MitoDrome2: a database of OXPHOS nuclear genes in Drosophila melanogaster, Drosophila pseudoobscura and Anopheles gambiae

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Motivation

Mitochondrial disorders are clinical phenotypes associated with abnormalities of oxidative phosphorylation (OXPHOS), the primary energy-producing process of all aerobic organisms. Disorders of OXPHOS are recognized as the most common inborn errors of metabolism affecting at least one in 5000 newborn children. Except for complex II, which is composed of proteins all encoded by nuclear genes, the other OXPHOS complexes are built up of both mitochondrial and nuclear DNA encoded proteins; so, assembling the OXPHOS complexes and fine tuning their activity require specialized regulatory mechanisms to optimize the cross-talk between the two genomes and ensure the coordinated expression of their relevant products. In this context, the characterization of nuclear genes encoding for mitochondrial proteins and of functional elements regulating their expression is of crucial importance to clarify real genetic causes of mitochondrial diseases, to assess the correct diagnosis and set up new and effective therapies. Despite the long evolutionary divergent time, many key pathways that control development and cellular physiology are conserved between Drosophila and humans, and about 70% of the genes associated with human diseases have direct counterpart in the Drosophila genome. To investigate on the functional constraints acting on the evolution and on the regulatory mechanism coordinating the expression of OXPHOS genes we have identified and characterized sequence and structure of these genes in three species of diptera, D. melanogaster, D. pseudoobscura and A. gambiae, and compared them with their human counterparts. Data obtained from this study have been annotated in the MitoDrome2 database. The availability of data produced by our study in MitoDrome2 is expected to be particularly useful for biologists and clinicians interested in studies of functional genomics related to mitochondrial biogenesis, metabolism and to their pathological dysfunctions.

Methods

D. melanogaster OXPHOS genes have been identified through the comparison of Human mitochondrial proteins available in SWISSPROT vs. the Drosophila genome, ESTs and cDNA sequence data available in the FlyBase database. To identify the putative counterparts of D. melanogaster OXPHOS genes in D. pseudoobscura and A. gambiae, we performed a TBLASTN search on the whole genome sequence of these two organisms using the amino-acid sequences of D. melanogaster as queries. Sequencing giving the best reciprocal BLAST hits were tentatively assumed to identify functional counterpart if they could be aligned over at least 60% of the gene length and the BLAST E-score was less than 10-30. The annotation of genes has been carried out by taking into account conservation in amino acid sequence, intron/exon structure, intron length, and presence of duplications in the genome. Data on genes, transcripts and proteins have been integrated with the data of the comparative analysis in a MySQL relational database.

The database also contains a list of mutant insertion alleles of D. melanogaster genes which has mostly been compiled using information available from FlyBase and from the BDGP P-Element Gene Disruption Project. A Web interface to query and retrieve the database content and to export sequences has been developed in PHP and BioPerl running on an Apache HTTP Server.

Results

We present MitoDrome2, a database which collects data derived from comparative analysis and manual annotation of OXPHOS nuclear genes and encoded products in D. melanogaster, D. pseudoobscura and A. gambiae. In order to make MitoDrome2 a useful tool supporting studies aimed to functional characterization of OXPHOS related bio-sequences we have developed a user-friendly Web interface providing a wide range of query/retrieval and sequence-export facilities. MitoDrome2 can be queried and retrieved through two different search modes: 1) from the home page, by organism, functional features, P-Insertion mutant of D. melanogaster, Cluster of orthologous/paralogous genes and 2) from the MitoDrome2 search page, combining different search criteria such as entry and gene name, subcellular localization, protein function and chromosome location. Users can extract sequences and sub-sequences (protein, transcript, gene, flanking gene regions, CDS, signal pepetide, UTRs, intron, exon) in different file formats (FASTA, GenBank, EMBL) thanks to an export management system integrated in the search data tool. Up to date MitoDrome2 contains, for each of the three Diptera, 78 OXPHOS nuclear genes and a total of 47 duplicates.

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