Newsletter
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Society News

The 10th Annual Meeting of the DGNG (11th workshop Neurogenetics in Germany) will be held in Hamburg from September 9 to September 11, 2004. The conference will be organized by Drs. Ulrich Finckh, Alexander Münchau, and Alexander Spauschus. Emphasis of the meeting will be on neurodegeneration, dementia, cognition, and dystonia. A link to details of the conference and registration forms will be available on the DGNG web site shortly.

We are pleased to announce that Professor Peter Propping/Bonn, the first vice president of our society has been honoured with the Mendel-Medaille der Leopoldina for his "Verdienste in der genetischen Analyse complexer Krankheiten". Society member Professor Lehmann-Horn/Ulm, the organizer of the second annual meeting of our society (third workshop on neurogenetics in Germany) in 1996 has received an honorary doctorate from the University Debrecen/Hungary for his "profound international achievements".

10th Workshop on Neurogenetics, 9th Annual Meeting of the Deutsche Gesellschaft für Neurogenetik e.V., Tübingen, September 21st-23rd 2003.

The 2003 annual workshop focussed on Parkinson's disease, trinucleotide repeat disorders, and on approaches to the analysis of complex diseases. Abstracts of all contributions to the meeting have been published in Medizinische Genetik 15: 235-246, 2003.

The highlight of the meeting was the keynote lecture of Ryosuke Takahashi (Saitama/Japan) on the genetics of Parkinson disease. He gave an overview of our current understanding of the role of parkin in Parkinson's disease. A wealth of findings points to a crucial role of the endoplasmatic reticulum (ER) in parkin-induced neuronal cell death. Thus the parkin ligand Pael (parkin-associated endothelin receptor-like)-receptor (R) that was discovered in a yeast-two hybrid screen is a G-protein-coupled trans-membrane protein located in the ER. In humans, Pael-R is highly expressed in the substantia nigra. Takahashi demonstrated that the Pael-R unfolds, becomes insoluble and is ubiquitinated when overexpressed in eucaryotic cells in vitro thus causing ER stress-induced cell death. (Abnormal accumulation of unfolded proteins in the ER is a major threat to cell viability. This is called "unfolded protein stress" or ER stress). Furthermore, Takahashi showed that wild-type parkin is involved in ubiquitination of the Pael-R in the presence of ER-resident E2s, i.e. ubiquitin-conjugating enzymes. Parkin promotes the degradation of unfolded Pael-R, thus suppressing cell death that is induced by the accumulation of unfolded Pael-R in the ER. Consistent with these in vitro findings, Takahashi detected that the insoluble

(unfolded) form of Pael-R accumulates in the brains of patients with autosomal recessive juvenile parkinsonism caused by mutations in parkin.

The findings by Takahashi were complemented by discoveries reported by Michael Schlossmacher (Boston, USA). Schlossmacher demonstrated primate-specific glycosylation of ?-synuclein (Park1) that is required for interactions with parkin's ubiquitin ligase activity. Strikingly, this specific glycosylation was most prominent in substantia nigra, whereas in cortical preparations ?-synuclein was glycosylated to a lesser extent. This work suggests functional, primate-specific links between ?-synuclein (PARK1) and parkin (PARK2) pathophysiology even in sporadic cases.

(contributed by Peter Bauer)

Research News

Type 2 myotonic dystrophy originated by founder effect in European populations. Myotonic dystrophy (DM) is a genetically heterogeneous autosomal dominant disorder. Clinical features include myotonia, muscular dystrophy, cardiac conduction defects, cataracts, and endocrine abnormalities. To date two disease genes have been identified in DM, one on chromosome 19 (DM1), the other one on chromosome 3 (DM2). The more common DM1 is caused by a CTG expansion in the 3´untranslated region of the dystrophia myotonica-protein kinase (DMPK) gene. The genetic defect in DM2 is a CCTG expansion in intron 1 of zinc finger protein 9 (ZNF9). It has been known for some time that DM1 originated from a single 30 kb haplotype in individuals of European ancestry. Now two studies (Liquori et al., 2003; Bachinski et al., 2003) demonstrate that DM2 also derived from a common founder in European populations. The structure of the DM 2 repeat in ZNF9 is $(TG)_n$ $(TCTG)_n(CCTG)_n$ GCTG CCTG TCTG $(CCTG)_n$ in the general population. In patients, however, the CCTG portion of the repeat is uninterrupted, greatly elongated, and highly unstable. Liquori et al. detected that a single haplotype flanks the CCTG expansion in affected individuals of Northern European ancestry. They also found an uninterrupted $(CCTG)_{20}$ on a haplotype identical to the most common affected haplotype. This might represent a premutation of the disease and indicates that loss of interruptions within CCTG predisposes to further repeat expansion. Bachinski et al. also describe that DM2 individuals share a common haplotype. The authors estimate that the founding haplotype and the DM2 CCTG expansion mutation originated 200-540 generations ago.

Bachinski LL *and 22 co-authors* (2003) Confirmation of the type 2 myotonic dystrophy $(CCTG)_n$ Expansion mutation in patients with proximal myotonic myopathy/proximal myotonic dystrophy of different European origins: a single shared haplotype indicates an ancestral founder effect. Am J Hum Genet 73: 835-848.

Liquori CL, Ikeda Y, Weatherspoon M, Ricker K, Schoser BGH, Dalton JC, Day JW, Ranum LPW (2003) Myotonic dystrophy type 2: human founder haplotype and evolutionary conservation of the repeat tract. Am J Hum Genet 73: 849-862.

Potential modifiers of age at onset in Huntington disease. Huntington disease (HD) is caused by a CAG expansion in exon 1 of the huntingtin gene. A correlation between age at onset and repeat size has been well established by the analysis of large cohorts of patients. However, repeat size does not predict age at onset at the level of the individual and great variation exists in carriers of repeats of the same length. This suggests the existence of additional factors modifying age of onset in HD. Given that the unexplained variation in age at onset is strongly heritable, the

genetic background is thought to play an important role. Li et al. (2003) have performed a whole genome scan to search for loci modifying the age at onset in the disease. They studied 629 affected sib pairs and found evidence of such loci on both the long and the short arm of chromosome 6 and – less significantly – on the short arm of chromosome 4, the location of the huntingtin gene. These findings are a first step towards the identification of genes that modify age of onset in HD which would allow more precise prediction of disease onset in individual carriers of CAG expansions.

Li J-L *and 38 co-authors* (2003) A genome scan for modifiers of age at onset in Huntington disease: the HD MAPS study. Am J Hum Genet 73: 682-687.

Synphilin-1 mutations in sporadic Parkinson disease. Synphilin-1 is encoded by the gene *synphilin-1* on chromosome 5p and is implicated in the pathogenesis of Parkinson disease (PD). It interacts with ?-synuclein (PARK1) and parkin (PARK2) and is a component of Lewy bodies (LB) in brains of sporadic PD patients. Marx et al. screened 328 German familial and sporadic PD patients and found a mutation in *synphilin-1* in two apparently sporadic patients. The mutation, a C to T transition at position 1861 of the *synphilin-1* gene results in an arginine to cysteine subsitution at position 621 (R621C) of the protein. Transfection experiments of HEK293 and SH-SY5Y cells demonstrated that mutant synphilin-1 produced significantly fewer cytoplasmic inclusions than did the wild-type gene (Marx et al., 2003). Furthermore, SH-SY5Y cells transfected with mutant *synphilin-1* were more susceptible to staurosporine-induced cell death than cells transfected with wild type *synphilin-1*. This indicates that the mutation in *synphilin-1* increases susceptibility of neurons to cellular stress and suggests that formation of intracytoplasmic inclusions is not linked to cell death.

Marx FP, Holzmann C, Strauss KM, Li L, Eberhardt O, Cookson MR, Hernandez D, Farrer MJ, Kachergus J, Engelender S, Ross CA, Berger K, Schöls L, Schulz JB, Riess O, Krüger R (2003) Identification and functional characterization of a novel R621C mutation in the synphilin-1 gene in Parkinson's disease. Hum Mol Gen 12: 1223-1231.

(*contributed by Rejko Krüger*)

Molecular defect in X-linked dystonia parkinsonism syndrome (XDP). The X-linked dystonia-parkinsonism syndrome (XDP) is a severe adult onset movement disorder characterized by both dystonia and parkinsonism. The disease originated by founder effect in the Philippines. Nolte et al. (2003) delineated the region harbouring the disease gene within a 300 kb interval in Xq13.1 of known DNA sequence. After exclusion of mutations in all known genes annotated to this region, sequencing of the entire interval in a patient revealed disease-specific single-nucleotide changes (DSCs). These DSCs were found to be located in a previously not known complex transcript system (*DYT3*). Portions of *DYT3* utilize exons of *TAF1*, a gene encoding TATA box binding protein associated factor 1. Although the function of *DYT3* is not yet known, the findings facilitate differential, predictive and prenatal diagnosis in this disorder.

Nolte D, Niemann S, Müller U (2003) Mutation in novel gene DYT3 is associated with X-linked dystonia parkinsonism (XDP). Proc Natl Acad Sci USA 100: 10347-10352.

With the best wishes for a successful New Year

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