

CLAIMS

1. ~~—A method for generating a tagged genomic library comprising:
(a) treating fragmented genomic DNA with end-repair enzymes to generate fragmented end-repaired genomic DNA; and
(b) ligating a random nucleic acid tag sequence, and optionally a sample code sequence and/or a PCR primer sequence to the fragmented end-repaired genomic DNA to generate the tagged genomic library.~~
2. ~~—The method of any of the preceding claims, wherein the random nucleic acid tag sequence is from about 2 to about 100 nucleotides.~~
3. ~~—The method of any of the preceding claims, wherein the random nucleic acid tag sequence is from about 2 to about 6 nucleotides.~~
4. ~~—The method of any of the preceding claims, wherein the fragmented end-repaired genomic DNA contains blunt ends.~~
5. ~~—The method of any of the preceding claims, wherein the blunt ends are further modified to contain a single base pair overhang.~~
6. ~~—The method of any of the preceding claims, wherein the ligating comprises ligating a multifunctional adaptor module to the fragmented end-repaired genomic DNA to generate the tagged genomic library, wherein the multifunctional adaptor molecule comprises:
(i) ~~—a first region comprising a random nucleic acid tag sequence;~~
(ii) ~~—a second region comprising a sample code sequence; and~~
(iii) ~~—a third region comprising a PCR primer sequence.~~~~
7. ~~—The method of any of the preceding claims, further comprising hybridizing a tagged genomic library with a multifunctional capture probe module to form a complex,~~

~~wherein the multifunctional capture probe module hybridizes to a specific genomic target region in the genomic library.~~

~~8.——The method of any of the preceding claims, further comprising isolating the tagged genomic library-multifunctional capture probe module complex.~~

~~9.——The method of any of the preceding claims, further comprising 3'-5' exonuclease enzymatic processing of the isolated tagged genomic library-multifunctional capture probe module complex to remove the single stranded 3' ends.~~

~~10.——The method of any of the preceding claims wherein the enzyme for use in the 3'-5' exonuclease enzymatic processing is T4 DNA polymerase.~~

~~11.——The method of any of the preceding claims, further comprising performing PCR on the 3'-5' exonuclease enzymatically processed complex from the preceding claims, wherein the tail portion of the multifunctional capture probe molecule is copied in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the genomic target region capable of hybridizing to the multifunctional capture probe module and the complement of the multifunctional capture probe module tail sequence.~~

~~12.——A method for targeted genetic analysis comprising:~~

~~(a) hybridizing a tagged genomic library with a multifunctional capture probe module complex, wherein the multifunctional capture probe module selectively hybridizes to a specific genomic target region in the genomic library;~~

~~(b) isolating the tagged genomic library-multifunctional capture probe module complex from a);~~

~~(c) performing 3'-5' exonuclease enzymatic processing on the isolated tagged genomic library-multifunctional capture probe module complex from b) using an enzyme with 3'-5' exonuclease activity to remove the single stranded 3' ends;~~

(d) performing PCR on the enzymatically processed complex from c) wherein the tail portion of the multifunctional capture probe molecule is copied in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the genomic target region capable of hybridizing to the multifunctional capture probe module and the complement of the multifunctional capture probe module tail sequence; and

(e) performing targeted genetic analysis on the hybrid nucleic acid molecule from d).

13. — The method of claim 12, wherein steps a) through d) are repeated at least about twice and the targeted genetic analysis of e) comprises a sequence alignment of the hybrid nucleic acid molecule sequences obtained from the at least two d) steps.

14. — The method of claim 13, wherein at least two different multifunctional capture probe modules are used in the at least two a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.

15. — The method of claim 14, wherein at least one multifunctional capture probe module hybridizes downstream of the genomic target region and at least one multifunctional capture probe module hybridizes upstream of the genomic target region.

16. — A method for determining copy number of a specific genomic target region comprising:

(a) hybridizing a tagged genomic library with a multifunctional capture probe module complex, wherein the multifunctional capture probe module complex selectively hybridizes to a specific genomic target region in the genomic library;

(b) isolating the tagged genomic library multifunctional capture probe module complex from a);

(c) performing 3'-5' exonuclease enzymatic processing on the isolated tagged genomic library multifunctional capture probe module complex from b) using an enzyme with 3'-5' exonuclease activity to remove the single stranded 3' ends;

(d) performing a PCR reaction on the enzymatically processed complex from e) wherein the tail portion of the multifunctional capture probe molecule is replicated in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the genomic target region capable of hybridizing to the multifunctional capture probe module and the complement of the multifunctional capture probe module tail sequence;

(e) performing PCR amplification of the hybrid nucleic acid molecule in d);

and

(f) quantitating the PCR reaction in e), wherein the quantitation allows for a determination of copy number of the specific genomic target region.

17.——The method of claim 16, further comprising obtaining the sequences of the hybrid nucleic acid molecules from step e).

18.——The method of claim 17, wherein steps a) through e) are repeated at least about twice and a sequence alignment is performed using the hybrid nucleic acid molecule sequences obtained from the at least two e) steps.

19.——The method of claim 18, wherein at least two different multifunctional capture probe modules are used in the at least two a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.

20.——The method of claim 19, wherein at least one multifunctional capture probe module hybridizes downstream of the genomic target region and at least one multifunctional capture probe module hybridizes upstream of the genomic target region.

21.——A method for determining copy number of a specific genomic target region comprising:

(a) hybridizing a tagged genomic library with a multifunctional capture probe module complex, wherein the multifunctional capture probe module complex selectively hybridizes to a specific genomic target region in the genomic library;

~~(b) isolating the tagged genomic library-multifunctional capture probe module complex from a);~~

~~(c) performing 3'-5' exonuclease enzymatic processing on the isolated tagged genomic library-multifunctional capture probe module complex from b) using an enzyme with 3'-5' exonuclease activity to remove the single stranded 3' ends;~~

~~(d) performing a PCR reaction on the enzymatically processed complex from c) wherein the tail portion of the multifunctional capture probe molecule is replicated in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the genomic target region capable of hybridizing to the multifunctional capture probe module and the complement of the multifunctional capture probe module tail sequence; and~~

~~(e) performing PCR amplification of the hybrid nucleic acid molecule in d).~~

~~22.—The method of claim 21, further comprising obtaining the sequences of the hybrid nucleic acid molecules from step e).~~

~~23.—The method of claim 22, wherein steps a) through e) are repeated at least about twice and a sequence alignment is performed using the hybrid nucleic acid molecule sequences obtained from the at least two e) steps.~~

~~24.—The method of claim 23, wherein at least two different multifunctional capture probe modules are used in the at least two a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.~~

~~25.—The method of claim 24, wherein at least one multifunctional capture probe module hybridizes downstream of the genomic target region and at least one multifunctional capture probe module hybridizes upstream of the genomic target region.~~

~~26.—A method for determining copy number of a specific genomic target region comprising:~~

(a) hybridizing a tagged genomic library with a multifunctional capture probe module complex, wherein the multifunctional capture probe module comprises selectively hybridizes to a specific genomic target region in the genomic library;

(b) isolating the tagged genomic library-multifunctional capture probe module complex from a);

(c) performing 3'-5' exonuclease enzymatic processing on the isolated tagged genomic library-multifunctional capture probe module complex from b) using an enzyme with 3'-5' exonuclease activity to remove the single-stranded 3' ends;

(d) performing a PCR reaction on the enzymatically processed complex from c) wherein the tail portion of the multifunctional capture probe molecule is replicated in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the genomic target region capable of hybridizing to the multifunctional capture probe module and the complement of the multifunctional capture probe module tail sequence;

(e) performing PCR amplification of the hybrid nucleic acid molecule in d);

and

(f) performing targeted genetic analysis on the hybrid nucleic acid molecule from e).

27.—The method of claim 26, wherein steps a) through e) are repeated at least about twice and the targeted genetic analysis of f) comprises performing a sequence alignment of the hybrid nucleic acid molecule sequences from the at least two e) steps.

28.—The method of claim 27, wherein at least two different multifunctional capture probe modules are used in the at least two a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.

29.—The method of claim 28, wherein at least one multifunctional capture probe module hybridizes downstream of the genomic target region and at least one multifunctional capture probe module hybridizes upstream of the genomic target region.

30. — A method for targeted genetic analysis comprising:

- (a) hybridizing a tagged genomic library with a multifunctional capture probe hybrid module complex, wherein the multifunctional capture probe hybrid module selectively hybridizes to a specific genomic target region in the genomic library;
- (b) isolating the tagged genomic library-multifunctional capture probe hybrid module complex from a);
- (c) performing 5' to 3' DNA polymerase extension of the multifunctional capture probe on the complex from b) to replicate a region of the captured, tagged genomic target region that is 3' of the multifunctional capture probe in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the multifunctional capture probe hybrid module and the complement of a region of the tagged genomic target region that is located in the 3' direction from the location where the multifunctional capture probe hybrid module hybridizes to the genomic target region; and
- (d) performing targeted genetic analysis on the hybrid nucleic acid molecule from c).

31. — The method of claim 30, wherein steps a) through c) are repeated at least about twice and the targeted genetic analysis of d) comprises a sequence alignment of the hybrid nucleic acid molecule sequences obtained from the at least two d) steps.

32. — The method of claim 31, wherein at least two different multifunctional capture probe modules are used in the at least two a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.

33. — The method of claim 32, wherein at least one multifunctional capture probe module hybridizes downstream of the genomic target region and at least one multifunctional capture probe module hybridizes upstream of the genomic target region.

34. — A method for determining copy number of a specific genomic target region comprising:

~~(a) hybridizing a tagged genomic library with a multifunctional capture probe hybrid module complex, wherein the multifunctional capture probe hybrid module selectively hybridizes to a specific genomic target region in the genomic library;~~

~~(b) isolating the tagged genomic library-multifunctional capture probe hybrid module complex from a);~~

~~(c) performing 5' to 3' DNA polymerase extension of the multifunctional capture probe on the complex from b) to replicate a region of the captured tagged genomic target region that is 3' of the multifunctional capture probe in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the multifunctional capture probe hybrid module and the complement of a region of the tagged genomic target region that is located in the 3' direction from the location where the multifunctional capture probe hybrid module hybridizes to the genomic target region; and~~

~~(d) performing PCR amplification of the hybrid nucleic acid molecule in c);~~
~~and~~

~~(e) quantitating the PCR reaction in d), wherein the quantitation allows for a determination of copy number of the specific genomic target region.~~

~~35.—The method of claim 34, further comprising obtaining the sequences of the hybrid nucleic acid molecules from step d).~~

~~36.—The method of claim 35, wherein steps a) through d) are repeated at least about twice and a sequence alignment of the hybrid nucleic acid molecules from the at least two d) steps.~~

~~37.—The method of claim 36, wherein at least two different multifunctional capture probe modules are used in the at least two a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.~~

38.—~~The method of claim 37, wherein at least one multifunctional capture probe module hybridizes downstream of the genomic target region and at least one multifunctional capture probe module hybridizes upstream of the genomic target region.~~

39.—~~The method of any of the preceding claims wherein the targeted genetic analysis is sequence analysis.~~

40.—~~The method of any of the preceding claims wherein the tagged genomic library is amplified by PCR to generate an amplified tagged genomic library.~~

41.—~~The method of any of the preceding claims wherein the genomic DNA is from a biological sample selected from the group consisting of blood, skin, hair, hair follicles, saliva, oral mucous, vaginal mucous, sweat, tears, epithelial tissues, urine, semen, seminal fluid, seminal plasma, prostatic fluid, pre-ejaculatory fluid (Cowper's fluid), excreta, biopsy, ascites, cerebrospinal fluid, lymph, and tissue extract sample or biopsy sample.~~

42.—~~A tagged genomic library comprising tagged genomic sequences, wherein each tagged genomic sequence comprises:~~

- ~~(a) fragmented end-repaired genomic DNA;~~
- ~~(b) a random nucleotide tag sequence;~~
- ~~(c) a sample code sequence; and~~
- ~~(d) a PCR primer sequence.~~

43.—~~A hybrid tagged genomic library comprising hybrid tagged genomic sequences for use in targeted genetic analysis, wherein each hybrid tagged genomic sequence comprises:~~

- ~~(a) fragmented end-repaired genomic DNA;~~
- ~~(b) a random nucleotide tag sequence;~~
- ~~(c) a sample code sequence;~~
- ~~(d) a PCR primer sequence;~~
- ~~(e) a genomic target region; and~~

~~(f) a multifunctional capture probe module tail sequence.~~

44. — ~~A multifunctional adaptor module comprising:~~

~~(a) a first region comprising a random nucleotide tag sequence;~~

~~(b) a second region comprising a sample code sequence; and~~

~~(c) a third region comprising a PCR primer sequence.~~

45. — ~~A multifunctional capture probe module comprising:~~

~~(a) a first region capable of hybridizing to a partner oligonucleotide;~~

~~(b) a second region capable of hybridizing to a specific genomic target region; and~~

~~(c) a third region comprising a tail sequence.~~

46. — ~~The multifunctional capture probe module of any of the preceding claims wherein the first region is bound to a partner oligonucleotide.~~

47. — ~~A multifunctional adaptor probe hybrid module comprising:~~

~~(a) a first region capable of hybridizing to a partner oligonucleotide and capable of functioning as a PCR primer and~~

~~(b) a second region capable of hybridizing to a specific genomic target region.~~

48. — ~~The multifunctional capture probe hybrid module of any of the preceding claims, wherein the first region is bound to a partner oligonucleotide.~~

49. — ~~The method of any of the preceding claims, wherein the partner oligonucleotide is chemically modified.~~

50. — ~~A composition comprising a tagged genomic library, a multifunctional adaptor module and a multifunctional capture probe module.~~

~~51.——A composition comprising a hybrid-tagged genomic library according to any of the preceding claims.~~

~~52.——A reaction mixture for performing the method of any one of the preceding claims.~~

~~53.——A reaction mixture capable of generating a tagged genomic library comprising:
(a) fragmented genomic DNA; and
(b) DNA end-repair enzymes to generate fragmented end-repaired genomic DNA.~~

~~54.——The reaction mixture of any of the preceding claims, further comprising a multifunctional adaptor module.~~

~~55.——The reaction mixture of any of the preceding claims, further comprising a multifunctional capture probe module.~~

~~56.——The reaction mixture of any of the preceding claims, further comprising an enzyme with 3' 5' exonuclease activity and PCR amplification activity.~~

~~57.——A method for DNA sequence analysis comprising:
(a) obtaining one or more clones, each clone comprising a first DNA sequence and a second DNA sequence, wherein the first DNA sequence comprises targeted genomic DNA sequence and the second DNA sequence comprises a capture probe sequence;
(b) performing a paired-end sequencing reaction on the one or more clones and obtaining one or more sequencing reads; and
(c) ordering or clustering the sequencing reads of the one or more clones according to the probe sequence of the sequencing reads.~~

~~58.——A method for DNA sequence analysis comprising:~~

~~(a) obtaining one or more clones, each clone comprising a first DNA sequence and a second DNA sequence, wherein the first DNA sequence comprises targeted genomic DNA sequence and the second DNA sequence comprises a capture probe sequence;~~

~~(b) performing a sequencing reaction on the one or more clones in which a single long sequencing read of greater than about 100 nucleotides is obtained, wherein the read is sufficient to identify both the first DNA sequence and the second DNA sequence; and~~

~~(c) ordering or clustering sequencing reads of the one or more clones according to the probe sequence of the sequencing reads.~~

~~59.—The method of claim 57 or claim 58, wherein the sequences of the one or more clones are compared to one or more human reference DNA sequences.~~

~~60.—The method of claim 59, wherein sequences that do not match the one or more human reference DNA sequences are identified.~~

~~61.—The method of claim 60, wherein non-matching sequences are used to create a *de novo* assembly from the non-matching sequence data.~~

~~62.—The method of claim 61, wherein the *de novo* assemblies are used to identify novel sequence rearrangements associated with the capture probe.~~

~~63.—A method for genomic copy number determination analysis comprising:~~

~~(a) obtaining one or more clones, each clone comprising a first DNA sequence and a second DNA sequence, wherein the first DNA sequence comprises a random nucleotide tag sequence and a targeted genomic DNA sequence and the second DNA sequence comprises a capture probe sequence;~~

~~(b) performing a paired-end sequencing reaction on the one or more clones and obtaining one or more sequencing reads; and~~

~~(c) ordering or clustering the sequencing reads of the one or more clones according to the probe sequence of the sequencing reads.~~

~~64.—A method for genomic copy number determination analysis comprising:~~

~~(a) obtaining one or more clones, each clone comprising a first DNA sequence and a second DNA sequence, wherein the first DNA sequence comprises a random nucleotide tag sequence and a targeted genomic DNA sequence and the second DNA sequence comprises a capture probe sequence;~~

~~(b) performing a sequencing reaction on the one or more clones in which a single long sequencing read of greater than about 100 nucleotides is obtained, wherein the read is sufficient to identify both the first DNA sequence and the second DNA sequence; and~~

~~(c) ordering or clustering sequencing reads of the one or more clones according to the probe sequence of the sequencing reads.~~

~~65.—The method of claim 63 or claim 64, wherein the random nucleotide tag sequence is about 2 to about 50 nucleotides in length.~~

~~66.—The method of claim 63 or claim 64, further comprising analyzing all sequencing reads associated with a second read sequence by:~~

~~(a) determining the distributions of unique and redundant sequencing reads;~~

~~(b) counting the number of times a unique read is encountered;~~

~~(c) fitting a frequency distribution of the unique reads to a statistical distribution;~~

~~(d) inferring a total number of unique reads; and~~

~~(e) normalizing the total number of inferred unique read to an assumption that most human genetic loci are generally diploid.~~

~~67.—The method of claim 66, wherein an inferred copy number of one or more targeted loci are determined.~~

~~68.—The method of claim 67, wherein the one or more target loci that deviate from an expected copy number value are determined.~~

~~69.—The method of claim 67, wherein the one or more targeted loci of a gene are grouped together in a collection of loci and the copy number measurements from the collection of targeted loci are averaged and normalized.~~

~~70.—The method of claim 67, wherein the inferred copy number of a gene is represented by the normalized average of all the target loci representing that gene.~~

~~71.—A method for generating a tagged RNA expression library comprising:
(a) fragmenting a cDNA library;
(b) treating the fragmented cDNA library with end repair enzymes to generate fragmented end-repaired cDNA; and
(c) ligating a multifunctional adapter molecule to the fragmented end-repaired cDNA to generate a tagged RNA expression library.~~

~~72.—A method for generating a tagged RNA expression library comprising:
(a) preparing a cDNA library from the total RNA of one or more cells;
(b) fragmenting the cDNA library;
(c) treating the fragmented cDNA with end repair enzymes to generate fragmented end-repaired cDNA; and
(d) ligating a multifunctional adapter molecule to the fragmented end-repaired cDNA to generate a tagged RNA expression library.~~

~~73.—The method of claim 71 or claim 72, wherein the cDNA library is an oligo-dT primed cDNA library.~~

~~74.—The method of claim 71 or claim 72, wherein the cDNA library is primed by random oligonucleotides comprising about 6 to about 20 random nucleotides.~~

~~75.—The method of claim 71 or claim 72, wherein the cDNA library is primed by random hexamers or random octamers.~~

~~76.—The method of claim 71 or claim 72, wherein the cDNA library is fragmented to a size of about 250 bp to about 750 bp.~~

~~77.—The method of claim 71 or claim 72, wherein the cDNA library is fragmented to a size of about 500 bp.~~

~~78.—The method of any one of claims 71 to 77, wherein the multifunctional adaptor module comprises:~~

~~(i) —a first region comprising a random nucleic acid tag sequence, and optionally;~~

~~(ii) —a second region comprising a sample code sequence, and optionally~~

~~(iii) —a third region comprising a PCR primer sequence.~~

~~79.—The method of any one of claims 71 to 78, wherein the multifunctional adaptor module comprises a first region comprising a random nucleic acid tag sequence, a second region comprising a sample code sequence, and a third region comprising a PCR primer sequence.~~

~~80.—The method of any one of claims 71 to 78, further comprising hybridizing a tagged cDNA library with a multifunctional capture probe module to form a complex, wherein the multifunctional capture probe module hybridizes to a specific target region in the cDNA library.~~

~~81.—The method of any one of claims 71 to 78, further comprising isolating the tagged cDNA library-multifunctional capture probe module complex.~~

82.—~~The method of any one of claims 71 to 78, further comprising 3'-5' exonuclease enzymatic processing of the isolated tagged cDNA library multifunctional capture probe module complex to remove the single stranded 3' ends.~~

83.—~~The method of claim 82, wherein the enzyme for use in the 3'-5' exonuclease enzymatic processing is T4 DNA polymerase.~~

84.—~~The method of claim 82 or claim 83, further comprising performing PCR on the 3'-5' exonuclease enzymatically processed complex, wherein a tail portion of the multifunctional capture probe molecule is copied in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the cDNA target region capable of hybridizing to the multifunctional capture probe module and the complement of the multifunctional capture probe module tail sequence.~~

85.—~~A method for targeted gene expression analysis comprising~~
~~(a) hybridizing a tagged RNA expression library with a multifunctional capture probe module complex, wherein the multifunctional capture probe module selectively hybridizes to a specific target region in the tagged RNA expression library;~~
~~(b) isolating the tagged RNA expression library multifunctional capture probe module complex from a);~~
~~(c) performing 3'-5' exonuclease enzymatic processing on the isolated tagged RNA expression library multifunctional capture probe module complex from b) using an enzyme with 3'-5' exonuclease activity to remove the single stranded 3' ends;~~
~~(d) performing PCR on the enzymatically processed complex from c) wherein the tail portion of the multifunctional capture probe molecule is copied in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the target region capable of hybridizing to the multifunctional capture probe module and the complement of the multifunctional capture probe module tail sequence; and~~
~~(e) performing targeted gene expression analysis on the hybrid nucleic acid molecule from d).~~

86.——A method for targeted gene expression analysis comprising:

(a) hybridizing a tagged RNA expression library with a multifunctional capture probe hybrid module complex, wherein the multifunctional capture probe hybrid module selectively hybridizes to a specific target region in the RNA expression library;

(b) isolating the tagged RNA expression library-multifunctional capture probe hybrid module complex from a);

(c) performing 5' to 3' DNA polymerase extension of the multifunctional capture probe on the complex from b) to replicate a region of the captured, tagged target region that is 3' of the multifunctional capture probe in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the multifunctional capture probe hybrid module and the complement of the tagged target region that is located in the 3' direction from the location where the multifunctional capture probe hybrid module hybridizes to the target region; and

(d) performing targeted genetic analysis on the hybrid nucleic acid molecule from c);

87.——A method for targeted gene expression analysis comprising:

(a) hybridizing a tagged cDNA library with a multifunctional capture probe hybrid module complex, wherein the multifunctional capture probe hybrid module selectively hybridizes to a specific target region in the cDNA library;

(b) isolating the tagged cDNA library-multifunctional capture probe hybrid module complex from a);

(c) performing 5' to 3' DNA polymerase extension of the multifunctional capture probe on the complex from b) to replicate a region of the captured, tagged target region in the cDNA library that is 3' of the multifunctional capture probe in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the multifunctional capture probe hybrid module and the complement of the tagged target region in the cDNA library that is located in the 3' direction from the location where the multifunctional capture probe hybrid module hybridizes to the target region; and

(d) performing targeted genetic analysis on the hybrid nucleic acid molecule from c);

88.——The method of any one of claims 85 to 87, wherein at least two different multifunctional capture probe modules are used in the at least two (a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.

89.——The method of claim 88, wherein at least one multifunctional capture probe module hybridizes downstream of the target region and at least one multifunctional capture probe module hybridizes upstream of the target region.

90.——A method for cDNA sequence analysis comprising:

(a) obtaining one or more clones, each clone comprising a first cDNA sequence and a second cDNA sequence, wherein the first cDNA sequence comprises targeted genomic cDNA sequence and the second cDNA sequence comprises a capture probe sequence;

(b) performing a paired-end sequencing reaction on the one or more clones and obtaining one or more sequencing reads; and

(c) ordering or clustering the sequencing reads of the one or more clones according to the probe sequence of the sequencing reads.

91.——A method for cDNA sequence analysis comprising:

(a) obtaining one or more clones, each clone comprising a first cDNA sequence and a second cDNA sequence, wherein the first cDNA sequence comprises targeted genomic DNA sequence and the second cDNA sequence comprises a capture probe sequence;

(b) performing a sequencing reaction on the one or more clones in which a single long sequencing read of greater than about 100 nucleotides is obtained, wherein the read is sufficient to identify both the first cDNA sequence and the second cDNA sequence; and

~~(c) ordering or clustering sequencing reads of the one or more clones according to the probe sequence of the sequencing reads.~~

~~92.—The method of claim 90 or claim 91, further comprising analyzing all sequencing reads associated with a second read sequence by:~~

~~(a) determining the distributions of unique and redundant sequencing reads;~~
~~(b) counting the number of times a unique read is encountered;~~
~~(c) fitting a frequency distribution of the unique reads to a statistical distribution;~~

~~(d) inferring a total number of unique reads; and~~
~~(e) converting unique read counts into transcript abundance using normalization to the total reads collected within each cDNA library sample.~~

~~93. A method for targeted genetic analysis comprising:~~

~~(a) hybridizing a tagged DNA library with a multifunctional capture probe hybrid module complex, wherein the multifunctional capture probe hybrid module selectively hybridizes to a specific target region in the DNA library;~~

~~(b) isolating the tagged DNA library multifunctional capture probe hybrid module complex from a);~~

~~(c) performing a concerted enzymatic processing of the tagged DNA library-multifunctional capture probe hybrid module complex from b) that includes 5' FLAP endonuclease activity, 5' to 3' DNA polymerase extension, and nick closure by a DNA ligase to join the complement of the multifunctional capture probe to the target region that is 5' of the multifunctional capture probe binding site in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the complement of the multifunctional capture probe hybrid module and a region of the tagged target region that is located 5' of the location where the multifunctional capture probe hybrid module hybridizes to the genomic target region; and~~

~~(d) performing targeted genetic analysis on the hybrid nucleic acid molecule from c).~~

94.—The method of claim 93, wherein steps a) through c) are repeated at least about twice and the targeted genetic analysis of d) comprises a sequence alignment of the hybrid nucleic acid molecule sequences obtained from the at least two d) steps.

95.—The method of claim 94, wherein at least two different multifunctional capture probe modules are used in the at least two a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.

96.—The method of claim 95, wherein at least one multifunctional capture probe module hybridizes downstream of the target region and at least one multifunctional capture probe module hybridizes upstream of the target region.

97.—A method for determining copy number of a specific target region comprising:
(a) hybridizing a tagged DNA library with a multifunctional capture probe hybrid module complex, wherein the multifunctional capture probe hybrid module selectively hybridizes to a specific target region in the genomic library;
(b) isolating the tagged DNA library-multifunctional capture probe hybrid module complex from a);
(c) performing a concerted enzymatic processing of the tagged DNA library-multifunctional capture probe hybrid module complex from b) that includes 5' FLAP endonuclease activity, 5' to 3' DNA polymerase extension, and nick closure by a DNA ligase to join the complement of the multifunctional capture probe to the target region that is 5' of the multifunctional capture probe binding site in order to generate a hybrid nucleic acid molecule, wherein the hybrid nucleic acid molecule comprises the complement of the multifunctional capture probe hybrid module and a region of the tagged target region that is located 5' of the location where the multifunctional capture probe hybrid module hybridizes to the target region; and
(d) performing PCR amplification of the hybrid nucleic acid molecule in c);
and

~~(e) quantitating the PCR reaction in d), wherein the quantitation allows for a determination of copy number of the specific target region.~~

~~98.—The method of claim 97, further comprising obtaining the sequences of the hybrid nucleic acid molecules from step d).~~

~~99.—The method of claim 98, wherein steps a) through d) are repeated at least about twice and a sequence alignment of the hybrid nucleic acid molecules from the at least two d) steps.~~

~~100.—The method of claim 99, wherein at least two different multifunctional capture probe modules are used in the at least two a) steps, wherein the at least two a) steps employ one multifunctional capture probe module each.~~

~~101.—The method of claim 100, wherein at least one multifunctional capture probe module hybridizes downstream of the genomic target region and at least one multifunctional capture probe module hybridizes upstream of the genomic target region.~~

~~102.—The method of any one of claims 93 to 101, wherein the targeted genetic analysis is sequence analysis.~~

~~103.—The method of any one of claims 93 to 102, wherein the target region is a genomic target region and the DNA library is a genomic DNA library.~~

~~104.—The method of any one of claims 93 to 103, wherein the target region is a cDNA target region and the DNA library is a cDNA library.~~

1. A plurality of compositions for generating a captured library comprising hybrid nucleic acid molecules, the plurality of compositions comprising:

(a) a first composition comprising a multifunctional adaptor module comprising:

(i) a first region comprising a random nucleotide tag sequence,

(ii) a second region comprising a sample code sequence, and
(iii) a third region comprising a PCR primer sequence;
characterized in that the multifunctional adaptor module is capable of ligating to each
end of a DNA fragment, and

(b) a second composition comprising a multifunctional capture probe module
comprising:

(i) a first region capable of hybridizing to a partner oligonucleotide, and
(ii) a second region capable of hybridizing to a specific genomic target region in the
DNA fragment.

2. The plurality of compositions of claim 1, wherein the first composition
comprises a plurality of multifunctional adaptor modules.

3. The plurality of compositions of claim 2, wherein each multifunctional adaptor
module of the plurality of multifunctional adaptor modules comprises a random nucleotide tag
sequence, wherein the multifunctional adaptor module and a nucleic acid sequence of the
DNA fragment ligated thereto is capable of being sequenced to obtain one or more sequencing
reads, and wherein a quantity of random nucleotide tag sequences determined in the
sequencing reads indicates the copy number of the nucleic acid sequence.

4. The plurality of compositions of claim 2 or claim 3, wherein the PCR primer
sequence of each multifunctional adaptor module of the plurality of multifunctional adaptor
modules is the same.

5. The plurality of compositions of any one of claims 1-4, wherein the
sample code sequence is capable of identifying a DNA sample from which the hybrid tagged
DNA library is generated.

6. The plurality of compositions of any one of claims 1-5, wherein the
multifunctional adaptor module comprises a ligation strand and a complementary strand,
wherein the complementary strand is hybridized to the 3' end of the ligation strand and forms
a partial duplex therewith.

7. The plurality of compositions of claim 6, wherein the duplexed region of the multifunctional adaptor module is blunt ended.

8. The plurality of compositions of claim 6, wherein the duplexed region of the multifunctional adaptor module comprises an overhang at the 3' end of the ligation strand, wherein the overhang is complementary to a 3'-overhang of a DNA fragment to be ligated thereto.

9. The plurality of compositions of any one of claims 1-8, wherein the partner oligonucleotide comprises a specific member of a binding pair that is configured to facilitate isolation and/or purification of a complex comprising the multifunctional capture probe module hybridized to the DNA fragment, wherein the specific member of a binding pair is a biotin or a hapten.

10. The plurality of compositions of claim 9, wherein the hapten is a dinitrophenol molecule, or a digoxigenin molecule.

11. The plurality of compositions of any one of claims 1-10, wherein the first region of the multifunctional capture probe module comprises a tail sequence at the 5' end.

12. The plurality of compositions of any one of claims 1-10, wherein the multifunctional capture probe module comprises a third region comprising a tail sequence at the 5' end.

13. The plurality of compositions of claim 11 or claim 12, wherein the tail sequence comprises a PCR primer binding site.

14. A complex comprising:
(a) a tagged DNA molecule comprising a DNA fragment, wherein each end of the DNA fragment is ligated to a multifunctional adaptor module comprising:
(i) a first region comprising a random nucleotide tag sequence;

(ii) a second region comprising a sample code sequence; and
(iii) a third region comprising a PCR primer sequence; and
(b) a hybrid nucleic acid molecule hybridized to the tagged DNA molecule, wherein the hybrid nucleic acid molecule comprises, from 5' to 3':

(i) a tail sequence comprising a PCR primer binding site;
(ii) a capture probe to which a portion of the DNA fragment is hybridized; and
(iii) the complement of a region of the DNA molecule that is located 3' to the capture probe, wherein the region comprises a multifunctional adaptor module.

15. The complex of claim 14, further comprising:

(c) a partner oligonucleotide hybridized to the 5' end of the hybrid nucleic acid molecule.

16. The complex of claim 14 or 15, wherein the random nucleotide tag sequence is configured to designate the DNA fragment ligated thereto.

17. The complex of any one of claims 14-16, wherein the DNA fragment is derived or isolated from a DNA sample, wherein the sample code sequence is capable of identifying the DNA sample.

18. The complex of any one of claims 14-17, wherein the partner oligonucleotide comprises a specific member of a binding pair that is configured to facilitate isolation and/or purification of the complex, wherein the specific member of a binding pair is a biotin or a hapten.

19. The complex of claim 18, wherein the hapten is a dinitrophenol molecule, or a digoxigenin molecule.

20. A complex comprising:

(a) a multifunctional capture probe module comprising, from 3' to 5':

(i) a first region capable of hybridizing to a partner oligonucleotide;

(ii) a second region capable of hybridizing to a specific genomic target region in a DNA fragment; and

(iii) a third region comprising a tail sequence; and

(b) a tagged DNA molecule comprising the DNA fragment, wherein the tagged DNA molecule is hybridized to the multifunctional capture probe module,

wherein the 5' end of the DNA fragment is ligated to a multifunctional adaptor module comprising:

(i) a first region comprising a random nucleotide tag sequence;

(ii) a second region comprising a sample code sequence; and

(iii) a third region comprising a PCR primer sequence;

wherein the 3' end of the DNA molecule comprises the complement of the third region of the multifunctional capture probe module.

21. The complex of claim 20, further comprising:

(c) a partner oligonucleotide hybridized to the first region of the multifunctional capture probe module.

22. The complex of claim 21, wherein the random nucleotide tag sequence is configured to designate the DNA fragment ligated thereto.

23. The complex of any one of claims 20-22, wherein the DNA fragment is derived or isolated from a DNA sample, wherein the sample code sequence is capable of identifying the DNA sample.

24. The complex of any one of claims 20-23, wherein the partner oligonucleotide comprises a specific member of a binding pair that is configured to facilitate isolation and/or purification of the complex, wherein the specific member of a binding pair is a biotin or a hapten.

25. The complex of claim 24, wherein the hapten is a dinitrophenol molecule, or a digoxigenin molecule.

26. A complex comprising:
- (a) a tagged DNA molecule comprising a DNA fragment, wherein each end of the DNA fragment is ligated to a multifunctional adaptor module;
- wherein the multifunctional adaptor module comprises:
- (i) a first region comprising a random nucleotide tag sequence;
- (ii) a second region comprising a sample code sequence; and
- (iii) a third region comprising a PCR primer sequence; and
- (b) a multifunctional capture probe module comprising:
- (i) a first region capable of hybridizing to a partner oligonucleotide; and
- (ii) a second region capable of hybridizing to a specific target region in the DNA fragment;
- wherein the tagged DNA molecule is hybridized to the multifunctional capture probe module.
27. The complex of claim 26, wherein the random nucleotide tag sequence is configured to designate the DNA fragment ligated thereto.
28. The complex of claim 26 or claim 27, wherein the sample code sequence is capable of identifying a DNA sample from which the tagged DNA molecule is derived or isolated.
29. The complex of any one of claims 26-28, wherein the partner oligonucleotide comprises a specific member of a binding pair that is configured to facilitate isolation and/or purification of the complex, wherein the specific member of a binding pair is a biotin or a hapten.
30. The complex of claim 29, wherein the hapten is a dinitrophenol molecule, or a digoxigenin molecule.
31. The complex of any one of claims 26-30, wherein the first region of the multifunctional capture probe module comprises a tail sequence.

32. The complex of any one of claims 26-31, wherein the multifunctional capture probe module comprises a third region comprising a tail sequence.

33. The complex of claim 31 or claim 32, wherein the tail sequence comprises a PCR primer binding site.