Capture And Long Read Sequencing And Genotyping Of The HLA Region

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CONTACT

Jeff M. Jackson

jjackso6@ucsc.edu

tel: .



INVENTORS

- Cornejo, Omar

OTHER INFORMATION

KEYWORDS

long read sequencing, target enrichment, HLA genotyping, nanopore sequencing, tagmentation

CATEGORIZED AS

- **Biotechnology**
  - Genomics

RELATED CASES

2025-948-0

BACKGROUND

The Major Histocompatibility Complex (MHC), is a genomic region that expresses proteins involved in immune system functions and that are important for organ transplantation. In humans, this type of gene is referred to as the Human Leukocyte Antigen (HLA). The HLA region is haplotypic, with all of the region inherited from one parent. HLA is highly polymorphic within the human population, both in terms of protein structure as well as genomic variability.This high genomic diversity makes accurate genotyping difficult using methods such as short-read sequencing. That said, current long-read sequencing methods and analysis can yield incomplete and inaccurate results.

TECHNOLOGY DESCRIPTION

Accurate genotyping of highly polymorphic genomic regions such as the HLA can be achieved using a new process developed by Omar Cornejo's lab at UC Santa Cruz.

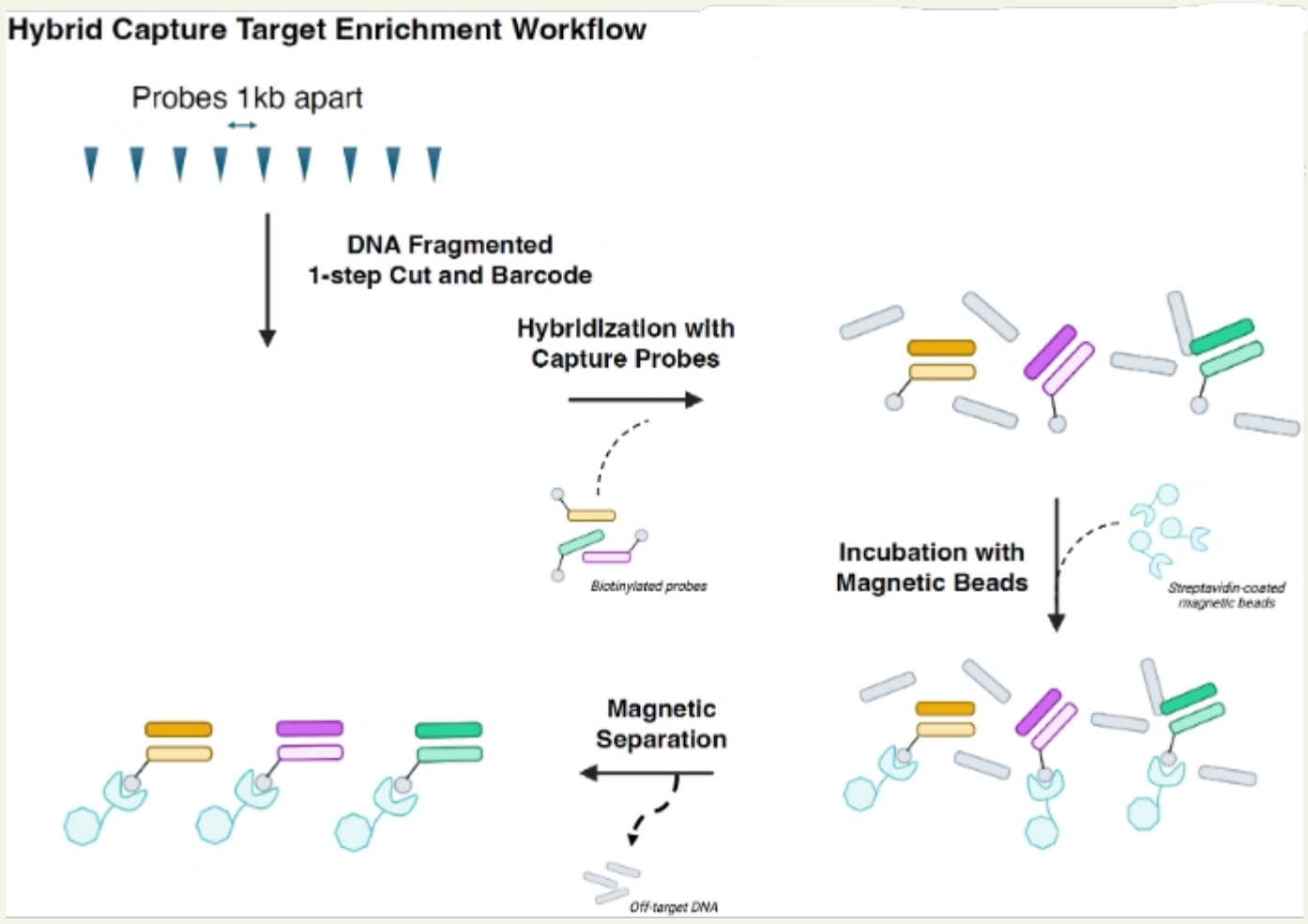
First, genomic DNA was tagmented using a transposase bound to a barcoded adapter. This produced fragments of 5-10 kb with the barcoded adapter ligated to each end. The gap produced by the tagmentase is filled in with a polymerase. The tagmented DNA is then subjected to hybrid capture without further enzymatic treatment

The use of a single barcoded adapter in tagmentation results in all tagmented molecules being available for PCR amplification. Other approaches use two transposases (each bound with a different adapter) which results in one quarter of molecules having two ends with one adapter, one quarter of molecules having two ends with the other adapter, and only half of molecules with one of each adapter at each end. This means that an intermediate PCR step prior to hybrid capture is unnecessary.

Hybrid capture is then used to enrich the tagmented DNA for seqences within the region of interest and the resulting enriched libraries sequenced using long read sequencing using e.g. the Oxford Nanopore MinION or PromethION or the PacBio Revio. High coverage of the region is achieved with a different 700 fold position wide enrichment of the targeted region.

A new software workflow was also developed to identify and annotate HLA alleles and can identify paternal and maternal haplotypes. Furthermore, complex duplications with high similarity can be discerned accurately.

An illustration of the target enrichment method is as follows:



APPLICATIONS

- Target enrichment and long read sequencing of complex genomic regions
- Accurate and high resolution identification of MHC haplotype

ADVANTAGES

- Single barcoded adapter eliminates intermediate PCR step
- 700x enrichment of targetec genomic area of interest
- Parental haplotypes readiliy determined
- Complex duplications with high similarity can be differentiated

INTELLECTUAL PROPERTY INFORMATION

Patent Pending

RELATED MATERIALS

University of California, Santa Cruz
Industry Alliances & Technology Commercialization
Kerr 413 / IATC,
Santa Cruz,CA 95064

Tel: 831.459.5415
innovation@ucsc.edu
https://officeofresearch.ucsc.edu/
Fax: 831.459.1658

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