

Newsletter der Deutschen Gesellschaft für Neurogenetik

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Society News

The German Society for Neurogenetics held its 12th Annual Meeting October 13 to 15 in the beautiful "Gate to the Baltic Sea" town of Rostock. As is customary, the organisation was in the hands of the local organizational committee, which put together an exciting programme with many internationally renowned speakers. Main topics this year included Genetics of stroke, movement disorders, and leukodystrophies, but also the use of stem cells in the treatment of neurodegenerative diseases. The topics nicely reflected the research interests of the host department. During the symposium it became clear that neurogenetics is still advancing in the field of rare monogenic disorders, in particular as far as translation of genetic findings into a deeper understanding of molecular pathogenesis is concerned. This was the focus of the talk of Olaf Riess, Tübingen, on the molecular mechanisms of ataxias. Ever more refined animal models play a crucial role in these advances. On the other hand, there is palpable progress in the genetics of complex neurogenetic disorders. This was highlighted for example in the talk of Matthew Farrer from the Mayo Clinic on "genetic lessons from Parkinson's disease, who emphasised the importance of findings in monogenic forms of parkinsonism to the population of sporadic PD patients as a whole, and of course also in several talks about stroke genetics.

The meeting can only be fully appreciated by taking into

consideration the beautiful venue in a nice new conference center and the charming social programme, with a relaxed evening at a renovated railway yard, which gave us the opportunity to meet up with old friends and make new ones.

The society will continue this cherished tradition, with the **13th Annual Meeting of the Society for Neurogenetics**, to be held in **Munich, October 11 to 13, 2006**. As always the programme will be stimulating.

Main topics will include:

- Migraine
- Epilepsy
- Dementia
- Myopathies / Neuropathies
- Mitochondrial disorders

The deadline for early registration and submission of Abstracts is **15th July 2007**.

In an effort to encourage young colleagues to attend the meeting, the DGNG will this year provide

3 travel-stipends poster-prizes:

- 1. Prize: travel-stipend of 500 €**
- 2. Prize: travel-stipend of 250 €**
- 3. Prize: travel-stipend of 250 €**

Please visit the registration site at: <http://www.dgng.de/>. The board of the society is looking forward to meeting you all there.

Thomas Gasser
President of the DGNG

Research News

Mitochondria back in the focus of Parkinson's disease research

The role of mitochondrial dysfunction in the pathogenesis of Parkinson's disease has been controversially discussed since the 1980s, when the groups of Heinz Reichmann and Yoshi Mizuno found defective enzyme activities of the mitochondrial respiratory chain in peripheral tissues of PD patients, such as blood platelets and muscle biopsies. However, these results could not be replicated by all groups and so their significance remained uncertain. It was well established, however, that at least a mitochondrial complex 1 defect in the substantia nigra is a consistent feature in PD, although it remained unknown whether this was primary or secondary.

Recently, a number of genetic discoveries have put the mitochondria back into the focus of PD research.

Particularly striking is the fact that the three recessive PD genes, which have been identified, all seem to be linked to mitochondrial function. As these recessive genes probably act via loss of function mechanisms.

The first recessive PD gene, parkin (PARK2) which is the gene most commonly mutated in patients with early-onset recessive parkinsonism. It encodes a predominantly cytoplasmic protein which functions as a E3-protein ligase. E3-ligases are important components in the proteasomal protein degradation process, which eliminates misfolded or otherwise damaged proteins. Recently however, parkin has clearly been linked to mitochondrial function: for example, a drosophila model lacking the parkin gene have been shown to exhibit reduced lifespan, locomotor defects, and male sterility. The locomotor defects derive from apoptotic cell death of muscle

subsets, and a mitochondrial pathology is the earliest manifestation of muscle degeneration in parkin mutants. These results indicate that the tissue-specific phenotypes observed in *Drosophila* parkin mutants result from mitochondrial dysfunction and raise the possibility that similar mitochondrial impairment triggers the selective cell loss observed in AR-JP (1).

The second recessive PD gene to be identified was Pten-induced Kinase 1 (PINK-1). This protein contains a mitochondrial targeting sequence and has been shown to locate to mitochondria (2). The third PD-gene DJ-1, also appears to be a sensor for oxidative stress, again a process intimately linked to mitochondrial function, as mitochondria are the major source of radical oxygen species (3).

The fact that the three "loss-of-function" PD genes are closely linked to mitochondrial integrity suggests that mitochondria play a pivotal and primary role in the pathogenic process of PD.

In support of this hypothesis, a recent study by Bender et al., showed that in substantia nigra neurons from both aged controls and individuals with Parkinson disease, there is a high level of deleted mitochondrial DNA (mtDNA) (controls, 43.3% +/- 9.3%; individuals with Parkinson disease, 52.3% +/- 9.3%). These mtDNA mutations are somatic, with different clonally expanded deletions in individual cells, and high levels of these mutations are associated with respiratory chain deficiency. These studies suggest that somatic mtDNA deletions are important in the selective neuronal loss observed in brain aging and in Parkinson disease. (4)

1. J. C. Greene *et al.*, *PNAS* **100**, 4078 (2003).
2. E. M. Valente *et al.*, *Ann Neurol* **56**, 336 (2004).
3. N. Lev, *et al.*, *J Mol Neurosci* **29**, 215 (2006).
4. A. Bender *et al.*, *Nat Genet* **38**, 515 (2006).