rs7294919 is an intergenic SNP associated with hippocampal volume. The SNP is located between two genes, HRK (1) and FBXW8 (2), but evidence suggests that it influences the expression level of a gene 3' to FBXW8, TESC (3). Each copy of the T allele was associated with a 107.8 mm^3 decrease in hippocampal volume (4). In European populations, the effect allele (T) is found at frequency of 0.898 (5). The minor allele (C) is found at a frequency of 0.102.

The hippocampus is a critical brain structure involved in learning and memory. In particular, it is associated with the ability to form long-term memories of facts and events (6). This is in contrast to short-term and working memory, which have been shown to be independent of the hippocampus (7). Hippocampal size decreases with age and is diminished in several disorders including Alzheimer's Disease (8), Major Depressive Disorder (9), Post-traumatic Stress Disorder (10), and Schizophrenia (11). Moreover, the size of the structure is heritable, with estimates of heritability ranging from 40-70% (10, 12).

Two major studies were conducted which found an association between rs7294919 and hippocampal volume. They were published in the April 15th, 2012 issue of *Nature Genetics* (4, 13). Though the P-values and regression slopes differ, both studies, together comprising tens of thousands of individuals, agree that the T allele is negatively associated with hippocampal volume.

The first study uses the CHARGE consortium (Cohorts for Heart and Aging Research in Genomic Epidemiology) as its discovery cohort (4). CHARGE comprises 8 sub-cohorts representing 9,232 people with an average age of 67.1 years. Most of the sub-cohorts were from Europe and hippocampal volume was determined using MRI. Second stage verification/replication was performed on two cohorts comprising 2,318 subjects. This study found that rs7294919 was associated with hippocampal volume with a meta-P value (combining the discovery and replication cohorts) of 2.9×10^{-11} and a regression slope (β) of -107.8 mm^3 hippocampal volume.

The authors provide some speculation about the SNP's mechanism of action by reviewing the neighboring two genes. HRK is involved in apoptosis of neurons and is thought to play a role in ischemia-induced apoptosis. FBXW8 targets an E3 ubiquitin ligase to protein aggregates and has been shown to be involved in hippocampal neuron dendrite growth. Potential pitfalls of this study include the older age of the participants, the mixture of both computerized and manual hippocampus tracing in MRIs, and the predominantly European ethnic makeup of the cohorts.

The second study's discovery cohort comprised 17 European-ancestry cohorts representing 5,775 healthy people with a mean age of 34.8 years (13). An additional 2,020 people with various neuropsychiatric disorders were also included to determine whether the SNPs had disease-specific effects. To verify/replicate their findings, they used several cohorts comprising both European-ancestry and non-European populations (Yoruba and Los Angeles Mexican).

The study found that rs7294919 was associated with hippocampal volume with a combined P value of 1.99×10^{-7} with a regression slope of -42.74 mm^3. The authors also examined the association of the SNP with IQ. While no association was found with full-scale IQ, a small association was found between having the C (minor) allele and an increase in verbal IQ ($P = 0.043$, $\beta = 0.126$). Using data from existing databases (14), rs7294919 (really rs4767492, a SNP used to impute rs7294919) was associated with expression of tescalin (TESC), a gene which lies 3' to FBXW8 in the brain. The T allele (associated with lower hippocampal volume) was associated with higher expression levels of TESC. TESC itself is expressed during brain development and is thought to regulate differentiation and proliferation. However, it is still not clear how increased TESC levels could be responsible for a decrease in hippocampal volume without additional studies.

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