Newsletter

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Deutschen Gesellschaft für Neurogenetik

July, 1997
DGNG News No. 6

Society News

4th Workshop Neurogenetics in Germany, 3rd Annual meeting of the DGNG

The 4th workshop Neurogenetics in Germany and 3rd Annual Meeting of the DGNG will be held in Bochum from October 2-4, 1997. Deadline for abstracts is August 10, 1997. For further details contact the organizer, Professor J.T. Epplen, email: epplejbz@rubc.rz.ruhr-uni-bochum.de

Program

Thursday, October 2, 1997

17^{00} ***Opening remarks (J.T. Epplen)***

Key note lecture (introduction: J.T. Epplen)

17^{15} C. Ross (Baltimore): Dynamic mutations and damaging proteins

19^{00} ***Reception***

20^{00} ***Business meeting*** (Deutsche Gesellschaft für Neurogenetik)

Friday, October 3, 1997

Trinucleotide diseases (chair: H. Przuntek)

9^{00} W. Doerfler (Cologne): Trinucleotide binding proteins

9^{30} M. Koenig (Strassbourg): Friedreich ataxia

10^{00} Coffee/tea break

10^{30} O. Rieß (Bochum): Research and patient care in the Huntington Center NRW

11^{00} L. Schöls (Bochum): SCA, genotype - phenotype

11^{30} K. Johnson (Glasgow): Myotonic dystrophy

12^{00} Lunch break

13^{00} ***Poster session***

15^{00} Coffee/tea break

Multiple Sclerosis (chair: W. Gehlen)

15^{30} R. Martin (Bethesda): MS, causal pathogenesis

16^{15} C. Epplen (Bochum): MS, genetic predisposition

17^{00} D. Pöhlau (Bochum): MS, clinical aspects and therapy

17^{30} Coffee and tea

19^{00} ***Meeting dinner***

Saturday, October 4, 1997

Hereditary dystonias, neuropathies, regeneration, CADASIL (chair: J.-P. Malin)

8^{30} U. Müller (Gießen): Genetics of dystonia parkinsonism syndromes

9^{00} E. Nelis (Antwerp): Molecular genetics of M. Charcot-Marie-Tooth and related peripheral neuropathies

9^{45} F. Stögbauer (Münster): Linkage studies in hereditary neuralgic amyotrophy (HNA)

10^{00} M. Dichgans (Munich): CADASIL

10^{15} F.-W. Schwaiger (Martinsried): Genes in neuronal regeneration

10^{30} Late breaking stories

11^{00} Coffee/tea break

Experimental animal models for neurogenetic diseases (chair: U. Eysel)

11^{20} W. Wurst (Neuherberg): Genetic network controlling mid-/hindbrain development

11^{50} K. Nave (Heidelberg): Transgenic models of human myelin diseases

12^{20} R. Kühn (Cologne): Gene targeting in the brain of the mouse

13^{00} End

Neurogenetics online

The new journal Neurogenetics is now online. All papers of the first issue can be downloaded without charge in PDF-format (http://www.oup.co.uk/neugen).

Hungarian Society of Neurogenetics founded

The Hungarian Society of Neurogenetics was founded on May 9, 1997, in Szombathely/Hungary during a scientific meeting entitled „Neurogenetical disorders - diagnosis and therapy“. In addition to Hungarian clinicians and scientists, speakers from Canada, France and Germany participated in the conference. Dr. Graeber delivered a talk on "Neurogenetics in Germany" in which the development of the DGNG was reviewed. Close interaction and co-operation between the two societies has been agreed upon.

Neurogenetics on the Web

The World Wide Web is undoubtedly developing into one of the most important and useful sources of information. The information provided is already more up-to-date and in many instances more comprehensive than that found in leading libraries. In addition, the Web offers unparalleled directory functions. We were interested in learning to what extent Neurogenetics is represented on the Web. A search using the AltaVista Web Pages via YAHOO (http://www.yahoo.com/) resulted in 3080 matches containing „neurogenetics“. Obviously, this number of hits is far too high to allow for a detailed review of all Web sites or documents that were retrieved. However, it should be mentioned that the DGNG is represented very well, i.e., many listings among the „top hits“ which is probably due to the fact that the abstracts of the First Annual Meeting were published on the Web as early as 1995. A review of sites which are of interest to DGNG members follows.

It may be appropriate to start this review with the Web site of one of the early neurogeneticists, James Gusella of the Molecular Neurogenetics Unit at Massachusetts General Hospital (http://www.mgh.harvard.edu/depts/molneur/). There is an animated (turning) DNA helix on the introductory page which is worth looking at but there is also very useful information such as a list of diseases the Unit is working on (http://www.mgh.harvard.edu/depts/molneur/diseases.html). The topics listed provide links to many related sites.

Another more clinical Neurogenetics site is located at the University of Pennsylvania Medical Center (http://www.med.upenn.edu/~penngen/neurogenetics.html). Pediatricians specialising in Neurogenetics may find their site at the Behavioral Neurogenetics and Neuroimaging Research Center of the Kennedy Krieger Institute in Baltimore (http://sol.med.jhu.edu/); a well-developed topic of this page concerns the fragile X syndrome.

A potentially very useful brain atlas/data collection on different strains of mice can be found at http://mickey.utmem.edu/neuron.html. As the authors of these pages state, the aim of their Mouse Brain Atlas Project is to provide high-resolution images of sections through the brains of several common (and some uncommon) strains of mice. For instance, a summary of the main results of an analysis of the retinal ganglion cell population of over 573 mice belonging to 62 strains is given. A somewhat cluttered page containing numerous links to various genetics resources can be found at http://neurogen-www.uia.ac.be/neurogen_links.html.

Finally, the Web site of DGNG member K.-F. Fischbach at http://filab.biologie.uni-freiburg.de/ should be mentioned. Apart from useful

information on the drosophila nervous system, an online text („Scriptum“) of Neurogenetics can be found at this site.

Please, let us know if you are aware of especially interesting Neurogenetics Web sites or, even better, write a review about them!

Research News

Parkinson Disease

Linkage analyses in autosomal dominant and autosomal recessive forms of Parkinson disease (PD). PD is a common neurodegenerative disorder that affects approximately 1% of the population older than 50 years. The great majority of PD cases has a multifactorial etiology, i.e., ill-defined genetic and environmental factors contribute to disease development. Recurrence risk to sibs is dependent on the age of disease onset of the proband. It ranges from 8% for siblings of an affected person younger than 45 years to less than 2% to first degree relatives of a proband with disease onset at age 65 or thereafter. In a minority of cases, parkinsonism can be inherited as a Mendelian trait, following either an autosomal dominant or an autosomal recessive mode of inheritance. Now gene loci have been mapped by linkage analysis in both an autosomal dominant and in an autosomal recessive form of PD. Polymeropoulos and co-workers (2) studied a large family in which PD segregated as an autosomal dominant trait with an average age of disease onset of 46 ± 13 years. Performing a genome screen with a total of 140 polymorphic markers spaced at intervals of approximately 20 cM, they were able to establish linkage between the disease locus and chromosome 4q markers. The highest lod score (Zmax = 6.0) was obtained with marker D4S2380. Additional linkage analyses assigned the PD locus to 4q21-q23 in this family. Unfortunately, no obvious candidate genes of the disorder were found within this interval. In another study, Matsumine et al. (1) performed linkage analysis in an autosomal recessive form of parkinsonism that is characterized by „highly selective degeneration of dopaminergic neurons in the zona compacta of the substantia nigra“. They found linkage with the Mn-superoxide dismutase gene and established linkage to the distal long arm of chromosome 6 (6q25.2-q27) in 13 families. Haplotype and multipoint linkage analyses assigned the disease gene to a 17 cM interval flanked by markers D6S437 and D6S264.

1) Matsumine H, Saito M, Shimoda-Matsubayashi S, Tanaka H, Ishikawa A, Nakagawa-Hattori Y, Yokochi M, Kobayashi T, Igarashi S, Takano H, Sanpei K, Koike R, Mori H, Kondo T, Mizutani Y, Schäffer AA, Yamamura Y, Nakamura S, Kuzuhara S, Tsuji S, Mizuno Y (1997) Localization of a gene for an autosomal recessive form of juvenile Parkinsonism to chromosome 6q25.2-27. *Am.J.Hum.Genet.* **60:** 588-596

2) Polymeropoulos MH, Higgins JJ, Golbe LI, Johnson WG, Die SE, Di Iorio G, Sanges G, Stenroos ES, Pho LT, Schaffer AA, Lazzarini AM, Nussbaum RL, Duvoisin RC (1996) Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. *Science* **274:** 1197-1199

Nurr1 is essential in differentiation and function of dopamine midbrain neurons. Nurr1 is a member of the steroid hormone nuclear receptor superfamily whose ligands are not yet known ("orphan" receptor). Nurr1 RNA is expressed in dopamine neurons of the substantia nigra and the requirement of Nurr1 for the differentiation of midbrain dopamine neurons has recently been shown in Nurr1 knock-out mice (1). Homozygote (Nurr1-/-) mice were born hypoactive and displayed movement abnormalities. They died within 2 days of birth due to their inability to suckle. There were no gross morphological abnormalities of brain or other organs. However, dopamine neurons of the ventral midbrain were absent as shown by lack of

tyrosine-hydroxylase immunoreactivity. Furthermore, dopamine metabolite DOPAC was found to be absent in tissue sections of the striatum and ventral midbrain of Nurr1 -/- mice. The observation in heterozygotes of reduced levels of DOPAC in both newborns and adults suggests that Nurr1 is not only required for differentiation but also for maintenance of function of dopamine neurons. It is tempting to speculate that Nurr1 malfunction, e.g., caused by mutations or by interactions with toxins, plays a role in the development of Parkinson disease.

1) Zetterstrom RH, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T (1997) Dopamine neuron agenesis in NURR1-deficient mice. *Science* **276:** 248-250

Fragile X syndrome

Reassessment of prevalence of fragile X syndrome. The frequency of the fragile X syndrome (mental retardation, characteristic facies with large ears and prominent chin, macroorchidism in males and a fragile site at Xq27.3) has been estimated at 1/1000-1/2000 in both males and females. These estimates are based on various population- based clinical and cytogenetic analyses in several countries including Great Britain, Finland, Australia, and Sweden. The British study was performed on school children in the city of Coventry in 1986 and arrived at a prevalence of 1/952 (4). Since this study was performed, the molecular basis of the fragile X syndrome has been elucidated and a CGG expansion in the gene *FMR1* was found as the cause of the fragile X syndrome. This discovery has facilitated the exact molecular analysis of the syndrome. Using molecular tests, Morton et al. (2) have reinvestigated the children diagnosed as having fragile X syndrome in the Coventry study. Of the original 29 patients, CGG expansions were only found in 7, 18 did not have fragile X syndrome, and 4 were lost to follow up. The revised prevalence figures of the syndrome now lie between 1/2720 (range 1/2198-1/3089) and 1/5714 (range 1/4762-1/6349). The lower figure is based on the assumption that the patients lost to follow up also did not have fragile X syndrome. The new data are comparable to other molecular studies which arrived at frequencies of fragile X syndrome ranging from 1/4130 (3) to 1/9000 (1).

1) Jacobs PA, Bullman H, Macpherson J, Youings S, Rooney V, Watson A, Dennis NR (1993) Population studies of the fragile X: a molecular approach. *J Med Genet* **30:** 454-459

2) Morton JE, Bundey S, Webb TP, MacDonald F, Rindl PM, Bullock S (1997) Fragile X syndrome is less common than previously estimated. *J Med Genet* **34:** 1-5

3) Slaney SF, Wilkie AO, Hirst MC, Charlton R, McKinley M, Pointon J, Christodoulou Z, Huson SM, Davies KE (1995) DNA testing for fragile X syndrome in schools for learning difficulties. *Arch Dis Child* **72:** 33-37

4) Webb TB, Bundey S, Thake A, Todd J (1986) The frequency of the fragile X chromosome among schoolchildren in Conventry. *J Med Genet* **23:** 396-399

Neurobiology of the fragile X syndrome. Neuroanatomical changes were analysed in fragile X knockout mice. Spines on apical dendrites of layer V pyramidal cells in occipital cortex were longer in knock-out than in wild-type mice. They were often thin and tortuous, similar to those observed in the human syndrome. The findings suggest that expression of the fragile X mental retardation protein (FMRP) is required for normal spine structural development. Moreover, spine density along the apical dendrite was greater in the knockout mice, which may reflect impaired developmental organizational processes of synapse stabilization and elimination or pruning (1). In addition, it was suggested that rapid production of FMRP near synapses in response to activation may be important for normal maturation of synaptic connections. Support for this comes from the

finding that FMRP is translated locally in distal dendrites and that FMRP is increased in response to metabotropic glutamate receptor (mGluR1) stimulation (2).

1) Comery TA, Harris JB, Willems PJ, Oostra BA, Irwin SA, Weiler IJ, Greenough WT (1997) Abnormal dendritic spines in fragile X knockout mice: maturation and pruning deficits. *Proc Natl Acad Sci USA* **94:** 5401-5404

2) Weiler IJ, Irwin SA, Klintsova AY, Spencer CM, Brazelton AD, Miyashiro K, Comery TA, Patel B, Eberwine J, Greenough WT (1997) Fragile X mental retardation protein is translated near synapses in response to neurotransmitter activation. Proc Natl Acad Sci USA **94:** 5395-5400

We are looking forward to seeing you in Bochum!

Sincerely yours,

Ulrich Müller

Peter Propping

Manuel B. Graeber

Call for collaboration

Refinement of the hereditary neuralgic amyotrophy (HNA) locus

Hereditary neuralgic amyotrophy (HNA) is an autosomal dominant, recurrent focal neuropathy characterized by episodes of painful brachial plexus neuropathy with muscle weakness and atrophy, as well as sensory disturbances. Single episodes are commonly preceded by nonspecific infections or immunization, or are associated with parturition. Minor facial dysmorphic features are present in some pedigrees but do not clearly segregate with the disease. To confirm the recently described HNA locus on distal chromosome 17q, we performed a genetic linkage study in an extended Turkish pedigree. We were able to delineate the HNA locus on chromosome 17q24-q25 in a 16 cM region (Stögbauer et al., Hum. Genet. 99:1997:685-687). In order to further refine the locus we are searching for more HNA families to find more recombination events. We would be grateful for collaboration with other groups who are aware of HNA families.

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