CRISPRware

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BACKGROUND

Clustered regularly interspaced short palindromic repeats (CRISPR) screening is a cornerstone of functional genomics, enabling genome-wide knockout studies to identify genes involved in specific cellular processes or disease pathways. The success of CRISPR screens depends critically on the design of effective guide RNA (gRNA) libraries that maximize on-target activity while minimizing off-target effects. Current CRISPR screening lacks tools that can natively integrate next-generation sequencing (NGS) data for context-specific gRNA design, despite the wealth of genomic and transcriptomic information available from modern sequencing approaches. Traditional gRNA design tools have relied on static libraries with limited genome annotations and outdated scoring methods, lacking the flexibility to incorporate context-specific genomic information. Off-target effects are also a concern, with CRISPR-Cas9 systems tolerating up to three mismatches between single guide RNA (sgRNA) and genomic DNA, potentially leading to unintended mutations that could disrupt essential genes and compromise genomic integrity. Additionally, standard CRISPR library preparation methods can introduce bias through PCR amplification and cloning steps, resulting in non-uniform gRNA representation.

TECHNOLOGY DESCRIPTION

To help address these current limitations, researchers at UC Santa Cruz (UCSC) have developed a computational tool with native support for contextual NGS data integration, allowing researchers to design gRNA libraries that account for cell type-specific gene expression, chromatin accessibility, and genetic variation. Named CRISPRware, a key UCSC innovation is the tool's ability to perform allele-specific guide design on a genome-wide scale by leveraging genetic variants to discriminate between alleles, demonstrated through successful targeting of strain-specific alleles in hybrid mouse cell lines. UCSC's CRISPRware also introduces an "active genome" indexing approach that restricts off-target analysis to accessible chromatin regions, substantially increasing the number of suitable gRNAs available for targeting while maintaining specificity.

APPLICATIONS

- agricultural research
- gene editing/therapy
- proteomics
- drug discovery
- bioinformatics

FEATURES/BENEFITS

- Supports RNA-seq, ATAC-seq, ChIP-seq, and Ribo-seq data to inform target selection, enabling context-specific library design that reflects the actual biological state of experimental systems.
- Advanced scoring algorithms, including Ruleset 3 for on-target efficiency and GuideScan2 for off-target assessment, with compatibility for ensemble scoring approaches that combine multiple prediction methods for improved reliability.
- Features optimized batch-size parameters that allow efficient gRNA scoring even on personal computers with limited computational resources.
- Facilitates targeting of non-canonical open reading frames identified through ribosome profiling data, expanding the scope of functional screening beyond traditional protein-coding genes to include regulatory peptides and previously uncharacterized translated regions.

RELATED MATERIALS

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OTHER INFORMATION

KEYWORDS

CRISPR, genomics, guide RNA, gRNA, next-generation sequencing, NGS, genes, allele, active genome, active genome indexing, CRISPRware

CATEGORIZED AS

- **Biotechnology**
  - Bioinformatics
  - Genomics
  - Other
  - Proteomics
- **Computer**
  - Software
- **Medical**
  - Gene Therapy
  - Research Tools

RELATED CASES

2024-824-0

- CRISPRware: an efficient method for contextual gRNA library design - 06/22/2024

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Methods and Compositions for Treating Inflammatory Diseases
- Hek293 Cell Line Producing Murine GM-CSF

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