Newsletter

der

Deutschen Gesellschaft für Neurogenetik

January, 1997
DGNG News No. 5

Society News

Annual meetings of the DGNG

1996:

The third workshop Neurogenetics in Germany, and the second annual meeting of the DGNG was held in Ulm from October 10-12, 1996 and organized by Professors F. Lehmann-Horn, W. Krone, and W. Vogel. The conference focussed on trinucleotide repeat disorders, ion channel diseases and neural tumors. The first session featured the following speakers: M. DiFiglia, Boston, with a report on the pathophysiology of Huntington disease; P. Steinbach, Ulm, with a contribution on fragile X syndrome; H. Orr, Minneapolis, with a lecture on spinocerebellar ataxia in transgenic mice and B. Wieringa, Nijmegen, with a comprehensive review of myotonic dystrophy. Speakers of the second session included R. Rüdel, Ulm, with a comprehensive introduction to the molecular basis of Cl^- channel disorders; H. Lerche and K. Jurkat-Rott from Lehmann-Horn´s lab with contributions on „Na^+ and Ca^{2+} ion channel disorders (myotonias, periodic paralyses)“; M. Litt, Portland, with a report on the molecular basis of ataxias, among other diseases; and O. Steinlein, Bonn, with a summary of acetylcholine receptor disorders. The third topic, neural tumors, was covered by W. Krone, Ulm, with a summary on the molecular basis of neurofibromatosis 1 and 2; J. Green, Cambridge, England, with an excellent overview of the various types of tuberous sclerosis; Y. Shiloh, Tel Aviv, with a report on the current state of research into ataxia telangiectasia; and A. von Deimling, Bonn, with a discussion of molecular findings in gliomas. There were also free oral presentations and a poster exhibit. In addition, the meeting included two exciting key note lectures, one by E. Hoffman, Pittsburgh, on therapeutic strategies for progressive muscular dystrophies, the other by D. Wildenauer, Munich, on mapping of schizophrenia genes. The lively discussions and the responses of many of the more than 100 participants of the conference suggest that the meeting was a great success and met a major goal of the DGNG, to bring together leading scientists in neurogenetics.

1997:

The fourth Workshop Neurogenetics in Germany and the third annual meeting of the DGNG will be held in Bochum from October 2-4, 1997. Deadline for abstracts is August 10, 1997. Abstracts should be sent to the organizers at Abteilung für Molekulare Humangenetik der Ruhr-Universität Bochum, Gebäude MA 5 Nord, Universitätsstr. 150, D-44801 Bochum. The meeting will focus on trinucleotide disorders, hereditary ataxias, hereditary motor and sensory neuropathies, multiple sclerosis and animal models of neurogenetic diseases. More details on the meeting will be given in Newsletter 6.

Membership

The number of members of the DGNG is increasing steadily and has reached 140 as of January 1997. A register of members is appended to the mailing of this newsletter.

Neurogenetics, a new journal

The field of Neurogenetics now has its own publication. The journal, *Neurogenetics*, will be published by Oxford University Press. The first issue of the journal will be available by April 1997. For further details visit the journal´s home page at

„http://www.oup.co.uk/neugen/“

Research Highlights

More on Friedreich ataxia (FRDA). In Newsletter No. 4 we reported on the discovery of the gene defect in FRDA and described a GAA expansion in intron 1 of the gene *X25* as the underlying cause of the disease. This gene is composed of 7 exons, 6 translated and one untranslated. More recent data suggest that *X25* is much larger and that it includes the proximally adjacent gene *STM7* which encodes the catalytic domain of a phosphatidylinositol-4-posphate 5 kinase. According to this finding, the FRDA gene is composed of at least 24 exons, the 7 exons of *X25* (now exons 18-24) plus 17 exons of *STM7*. Expression of *STM7/X25* is complex. There are different splicing variants that may code for different isoforms of phosphatidylinositol phosphate (PIP) kinases. In contrast to the previous report by Campuzano et al. (see Newsletter No. 4), Carvajal et al. detected no transcript of 1.3 kb that was composed of *X25* exons only. Given that *STM7* codes for a PtdIns(4)P-5-kinase, the FRDA gene product might be essential in the phosphatidylinositid pathway. In this context it might be significant that a PI-3 kinase encoded by chromosome 11 is mutated in another ataxia, ataxia telangiectasia.

Carvajal JJ, Pllk MA, dos Santos M, Doudney K, Hillermann R, Minogue S, Willimson R, Hsuan JJ, Chamberlain S (1996) The Friedreich´s ataxia gene encodes a novel phosphatidylinositol-4-phosphate 5-kinase. Nature Genetics 14: 157-162.

Further reading:

Liscovitch M. and Cantley L.C. (1995) Signal transduction and membrane traffic: The PITP/Phosphoinositide connection. Cell 81, 659-662

De Camilli P, Emr SD, McPherson PS, Novick P (1996) Phosphoinositides as regulators in membrane traffic. Science 271: 1533-1539.

Genetic basis of multiple sclerosis. Molecular approaches have facilitated the unravelling of many monogenic neurological disorders including Huntington disease, Duchenne muscular dytrophy and several hereditary ataxias. In contrast, the molecular analysis of multifactorial diseases, i.e., disorders caused by genetic and environmental factors is still in its infancy. Recently, the first findings have been reported aiming at the elucidation of the genetic basis of the multifactorial neurogenetic disorder multiple sclerosis (MS). It has been recognized for many years that this demyelinating disorder is more common among relatives of affecteds than in the general population. While the prevalence is up to 1/1000 in high risk populations, i.e., individuals of Northern European descent, the disease frequency is increased by 10-20 fold in first degree relatives of affecteds. Thus, the recurrence risk is about 0.6% for a son of a male index patient, 1.2% for a daughter, up to 3.8% for a brother, and 1.5% for a sister. In the case of a female index patient the recurrence risks for a son are 0.8%, for a daughter 0.4%, for a brother 1.9%, and for a sister 2.2% (Sadovnick AD, McLeod PM (1981) The familial nature of multiple sclerosis: empiric recurrence risks for first, second-, and third-degree relatives of patients. Neurol. 31: 1039-1041). There is an association of the disorder with certain HLA class II alleles within the major histocompatibility complex on the short arm of chromosome 6. This association, however, is weak and not useful for predictive and diagnostic purposes. Now three groups have reported on whole genome screens for susceptibility genes of MS. The families analysed were from Canada, the USA and Europe. The three studies did not reveal consistent data for

most regions thought to be critical for the development of MS. The studies showed two regions, however, that were consistent with a region of higher susceptibility to MS. One was the HLA region in 6p, the other a region in the short arm of chromosome 5. Thus all three groups (The Multiple Sclerosis Genetics Group, 1996 and Ebers et al., 1996; Kuokkanen et al., 1996 and previous results from this group) obtained data compatible with an association of susceptibility genes in 6p. Furthermore, the three groups (The Multiple Sclerosis Genetics Group, 1996, Ebers et al., 1996, and Kuokkanen et al., 1996) obtained some evidence of an association with markers on 5p. However, the highest degree of association was not found with identical loci of 5p in all three studies. The three investigations are exciting since they are a first attempt at the unravelling of the genetic basis of the multifactorial neurogenetic disorder MS. They do, however, only represent the „trail head" of an arduous path that might eventually result in the isolation of susceptibility genes for this debilitating disorder.

The multiple sclerosis genetics group (1996) A complete genomic screen for multiple sclerosis underscores a role for the major histocompatibility complex. Nat. Genet. 13: 469-471

Ebers GC et al. (1996) A full genome search in multiple sclerosis. Nat. Genet. 13: 472-476

Kuokkkanen S et al. (1996) A putative vulnerability locus to multiple sclerosis maps to 5p14-p12 in a region syntenic to the murine locus Eae2. Nat. Genet. 13: 477-480

Further reading:

Ebers GC (1996) Genetic epidemiology of multiple-sclerosis. Curr. Opin. Neurol. 9: 155-158

The response to nervous system trauma is influenced by genetic factors. Traumatic injury of the central and peripheral nervous system (head and spinal cord injury, lesions of peripheral nerves) affects hundreds of thousands of people each year. In general, since trauma is, by definition, caused by extrinsic agents, the role of genetic factors is not commonly considered in this context. Yet, a number of recent studies show that the genetic background of the affected individual may play an important role in the way in which the consequences of traumatic injury are dealt with.

The laboratory of O. Steward has recently demonstrated genetic influences on the cellular reactions to spinal cord injury in mice (Fujiki et al., 1996). Using an extradural approach, crush injuries were produced at the T8 level of the spinal cord and the animals allowed to survive for 2 days to 12 weeks after the injury. Subsequently, the cellular reactions were studied using immunohistochemistry. In mice carrying the Wld(s) genetic defect which slows down Wallerian degeneration, the accumulation of macrophages at the site of injury was delayed. In addition, these mice also showed a slower response of astrocytes which did not increase in immunostaining for the glial fibrillary acidic protein (GFAP) until 2-3 weeks after trauma. In a second study (Zhang et al., 1996), Steward and co-workers demonstrated that progressive tissue necrosis, a process unique to the injured mammalian spinal cord, is more severe in Wld(s) than in C57BL mice, resulting in more severe cavitation of the tissue and larger lesions. Thus, the Wld(s) gene which maps to mouse chromosome 4 (Lyon et al., 1993) appears to play an important role in the cellular reactions leading to central nervous system repair. Dependence of the result of regeneration on genetic factors has also been demonstrated for the peripheral nervous system (Brown et al., 1991; Rath et al., 1995).

The well-established link between Alzheimer's disease and head injury deserves mention in this context. The apolipoprotein E epsilon 4 allele is associated with betaA4 deposition in the brain parenchyma following head injury, and individuals carrying the epsilon 4 allele are more likely to die from head trauma (Nicoll et al., 1995; Sorbi et al., 1995). Furthermore, experimentally induced focal injury to the white matter causes a robust increase in expression of the presenilin-1 gene in non-neuronal cells

immediately surrounding the site of injury, underscoring the epidemiological evidence that implicates head injury as a risk factor for Alzheimer disease and suggesting a possible role for presenilin-1 in this capacity (Cribbs et al., 1996).

A link between the phenotype of brain injuries and genetic factors has also been demonstrated for perinatal hypoxia-ischemia the manifestation of which depends on the level of expression of the copper/zinc-superoxide dismutase gene (Ditelberg et al., 1996). Similarly, attenuated hippocampal damage has been described following global cerebral ischemia in mice carrying a defunct gene for neuronal nitric oxide synthase (Panahian et al., 1996).

In conclusion, there is increasing evidence that genetic factors play an important role in the nervous system response to traumatic injury.

References

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Cribbs, D.H., L.S. Chen, C.W. Cotman and F.M. Laferla (1996) Injury induces presenilin-1 gene-expression in mouse-brain. NeuroRep., 7:1773-1776.

Ditelberg, J.S., R.A. Sheldon, C.J. Epstein and D.M. Ferriero (1996) Brain injury after perinatal hypoxia-ischemia is exacerbated in copper/zinc superoxide dismutase transgenic mice. Pediatric Research, 39:204-208.

Fujiki, M., Z.Y. Zhang, L. Guth and O. Steward (1996) Genetic influences on cellular reactions to spinal-cord injury - activation of macrophages/microglia and astrocytes is delayed in mice carrying a mutation (Wld(s)) that causes delayed Wallerian degeneration. Journal of Comparative Neurology, 371:469-484.

Lyon, M.F., B.W. Ogunkolade, M.C. Brown, D.J. Atherton and V.H. Perry (1993) A gene affecting Wallerian nerve degeneration maps distally on mouse chromosome 4. Proceedings of the National Academy of Sciences USA, 90:9717-9720.

Nicoll, J.A., G.W. Roberts and D.I. Graham (1995) Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. Nature Medicine, 1:135-137.

Panahian, N., T. Yoshida, P.L. Huang, E.T. Hedley-Whyte, T. Dalkara, M.C. Fishman and M.A. Moskowitz (1996) Attenuated hippocampal damage after global cerebral ischemia in mice mutant in neuronal nitric oxide synthase. Neuroscience, 72:343-354.

Rath, E.M., D. Kelly, T.W. Bouldin and B. Popko (1995) Impaired peripheral nerve regeneration in a mutant strain of mice (Enr) with a Schwann cell defect. Journal of Neuroscience, 15:7226-7237.

Sorbi, S., N. Nacmias, S. Piacentini, A. Repice, S. Latorraca, P. Forleo and L. Amaducci (1995) ApoE as a prognostic factor for post-traumatic coma. Nature Medicine, 1:852.

Zhang, Z.Y., M. Fujiki, L. Guth and O. Steward (1996) Genetic influences on cellular reactions to spinal cord injury - a wound-healing response present in normal mice is impaired in mice carrying a mutation (Wld(s)) that causes delayed Wallerian degeneration. Journal of Comparative Neurology, 371:485-495.

With the best wishes for a successful NEW YEAR.

Sincerely yours,

Ulrich Müller

Peter Propping

Manuel B. Graeber