J Neural Transm (2000) 107: 31–40

Journal of Neural Transmission

Involvement of α-synuclein in Parkinson's disease and other neurodegenerative disorders

R. Krüger[1], **T. Müller**[1], and **O. Riess**[2]

[1] Department of Neurology, St. Josef-Hospital, Ruhr-University, Bochum, and
[2] Department of Medical Genetics, Children's Hospital, University Rostock, Rostock, Federal Republic of Germany

Received April 9, 1999; accepted June 16, 1999

Summary. A major step in the elucidation of the pathogenesis of neurodegenerative disorders was the identification of a mutation in the α-synuclein gene in autosomal dominant Parkinson's disease (PD). α-Synuclein is the main component of Lewy bodies (LB), the neuropathological hallmark of PD. Moreover, a fragment of α-synuclein (NAC) is the second major component of amyloid plaques in Alzheimer's disease (AD). Recent studies of other neurodegenerative disorders such as dementia with LB (DLB), multiple system atrophy (MSA) and amyotrophic lateral sclerosis (ALS) also revealed intracellular accumulations of α-synuclein in affected brain regions. This may indicate that these disorders partially share common pathogenic mechanisms. Recent data provide first insights into the physiological function of α-synuclein and support the concept of an essential role of α-synuclein in neurodegeneration. Increasing knowledge on the pathogenic molecular mechanisms of neurodegeneration and of the pathophysiological function of α-synuclein in particular may influence future development of therapeutic strategies in neurodegenerative disorders.

Keywords: Alzheimer's disease, α-synuclein, neurodegeneration, Parkinson's disease.

Genetics of PD

Parkinson's disease (PD) is a common neurodegenerative disorder, which afflicts about 1% of a population over the age of 50. The progressive neurodegeneration predominantly affects dopaminergic neurons of the substantia nigra (SN). The neuropathological hallmark of PD is the increased appearance of intracellular inclusions, so-called Lewy bodies (LB). LB are located in many brain regions including the substantia nigra. Sporadic and familial forms of PD occur. Several lines of evidence suggest a multifactorial

pathogenesis of sporadic PD in genetically predisposed aging individuals. Several authors controversially discuss the putative genetic influence on the pathogenesis of PD (Duvoisin, 1986; Lazzarini et al., 1994). Earlier studies showed no increased concordance of PD in monozygotic compared to dizygotic twins (Duvoisin et al., 1981; Marttila et al., 1988), but design of these studies was limited. Previous trials on concordance rates of twins, detecting presymptomatic PD with the determination of striatal ^{18}fluorodopa uptake by positron emission tomography, support the view of a genetic influence on the occurrence of PD (Burn et al., 1992). Further evidence for a genetic contribution to PD has been provided by the identification of families with an autosomal dominant (ADPD) and autosomal recessive (ARJP) trait of the disease. Subsequently, four gene loci have been identified by linkage analysis on human chromosome 4q21–23 (PARK1), 6q25–27 (PARK2), 2p13 (PARK3), and 4p15 (Polymeropoulos et al., 1996; Matsumine et al., 1997; Gasser et al., 1998; Farrer et al., 1999). For the PARK2 locus a gene, parkin, has been isolated and mutations causing ARJP have been identified (Kitada et al., 1998). While little is known on the function of parkin, there is increasing knowledge on α-synuclein which is mutated in some rare forms of ADPD (Polymeropoulos et al., 1997; Krüger et al., 1998).

α-Synuclein in PD

Search for mutations in the *α-synuclein* gene localized on human chromosome 4q21–23 (Polymeropoulos et al., 1997) identified a missense G209A mutation. This results in an amino acid (aa) exchange from alanine to threonine at position 53 of the protein. This mutation marks PD of all affected family members except one (Polymeropoulos et al., 1997). Five Greek ADPD families also showed this mutation. In two of them asymptomatic carriers over the expected age at onset are decribed, which may indicate incomplete penetrance of the autosomal-dominant mutation in the *α-synuclein* gene (Papadimitriou et al., 1999). Colonization of Southern Italy by ancient Greeks and migration between Greece and Italy in former times may suggest a common ancestor of the Italian and Greek families and might therefore reflect a founder effect. The alanine residue in position 53 is not well conserved through evolution. Threonine is present at position 53 of α-synuclein in mouse, rat and canary (George et al., 1995). Nevertheless, the identification of an alanine-to-proline substitution at aa position 30 of the α-synuclein protein in a German family with ADPD provided further evidence for the involvement of α-synuclein in the pathogenesis of PD (Krüger et al., 1998). The A30P substitution occurs in a repeat motif which is highly conserved throughout all investigated species and in the synuclein gene family. Subsequent studies failed to identify the A53T and the A30P mutation in other ADPD families or in patients with sporadic PD (Chan et al., 1998; Krüger et al., 1998; Zareparsi et al., 1998). Moreover, sequence analysis of the entire gene in further 36 European and American ADPD families did not identify other mutations in the α-synuclein gene so far (Farrer et al., 1998; Vaughan et al., 1998). Nevertheless, these results suggest that α-synuclein may participate in the pathogenesis of rare forms of ADPD. However, the

pathogenic effect of the A53T mutation in humans needs further verification. One explanation might be that wild type α-synuclein with an alanine at position 53 in combination with the T53 α-synuclein enhances protein oligomerization in the presence of other proteins. Self-oligomerization of α-synuclein in the presence of Aβ, possibly catalyzed by transglutaminases, was demonstrated in amyloid of AD subjects and in LBs (Iwai et al., 1995; Paik et al., 1998). Moreover additional factors may influence onset, course and progression of PD regarding the variable phenotype of mutation carriers (Krüger et al., 1998; Papadimitriou et al., 1999). Identification of mutations of the *α-synuclein* gene stimulated its immunohistochemical characterisation in Parkinsonian brains. LBs in brains of affected family members of the Contursi kindred showed a strong staining with antibodies against α-synuclein. Moreover studies in brains of sporadic Parkinsonian patients and subjects with dementia with LB (DLB) also identified α-synuclein as the major component of LB (Spillantini et al., 1998). Therefore α-synuclein beside staining for ubiquitin may represent a further sensitive marker for LB and Lewy neurites. In this context it is noteworthy, that components located in LBs and in dystrophic neurites, such as α-synuclein, neurofilament, ubiquitin, and many others accumulate only in a subset of cells (Spillantini et al., 1998).

α-Synuclein in other neurodegenerative disorders

Ueda and colleagues studied proteins participating in the formation of amyloid plaques in Alzheimer's disease (AD) and identified a peptide called NAC, for non-Aβ component of AD amyloid (Ueda et al., 1993). NAC is the second major component of AD plaques and amounts to less than 10% of the Aβ peptide. The precursor protein was named NACP and was homologous to the α-synuclein protein of the rat (Jensen et al., 1997). NAC has been shown to be involved in protein aggregation in AD (Jensen et al., 1997). Both, NAC and α-synuclein, stimulate the formation of Aβ aggregates *in vitro* (Jensen et al., 1997). NAC itself has a tendency to form insoluble β-pleated sheet structures. α-synuclein binds NAC and Aβ and subsequently to amyloid plaques in AD (Paik et al., 1998). These biochemical data support the hypothesis of an involvement of α-synuclein in the pathogenesis of AD. However, a detailed mutation analysis of the α-synuclein gene in 26 unrelated patients with familial early-onset AD identified no disease causing alteration (Campion et al., 1996).

The presence of insoluble protein aggregations in affected brain regions is a common feature of several neurodegenerative disorders. This led to the hypothesis of a participation of α-synuclein in protein aggregations in other neurodegenerative disorders.

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder with a great variety of clinical symptoms, such as parkinsonism, ataxia, corticospinal motor signs, and autonomic failure. Neuropathological hallmarks are glial and neuronal cytoplasmic argyrophilic inclusions (Lantos et al., 1994). Several studies consistently demonstrated that antibodies against α-synuclein stain these characteristic neuropathological structures (Tu et al., 1998; Wakabayashi et al., 1998). These α-synuclein-positive glial cytoplasmic

inclusions (GCI) represent no specific biomarker of MSA. Astrocytes and Schwann cells of subjects with amyotrophic lateral sclerosis (ALS) also show protein inclusions, reacting with antibodies against α-synuclein (Mezey et al., 1998). Moreover antibodies to α-synuclein stained GCI in the white matter as well as neuronal cytoplasmic inclusions in the gray matter of cingulate cortex and putamen in one case of Hallervorden-Spatz disease (Tu et al., 1998). This might indicate that aggregation of α-synuclein is a common and therefore unspecific phenomenon in neurodegeneration. However, α-synuclein-positive protein aggregations were not identified in other neurodegenerative disorders such as Guam parkinsonism/dementia complex, progressive supranuclear palsy, corticobasal degeneration and Pick's disease up to now.

The role of the glial accumulation of α-synuclein in the above mentioned disorders either as initial event causing impaired glial function and/or as secondary phenomenon due to neuronal damage is still unknown. α-Synuclein is also present in neurons of healthy subjects. Therefore GCIs may reflect a pathologic upregulation of glial α-synuclein expression or impairment of protein degradation. Both may induce the aggregation of either previously lowly expressed glial α-synuclein and/or neuronal α-synuclein.

These findings suggest the characterisation of the above mentioned neurodegenerative disorders as α-synucleinopathies due to the involvement of α-synuclein in the pathophysiological mechanisms leading to glial and neuronal dysfunction and death.

The synuclein family

Earlier studies revealed localisation of α-synuclein in presynaptic nerve terminals and portions of the nuclear envelope (Maroteaux et al., 1988). The nuclear localization has not been confirmed by later studies (Goedert, 1997). Subsequently, other proteins with high homology to α-synuclein have been identified. Currently three members of the synuclein protein family-α, β and γ-synuclein- are known (Chen et al., 1995; Spillantini et al., 1995; Lavedan et al., 1998).

All are highly expressed in the human brain with α- and γ-synuclein compared to β-synuclein in a more widespread fashion (Ueda et al., 1993; Jakes et al., 1994; Lavedan et al., 1998). The striking structural elements throughout the synuclein protein family are variants of an 11 amino acid consensus motif (XKTKEGVXXXX) in the amino terminal region, which are highly conserved among all members. This element resembles to those found in the amphipathic helices of apolipoproteins mediating interactions with lipid membranes (George et al., 1995). Biophysical studies on these synucleins indicate, that they have a natively unfolded structure and therefore may potentiate protein-protein interactions and/or play a role in cell regulation (Weinreb et al., 1996). α and β-synuclein selectively inhibit phosphatidylcholine-specific phospholipase D2 (PLD2) (Jenko et al., 1998). PLD2 activiation stimulates cell growth, differentiation, and neurotransmitter release (Klein et al., 1995). This suggests that regulation of phospholipase D2 may play a role in the pathophysiology of PD. Furthermore α-synuclein is a

substrate for phosphorylation by Ca^{2+}-calmodulin-dependent protein kinase (Nakajo et al., 1993). Ca^{2+}-calmodulin-dependent protein kinase-II is another component of LB (Iwatsubo et al., 1991). Therefore Ca^{2+}-dependent phosphorylation may relieve synuclein inhibition of PLD2 and represent an essential key event of LB formation. Recent studies show an increased expression of α-synuclein in rat Sertoli cells indicating a possible role in the meiosis of spermatogonia. γ-synuclein, described as the breast cancer specific gene 1 (BCSG1), seems to be involved in breast cancer progression (Ji et al., 1999). α-synuclein may influence neuronal plasticity, because expression of the α-synuclein homologue synelfin accompagnies song learning of birds (George et al., 1995).

The central region of α-synuclein comprising the NAC fragment is hydrophobic and the carboxy-terminus is enriched in acidic amino acids. Some homologies between a small region of α-synuclein (66–73), the C-terminus of the Aβ (protein (Aβ(36–42), and a sequence in the prion protein (PrP117–124) appear (Han et al., 1995). Similarities in the pathogenesis of PD, AD, and prion diseases were reviewed and discussed in the context of chaperone mediated protein aggregation, but little information is available on α-synuclein (Welch and Gambetti, 1997).

A protein, called synphilin1, interacts with α-synuclein according to *in vitro* and *in vivo* trials (Engelender et al., 1998). Synphilin1 contains 4 ankyrin-like repeats and an ATP/GTP binding domain. Synphilin1 appears in many brain areas including the substantia nigra. α-Synuclein co-immunoprecipitated with synphilin1 from brain extracts. Future studies will evaluate the possibility of synphilin1 being a component of LBs in PD.

α-Synuclein and neurodegeneration

0.5%–1% of the cytosolic protein is α-synuclein in brain homogenates. α-Synuclein is localized in the synaptophysin-immunoreactive presynaptic terminals (Iwai et al., 1995). This suggests a role of α-synuclein in presynaptic function, such as regulation of synaptic vesicles. The highly conserved amino-terminal repeat region of α-synuclein supports this hypothesis of the involvement of α-synuclein in the function of synaptic vesicles, because natively unfolded protein adopts approximately 80% helical structure when bound to lipid membranes (Davidson et al., 1998). Recent studies demonstrated that α-synuclein containing the Ala30Pro mutation is devoid of significant vesicle binding activity (Jensen et al., 1998). Therefore this mutation may accumulate and induce the formation of LB. α Synuclein with either the A53T or the A30P mutation promotes its own fibrillization *in vitro*, forming β-sheet structure and mature filaments (El-Agnaf et al., 1998). This represents an analogy to AD, where mutations in the APP gene resulted in an increased Aβ fibrillization.

Mutations in the *α-synuclein* gene may cause failure to mature along the normal folding pathway leading to a loss of solubility, which may affect the protein degradation pathway. One pathway supporting the degradation of misfolded proteins is the ubiquitin/proteasome pathway (Finley et al., 1991).

Ubiquitin is conjugated to lysine residues of a target protein by an ubiquitin-conjugating enzyme. Polyubiquitinated proteins are recognized and rapidly degraded by a complex of proteinases, the 26S proteasome (for review: Ashkenas and Byers, 1997). Ubiquitin represents a component of degenerating neurites in PD as well as in LB, AD plaques and GCI in MSA (Tamaoka et al., 1995) implicating a common pathophysiological disease process related to interference by protein degradation.

These findings suggest that both abnormal function and/or abnormal compartmentalization of α-synuclein may play a role during the progression of LB diseases. A disruption of perikaryal transport may cause neuronal cell death, because of appearance of LBs in neuronal cell bodies or blockage of axonal transport by LB proteins due to aggregation in dystrophic neurites (Trojanowski and Lee, 1998).

Conclusion

The identification of mutations in the *α-synuclein* gene as markers for ADPD represents a major step towards the elucidation of the pathogenesis of PD. α-Synuclein is the main component of LB also in sporadic PD and appears in cellular protein aggregations in ALS, HSD and MSA. Therefore α-synuclein may represent a key substrate in neurodegeneration of these disorders. The way how wild type synuclein may be involved in protein agreggation need still to be elucidated. A recent *in vitro* study indicates that oxidative stress induces amyloid-like aggregate formation of wild type α-synuclein (Hashimoto et al., 1999). Several studies indicate that oxidative stress due to the presence of free radicals plays an important role in neurodegeneration (Olanow, 1993). Further studies will reveal regulatory elements of the *α-synuclein* gene and identify variations of the transcript level similar to the role of APP in AD. Recent data indicate a positive association of a dinucleotide repeat marker in the promoter region of the *α-synuclein* gene with sporadic PD with a 2.7 fold increased risk to develop PD (Krüger et al., 1999). One allele of the same marker may represent a protective factor in the pathogenesis of AD (Xia et al., 1997). These results suggest the presence of DNA polymorphisms in regulatory elements of the *α-synuclein* gene and emphasize the relevance and necessity of a detailed mutation analysis in the *α-synuclein* promoter region in the above mentioned disorders. Moreover the recent discovery of a Ile93Met mutation in the *ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1)* gene in one German pedigree with ADPD demonstrates the relevance of aberration in the cellular protein degradation pathway for neurodegenerative processes (Leroy et al., 1998). This implies a great variety of candidate genes which may influence protein aggregation as a causative event of neurodegeneration in humans. Further investigations will have to enlighten these phenomena and regulatory processes.

Acknowledgements

We would like to thank numerous colleagues for continues support, in particular Prof. Przuntek and Prof. Epplen. Work in the laboratory of OR is supported by the DFG.

References

Arai H, Lee VMY, Hill WD, Greenberg BD, Trojanowski JQ (1992) Lewy bodies contain beta-amyloid precursor proteins of Alzheimer's disease. Brain Res 585: 386–390

Ashkenas J, Byers P (1997) The final step of gene expression: chaperones and the regulation of protein fate. J Hum Genet 61: 267–272

Burn DJ, Mark MH, Playford ED, Maraganore DM, Zimmerman TR Jr, Duvoisin RC, Harding AE, Marsden CD, Brooks DJ (1992) Parkinson's disease in twins studied with ^{18}F-Dopa and positron emission tomography. Neurology 42: 1894–1900

Campion D, Martin C, Heilig R, Charbonnier F, Moreau V, Flaman JM, Petit JL, Hannequin D, Brice A, Frebourg T (1995) The NACP/synuclein gene: chromosomal assignment and screening for alterations in Alzheimer disease. Genomics 26: 254–257

Chan P, Tanner CM, Jiang X, Langston JW (1998) Failure to find the (-synuclein gene missense mutation (G209A) in 100 patients with younger onset Parkinson's disease. Neurology 50: 513–514

Chen X, de Silva HA, Pettenati MJ, Rao PN, St. George-Hyslop P, Roses AD, Xia Y, Horsburgh K, Ueda K, Saitoh T (1995) The human NACP/α-synuclein gene: chromosome assignement to 4q21.3–q22 and TaqI RFLP analysis. Genomics 26: 425–427

Davidson WS, Jonas A, Clayton DF, George F (1998) Stabilization of alpha-synuclein secondary structure upon binding to synthetic membranes. J Biol Chem 273: 9443–9449

Duvoisin RC (1986) On heredity, twins, and Parkinson's disease. Ann Neurol 19: 409–411

Duvoisin RC, Eldridge R, Williams A, Nutt J, Calne D (1981) Twin study of Parkinson's disease. Neurology 31: 77–80

El-Agnaf OM, Jakes R, Curran MD, Wallace A (1998) Effects of the mutations Ala30 to Pro and Ala53 to Thr on the physical and morphological properties of alpha-synuclein protein implicated in Parkinson's disease. FEBS Lett 440: 67–70

Engelender S, Guo X, Hoffman BE, Lee MK, Sharp AH, Zhang C, Cooper JK, Herring WJ, Troncoso JC, Price DL, Lanahan A, Worley P, Dawson VL, Dawson TM, Ross CA (1998) Alpha-synuclein interacts in vivo with a novel protein (synphilin1). Mov Disord 13: 87(Abstract)

Farrer M, Wavrant-De Vrieze F, Crook R, Boles L, Perez-Tur J, Hardy J, Johnson WG, Steele J, Maraganore D, Gwinn K, Lynch T (1998) Low frequency of α-synuclein mutations in familial Parkinson's disease. Ann Neurol 43: 394–397

Farrer M, Gwinn-Hardy K, Muenter M DeVrieze FW, Crook R, Perez-Tur J, Lincoln S, Maraganore D, Adler C, Newman S, MacElwee K, McCarthy P, Miller C, Waters C, Hardy J (1999) A chromosome 4p haplotype segregating with Parkinson's disease and postural tremor. Hum Mol Genet 8: 81–85

Finley D, Chau V (1991) Ubiquitination. Ann Rev Cell Biol 7: 25–69

Gasser T, Muller-Myhsok B, Wszolek ZK, Oehlmann R, Calne DB, Bonifati V, Bereznai B, Fabrizio E, Vieregge P, Horstmann RD (1998) A susceptibility locus for Parkinson's disease maps to chromosome 2p13. Nature Genet 18: 262–265

George JM, Jin H, Woods WS, Clayton DF (1995) Characterization of a novel protein regulated during the critical period for song learning in the zebra finch. Neuron 15: 361–372

Goedert M (1997) The awakening of α-synuclein. Nature 388: 232–233

Han H, Weinreb PH, Lansbury PT (1995) The core Alzheimer's peptide NAC forms amyloid fibrils which seed and are seeded by beta-amyloid: is NAC a common trigger or target in neurodegenerative disorders? Chem Biol 2: 163–169

Iwai A, Masliah E, Yoshimoto M, Ge N, Flanagan L, de Silva HA, Kittel A, Saitoh T (1995) The precursor protein of non-Aβ component of Alzheimer's disease amyloid is a presynaptic protein of the central nervous system. Neuron 14: 467–475

Iwai A, Yoshimoto M, Masliah E, Saitoh T (1995) Non-Aβ component of Alzheimer's disease amyloid (NAC) is amyloidogenic. Biochemistry 34: 10139–10145

Iwatsubo T, Nakano I, Fukunaga K, Miyamoto E (1991) Ca^{2+}-calmodulin-dependent protein kinase-II immunoreactivity in Lewy bodies. Acta Neuropathol 82: 159–163

Jakes R, Spillantini MG, Goedert M (1994) Identification of two distinct synucleins form human brain. FEBS Lett 345: 27–32

Jenko JM, Rawlingson A, Daniels B, Morris AJ (1998) Regulation of phospholipase D2: selective inhibition of mammalian phospholipase D isoenzymes by α- and β-synucleins. Biochemistry 37: 4901–4909

Jensen PH, Sorensen ES, Petersen TE, Gliemann J, Rasmussen LK (1995) Residues in the synuclein consensus motif of the α-synuclein fragment, NAC, participate in transglutaminase-catalysed cross-linking to Alzheimer-disease amyloid bA4 peptide. Biochem J 310: 91–94

Jensen PH, Hojrup P, Hager H, Nielsen MS, Jacobsen L, Olesen OF, Gliemann J, Jakes R (1997) Binding of Abeta to alpha- and beta-synucleins: identification of segments in alpha-synuclein/NAC precursor that bind Abeta and NAC. Biochem J 323: 539–546

Jensen PH, Nielsen MS, Jakes R, Dotti CG, Goedert M (1998) Binding of alpha-synuclein to brain vesicles is abolished by familial Parkinson's disease mutation. J Biol Chem 273: 26292–26294

Ji H, Liu YE, Liu J, Shi YE (1999) Stimulation of breast cancer invasion and metastasis by synuclein gamma. Cancer Res 59: 742–747

Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392: 605–608

Klein J, Chalifa V, Liscovitch M, Loffelholz K (1995) Role of phospholipase D activation in nervous system physiology and pathophysiology. J Neurochem 65: 1445–1455

Krüger R, Kuhn W, Müller Th, Woitalla D, Graeber M, Kösel S, Przuntek H, Epplen JT, Schöls L, Riess O (1998) Ala30Pro mutation in the gene encoding α-synuclein in Parkinson's disease. Nat Genet 18: 106–108

Krüger R, Kuhn W, Müller T, Kühnl N, Fuchs GA, Berg D, Storch A, Hungs M, Woitalla D, Przuntek H, Epplen JT, Schöls L, Riess O (1998) Increased susceptibility to sporadic Parkinson's disease by a certain combined α-synuclein/apolipoprotein E genotype. Ann Neurol 45: 611–617

Lantos PL, Papp MI (1994) Cellular pathology of multiple system atrophy: a review. J Neurol Neurosurg Psychiatry 57: 129–133

Lavedan C, Leroy E, Dehejia A, Buchholtz S, Dutra A, Nussbaum RL, Polymeropoulos MH (1998) Identification, localization and characterization of the human γ-synuclein gene. Hum Genet 103: 106–112

Lazzarini AM, Myers RH, Zimmerman TR, Mark MH, Golbe LI, Sage JI, Johnson WG, Duvoisin RC (1994) A clinical genetic study of Parkinson's disease: evidence for dominant transmission. Neurology 44: 499–506

Leroy E, Boyer R, Auburger G, Leube B, Ulm G, Mezey E, Harta G, Brownstein MJ, Jonnalagada S, Chernova T, Dehejia A, Lavedan C, Gasser T, Steinbach PJ, Wilkinson KD, Polymeropoulos MH (1998) The ubiquitin pathway in Parkinson's disease. Nature 395: 451–452

Maroteaux L, Campanelli JT, Scheller RH (1988) Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminals. J Neurosci 8: 2804–2815

Marttila RJ, Kaprio J, Koskenvuo M, Rinne UK (1988) Parkison's disease in a nationwide twin cohort. Neurology 38: 1217–1219

Matsumine H, Saito M, Shimoda-Matsubayashi S, Tanaka H, Ishikawa A (1997) Localization of a gene for an autosomal recessive form of juvenile Parkinsonism to chromosome 6q25.2–27. Am J Hum Genet 60: 588–596

Mezey E, Dehejia A, Harta G, Papp MI, Polymeropoulos MH, Brownstein MJ (1998) Alpha synuclein in neurodegenerative disorders: murderer or accomplice? Nat Med 4: 755–756

Nakajo S, Tsukada K, Omata K, Nakamura Y, Nakaya, K (1993) A new brain-specific 14-kDa protein is a phosphoprotein. Its complete amino acid sequence and evidence for phosphorylation. Eur J Biochem 217: 1057–1063

Olanow CW (1993) A radical hypothesis for neurodegeneration. Trends Neurosci 16: 439–444

Paik SR, Lee JH, Kim DH, Chang CS, Kim YS (1998) Self-oligomerization of NACP, the precursor protein of the non-amyloid β/A4 protein (Aβ) component of Alzheimer's disease amyloid, observed in the presence of a C-terminal Aβ fragment (residues 25–35). FEBS Lett 421: 73–76

Papadimitriou A, Veletza V, Hadjigeorgiou GM, Patrikiou A, Hirano M, Anastasopoulos I (1999) Mutated α-synuclein gene in two Greek kindreds with familial PD: incomplete penetrance? Neurology 52: 651–654

Polymeropoulos MH, Higgins JJ, Golbe LI, Johnson WG, Ide SE, Di Iorio G, Sanges G, Stenroos ES, Pho LT, Schafffer AA, Lazzarini AM, Nussbaum RL, Duvoisin RC (1997) Mapping of a gene for Parkinson's disease to chromosome 4q12–q23. Science 274: 1197–1199

Polymeropoulos MH, Laavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL (1997) Mutation in the α-synuclein gene identified in families with Parkinson's disease. Science 276: 2045–2047

Spillantini MG, Divane A, Goedert M (1995) Assignement of human α-synuclein (SNCA) and β-synuclein (SNCB) genes to chromosomes 4q21 and 5q35. Genomics 27: 379–381

Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M (1998) α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. Proc Natl Acad Sci USA 95: 6469–6473

Tamaoka A, Mizusawa H, Mori H, Shoji S (1995) Ubiquitinated alpha B-crystallin in glial cytoplasmic inclusions from the brain of a patient with multiple system atrophy. J Neurol Sci 129: 192–198

Trojanowski JQ, Lee VMY (1998) Aggregation of neurofilament and α-synuclein proteins in Lewy bodies. Arch Neurol 55: 151–152

Tu P-H, Galvin JE, Baba M, et al. (1998) Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble α-synuclein. Ann Neurol 44: 415–422

Ueda K, Fukushima H, Masliah E, Xia Y, Iwai A, Yoshimoto M, Otero DA, Kondo J, Ihara Y, Saitoh (1993) Molecular cloning of cDNA encoding an unrecognized component of amyloid in Alzheimer disease. Proc Natl Acad Sci USA 90: 11282–11286

Vaughan JR, Farrer MJ, Wszolek ZK, Gasser T, Durr A, Agid Y, Bonifati V, DeMichele G, Volpe G, Lincoln S, Breteler M, Meco G, Brice A, Marsden CD, Hardy J, Wood NW (1998) Sequencing of the α-synuclein gene in a large series of cases of familial Parkinson's disease fails to reveal any further mutations. Hum Mol Genet 7: 751–753

Wakabayashi K, Yoshimoto M, Tsuji S, Takahashi H (1998) Alpha synuclein immunorectivity in glial cytoplasmic inclusions in multiple system atrophy. Neurosci Lett 249: 180–182

Weinreb PH, Zhen W, Poon AW, Conway KA, Landsbury PT (1996) NACP, a protein implicated in Alzheimer's disease and learning, is natively unfolded. Biochemistry 35: 13709–13715

Welch WJ, Gambetti P (1998) Chaperoning brain diseases. Nature 392: 23–24

Xia Y, Rohan de Silva HA, Rosi BL, Yamaoka LH, Rimmler JB, Pericak-Vance MA, Roses AD, Chen X, Masliah E, DeTeresa R, Iwai A, Sundsmo M, Thomas RG, Hofstetter CR, Gregory E, Hansen LA, Katzman R, Thal LJ, Saitoh T (1996) Genetic studies in Alzheimer's disease with an NACP/alpha-synuclein polymorphism. Ann Neurol 40: 207–215

Zareparsi S, Kaye J, Camicioli R, Kramer P, Nutt J, Bird T, Litt M, Payami H (1998) Analysis of the α-synuclein G209A mutation in familial Parkinson's disease. Lancet 351: 37–38

Authors' address: R. Krüger, MD, Department of Neurology, St. Josef-Hospital, Ruhr-University, D-44780 Bochum, Federal Republic of Germany, email: rejko.krueger@ruhr-uni-bochum.de