

CLAIMS

1. A method for detecting genomic variations in the genome of an organism, the method comprising:
 - (1) fragmenting genomic DNA of the organism to generate a plurality of genomic DNA fragments;
 - (2) tagging the ends of the genomic DNA fragments with a tag sequence;
 - (3) ligating tagged ends of the genomic DNA fragments, under a condition that promotes blunt-end intramolecular ligation, to generate a plurality of circularized genomic DNA fragments with ligated tag sequence;
 - (4) fragmenting the plurality of circularized genomic DNA fragments by shotgun fragmentation, to generate:
 - (a) a plurality of mate-pair (MP) fragments, each comprising the ligated tag sequence flanked by flanking genomic DNA; and,
 - (b) a plurality of shotgun (SG) fragments;
 - (5) determining the sequences of the MP fragments and the SG fragments;and,
 - (6) identifying said genomic variations in the genome of the organism based on both the sequences of the SG fragments and the sequences of the MP fragments.
2. The method of claim 1, wherein said genomic variations comprise one or more of: single nucleotide polymorphisms (SNPs); small insertions or deletions (indels); tandem base mutations (TBM); copy number variations (CNVs); structural variations (SVs); and combination thereof.
3. The method of claim 1, wherein steps (1) and (2) are carried out simultaneously, preferably by transposon-mediated tagmentation, wherein said transposon-mediated tagmentation is optionally carried out by a Tn5 transposase.
4. The method of claim 1, wherein the plurality of genomic DNA fragments is size-selected prior step (3), wherein preferably, genomic DNA fragments of about 4-10 kb, or about 6-8 kb, are size-selected.
5. The method of claim 1, wherein uncircularized or linear genomic DNA fragments are removed by DNA exonuclease digestion prior to steps (4)-(6).

6. The method of claim 1, wherein sequences of the MP fragments and the SG fragments are determined separately or simultaneously.
7. The method of claim 1, wherein the SG fragments have an average size of about 400 bp, 450 bp, or 500 bp; or wherein the MP fragments have an average size of about 400 bp, 450 bp, or 500 bp.
8. The method of claim 1, wherein the MP fragments and the SG fragments are either isolated or not isolated from each other before step (5).
9. The method of claim 1, wherein tagged ends of the genomic DNA fragments are repaired to promote blunt end ligation prior to step (3).
10. The method of claim 1, wherein step (6) comprises mapping the sequences of the flanking genomic DNA and the sequences of the shotgun fragments to the genomic sequence of the organism.
11. The method of claim 1, wherein the sequences of the genomic DNA are determined by high-throughput sequencing.
12. The method of claim 11, wherein the high-throughput sequencing is selected from the group consisting of: single-molecule real-time sequencing; ion semiconductor (Ion Torrent) sequencing; pyrosequencing (454); sequencing by synthesis (Illumina); sequencing by ligation (SOLiD sequencing); polony sequencing; massively parallel signature sequencing (MPSS); DNA nanoball sequencing; single molecule nanopore sequencer; and Heliscope single molecule sequencing.
13. The method of claim 11, wherein the high-throughput sequencing produces 30-, 40-, 50-, 60-, 70-, 80-, 90-, 100- or more fold of coverage for the flanking genomic DNA and/or the shotgun fragments.
14. The method of claim 1, wherein the organism is a human, a non-human primate, a mammal, a rodent (rat, mouse, hamster, rabbit), livestock animal (cattle, pig, horse, sheep, goat), a bird (chicken), a reptile, an amphibians (*Xenopus*), a fish (zebrafish (*Danio rerio*), puffer fish), an insect (*Drosophila*, mosquito), a nematode, a parasite, a fungus (yeast, such as *S. cerevisiae* or *S. pombe*), a plant, a bacterium, or a virus.

15. The method of claim 1, wherein the organism is a human having a disease or condition selected from the group consisting of: autism (autism spectrum disorder (ASD)), cancer, or hereditary disease.