Newsletter
der
Deutschen Gesellschaft für Neurogenetik

July, 2000
DGNG News No. 12

Society News

7th Workshop Neurogenetics in Germany, 6th Annual Meeting of the DGNG

The 7th Workshop Neurogenetics in Germany and 6th Annual Meeting of the DGNG will be held in Dresden from September 14th to 16th, 2000. The organizers of the meeting are Heinz Reichmann, Janet Schmiedel, and Peter Seibel. One major topic of the meeting will be mitochondrial disorders. For more information visit the homepage at http://www.fnz.med.tu-dresden.de/dgng/. Please, note that the deadline for submission of abstracts is June 10, 2000.

Research News

Modelling of neurodegenerative disorders in drosophila. Drosophila is becoming increasingly relevant to the study of human neurodegenerative disorders. About two years ago, it was shown that introduction of expanded stretches of CAG repeats as found in Huntington disease and in many forms of spinocerebellar ataxias mimic the hallmarks of these diseases, i.e. late-onset progressive neuronal degeneration and formation of intranuclear inclusions. The latter arise by abnormal aggregation of polypeptides containing large polyglutamine expansions (see DGNG News No. 9). Similar to humans, severity of neural degeneration and age of onset correlated with repeat length (Jackson et al., 1998; Warrick et al., 1998).

Recently, Parkinson disease (PD), the second most common neurodegenerative disorder in humans, was modelled in drosophila. Feany and Bender (2000) expressed wild type α-synuclein and the two mutant proteins linked to familial PD, A30P and A53T α-synuclein in flies (see also DGNG News No. 7, 8). The authors placed wild-type and mutant c-DNA constructs downstream to multiple binding sites for GAL4. Transgenic animals carrying the GAL4-responsive constructs were crossed to well characterized lines that express the GAL4 activator in various tissue - and cell type - specific patterns. Although the expression of human α-synuclein did not impair gross development in drosophila, an age-dependent specific loss of dopaminergic neurons was found in flies expressing wild-type, A30P or A53T α-synuclein. Loss of other neurons was not observed. Significantly, the authors detected intracellular aggregates of α-synuclein resembling Lewy bodies, a characteristic finding in brains of patients with PD. Similarly, overexpression of wild-type α-synuclein resulted in progressive accumulation of α-synuclein, loss of dopaminergic terminals in the basal ganglia, and motor impairment in transgenic mice (Masliah et al., 2000). In addition to neuropathological changes, Feany and Bender demonstrated characteristic behavioral anomalies in flies expressing the three forms of α-synuclein. Applying a well-established climbing test, they found that the ability to climb declined more rapidly over time in transgenic than in control animals. The time course of locomotor dysfunction correlated well with loss of dopaminergic neurons and the appearance of α-synuclein inclusion bodies.

Thus α-synuclein transgenic flies model all characteristics of PD, i.e. adult-onset specific depletion of dopaminergic neurons, formation of inclusion bodies and locomotor anomalies paralleling the neuropathological finding.

The accurate modelling of these and other neurodegenerative disorders makes drosophila an ideal model organism for further investigations into the pathological mechanisms underlying these disorders and for the development and testing of causal therapies.

1. Feany MB, Bender WW (2000) A drosophila model of Parkinson's disease. Nature 404: 394-398.
2. Jackson GR, Salecker I, Dong X, Yao X, Arnheim N, Faber PW, MacDonald ME, Zipursky SL (1998) Polyglutamine-expanded human huntingtin transgenes induce degeneration of drosophila photoreceptor neurons. Neuron 21:633-642.
3. Warrick JM, Paulson HL, Gray-Board GL, Bui QT, Fischbeck KH, Pittman RN, Bonini NM (1998) Expanded polyglutamine protein forms nuclear inclusions and causes neural degeneration in drosophila. Cell 93: 939-949.
4. Masliah E, Rockenstein E, Veinbergs I, Mallory M, Hashimoto M, Takeda A, Sagara Y, Sisk A, Mucke L (2000) Dopaminergic loss and inclusion body formation in α-synuclein mice: Implications for neurodegenerative disorders. Science 287: 1265-1269.

Huntington's disease and the problem with Huntington-like disorders. The identification of new gene loci in neurological diseases is a permanent challenge for physicians and scientists. In particular, the increasingly recognized genetic heterogeneity of phenotypically identical diseases requires both careful molecular analyses and interpretation of data. Until recently, Huntington's disease was one of the few neurological diseases with a clearly defined phenotype which could be diagnosed by a relatively simple DNA test (detection of a CAG expansion in the 5'translated region of the gene). However, the first doubts about the homogeneity of the disease were raised as early as 1994 (Andrew et al. 1994). Now, two groups mapped these Huntington-like diseases to chromosome 20p (autosomal dominant inheritance, Xiang et al. 1998) and to chromosome 4p15.3 (autosomal recessive, Kambouris et al. 2000). These new findings might explain some of the conflicting mapping data which troubled the fine-mapping of Huntington's disease a decade ago (Doggett et al. 1989). Although these Huntington-like diseases seem to be rather rare, we draw your attention to these data as it will have implications for genetic counseling of persons at risk. It also highlights the need to test affected family members for the HD CAG repeat expansion before predictive testing is offered to unaffected individuals.

There is also news for HD patients and mutation carriers. Van Dellen and coworkers (2000) exposed transgenic mice carrying the CAG repeat expansion to a stimulating environment. Strikingly, the onset of neurological signs in these mice was significantly delayed as compared to mice kept in the absence of an enriched environment. In an elegant experiment René Hen and colleagues (Yamamoto et al., 2000) generated a conditional model of HD by using the tet-regulated system which has been developed by Bujard and co-workers in Heidelberg. This system requires the generation of double transgenic mice. One of the transgenic lines expresses the tetracycline-regulated transactivator under control of a specific promoter (this group used the well characterized CamKIIα-promoter trans-genic mouse line of E. Kandel), the other one the gene of interest (here exon 1 of the HD gene with 94 CAG repeats). The tetracycline-regulated transactivator binds specifically to the tetO operator and induces transcription from an adjacent CMV promoter. Using this approach, Hen and colleagues (Yamamoto et al., 2000) generated double transgenic mice which developed progressive motor dysfunction

and characteristic neuropathology including neuronal inclusions. Down regulation of the expression by administration of tetracycline led to disappearance of inclusions and an amelioration of the phenotype. The disappearance of inclusions was unexpected since biochemical analysis had indicated that the aggregates were extremely stable (Kazantsev et al., 1999). The other striking finding was the reversion of the phenotype suggesting that therapeutic approaches to destroy or inactivate mutant huntingtin might be effective. Another recent paper reported that aggregation and nuclear localization of expanded polyglutamine proteins can be modulated by the glucocorticoid receptor (Diamond et al., 2000). These cell culture studies will undoubtedly lead to tests of glucocorticoid effects in mice transgenic for mutated huntingtin.

1. Andrew SE, Goldberg YP, Kremer B, Squitieri F, Theilmann J, Zeisler J, Telenius H, et al. (1994) Huntington disease without CAG expansion: phenocopies or errors in assignment? Am J Hum Genet 54:852-863.
2. Diamond MI, Robinson MR, and Yamamoto KR (2000) Regulation of expanded polyglutamine protein aggregation and nuclear localization by the glucocorticoid receptor. Proc Natl Acad Sci USA 97:657-661.
3. Doggett NA, Cheng JF, Smith CL, and Cantor CR (1989) The Huntington disease locus is most likely within 325 kilobases of the chromosome 4p telomere. Proc Natl Acad Sci USA 86:10011-10014.
4. Kambouris M, Bohlega S, Al-Tahan A, and Meyer BF (2000) Localization of the gene for a novel autosomal recessive neurodegenerative Huntington-like disorder to 4p15.3. Am J Hum Genet 66:445-452.
5. Kazantsev A, Preisinger E, Dranovsky A, Goldgraber D, and Housman D (1999) Insoluble detergent-resistent aggregates form between pathological and nonpathological lengths of polyglutamine in mammalian cells. Proc Natl Acad Sci USA 96:11404-11409.
6. Xiang F, Almqvist EW, Huq M, Lundin A, Hayden MR, Edström L, Anvret M, and Zhang Z (1998) A Huntinton disease-like neurodegenerative disorder maps to chromosome 20p. Am J Hum Genet 63:1431-1438.
7. Yamamoto A, Lucas JJ, and Hen R (2000) Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. Cell 101: 57-66.
8. Van Dellen A, Blakemore C, Deacon R, York D, and Hannan AJ (2000) Delaying the onset of Huntington's in mice. Nature (London) 404:721-722.

Pronounced locus heterogeneity in autosomal dominant pure spastic paraplegia and identification of a disease gene in 2p. Spastic paraplegias are relatively mild neurodegenerative disorders of the spinal cord. The predominant clinical sign is a slowly progressive gait anomaly due to spasticity and weakness of the legs. Pure forms can be distinguished from complex forms of spastic paraglegia. The latter are characterized by associated signs such as peripheral neuropathy, epilepsy, extrapyramidal disturbances, ataxia, dementia, skin lesions, optic neuropathy, retinopathy, and deafness. The group of disorders is genetically heterogeneous. Presently, 7 loci have been identified in autosomal dominant pure spastic paraplegias and one in a complex form associated with cataract. There are two loci on chromosome 2, one on 2p (SPG4), and another one on 2q (Fontaine et al., 2000). Additional loci were assigned to chromosomes 8q (SPG 8; Reid et al, 1999b; Hedera et al., 1999), 12q (SPG10, Reid et al. 1999a), 14q (SPG3, Hazan et al., 1993), 15q (SPG6, Fink et al., 1995), and 19q (SPG12, Reid et al., 2000). The complex spastic paraplegia SPG9 was assigned to 10q23.3-q24.2 (Seri et al., 1999).

The gene causing SPG4, the most common form of autosomal dominant spastic paraplegia, has recently been identified by

a positional cloning approach. The entire critical interval in 2p21-p22 as defined by linkage analyses was sequenced. In a region of approximately 1.5Mb, Hazan et al. (1999) identified 14 putative transcription units, 5 of which had previously been unknown. The putative product of one of these transcription units showed homology with the AAA family of proteins, members of which are ATPases involved in diverse cellular functions. The gene (transcription unit) was found to span approximately 90kb of DNA and was shown to be composed of 17 exons. Its full-length cDNA comprises 3,263 bp. Mutation analysis in patients with SPG4 revealed various base changes including missense, nonsense, and frameshift mutations. This identified it as the disease gene in SPG4 and its product was named spastin. Although the function of spastin is presently unknown its homology with the 26S proteasome subunit amino-acid sequence and the presence of two leucine-zipper domains and a coiled-coil dimerization motif suggest that it participates in protein complexes. As such spastin might have a function in the regulation of gene expression by triggering proteolytic activation or degradation of transcription factors.

1. Fink JK, Wu CT, Jones SM, Sharp GB, Lange BM, Lesicki A, Reinglass T, et al. (1995) Autosomal dominant familial spastic paraplegia: tight linkage to chromosome 15q. Am J Hum Genet 56:188-192.
2. Fontaine B, Davoine C-S, Dürr A, Paternotte C, Feki I, Weissenbach J, Hazan J, Brice A (2000) A new locus for autosomal dominant pure spastic paraplegia, on chromosome 2q24-q34. Am J Hum Genet 66:702-707.
3. Hazan J, Fonknechten N, Mavel D, Paternotte C, Samson D, Artiguenave F, Davoine C-S et al. (1999) Spastin, a new AAA protein, is altered in the most frequent form of autosomal dominant spastic paraplegia. Nat Genet 23:296-303.
4. Hazan J, Lamy C, Melki J, Munnich A, de Recondo J, Weissenbach J (1993) Autosomal dominant familial spastic paraplegia is genetically heterogeneous and one locus maps to chromosome 14q. Nat Genet 5:163-167.
5. Hedera P, Rainier S, Alvarado D, Zhao X, Williamson J, Otterud B, Leppert M et al. (1999) Novel locus for autosomal hereditary spastic paraplegia, on chromosome 8q. Am J Hum Genet 64:563-569.
6. Reid E, Dearlove AM, Osborn O, Rogers MT, Rubinsztein DC (2000) A locus for autosomal dominant "pure" heteditary spastic paraplegia maps to chromosome 19q13. Am J Hum Genet 66:728-732.
7. Reid E, Dearlove AM, Rhodes M, Rubinsztein DC (1999a) A new locus for autosomal dominant "pure" hereditary spastic paraplegia mapping to chromosome 12q13, and evidence for further genetics heterogeneity. Am J Hum Genet 65:757-763.
8. Reid E, Dearlove AM, Whiteford ML, Rhodes M, Rubinsztein DC (1999b) Autosomal dominant spastic paraplegia: refined SPG8 locus and further genetic heterogeneity. Neurology 53:1844-1849.
9. Seri M, Cusano R, Forabosco P, Cinti R, Caroli F, Picco P, Bini R et al. (1999) Genetic mapping to 10q23.3-q24.2, in a large Italian pedigree, of a new syndrome showing bilateral cataracts, gastroesophageal reflux, and spastic paraparesis with amyotrophy. Am J Hum Genet 64:586-593.

We are looking forward to seeing you in Dresden.

Sincerely yours,

Ulrich Müller
Olaf Riess
Manuel B. Graeber