

ChimeraLM filters amplification artifacts for accurate structural variant calling in long-read single-cell sequencing

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Abstract

Single-cell genomics provides unprecedented insights into cellular heterogeneity, but **Whole Genome Amplification (WGA)**—required to obtain sufficient DNA—introduces chimeric artifacts that generate false-positive **Structural Variations (SVs)** and undermine biological interpretations. Current computational methods cannot reliably distinguish amplification-induced artifacts from genuine rearrangements. Here we present ChimeraLM, a genomic language model that learns sequence-level features to discriminate biological sequences from **WGA** artifacts. Validated on nanopore long-read data, ChimeraLM achieves 95% recall with 70% precision, reduces chimeric reads by $\sim 90\%$, and preserves 72–92% of true **SVs**. This improves **SV** validation rates 8–11 fold and eliminates artifactual **inversion (INV)** bias, restoring **SV** type distributions to bulk-like profiles. Attention visualization reveals that ChimeraLM focuses on chimeric junction regions, learning mechanistically interpretable features that generalize across sequencing platforms. By enabling reliable **SV** detection at single-cell resolution, ChimeraLM addresses a critical data quality barrier in cancer genomics, developmental biology, and somatic mosaicism studies. ChimeraLM is available at <https://github.com/ylab-hi/ChimeraLM>.

Keywords: Whole Genome Amplification, Single Cell, Genomic Language Model,
Structural Variation

Main

Single-cell genomics has revolutionized our resolution of biological heterogeneity, enabling the discovery of rare cell types and the reconstruction of clonal evolution in cancer and development [1–3]. However, a single cell contains only 6–7 picograms of DNA—approximately two genome copies—posing significant technical challenges for comprehensive genomic analysis [4, 5]. Consequently, WGA remains an unavoidable prerequisite, amplifying DNA 1,000- to 10,000-fold for high-coverage sequencing [6–8]. While WGA provides necessary material for downstream analysis, it introduces systematic errors that severely compromise genomic fidelity, particularly for SV detection [9–11].

The most pernicious of these errors are chimera artifacts—artificial DNA constructs formed when highly processive polymerases, such as phi29 in Multiple Displacement Amplification (MDA) [12], switch templates during amplification [9–11, 13]. These chimeras join discontinuous genomic loci into single molecules, mimicking the structural signatures of biological translocations (TRAs) and INVs [10]. In long-read sequencing, which is otherwise ideal for resolving complex SVs, chimeric reads can constitute 42–76% of the WGA data [9], rendering standard SV callers unreliable [14–19]. Because these tools rely on alignment heuristics and coverage deviations [14, 20], they frequently misclassify artificial chimeras as genuine variants [21].

Distinguishing biological rearrangements from amplification artifacts remains a major computational bottleneck. Current quality control methods rely on hand-crafted features—such as read-pair orientation or localized coverage drops—that fail to capture the sequence-intrinsic patterns of WGA errors [11, 13, 22]. This limitation blocks the application of single-cell long-read sequencing in contexts where precision is paramount, such as tracking somatic mosaicism or validating CRISPR off-target effects.

We reasoned that WGA artifacts possess latent sequence motifs and structural patterns distinct from genomic sequences, learnable without reliance on reference alignment. Here, we present ChimeraLM, a platform-agnostic Genomic Language Model (GLM) to identify and filter WGA artifacts with single-read resolution.

Leveraging advances in DNA foundation models [23–26], ChimeraLM treats artifact detection as a sequence modeling task rather than an alignment problem. By attending to long-range dependencies and contextual features within raw reads [23–28], ChimeraLM achieves ~90% reduction in chimeric reads while preserving 72–92% of true SVs. We demonstrate that this approach restores the fidelity of single-cell SV calling, enabling robust characterization of genomic heterogeneity at the single-cell level.

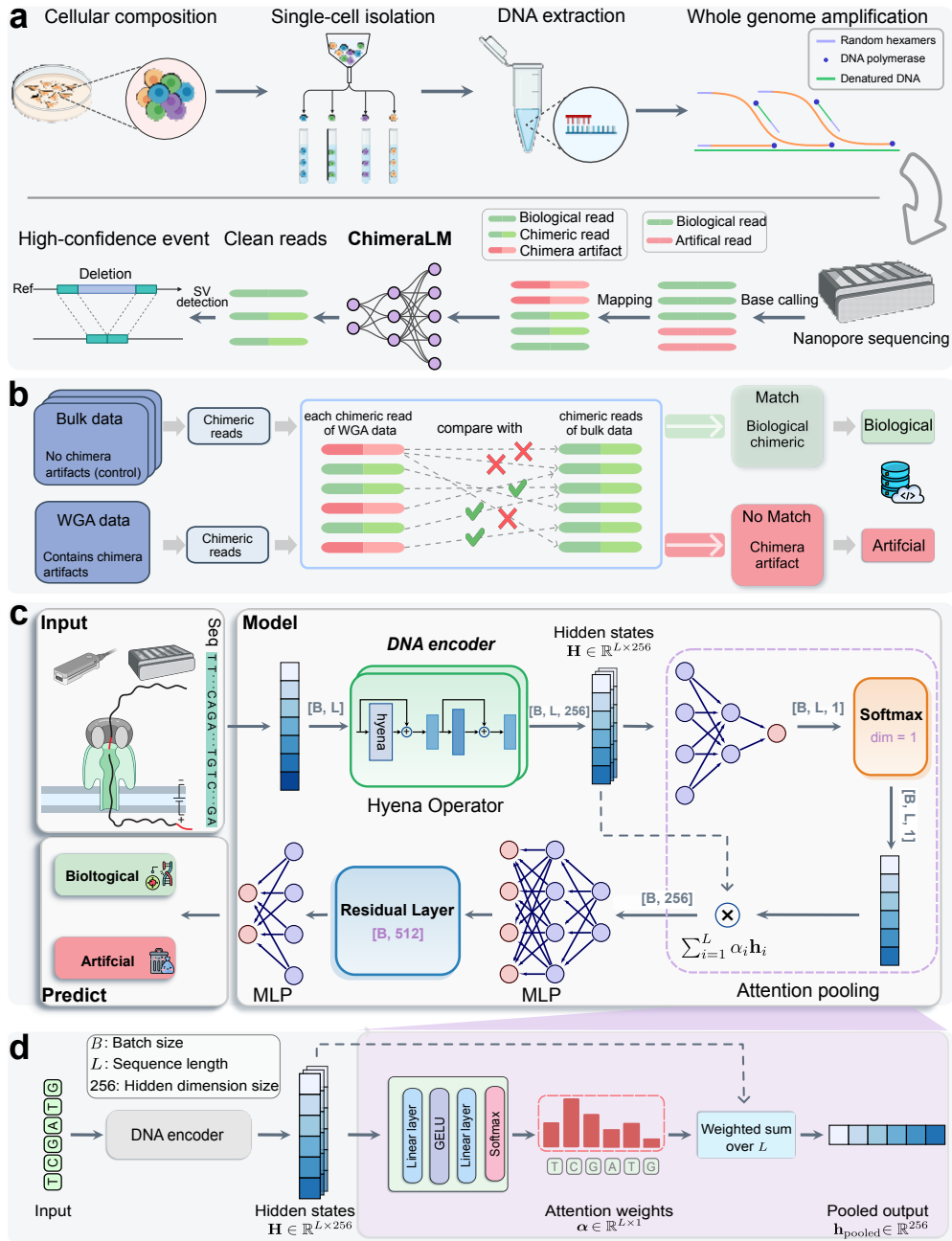


Fig. 1 ChimeraLM workflow and architecture for detecting WGA artifacts. (a) Single-cell genomic workflow and ChimeraLM integration. Single cells are isolated, followed by DNA extraction and WGA. Template switching during amplification generates chimeric artifacts (red) alongside biological reads (green). After base calling and mapping, ChimeraLM classifies chimeric reads as biological or artificial, enabling downstream SV detection on filtered data. (b) Ground truth label generation. Chimeric reads from WGA data are compared against chimeric reads from bulk sequencing of the same cell line. Reads matching bulk data are labeled biological (green); non-matching reads are labeled artificial (red). (c) ChimeraLM architecture. Input DNA sequences (batch size B , sequence length L) are tokenized at single-nucleotide resolution and encoded into hidden states $H \in \mathbb{R}^{L \times 256}$ through DNA encoder (HyenaDNA [23]). Hyena operators capture long-range dependencies. Attention pooling aggregates position-specific features, and multilayer perceptron (MLP) layers with residual connections process pooled representations for binary classification. (d) Attention pooling mechanism. Attention weights $\alpha \in \mathbb{R}^{L \times 1}$ are computed through linear layers with GELU activation and softmax normalization, assigning importance scores to each position. The weighted sum produces a fixed-dimensional representation $h_{\text{pooled}} \in \mathbb{R}^{256}$. Created with BioRender.com.

Results

Overview of ChimeraLM workflow and model architecture

Single-cell genomics relies on WGA to obtain sufficient DNA for sequencing (Fig. 1a). The standard workflow includes single-cell isolation, DNA extraction, WGA, long-read sequencing (e.g., Oxford Nanopore Technologies (ONT)), base calling, and alignment to the reference genome. During amplification, template-switching events introduce artificial chimeric reads, resulting in alignment files containing a mixture of authentic and artificial sequences that can mimic SVs and confound variant detection.

ChimeraLM integrates directly into this pipeline as a pre-processing filter, operating after read alignment but before SV detection (Fig. 1a). It evaluates each chimeric read—sequences with multiple alignments to distant genomic locations—and classifies it as either biological (genuine) or artificial (WGA-induced). This binary classification enables retention of authentic genomic sequences while removing amplification artifacts prior to variant calling.

Supervised training required a high-confidence labeled dataset (Fig. 1b; Extended Data Fig. 1a). We constructed this dataset using sequencing data from the PC3 prostate cancer cell line, which provides both WGA-amplified and non-amplified (bulk) genomic data. The key assumption is that bulk sequencing contains only genuine genomic sequences, whereas WGA data includes both genuine and artificial chimeras. Chimeric reads from the PC3 WGA PromethION dataset were systematically compared against three independent bulk datasets (ONT PromethION, ONT MinION, and Pacific Biosciences (PacBio); see Methods). WGA reads whose chimeric structures were absent from all three bulk datasets were labeled artificial; reads with structures validated in one or more bulk datasets were labeled biological.

This labeling strategy identified 12,670,396 artificial chimeric reads (zero bulk matches) and 293,180 biological chimeric reads from the WGA dataset (Extended Data Fig. 1b). To construct the training dataset, we retained all 293,180 biological reads, subsampled an equal number of artificial reads, and augmented the biological class with 178,748 chimeric reads sampled directly from bulk sequencing data—genuine structural rearrangements unaffected by amplification. This intentional class imbalance prioritizes recall of true biological reads, minimizing loss of genuine variants during filtering. The final dataset of 765,108 labeled reads was partitioned into training (70%), validation (20%), and internal test (10%) sets using stratified splitting.

The ChimeraLM architecture (Fig. 1c) addresses three technical challenges inherent to long-read classification: processing variable-length sequences spanning tens of kilobases, maintaining single-nucleotide resolution to detect abrupt compositional changes at chimeric junctions, and aggregating variable-length representations into fixed-dimensional classification outputs. Input sequences are tokenized at single-nucleotide resolution to preserve complete sequence information. The encoder employs Hyena operators [29], which achieve subquadratic scaling with sequence length, enabling analysis of full-length reads without fragmentation. We initialized the DNA encoder with weights from HyenaDNA [23], a genomic foundation model pre-trained on diverse DNA sequences. An attention pooling mechanism (Fig. 1d) aggregates

information across the entire read by computing learned, position-specific weights, producing a fixed-dimensional representation. This representation is processed through MLP layers with residual connections, and a final softmax layer outputs classification probabilities.

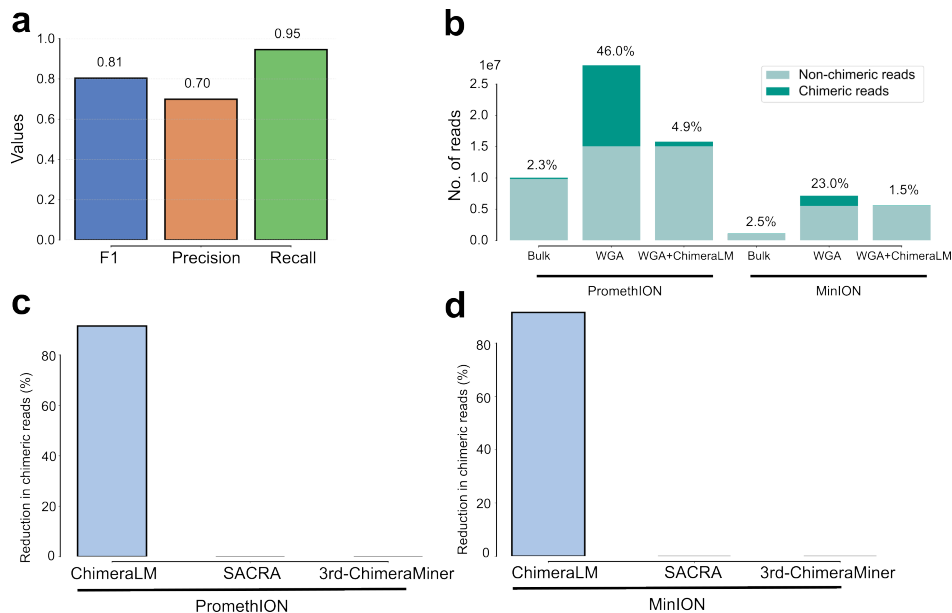


Fig. 2 ChimeraLM accurately identifies and removes WGA-induced chimeric artifacts. (a) Classification performance on held-out test data. ChimeraLM achieves recall of 0.95, precision of 0.70, and F1 score of 0.81. (b) Chimeric read reduction across sequencing platforms. Stacked bars show proportions of chimeric (dark teal) and non-chimeric (light teal) reads in bulk, WGA, and ChimeraLM-filtered samples. ChimeraLM reduces chimeric read frequencies from 46.0% to 4.9% (PromethION) and from 23.0% to 1.5% (MinION), approaching bulk levels (2.3% and 2.5%, respectively). (c,d) Benchmarking against existing methods on PromethION (c) and MinION (d). ChimeraLM achieves approximately 90% reduction in chimeric reads on both platforms; SACRA and 3rd-ChimeraMiner show no detectable reduction.

ChimeraLM achieves high accuracy and reduces artifacts to near-bulk levels across platforms

We evaluated ChimeraLM's classification accuracy on the held-out test set, which comprised reads with known biological or artificial status (Fig. 2a). The model achieved an F1 score of 0.81, with recall of 0.95 indicating that 95% of chimeric artifacts were correctly identified—critical for minimizing downstream false-positive SV calls—and precision of 0.70 confirming that the majority of flagged reads were true artifacts.

We next assessed practical effectiveness on the full PC3 WGA datasets across PromethION and MinION platforms (Fig. 2b). Bulk sequencing established low baseline chimeric read rates (2.3% for PromethION; 2.5% for MinION), whereas WGA

231 increased artifact load to 46.0% and 23.0%, respectively. After ChimeraLM filtering,
232 chimeric content dropped to 4.9% (PromethION) and 1.5% (MinION)—10- to 15-
233 fold reductions—while retaining 15.8 million and 5.6 million biological reads. This
234 restoration to near-bulk levels demonstrates effective separation of genuine reads from
235 WGA-induced artifacts.

236 We benchmarked ChimeraLM against SACRA [22] and 3rd-ChimeraMiner [13],
237 existing tools for detecting amplification-induced chimeras (Fig. 2c,d). ChimeraLM
238 achieved approximately 90% reduction in chimeric reads on both platforms; neither
239 SACRA nor 3rd-ChimeraMiner showed detectable reduction (0%).

240 The MinION results are particularly notable: this platform served as a com-
241 pletely independent test set, as the model was trained exclusively on PromethION
242 data. Effective generalization to MinION confirms that ChimeraLM learns universal
243 sequence-level features of WGA-induced artifacts rather than platform-specific signa-
244 tures. This cross-platform robustness suggests applicability beyond nanopore to other
245 long-read and short-read sequencing technologies.

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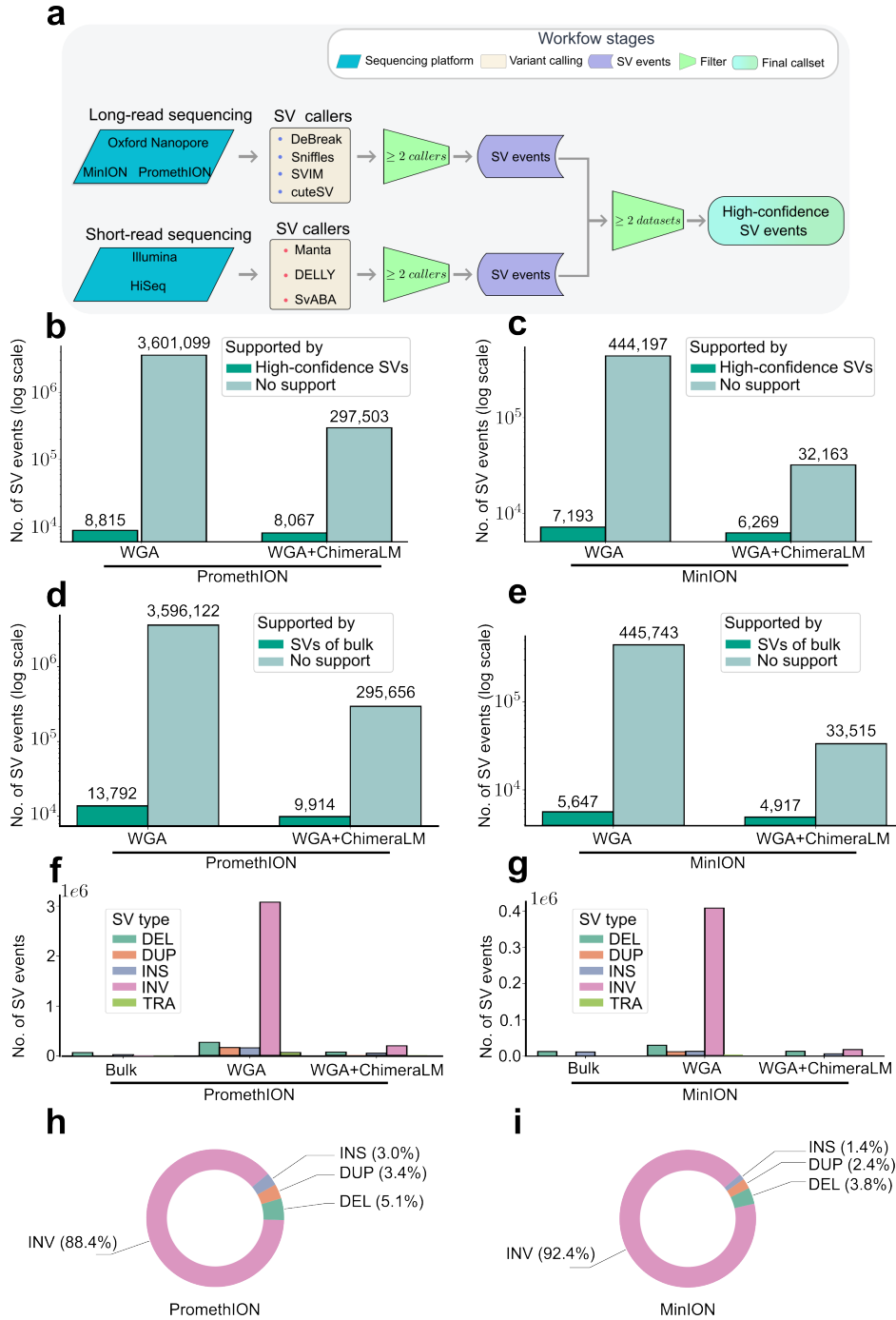


Fig. 3 ChimeraLM improves structural variant detection accuracy. (a) Construction of high-confidence SV reference dataset. PC3 bulk DNA was sequenced on multiple platforms (ONT PromethION, MinION, and Illumina HiSeq) and analyzed with multiple SV callers. Events detected by ≥ 2 callers on the same platform and supported by both long-read and short-read data were designated as gold standard SVs. (b,c) SV validation against gold standard for PromethION (b) and MinION (c). Stacked bars show SV calls (log scale) classified as gold standard-supported (dark teal) or unsupported (light teal). ChimeraLM reduces unsupported calls while preserving validated events. (d,e) SV validation against platform-matched long-read bulk sequencing for PromethION (d) and MinION (e). This reference captures true variants that may be missed by short-read data. (f,g) SV type distribution for PromethION (f) and MinION (g). Unfiltered WGA shows elevated INVs, which are reduced to bulk-like levels after ChimeraLM filtering. (h,i) Composition of artifact-supported SVs for PromethION (h) and MinION (i). Pie charts show SV types among events supported exclusively by chimeric reads, representing false positives eliminated by ChimeraLM.

ChimeraLM substantially reduces false-positive structural variant calls

To quantify ChimeraLM’s impact on SV calling accuracy, we compared variant calls from unfiltered and ChimeraLM-filtered WGA data against two independent reference standards (Fig. 3).

We first established a high-confidence gold standard SV dataset from bulk PC3 DNA sequenced on multiple platforms (ONT PromethION, ONT MinION, and Illumina HiSeq) and analyzed with multiple SV callers (Fig. 3a; Extended Data Table 1). SVs detected by ≥ 2 callers on the same platform and supported by both long-read and short-read data were retained as gold-standard events.

Unfiltered WGA data contained extensive false-positive SVs (Fig. 3b,c). On PromethION, raw WGA produced 3.6 million SV calls, of which only 8,815 (0.24%) matched gold standard events—over 99% were artifacts. After ChimeraLM filtering, total calls dropped to 305,570 while retaining 8,067 gold standard events (91.5% of true variants), raising the validation rate to 2.64% (11-fold improvement). MinION data showed similar improvements: calls reduced from 451,390 to 38,432 with validation rate increasing from 1.59% to 16.3% (10-fold improvement) while retaining 87.2% of true variants.

We next performed platform-matched validation, comparing WGA-derived SV calls against long-read bulk sequencing from the same platform (Fig. 3d,e). This reference captures true SVs that may be missed by short-read data, providing a more inclusive measure of recall. ChimeraLM increased validation rates from 0.38% to 3.24% on PromethION (8.5-fold improvement) and from 1.25% to 12.79% on MinION (10-fold improvement), while retaining 71.9% and 87.1% of bulk-supported events, respectively.

Together, ChimeraLM reduces false-positive SV calls by 8–11 fold while preserving 72–92% of true variants, substantially enhancing the signal-to-noise ratio in single-cell SV discovery.

ChimeraLM restores unbiased SV-type distributions

Amplification artifacts can distort the apparent spectrum of SVs. We compared SV type distributions across bulk, unfiltered WGA, and ChimeraLM-filtered datasets (Fig. 3f,g). Bulk sequencing showed balanced proportions of deletions (DELs), duplications (DUPs), insertions (INSs), INVs, and TRAs. Unfiltered WGA data exhibited dramatic overrepresentation of INVs on both platforms, consistent with amplification artifacts. After ChimeraLM filtering, SV distributions were restored toward bulk-like profiles: excessive INVs were markedly reduced while other categories remained stable, reflecting selective removal of artifact-supported INVs rather than indiscriminate loss of genuine signals.

To characterize the artifact composition, we analyzed SV calls supported exclusively by reads classified as chimera artifacts (Fig. 3h,i). These artifact-supported events were dominated by INVs, comprising 88.4% on PromethION and 92.4% on MinION—consistent with template-switching junctions producing inversion-like alignment signatures. Smaller fractions of DELs (5.1% and 3.8%), DUPs (3.4% and 2.4%), and INSs (3.0% and 1.4%) indicate that WGA-induced chimeras can mimic diverse SV categories.

Although **INVs** predominate, the presence of other **SV** types among chimeric events indicates that comprehensive filtering—rather than inversion-specific correction—is essential for accurate **SV** detection. By restoring biologically representative **SV** type distributions, ChimeraLM enables robust and interpretable characterization of **SV** in single cells.

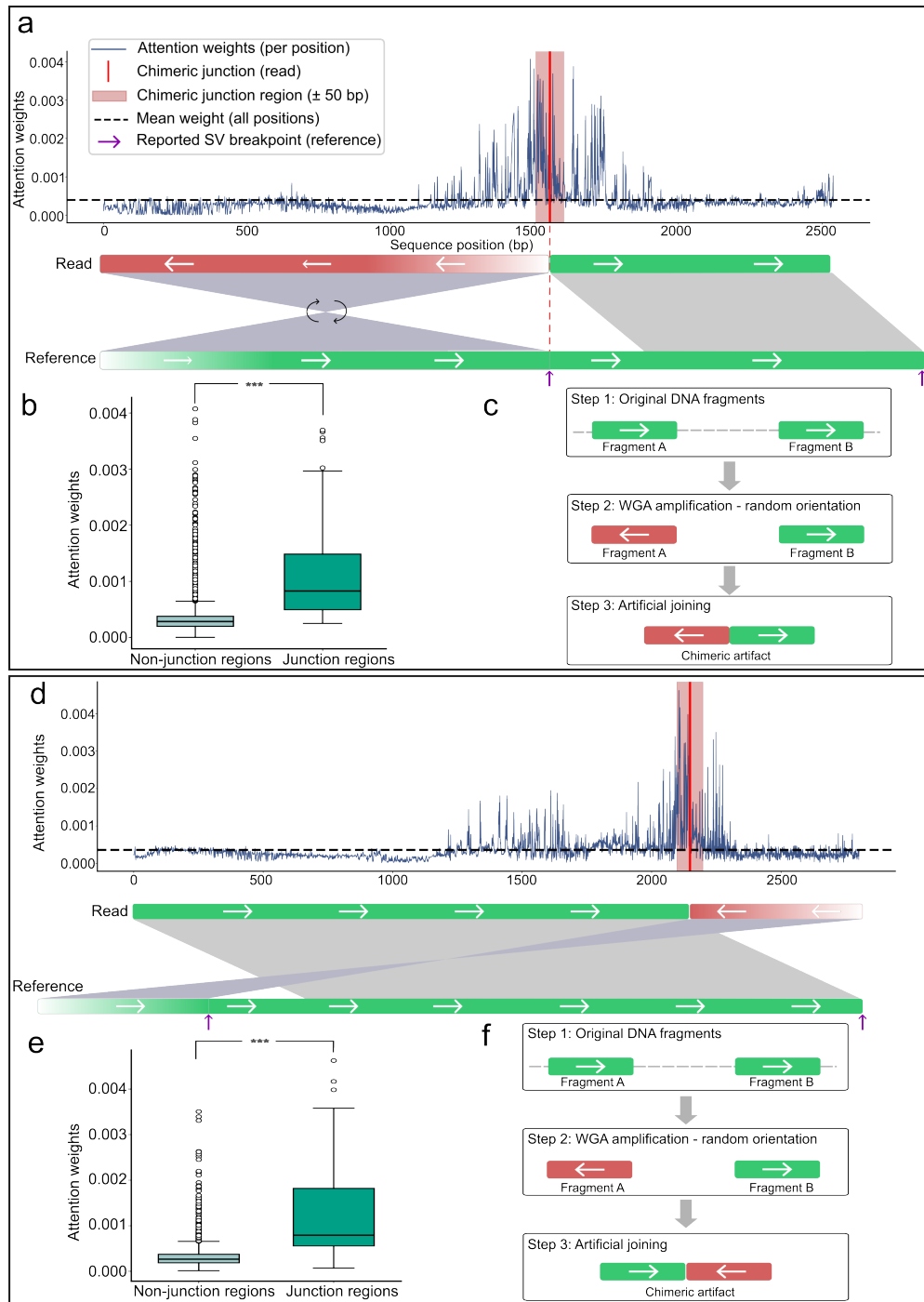


Fig. 4 ChimeraLM attention weights can localize to chimeric junction regions. (a,d) Attention weight profiles for two representative chimeric reads. Upper panels show attention weights per position (blue) with mean attention (dashed line). Red vertical lines mark junction positions; pink shading indicates junction region (± 50 bp). Lower panels show read alignments with orientation transitions at junctions (green = forward, red = reverse-complemented). (b,e) Quantitative analysis showing significantly elevated attention weights in junction versus non-junction regions ($P = 5.3 \times 10^{-14}$ and $P = 6.8 \times 10^{-15}$; Wilcoxon rank-sum test). (c,f) Proposed chimera formation mechanisms. During WGA, DNA fragments from distant loci undergo random strand orientation changes before template switching joins them with discordant orientations, producing inversion-like alignment signatures. The two examples illustrate forward-to-reverse and reverse-to-forward transitions.

Attention visualization reveals interpretable classification features

We investigated whether ChimeraLM’s attention mechanism highlights biologically meaningful regions (Fig. 4). For representative chimeric reads, attention weight profiles showed low baseline values across most positions but pronounced peaks at junction regions where template switching joins DNA fragments from distinct genomic loci (Fig. 4a,d). These peaks coincided with alignment breakpoints characterized by orientation changes between adjacent read segments—the defining signature of WGA-induced artifacts.

Attention weights within junction regions (± 50 bp) were significantly higher than in non-junction regions (Wilcoxon rank-sum test, $P = 5.3 \times 10^{-14}$ and $P = 6.8 \times 10^{-15}$; Fig. 4b,e), indicating that ChimeraLM learns mechanistically relevant features rather than spurious correlations.

Schematic reconstruction of the amplification process supports this interpretation (Fig. 4c,f). During WGA, DNA fragments from distant loci undergo random strand orientation changes before being joined by template switching, producing artificial junctions with discordant orientations that generate inversion-like alignment signatures. The model’s attention peaks effectively capture these orientation discontinuities, localizing chimeric junctions at single-nucleotide resolution.

Discussion

WGA enables genomic analysis from single cells but introduces chimeric artifacts that compromise SV detection. ChimeraLM addresses this challenge through sequence-level classification of biological versus artificial reads, providing an upstream filtering strategy that removes problematic sequences before downstream analysis rather than correcting errors post hoc.

Our results demonstrate several advantages for long-read single-cell sequencing: approximately 90% reduction in chimeric reads while retaining 72–92% of true SVs, 8–11 fold reduction in false-positive SV calls, and consistent performance across PromethION and MinION without platform-specific retraining. The complete failure of existing tools SACRA and 3rd-ChimeraMiner to reduce chimeric content underscores the inadequacy of current heuristic approaches and highlights the advantage of learning sequence-level features directly from data.

ChimeraLM’s effectiveness reflects deep learning’s ability to capture complex sequence patterns difficult to encode in rule-based filters. Traditional quality control methods rely on predefined metrics such as mapping quality or read depth [13, 22], which may not effectively distinguish chimeric artifacts from biological reads. By learning directly from sequence data, ChimeraLM discovers subtle compositional and structural features that differentiate authentic sequences from amplification artifacts. The model also offers interpretability through attention visualization: attention weights concentrate at junctions where template switching joins DNA fragments from distinct loci, matching the known mechanism of chimera formation and building confidence in predictions.

507 The improved reliability of SV detection has direct implications for single-cell
508 genomics. Studies of chromosomal instability, clonal evolution, and SV burden have
509 been constrained by high false-positive rates in WGA data [21, 30]. ChimeraLM
510 enables more confident identification of genuine SVs, supporting research in cancer
511 genomics, developmental biology, and aging where single-cell resolution is essential.

512 Several limitations warrant consideration. The current model processes reads
513 independently; integrating contextual features such as coverage or phasing infor-
514 mation may enhance accuracy. Graphics Processing Unit (GPU) resources are
515 recommended for large-scale datasets, though Central Processing Unit (CPU) infer-
516 ence remains feasible for smaller studies. Future work should prioritize validation
517 across diverse cell types, WGA protocols (Multiple Annealing and Looping-based
518 Amplification Cycles (MALBAC) [31], Linear Amplification via Transposon Insertion
519 (LIANTI) [5], Primary Template-directed Amplification (PTA) [19], and droplet-based
520 MDA (dMDA) [32]), and sequencing platforms including PacBio HiFi. The sequence-
521 level approach suggests effective transfer to other platforms, though fine-tuning may
522 optimize performance.

523 More broadly, ChimeraLM illustrates the potential of GLMs for data quality
524 control. The framework could extend to other amplification-dependent technologies,
525 including cell-free DNA analysis, ancient DNA studies, and metagenomic sequencing
526 from low-biomass samples. Attention-based interpretability also opens opportuni-
527 ties for mechanistic studies of template-switching dynamics, potentially guiding
528 development of improved amplification protocols.

529 In summary, ChimeraLM provides a practical and interpretable framework for
530 improving long-read single-cell genomic data quality, enhancing SV detection reliabil-
531 ity while revealing mechanistic features of amplification-induced artifacts.

532

533 Methods

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535 Cell culture, single-clone preparation, and nanopore sequencing

536

537 *Cell culture and single-clone establishment*

538 PC3 prostate cancer cells (ATCC[®] CRL-1435[™]) were cultured in RPMI-1640 medium
539 supplemented with 10% fetal bovine serum and 1% penicillin–streptomycin at 37 °C
540 with 5% CO₂. To minimize biological heterogeneity, a monoclonal population was
541 established by serial dilution in 96-well plates, ensuring that each culture originated
542 from a single cell. Mycoplasma contamination was routinely tested and confirmed
543 negative prior to DNA extraction.

544

545 *DNA extraction and whole-genome amplification*

546 From the monoclonal population, two types of DNA samples were prepared: a
547 bulk (non-amplified) control and ten single-cell MDA-amplified genomes. Bulk high-
548 molecular-weight DNA was extracted using the Monarch[®] HMW DNA Extraction
549 Kit for Cells & Blood (New England Biolabs). Individual cells were isolated using
550 1CellDish-60 mm (iBioscience) and amplified using the REPLI-g Advanced DNA Sin-
551 gle Cell Kit (Qiagen) following the manufacturer’s protocol. DNA concentration and
552

fragment integrity were assessed with a Qubit 4 fluorometer and Agilent TapeStation (DNA 1000/5000 ScreenTape). Only samples meeting quality standards were used for library construction.

Nanopore library preparation and sequencing

Sequencing libraries were prepared using the [ONT](#) Ligation Sequencing Kit V14 (SQK-LSK114) and sequenced on MinION Mk1C or PromethION P2 Solo devices with R10.4.1 flow cells according to the manufacturer’s genomic DNA workflow. Because all single-cell samples originated from the same monoclonal lineage, observed differences between amplified and bulk data primarily reflect MDA-induced artifacts rather than biological variation, providing a controlled experimental setting for downstream analyses.

Basecalling and read processing

Raw signal files (POD5) were basecalled using Dorado v0.5.0 with the high-accuracy model `dna_r10.4.1_e8.2.400bps_hac@v4.3.0` [33]. Reads with mean quality < 10 or length < 500 bp were removed. Residual adapters and concatemers were trimmed using Cutadapt v4.0 [34] in two-pass error-tolerant mode. Cleaned reads were aligned to the GRCh38.p13 reference genome using minimap2 v2.26 (`map-ont` preset) [35]. Resulting BAM files were sorted and indexed with SAMtools v1.16 [36]. Read length and mapping statistics were calculated using NanoPlot v1.46.1 [37]. All samples were processed under identical parameters to ensure consistency across datasets.

Chimeric read identification

Chimeric reads were identified based on the presence of supplementary alignments in BAM files using the [Supplementary Alignment \(SA\)](#) tag. The SA tag indicates that a read has additional alignments beyond the primary alignment, which is characteristic of chimeric sequences that map to multiple distant genomic locations. To ensure accurate identification, we applied stringent filtering criteria: reads were classified as chimeric only if they (1) were not unmapped, (2) contained the SA tag, (3) were not secondary alignments, and (4) were not supplementary alignments themselves. This filtering approach ensures that only primary alignments with supplementary mapping evidence are considered chimeric, avoiding double-counting of the same chimeric event and excluding low-quality or ambiguous alignments. Reads without the SA tag (single continuous alignments) were classified as non-chimeric. This approach leverages the standard BAM format specification to reliably identify reads with complex alignment patterns.

Training data construction

Data generation and sources

To construct the training dataset, we generated [WGA](#) and bulk sequencing data from PC3 cells. The [WGA](#) sample was amplified and sequenced on the PromethION P2 platform ([ONT](#)), while three independent bulk datasets were produced from non-amplified genomic DNA: bulk PromethION P2, bulk MinION Mk1c ([ONT](#)), and bulk PacBio.

599 These bulk datasets represent authentic biological sequences free from amplification-
600 induced artifacts. In contrast, WGA sequencing includes both genuine genomic reads
601 and artificial chimeras introduced during the amplification process. An additional
602 WGA dataset sequenced on the MinION Mk1c platform was reserved exclusively as
603 an independent test set for cross-platform evaluation.

604

605 *Ground truth annotation and class definition*

606 Ground truth labels were established by systematically comparing chimeric reads from
607 the WGA PromethION P2 dataset against those from the three bulk datasets. For
608 each WGA chimeric read, all alignment segments—defined by their genomic start
609 and end coordinates—were compared to the corresponding segments of bulk chimeric
610 reads. A WGA read was labeled as biological if every segment matched at least one
611 bulk chimeric read within a 1 kb positional tolerance, indicating that the structural
612 configuration is also present in non-amplified DNA. Reads lacking any matching pat-
613 tern across all bulk datasets were labeled as artificial chimeras, presumed to arise
614 from the amplification process. To ensure balanced class representation, additional
615 chimeric reads were randomly sampled from the bulk datasets and labeled as biologi-
616 cal, as these reads originate from genuine genomic rearrangements such as true SVs.
617 The final labeled dataset combined the annotated WGA PromethION P2 reads with
618 the subsampled bulk chimeric reads and was subsequently partitioned into training,
619 validation, and test sets as described below.

620

621 *Dataset partitioning and cross-platform validation*

622 The combined labeled dataset, derived from WGA PromethION P2 and bulk sequenc-
623 ing data, was divided into training (70%), validation (20%), and internal test (10%)
624 sets using stratified random sampling to maintain class balance. These subsets
625 were used respectively for model training, hyperparameter tuning, and performance
626 evaluation on data from the same sequencing platform.

627 To evaluate cross-platform generalization, the complete WGA MinION Mk1c
628 dataset was reserved as an independent external test set. This dataset, generated on a
629 different nanopore platform, was never used during model training or internal testing.
630 This two-level evaluation design allowed us to test whether ChimeraLM captures gen-
631 eral sequence features of amplification-induced chimeras rather than platform-specific
632 artifacts.

633

634 **Model architecture**

635

636 *DNA encoder*

637 ChimeraLM employs the pre-trained HyenaDNA model [23] as its DNA encoder. This
638 model was pre-trained on large-scale genomic data and provides robust sequence rep-
639 resentations. DNA sequences are tokenized at single-nucleotide resolution, with each
640 base (A, C, G, T, N) mapped to a unique integer token (7, 8, 9, 10, 11, respectively).
641 Special tokens include [CLS]=0, [PAD]=4, and others for sequence processing. Input
642 sequences are truncated at 32,768 bp or padded to enable batch processing.

643

644

For a tokenized input sequence $\mathbf{x} \in \mathbb{Z}^L$, the HyenaDNA generates contextualized hidden representations:

$$\mathbf{H} = \text{HyenaDNA}(\mathbf{x}) \in \mathbb{R}^{L \times 256}$$

where $\mathbf{H} = (\mathbf{h}_1, \mathbf{h}_2, \dots, \mathbf{h}_L)$ represents position-wise hidden states with dimension 256. The Hyena operators [29] efficiently capture both local sequence motifs and long-range dependencies essential for distinguishing biological sequences from chimeric artifacts.

Attention pooling

To aggregate variable-length sequence representations into fixed-size vectors, ChimeraLM implements attention-based pooling. For hidden states $\mathbf{H} \in \mathbb{R}^{L \times 256}$, attention weights are computed through a two-layer network:

$$\mathbf{e} = \text{GELU}(\text{Linear}_{256 \rightarrow 256}(\mathbf{H})) \in \mathbb{R}^{L \times 256}$$

$$\mathbf{s} = \text{Linear}_{256 \rightarrow 1}(\mathbf{e}) \in \mathbb{R}^{L \times 1}$$

$$\boldsymbol{\alpha} = \text{softmax}(\mathbf{s}) \in \mathbb{R}^{L \times 1}$$

The pooled representation is the weighted sum of hidden states:

$$\mathbf{h}_{\text{pooled}} = \sum_{i=1}^L \alpha_i \mathbf{h}_i \in \mathbb{R}^{256}$$

This mechanism assigns learned importance weights to each sequence position, enabling the model to focus on informative regions while accommodating natural variability in read lengths.

Classification head

The pooled representation is processed through a MLP with residual connections. The first layer expands dimensionality:

$$\mathbf{f}_1 = \text{Dropout}_{0.1}(\text{GELU}(\text{Linear}_{256 \rightarrow 512}(\mathbf{h}_{\text{pooled}}))) \in \mathbb{R}^{512}$$

Subsequent residual blocks with input $\mathbf{f}_{\text{in}} \in \mathbb{R}^{512}$ compute:

$$\mathbf{f}_{\text{out}} = \text{Dropout}_{0.1}(\text{Linear}_{512 \rightarrow 512}(\text{GELU}(\text{Linear}_{512 \rightarrow 512}(\mathbf{f}_{\text{in}})))) + \mathbf{f}_{\text{in}}$$

where the skip connection enables stable gradient flow during training. The final layer produces binary classification logits:

$$\mathbf{z} = [z_0, z_1] = \text{Linear}_{512 \rightarrow 2}(\mathbf{f}_{\text{final}}) \in \mathbb{R}^2$$

where z_0 and z_1 represent logits for biological and artificial chimeric classes, respectively. During inference, the predicted class is $\hat{y} = \text{argmax}_{i \in \{0,1\}} z_i$.

691 **Model summary**

692 The complete ChimeraLM pipeline processes DNA sequences through: (1) single-
693 nucleotide tokenization, (2) HyenaDNA backbone encoding to generate contextualized
694 representations, (3) attention pooling to aggregate position-specific features, (4) MLP
695 layers with residual connections to learn classification features, and (5) binary classi-
696 fication output. The entire model is trained end-to-end using labeled WGA and bulk
697 sequencing data.

699 **Model training and optimization**

701 *Training configuration*

702 ChimeraLM was trained using PyTorch [38] and PyTorch Lightning [39] frameworks.
703 Input sequences were tokenized using the tokenizer with maximum sequence length of
704 32,768 bp. Sequences longer than this threshold were truncated; shorter sequences were
705 padded to enable batch processing. Training employed mixed-precision computation
706 (bf16) to accelerate training while maintaining numerical stability.

708 *Optimization procedure*

709 We used the AdamW optimizer [40] with learning rate $\eta = 1 \times 10^{-4}$ and weight
710 decay $\lambda = 0.01$. AdamW implements adaptive learning rates with decoupled weight
711 decay, combining the benefits of Adam optimization with proper L2 regularization.
712 A ReduceLROnPlateau scheduler dynamically adjusted the learning rate based on
713 validation loss, reducing it by a factor of 0.1 when no improvement occurred for 10
714 consecutive epochs. Early stopping with patience of 10 epochs prevented overfitting
715 by terminating training when validation performance plateaued. A fixed random seed
716 (12345) ensured reproducibility across training runs.

717 The training objective used cross-entropy loss for binary classification. For a train-
718 ing example with true class label $y \in \{0, 1\}$ and model logits $\mathbf{z} = [z_0, z_1]$, the loss
719 is:

$$720 \quad \mathcal{L}(\mathbf{z}, y) = -\log \left(\frac{\exp(z_y)}{\exp(z_0) + \exp(z_1)} \right) = -z_y + \log(\exp(z_0) + \exp(z_1))$$

722 where z_0 and z_1 represent logits for biological and artificial chimeric classes, respec-
723 tively.

725 *Training implementation*

726 Training used batch size of 16 sequences with 30 parallel data loading workers. GPU
727 acceleration was employed for efficient processing, with training typically requiring 96-
728 120 hours depending on dataset size. Model checkpointing saved the best-performing
729 model based on validation metrics. Configuration management used Hydra [41] to
730 enable reproducible experimentation.

Model evaluation

Performance was monitored using accuracy, precision, recall, and F1 score on the validation set after each epoch:

$$\text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FP}}, \quad \text{Recall} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$
$$\text{F1} = \frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}}, \quad \text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}}$$

where TP (true positives) are chimeric reads correctly classified as artificial, TN (true negatives) are biological reads correctly classified as biological, FP (false positives) are biological reads misclassified as artificial, and FN (false negatives) are chimeric reads misclassified as biological. Final model selection was based on best validation performance as determined by early stopping.

Model inference and application

Inference pipeline

To apply ChimeraLM to new WGA sequencing data, the model takes a BAM file as input. Chimeric reads are identified using SA tags and filtered to exclude unmapped, secondary, or supplementary alignments. Each chimeric read sequence is tokenized using the tokenizer (maximum length 32,768 bp, with truncation or padding as needed). The trained model processes sequences in batches, generating two logits $[z_0, z_1]$ for each read corresponding to biological and artificial chimeric classes. Classification is determined by $\hat{y} = \text{argmax}(z_0, z_1)$. ChimeraLM outputs a filtered BAM file containing only reads classified as biological, which can be directly used for downstream analyses including SV calling.

Performance evaluation

Test set evaluation

Final model performance was evaluated on the held-out test set and the independent MinION Mk1c dataset. Metrics (precision, recall, F1 score, accuracy) were computed as described in the training section, where true positives represent chimeric reads correctly classified as artificial and true negatives represent biological reads correctly classified as biological.

SV calling

SVs were called using multiple tools to ensure comprehensive detection. For long-read data (ONT PromethION P2 and MinION Mk1c), we used Sniffles v2.5 [14, 15], DeBreak v1.2 [16], SVIM v2.0.0 [17], and cuteSV v2.1.1 [18]. For short-read data of the PC3 cell line, we used both the CCLE Illumina whole-genome sequencing dataset and the PRJNA361315 Illumina WGS dataset, processed with Manta v1.6.0 [42], DELLY v1.5.0 [43], and SvABA v1.1.0 [44]. All tools were executed with default recommended parameters.

783 **Gold standard SV dataset construction**

784 A high-confidence gold standard SV dataset was generated from bulk PC3 sequencing
785 data to evaluate the impact of ChimeraLM on SV detection accuracy (Fig. 3a). All
786 SV comparison and breakpoint correction were performed using OctopusSV v0.2.3 [45].
787 We used four datasets: bulk MinION Mk1c, bulk PromethION P2, the CCLE Illumina
788 WGS dataset, and the PRJNA361315 Illumina WGS dataset. Within each dataset, SV
789 events supported by at least two independent callers were retained. Variants supported
790 by two or more datasets were designated as gold standard SVs for benchmarking.

792 **SV benchmarking analysis**

793 To assess the impact of ChimeraLM on SV calling accuracy, we compared SV calls from
794 unfiltered WGA data and ChimeraLM-filtered WGA data against two references: (1)
795 the stringent multi-platform gold standard dataset, and (2) platform-matched long-
796 read bulk sequencing data. Benchmarking was performed using Truvari v4.2.2 [46]
797 with default parameters. SVs were considered supported if they matched reference
798 variants within the defined breakpoint tolerance. Validation rates were calculated as
799 the proportion of called SVs supported by the reference. This dual benchmarking
800 strategy quantifies both improvements in detecting high-confidence multi-platform
801 SVs and the retention of platform-specific true variants.

804 **Benchmarking against existing methods**

805 ChimeraLM was compared to two existing computational methods for detecting
806 amplification-induced chimeric artifacts: SACRA [22] (GitHub commit 9a2607e) and
807 3rd-ChimeraMiner [13] (GitHub commit 04b5233). Both tools were applied to WGA
808 data from PromethION P2 and MinION Mk1c platforms using default parameters as
809 recommended in their documentation. Performance was evaluated by measuring the
810 percentage reduction in chimeric reads relative to unprocessed WGA data. Chimeric
811 reads were identified using WGA tag-based alignment criteria (reads with SA tags
812 indicating split alignments), and reduction rates were calculated as the proportion of
813 chimeric reads removed by each method.

815 **Attention weight analysis**

816 To investigate ChimeraLM’s interpretability, we analyzed attention weights from
817 the pooling mechanism for representative chimeric reads. Attention weights indicate
818 the relative importance assigned to each sequence position during classification. For
819 selected reads, we extracted per-position attention weights and visualized them along-
820 side read alignments to identify whether the model focuses on mechanistically relevant
821 regions.

822 Chimeric junction positions were identified from alignment data (defined by break-
823 points in SA tags). A window of ± 50 bp surrounding each junction was designated as
824 the junction region. Attention weights within junction region were compared to non-
825 junction regions using the Wilcoxon rank-sum test [47], with statistical significance
826 assessed at $p < 0.001$.

828

Data visualization

Figures were generated using Python with Matplotlib [48] and Seaborn [49].

Computing resources

Computations were performed on a [High Performance Computing \(HPC\)](#) server with 64-core Intel Xeon Gold 6338 CPU, 256 GB RAM, and two NVIDIA A100 GPUs (80 GB memory each).

Extended Data Table 1 Sequencing and alignment statistics of PC3

Sample	Platform	Reads ($\times 10^6$)	Total bases (Gb)	Total bases aligned (Gb)	Fraction aligned	Mean length (bp)	Mean quality (Q)	Average identity (%)
WGA	MinION	9.11	14.6	10.4	0.7	1,603	14.3	97.6
WGA	PromethION	44.69	128.2	69.2	0.5	2,869	14.5	96.1
Bulk	MinION	0.97	8.1	7.1	0.9	8,310	17.2	97.3
Bulk	PromethION	8.00	69.9	62.4	0.9	8,732	18.5	97.7

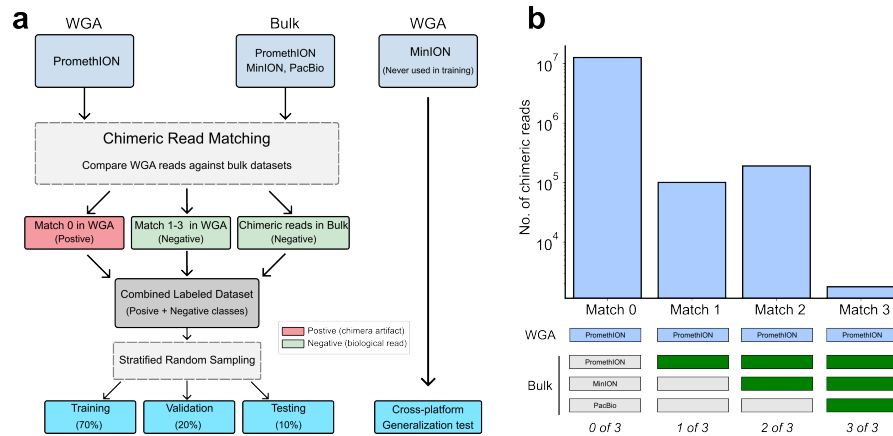
Supplementary information.

Acknowledgements. We thank Tingyou Wang for guidance on figure preparation. This project was supported in part by NIH grants R35GM142441 and R01CA259388 awarded to RY.

Declarations

Author Contributions. YL, QG and RY designed the study. YL and QG performed the analysis. QG performed the experiments. YL and QG designed and implemented the model. YL built the command-line tool and documentation. YL, QG and RY wrote the manuscript. RY supervised this work.

Data Availability. The raw sequencing data generated in this study have been deposited in the NCBI Sequence Read Archive (SRA) under BioProject accession PRJNA1354861. The dataset includes Oxford Nanopore long-read whole-genome sequencing of PC3 prostate cancer cells and MDA-amplified single-cell derivatives. The individual SRA accessions are as follows: PC3 bulk (MinION Mk1C), SRR35904028; PC3 bulk (PromethION P2), SRR35904029; PC3 10-cell WGA (MinION Mk1C), SRR35904026; PC3 10-cell WGA (PromethION P2), SRR35904027. We can access the data at the following link: <https://dataview.ncbi.nlm.nih.gov/object/PRJNA1354861?reviewer=viej6cv6mgbli3n7a9a5k1bsb3>



Extended Data Fig. 1 Training dataset construction and ground-truth labeling strategy. (a) Workflow for generating labeled training data. WGA PromethION data is compared against three independent bulk sequencing datasets (PromethION, MinION, and PacBio). Reads with no bulk matches (Match 0) are labeled artificial; reads matching one or more bulk datasets (Match 1–3) are labeled biological, along with chimeric reads sampled directly from bulk data. The labeled dataset is split into training (70%), validation (20%), and test (10%) sets. The WGA MinION dataset is reserved for independent cross-platform evaluation. (b) Distribution of chimeric read matches. Bar chart shows the number of WGA PromethION chimeric reads (log scale) by bulk dataset matches. Match 0 reads (~10⁷) lacking bulk validation are classified as artificial; Match 1–3 reads with bulk support are classified as biological. The substantial imbalance reflects high prevalence of WGA-induced artifacts.

Code Availability. ChimeraLM, implemented in Python, is open source and available on GitHub (<https://github.com/ylab-hi/ChimeraLM>) under the Apache License, Version 2.0. The package can be installed via PyPI (<https://pypi.org/project/chimeralm>) using pip, with wheel distributions provided for Windows, Linux, and macOS to ensure easy cross-platform installation. An interactive demo is available on Hugging Face (<https://huggingface.co/spaces/yangliz5/ChimeraLM>), allowing users to test DeepChopper’s functionality without local installation. For large-scale analyses, we recommend using ChimeraLM on systems with GPU acceleration. Detailed system requirements and optimization guidelines are available in the repository’s documentation (<https://ylab-hi.github.io/ChimeraLM/>).

Conflict of interest. RY has served as an advisor/consultant for Tempus AI, Inc. This relationship is unrelated to and did not influence the research presented in this study.

Acronyms

CPU Central Processing Unit 12

DEL deletion 8

dMDA droplet-based MDA 12

DUP duplication 8

GLM Genomic Language Model 2 , 12	921
GPU Graphics Processing Unit 12 , 16 , 19 , 20	922
	923
HPC High Performance Computing 19	924
	925
INS insertion 8	926
INV inversion 1 , 2 , 7–9	927
	928
LIANTI Linear Amplification via Transposon Insertion 12	929
	930
MALBAC Multiple Annealing and Looping-based Amplification Cycles 12	931
MDA Multiple Displacement Amplification 2	932
MLP multilayer perceptron 3 , 5 , 15 , 16	933
	934
ONT Oxford Nanopore Technologies 4 , 7 , 8 , 13	935
	936
PacBio Pacific Biosciences 4	937
PTA Primary Template-directed Amplification 12	938
	939
SA Supplementary Alignment 13 , 17 , 18	940
SV Structural Variation 1–3 , 5 , 7–9 , 11 , 12 , 14 , 17 , 18	941
	942
TRA translocation 2 , 8	943
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WGA Whole Genome Amplification 1–8 , 10–14 , 16–20	945
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