Mitochondrial DNA

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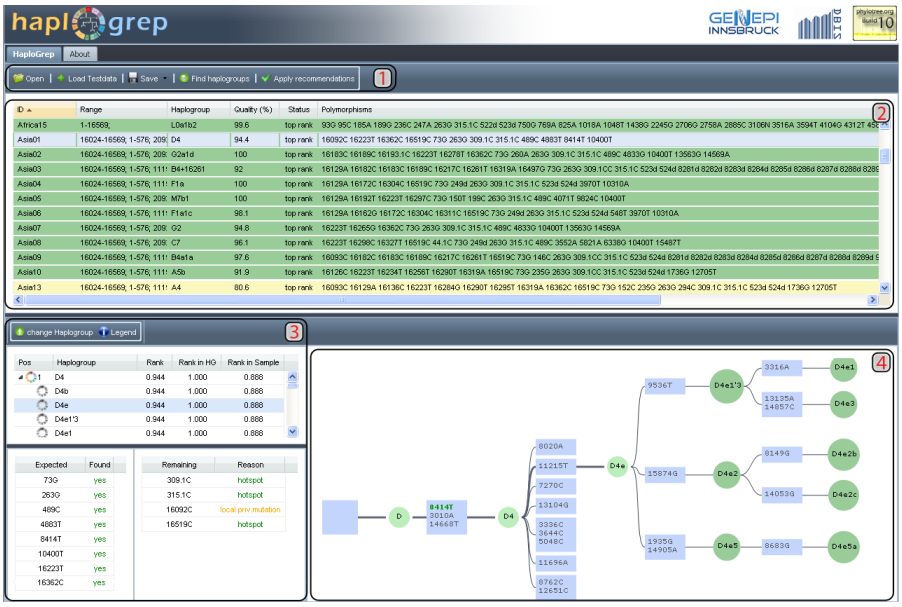
Background and previous findings

Human mitochondrial DNA (mtDNA) is routinely analyzed in various disciplines, such as medical genetics (searching for pathogenic mutations), population genetics (studying evolutionary patterns), and forensics (targeting degraded remains).

An ongoing source of controversy in mtDNA research is based on the detection of numerous errors in mtDNA profiles that led to erroneous conclusions and false disease associations. We developed **eCOMPAGT**, a database system which allows a successful data handling and quality assurance of mtDNA genotypes for medical genetics, population genetics and forensics.

The maternal inheritance of mtDNA results in a natural grouping of sequence haplotypes into monophyletic clusters, referred to as haplogroups. The members of a haplogroup carry a specific sequence motif as a consequence of sharing a common ancestor. For population genetic inferences, the identification of haplogroup affiliation of members of a population sample is crucial for inferring the demographic impact on human migrations. For clinical genetics, knowledge of the haplogroup can aid in finding disease-associated mutations.

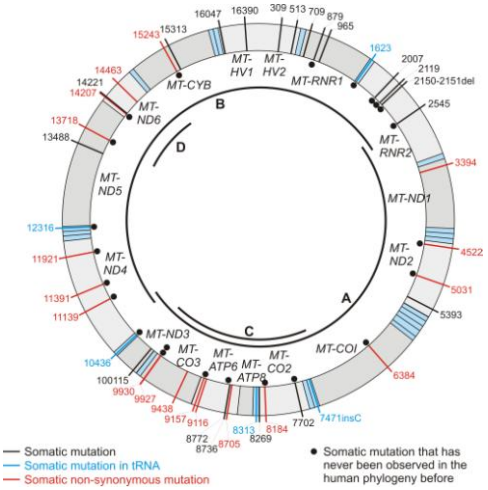
However, the determination of the haplogroup affiliation is time-consuming and error-prone. We therefore developed **HaploGrep**, a web-application designed to determine the most probable haplogroups of mtDNA haplotypes. With its sophisticated visualization tools, HaploGrep offers an all-in-one solution for quality assessment of mtDNA profiles in forensics, clinical and population genetics.



HaploGrep's Web interface: *(1) Toolbar of HaploGrep; (2) data and associated haplogroups are highlighted in different colors depending on the quality of the assignment; (3) 10 top hits for every sample are displayed with details on diagnostic and remaining polymorphisms. The remaining polymorphisms are further categorized into ''hotspot,'' ''local private mutation,'' ''global private mutation,'' and ''polymorphism out of range;'' (4) location of the sample within the human phylogenetic tree.*

Apart from their important role in phylogenetics, mitochondria have been implicated in the process of carcinogenesis because of their vital role in energy production and apoptosis. We aimed at studying the role of somatic mtDNA mutations in prostate cancer by applying a superior sequencing procedure. We sequenced the entire mitochondrial genome from 30 pairs of cancerous and benign cells from prostate cancer patients.

By examining both the frequency and types of somatic mtDNA mutations in prostate cancer patients we were able to identify several genetic changes having clinical significance. The most striking finding of our study was the association between somatic tRNA mutations and PSA levels at diagnosis. Patients with a somatic tRNA mutation had a significantly higher PSA value than did patients without a somatic tRNA mutation. These findings will potentially help others monitor malignant transformation, tumor progression, and metastasis.



Distribution of all observed somatic mutations over the mitochondrial genome. *Transfer RNAs are shaded in light blue. The location of the PCR fragments for the primary screen of entire mtDNA genomes (fragments A and B) and the secondary, targeted screen (fragments C and D) are indicated in the inner circle of the mtDNA.*

Ongoing work

- Somatic mtDNA mutations in oral carcinoma

Team members:

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Main collaborators:

Günther Specht, Helmut Klocker, Georg Schäfer, Frank Kloss

Selected Publications:

1. Kloss-Brandstätter A, Pacher D, Schönherr S, Weissensteiner H, Binna R, Specht G, Kronenberg F: HaploGrep: a fast and reliable algorithm for automatic classification of mitochondrial DNA haplogroups. ***Hum.Mutat.*** 32:25-32, 2011. [Pub-Med]
2. Kloss-Brandstätter A, Schäfer G, Erhart G, Hüttenhofer A, Coassin S, Seifarth C, Summerer M, Bektic J, Klocker H, Kronenberg F: Somatic mutations throughout the entire mitochondrial genome are associated with elevated PSA levels in prostate cancer patients. ***American Journal Human Genetics*** 87:802-812, 2010 [Pub-Med]
3. Weißensteiner H, Schönherr S, Specht G, Kronenberg F, Brandstätter A: eCOMPAGT integrates mtDNA: import, validation and export of mitochondrial DNA profiles for population genetics, tumour dynamics and genotype-phenotype association studies. ***BMC Bioinformatics*** 11:122, 2010. [Pub-Med]