

LONGITUDINAL EFFECTS OF ALZHEIMER'S DISEASE-ASSOCIATED RISK VARIANTS ON MEMORY, LANGUAGE, AND EXECUTIVE FUNCTION DOMAINS

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ABSTRACT

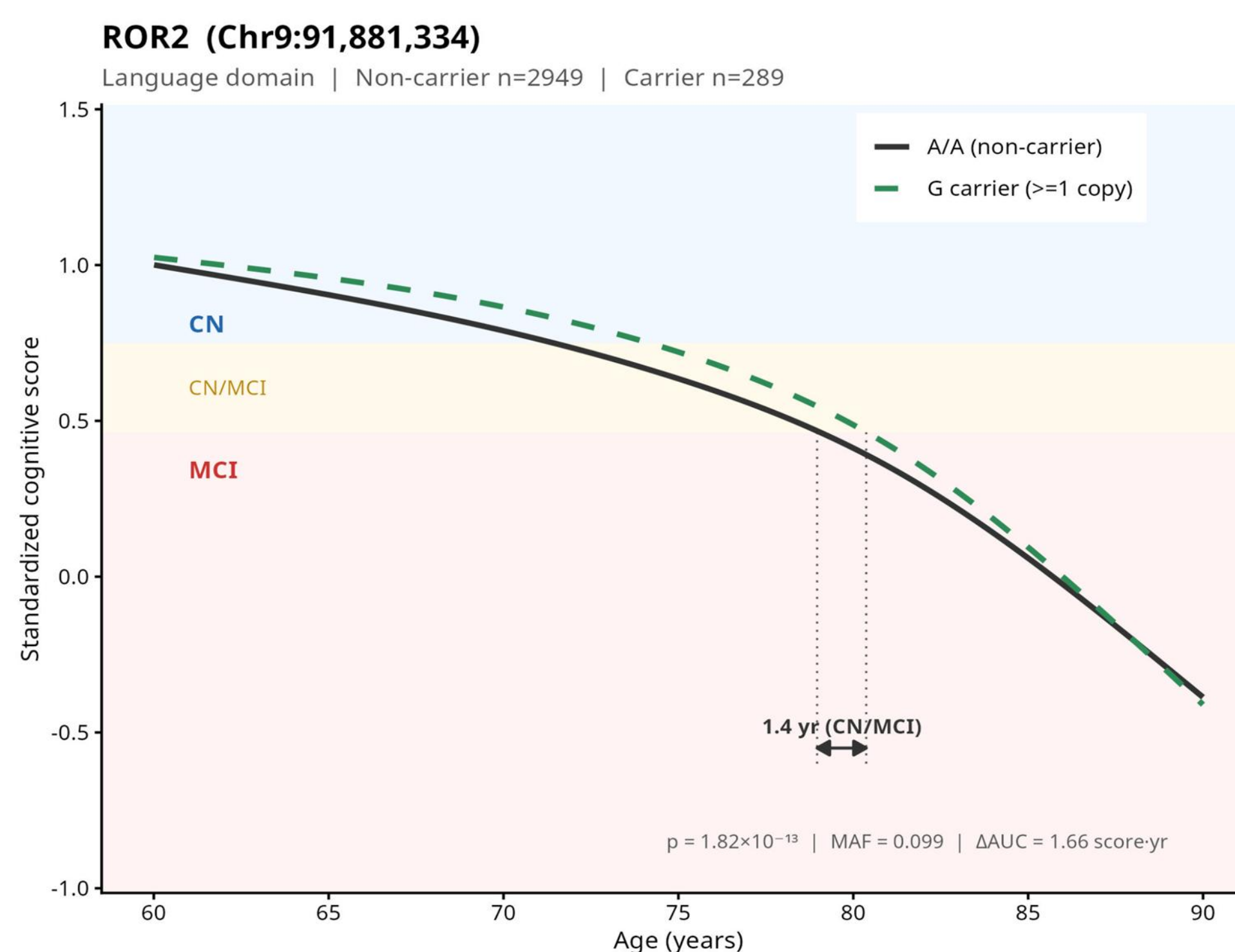
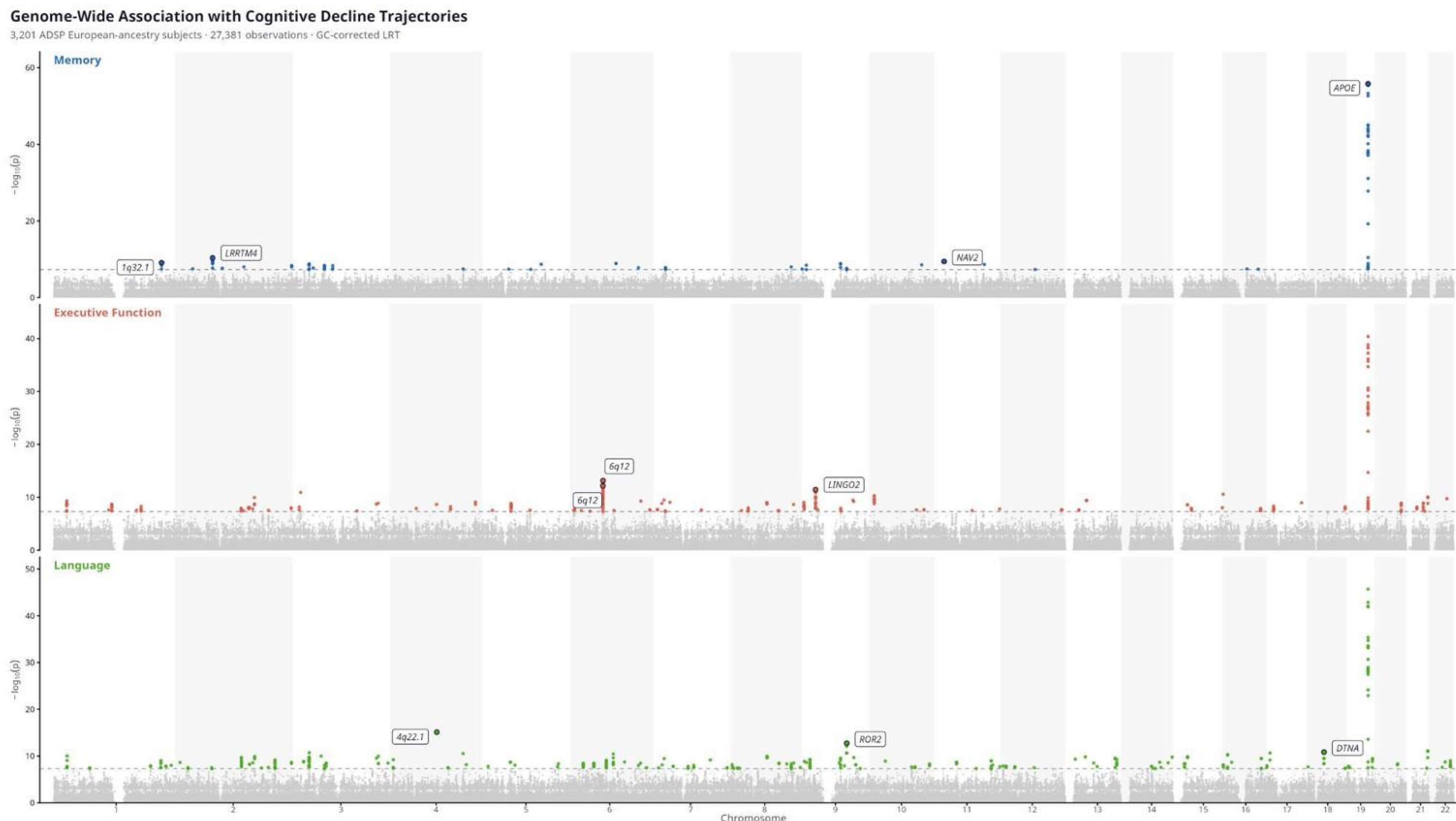
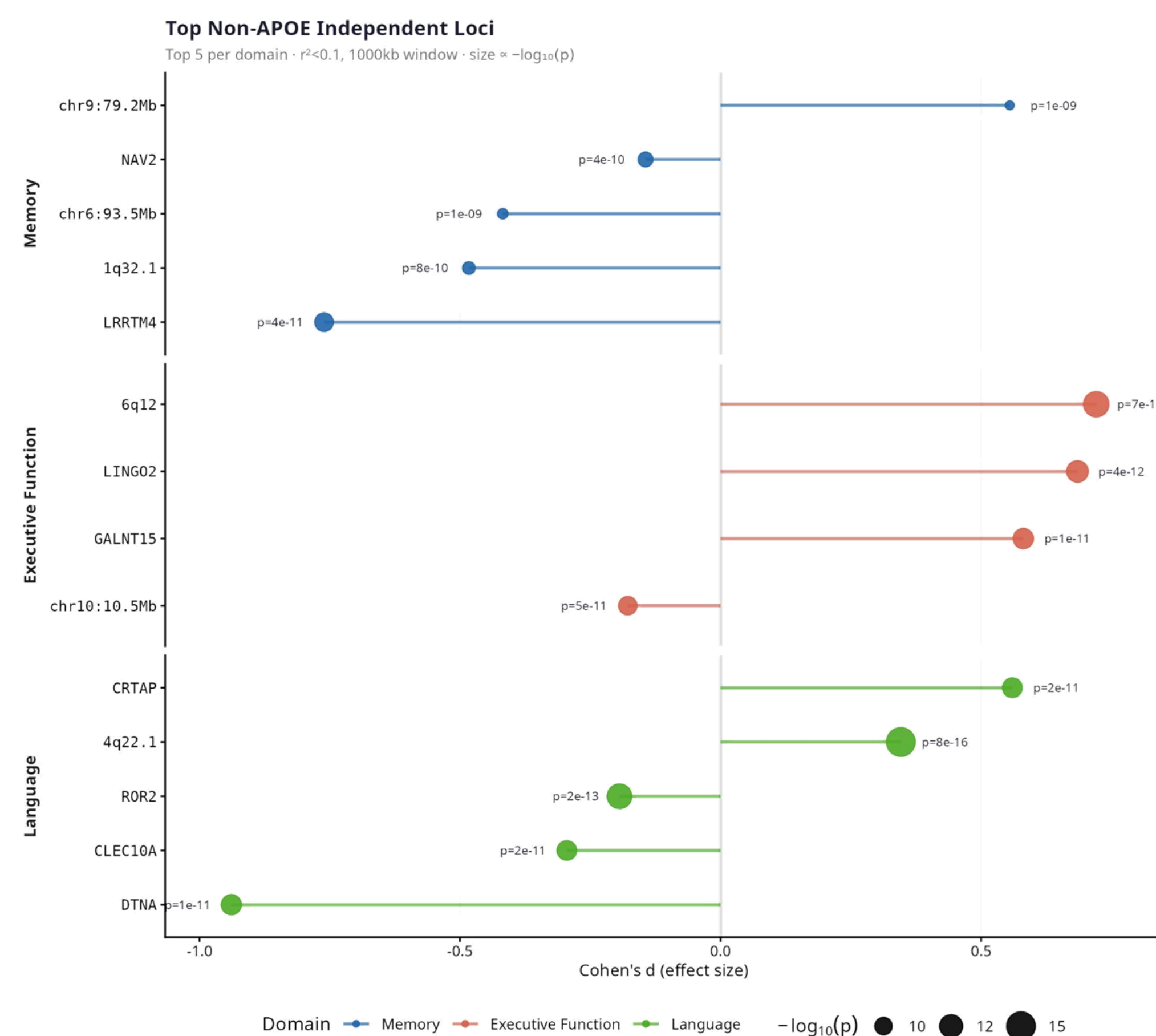
Building on a targeted analysis of 62 Bellenguez 2022 AD candidate loci that identified domain-specific cognitive trajectory effects, we extend this framework to genome-wide discovery across all 22 autosomes (~7M variants) in 3,201 ADSP European-ancestry subjects, identifying 232 independent loci that modify cognitive decline trajectories across memory, executive function, and language domains.

OBJECTIVE

Most analyses of cognitive measures over time use linear assumptions which may not fully characterize variation in disease trajectory. In this analysis, we applied hierarchical mixed-effects spline models across ~7M genetic variants to identify common variants that modify cognitive decline trajectories across memory, executive function, and language, with LD-based independent locus identification across the full genome. We specifically wanted to identify models undetectable with linear modeling approaches.

METHODS

- 3,201 ADSP European-ancestry subjects; 27,381 observations; memory, executive function, language
- Hierarchical LME: SNP×age interaction via natural splines (df=2–5, delta-SABIC selected); ML estimation
- Additive model; dominant fallback; LRT p-value for interaction term
- GW significance $p < 5 \times 10^{-8}$; GC correction for within-subject LRT inflation ($\lambda = 2.4\text{--}3.1 \rightarrow 1.2\text{--}1.3$)
- Trajectories reconstructed from spline coefficients at ADSP cohort knot positions



RESULTS AND EVALUATION

- Genome-wide discovery across 3,201 EUR-ancestry subjects, 27,381 observations: 232 GW-significant independent loci ($p < 5 \times 10^{-8}$, $r^2 < 0.1$) across all 22 autosomes
- Language most polygenic (127 loci), followed by executive function (74) and memory (31); 16 loci significant in ≥ 2 domains
- APOE region dominates top signals across all three domains (mem $p = 1.7 \times 10^{-56}$, lan $p = 2 \times 10^{-46}$, exf $p = 4 \times 10^{-41}$)
- Top novel loci: LINGO2 (exf, $p = 3.7 \times 10^{-12}$), ROR2 (lan, $p = 1.8 \times 10^{-13}$), DTNA (lan, $p = 1.4 \times 10^{-11}$), LRRTM4 (mem, $p = 4.5 \times 10^{-11}$), NAV2 (mem, $p = 3.8 \times 10^{-10}$)
- 75% of genome-wide significant loci are not significant when evaluated with linear models.

CONCLUSIONS

- Genome-wide hierarchical spline modeling identifies 232 independent loci modifying cognitive decline trajectories — a largely distinct architecture from standard AD onset/risk GWAS
- Language is the most genetically polygenic domain (127 loci); novel loci implicate synaptic adhesion (LRRTM4), axon guidance (ROR2), myelination (LINGO2), and cytoskeletal biology (DTNA, NAV2)
- ROR2 G-carriers show 1.4-year delay in language MCI threshold crossing ($p = 1.8 \times 10^{-13}$, $\Delta AUC = +1.66$ score·yr) — illustrating the clinical interpretability of trajectory-based discovery
- Effect directions balanced across domains; 16 loci significant in ≥ 2 domains suggest shared cross-domain regulatory mechanisms
- Limitation: Common variant focus (MAF $> 1\%$); low-frequency trajectory-modifying variants (TREML2) require targeted or multi-ancestry approaches

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References

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