HmtDB, the Human Mitochondrial Genomic Resource: developments in 2006

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Motivation

HmtDB is a Human Mitochondrial genomic resource based on variability studies supporting population genetics and biomedical research (Attimonelli et al.). Here a summary of the most recent improvements as regards both the database and the study of the variability resulting data is reported. In particular, data contained in HmtDB obtained by the application of site variability approaches were studied in order to: contribute in a more rigorous way to a quantitative estimation of the pathogenic proneness of the mutated sites; qualify the importance of the single point mutation in relation to multiple variations associated in one human mtDNA.

Methods

Genomes in HmtDB are analysed in order to estimate their site-specific variability. This is performed on the whole HmtDB dataset and on continent-specific subsets. It has been recently reported in a paper on Human mutation journal, submitted by the present research group and accepted for publication, that variability values can act as haplogroup markers. Further studies on variability data are in progress, in order to estimate the correlation between both nucleotidic and aminoacidic variability and the pathogenic proneness of a specific site. This analysis is also supported by the information available in MITOMAP and by studies of the influence of aminoacidic changes on the secondary and tertiary protein structure. In order to infer a relationship between the variability of a given position and the pathogenic potential of the corresponding mutation, HmtDB data resulting from the application of site variability approaches are compared both to MITOMAP data relative to polymorphic and pathological mutations, and to mtREV index. This last expresses the level of similarity between two aminoacids estimated on homologous multialigned mitochondrial proteins (Adachi and Hasegawa). Moreover, starting from site-specific variability data, changes in the 3D structure and physicochemical features of a modified protein can be investigated. The detection of the influence of single mutation on the whole protein 3D structure is investigated by using such software as Deep View Swiss-PDB Viewer and SWISS-MODEL available at EXPASY, NAMD and VMD, ANTHEPROT, and algorithms developed by the present research group, written in Delphi and C++ language running on the HP ProLiant ML150G2 with OS Linux RedHat and also on PC with WindowsXP.

Results

The current release of HmtDB contains 2155 human mitochondrial genomes of different geographical origin: 200 are from Africa, 660 Asians, 1031 Europeans, 85 from Oceania and 115 Native Americans. Moreover, 500 genomes from subjects affected by "mitochondrial disease" have been collected and will be stored in a separate section of HmtDB database. In 2005, the Query section of HmtDB database was developed by the present research group, and updating and browsing were improved. The Query section allows the extraction, from HmtDB database, of a set of genomes satisfying user-submitted query based on different criteria such as the subject's geographical origin, SNP position, age, sex etc.. As far as it concerns the pathogenic proneness of variated sites, preliminary results about variability, make it possible to postulate the presence of four different classes of variation type: pathological variant associated with disease, with low or average variability value and low mtREV index; rare polymorphic variant, with low variability value and high mtREV index; frequent polymorphic variant, with high variability value and high mtREV index; potential pathological variant, with low variability value and low mtREV index. As far as it concerns 3Dstructure, the calculations and simulations of the changes in the 3D structure of a modified protein suggest that a single aminoacidic substitution can lead to bigger structure alteration than it appears. Moreover, associations of single variations result in almost twice as big

structure changes than the ordinary sum of single punctual mutations. Furthermore, some relatively frequent and seemingly innocuous aminoacidic variations can destabilise the structure of the main part of the protein.

Availability: http://www.hmdb.uniba.it/

References

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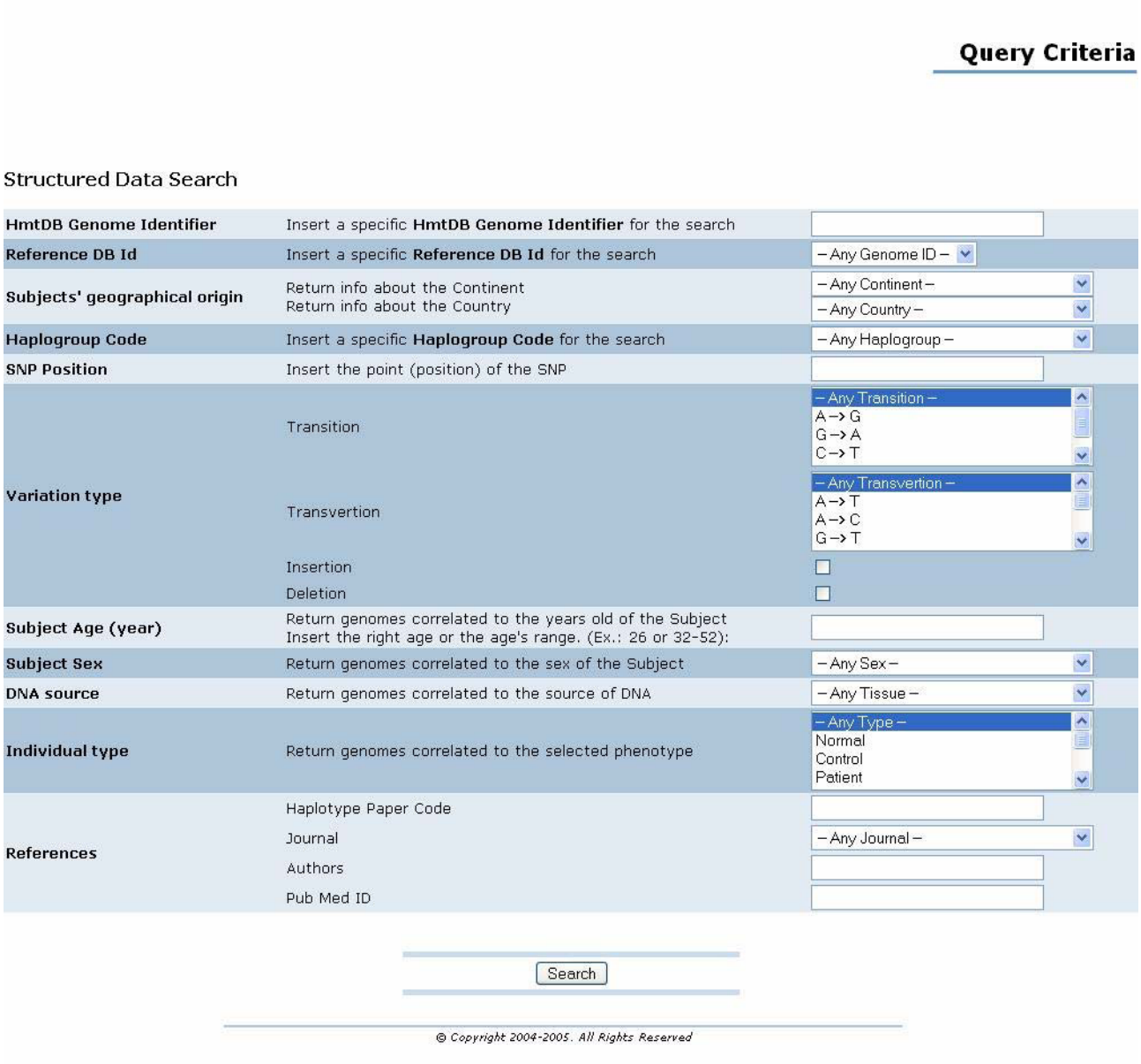

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