

SUMMARY

Provided herein is a method for analyzing polynucleotides such as genomic DNA. In certain embodiments, the method comprises: (a) treating chromatin isolated from a population of cells with a transposase and molecular tags to produce tagged fragments of polynucleotides; (b) sequencing a portion of the tagged fragments to produce a plurality of sequence reads; and (c) making an epigenetic map of a region of the genome of the cells by mapping information obtained from the sequence reads to the region.

In one aspect of the present disclosure, there is provided a method for analyzing a biological sample, comprising:

(a) contacting chromatin of a genome region of said biological sample with an insertional enzyme complex to produce tagged nucleic acid molecules, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin;

(b) performing a nucleic acid assay on said tagged nucleic acid molecules ; and

(c) generating a plurality of sequence reads comprising sequence information of said tagged nucleic acid molecules.

In some cases, the information is obtained using the nucleotide sequences at the beginning and, optionally, the end of a sequence read. In some cases, the information mapped in (c) is selected from one or more of: (i) cleavage sites for the transposase; (ii) the sizes of the fragments produced in step (a); (iii) sequence read length; (iii) the positions of sequence reads of a defined range in length; and (iv) sequence read abundance. In some instances, the fragments of a defined size range are nucleosome-free fragments.

In some instances, the epigenetic map shows one or more of: (i) a profile of chromatin accessibility along the region; (ii) DNA binding protein occupancy for a binding site in the region; (iii) nucleosome-free DNA in the region; (iv) positioning of nucleosomes along the region; and/or (v) chromatin states. In some cases, the method can further comprise measuring global occupancy of a binding site for the DNA binding protein. The DNA binding protein can, for example, be a transcription factor.

In some cases, the population of cells can be composed of about 500 to 100,000 cells. The cells can be isolated from an individual, such as from the blood of the individual. In some examples, the cells can be of the same cell type. In some examples, the cells can be FACS-selected cells.

In some instances, the treating step (a) can comprise: isolating nuclei from the population of cells; and combining the isolated nuclei with the insertional enzyme complex,

CLAIMS

What is claimed is:

1. A method for analyzing a biological sample, comprising:
 - (a) contacting chromatin of a genome region of said biological sample with an insertional enzyme complex to produce tagged nucleic acid molecules, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin;
 - (b) performing a nucleic acid assay on said tagged nucleic acid molecules; and
 - (c) generating a plurality of sequence reads comprising sequence information of said tagged nucleic acid molecules.
2. The method of claim 1, further comprising generating a representation of epigenetic features of said genome region at least in part by mapping said sequence information to said genome region.
3. The method of claim 1, wherein said biological sample is a cell or a nucleus.
4. The method of claim 3, further comprising lysing said cell or said nucleus.
5. The method of claim 3, further comprising permeabilizing said cell or said nucleus to permit said insertional enzyme complex to access said chromatin.
6. The method of claim 5, wherein said permeabilizing is configured to minimally perturb said chromatin of said cell or said nucleus.
7. The method of claim 5, wherein said cell or said nucleus is permeabilized with a reagent configured to permit said insertional enzyme complex to access said chromatin.
8. The method of claim 7, wherein said reagent comprises NP40, digitonin, tween, streptolysin, or a cationic lipid.

9. The method of claim 5, wherein said cell or said nucleus is permeabilized by hypotonic shock or ultrasonication.
10. The method of claim 1, wherein said insertional enzyme comprises a transposase.
11. The method of claim 10, wherein said transposase is a Tn5 transposase or derived from a Tn5 transposase.
12. The method of claim 11, wherein said transposase is a hyperactive Tn5 transposase.
13. The method of claim 1, wherein said insertional enzyme complex comprises a first and second adapter.
14. The method of claim 13, wherein said first and second adapters comprise sequencing adapters.
15. The method of claim 13, wherein said first sequencing adapter further comprises a barcode sequence.
16. The method of claim 14, wherein said second sequencing adapter further comprises a barcode sequence.

17. The method of any one of claims 1-16, further comprising adding a sequence that is compatible with a selected next generation sequencing platform to said tagged nucleic acid molecules.

18. The method of claim 17, further comprising amplifying said tagged nucleic acid molecules using a plurality of PCR primers that hybridize to said tagged nucleic acid molecules, wherein said PCR primers comprise a 5' tail that is compatible with said selected next generation sequencing platform.