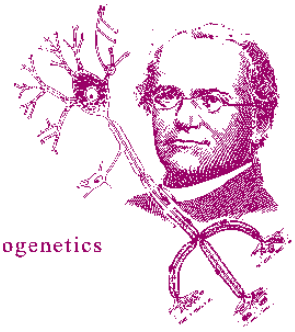
Newsletter 24 DGNG



German Society of Neurogenetics

Newsletter
der Deutschen Gesellschaft für Neurogenetik
Dezember 2007
DGNG News Nr. 24

The 13th annual meeting of the German Society of Neurogenetics was held from October 11 through October 13 at the Klinikum Großhadern in München. The local organisation committee was headed by Professor Ortrud Steinlein, Department of Human Genetics and Prof. Martin Dichgans, Department of Neurology, at the University of Munich.
Main topics this year included migraine, epilepsy, dementia, myopathies and mitochondrial disorders. These topics, and customary, were to some degree reflections of the major scientific interests of the hosts. As in previous years, internationally renowned speakers lectured on their topics and provided inside into to cutting-edge issues of neurogenetic research. A delightful social evening at the historical Anatomical Institute of the University of Munich completed this successful meeting.

Three poster prizes were awarded:
First prize to Andrea Seibel presenting a poster titled: A novel form of autosomal dominant pure spastic paraplegia (SP) maps to chromosome 12q23-24
Second prize to Ute Felbor presenting "Cerebral cavernous malformations: new pathogenetic insights."
Third prize to Oliver Rothfuss (Tübingen) presenting a poster titled: Parkin is associated to mtDNA D-Loop region and colocalizes with mitochondrial transcription factor TFAM in vivo.

At the annual business meeting, Dr. Ulrich Finckh stepped down from his position as vice president of the society due to his new obligations in private genetic practice. The membership elected PD Dr. Peter Bauer, Department of Human Genetics at the University of Tübingen as a new vice president. The board and the members of the DGNG are grateful to Dr. Finckh for his excellent services of the last years, and look forward to working with Dr. Bauer.

In this annual business meeting the board of the DGNG decided to announce an annual DGNG research award, to be presented each year to a junior researcher during the annual DGNG meeting. The first award will be announced early 2008.

Next years meeting will take place in September 26 to 28 in Lübeck and will be hosted by Prof. Christine Klein. Main topics will include Parkinson's genetics and neurodegeneration/regeneration. The board of the society is as always looking forward to meet you again in a years time to share the latest progress in neurogenetic research.

Thomas Gasser
President of the DGNG

Conference reports

57th Annual Meeting of the AMERICAN SOCIETY of HUMAN GENETICS (ASHG); San Diego

More than 5000 attendees withstood massive wildfires in southern California, while the annual ASHG meeting could take place as scheduled.

Within the "Genomics" session the advent of new sequencing technologies was discussed. Several genomic sequencers now empower us to resequence hundreds of megabases in individual samples.

A new paired-end method, presented by Urban and coworkers (Yale Univ., New Haven), investigated structural variation in two individual genomes based upon more than 10 million sequence reads. Several hundred structural variations – **copy number variations** - could be identified in healthy probands, ranging in size from 2kb to several Mb. Evidently, these individual genomic variations will contribute to human phenotypes.

Even resequencing the complete genome of an individual – Dr. James Watson – by Wheeler and coworkers (Baylor Univ. Huston) has been achieved and provided insights in individual SNP counts (2,1 Mio) and *indel* (70,000) counts. More than 6000 SNPs in this individual were classified as non-synonymous amino acid changes; 23 heterozygous alleles were found in the Human Gene Mutation Database; 70 *indels* were located in coding exons. Here again, functional implications are very suggestive. Although these data represent major technical breakthroughs, ethical implications have been discussed very open.

A lot of progress was reported investigating functional consequences of noncoding RNAs. For instance, the lack of a small C/D box nucleolar RNA (snoRNA) contributes to the Prader-Willi-Phenotype. Ding and colleagues (Stanford Univ., California) could show that a PWS mouse model with a small 150kb deletion of this snoRNA cluster leading to hyperphagia and motor learning deficits very similar to the human phenotype. Cheung and colleagues (Univ. Pennsylvania) were able to contribute similar observations in ataxia telangiectasia carriers. After expression profiling phenotypes with "recessive" and "dominant" types of action were identified and could be linked to altered microRNA expression which regulate these genes.

Moreover, Wang and coworkers from the Univ. of Miami were able to functionally link a well established risk allele in the 3' UTR of FGF20 at 8p21.3-22 in Parkinson's disease patients with a disrupted binding site for microRNA-433. In consequence FGF20 is downregulated and α-synuclein is upregulated. Wang argued that this mechanism might be effective in conferring a genetic risk for PD in those 10% of Caucasian that are genotyped homozygous for the TT allele in rs12720208.

(contributed by Peter Bauer, M.D.; Tübingen)

37th Annual Meeting of the Society for Neuroscience (SfN); San Diego

The **37th annual meeting of the Society for Neuroscience (SfN)** took place from November 3rd to November 7th 2007 in beautiful San Diego (California) directly after the disastrous bush fires were under control. As every year, this meeting was one of the largest meetings in the field of neuroscience with more than 31,000 participants and thousands of posters and presentations.

The conference was opened with the keynote lecture of Jeff Hawkins (the inventor of the Palm Pilot handheld computer) who gave examples, "why a

computer can't be more like a brain" and illustrated the borders and difficulties of the work on artificial intelligence.

Susan Lindquist from the Whitehead Institute for Biomedical Research (Cambridge, MA) reported about their study on **protein aggregation in yeast**. In a paper published last year in Science (Cooper *et al.*, 2006), this group had demonstrated that the ER stress caused by α -synuclein in yeast (especially in the A53T mutated form) is due to impaired vesicular trafficking from the ER to the Golgi apparatus. They identified the Rab GTPase YPT1 (Rab1 in mammals) which promoted the transport from the ER to the Golgi apparatus and therefore suppressed the α -synuclein toxicity in Yeast, Drosophila, C.elegans, and mammalian cells. They now screened a library of 150,000 compounds and identified seven compounds, which likewise ameliorated the ER-Golgi transport problem caused by α -synuclein and therefore might become a novel class of drugs for the treatment of Parkinson's disease.

The group of Roderic G. Eckenhoff (Dept. of Anesthesiology and Critical Care, Univ. Pennsylvania, Philadelphia, PA) presented their data on the **effects of the anesthetic isoflurane on the cognition of mice** carrying three transgenes involved in Alzheimer's disease. Isoflurane is routinely used for the anaesthesia of rodents. Mice at 2.5 months of age were treated with 1.5 % isoflurane for 2 hours once per week and showed after four weeks of treatment significant cognitive decline compared with controls possibly due to increased protein oligomerization. Halothane induced even stronger effects. That these effects are not only restricted to Alzheimer's disease but also apply to polyglutamine diseases was demonstrated in tissue culture. Striatal cells from transgenic Huntington's disease knock-in mice were treated with isoflurane, which induced spontaneous aggregation of huntingtin, and increased Ca^{2+} release from the ER while sevoflurane or desflurane had weaker effects. One therefore has to consider these effects when using Isoflurane as anesthetic.

A **treatment study for Spinocerebellar Ataxia Type 3 (SCA3)** was presented by the group of Ilya Bezprozvanny (Dept. of Physiology, UT Southwestern Medical Ctr., Dallas, TX). They used dantrolene (stabilizer of intracellular Ca^{2+} signalling) for the treatment of a transgenic SCA3 mouse model. Mice were treated starting at two months of age and performed significantly better during behavioural tests at 8-10 months of age than untreated controls. They also observed neuroprotection in the pons and substantia nigra. Interestingly, dantrolene is already used as a drug in humans as muscle relaxant or for the treatment of malignant hyperthermia.

A novel **inducible mouse model of synucleinopathies** was presented by X. Lin (National Institute of Aging, NIH, Bethesda, MD). He used the Tet-Off system to generate a transgenic mouse model expressing α -synuclein (carrying the A53T mutation) under the control of the CamKII promoter. The generated mice exhibit very high expression in the olfactory bulb, the striatum, the cortex, and the hippocampus. At two months of age, the mice showed increased motor activity and reduced body weight. At 6 months, Lewy body-like aggregates were detectable in multiple brain areas (cortex, hippocampus, and striatum) and a marked loss (>30 %) of dopaminergic neurons was apparent. X. Lin considers this mouse model as the first transgenic mouse model for Parkinson's disease with Parkinson's-like pathology. The Tet-Off systems allows turning off the expression of the

transgene using doxycyclin. However, after treatment of symptomatic mice with this antibiotic, no differences between treated or untreated mice were apparent. They will now try to treat their mice at earlier disease stages.

Several studies report that the polyglutamine stretch within ataxin-3, the protein affected in Spinocerebellar Ataxia Type 3 (SCA3), is cleaved from the remaining protein before the formation of intranuclear inclusion bodies. However, the actual **cleavage site within ataxin-3** is unknown and postulated to be located C-terminal of amino acid 191. For this reason, Veronica F. Colomer Gould (Department of Psychiatry, Johns Hopkins University, Baltimore, MD) generated mice transgenic for ataxin-3 lacking amino acids 190-220. They expected to prevent the cleavage of ataxin-3. However, the generated mice still developed behavioural symptoms and intranuclear aggregates containing cleavage fragments of ataxin-3. They therefore postulate that the cleavage of ataxin-3 occurs N-terminal of amino acid 190.

H. Sebastian Seung (Massachusetts Institute of Technology, Cambridge, MA) presented fascinating **insight into the future of digital brain imaging**. They generated in collaboration with Wolfgang Denk (Max Planck Institute for Medical Research, Heidelberg) a wiring diagram of the rabbit retina. Cross-sectional electron microscopical pictures were used to generate a 3D insight into the nerve fibers. For novel projects, they presently further improve their techniques since the imaging of just one human cortical column would currently take about three billion person years…

(contributed by Thorsten Schmidt, PhD, Tübingen)