Newsletter
der
Deutschen Gesellschaft für Neurogenetik

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Society News

Neurogenetics in Bonn

The 6th Workshop Neurogenetics in Germany, 5th Annual Meeting of the German Society of Neurogenetics, was held in Bonn from September 16- September 18, 1999. The meeting was organized by Dr. O. Steinlein, Professor P. Propping, and Professor T. Klockgether. As in previous workshops, there were comprehensive overviews of various topics by invited renowned speakers. The morning sessions of 9/17 were devoted to channelopathies. K. Jurkat-Rott (Ulm) reviewed sodium channel disorders. A. Ophoff (Leiden, now San Francisco) discussed the pathogenic role of mutations in calcium channels in migraine, ataxia, and epilepsy. D. Bertrand (Geneva) demonstrated the importance of nicotinic acetylcholine receptors in brain function, and T.J. Jentsch (Hamburg) summarized recent findings of his lab on KCNQ potassium channels and their role in disorders of the nervous system. The main talks of the afternoon sessions addressed the genetics of Friedreich ataxia (H. Puccio, Strassburg) and the genetics of dystonias (O. Bandmann, Marburg). On 10/18 there were two major talks on amyotrophic lateral sclerosis (N. Cole, Chicago) and on molecular misreading in Alzheimer disease (E. Hol, Amsterdam). In addition there were numerous short talks selected from submitted abstracts and poster presentations. The presentations covered a wide spectrum of topics ranging from clinical observations and mutation screening in neurogenetic disorders to methodological advances. Abstracts of presentations have been published in Med Genet 3: 443-462 (1999).

7th Workshop Neurogenetics in Germany, 6th Annual Meeting of the DGNG

The next workshop (7th Workshop Neurogenetics in Germany and the 6th Annual Meeting of the DGNG) will be organized by Prof. H. Reichmann, Dr. J. Schmiedel, and Dr. P. Seibel and held in Dresden. For further information, please, visit http://www.fnz.med.tu-dresden.de/dgng/.

Research News

Molecular genetics of schizophrenia. Schizophrenia is a potentially heterogeneous group of disorders characterized by delusions, hallucinations, paranoia, psychosis, impaired cognition and attention, and social withdrawal. The disorder has a multifactorial etiology with a strong genetic component. Thus recurrence risks are greatly increased in first degree relatives of affecteds as compared to controls. While schizophrenia occurs in slightly less than 1 % of the general population, the recurrence risk is approximately 9 % if a sib is affected, 13 % if a parent suffers from the disorder, and 45 % if both parents are schizophrenics. This situation has stimulated vast mapping efforts in order to identify gene variants contributing to the development of schizophrenia. Despite the assignment of various loci, notably on chromosomes 2, 5, 6, 8, 11, 13, 18, 22 (for review see Shastry, 1999), no candidate genes have been identified in schizophrenia so far. This together with frequent irreproducibility of locus assignments in different populations may in part be due to heterogeneity of the disorder. Another important factor that might make the identification of candidate genes difficult is the possibility of quantitative effects in gene expression. Such effects are not easily recognized in standard investigations of

candidate genes which usually focus on their structural analysis. Now, Mohn et al. provide strong evidence for the importance of quantitative gene effects in an animal model of schizophrenia. The authors constructed mice expressing only 5 % of the normal levels of subunit NMDAR1 (NR1) of N-methyl-D-aspartate receptors. This was accomplished by insertion of a neomycin resistance gene into intron 20 of *NR1*. This insertion resulted in greatly reduced expression of NR1 (7.3 % ± 1.4 % at protein level) and of NMDA receptors as compared to wild-type animals. Unlike complete NMDA receptor "knock-outs", which are lethal, the animals constructed were viable, were morphologically normal and lived into adulthood. Behavioural analyses in these animals, however, demonstrated an increase in motor activity and stereotypic behaviour. These symptoms are correlated with positive symptoms of schizophrenia (delusions, hallucinations, paranoia) (Corbett et al., 1995). In addition, there was social withdrawal, a typical negative symptom in schizophrenia. The motor symptoms could be successfully treated with the antipsychotic drugs haloperidol and clozapine and best attenuation of negative symptoms was achieved with clozapine. The findings reported by Mohn et al. convincingly demonstrate the importance of disturbances in quantitative gene expression in behavioural disorders. A good approach to the analysis of candidate genes in schizophrenia in humans might therefore be the quantitative analysis of vast amounts of genes in both schizophrenics and controls. Such an approach is feasible by the application of microarray technology, specifically by the interrogation of arrays of cDNAs of a great number of genes with fluorescently labelled RNAs from patients and controls.

1. Corbett R, Hartmann H, Kerman LL, Woods AT, Strupczewski JT, Helsley GC, Conway PC, Dunn RW (1993) Effects of atypical antipsychotic agents on soical behavior in rodents. Pharmacol Biochem Behav 45: 9-17

2. Shastry BS (1999) Recent developments in the genetics of schizophrenia. Neurogenetics 2: 149-154

3. Mohn AR, Gainetdinov RR, Caron MG, Koller BH (1999) Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. Cell 98: 427-436.

Hypocretin receptor 2 and narcolepsy.

Narcolepsy is a disorder of normal sleep regulation resulting in frequent episodes of daytime drowsiness. Characteristic symptoms are due to abnormal REM sleep and include episodes of skeletal muscle paralysis, atonia, and hypnagogic hallucinations (half-sleep dreams). In humans the disorder is usually sporadic thus rendering the analysis of the molecular basis of the disease difficult. In contrast to humans, however, narcolepsy occurs as a fully penetrant autosomal recessive trait in dogs. The disorder is particularly common in Doberman pinschers and in Labrador retrievers. Lin et al. (1999) have now used Doberman pinschers to identify the gene mutated in narcoleptic dogs. In a first step, they performed linkage analysis and identified a tightly linked marker, a human µ switch immunoglobulin variable heavy chain probe. This probe turned out to be a cross-reacting repeat sequence of unknown function not related to a dog immunoglobulin switch segment. The authors then constructed a dog BAC library and constructed a 1.8 Mb contig surrounding the tightly linked polymorphic marker and thus probably the narcolepsy locus, *canarc-1*, as well. They searched the data base for sequence homologies of BAC inserts with known sequences and found homology of one sequence with human *Myo6* that is located on the long arm of human chromosome 6. In situ hybridization with additional BAC clones identified a large region of synteny between human chromosome 6 and canine chromosome 12. This facilitated mapping of genes to the contig using human ESTs proximal and distal to *Myo6*. The authors thus identified additional canine BAC clones of the *canarc-1* critical region, isolated STRPs for fine mapping and characterized some canine homologs of human genes. Using the newly developed STRPs they further narrowed down the critical interval and found that one gene only, *Hctr2*, had previously been mapped to this region. This gene codes for a G protein-coupled receptor with high affinity for hypocretins (orexins). In order to characterize

the dog *Hctr2* gene, the authors designed degenerate primers based on the 5´and 3´sequences of published human and rat *Hctr2* cDNAs. Using these primers they found different products when amplifying cDNAs of narcoleptic dogs as compared to healthy litter mates. Sequence analysis of the amplicons then identified a 116bp deletion in the *Hctr2* transcript of affected animals. Further analyses demonstrated that this deletion is the result of abnormal splicing caused by the insertion of a canine short interspersed nucleotide element (SINE) in the intron preceding the fourth coding exon. A different splice site mutation was detected in narcoleptic labrador retrievers. The findings strongly suggest that mutations in the hypocretin receptor gene 2 are the underlying cause of narcolepsy in dogs. Hypocretin receptor 2 binds hypocretins 1 and 2, both of which are derived from a common preprohypocretin RNA and are highly expressed in the hypothalamus. Although hypocretins were initially thought to be primarily involved in the regulation of energy balance and feeding, neuroanatomical studies of hypocretins and their receptors suggest a wider role of these molecules. These roles include an important function in the regulation of sleep and wake, as this paper has convincingly demonstrated. The important role of the hypocretin (orexin) system was further demonstrated in orexin knock-out mice which also develop symptoms comparable to narcoleptic attacks (Chemelli et al., 1999).

1. Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, Yanagisawa M (1999) Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98: 437-451

2. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E (1999) The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98: 365-376

A new therapy for familial transthyretin-type amyloidoses?

Familial amyloidotic polyneuropthy is a rare autosomal dominant disorder characterized by extracellular deposition of insoluble transthyretin in peripheral nerves, muscle, heart, kidneys and vitreous body. Transthyretin is composed of 4 identical subunits with a high proportion of beta-structure and is synthesized in the liver, plexus choroideus and retina. The transthyretin gene comprises 4 exons and is located on chromosome 18. More than 60 mutations have been detected that result in precipitation as amyloid. They are associated with a decreased tetramer/monomer ratio of transthyretin. Liver transplantation is the only effective therapy known to date. Now Altland and Winter (1999) provide in vitro and in vivo evidence that sulfite raises the tetramer/monomer ratio of transthyretin by replacing sulfhydryls bound to the only cysteine (i.e. Cys10) of the primary structure. This is expected to cause a significant inhibitory effect on amyloid formation. Clinical studies have been initiated to verify the potentially beneficial effects of sulfite in patients.

1. Altland K, Winter P (1999) Potential treatment of transthyretin-type amyloidosis by sulfite. Neurogenetics 2:183-188

With the best wishes for a successful New Year.

Sincerely yours,

Ulrich Müller
Olaf Riess
Manuel B. Graeber

Protokoll der Mitgliederversammlung 1999 der Deutschen Gesellschaft für Neurogenetik

Ort: Unikliniken Venusberg - Neurozentrum der Universität Bonn

Zeit: Donnerstag, 16.09.1999

Beginn: 18:05 Uhr

Anwesend: 22 Mitglieder

TOP 1: Protokoll der letzten Mitgliederversammlung

Der Vorsitzende, Prof. Müller (Gießen), eröffnet die Mitgliederversammlung und stellt den Antrag auf Genehmigung des Protokolls der letzten Mitgliederversammlung. Das Protokoll wird ohne Gegenstimme angenommen.

TOP 2: Bericht des Präsidenten

Prof. Müller berichtet über die weiterhin positive Entwicklung der Mitgliederzahl der Gesellschaft.

Mit Bestürzung wird zur Kenntnis genommen, dass ein junges Mitglied nach kurzer Krankheit verstorben ist.

TOP 3: Bericht des Schriftführers

Dr. Graeber (Martinsried) erwähnt das anhaltende Interesse der Zeitschrift NATURE, DGNG-Mitgliedern vergünstigte Konditionen für die Subskription der Zeitschrift einzuräumen. Dr. Graeber kündigt an, dass er sein Amt als Schriftführer im nächsten Jahr zur Verfügung stellen wird, da er den Ruf auf den Lehrstuhl für Neuropathologie am Imperial College der Universität London angenommen hat.

TOP 4: Bericht der Schatz-Meisterin, Kassenprüfung

Drs. Klopstock (München) und Kostrzewa (Leipzig) werden zu Vertretern der abwesenden Kassenprüfer bestellt. Drs. Klopstock und Kostrzewa führen die Kassenprüfung durch. Die Schatzmeisterin, Frau Dr. Koehler (Gießen), legt die Einnahmen- und Ausgabenrechnung der Gesellschaft dar. Die Finanzen der Gesellschaft befinden sich in gutem Zustand (s. TOP 7). Prof. Müller stellt nach erfolgter Kassenprüfung den Antrag auf Entlastung der Schatzmeisterin, der ohne Gegenstimme angenommen wird.

Die gute Finanzlage der Gesellschaft ist auf Überschüsse zurückzuführen, die aufgrund der Freiburger Tagung entstanden sind. Nach überaus erfolgreichem "Fundraising" war Dr. Landwehrmeyer (Freiburg) nicht nur dazu in der Lage, den von der DGNG gewährten Tagungszuschuss zurückzuerstatten, sondern hat darüber hinaus verbliebene Mittel großzügigerweise ebenfalls der Gesellschaft gespendet. Dies wird von den Anwesenden mit großer Anerkennung vermerkt.

TOP 5: Vorstandwahl 2000

Die nächsten Wahlen für den Vorstand der DGNG werden im kommenden Jahr stattfinden. Alle Mitglieder der Gesellschaft sind aufgefordert, Vorschläge zu machen und zahlreich an der Wahl während der nächsten Mitgliederversammlung teilzunehmen.

TOP 6: Tagungsorte der DGNG-Meetings 2000 und 2001

Prof. Müller berichtet, dass Professor Reichmann (Neurologie Dresden) vom 14. bis 16. September 2000 die nächste DGNG-Tagung ausrichten wird. Prof. Riess (Rostock) schlägt für 2001 Hamburg und Berlin als mögliche Tagungsorte vor. Prof. Klockgether (Bonn) erwähnt Marburg als weitere Alternative. Der Vorstand wird mit möglichen Organisatoren am Ort Kontakt aufnehmen.

TOP 7: Verschiedenes

Es wird diskutiert, ob aufgrund der positiven Finanzlage (s. TOP 4) eine Medaille der Gesellschaft, ein Stipendien-artiger Zuschuss für junge Mitglieder oder ein Posterpreis gestiftet werden soll. Die Anwesenden beschließen nach eingehender Diskussion ohne Gegenstimme bei einer Enthaltung, je nach Finanzlage und Möglichkeit auf zukünftigen Tagungen 1-2 Posterpreise in Höhe von DM 1000,-- zu vergeben.

Die Mitgliederversammlung endet um 18:28 Uhr.

Bonn, den 16.09.1999

Manuel B. Graeber (Schriftführer) *Ulrich Müller (Präsident)*