

CLAIMS

1. A method for targeted genetic analysis of circulating cell-free DNA (cfDNA) comprising:

(a) hybridizing one or more capture probe modules to a target genetic locus in a tagged circulating cfDNA library to form one or more capture probe module-circulating cfDNA clone complexes,

wherein the one or more capture probe modules hybridizes to a specific DNA target region wherein the capture probe modules comprise capture probes that are substantially smaller than 60 nucleotides, and wherein the tagged circulating cfDNA library comprises circulating cfDNA ligated at each end to an adaptor module;

(b) isolating the one or more isolated capture probe module-circulating cfDNA complexes from (a):

(c) enzymatically processing the one or more isolated capture probe module-circulating cfDNA complexes from (b), wherein the enzymatic processing comprises performing 5'-3' DNA polymerase extension of the capture probe using the isolated circulating cfDNA clone in the complex as a template;

(d) performing PCR on the enzymatically processed complex of (c) to generate amplified hybrid nucleic acid molecules, wherein the amplified hybrid nucleic acid molecules comprise a target sequence in the target genetic locus capable of hybridizing to the capture probe and the complement of the capture probe module tail sequence; and

(e) performing a quantitative genetic analysis of on the amplified hybrid nucleic acid molecules.

2. The method of claim 1, wherein the adaptor module comprises

- (a) a primer binding site for amplification of the circulating cfDNA library;
- (b) one or more unique read codes;
- (c) one or more sequences for DNA sequencing; and, optionally,
- (d) one or more sample codes for sample multiplexing.

3. The method of claim 1, wherein a plurality of capture probe modules are hybridized to the target genetic locus in the tagged circulating cfDNA library.
4. The method of claim 1, wherein the targeted genetic analysis is performed on a plurality of target genetic loci.
5. The method of claim 1, wherein the capture probes are 40 nucleotides.
6. The method of claim 1, further comprising determining the number of genome equivalents in the circulating cfDNA library.
7. The method of any one of claims 1-6, wherein the quantitative genetic analysis comprises sequencing of the amplified hybrid nucleic acid molecules to generate a plurality of sequencing reads and performing bioinformatics analysis on the plurality of sequencing reads.
8. The method of claim 7, wherein the bioinformatics analysis is used to detect one or more genetic lesions with the targeted genetic locus.
9. The method of claim 8, wherein the one or more genetic lesions comprise a nucleotide transition or transversion, a nucleotide insertion or deletion, a genomic rearrangement or a change in copy number.
10. The method of any one of claims 1-9, wherein the circulating cfDNA is isolated from a biological sample of a subject selected from the group consisting of amniotic fluid, blood, plasma, serum, semen, lymphatic fluid, cerebral spinal fluid, ocular fluid, urine, saliva, stool, mucous, and sweat.

11. The method of any one of claims 1-10, wherein the quantitative genetic analysis is used to identify or detect one or more genetic lesions that cause or associated with a genetic disease.
12. The method of claim 11, wherein the genetic disease is cancer.
13. The method of any of claims 1-12, wherein the circulating cfDNA is extracellular DNA, DNA that has been extruded from cells, or DNA that has been released from necrotic or apoptotic cells.