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General Summary

Human herpesvirus is capable of establishing a lifelong latent infection of their host, is reactivated frequently. We are studying the molecular mechanism of latency and pathogenesis of human cytomegalovirus (HCMV) and human herpesvirus 6 (HHV-6), and find a novel latent protein of HHV-6 which associate with and mood disorders. We are also trying to apply HHV-6 and HHV-7 to the tools for studying the mechanism of fatigue. Salivary HHV-6 and HHV-7 DNA amounts increased with training and decreased with rest, suggesting usefulness as biomarkers of physiological fatigue. Additionally we study on cognitive impairment and Alzheimer's disease which we have previously shown the relationship to fatigue and herpesvirus reactivation.

Research Activities

HHV-6 and HHV-7 are biomarkers for fatigue which distinguish between physiological fatigue and pathological fatigue

Fatigue reduces productivity and is a risk factor for lifestyle diseases and mental disorders. Physiological fatigue occurs in everyone but decreases with rest. Pathological fatigue, however, greatly reduces quality of life and requires therapeutic interventions. Therefore, these 2 types of fatigue must be distinguished, but biomarkers for distinguishing them have not been identified. We report on the measurement of salivary HHV-6 and HHV-7 as biomarkers for quantifying physiological fatigue. We observed that salivary HHV-6 and HHV-7 increased with military training and work and rapidly decreased with rest. Our results suggest that macrophage activation and differentiation are necessary for virus reactivation. However, HHV-6 and HHV-7 did not increase in subjects with obstructive sleep apnea syndrome, CFS, and major depressive disorder, which are thought to cause pathological fatigue. Thus, HHV-6 and HHV-7 would be useful biomarkers for distinguishing between physiological fatigue and pathological fatigue. Our findings suggest a fundamentally new approach to evaluating fatigue and preventing fatigue-related diseases.

Caregiver burden and fatigue in caregivers of people with dementia: Measuring human HHV-6 and HHV-7 DNA levels in saliva

Purpose: We examined chronic fatigue, which has not been investigated in detail, in caregivers for family members with dementia.

Methods: The subjects of this study were 44 community-dwelling family caregivers and 50 elderly persons who were not caregivers. We measured salivary levels of HHV-6 and HHV-7 DNA and used the Chalder Fatigue Questionnaire (CFQ) to assess levels of fatigue; we also used the Center for Epidemiologic Studies Depression Scale, the Physi-

cal Activity Scale for the Elderly, the Zarit Caregiver Burden Interview, the Mini-Mental State Examination, the Assessment of Motor and Process Skills, and the Dementia Behavior Disturbance Scale.

Results: The salivary HHV-6 DNA levels and the CFQ scores were significantly higher in caregivers than in elderly persons. The salivary HHV-6 DNA levels in caregivers were significantly correlated with depressive symptoms, the cognitive function of the family members with dementia, and the activities of daily living/instrumental activities of daily living abilities of the patients. The CFQ scores in caregivers significantly correlated with caregiver burden, depression symptoms, leisure physical activity, the number of other family caregivers, the hours spent by caregiving per week, behavior disturbances, and activities of daily living/instrumental activities of daily living abilities.

Conclusions: The salivary HHV-6 DNA level is a new biomarker for caregiver exhaustion. To estimate the burden of caregivers of family members with dementia, fatigue assessments should be performed with a questionnaire, such as the CFQ, and the search for a biomarker, such as the salivary HHV-6 DNA level.

Publications

Suzuki A, Shibata N, Kasanuki K, Nagata T, Shinagawa S, Kobayashi N, Ohnuma T, Takeshita Y, Kawai E, Takayama T, Nishioka K, Motoi Y, Hattori N, Nakayama K, Yamada H, Arai H. Genetic Association between Presenilin 2 Polymorphisms and Alzheimer's Disease and Dementia of Lewy Body Type in a Japanese Population. *Dement geriatr cogn dis extra*. 2016; **6**: 90-7.

Osaki T, Morikawa T, Kajita H, Kobayashi N, Kondo K, Maeda K. Caregiver burden and fatigue in caregivers of people with dementia: Measuring human herpesvirus (HHV)-6 and -7 DNA levels in saliva. *Arch Gerontol Geriatr*. 2016; **66**: 42-8.

Shinagawa S, Kobayashi N, Nagata T, Kusaka A, Yamada H, Kondo K, Nakayama K. DNA methylation in the NCAPH2/LMF2 promoter region is associated with hippocampal atrophy in Alzheimer's disease and amnesic mild cognitive impairment patients. *Neurosci Lett*. 2016; **629**: 33-7.

Aoki R, Kobayashi N, Suzuki G, Kuratsune H, Shimada K, Oka N, Takahashi M, Yamadera

W, Iwashita M, Tokuno S, Nibuya M, Tanichi M, Mukai Y, Mitani K, Kondo K, Ito H, Nakayama K. Human herpesvirus 6 and 7 are biomarkers for fatigue, which distinguish between physiological fatigue and pathological fatigue. *Biochem Biophys Res Commun*. 2016; **478**: 424-30.

Takeshita Y, Shibata N, Kasanuki K, Nagata T, Shinagawa S, Kobayashi N, Ohnuma T, Suzuki A, Kawai E, Takayama T, Nishioka K, Motoi Y, Hattori N, Nakayama K, Yamada H, Arai H. Genetic association between RAGE polymorphisms and Alzheimer's disease and Lewy body dementias in a Japanese cohort: a case-control study. *Int J Geriatr Psychiatry*. Epub 2016 Oct 4.

Kobayashi N, Shinagawa S, Nagata T, Shimada K, Shibata N, Ohnuma T, Kasanuki K, Arai H, Yamada H, Nakayama K, Kondo K. Usefulness of DNA Methylation Levels in COASY and SPINT1 Gene Promoter Regions as Biomarkers in Diagnosis of Alzheimer's Disease and Amnesic Mild Cognitive Impairment. *PLoS one*. 2016; **11**: e0168816.