOP 7

Wegen der Umstellung der Währung auf Euro wird der Mitgliederbeitrag ab 2002 auf 17 € (33,25 DM) festgelegt. Damit erhöht sich der bisherige Beitrag von 30 DM (15,34 €) geringfügig. Der Festlegung der Beitragshöhe auf 17 € wurde einstimmig zugestimmt.

Dr. A. Köhler
(Vertreterin des Schriftführers)

Prof. Dr. U. Müller
(Präsident)