Newsletter
der
Deutschen Gesellschaft für Neurogenetik

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DGNG News No. 16

Society News

The 8th annual meeting of the society of Neurogenetics (9th workshop Neurogenetics in Germany) will be held in Ulm from Thursday September 5 to Saturday September 7, 2002. The conference will be organized by Drs. G. B. Landwehrmeyer, F. Lehmann-Horn, H. Lerche, A.C. Ludolph, C. O. Hanemann and W. Vogel. Major topics include „Model systems, Mechanisms of neurodegeneration, Motoneuron disorders, Epilepsie, Genetics of tumors of the CNS and PNS, Multifactorial traits". Details and registration forms are on the web (http://www.uni-ulm.de/klinik/neurologie/DGNG-Tagung). Deadline for abstracts is Sunday 06/30/2002.

Research News

Rapid changes in brain transcriptome drive human evolution. DNA sequences of humans and their closest evolutionary relatives, the chimpanzees, are 98.7 % identical. These findings prompted King and Wilson (1975) to suggest that regulatory rather than structural genetic changes underly the differences between these two closely related species. This has now been shown experimentally by Pääbo and coworkers (Enard et al., 2002). The authors studied the expression profiles of approximately 12,000 genes (Affymetrix U95A arrays) in brain and liver from 3 adult human males, from 3 adult male chimpanzees, and from one male orangutan, all of whom had died from natural causes. Brain RNA was gray matter from the left prefrontal lobe (Brodman area 9). Two independent RNA preparations were obtained from two adjacent areas of the two tissues analyzed. The results showed relatively small (12 % to 14 %) changes in gene expression between samples from the same individual. This allowed the calculation of differences in overall gene expression between the duplicates for each tissue sample. The results were given as trees depicting the overall differences in gene expression observed between individuals. The variation in gene expression within one species was substantial, e.g. one human brain sample differed more from the other human samples than the latter differed from the chimpanzee samples. However, when gene expression patterns are compared to that of the orangutan, humans and chimpanzees fell into two mutually exclusive groups. The differences in gene expression between humans and chimpanzees differed 3.8 fold in brain but only 1.7 fold in liver. The striking difference in brain gene expression between humans and chimpanzees was borne out in another experiment using RNA from neocortex samples from autopsies of seven humans, four chimpanzees, and two Rhesus macaques. In addition, liver samples from six humans, five chimpanzees, and four macaques, and blood samples from 10 humans, 10 chimpanzees, and 10 macaques were analyzed. The RNAs were tested on membrane based cDNA arrays harboring 21,504 DNA sequences of an average length of approx. 1,000 bp. The sequences corresponded to 17,997 genes. Relative evolutionary changes in transcription of the

three tissues were estimated, using the macaque as an outgroup. While differences in gene expression between humans and chimpanzees were small in liver and leukozytes, a 5.5 fold increase in the rate of change in gene expression level was found in human brain tissue. The authors also examined changes in transcription in brain and liver samples from three mouse species that are approximately as related to each other as are humans, chimpanzees, and orangutans. In these species, no acceleration in the expression pattern was found in the brain as compared to liver. Taken together, the findings demonstrate that changes in the expression profiles of related genomes in various tissues drive evolution and that rapid changes in gene expresssion levels in the brain are a characteristic of recent human evolution.

King MC, Wilson AC: Evolution at two levels in humans and chimpanzees. *Science* 188: 107-116 (1975).

Enard W, Khaitovich P, Klose, J, Zöllner S, Heissig F, Giavalisco P, Nieselt-Struwe K, Muchmore E, Varki A, Ravid R, Doxiadis GM, Bontrop RE, Pääbo S: Intra-and interspecific variation in primate gene expression patterns. *Science* 296: 340-343 (2002).

Frataxin, a potent antioxidant. Friedreich ataxia (FA) is an autosomal recessive neurodegenerative disorder characterised by limb ataxia, cerebellar dysarthria, skeletal deformities, and hypertrophic cardiomyopathy. In addition, deafness, blindness, diabetes mellitus, and an increased incidence of malignancies are observed. Onset is usually during the first or second decade, and the disorder is invariably fatal. FA is most frequently caused by expansions of the trinucleotide GAA in the first intron of the disease gene on chromosome 9 (see Newsletter 4). The GAA expansion results in reduced expression of the gene product, frataxin. Frataxin is a mitochondrial protein that has been conserved during evolution with a high degreee of homology among yeast and other eukaryotic frataxins, and the corresponding proteins encoded by bacteria. Mitochondria lacking frataxin accumulate iron thus suggesting that frataxin is required for iron homeostasis. This is supported by x-ray diffraction data that demonstrated binding of one iron atom per frataxin molecule. There are many findings suggesting that frataxin acts as a cellular antioxidant. These findings include increased sensitivity of fibroblasts from FA patients to radiation and to reactive oxygen species (ROS); an increase in the mutation rate of DNA from patients; and the observation of depletion of iron-sulfur clusters in heart and neuronal tissues from patients by ROS. In order to investigate whether frataxin functions directly as an antioxidant Shoichet et al. (2002) overexpressed human frataxin in murine fibroblasts. Studying its role in antioxidant defense they found that frataxin 1) increases cellular resistance to oxidative stress; 2) decreases intracellular levels of free radicals; 3) promotes antioxidant defense via glutathione and its peroxidase; and 4) inhibits colony formation (as indicator of malignant transformation) after exposure to ROS. These findings convincingly demonstrate that frataxin is an antioxidant important to maintain normal cellular integrity. In particular frataxin might play a role in the prevention of cancer induction.

Shoichet SA, Bäumer AT, Stamenkovic D, Sauer H, Pfeiffer AFH, Kahn CR, Müller-Wieland D, Richter C, Ristow M: Frataxin promotes antioxidant defense in a thiol-dependent manner resulting in diminished malignant transformation in vitro. *Hum. Mol. Genet.* 11: 815-821 (2002).

HAP-1 is essential for normal postnatal feeding. In a previous Newsletter (No. 3) we reported on the identification of a huntingtin-associated protein, referred to as HAP-1. The physiological role of this protein has now been elucidated by targeted disruption of its mouse homologue Hap-1. While prenatal development is not disturbed in homozygous Hap-1 knock-out mice (Hap1-/-), there is a pronounced decrease in feeding starting at birth. This results in malnutrition, dehydration, and premature death (between postnatal days 2 and 8). Consistent with its putative role as regulator of feeding, Hap-1 is enriched in the hypothalamus of control mice and absent in Hap1-/-animals. Although the role of HAP-1 in the pathogenesis of Huntington disease (HD) remains unclear, the authors make several suggestions as to its possible function. Thus HAP-1 localization might be altered in the hypothalamus by increased binding to huntingtin in patients. This might contribute to enhanced dopaminergic activity with altered hormonal release and/or to neuronal degeneration. Abnormal Hap-1 function may also be involved in the overall weight loss in HD patients that occurs despite good appetite of these patients. Clearly, more studies are necessary to show what role if any Hap-1 plays in the pathogenesis of HD.

Chan EYW, Nasir J, Gutekunst C-A, Coleman S, Maclean A, Maas A, Metzler M, Gertsenstein M, Ross CA, Nagy A, Hayden MR: Targeted disruption of Huntingtin-associated protein-1 (Hap1) results in postnatal death due to depressed feeding behavior. *Hum. Mol. Genet.* 11: 945-959 (2002).

Sincerely yours,

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