Genome-wide meta-analyses of cognitive decline across neurocognitive domains in older adults stratified by *APOE* genotype

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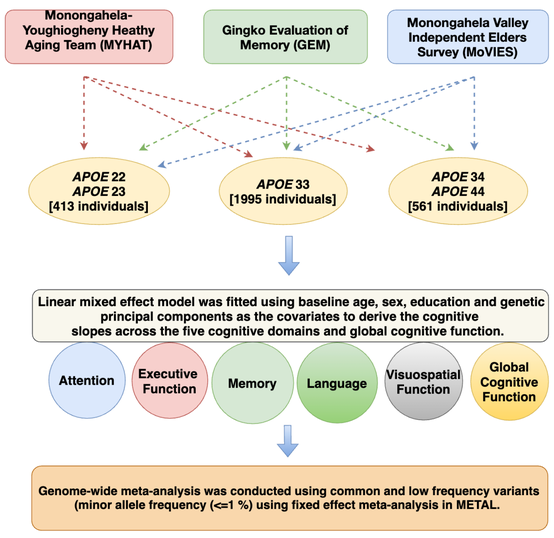
BACKGROUND

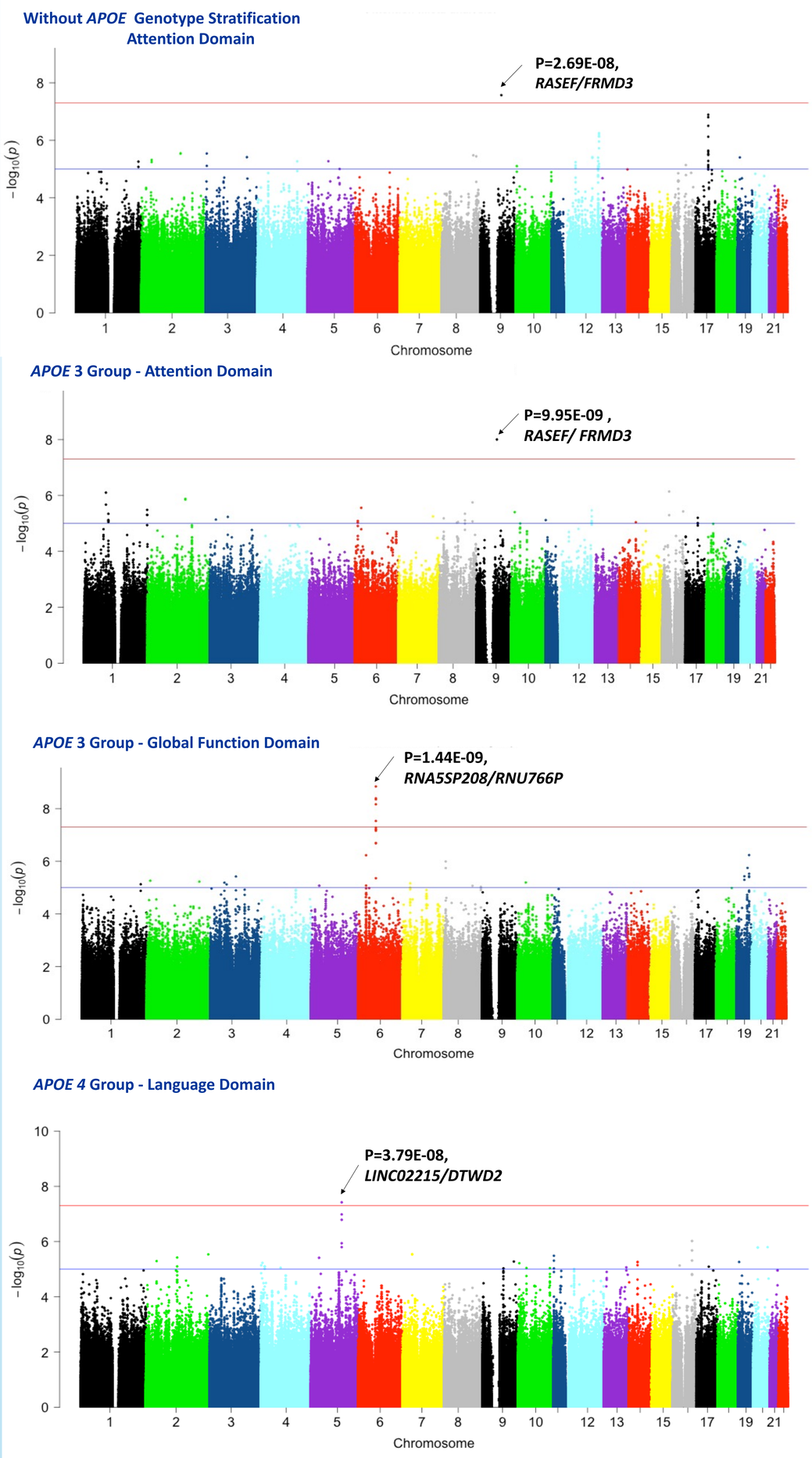
- Apolipoprotein (*APOE*) is one of strongest risk factors for late-onset Alzheimer's disease (LOAD).
- The *APOE* polymorphism is determined by three alleles (*E2*, *E3* and *E4*), resulting into six genotypes: *APOE* 22, 23, 24, 33, 34 and 44.
- *APOE* polymorphism has a differential effect on the risk of LOAD such that the *E4* allele is associated with increased and *E2* with decreased risk of AD as compared to E3 allele.[1]
- *APOE*4 allele has also been associated with cognitive decline in healthy adults, especially with decline of memory, executive function and global cognitive function. [2,3]
- The strong effect of *APOE4* might mask the effect of other genetic factors of cognitive aging.
- In order to identify novel genetic markers associated with age-related cognitive decline, we conducted genome-wide meta-analyses in three *APOE* groups: E2 (22/23 genotypes), E3 (33 genotype) E4 (34/44 genotypes); subjects with 24 genotype were excluded.

METHODS



- Individuals aged 65 and above from three longitudinal cohorts were assessed for the intra-individual variation in cognition.

RESULTS



- A previously described novel signal for decline of attention on Chr9q21.32 in this sample without *APOE* genotype stratification (top Figure) was found to be confined in the *APOE* 3 group at genome-wide significance (GWS) level (β= -0.288; P=9.95E-09; 2nd from top Figure).
- In the *APOE* 3 group, we identified a novel GWS signal for decline of global cognitive function on Chr6q12 (β= -0.507; P=1.44E-09) in the intergenic region (3rd from top Figure). The same signal was also observed at a nominal significance in the *APOE* 23/22 group, but in the opposite direction (β= 0.57; P= 2.75E-03).
- In the *APOE*4 group, we observed a novel signal for decline of language on Chr5q23.1 (β= 0.693; P=3.79E-08) in the intergenic region (bottom Figure).

DISCUSSION

- As described previously, the Chr9q21.32 signal is an eQTL for the nearby genes, *RASEF*, *KIF27* and *IDNK* in blood and brain tissues and these genes play a role in RNA-binding. [2]
- The intergenic signal near *RNA5SP208* and *RNU766P* on chromosome 6 in the *APOE* 3 group, which is associated with global cognitive decline, is found to be in linkage disequilibrium (LD) with reported significant SNPs associated with educational attainment[4] and cognitive decline in AD.[5]
- *RNA5SP208* is a ribosomal pseudogene and *RNU766P* codes for the U7-small nucleolar pseudogene, both of which are expressed in the brain. Although pseudogenes have been thought to be non-functional, recent studies suggest pseudo-genes might be expressed in a tissue-specific manner and could be involved in gene-silencing.
- The chromosome 5 signal associated with decline of language in *APOE4* group is an eQTL for *HSD17B4* (p=1.92E-08), *DTWD2* (p=0.0048) and *DMXL1* (p=0.0052) in blood. Interestingly, *HSD17B4* is a known risk gene for Perrault syndrome, an autosomal recessive disorder with hearing loss, intellectual disability and cerebral ataxia [6] and a variant eQTL for *DTWD2,* rs421765 , has been previously associated with severe otitis media, severe ear infection, in an Australian Aboriginal population.[7]
- Children with congenital hearing loss also manifest language delay and cognitive impairment. The association of genes involved in auditory loss and infection with decline of language in older adults suggests the potential role of these genetic variants in the decline of language in older age.

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