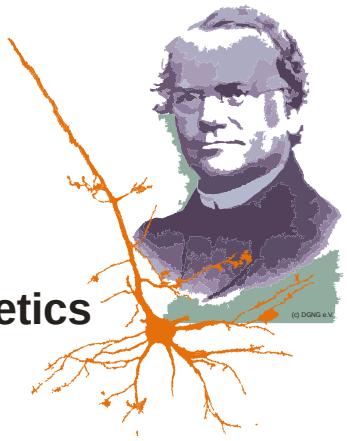
Newsletter 25 DGNG

German Society of Neurogenetics



Newsletter
der Deutschen Gesellschaft für Neurogenetik
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DGNG News Nr. 25

Society News

THE German Society for Neurogenetics (DGNG) strives to promote all areas of neurogenetic research. Neurogenetics is a constitutively interdisciplinary field, which depends heavily on a close collaboration between clinical neurologists, neuroscientists and human geneticists. This is becoming more and more evident, as technologies advance and our knowledge on genes and genomes and everything beyond becomes more and more complex.
Prerequisite for this collaboration is, before all, a mutual understanding. Despite best efforts on all sides, this is sometimes not easy, as clinicians and basic scientists seem to talk in different languages.
The annual congress of the Society, as well as the biannual newsletters, attempt to bridge this gap between science and clinical practice, bench and bedside.
In a **"DGNG - Minireview"**. this newsletter therefore summarizes the latest advances in one of the most active fields in neurogenetics, the genetics of spastic paraplegias, as viewed by a clinical neurologist working also at the lab bench.

With this issue, the board of the society wants to start a tradition of contributions of this sort, provided by members of the society, both from neurology and from human genetics, attempting to appeal to both crowds.

AS a complementation of its existing activities, the German Society for Neurogenetics is particularly committed to promoting young researchers. The society therefore announces an

Annual Junior Research Award of the German Society for Neurogenetics

to be awarded for the first time at the annual meeting, to be held from Sept 24 to 27, in Lübeck. 2000 Euro will be awarded for a paper, published within the last year or submitted to a peer-reviewed journal. Submission of papers resulting from a collaboration of clinical neurologists and human geneticists are particularly encouraged. **Submission deadline is August 15, 2008.** (submissions, contained in a single pdf-file including a cover-letter, the full paper and a brief CV of the applicant should be sent to the

secretariat of the DGNG (Elvira.Biesienger@uni-tuebingen.de)

With this Newsletter, the board also invites all members of the DGNG to attend the **annual business meeting** of the society, which will be held during the Annual Meeting, on Sept. 26th, 2008, at 1 p.m.

Agenda:

1. President's report
2. Secretary's report
3. Junior Research Award
4. Working group on hereditary movement disorders
5. DNA repositories
6. Development of the homepage of the DGNG
7. Further issues

The board of the DGNG is looking forward and the local organizers are looking forward to seeing you all in Lübeck.

Thomas Gasser
President of the DGNG

Peter Bauer
Vice-President of the DGNG

Daniela Berg
Secretary of the DGNG

DGNG Mini-Review

Autosomal Recessive Hereditary Spastic Paraplegia (AR-HSP)

In the dynamic field of genetically heterogeneous hereditary spastic paraplegias (HSP) it is hard to keep updated on the ever growing number of genetic loci and genes.

In autosomal dominant HSP, known HSP genes account for >70% of familial cases, SPG4, SPG3, SPG31 and SPG10 being the major players (in decreasing order of frequency).

In autosomal recessive HSP (AR-HSP), the number of published loci has increased to 15 [1]. Until recently however, only three recessive HSP genes were known: the SPG7 gene paraplegin, which accounts for about 5% of AR-HSP, spartin (SPG20) and maspardin (SPG21), mutations in which are rarely found outside the Amish population.

Since 2007 however, two major genes for autosomal recessive complicated HSP have been published: SPG11 and SPG15.

SPG11 is the most common cause of AR-HSP with thin corpus callosum (TCC) and cognitive impairment

The SPG11 locus has been originally mapped to chromosome 15q 9 years ago [2]. In 2007, G. Stevanin and colleagues from the Alexis Brice group, Paris, succeeded in identification of the SPG11 gene [3]. 10 different mutations in spatacsin, a 40 exon gene on chr. 15q21.1, were reported in 11 SPG11-linked families. Since then, a number of mutation screenings has identified further mutations in SPG11 linked families as well as sporadic cases [4-6].

Age at onset in SPG11 mutation carriers varied between 2 and 31 years of age. A thin corpus callosum (TCC), especially in its rostral parts, is the

hallmark of the SPG11 phenotype. It is present in the vast majority of reported SPG11 cases (>90%) and is the best single indicator for SPG11 in complex HSP [5]. Other MRI features include frontal cortical atrophy and bilateral periventricular white matter changes.

Clinically, mental retardation is commonly present and reported to worsen with disease progression [3, 4]. Other prominent features include pseudobulbar dysarthria (54-85%), marked atrophy of intrinsic hand muscles (~45%) and presence of a mixed axonal demyelinating peripheral neuropathy (56-72%). Other complicating signs like cataract, retinitis pigmentosa, cerebellar signs or optic atrophy have been infrequently reported.

So far only selected cases with complicated HSP fitting the initial description of the SPG11 phenotype have been included in screenings; the actual phenotypic spectrum of SPG11 might therefore be broader than so far published.

The spectrum of spatacsin mutations observed in SPG11 indicates a loss-of-function disease mechanism. About 50 different spatacsin mutations have been reported; they are spread over almost all exons and are mostly private mutations. The majority of mutations is truncating, including nonsense mutations (21%), small deletions or insertions leading to a consecutive frameshift (66%) and splice site mutations (13%).

SPG11 accounts for 59% of AR-HSP with cognitive impairment and TCC; it is as rare as 4.5% however in cases without TCC [5].

The SPG15 phenotype is very similar to the SPG11 phenotype

SPG15 was first mapped to chromosome 14q by C.A. Hughes and colleagues [7]. A few months ago, the SPG15 gene was identified [8]. Spastizin, the product of the 42 exon gene ZFYVE26, belongs to the FYVE domain containing family of proteins that is involved in regulation of endocytic membrane trafficking [8].

Six different truncating ZFYVE26 mutations were reported in eight consanguineous SPG15-linked families, including two nonsense mutations, one frameshift deletion, one splice site mutation and one complex indel-inversion rearrangement.

As SPG15 has been only examined in linked families so far, frequency of this form of complex AR-HSP is unknown.

The phenotype of SPG15 is virtually indistinguishable from SPG11. Age at onset ranges from 5-19 years. Cognitive impairment (73%), peripheral neuropathy (67%), TCC (64%) and white matter abnormalities (36%) occur at similar frequencies as in SPG11. Additionally mild cerebellar signs (36%) and less frequently other signs or symptoms like hearing deficits or retinal degeneration have been described.

In conclusion, SPG11 as well as SPG15 have to be considered in autosomal recessive or sporadic cases of young onset (<40 years) HSP with TCC with or without further complicating features like mental retardation or peripheral neuropathy.

As mutation types in both genes indicate a loss of function mechanism, it would be certainly worthwhile to screen for larger deletions as well. An MLPA assay however, that has been implemented in routine diagnostic testing for SPG3/4/31 at many institutions, is not yet available.

1. Dick, K.J., et al., A novel locus for an autosomal recessive hereditary spastic paraplegia (SPG35) maps to 16q21-q23. Neurology, 2008.

2. Martinez Murillo, F., et al., Genetic localization of a new locus for recessive familial spastic paraparesis to 15q13-15. Neurology, 1999. 53(1): p. 50-6.

3. Stevanin, G., et al., Mutations in SPG11, encoding spatacsin, are a major cause of spastic paraplegia with thin corpus callosum. Nat Genet, 2007. 39(3): p. 366-72.

4. Hehr, U., et al., Long-term course and mutational spectrum of spatacsin-linked spastic paraplegia. Ann Neurol, 2007. 62(6): p. 656-65.

5. Stevanin, G., et al., Mutations in SPG11 are frequent in autosomal recessive spastic paraplegia with thin corpus callosum, cognitive decline and lower motor neuron degeneration. Brain, 2008. 131(Pt 3): p. 772-84.

6. Paisan-Ruiz, C., et al., SPG11 mutations are common in familial cases of complicated hereditary spastic paraplegia. Neurology, 2008. 70(16 Pt 2): p. 1384-9.

7. Hughes, C.A., et al., SPG15, a new locus for autosomal recessive complicated HSP on chromosome 14q. Neurology, 2001. 56(9): p. 1230-3.

8. Hanein, S., et al., Identification of the SPG15 gene, encoding spastizin, as a frequent cause of complicated autosomal-recessive spastic paraplegia, including Kjellin syndrome. Am J Hum Genet, 2008. 82(4): p. 992-1002.

(contributed by Rebecca Schüle, M.D., Tübingen)