ABSTRACT

The exact cause of age-related dementia is still unknown due to involvement of multifactorial genes. Linkage analysis is most pragmatic way to clarify the cause of disease in recent days. Senescence accelerated mouse prone 8 (SAMP8) strain exhibits age-related learning and memory deficits (LMD) at 2 months of age well before the median age of survival (17.2 months), which further aggravates with advancing age without displaying other signs of premature aging. Japanese fancy mouse (JF1) strain derived from Japanese wild mouse (*Mus musculus molossinus*) showing normal learning and memory function. In step-through passive avoidance response with 264 F2 intercross SAMP8 x JF1 mice, SAMP8 exhibiting short retention time while JF1 exhibiting normal long retention time. From genetic analysis of SAMP8 mouse using the whole genome scan for quantitative trait loci (QTL) to specify the impairment in step-through passive avoidance test, five loci have been identified with significant linkage to chromosomes 1, 12, 13 and 15 related to manifestations of LMD. Three of them on chromosomes 1, 12 and 13 are due to SAMP8 background while two of them on chromosome 15 are derived from JF1 background despite parental JF1 strain shows normal phenotype. The aim of this work is to search for the candidate genes related with learning and memory dysfunction in SAMP8 mice. RNA-seq and micro array analysis of LMD locus on Chromosome 13 identified *Hcn*1 gene out of 29 genes. Hcn1 in SAMP8 strain showed 15 times less polyglutamine repetition compared to JF1. Whole cell patch clamp analysis showed that Hcn1 ion conductivity was significantly lower in SAMP8 compared to that of JF1, which may be associated with learning and memory deficiency. Although Senescence-resistant strain 1 (SAMR1) did not show any severe learning and memory dysfunction, SAMR1 has the same length of CAG repetition like SAMP8 mice. Considering SAMP8 has other LMD loci, *Hcn1* is not enough to cause

learning and memory dysfunction alone thoroughly in SAMR1 strain. Combination with genes from other loci may affect learning and memory deficiency in SAMP8 mice. Therefore, I have searched for the genes possessing differences between SAMP8 and SAMR1 strains in other loci from SAMP8 background. In this purpose, transcriptome analysis of LMD region containing 218 genes on Chromosome 12 was performed. Micro array analysis of these genes showed no significant differences in the level of gene expression between SAMP8, SAMR1 and JF1 strains. However, RNA-seq analysis showed that 3 genes possess SAMP8 specific SNPs while 1 gene was found with extremely low level expression in SAMP8 compared to SAMR1 and JF1 strains. Finally, 4 genes were sorted out to be possible candidate gene in relation with learning and memory dysfunction which requires more studies in details to narrow down the most reliable candidate gene.