Alpha-synuclein and familial Parkinson's disease

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SNCA multiplication is a cause for familial Parkinson's disease (PD). We have identified several families with SNCA multiplication. Molecular characterization was performed using real-time PCR, SNP arrays, and haplotype analysis. We further studied those patients who were found to harbor SNCA duplication with olfactory function tests, polysomnography, and PET. We identified six families and one sporadic patient with SNCA duplication, and one family with SNCA triplication, respectively. The lifetime estimate of overall penetrance was ca. 40%. FDG-PET study of symptomatic patients showed hypometabolism in the occipital lobe, whereas asymptomatic carriers of SNCA duplication demonstrated normal glucose metabolism. Symptomatic patients showed abnormal olfactory function and polysomnography and asymptomatic carriers showed normal results. The clinical features of SNCA duplication include parkinsonism with or without dementia. Asymptomatic carriers displayed normal test results with the eldest individual aged 79 years; thus, even a carrier of SNCA duplication may escape the development of PD. This difference in age-associated penetrance may be due to the genetic background or environmental exposures. Further studies of SNCA multiplication carriers will help identify disease-modifiers and may open novel avenues for future treatment. IN addition to SNCA multiplication, we have identified homozygous A53V mutation. This is the first homozygous missense mutation. Clinical features revealed mild phenotypes even though the presence two allele mutations. In this symposium, I will discuss the relationship between clinical phenotypes and genotypes including gene dosage.