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Mitochondrial Genetics And Stroke Recovery

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Introduction: Spontaneous recovery after stroke is variable and incomplete. Some of this variability might arise from genetic factors. We previously described a significant association between poorer stroke recovery and presence of either BDNF val66met or ApoE4 polymorphism. Another set of genetic factors of potential interest pertains to mitochondrial haplotype. Variation in mitochondrial haplotype is important to cellular energy metabolism and thus potentially to brain reformatting after stroke, and has significant clinical associations e.g., increased longevity and risk of degenerative disease. The current study examined the hypothesis that variation in mitochondrial DNA (mtDNA) haplotype is associated with degree of recovery from stroke. **Methods:** This study examined data from 241 patients from the Glycine Antagonist In Neuroprotection (GAIN) studies. Inclusion criteria included treatment started within 6 hr of stroke symptom onset, age >= 18 yr, and limb weakness. Determination of mtDNA haplotype in stored blood samples was carried out by analysis of the hypervariable sequences of the non-coding region and by PCR-RFLP of the mtDNA. Behavioral data acquired during the trial were used to evaluate recovery in relation to genotype. The primary endpoint was change in the NIH Stroke Scale (NIHSS) score from acute to 1 month after stroke, with secondary endpoints examining change to 3 months post-stroke as well as change in modified Rankin Scale (mRS) and Barthel Index (BI). NIHSS was assessed acutely (immediately prior to treatment) as well as 1 and 3 months post-stroke; mRS was estimated pre-stroke then assessed 1 month and 3 months post-stroke; BI was assessed 1 week, 1 month, and 3 months post-stroke. **Results:** Sufficient DNA was available to determine the mtDNA haplotype in 227/241 subjects. Across the 6 mtDNA haplotypes, Kruskal-Wallis testing did not find a difference in relation to change in the primary endpoint or in any of the secondary endpoints. When each of the 6 haplotypes was examined separately, results suggested an effect of one haplotype: subjects with the R0 mtDNA haplotype (n=102) had a higher change in the primary endpoint compared to subjects (n=125) without the R0 mtDNA haplotype (median improvement in NIHSS score from acute to 1 month post-stroke 5 vs. 4 points, $P<0.005$, Wilcoxon Rank Sums test). **Conclusions:** Mitochondria generate cellular energy as well as reactive oxygen species. Variation in mitochondrial genetics might therefore influence recovery from stroke, a possibility suggested by the association that genetic variability in other pathways has with recovery from stroke in human subjects. The current findings suggest this might be true in relation to the R0 mtDNA haplotype. These findings might be of value to stroke trials, for example for stratification, and might suggest future avenues for treatment strategies according to individual genotype.

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