3D Chromatin Condensates & Non-B DNA | Signal Rating: 4/5 Stars | Oct 29, 2026 | 11 min read

Chromosome 19q13.32 APOE-TOMM40-APOC1 G-Quadruplex Condensates & Pangenome VNTR Phase-Switching

High-resolution non-B DNA complexity, 94-haplotype pangenome walk topology, and 3D Micro-C condensate compaction across the 320 kb human 19q13.32 apolipoprotein locus.

Combining non-B DNA complexity scanning, 94-haplotype pangenome graph topology, and 3D Micro-C chromatin modeling across 320 kb of human chromosome 19q13.32 suggests that the GC-rich APOE Exon 4 CpG/G-quadruplex island and the TOMM40 Intron 6 poly-T tandem repeat co-localize in modeled 3D space with the downstream APOC1 enhancer. On the APOE4 haplotype, the linked Very-Long intronic repeat correlates with higher modeled splice-junction divergence and a +69.4% shift in simulated 3D contact connectivity.

1. High-Resolution Compositional & Non-B DNA Architecture of the 19q13.32 Apolipoprotein Cluster

The human chromosome 19q13.32 apolipoprotein locus houses a tightly linked 60 kb core regulatory neighborhood comprising TOMM40 (outer mitochondrial membrane translocase 40), APOE (apolipoprotein E), APOC1 (apolipoprotein C-I), the tissue-specific multienhancers ME.1 and ME.2, and the segmentally duplicated pseudogene APOC1P1 . While clinical genetics has historically focused on the two non-synonymous SNPs within APOE Exon 4 -- rs429358 (c.388T>C , p.Cys130Arg / mature p.Cys112Arg) and rs7412 (c.526C>T , p.Arg176Cys / mature p.Arg158Cys) -- single-nucleus RNA-seq from Alzheimer's disease cortex suggests that the APOE4 haplotype also exhibits altered astrocytic and disease-associated microglial (DAM) transcriptional kinetics compared with APOE3 haplotypes in identical cellular states.

To resolve the physical sequence grammar governing 19q13.32 chromatin topology, we partitioned the verified NCBI RefSeq GRCh38 genomic slice (NC_000019.10:44,890,001-44,950,000 , 60,000 bp) into six functional subwindows and evaluated dinucleotide Shannon entropy (H 2), Lempel-Ziv -76 normalized complexity (LZ76), DNA-walk Hurst long-range correlation (H), G4Hunter G-quadruplex propensity (25-nt sliding window, threshold | S | >= 1.45), and Z-DNA propensity.

| Window ID | | GRCh38 Coordinates | | Genomic Feature & Regulatory Role | | Length (bp) | | GC (%) | | CpG O/E | | H2 (bits) | | LZ76 Norm | | Hurst (H) | | G4 Motifs | | G4 Max |S| | | Z-DNA Score | | Anomaly Z (SD) |

| WIN-01-TOMM40-BODY | | NC_000019.10:44890569-44899500 | | TOMM40 Exons 1-5 & Proximal Introns | | 8932 | | 56.66 | | 0.3963 | | 3.9117 | | 0.9140 | | 0.6508 | | 220 | | 2.32 | | 0.6382 | | 3.38 |

| WIN-02-TOMM40-IVS6-VNTR | | NC_000019.10:44899501-44903689 | | TOMM40 Intron 6 rs10524523 Poly-T/G4 Switch & Exons 6-10 | | 4189 | | 55.38 | | 0.2991 | | 3.9085 | | 0.9062 | | 0.6147 | | 92 | | 2.60 | | 0.4774 | | 3.34 |

| WIN-03-APOE-PROM-EX1-3 | | NC_000019.10:44905001-44907750 | | APOE Proximal Promoter, Bipartite Enhancer & Exons 1-3 | | 2750 | | 57.42 | | 0.3314 | | 3.8928 | | 0.9078 | | 0.6475 | | 248 | | 2.72 | | 0.1091 | | 3.72 |

| WIN-04-APOE-EXON4-CPG-G4 | | NC_000019.10:44907751-44909393 | | APOE Exon 4 Ultradense CpG/G4 Island (Codons 112/136/158/236) | | 1643 | | 66.10 | | 0.6145 | | 3.7786 | | 0.8940 | | 0.7817 | | 56 | | 2.20 | | 1.1564 | | 4.64 |

| WIN-05-APOC1-ME1-ENHANCER | | NC_000019.10:44914247-44921500 | | APOC1 Gene Body & Multienhancer ME.1/ME.2 Condensate Hub | | 7254 | | 51.27 | | 0.3299 | | 3.9319 | | 0.8407 | | 0.6219 | | 151 | | 2.28 | | 0.3722 | | 2.63 |

| WIN-06-APOC1P1-PSEUDOGENE | | NC_000019.10:44926900-44931500 | | APOC1P1 Segmentally Duplicated Pseudogene Paralog | | 4601 | | 52.25 | | 0.3394 | | 3.9211 | | 0.8383 | | 0.6480 | | 53 | | 1.96 | | 0.4130 | | 2.50 |

Generated by: Native Rust Sliding-Window Information-Theoretic & Non-B DNA Scanner (complexity.rs : Shannon H3 + LZ76 + DFA + G4Hunter + Z-DNA) * Native Rust Codon dN/dS, Selection Relaxation (RELAX k) & Trait-Loss Engine (pseudo_pancryptic.rs) * Native Rust 3D Chromatin Graph Laplacian & RNA Phase-Separation Scaffolder Engine (coevo_condensate_clonal.rs)

Two quantitative features stand out across the 60 kb window. First, WIN-04-APOE-EXON4-CPG-G4 (NC_000019.10:44,907,751-44,909,393) is a coding CpG island (66.10% GC overall and 74.2% GC across the central 860 bp coding core; CpG O/E = 0.6145) with the highest DNA-walk persistent memory in the cluster (Hurst H = 0.7817) and a Z-DNA alternating purine- pyrimidine score of 1.1564 (Z = +4.64 SD). Furthermore, replacing thymine with cytosine at codon 112 in APOE4 (TGC -> CGC , rs429358) creates an additional methylatable CpG dinucleotide inside a GC-rich G-quadruplex stem. Second, the proximal APOE promoter and Intron 1 enhancer (WIN-03-APOE-PROM-EX1-3) harbor 248 overlapping G4Hunter windows reaching | S | = 2.72, while TOMM40 Intron 6 (WIN-02-TOMM40-IVS6-VNTR) reaches | S | = 2.60 immediately flanking the polymorphic rs10524523 poly-T tract.

2. Diagnostic Power Profile & Empirical Assay Failure Boundaries at 19q13.32

Before modeling 3D chromatin phase separation, we evaluated the diagnostic resolution and empirical failure boundaries of standard sequencing and genotyping assays across the TOMM40 - APOE - APOC1 locus . Because APOE Exon 4 combines extreme GC content (up to 74.2% GC) with downstream segmental duplication between APOC1 and APOC1P1 (91.8% sequence identity across 4.6 kb), conventional short-read and unanchored amplicon workflows suffer systematic dropout and paralog collapse.

| Genomic Element | | Optimal Diagnostic Window | | Empirical Failure Boundary | | Corrective Assay Rescue Protocol |

| APOE Exon 4 Coding Core (NC_000019.10:44908672-44908839 ; Codons 108-163) | | Definitive resolution of canonical 2 (Cys112/Cys158), 3 (Cys112/Arg158), 4 (Arg112/Arg158), and Christchurch (Arg136Ser) alleles (H d = 0.8301, 96.5% bootstrap when phased). | | 1. Upstream Exon 2-3 amplicon blindness: Amplicons targeting Exon 3 (NM_000041.4:180-341) yield d K2P = 0.0000 across 2/ 3/ 4 (gap = 0.0042, 46% bootstrap). 2. High-GC PCR allelic dropout: 74.2% GC core and G4 stems

(| S | = 2.20) stall standard Taq polymerase on the CGC (4) template. | | Span full Exon 4 codons 112-251 with betaine/DMSO or 7-deaza-dGTP G4-resolving mastermix, or use long-read PacBio HiFi / ONT cis-phasing across rs429358 - rs10524523 - rs7412 . |

| TOMM40 Intron 6 Poly-T / G4 VNTR (rs10524523 ; NC_000019.10:44899790-44899835) | | Stratifies Short (S, < 20 T), Long (L, 20-29 T; linked to APOE4), and Very-Long (VL, >= 30 T) cis-regulatory haplotypes (H walk = 5.64 bits) that modulate AD age-of-onset and cryptic splicing (JSD = 0.348 bits). | | Polymerase slippage & stutter shadow: Standard Illumina short-read calling and capillary PCR across >= 30 dT homopolymers flanked by G4 tracts (| S | = 2.60) produce +/-3-6 nt indel stutter and fail to phase rs10524523 with APOE Codon 112 (9.8 kb away). | | Use amplification-free Cas9-targeted nanopore/HiFi long reads spanning the 15 kb TOMM40 - APOE interval and align directly to the 94-haplotype HPRC GFA pangenome graph. |

| APOC1 vs. APOC1P1 Enhancer Duplication (NC_000019.10:44914247-44931500) | | Captures hepatic and astrocytic multienhancer (ME.1/ME.2) 3D chromatin loop anchors and ChIP-seq/Micro-C regulatory occupancy. | | Segmental duplication paralog collapse: Unanchored 150 bp short reads share 91.8% sequence identity between functional APOC1 and pseudogene APOC1P1 , collapsing isoform/enhancer attribution (mapping JSD = 0.0312 bits, 44% bootstrap). | | Require >= 2.5 kb mate-pair or long-read anchoring across the unique intergenic ME.1/ME.2 spacer and filter multi-mapped reads at MAPQ >= 30 . |

3. Pangenome Bubble Topology, 3D Micro-C Condensate Compaction & In Silico Hybridization Modeling

Mapping 94 phased assemblies from the Human Pangenome Reference Consortium (HPRC) across the 320 kb 19q13.32 window (NC_000019.10:44,750,001-45,070,000) reveals a complex structural bubble centered on TOMM40 Intron 6 through the APOC1 multienhancer (142 GFA nodes, 179 edges, cyclomatic complexity beta 1 = 38, topological walk entropy H walk = 5.64 bits). On haplotypes carrying the Short (S, 14-19 T) rs10524523 repeat (predominantly linked to APOE3), RNA Polymerase II is modeled to traverse TOMM40 Intron 6 without stalling, consistent with canonical splicing of TOMM40 Exons 6-7 and a dynamically equilibrated 3D chromatin loop at the downstream APOC1 ME.1/ME.2 enhancer (Fiedler algebraic connectivity 2 = 0.284, von Neumann graph entropy S vN = 3.42 bits).

In contrast, when the Long (L, 22-29 T) or Very-Long (VL, 30-39 T) rs10524523 allele is paired in cis with the 74.2%-GC APOE4 Exon 4 CpG island, sequence-structure modeling across the G-rich non-template strand of TOMM40 Intron 6 predicts a stable parallel G-quadruplex / DNA:RNA hybrid motif (G4Hunter | S | = 2.60) that correlates with two modeled structural shifts:

* Modeled Splice-Junction Divergence in TOMM40 : Sequence-motif scoring at the Intron 6 G4/poly-T boundary correlates with elevated TOMM40 exon-6/7 alternative splice junction divergence (Jensen-Shannon divergence JSD = 0.348 bits vs. Short alleles).

* 3D Micro-C Contact Compaction (+69.37% 2 Shift): Spectral Laplacian evaluation of the 60 kb TOMM40 - APOE - APOC1 contact matrix indicates that simulated G4/R-loop

bridging between TOMM40 Intron 6 (WIN-02), the APOE promoter/Exon 4 G4 island (WIN-03 / WIN-04), and the APOC1 ME.1/ME.2 enhancer (WIN-05) shifts Fiedler algebraic connectivity from 2 = 0.284 to 2 = 0.481 (+69.37% compaction; von Neumann entropy shift Delta S vN = 0.71 bits to 2.71 bits).

| 19q13.32 Cis-Haplotype State | | rs10524523 Poly-T Length (nt) | | APOE Exon 4 Codon 112/158 | | Pangenome Walk Entropy (bits) | | TOMM40 Splicing JSD (bits) | | Micro-C Fiedler Lambda2 | | Condensate Shift vs WT (%) | | Von Neumann Entropy (bits) | | Modeled Burst Ratio | | In Silico Hybridization DeltaDeltaG (kcal/mol) |

| HPRC-E3-Short (Baseline Reference) | | 16 | | Cys112 / Arg158 | | 4.12 | | 0.042 | | 0.2840 | | 0.00 | | 3.4210 | | 1.00 | | -4.20 |

| HPRC-E2-Long (E2 Haplotype) | | 24 | | Cys112 / Cys158 | | 4.68 | | 0.118 | | 0.3120 | | 9.86 | | 3.2840 | | 1.18 | | -6.80 |

| HPRC-E3-VeryLong (E3-VL Haplotype) | | 33 | | Cys112 / Arg158 | | 5.38 | | 0.294 | | 0.4320 | | 52.11 | | 2.8650 | | 1.76 | | -14.10 |

| HPRC-E4-Long (E4-L Haplotype) | | 27 | | Arg112 / Arg158 | | 5.49 | | 0.312 | | 0.4560 | | 60.56 | | 2.7920 | | 1.94 | | -14.85 |

| HPRC-E4-VeryLong (E4-VL Haplotype) | | 35 | | Arg112 / Arg158 | | 5.64 | | 0.348 | | 0.4810 | | 69.37 | | 2.7110 | | 2.14 | | -15.60 |

| HPRC-E4-VL (In Silico Unfolded G4 Control) | | 35 | | Arg112 / Arg158 | | 5.64 | | 0.068 | | 0.2990 | | 5.28 | | 3.3640 | | 1.08 | | -15.60 |

Generated by: Native Rust Haplotype Clustering & Minimum Spanning Network Engine (haplo.rs) * Native Rust GFA Pangenome Graph Topology, Residue-Interaction Network (RIN) & Cryptic Cavity Engine (pseudo_pancryptic.rs) * Native Rust 3D Chromatin Graph Laplacian & RNA Phase-Separation Scaffolder Engine (coevo_condensate_clonal.rs)

4. Focal Sequence Alignment & Structural Cladogram of the 19q13.32 Regulatory Haplotypes

To annotate sequence conservation across the 19q13.32 cluster, we aligned the APOE Exon 4 diagnostic core (NC_000019.10:44,908,672-44,908,767) across human haplotypes and non-human primate reference assemblies, alongside the neighbor-joining topology of the six 19q13.32 cis-regulatory haplotypes. The alignment highlights how the c.388T>C (Cys112Arg) substitution at nt 44,908,684 introduces an extra CpG dinucleotide (GTGCGC) directly inside Helix 3.

Generated by: Native Rust Gotoh 3-State Affine-Gap & 9-mer Anchor Multiple Sequence Aligner (phylo.rs) * Native Rust Somatic Coalescent, 96-Channel Mutational JSD & Synthetic Lethality Engine (coevo_condensate_clonal.rs)

Generated by: Native Rust K2P / TN93 Distance, Neighbor-Joining & ABGD Systematics Engine (phylo.rs) * Native Rust Haplotype Clustering & Minimum Spanning Network Engine (haplo.rs)

Generated by: Native Rust K2P / TN93 Distance, Neighbor-Joining & ABGD Systematics Engine (phylo.rs)

Discussion & Key Takeaways

Candidate Cis-Regulatory Condensate Hypothesis for TOMM40 rs10524523 Across APOE4 and APOE3 Backgrounds: Clinical cohorts have reported that individuals homozygous for APOE3 who carry the Very-Long (VL, >= 30 T) TOMM40 rs10524523 repeat may experience earlier cerebral amyloidosis than APOE3 carriers with Short (S, < 20 T) alleles, while APOE4 alleles are frequently inherited in linkage with L/VL repeats. Our 320 kb chromosome 19q13.32 analysis offers one computational line of evidence suggesting a candidate mechanism for further human investigation: high G-quadruplex density across TOMM40 Intron 6 and the APOE Exon 4 CpG island correlates with increased modeled 3D contact connectivity toward the downstream APOC1 ME.1/ME.2 multienhancer (+52.11% to +69.37% 2 shift) and elevated TOMM40 intron-6 splice-junction divergence (JSD = 0.294-0.348 bits).

In Silico Thermodynamic Profile of the Intron-6 G4/Poly-T Boundary: Sliding-window nearest-neighbor hybridization scoring across the TOMM40 Intron 6 G-quadruplex boundary highlights an 18-nt window (NC_000019.10:44,899,795-44,899,812 , predicted DeltaDelta G = 15.60 kcal/mol) where secondary-structure unfolding is modeled to reduce simulated contact connectivity toward baseline levels (2 = 0.2990). Together with the Exon 4 and rs10524523 diagnostic failure boundaries mapped in Table 2, these computational informatics findings provide specific sequence coordinates and long-read phasing parameters that can contribute to functional genomics, neurogenetics cohort phasing, and clinical sequencing assay design.

5. Data Provenance & Verification Ledger

| Accession / Identifier | | Organism & Assembly | | Genomic Coordinates / Length | | Verification Status |

| NC_000019.10:44890001-44950000 | | Homo sapiens (GRCh38.p14 Primary Assembly Chr 19) | | 60000 | | NCBI RefSeq Verified (SHA-256 Cached) |

| NM_000041.4 | | Homo sapiens APOE mRNA Transcript Variant 1 | | 1226 | | NCBI RefSeq Verified (SHA-256 Cached) |

| NC_006486.4:44410001-44415000 | | Pan troglodytes (Clint_PTRv2 Chr 19 APOE Ortholog) | | 5000 | | NCBI RefSeq Verified (SHA-256 Cached) |

| NC_041772.1:49222001-49227000 | | Macaca mulatta (Mmul_10 Chr 19 APOE Ortholog) | | 5000 | | NCBI RefSeq Verified (SHA-256 Cached) |

Generated by: NCBI Entrez E-Utilities (efetch.fcgi) * CRV Science Labs PoliteCacheManager (fetch.rs)

6. References & Primary Literature

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