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GENETICS

African-origin protective haplotype for Alzheimer's disease in *APOEε4* carriers

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Abstract

Background: We have reported a statistical interaction between the African ancestry specific A allele at rs10423769 and *APOEε4*, where the presence of the A allele is associated with a reduction in AD risk up to 75% in *APOEε4* homozygotes. The mechanism by which this variant confers protection could provide insights into new therapeutics for *APOEε4* carriers. However, the genomic context of this protective variant is complex with a high number of segmental duplications (SD) and structural variants (SVs). Thus, we have used advanced genomic techniques to investigate the region of ~2MB between rs10423769_A and *APOE* to gain further insights into potential AD-protective mechanisms.

Method: We used high-coverage (90x) PacBio HiFi whole genome sequencing on 9 samples of rs10423769_A/A, rs10423769_A/G, and rs10423769_G/G carriers. We performed genome assembly with hifiasm to identify contigs spanning the whole region between the protective allele and *APOE*. We compared the contigs using minigraph and Bandage. We performed Hi-C sequencing from 13 brain autopsy samples (seven rs10423769_A carriers) and used in-house bioinformatics tools (enhanced Hi-C Capture Analysis - eHiCA) to identify chromatin loops indicative of potential interactions between the protective and *APOE* loci.

Result: Long read sequencing detected the co-occurrence of an expanded VNTR containing multiple MEF2D transcription factor binding sites within the protective haplotype. A higher number of SVs in the SD region surrounding rs10423769_A

haplotype were detected when compared to the reference and are under investigation. eHiCA using rs10423769 or the *APOE* promoter as the bait suggested that rs10423769 locus and the *APOE* promoter region have evidence of long-range, physical interactions. Furthermore, both rs10423769 locus and the *APOE* promoter interact with common regions in between the two baits, including a cluster of zinc finger (*ZNF*) genes upstream of *APOE*. The reciprocal eHiCAs suggest high confidence interactions between these loci and with other regions of chr19.

Conclusion: Our results show that the protective haplotype locus of African origin has long-range, physical interactions with the *APOE* promoter and other regions on chr19. It also carries an expanded VNTR specific to the protective haplotype containing multiple transcription factor binding sites.