# Newsletter
# der
# Deutschen Gesellschaft für Neurogenetik

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## *Society News*

The 10th Annual Meeting (11th Workshop "Neurogenetics in Germany") was held in Hamburg from Sept 9 to 11, 2004. At this meeting, the founding president of the Society, Prof. Ulrich Müller, Giessen, stepped down after ten years of outstanding service. Under his leadership, the Society became a well-known and respected institution in Germany. He shaped the unique format of the Annual Conferences, where young German scientists interested in Neurogenetics got the chance to present their data and to discuss research with internationally recognized experts in the field. Key-note speakers at these conferences included such illustrious names as Chris Ross (Baltimore) in 1997 in Bochum on "dynamic mutations", Konrad Beyreuther (Heidelberg) in 2000 in Dresden on Alzheimer's disease, or Anders Björklund (Lund) in 2001 in Magdeburg on the use of stem cells for brain repair. The experience of the Annual meetings has become a cherished tradition to many of us.

The Neurogenetics community in Germany owes, in good part, to Ulrich Müller that this field is widely recognized as one of the most dynamic and fascinating fields in modern biomedical research, that talented young researchers are attracted, and that German science plays an internationally visible role.

The other members of the board, Vice-president Prof. Riess, Tübingen, and Prof. Landwehrmeyer, Ulm, also stepped down after fulfilling their term. We are grateful to both of them for their tireless support. The Society is also particularly indebted to Dr. Angelika Köhler, who served as treasurer, and who can claim the credit for the Society being financially sound.

At the Hamburg meeting, a new board has been elected. Incoming president, Prof. Thomas Gasser, Tübingen, Vice-President PD Dr. Ulrich Finckh, Hamburg, and secretary Prof. Matthias Riemenschneider, München, thanked Prof. Müller and his team in the name of the entire membership of the Society for their outstanding service and pledged to continue the work in their spirit. As the new treasurer of the society, PD Dr. Daniela Berg was elected, and the new board expressed its gratitude that she will take on this laborious task.

These changes will not have any technical consequences for the members. Although the new location of the Society will be Tübingen, all financial affairs will be transacted via the same accounts as before

The leadership of the Society has changed, but the challenge to promote Neurogenetics in Germany, remains.

The 11th Annual Meeting (12th Workshop "Neurogenetics in Germany" will be held in Münster from September 8th to September 10th. Main topics will be: hereditary neuropathies, multiple sclerosis and stroke. As in the previous meetings, a number of outstanding and internationally renowned speakers, will provide an up-to-date overview of the field, and will be available to discuss

novel findings with the congress participants. The new board of the Society is looking forward to meeting you all there.

Thomas Gasser
Ulrich Finckh
Matthias Riemenschneider

# *Research News*

***LRRK2-mutations are common in autosomal-dominant Parkinson's disease***

The latest addition to the growing list of cloned genes that cause monogenic forms of Parkinson's disease (PD) is the LRRK2-gene (leucine rich repeat kinase 2) on chromosome 12 (PARK8). This locus had been mapped in a Japanese family with a dominant form of PD. Recently, mutations in the gene for LRRK2 were simultaneously reported by two groups (Paisan-Ruiz et al., 2004; Zimprich et al., 2004). The gene spans a genomic region of 144 Kb, with 51 exons encoding 2527 amino acids. The gene is expressed in all tissues examined, although at low levels (Genbank entry number AY792511).

LRRK2-associated Parkinson's disease is remarkable for several reasons. Mutations in the LRRK2 gene appear to be the most common cause of autosomal-dominantly inherited parkinsonism detected so far. Four different mutations were detected in five of 34 dominant families studied by Zimprich et al. The same codon was affected in the group of Basque families studied by Paisan-Ruiz et al., but this mutation resulted in a different amino acid exchange. Paisan-Ruiz et al described a founder-mutation occurring in a considerable proportion of patients with dominantly inherited PD from the Basque population.

Another particularly common mutation, Gly2019Ser, was found on a founder haplotype in several European populations (Kachergus et al., 2005) and in up to 5–6% of several large cohorts of families with dominant parkinsonism, and even in 1–2% of patients with sporadic late-onset disease wood (Gilks et al., 2005). It will take some time until the full spectrum of mutations in this very large gene will be elucidated in different populations, but based on the present knowledge it already can be expected that their clinical relevance will surpass that of previously detected PD-mutations, particularly with respect to genetic counselling..

Clinical signs and symptoms of LRRK2-related PD resemble typical sporadic Parkinson's disease in most families. This is true also for age of onset, which is on average in the late 50s and 60s in the families described so far, but seems to be highly variable, as is the severity of the disease, even within single families. Therefore, of the Parkinson's disease genes identified so far, LRRK2 is the one most likely to play a role in the setting of typical sporadic late-onset Parkinson's disease.

Another interesting aspect of LRRK2-associated PD is that the associated pathology is remarkably variable. Pathologic changes include abnormalities consistent with Lewy body Parkinson's disease, diffuse Lewy body disease, nigral degeneration without distinctive histopathology and progressive supranuclear palsy-like tau aggregation. LRRK2 mutations may therefore be an upstream event in the cascade leading to neurodegeneration with different pathologies.

By sequence homology, LRRK2 can be assigned to the group of recently identified ROCO-proteins and contains a highly-conserved protein kinase domaine which belongs to the MAPKKK-class of kinases, suggesting a role in intracellular signalling

pathways, but its precise function remains to be determined.
It will be interesting to see the molecular pathways involved in the LRRK2-signalling cascade being unravelled. As many of the most common mutations affect the kinase domaine, this function may be critical in the molecular pathogenesis of PD, and may be even promise for pharmacologic manipulation.

Gilks WP, Abou-Sleiman PM, Gandhi S, Jain S, Singleton A, Lees AJ, et al. A common LRRK2 mutation in idiopathic Parkinson's disease. Lancet 2005; 365: 415-6.

Kachergus J, Mata IF, Hulihan M, Taylor JP, Lincoln S, Aasly J, et al. Identification of a Novel LRRK2 Mutation Linked to Autosomal Dominant Parkinsonism: Evidence of a Common Founder across European Populations. Am J Hum Genet 2005; 76: 672-80.

Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der Brug M, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 2004; 44: 595-600.

Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, et al. Mutations in LRRK2 Cause Autosomal-Dominant Parkinsonism with Pleomorphic Pathology. Neuron 2004; 44: 601-7.

### *SNPs in FKBP5, a co-chaperone of the glucocorticoid-receptor, are associated with response to antidepressants*

The genetic basis of affective disorders is one of the most challenging topics in Neurogenetics. Despite unequivocal evidence for a major genetic contribution to this common group of disorders, the underlying genetic variants have remained elusive. However, the long and hard work put into defining the genetic basis of complex neurobehavioural and psychiatric disorders by carefully selecting and characterizing patient populations over many years finally seems to pay off. In a recent study, a consortium funded within the National Genome Network (NGFN) by the German Ministry of Education and Research (BMBF) has identified, through a candidate gene association study approach, SNPs in the gene for FKBP5, a co-chaperone of the glucocorticoid receptor (Binder et al., 2004) to be highly associated with the response of depressive symptoms towards pharmacotherapy. The endocrine action of glucocorticoid, particularly cortisone, as “stress hormone” have long been implicated in the regulation of affect and mood, and a dysregulation of the pituitary-pituitary-adrenal axis (HPA axis) is known as a biological marker for depression, although its causal role is still uncertain. The results of this study, showing an association with a p-value of 5.5x10-6 and an odds ration of 28, suggest that individuals carrying the associated genotypes had less HPA-axis hyperactivity during the depressive episode and that the FKBP5 variant-dependent alterations in HPA-axis regulation could be related to the faster response to antidepressant drug treatment and the increased recurrence of depressive episodes observed in this subgroup of depressed individuals. These findings support a central role of genes regulating the HPA axis in the causality of depression and the mechanism of action of antidepressant drugs.
The identified variant SNPs also seem to be associated with an alteration of the expression level of the FKBP5 protein, providing at least a testable biologic basis for this observation.
This remarkable study also demonstrates that association studies can be a highly effective way to identify genetic contributions to complex phenotypes once the prerequisites for a successful association study are

fulfilled: a clear and well-founded biologic hypothesis, a sufficient sample size of carefully characterized patients and controls, and a replication sample (for this study still unpublished, but successfully examined; S. Lucae, personal communication).

Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, Putz B, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet 2004; 36: 1319-25.

***Recovery from Polyglutamine-induced neurodegeneration***

Pathologic expansion of polyglutamine domains in a number of proteins are associated with several neurodegenerative diseases, such as Huntington's disease and the spinocerebellar ataxias. It is thought that, following cleavage by caspases, the polyglutamine-containing fragment translocates to the cell nucleus, where it aggregates and exerts its deleterious action, leading to a cell-type specific and progressive neurodegenerative process. These findings have lead to significant process in the diagnosis and classification of the heterogeneous group of neurodegenerative diseases, but unfortunately so far have not translated into novel successful treatment strategies. This is due to the fact that the mechanisms by which polyglutamine expansions cause cellular damage have been subject to a large number of studies in different models, but essentially remain unknown. Recently, Tao Zu and colleagues from the group of Harry Orr have taken those studies a step further, and have provided hope that the progress in Neurogenetics may eventually translate into tangible improvement of therapy for the patients. Zu et al. have constructed a transgenic mouse line that expresses the SCA1-gene (ataxin 1) with an expanded polyglutamine (82Q) in P Purkinje-cells in a tetracycline-dependent manner (Tet-Off-System). By adding tetracycline or its derivative doxicycline to the diet of the animals, the transgene expression can be turned off nearly completely. (Zu et al., 2004). After cessation of SCA1[82Q] transgene expression, mutant ataxin-1, including that in nuclear inclusions, was cleared rapidly from Purkinje cells. At an early stage of disease, Purkinje cell pathology and motor dysfunction were completely reversible. After halting SCA1 expression at later stages of disease, only a partial recovery was seen. Interestingly, restoration of the ability to perform a complex motor task, the accelerating Rotarod, correlated with localization of mGluR1alpha to the Purkinje cell-parallel fiber synapse. These results show that the progression of SCA1 pathogenesis is dependent on the continuous expression of mutant ataxin-1. Of note, even at a late stage of disease, Purkinje cells retain at least some ability to repair the damage caused by mutant ataxin-1. A similar approach several years ago using the mutant Huntingtin gene has provided similar results (Yamamoto et al., 2000). Findings like these are beginning to bridge the gap between the astonishing progress that Neurogenetics has made in the analysis of the genetic mechanisms underlying these diseases and the relative lack of therapeutic options.

Yamamoto A, Lucas JJ, Hen R. Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. Cell 2000; 101: 57-66.

Zu T, Duvick LA, Kaytor MD, Berlinger MS, Zoghbi HY, Clark HB, et al. Recovery from polyglutamine-induced neurodegeneration in conditional SCA1 transgenic mice. J Neurosci 2004; 24: 8853-61.