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RIN3 Protein Mutation and Astrocyte Dynamics in the Hippocampus: Implications for Alzheimer's Disease

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Extended Abstract

Alzheimer's Disease (AD), a progressive neurodegenerative disorder, is the leading cause of dementia and deteriorates memory and cognitive function. As found in the pathogenesis of AD, if the amyloid-precursor protein (APP) aggregates to form amyloid plaques at abnormal levels [1], the synaptic communication and cellular trafficking processes could be potentially disrupted [2]. Guanine nucleotide exchange factor Ras and Rab Interactor 3 (RIN3) also plays a significant role in the regulation of endocytic pathways, strengthening the aggregation of APP formation [2][3][4]. Of all researched AD cases, an estimated 5-6% are diagnosed with a specific type of AD disease, Early-Onset Alzheimer's Disease, which occurs when symptoms present and diagnosis are made prior to age 65 [5]. It has been determined in previous studies that the missense mutation in protein RIN3, known as W63C, plays a predominant role in patients with early-onset AD [2][4]. The altered function of RIN3 could be a potential factor for the loss of synaptic communication observed in patients with AD [2][4]. This study focuses on analyzing the astrocytes in the hippocampus of mouse models with various genotypes of the W63C mutation to further predict the role of this variant in brain cell health and memory.

Brain tissue samples were collected from five mice, categorized into three genotypic groups: Wild Type (WT), Homozygous (HOMO) for the RIN3 W63C mutation, and Heterozygous (HET) for the same mutation. One mouse was assigned to the WT group, while the HOMO and HET groups each included two mice, in order to investigate astrocyte proliferation in the hippocampus. The use of immunohistochemistry enabled the observation of astrocyte intensities with red fluorescent labeling, utilizing GFAP—a type of glial cell marker in the central nervous system (CNS)—which indicates astrogliosis and contributes to the formation of intermediate filaments. After collecting the images, the intensities across the genotypic variants of the hippocampus were compared, followed by a Two-Way ANOVA statistical analysis and post-hoc familywise comparison tests to identify any significant differences. Intensity of astrocyte signals in hippocampal regions was manually measured and cross-checked for consistency between individuals. Normalized intensities were calculated by dividing the total intensity by the total area of the selected regions, allowing for comparison between various genotypes.

This project aims to identify the specific effects of the RIN3 protein mutation, W63C, in Alzheimer's Disease, contributing to the ongoing research aimed at preventing brain cell function and memory decay in individuals with AD. The project hypothesized that the W63C point mutation in RIN3 is implicated in an increased number of activated astrocytes in hetero or/and homozygous animals compared to wild type. However, the results did not show a significant difference between the conditions and categories. Nonetheless, the data revealed a trend: the HOMO group exhibited a higher range of intensity values compared to the HET and WT groups. This suggests that astrocytes may be increased in homozygotes for the RIN3 mutation to compensate for dysfunctional neuronal cells.

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