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Rhine Westfalia (the county of the index patient) or in 90 controls from Saxony-Anhalt, the county of origin of the pedigree (data not shown).

In summary, according to the criteria of the UK Parkinson's Disease Society Brain Bank, definitive PD was diagnosed in two sibs and the deceased mother. As the mutation co-segregates with the disease in the pedigree but was not detected in a total of 1140 chromosomes of control individuals, we conclude that the Ala30Pro substitution is the cause of PD in this family.

It is not known how the Ala30Pro substitution affects the function of the α-synuclein protein. In Alzheimer's disease, α-synuclein was originally identified as the precursor protein for the non-β–amyloid component of amyloid plaques[6]. The normal function of human α-synuclein is unknown, but experiments with song-learning in the zebra finch indicates a role in neuronal plasticity[4]. The mutation described here is located in the terminal position of the second of seven repetitive motifs, a residue that is highly conserved in animals and in the synuclein gene family. The N-terminus of α-synuclein may be involved in interactions with a membrane cytoplasmic surface[7]. Thus, the mutation may affect binding to synaptic vesicles[8]. α-synuclein appears to be natively unfolded and therefore lacks defined secondary structure[7]. It has been suggested that the protein can adopt secondary structures when bound to other proteins[7]. Proline residues are completely absent in the N-terminal part of the normal protein but as proline is involved in protein secondary structure acquisition[9], the Ala30Pro substitution might influence its secondary structure, and perhaps result in an increased tendency to aggregate. Aggregation could lead to abnormal transport and accumulation of synaptic proteins or abnormal processing and degradation of α-synuclein, a property that may lead to the formation of Lewy bodies.

No other mutations or polymorphisms beside the Ala30Pro substitution were identified in the coding region of α-synuclein in the sporadic and familial PD patients investigated here. Also, linkage analysis in large ADPD families has excluded the chromosomal region 4q21–23 as a candidate region for familial PD[10,11]. Our results support the hypothesis that mutations in *SNCA* participate in the pathogenesis of some rare forms of ADPD.

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Rejko Krüger[1,2], Wilfried Kuhn[1], Thomas Müller[1], Dirk Woitalla[1], Manuel Graeber[3], Sigfried Kösel[4], Horst Przuntek[1], Jörg T. Epplen[2], Ludger Schöls[1] & Olaf Riess[2]

[1]Neurological University Hospital and [2]Department of Molecular Human Genetics, Ruhr-University, 44780 Bochum, Germany. [3]Department of Neuromorphology, Max-Planck-Institute for Psychiatry, 82152 Martinsried, Germany. [4]Institute of Molecular Neuropathology, 80337 Munich, Germany. Correspondence should be addressed to O.R. e-mail: olaf.riess@ruhr-uni-bochum.de

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Supersonic congenics?

I read with interest the paper by Markel *et al.*[1] on the generation of congenic mouse strains using molecular genetic tools to reduce the amount of time typically taken to produce these valuable mouse strains. I was impressed with the theory, the use of molecular markers, and the math involved with the 'speed congenic' method. However, there is an alternative method that is as quick but much simpler.

Female prepubertal mice (approximately three-weeks–old) are routinely superovulated with hormones to produce fertilized eggs for embryo transfer. Thus, it is not necessary to wait until a female is sexually mature to initiate the next generation. Therefore, if one starts with a fertilized egg, it takes three weeks to produce a pup and then another three weeks to produce a female for superovulation and embryo transfer. Thus, from egg to the next backcross generation is only six weeks. At six weeks per generation for ten backcross generations, one can deduce that a congenic strain can be generated in a little over one year (sixty weeks). The only requirements would be the ability to determine which females carried the mutation of interest prior to superovulation and ten embryo transfer sessions. No comprehensive genotyping of numerous animals would be required. One potential concern is that different inbred strains superovulate with different efficiencies. Potentially, the speed congenic and the superovulation methods could be combined to generate supersonic congenic mice in about eight months (thirty weeks). Sometimes the genome can be so dazzling that simpler less sophisticated alternatives are overlooked.

Richard Behringer

Department of Molecular Genetics, M. D. Anderson Cancer Center, Houston, Texas, USA. e-mail: bhr@molgen.mda.uth.tmc.edu

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