Mapping of mitochondrial DNA deletions and duplications using deep sequencing

Abstract : Duplication and deletion in mitochondria genome leads to variety of rare disorders which cause and related to diseases such as cancer ,diabetes type 2 and age related disorder so they set up a computational method that can accurately map and classify mtDNA deletions and duplications using high-throughput sequencing, Mitochondrial structure alterations used for accurate identification, quantification and visualization of mtDNA deletions and duplications from genomic sequencing data, they tested on human samples with single deletion and duplication and for application this methodology they use mouse models maintenance disease that show the ability to detect this events at low levels of heteroplasm.

Introduction : Mitochondria have their own genome, which encodes the oxidative phosphorylation system's essential subunits as well as the RNA molecules needed for mitochondrial translation. Human mtDNA is a small circular molecule of 16.6 billion base pairs with few non-coding regions. Mitochondrial gene activity is almost disrupted when mtDNA events is happened. These structural alteration may occur naturally or as a result of mutations(deletion or duplication in the gene sequence) in the nuclear-encoded mtDNA maintenance machinery. Mitochondrial disorders are often caused by deletions which related to these diseases : Cancer, diabetes, neurodegenerative diseases, and the ageing process. Duplications are less common mutation, but nearly have been described in patients with disease-causing mutations in MGME1 or mice expressing a proof-reading-deficient variant of Pol.

Most mtDNA alterations are heteroplasmic, which means that wild-type mtDNA coexists with mutant variants and because of the complexity of the DNA landscape, it is difficult to characterise mtDNA variants with Low-level heteroplasmic that are explicitly hard to detect .The detection methods Southern blotting and longrangePCR have limited resolution ,even a variant present at high levels can remain undetected relying on the primers, probes, or restriction enzymes and beforehand these methods duplications have been incorrectly classified as deletions .

To solve this and for more accurate mapping of these alterations they use high-throughput sequencing , It permit for the survey of mtDNA deletions and duplications in a large body of preceding sequenced data. Identification of discordant paired-end reads or gapped alignment of individual reads to the reference genome are the fundamental bioinformatics principles for determining structural alterations from short read sequencing. However, implementation details may have a significant impact but the small size of the mitochondrial genome simplifies the problem that mitochondrial deletions often occur near repeated sequences which makes it more difficult, and mapping structural events on a circular genome adds to the difficulty.

Many methods for identifying mtDNA deletions have recently been developed from high-throughput short read sequencing,including MitoDel,Splice-Break , eKLIPse , MitoMut and a PERL script, These methods depend on gapped and split alignments to predict deletions, but fail to recognize that every event affecting the arc complementary to the deleted part. Finaly we must know that duplications can form as a result of mutations in mitochondrial replication factors, and correct identification and classification of such alterations is thus an important requirement for any bioinformatics method concern to mtDNA structural changes analysis.