Applications of Mitochondrial DNA in Forensic Science

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Abstract

Mitochondria is an intracellular double-membraned organelle that exists inside each nucleated cell of mammals. Mitochondrial DNA (mtDNA) is a tiny 16.6 kilobase (kb) dsDNA circle coding 13 critical respirational chain components. The displacement loop (D-Loop) of mtDNA or control region is a noncoding region with 1.1 kb size that controls molecule transcription and replication. The D-Loop includes three short regions with a highly variable population sequence relative to the rest of the genome: a hypervariable HVS-I, HVS-II, and a HVS-III. mtDNA is strongly preserved, and it is recombined with what would be similar copies of itself when it is recombined. However, the mutation rate of mitochondrial DNA is tenfold greater than the DNA of the nucleus. This property makes the creation of species extremely useful in the matrilineal line for several generations and utilized in several forensic investigations. Therefore, mitochondrial DNA profiling is one of the most important tools in maternal dispute and child swapping cases.

Keywords

mtDNA · D-Loop · Profiling · Forensic · Recombination

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16.1 Introduction

16.1.1 Mitochondria

Mitochondria's are intracellular double-membrane organelles that exist inside each nucleated cell of mammals. On an organizational level, the established picture that mitochondria are a bean-shaped or cigar-shaped small structure is possibly ingenuous, and it is more precise to consider mitochondria as an endoplasmic reticulum-like budding and fusing network (Iborra et al. 2004). Mitochondria are closely enmeshed in homeostasis on the cellular. They play a role among other functions in intracellular signaling and apoptosis, intermediary metabolism, and in the metabolism of lipids, amino acids, steroids, cholesterol, and nucleotides. Likewise, mitochondria also perform a vital role in the metabolism of cellular energy. This process involves the development of carboxylic acid β-oxidation, the urea process, and the definitive important nucleotide pathway (ATP)—the respirational chain. The mitochondrial respirational chain is a combination of complexes of five enzymes located on the membrane inside mitochondria. Each of the complexes comprises of several subunits, the most important being complex I consisting of over 40 components of polypeptides. NADH and FADH2 are reduced cofactors produced by the intermediate break down of carbohydrates, fats, and proteins giving complex I and II electrons. Such electrons migrate downwards and are electrochemical gradients between complexes III and IV and two mobile electron carriers, ubiquinone and cytochrome. The e-transfer purpose of complexes I–IV is achieved through subunits harboring prosthetic groups (e.g. iron-sulfur groups in complexes I, II, and III and heme iron in cytochrome c and in complex IV). Mitochondrial subunits containing prosthetic groups, i.e., heme iron in cytochrome (c) and complex IV), sulfur iron group in complexes I, II, and III and the electron transference function of complexes I–IV is carried out. Complexes I, III, and IV use the released energy to transmission protons from the mitochondrial matrix into the vacuum between the intermembrane. This proton gradient is connected by complex V to synthesize ATP from adenosine diphosphate (ADP) and inorganic phosphate, which produces the bulk of the mitochondrial membrane potentials. Oxidative phosphorylation (OXPHOS) is the basic method. ATP is a high-energy source used by virtually all-important metabolic processes in the cell. In exchange for cytosolic ADP, it must be released from the mitochondrion. Adenine nucleotide (ANT), which comprises a

Fig. 16.1 Location of mtDNA within the cell
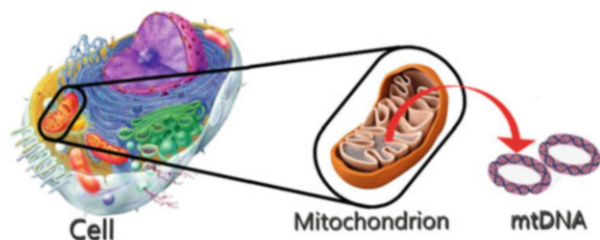
variety of tissue exclusive isoforms, is used for this purpose (Bandelt et al. 2006) (Fig. 16.1).

16.1.2 Mt Genome (Location and Structure)

Mitochondrial DNA is a tiny 16.6 kb dsDNA circle coding 13 critical respirational chain components. Seven subunits of complex 1 are encoded by ND1-ND6 and ND4 L. The cytb-compound (ubiquinol cytochrome c reductase) is a single mitochondrial DNA-encrypted III complex subunit. CO (I)-CO (III) encrypt3 complex IV subunits (cytochrome c oxidase) with two complex V-subunits (ATP synthesis) encoding for ATP6 and ATP8 genes. Besides, mtDNA codes for two ribosomal RNAs (rRNAs) genes and 22 genes of transfer RNAs (tRNAs), which provide RNA components for intra-mitochondrial protein synthesis.

The displacement loop (D-Loop) of mtDNA or control region is a noncoding region with 1.1 kb size that controls molecule transcription and replication. D-loop stretches from 576 nt to16,024 nt in mtDNA and is the major region not influenced by the production of polypeptides in the chain. There are a variety of small and single-base genome segments that don't engage in RNA or protein coding directly. The D-Loop includes three short regions with a highly variable population sequence relative to the rest of the genome: a hypervariable HVS-I, a HVS-II, and a HVS-III, corresponding in other references (Brandstätter et al. 2004a). The precise description of the various hypervariable sequences differs between contexts. The forensic group historically took HVS-I in 16,024–16,365, HVS-II in 73–340, and HVS-III in 438–576 (Brandstätter et al. 2004b). New population genetic studies, on the other hand (Brandstätter et al. 2004b). To depict the phylogenetically significant positions 16,390, 16,391, and 16,399 (HVS-I 16,024–16,400, HVS-II 44–340, and HVS-III 438–576), take extensive ranges, in particular in HVS-I. The full purpose of these three hypervariable regions is not understood, but they tend to be essential for replication of genome and transcriptions and either one contain or close to the source of mtDNA replication by heavy strand and light strand: O_H and O_L. The genetic code of mtDNA varies in many ways from the worldwide genetic code (Anderson et al. 1981). In human mtDNA, AUG codon codes for methionine, but not for isoleucine, and the termination codons, i.e., AGA and AGG codes for Arginine, and tryptophan is coded with UGA unlike nuclear DNA. Ultimately, the codons of initiation are AUA and AUG. Early trials established the molecular asymmetric stranding with a "weighty " strand rich in guanosine or "H-Strand" and "light" Strandor" L-strand rich in cytosine. In the custom, mtDNA is tote up according to the original CRS— Cambridge Reference Sequence of mtDNA in reference to the light strand. The revised Cambridge Reference Sequence as the novel light strand system of numbering should be preserved for reserach purposes (Andrews et al. 1999) (Fig. 16.2).
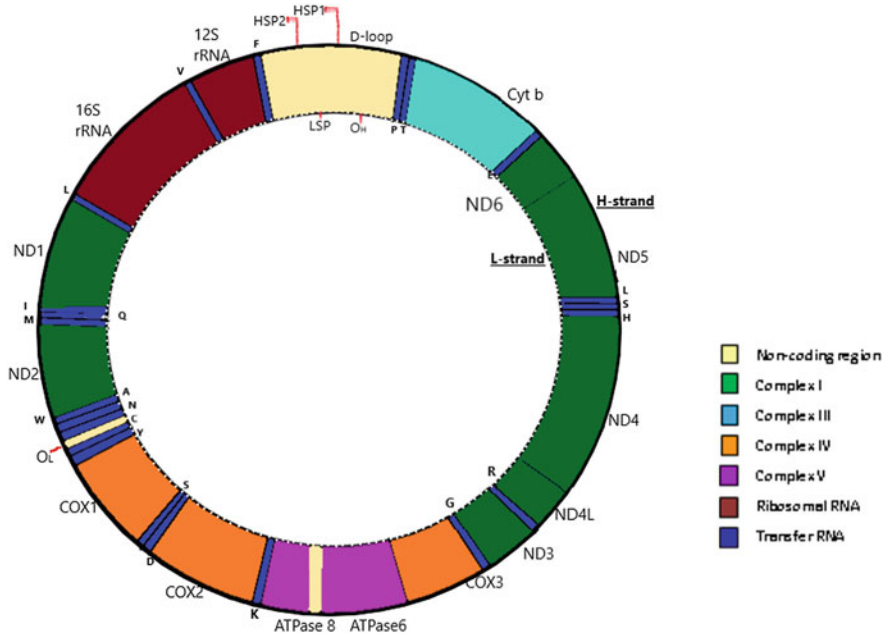
Fig. 16.2 Mitochondrial genome

16.2 Transcription, Translation, and Replications in mtDNA

The human mitochondrial DNA was revealed in the 1980s as the fundamental mechanism for transcription (Clayton 1982). Two main sites are launched for transcript: ITH1 and ITL, both in the noncoding region at 150 bp. Strong beach transcription begins at position 561 in a strong beam promoter; light beach transcriptions start at position 407 inside a light beach, along with elements of enhancer right upstream binding the mitochondrial transcript factor A (TFAM or mtTFA). TFAM allows a two-way version, isolated from the DNA template.

In stoichiometry, theBM1 and BM2 transcription factors join 1:1 to the heart and perform a critical part when the transcription begins (Falkenberg et al. 2002). The beam is transliterated as a solo polycistronic precursor that is later sort out and improved until the proteins encoded by mtDNA are synthesized on mitochondrial ribosomes in the mitochondrial matrix. While the fundamental processes following this phase are familiar, the monitoring processes are merely explained (Gagliardi et al. 2004).

In comparison to nuclear DNA that only repeats one time in the course of each cell cycle, mt DNA is processed constantly in non-tissues, for instance, the muscle of the skeleton and the brain (Bogenhagen and Clayton 1977; Birky 2001). Consequently, mitochondrial DNA is self-contained of cell cycle replication. The correct

replication process of mtDNA is asymmetrical to the strand. The heavy strand leads to a replication process starting at OH according to this model (Clayton 1982) with rift of an initial transcript synthesized with the light beam promoter. As the heavy strand reproduction reaches the origin of replication for the light strand, the light strand is synthesized in the opposite direction. Current experimental data does support a substitutional symmetric or rolling-circulation strand model, which starts to replicate MtDNA in a crucial 5.5 kb region flanked by the D-Loop and the ND4 gene at various points (Bowmaker et al. 2003). Such duplication bubbles then continue bidirectionally, ending at O_H and stopping succinctly in the O_L region, until the replication process is completed, and the rear strand rates the binding of Okazaki fragments.

16.3   Pathogenic Mutations of mtDNA-Heteroplasmy

Earlier studies in 1980s, reported the pathogenic mutations in mitochondrial DNA. The cases with long-lasting, developing, outward ophthalmoplegia and (KSS) Kearns Sayre Syndrome (Holt et al. 1988; Zeviani et al. 1988) large-scale deletions of mitochondrial DNA, together with deleting tRNAs and functional genes, occurred in the muscles of skeleton. In a case suffering from mitochondrial encephalomyopathy along with stroke (Goto et al. 1990) as well as Leber Inherited Optic Neuropathy (LION), point mutations of mitochondrial DNA were identified (Wallace 1997).

The prevalence of initial pathogenic mitochondrial DNA mutations in affected individuals remain heteroplasmic by means of different quantities of mutated mitochondrial DNA in the similar organism. While the majority of humans hold two copies of nuclear DNA, they have much extra copies of mtDNA (depending on the cell type from 1000 to 100,000). All of these exist frequently same in salubrious birth persons (homoplasmas), but a certain mixture (heteroplasmas) can occur, particularly involving polycytosine stretch hypervariable sites and polymorphs in duration. In reality, the altered and the wild type mitochondrial DNA often interact in patients who have pathogenic mtDNA defects (Holt et al. 1988; Wallace 1997). There is a major difference between different cases and in tissues of various organs and also within the cells of the same person in the percentage of mutated mtDNA. The bulk of mutated mitochondrial DNA mutations remain strongly recessive in in vitro experiments using the "trans-mitochondrial cytoplasmic hybrid" cells (King and Attardi 1988). In other words, before a biochemical fault within the respirational chain was created, cells could tolerate high level of mutilated mtDNA (typically 70–90%). The emergence of Heteroplasmy and sequencing of D-Loop suggests a recent transformation at the same site from population genetics perspective (Man et al. 2003).

16.4   Inheritance of mtDNA

It is common to say, but recently this has been called into question, that mitochondrial DNA is transmitted only along the matrilineal lines (Giles et al. 1980). The problem of paternal transmission was posed by a surplus of homoplasms and the apparent inversion of the intermolecular mtDNA rebound rate with the genetic gap (Awadalla et al. 1999), and by the fact that paternalistic mtDNA is associated with the analyses of individual development (Awadalla et al. 1999).

Post Studies after above findings created questions on the explanations given. The excessive homoplasmy identified in earlier reports is clarified in different recombinant measures in various data sets (Mcaulay et al. 1999; Elson et al. 2001) along with sequencing artifacts (Hagelberg et al. 1999). The latest study of the deletion of paternal small pathogenic mtDNA found that paternal mtDNA leakage can occur (Schwartz and Vissing 2002).

Indeed, in the past decade several substantial number of families with mtDNA disease were researched around the world and other cases of paternal transmission have not been reported. Therefore, there is little evidence that mtDNAs are recovered in vivo (Howell 1997). Latest research of Kraytsberg and his colleagues has provided an exciting proof of recombination in vivo (Kraytsberg et al. 2004), which, however, is also used to create entities that may perhaps yield confusing outcomes (Bandelt et al. 2006).

In addition, the available evidence suggests that paternal mtDNA leaking is extremely rare, and while it does occur, a major recombination of paternal and maternal mtDNAs is highly unlikely. So there seems to be no reason to question, nevertheless as of the population genetics perspective, the conventional doctrine of maternal transmission.

The findings are still vital on the way to explain the exact molecular mechanisms in the rear of strict motherly transmission. Although paternal mitochondria were originally thought to not have entered the oocyte, this is not the case. In a study, the recently implanted embryo in uterus have found paternal mtDNA molecules in them (St John et al. 2000). The father's mitochondrial DNA is likely to be killed by an effective ubiquitis process (Sutovsky et al. 1999).

16.5   Forensic Applications of mtDNA

Mitochondria exists as a key organelle intended for the manufacture of ATP in the form of energy for cells. Human beings contain DNA in mitochondria as mtDNA, which is around 16,500 base pairs as well as individual-specific. This makes mtDNA useful when DNA is compromised or degraded in forensic science. Human mtDNA is highly preserved, and it is recombined with similar copies of itself when recombine. However, the mutation rate of mitochondrial DNA is tenfold greater than DNA of nucleus. This property makes the creation of species extremely useful in the matrilineal line for several generations. Some of the most important applications of mtDNA in forensic science are as follows:

1. Identification of largely decayed bodies where only the teeth, bones, or hair is available.
2. Maternal dispute cases.
3. Baby swapping.
4. Identification of ancient DNA.
5. Phylogenetic studies.

16.6   Mitochondrial DNA Sequencing Approaches

The first DNA sequence research (Sanger et al. 1977), also regarded as the first-generation sequences, was published by Sanger in 1977. The incorporation of ddNTPs into the freshly synthesized DNA molecules contributes to the completion of the stretching cycle and subsequent awareness of the individual nucleotide in each location in the chain. The method of Sanger sequencing can generate readings of 25–1200 nucleotides, which allow reading of up to 96 kb of nucleotides within 2 h. Since 2005, modern methods of DNA sequencing were developed (Bruijns et al. 2018), often referred to as next-generation sequencing (NGS).

The synthesis-sequence approaches, for instance Roches "454" pyrosequencing approach and Illuminas "HiSeq," enable sequencing within 1–2 week, capable of analyzing 80 million bp in 2 h, and able to analyze 6 billion base pairs. Sequencing through hybridization and ligation, for instance-ABI SOLiD 3plus, results in 60 gb per exercise of functional deoxyribose nucleic acid details. The sequenced DNA fragments will vary from 35 to 75 nt while in the analysis with SOLiD with 453 pyrosequencing and major parallel sequencing (MPS) technologies (Bruijns et al. 2018; Ondov et al. 2010; Shendure et al. 2005) the fragments are 100–1000 nts long. (Bruijns et al. 2018; Dames et al. 2010). Personal Genome Machine™ (PGM) via Ion Torrent utilizes a pH-based identification technique by introducing a radio-active material to a series (Rothberg et al. 2011). Once this occurs, protons are emancipated and a proportional electrical signal is produced. Data processing is performed via the CMOS (Complementary Metal Oxide Semiconductor) capable of calculating millions to billions instantaneous sensing responses, with a sensor surface on the bottom of the well layer. Finally, a portable real-time sequence device (MION) (Oxford Nanopore Technologies) enables extremely long reading lengths in hundered kb. In forensics the NGS tools were easily used (Bruijns et al. 2018). In the form of forensic sampling (Parson et al. 2013) and heteroplasm experiments (Magalhães et al. 2015), for example, Ion Torrent's PGM device was used. Though PGM has proven resilient and accurate to detect and measure mixture and heteroplasm, the reporting of the mtDNA in certain regions with significant feature biases and fake positive results mainly triggered by problems of alignment in the research algorithms has been troublesome. In recent years, the accurate identification of mitochondrial DNA Complete Genome Panel (Woerner et al. 2018) was used with S5 Ion Technique (Thermo Fisher Scientific) and Desktop MiSeqFGx Sequencer (Ilumina). Both structures provide consistent mtDNA haplotypes estimate. Some additional findings on the usage of forensic molecular genetics

technology and mitochondrial DNA examination have been circulated (Templeton et al. 2013; Just et al. 2014; Chaitanya et al. 2015; Lopopolo et al. 2016; Ovchinnikov et al. 2016; Hollard et al. 2017; Marshall et al. 2017; Park et al. 2017; Young et al. 2017; Churchill et al. 2018; Ma et al. 2018).

Nonetheless, more feasibility studies and advanced forensic-based software capabilities need to be created to allow NGS analysis to be integrated into traditional legal purposes (Amorim and Pinto 2018; Peck et al. 2016). Although, Sanger sequence appears as an effective tool for mtDNA research for the forensic detection of individuals, and is used in most cases work laboratories around the world, in keeping with existing universal recommendations (Parson et al. 2014; Prinz et al. 2007; Ballard 2016). A number of forensic science laboratories conduct the sequencing using Sanger method of the whole control zone as a standard technique (Chaitanya et al. 2016; Poletto et al. 2019; Turchi et al. 2016; Yasmin et al. 2017), although others have also expanded the analysis to HVIII and, in modern years, nearly all forensic science laboratories applies amplifications of the whole control region in standard technique. Over the last decade, several experiments have been based on applying research of the whole mtDNA genomes in an effort of enhance the role of mtDNA in human identifying (Duan et al. 2019; Strobl et al. 2018; Woerner et al. 2018).

Amorim and Pinto (2018), contribute details as of the complete genome of mtDNA to enhance the identity obtained by the HVI, HVII and HVII analysis or from the complete control region without modifying the previous findings on separate haplogroups with an entirely different regional ancestry.

16.7   Current Trends of mtDNA Analysis: Hybridization Enrichment Coupled with Massively Parallel Sequencing (MPS)

Control region sequencing using Sanger method possibly will be a concern in forensic examination of mitochondrial DNA of disintegrated human remains and with PCR-based Sanger sequencing the obtained DNA evidences are incredibly small. Enrichment of hybridization coupled with next-generation sequencing –massively parallel sequencing (MPS) provides an efficient way to retrieve fragments from poorly preserved samples of DNA as minute as 30 base pairs (bp). Cases where human identifications are required from extremely disintegrated and fragmented DNAs (< 100 bp) are mostly solved by analysis of mtDNA, and also in cases where persons missing from longer time, immigrant problems, Disaster Victim Identification, etc. Also, with poor amplification of PCR has been observed due to high rates of fragmented DNA, i.e. which are below required size of amplicon, requires hybridization for better analysis (Gilbert et al. 2003; Maciejewska et al. 2013; Chaitanya et al. 2015).

The performance of mtDNAPCR is linked to the input of DNA, which indicates that low DNA quantity PCR-based approaches have failed (Just et al. 2015). Targeted hybridization enhancement (Templeton et al. 2013; Hofreiter et al. 2015)

coupled with MPS provides a range of advantages in contrast to the PCR-based analytical approaches for decomposed DNA. They are capable of obtaining sequence facts from pieces of DNA as petite as 30 base pair, fairly beneath the minimum PCR level and identifying single fragments of DNA, thereby reducing PCR-related problems.

Enrichment of hybridizing involves conversion by bar-coded adjusters of disintegrated genomic DNA to the DNA lending library. The PCR primers are used to immortalize the DNA, complementing the adapters, until enrichment is hybridized. Biotinylated ssRNA or DNA hybridization dressings are consequently utilized so as to separate from the library the relevant sequences (in this case human mtDNA).

Various forms of DNA like well preserved DNA, decomposed DNA, chemically treated DNA, telogen-rested blood, skeletal remain traces, and archaeological specimens have been examined and used in forensic analysis (Templeton et al. 2013; Marshall et al. 2017; Shih et al. 2018). (MDNA) To enhance and sequence of the mitochondrial DNA (mtDNA) control regions, Eduardoff et al. (2017) used primary extension capture (PEC) from superior quality DNA, human hairs samples and ancient human skeletal remains.

Hybridization enrichment can therefore be said to have a new ability and capacity to distinguish traces and highly damaged DNA based on expert DNA. In this latest strategy, trace sources will be enhanced, decomposed human remains are more accurately detected, and uncertain sample detection costs and delay are reduced, thereby improving criminal and coronal investigative findings (Fig. 16.3).

16.8 Mitochondrial DNA Population Data and Databases

If two mitochondrial DNA sequences, one commencing from a sample proof and one as of a reference lending library, cannot be ruled out as they come from precisely the similar resource, some detail on the rarities of the mtDNA profile should be given. The traditional method is to calculate how many times in a population sample a given order is found (Budowle et al. 1999). In general, the population databanks utilized in forensics include numerous convenient specimens which reflect, in terms of facts, the main populations of possible contributors. The EDNAP Mitochondrial DNA Population Database is the most important mtDNA Haplotype database (EMPOP, http://www.empop.org).

EMPOP was developed and planned in its early stages to function like a population reference databank exclusively for assessment of mitochondrial DNA proof throughout the world, with the purpose to endow mtDNA data with the superior quality. The design and research capabilities of this online database have developed over the past few years, while mtDNA data consistency remains the key objective of the EMPOP database. EMPOP is not just a population reference resource but also a direct result intended for forensic genetics researchers as well as other disciplines. It also acts as a quality control device. EMPOP is the most robust dataset, especially from the point of view of community covered by this database, although there is a
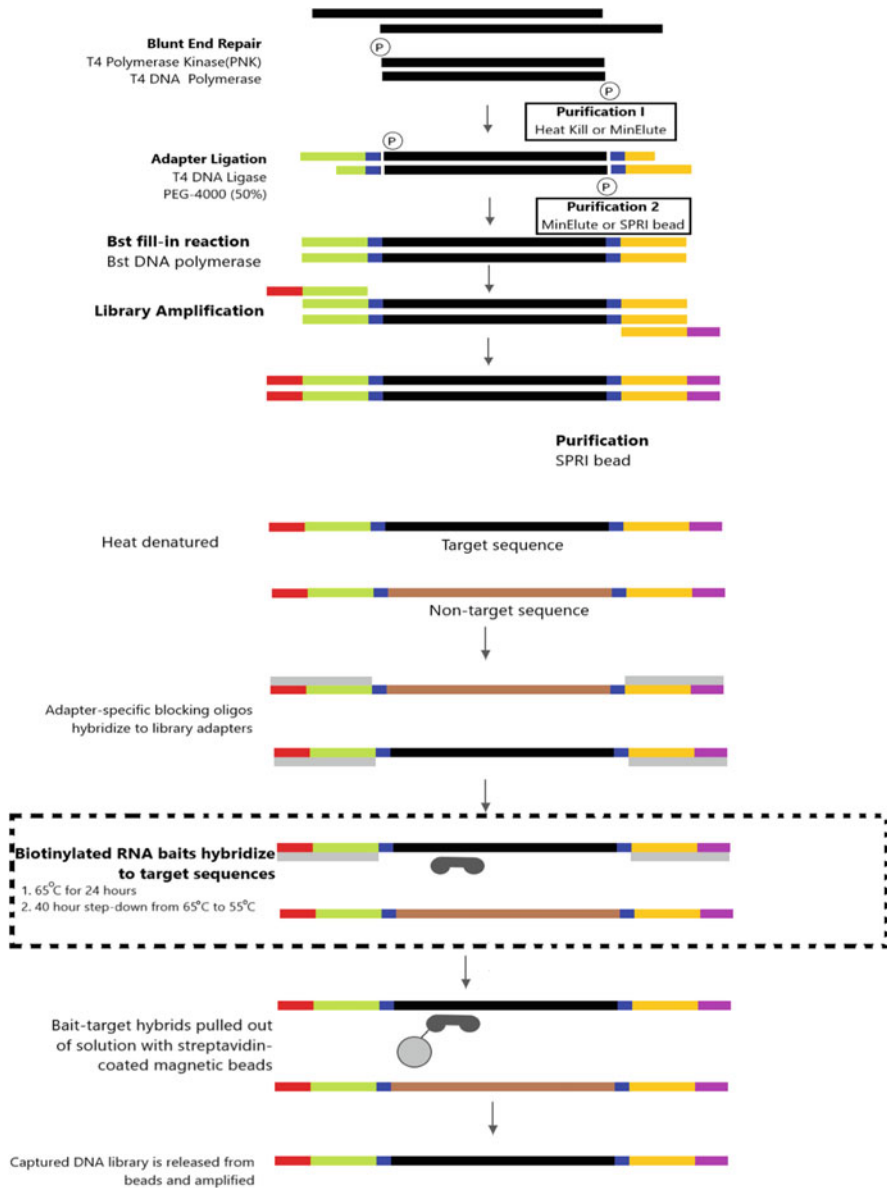
Fig. 16.3 Steps of massively parallel sequencing (MPS) with coupling of hybridization enrichment

significant amount of standard reference populations meant for the purpose of forensic comparisons (Parson et al. 2014). EMPOP utilizes a sequence-based SAM search algorithm that transforms enquiry and database arrangements on nuclear sequences that are alignment safe, thus ensuring that a haplotype is identified in an

unchecked database application. SAM-E is already in operation. It is an improved SAM variant and uses InDels block as phylogenetic cases. In EMPOP the tool haplogroup explorer represents in convenient searchable formats all known Phylotree Haplogroups and offers the number of the EMPOP sequence allocated toward the respective category by means of the maximum probability method EMMA to estimate mitochondrial DNA Haplogroups (Röck et al. 2013). As described earlier, more current common ancestor (MRCA) haplogroups are valid for many potential haplogroups. PhyloTree offers a revised full phylogenetics of a global human variant of mtDNA centered on mutations in the coding regions and control regions (Van Oven and Kayser 2008).

The entire mitochondrial DNA phylogenetic tree is accessible at http://www.phylotree.org, which contains both recently documented populations and newly found haplogroups. EMPOP offers spatial haplogroup variations to imagine and appreciate the regional distribution of the graphs. Mitomap (Ruiz-Pesini et al. 2007) is another significant mtDNA human database.

This database was created in 1996 as an electronic database (http://www.mitomap.org) comprising reported differences of human mtDNA, along with different variants of geography and disease. Today, Mitomap is manually designed with the aid of superior quality human mitochondrial DNA used for medical professionals, researchers, and molecular biologists (Ruiz-Pesini et al. 2007) and modified to technically rich tools. Mitomap has three primary use groups. This provides certain relevant details on human mtDNA, including the overall distribution of mitochondrial DNA haplogroups and their frequency.

In addition, consumers can include details on certain repositories, applications, and helpful services unique to mtDNA. Mitomap shops all healthy people and doctors to annotate mtDNA variations. The mutation frequency is determined from the GenBank's human mitogenomes. Thus, users can access the details and save the most significant information on loci, the nucleotide shift, codon location, and number in various file sizes. Mitomap includes the computational method Mitomaster, which actually offers the computer programming interface.

The key purpose of this method is to classify polymorphic locations, to quantify variant statistics and to assign complete or partial mitogenomes to haplogroups. Such a question may be achieved by repeating to mtDNA, GenBank, or single nucleotides (Brandon et al. 2009). Such a question will not be feasible. Throughout the application of mtDNA databases, ethical and legal concerns can emerge from another viewpoint. Study of mtDNA may produce knowledge regarding privacy concerns (Guillen et al. 2000; Wallace et al. 2014).

Main mitochondrial disorder is a mutation that can be transmitted in most men. Consequently, knowledge regarding the structure of the mitochondrial genome will classify a person's current or potential safety. The study of MtDNA can only be conducted in noncoding regions, where no illness or phenotypical details has been identified with it.

16.9   Conclusion

For the past 25 years, mitochondrial DNA typing is used internationally to address various human identity problems linked to organized crime, small offences, criminal attacks, major accidents, and incidents of disappearances. Advances in mtDNA typing are incredible, varying from analyzing tiny fragments within days to decoding many entire mtDNA genomes in a few hours. The mtDNA genome may include details on ancestors, including knowledge on health/disease, as a genetic marker of lineage. While there are many widely recognized explanations for researchers to collect knowledge on the possible history of a suspected perpetrator, others nevertheless consider it unethical to establish the genetic structure behind such diseases. Therefore, emerging technologies that enable the sequencing of mitochondrial DNA should be wisely utilized in the field of forensic identification and for the purposes expected. These remain issues with respect, in particular, to the topic of heteroplasmy and in recent times with the flexibility of biparental heirlooms, the allowability of mtDNA research in court. Clear explanation of biparental ancestry molecular pathways for mtDNA, the capacity to evaluate the conditions when this happens, and the potential to extremely reliably diagnose and classify the heteroplasmy are big challenges that need to be dealt with in order to render mtDNA a viable alternate resource in forensic identification of humans.

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