

# Newsletter der Deutschen Gesellschaft für Neurogenetik

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## *Society News*

The German Society for Neurogenetics is continuing to flourish. The society is intensifying its connection with other scientific societies, for example by participating in the organization of a symposium at the XX. International Congress of Genetics in Berlin in 2008. The society is also active in the communication with other societies within the VdBiol (Verband Deutscher Biologen e.V.).

The 11<sup>th</sup> Annual Meeting of the Society was held in Münster, from Sept 8 to 10, 2005. As in the previous meetings, a number of outstanding and internationally renowned speakers, have covered interesting topics in the rapidly moving field of Neurogenetics. As is customary during the annual meetings, one or several of the topics reflects the scientific interests of the host institution. During the last conference, the genetics of hereditary neuropathies, an area that has received major input from the Münster group, was reviewed by several internationally known speakers. In addition to clinical and molecular aspects of the increasingly complex family of CMT-disorders, the emerging role of genomic duplications in the aetiology of complex neurological phenotypes was covered by Dr. Lupski from Houston, USA. Further featured topics included the genetics of multiple sclerosis and of stroke syndromes.

As in previous years, the meeting provided an up-to-date overview of the field, allowed young researchers to network with accomplished scientists in the field, and, last not least, gave us all

the opportunity to meet some old friends. The society will continue this cherished tradition, with the **12<sup>th</sup> Annual Meeting of the Society for Neurogenetics**, to be held in **Rostock, October 12 to 15, 2006**. As always the programme will be stimulating. Please visit the registration site at: <http://www.dgng.med.uni-rostock.de/>. The board of the society is looking forward to meeting you all there.

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Matthias Riemenschneider

## *Research News*

### ***Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study***

Anderson-Fabry disease is an X-linked lysosomal storage disease that results from a deficiency of the enzyme  $\alpha$ -galactosidase ( $\alpha$ -GAL) leading to accumulation of glycosphingolipids, primarily globotriasylceramide (Gb3/GL3). Without this enzyme, GL-3 accumulates within the vascular epithelium, kidneys, cornea, heart, and other tissues, causing renal failure, painful acroparesthesias, typical angiokeratoma, hypohydrosis, and cardiac failure. In the central nervous system (CNS), diffuse storage occurs in the vascular endothelium. The incidence of stroke together with

vessel ectasia is about 40% in hemizygous males; mainly younger subjects seem to be affected. The cerebrovascular manifestations consist of large-vessel ectasia, large vessel occlusive disease, and small vessel disease; the vascular diathesis is reported to have a vertebrobasilar circulation distribution, although the reason for this is unclear. PET investigations suggest a chronic alteration of the nitric oxide pathway. On the other hand there exists an increased endothelium-mediated vascular reactivity, where the increased vessel response to acetylcholine suggests altered function of non-NO endothelium-dependent vasodilatory pathways. Recently, enzyme replacement therapy (ERT) has become available.

The worldwide incidence of stroke in young adults (aged 16-55) is estimated to be nine to 14 per 100.000 people. In the United States the National Survey of Stroke reports that 3.7% of all strokes occur in patients aged 15 to 45 years. Approximately 20 - 30% of ischemic stroke is considered cryptogenic, ie, no specific cause can be identified.

721 German adults aged 18 to 55 years suffering from acute cryptogenic stroke were screened for Fabry disease. The plasma  $\alpha$ -galactosidase activity in men was measured followed by sequencing of the entire  $\alpha$ -GAL gene in those with low enzyme activity. By contrast, the entire  $\alpha$ -GAL gene was genetically screened for mutations in women even if enzyme activity was normal.

21 of 432 (4.9%) male stroke patients and seven of 289 (2.4%) women had a biologically significant mutation within the  $\alpha$ -GAL gene. The mean age at onset of symptomatic cerebrovascular disease was 38.4 years (SD 13.0) in the male stroke patients and 40.3 years (13.1) in the female group. The higher frequency of infarctions in the

vertebrobasilar area correlated with more pronounced changes in the vertebrobasilar vessels like dolichoectatic pathology (42.9% vs 6.8%).

The most important result of the study is the high frequency of Fabry disease (4%, 28/721) in this cohort of stroke patients with cryptogenic stroke aged between 18 and 55 years. Fabry disease must be considered in all cases of unexplained stroke in young patients, especially in cases with the combination of infarction in the vertebrobasilar artery system and proteinuria.

In an accompanying editorial Schiffmann and Ries from the NINDS have stated that the prediction made by Rolfs and co-workers that Fabry disease might correspond to a prevalence of about 1.2% in the general stroke population aged 18–55 years seems to underestimate the real situation. Fabry's disease is itself a risk factor for accelerated atherosclerosis and cardiac and renal disease, which can lead to emboli and hypertension. According to the authors it is therefore unlikely that patients with Fabry's disease would not be found among patients with stroke of known cause. Thus the group studied seems to have shared many clinical characteristics with the general stroke population.

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Rolfs et al., Lancet, 2005, 366, 1794-1796

### ***Positional cloning and functional analysis of a third gene for familial hemiplegic migraine***

Familial hemiplegic migraine (FHM) is a rare and severe subtype of migraine with aura; it is characterized by an autosomal-dominant mode of inheritance and the presence of some degree of hemiparesis during the aura. Previously, mutations in two different genes, *CACNA1A* encoding a neuronal

voltage-gated calcium channel (FHM1) (Ophoff et al. 1996) and *ATP1A2* encoding an astrocytic Na<sup>+</sup>/K<sup>+</sup>-pump (FHM2) (De Fusco et al. 2003) have been reported in affected pedigrees.

Recently, genome-wide linkage analysis in two families without mutations in *CACNA1A* and *ATP1A2* led to the identification of a novel genetic locus for FHM on chromosome 2q24 (FHM3). Sequencing analysis of candidate genes revealed a heterozygous missense mutation (Q1489K) in exon 23 of *SCN1A* in the two families used for genome-wide linkage as well as one additional family (Dichgans et al. 2005). Meanwhile, further mutations have been detected in other families (*unpublished data*).

*SCN1A* encodes the pore-forming alpha subunit of a voltage-gated sodium channel which is expressed on cortical neurons and is responsible for the generation and propagation of action potentials in the human brain. The Q1489K mutation affects a highly conserved amino acid residue within a short cytoplasmic linker domain which connects the third and fourth transmembrane domain of *SCN1A*; this region is known to be critical for fast inactivation of sodium channels by a so called 'hinged-lid' mechanism.

The functional properties of the Q1489K mutation were studied electrophysiologically using an expression construct of the highly homologous human *SCN5A* sodium channel, which is expressed in the myocardium and has similar functional properties as *SCN1A*. Patch-clamp experiments revealed a 2- to 4-times faster recovery of mutant *SCN5A* channels from fast inactivation (Dichgans et al. 2005).

This finding fits into current concepts of migraine pathophysiology. The migraine aura is thought to be caused by a phenomenon called cortical spreading depression (CSD); CSD consists of an initial brief spike of

increased neuronal activity followed by long-lasting suppression which spreads across the cortex at 1 – 3 mm/s. The faster recovery of mutant sodium channels from inactivation, as observed with the *SCN5A* homologue, is predicted to allow higher action potential rates and thus may cause an increased susceptibility for CSD.

Mutations in *SCN1A* have previously been associated with two severe hereditary epilepsy syndromes (GEFS+ type 2 and SMEI); the functional consequences of these mutations are usually more pronounced than that of *SCN1A* Q1489K, which would account for the more severe clinical phenotype.

The phenotype of all FHM families with *SCN1A* mutations studied so far is that of 'pure' FHM. In other words, interictal cerebellar signs, as described for about 50% of families with FHM1, are not present in patients with FHM3.

Future studies will have to investigate the significance of *SCN1A* for sporadic hemiplegic migraine (SHM) as well as for the more common, genetically complex forms of migraine, i.e. migraine with and without aura.

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De Fusco, et al. Haploinsufficiency of *ATP1A2* encoding the Na<sup>+</sup>/K<sup>+</sup> pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet* 2003; 33(2): 192-6.

Dichgans et al, Mutation in the neuronal voltage-gated sodium channel *SCN1A* in familial hemiplegic migraine. *Lancet* 2005; 366(9483): 371-7.

Ophoff et al., Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca<sup>2+</sup> channel gene *CACNL1A4*. *Cell* 1996; 87(3): 543-52.

## Genetics of multiple sclerosis

Numerous genes have been analyzed in regard to contribute to multiple sclerosis (MS) susceptibility. So far eleven genome wide linkage analyses have been performed in MS using microsatellite markers (density 10 cM). None of these studies showed a

genome wide significance for a defined gene region. Recently, a linkage analysis in MS was published with 4506 SNP markers in 2692 individuals from 730 families with multiple individuals with MS from Australia, Scandinavia, England and USA. (Sawcer et al., 2005). Linkage was only found for the major histocompatibility complex (MHC, 6p21, Maximum LOD Score 11.66). The authors underscore that the lack of evidence for additional genetic loci besides MHC does not rule out that these have an influence on MS, but all studies which have been done so far have insufficient power.

The MHC influence in MS was first reported in the 70ies. There has been a long standing debate on which genes within the MHC are associated with MS (MHC in man is called HLA and is a 3.6 Mb region with about 120 expressed genes). Recently ample evidence with SNP markers covering the complete MHC region was obtained indicating that the main disease association exists for the MHC class II genes and mainly with *HLA-DRB1* (Lincoln et al., 2005). *HLA-DRB1\*15* and to a lower degree *HLA-DRB1\*17* are positively associated with MS and *HLA-DRB1\*14* is negatively associated with MS (Dyment et al., 2005). MS patients with *HLA-DRB1\*1501* have a more severe disease course compared with other haplotypes (Barcellos et al., 2003).

In order to define genes outside the MHC contributing to MS susceptibility a very interesting study was performed in which variations in the incidence of MS in populations with different ethnic and geographic background were analysed (admixture scan). In African Americans an association with a locus on chromosome 1 was found (Reich et al, 2005).

In summary and perspective the only definite genetic association exists for

the MHC class II genes in MS. All other reported linkages and associations for genes or gene regions with MS are not valid due too small numbers of analyzed individuals (false positives). In the future associations studies have to be performed with very large cohorts. The reported approach with 'admixture scans' will possibly contribute to map genes outside the MHC region. Additionally genetic analysis of animal models of MS (experimental autoimmune encephalomyelitis, EAE) by using crosses of susceptible and non-susceptible strains of mice or rats seems to be a promising tool to map genes which contribute to susceptibility and disease course. Subsequently, genes with influence in EAE can be analyzed in MS patients and controls with association studies. Furthermore it is of outstanding importance to define the functional influence of MHC on the molecular level in MS. A better understanding of MHC function might ultimately open up new avenues for therapeutic interventions in MS.

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Barcellos et al, 2003. HLA-DR2 dose effect on susceptibility to multiple sclerosis and influence on disease course. *Am J Hum Genet* 72:710-716.

Dyment et al, 2005. Complex interactions among MHC haplotypes in multiple sclerosis: susceptibility and resistance. *Hum Mol Genet* 14:2019-2026.

Lincoln et al., 2005. A predominant role for the HLA class II region in the association of the MHC region with multiple sclerosis. *Nat Genet* 37:1108-1112.

Reich et al., 2005. A whole-genome admixture scan finds a candidate locus for multiple sclerosis susceptibility. *Nat Genet* 37:1113-1118.

Sawcer et al, 2005. A high-density screen for linkage in multiple sclerosis. *Am J Hum Genet* 77:454-467.