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THE GENE VARIABILITY OF NEURONAL NITRIC OXIDE SYNTHASE AFFECTS COGNITIVE FUNCTIONING AND SURVIVAL IN THE ELDERLY

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Nitric oxide (NO) is an important endogenous mediator involved in the regulation of the cardiovascular, nervous and immune systems. In mammals, NO is synthesized by a complex family of enzymes named NO synthases (NOS), encoded by 3 distinct NOS genes, including: neuronal (*nNOS or NOS-1*), inducible (*iNOS or NOS-2*) and endothelial (*eNOS or NOS-3*). The regulation of NO production is a crucial process to ensure homeostasis in tissues and apparatus. NO is involved in the regulation of many metabolic pathways, and in particular seems to play a crucial role in the process of brain aging. Indeed, at the level of CNS, NO, synthesized by *NOS-1*, acts as neurotransmitter, neuromodulator, or intracellular signaling molecule. The variability of *NOS-1* gene has been proved to affect both pathological and normal phenotypes correlated to cognitive function. Since the maintenance of cognitive abilities is an important factor for successful aging and it is a major component of the quality of life in the elderly, we tested the association between two selected SNPs (rs1879517 and rs2683826) falling in the *NOS-1* gene and the preservation of cognitive function in the elderly, and its possible effects on survival. Cognitive function was measured by Mini Mental State Examination (MMSE), corrected for age and school-attendance rate. A sample of 624 subjects from southern Italy (age range 60-107 years) was screened for *NOS-1* variability. We found that within the 65-89 years age range (the prevalence of cognitive impairment is greatest in this age group) the C/C genotype relative to the rs1879517 is overrepresented in subjects with impaired cognitive function (MMSE < or = 23) compared to those with conserved cognitive function (MMSE > 23) ($p=0.04$). As cognitive functions have a crucial role in survival chance in the elderly, the correlation between these polymorphisms and survival was then analyzed in a larger sample divided into two specific age groups (subjects aged from 60 to 85 years and subjects aged over 85). A significant association was found under the recessive model for minor allele C of rs1879517 ($p=0.004$) suggesting the C/C genotype to be detrimental for survival in the elderly. The rs1879517 variant it is located in the promoter region, but there are no data indicating its functional role. *In vitro* studies will be carried out to clarify this point.