Supplementary Table S1: Supplementary_Table_S1.xlsx

Quality control metrics for Hi-C datasets used in this study. This table summarizes key quality control (QC) statistics for the three Hi-C datasets analyzed in this study: in-house NPC Hi-C**,** public NPC Hi-C, and microglia Hi-C. Metrics include sequencing depth, mapping efficiency, PCR duplication rate, and contact composition, providing an overview of data quality and usability for downstream 3D genome analyses.

- **N1 (# of raw reads):** Total number of sequenced read pairs generated.
- **N2 (# of uniquely mapped reads, MAPQ ≥ 30):** Read pairs uniquely aligned to the reference genome with high mapping confidence.
- **N3 (# of reads after PCR duplicate removal):** Uniquely mapped read pairs remaining after removal of PCR duplicates.
- **N4 (# of inter-chromosomal reads):** Valid Hi-C read pairs mapping to different chromosomes.
- **N5 (# of intra-chromosomal reads):** Valid Hi-C read pairs mapping within the same chromosome.
- **N6 (# of intra-chromosomal reads < 20 kb):** Short-range intra-chromosomal contacts (<20 kb).
- **N7 (# of intra-chromosomal reads ≥ 20 kb):** Long-range intra-chromosomal contacts (≥20 kb).

Derived metrics:

- **% of inter-chromosomal reads (N4/N3):** Fraction of inter-chromosomal contacts among non-duplicated reads.
- **% of intra-chromosomal reads ≥ 20 kb (N7/N5):** Proportion of long-range intra-chromosomal contacts, indicative of library quality for higher-order chromatin structure analysis.
- **PCR duplication rate (1 − N3/N2):** Estimated fraction of duplicated reads.
- **Data usage (N7/N1):** Fraction of raw reads contributing to long-range intra-chromosomal contacts used for downstream analyses.

Supplementary Table S2: Supplementary_Table_S2.xlsx

CTCF motif–mutated regions and intersecting NPC test regions. This table summarizes the genomic coordinates of CTCF motif–mutated regions and their intersections with NPC Hi-C test regions used for *in silico* mutagenesis and disruption analysis in this study.

Sheet 1: CTCF mutated regions and intersected NPC test regions

This sheet lists all CTCF motif instances selected for mutagenesis and the corresponding NPC test regions in which they reside.

Sheet 2: CTCF mutated regions and top disrupted NPC test regions

This sheet reports a subset of CTCF-mutated regions paired with the top three NPC test regions showing the strongest predicted disruption.

Supplementary Table S3: Supplementary_Table_S3.xlsx

Disruption scores of CTCF motif–mutated regions.

This table summarizes the predicted impact of CTCF motif mutations on 3D chromatin organization across NPC test regions. Each row corresponds to a genomic region containing a mutated CTCF motif and reports the magnitude of structural and signal-level perturbation predicted by the iNeuroAkita model.

Supplementary Table S4: Supplementary_Table_S4.xlsx

Functional variant input dataset. This table lists experimentally supported functional genetic variants used as input for downstream analyses in this study. Variants were curated from prior functional assays, including MPRA, CROP-seq, and CRISPR-based

perturbation experiments, and represent AD- and PSP-associated regulatory variants with reported transcriptional or regulatory effects.

Supplementary Table S5: Supplementary_Table_S5.xlsx

Disruption scores for functional regulatory variants. This table summarizes predicted 3D chromatin disruption scores for 42 experimentally supported functional variants**,** computed using the iNeuroAkita model. Scores quantify the impact of each variant on predicted chromatin contact maps and integrate multiple disruption metrics into a composite measure.

Supplementary Table S6: Supplementary_Table_S6.xlsx

Fine-mapped significant microglial eQTLs. This table lists fine-mapped, statistically significant eQTL variants in microglia. These eQTLs were used to link AD-associated variants and predicted 3D chromatin perturbations to transcriptional regulation in disease-relevant brain cell types.

Supplementary Table S7: Supplementary_Table_S7.xlsx

Top microglial eQTLs ranked by predicted 3D chromatin disruption. This table reports the top 37 microglial eQTL variants ranked by their predicted impact on 3D chromatin organization, as quantified by the iNeuroAkita model. Variants were prioritized based on a composite disruption score integrating multiple structural perturbation metrics derived from in silico mutagenesis.

Supplementary Table S8: Supplementary_Table_S8.xlsx

AD and ADRD-associated structural variants used as model input.

This table lists Alzheimer's disease (AD) and Alzheimer's disease–related dementia (ADRD)–associated structural variants (SVs) used as input for in silico mutagenesis and 3D genome disruption analyses in this study. Variants were curated from published large-scale SV studies and represent deletions and duplications overlapping or proximal to genes implicated in AD/ADRD risk.

Supplementary Table S9: Supplementary_Table_S9.xlsx

Genome-wide predicted disruption scores for AD/ADRD structural variants.

This table reports predicted 3D chromatin disruption scores for all Alzheimer's disease (AD) and AD-related dementia (ADRD)–associated structural variants (SVs) analyzed in this study. Scores were computed using iNeuroAkita by comparing predicted Hi-C contact maps between reference and mutated sequences generated by in silico mutagenesis. Variants are sorted by overall impact MSE score, highlighting SVs with the strongest predicted effects on chromatin architecture.