Neurol Sci (2003) 24:159–160
DOI 10.1007/s10072-003-0108-0

DJ-1 (*PARK7*), a novel gene for autosomal recessive, early onset parkinsonism

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Abstract Four chromosomal loci (*PARK2, PARK6, PARK7,* and *PARK9*) associated with autosomal recessive, early onset parkinsonism are known. We mapped the *PARK7* locus to chromosome 1p36 in a large family from a genetically isolated population in the Netherlands, and confirmed this linkage in an Italian family. By positional cloning within the refined *PARK7* critical region we recently identified mutations in the *DJ-1* gene in the two PARK7-linked families. The function of DJ-1 remains largely unknown, but evidence from genetic studies on the yeast *DJ-1* homologue, and biochemical studies in murine and human cell lines, suggests a role for DJ-1 as an antioxidant and/or a molecular chaperone. Elucidating the role of DJ-1 will lead to a better understanding of the pathogenesis of DJ-1-related and common forms of Parkinson's disease.

By genome-wide scan and homozygosity mapping, we identified the *PARK7* locus in a large consanguineous family with four affected individuals, belonging to a genetically isolated population in the south west of the Netherlands [1]. Linkage to the same region was later confirmed in a consanguineous pedigree from central Italy with three affected members [2]. The phenotype in both families is characterized by parkinsonism of early onset (ranging from age 27 to 40 years), good levodopa response, and slow progression. Behavioral and psychic disturbances and dystonic features (including blepharospasm) are also present, and a positron emission tomography study in the Dutch family showed dopaminergic presynaptic dysfunctions [1–3].

Fine mapping studies and a positional cloning strategy led us to the identification of homozygous mutations in the *DJ-1* gene showing complete cosegregation with the disease haplotype and absence from large numbers of control chromosomes: a ~14-kb deletion removing a large part of the *DJ-1* coding region in the Dutch family and a missense mutation (Leucine166Proline, L166P) in the Italian family (Fig. 1) [4].

The expression of the *DJ-1* gene is abolished by the homozygous deletion in the patients of the Dutch family, indicating that the loss of DJ-1 function is pathogenic. The L166P mutation is also likely to severely affect the function of DJ-1 because: (1) it replaces a highly conserved residue in the DJ-1 protein, (2) it destabilizes the carboxy-terminal a-helix of the DJ-1 protein as predicted by structural models, and (3) it dramatically changes the subcellular localization of the DJ-1 protein in transfection experiments [4].

The human *DJ-1* is organized in eight exons distributed over 24 kb. The first two exons are non-coding and alternatively spliced in the mRNA. *DJ-1* is ubiquitously and highly expressed in the brain areas and extra-cerebral tissues. The human DJ-1 protein has 189 amino acids and belongs to the ThiJ/PfpI family. The exact function of the DJ-1 protein is unknown, but previous reports suggested an involvement in multiple cellular processes, including oncogenesis, regulation of RNA-binding protein complexes, sperm maturation and fertilization in rodents, and regulation of androgen receptor-mediated transcriptional activity [4]. Interestingly, studies in murine and human cell lines showed that the DJ-1 protein is converted into a more-acidic variant in response to oxidative stress, suggesting a role as an antioxidant [5]. Moreover, the yeast *DJ-1* homologue is transcribed during the oxidative stress response and during the response to protein misfolding (which in turn is associated with oxidative stress), raising the question of whether DJ-1 also plays a role as a molecular chaperone [6, 7]. DJ-1 might therefore be involved in the cellular response to stress at multiple levels. It might directly react to stress signals by chemical shifts and/or change in multimerization state; it might also modulate the gene expression of the stress response at transcriptional and/or post-transcriptional levels [4]. Although an involvement of human DJ-1 in the oxidative stress response, or in the response to protein misfolding, remains to be

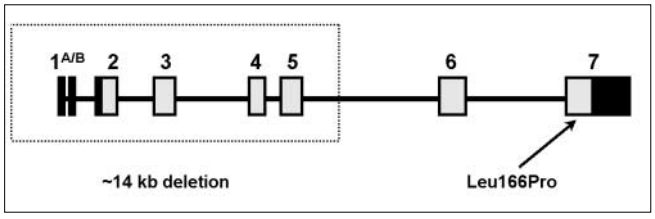

Fig. 1 Genomic structure of the *DJ-1* gene showing the two mutations identified [4]. *Black* and *grey boxes* indicate non-coding and coding exonic sequences, respectively

proven, the proposed model is intriguing in the light of the oxidative stress and protein misfolding documented in the brains of patients with Parkinson's disease (PD).

Mutational analyses in large series of patients with early onset PD are currently in progress to evaluate the frequency of *DJ-1* mutations, pinpoint functionally important domains in the DJ-1 protein, and allow accurate genotype-phenotype correlation studies. Although brain material from patients with *DJ-1*-related forms is not currently available, the presence of the DJ-1 protein is being investigated in brains from patients with Lewy body disease, as well as other neurodegenerative diseases. These studies might provide clues on the involvement of DJ-1 in common forms of neurodegeneration. Lastly, functional studies are in progress to elucidate further the role of DJ-1, identify its interacting partners, and explore possible relationships with the proteins encoded by the other genes firmly implicated in PD: *α-synuclein* and *parkin* [8]. Understanding the role of DJ-1 in the brain and the *DJ-1*-related disease might shed light on the mechanisms of brain maintenance and the pathogenesis of classical PD.

Acknowledgements We thank the families studied for their cooperation and understanding, and the members of the "Italian Parkinson Genetics Network" for their contributions. The work described in this paper was supported in part by the Parkinson Disease Foundation/National Parkinson Foundation (USA), the Princes Beatrix Foundation (NL), and the "Ministero dell'Istruzione, Universita' e Ricerca" (MIUR, IT).

References

1. van Duijn CM, Dekker MC, Bonifati V et al (2001) Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. Am J Hum Genet 69:629–634
2. Bonifati V, Breedveld GJ, Squitieri F et al (2002) Localization of autosomal recessive early-onset parkinsonism to chromosome 1p36 (PARK7) in an independent dataset. Ann Neurol 51:253–256
3. Dekker M, Bonifati V, van Swieten J et al (2003) Clinical features and neuroimaging of PARK7-linked parkinsonism. Mov Disord (in press)
4. Bonifati V, Rizzu P, van Baren MJ et al (2003) Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 299:256–259
5. Mitsumoto A, Nakagawa Y, Takeuchi A et al (2001) Oxidized forms of peroxiredoxins and DJ-1 on two-dimensional gels increased in response to sublethal levels of paraquat. Free Radic Res 35:301–310
6. de Nobel H, Lawrie L, Brul S et al (2001) Parallel and comparative analysis of the proteome and transcriptome of sorbic acid-stressed Saccharomyces cerevisiae. Yeast 18:1413–1428
7. Trotter EW, Kao CM, Berenfeld L et al (2002) Misfolded proteins are competent to mediate a subset of the responses to heat shock in Saccharomyces cerevisiae. J Biol Chem 277:44817–44825
8. Dawson TM, Dawson VL (2003) Rare genetic mutations shed light on the pathogenesis of Parkinson disease. J Clin Invest 111:145–151