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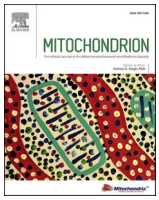

mitoPADdb: A database of mitochondrial proteins associated with diseases

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ABSTRACT

Mitochondrial protein/gene mutations and expression variations contribute to the pathogenesis of various diseases, such as neurodegenerative and metabolic diseases. Detailed studies on mitochondrial protein-encoding (MPE) genes across diseases can provide clues for novel therapeutic strategies. Here, we collected, compiled, and manually curated the MPE gene mutation and expression variations data and their association with diseases in a single platform named mitoPADdb. The database contains 810 genes with 18,356 mutations and 1284 qualitative expression variations associated with 1793 diseases, grouped into 15 categories. It allows users to perform a comparative quantitative gene expression analysis for 317 transcriptomic studies across disease categories. Further, it provides information on MPE genes-associated molecular pathways. The mitoPADdb is a valuable resource for investigating mitochondrial dysfunction-related diseases. It can be accessed via http://bicresources.jcbose.ac.in/ssaha4/mitopaddb/index.html.

1. Introduction

The mutation and expression variation of MPE genes were found to have a correlation with several diseases pathogenesis (Gorman et al., 2016; Javadov et al., 2020; Scharfe et al., 2009; Télot et al., 2018; Wang et al., 2022). For instance, the mutation and downregulated expression of FXN gene were linked to Friedreich ataxia (Clark et al., 2019; Deutsch et al., 2010), while upregulated expression of PRDX3 gene was associated with dilated cardiomyopathy (Roselló-Lletí et al., 2014). There are several mitochondrial databases available containing human diseases information; these are MITOP (Scharfe et al., 2000), MITOMAP (Brandon, 2004), Mito Phenome (Scharfe et al., 2009), MitoDB (Scheibye-Knudsen et al., 2013), MSeqDR (Falk et al., 2015), and MitoPhen (Ratnaike et al., 2021). However, the diseases-associated expression variation and comprehensive mutation data on MPE genes are lacking in these available databases. The MPE genes are worth investigating in data sciences for identifying novel therapeutic strategies. Keeping this in mind, we collected, compiled and curated the MPE genes' mutations, expression variations, and associated diseases on a single platform, named mitoPADdb. It includes data from the last three decades of progress in clinical mitochondrial research to comprehend the role of mitochondrial and nuclear-encoded MPE genes in terms of mutation and expression variation associated with diseases. It can help researchers investigate mitochondrial dysfunction-related diseases.

2. Methods

2.1. Data procurement of mitoPADdb

We have collated and curated a comprehensive pathogenic mutation dataset of MPE genes from the literature and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). We have also collected the qualitative expression variations data of MPE genes, with at least 1.5-fold upregulated or downregulated in the disease state compared to the control in the same experiment and p-value < 0.05 as shown in the literature. The 810 MPE genes with diseases associated information were manually sourced from 1032 published scientific case studies and clinical research articles (Supplementary Figure S5) from NCBI-PubMed, and NCBI-ClinVar datasets, ensuring a well-rounded dataset (Supplementary Figure S6). The curated diseases were grouped into 15 standard disease categories. This information is current as of July 2023. Supplementary Methods S1 and S2 describe the MPE gene selection and disease grouping strategy. Supplementary Table S4 provides 810 MPE genes' localization annotation to mitochondria or mitochondria-associated function (Mitochondrial protein annotation type) and the evidence from the UniProtKB/Swiss-Prot annotation, GO CC/GO BP annotation,

Abbreviations: MPE gene, mitochondrial protein-encoding gene; OXPHOS, oxidative phosphorylation.

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PubMed literature, and the MitoCarta3.0 annotation. This database will be updated with new evidence of mitochondrial protein localization, mutation, and expression variation-associated disease at one or two-year intervals.

2.2. Meta-analysis of transcriptomic data for differential gene expression study across diseases

We performed multiple searches in GEO (https://www.ncbi.nlm.nih.gov/geo/) with relevant selected keywords of curated human diseases (e.g., Friedreich ataxia, Leigh syndrome) from disease categories (list of keywords in Supplementary Table S3). A *meta*-analysis was conducted on the data from 317 transcriptomic GEO studies across 14 categories of diseases (excluding 'Others'), which comprised of 165 unique GEO accessions. Studies were manually selected based on the presence of both disease and control data, with similar samples, techniques and conditions/states as diseases, and excluding drug-treated groups (Supplementary Methods S3).

2.3. Pathway enrichment analysis

The mitoPADdb provides enriched pathways obtained from two popular databases, Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa et al., 2017) and MitoCarta3.0 (Rath et al., 2021). The pathway enrichment analysis utilizing 810 MPE genes set in the Enrichr tool (Kuleshov, 2016) was used to select the KEGG pathways. From this analysis, we identified 89 enriched pathways with a p-value < 0.05, included in this database. For the selection of MitoCarta3.0 pathways, we performed gene-pathway mapping using 810 genes set to all 149 mito-pathways on MitoCarta3.0. Subsequently, we identified 131 mito-pathways and included those in mitoPADdb.

2.4. Database content

The mitoPADdb has five data types, these are i) the basic information of MPE genes and diseases, ii) curated pathogenic mutation, iii) curated disease associated expression variation, iv) enriched pathway, and v) GEO studies. The basic/common information includes gene symbol, UniProt accession ID, Gene Ontology Cellular Component (GO CC), Molecular Function (GO MF) and Biological Process (GO BP), disease name, disease category, external disease accession IDs (e.g., MeSH ID, MedGen ID), MeSH tree number, and protein-disease associations. The curated pathogenic mutation includes nucleotide change, amino acid change, dbSNP ID, and source ID (PubMed or ClinVar). The curated disease associated expression variation includes expression variation (upregulation or downregulation), expression molecule, sample, method, remarks, and PubMed ID. The enriched pathway includes pathway type (KEGG or MitoCarta3.0), pathway name, pathway ID, adjusted p-value, pathway gene association, and gene disease association. The GEO studies includes comparative heatmap and studies information such as study ID, disease category, disease name, sample, $\log_2$ fold change subjects with sample size, condition/state, and GEO accession.

2.5. Data statistics of mitoPADdb

The mitoPADdb contains information on 810 MPE genes with a total of 18,356 mutations and 1284 expression variations entries that are linked to 1793 disease terms which are grouped into 15 broad categories. It also provides users with a comparative gene expression heatmap for 317 GEO studies across diseases. Detailed statistics of mitoPADdb is shown in Table 1.

2.6. Data architecture of mitoPADdb

The mitoPADdb was implemented using MySQL (version 5.1.69) and was deployed using the Apache HTTP web server (version 2.2.15). The web interface was designed with PHP 5.3.3, HTML, JavaScript, and CSS. In mitoPADdb, the curated 810 MPE genes were hyperlinked with their respective UniProt accession IDs (The UniProt Consortium et al., 2021). The disease terms-associated MPE genes' high-throughput and low-throughput expression and mutations curated source IDs were hyperlinked with their respective PubMed, ClinVar, and GEO. In addition, the pathways were hyperlinked to KEGG (Kanehisa et al., 2017). Fig. 1 depicts the mitoPADdb implementation strategy.

Table 1
Statistics table of the mitoPADdb.

Disease category (No. of diseases)*	Gene (Mutation) entries	Gene (Expression variation) entries**	GEO studies entries***
1. Cardiovascular Diseases (45)	**35 (139)**	**197 (296)**	**11**
2. Congenital, Hereditary, and Neonatal Diseases and Abnormalities (89)	**149 (1480)**	**13 (20)**	**11**
3. Digestive System Diseases (39)	**24 (445)**	**7 (12)**	**34**
4. Eye Diseases (48)	**34 (255)**	**0 (0)**	**31**
5. Hemic and Lymphatic Diseases (32)	**21 (216)**	**47 (50)**	**19**
6. Mental Disorders (21)	**52 (68)**	**5 (5)**	**18**
7. Musculoskeletal Diseases (147)	**107 (854)**	**39 (73)**	**19**
8. Neoplasms (150)	**47 (5060)**	**18 (26)**	**32**
9. Nervous System Diseases (438)	**255 (4198)**	**218 (414)**	**36**
10. Nutritional and Metabolic Diseases (246)	**183 (1402)**	**102 (208)**	**35**
11. Otorhinolaryngologic Diseases (22)	**19 (58)**	**11 (15)**	**7**
12. Pathological Conditions, Signs and Symptoms (18)	**19 (90)**	**6 (6)**	**17**
13. Respiratory Tract Diseases (7)	**5 (10)**	**13 (13)**	**12**
14. Urogenital Diseases (52)	**40 (523)**	**13 (16)**	**35**
15. Others (439)	**290 (3558)**	**84 (130)**	**0**

* The number of diseases found in the database for each broad category.
** Qualitative gene expression (upregulated or downregulated) studies entries as reported in the literature.
*** Comparative quantitative expression analysis of 810 MPE genes across mentioned GEO studies entries.

3. Implementation

The mitoPADdb is open-access, user-friendly with search and browse options, and does not require login password for database access.

3.1. Search options

The Search options are accessible from the home page. Users can search the database in three ways using proper keywords, gene symbol (e.g. FXN, NDUFB11), UniProt accession ID (e.g. P00846, P00395), or any (UniProt accession ID or gene symbol) as shown in Supplementary Figure S1.

3.2. Information on the search output page

The mitoPADdb comprises two output pages: the protein page and the disease page.

3.2.1. Protein page

The protein page is composed of five sections, namely protein information, protein-disease associations, protein-pathway associations, disease-associated mutations, and disease-associated expression

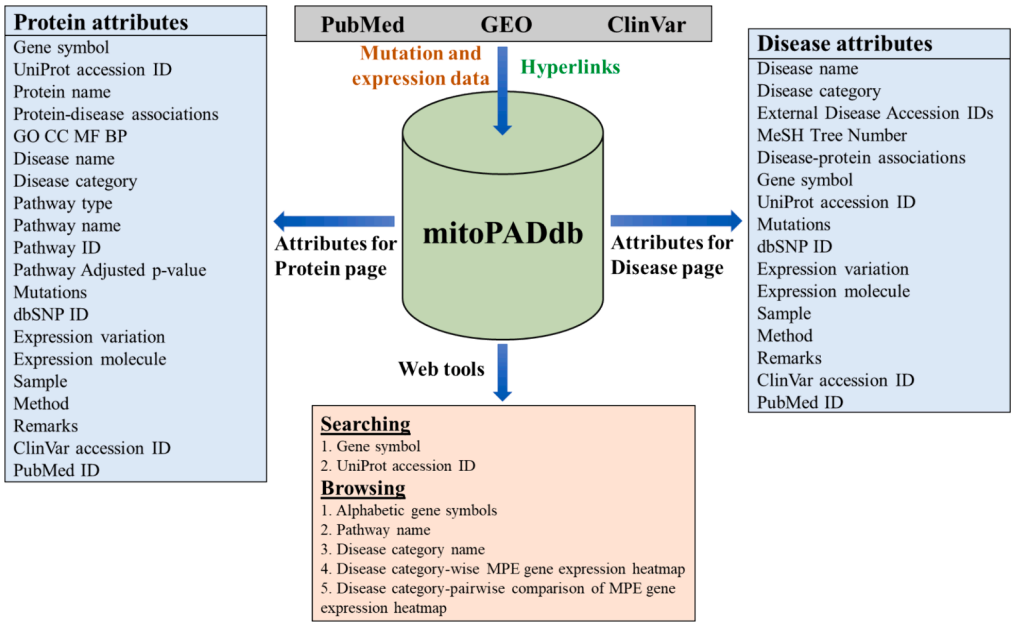

Fig. 1. A schematic workflow and data architecture of mitoPADdb.

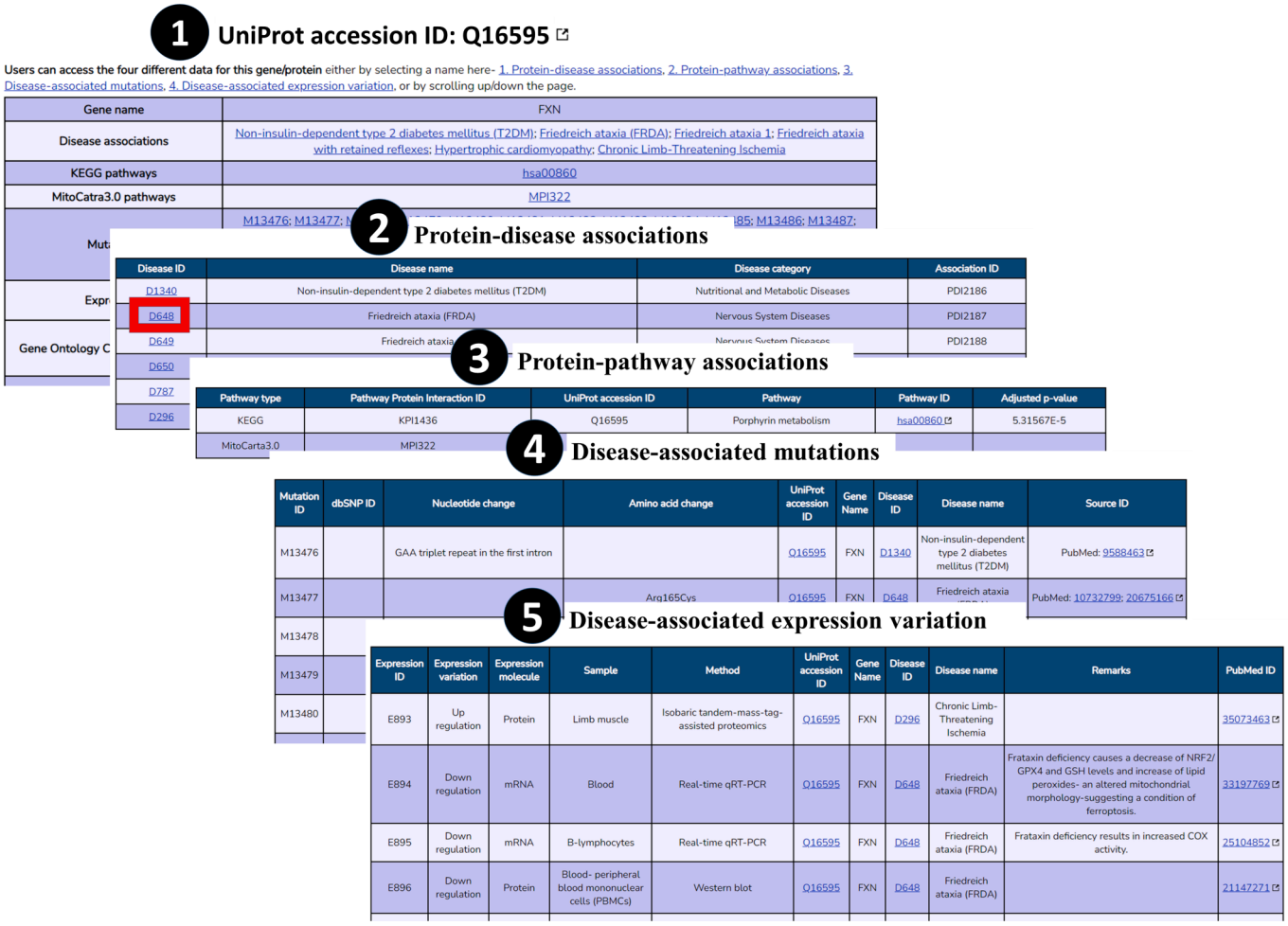

Fig. 2. Snapshot of the output protein page after search with FXN gene symbol. The protein page is composed of five sections: 1) protein information, 2) Protein-disease associations, 3) Protein-pathway associations, 4) Disease-associated mutations, and 5) Disease-associated expression variation.

variation as shown in Fig. 2 after search with FXN gene (see Supplementary Figure S1). 1) The protein information section contains UniProt accession ID, gene name, Gene Ontology (GO) annotations and an overview of the protein's association with diseases, pathways, mutations, and expressions. 2) The protein-disease associations section contains MPE-gene associated disease names, disease IDs, disease categories, and association IDs. 3) The protein-pathway associations section contains pathway types (KEGG or MitoCarta3.0), pathway names, pathway IDs, adjusted *p*-values. 4) The disease-associated mutations section contains mutation IDs, dbSNP IDs, nucleotide changes, amino acid changes, and source IDs (PubMed, ClinVar). 5) The disease-associated expression variation section contains expression IDs, expression variations (upregulation or downregulation), expression molecules (e.g., protein, mRNA), samples, methods, remarks, and PubMed IDs.

3.2.2. *Disease page*

The disease page can be accessed from the protein page by selecting the disease ID as shown D648 marking red box for Friedreich ataxia (FRDA) in protein page (see Fig. 2) at protein-disease associations section. This page encompasses four sections (Supplementary Figure S2), namely disease information, disease-protein associations, disease-associated mutations, and disease-associated expression variation. 1) The disease information section provides disease name, disease ID, disease category, external disease accession IDs, MeSH tree number, and an overview of the disease's association with proteins, mutation, and expression. 2) The disease-protein associations section provides disease associated gene symbols, UniProt accession IDs, and association IDs. 3) The disease-associated mutations and 4) disease-associated expression variation sections provide the information as described earlier in protein page, but specific for a disease.

3.3. *Browse options*

The browse option of mitoPADdb offers five distinct ways to access the data (see Supplementary Figure S3 and S4). These include browse by gene symbol, pathway name, disease category name, disease category-wise MPE gene expression heatmap, and disease category-pairwise comparison of MPE gene expression heatmap. Upon selection, each of these sections provides users with access to specific data sets, which are outlined on the database browse page.

When utilizing the gene symbol option, users can get protein/gene information curated in this database (see 1. gene symbol section in Supplementary Figure S4). Alternatively, the pathway name option allows users to explore connections among pathways, genes, and diseases as shown KEGG pathway marking with red box in Fig. 3A. Upon selection of KEGG pathway, it will provide a list of pathways. Users need to double-click on a pathway (e.g., ABC transporters, marking with black-box) to get a list of genes associated with that pathway followed by double-click on a gene (e.g., ABCB6, marking with blue-box) to get a list of diseases associated with that gene as shown in Fig. 3B. In the case of disease category name, users can browse disease and disease category information curated in mitoPADdb (see 3. disease category name section in Supplementary Figure S4). Upon utilizing Disease category-wise MPE gene expression heatmap options, users can obtain a list of all GEO studies of a disease category (e.g., Eye diseases). The list contains study IDs, disease category, disease names, samples, $\log_2$ fold change subjects with sample size, conditions/states, and GEO accession IDs as shown Eye diseases category marking with red box in Fig. 4A. Users can visualize the heatmap of differential transcript expression of MPE genes associated with that disease category by selecting 'Get expression heatmap' in top or bottom of the list. The heatmap will open in a new page, users need to select an alphabet (A-Z) provided below to visualize the heatmap of selected genes starting with a particular alphabet as shown 'A' marking with black-box in Fig. 4B. Finally, using Disease category-pairwise comparison of MPE gene expression heatmap option, users can visualize the heatmap of differential transcript expression of all MPE genes (810) available in mitoPADdb across all (317) GEO studies by selecting two disease categories (e.g., I. Cardiovascular diseases category and II. Congenital, hereditary, and neonatal diseases and abnormalities category) at a time followed by selecting 'Get heatmap' at right side. The heatmap will open in a new page for genes starting with 'A' by default, users need to select other alphabets (A-Z) to obtain the heatmap of their choice of genes as shown 'B' marking with grey-box in Supplementary Figure S4 at disease category-pairwise comparison of MPE gene expression heatmap section. A legible tutorial was given on database pages on how to access the data step by step.

In the browsing section, users can download the result file of heatmap images in JPG format, as well as the $\log_2$ fold change value of heatmaps in CSV format by clicking on 'Download Result'.

4. Comparison with the existing related databases

There are a few mitochondrial databases available with human diseases information. These are MITOP, MITOMAP, Mito Phenome, MitoDB, MSeqDR, and MitoPhen. However, the mitoPADdb is distinct due to its focus on diseases associated MPE genes storage. The database contains a vast collection of MPE genes that were thoroughly curated

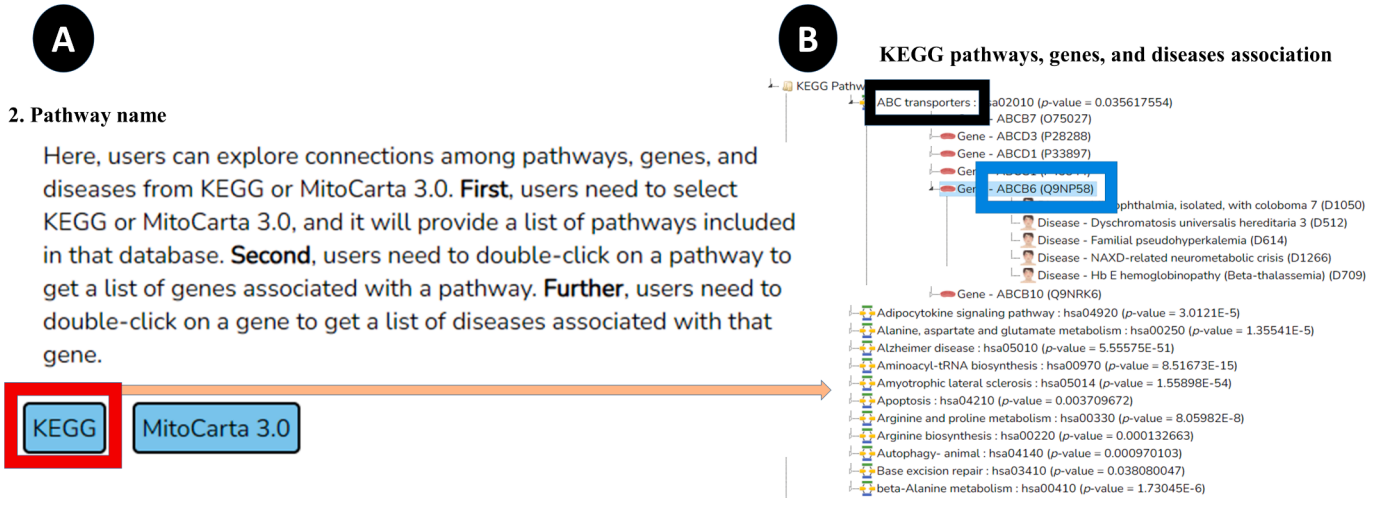

Fig. 3. Snapshot of the output page after browse by pathway name. A) The pathway name section of the browse page. B) KEGG pathways (e.g., ABC transporters), genes (e.g., ABCB6), and diseases association.

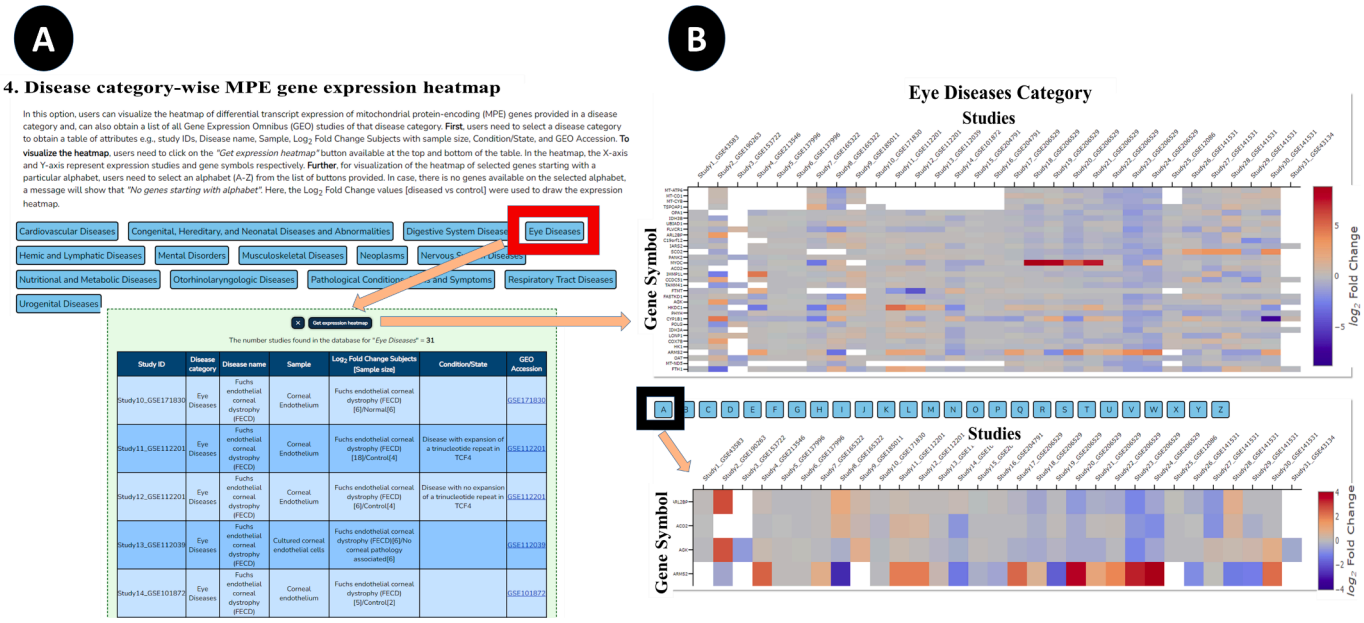

Fig. 4. Snapshot of the output page after browse by disease category-wise MPE gene expression heatmap. A) Disease category-wise MPE gene expression heatmap section of the browse page with metadata table of GEO studies of Eye diseases category (Red box). B) Heatmap of quantitative transcript expression of MPE genes across all GEO studies in Eye diseases category (above) and visualize the heatmap of selected genes starting with 'A' (below), marked with black box.

Table 2
Comparison of mitoPADdb with six existing mitochondrion and disease-related databases.

Attributes	**mitoPADdb**	MITOP	MITOMAP	Mito Phenome	MitoDB	MSeqDR	MitoPhen
MPE genome: nuclear or mitochondrial encoded	Both	Both	Mitochondrial only	Nuclear only	×	Both	Mitochondrial only
Disease-associated MPE genes	810	85	13	174	×	279	13
Variants type of MPE genes: non-pathogenic and pathogenic	Pathogenic	×	Both	×	×	Both	Pathogenic
Pathogenic mutation entries of MPE genes	18,356	×	1018	×	×	✓	40
Disease-associated qualitative expression variation data[#]	✓	×	×	×	×	×	×
Disease-associated comparative quantitative gene transcript expression analysis of MPE genes[#]	✓	×	×	×	×	×	×
Diseases/HPO terms	1793	110	✓	191	257	284	26,348 HPO
Diseases classification into categories	✓	×	×	✓	×	×	×
Organism	Human	Human, Mouse, Yeast, *C. elegans*, *N. crassa*	Human	Human	Human	Human	Human
Pathway	✓	✓	×	✓	×	×	×
Publication	Present study	(Scharfe et al., 2000)	(Brandon, 2004)	(Scharfe et al., 2009)	(Scheibye-Knudsen et al., 2013)	(Falk et al., 2015)	(Ratnaike et al., 2021)
Database URL status	Active	Inactive	Active	Inactive	Active	Active	Active

[#]Indicates the unique attributes of mitoPADdb.

and found to be associated with various diseases. The content of these six databases was studied and compared with the mitoPADdb, as shown in Table 2. The unique attributes that are present in mitoPADdb in comparison with these available databases include disease-associated qualitative expression variation data and disease-associated comparative quantitative gene transcript expression analysis of MPE genes, marked as [#] in Table 2. In addition, 325 MPE genes, having manually curated mutation in mitoPADdb, were compared with DisGeNET curated gene sets (Piñero et al., 2020). We identified 44 unique disease-associated MPE genes (with 622 mutation hits) based on manual curation from literature, which are not found in the DisGeNET database (see Supplementary Table S5). Overall, it shows that the mitoPADdb is enriched with more attributes and mutational entries than other existing mitochondrial resources associated with diseases.

5. Utility of mitoPADdb

The mitoPADdb contains large number of curated MPE genes that are associated with diseases. This database can be tremendously useful for researchers/academicians exploring mitochondrial role in health and disease biology. The prime utility of mutation, expression data, pathway and comparative gene transcripts analysis studies from mitoPADdb includes investigating mitochondrial dysfunction-related diseases and probable affected pathways and developing mitochondrial protein

targeted therapy for such diseases. Researcher can look for their gene of interest on mitoPADdb and identify the similar trends of mutations, qualitative expressions, and quantitative transcript expression in heatmap across disease and disease categories. For example, comparison of mutations table from the output page of this database, the six different disease terms are associated with six different mutations of the NDUFB11 gene. Among them, the c.262C > T (p.Arg88Ter) [dbSNP ID: 786205225] mutation is common in four different diseases terms (marked with four red boxes in Supplementary Figure S7A). While, comparing the qualitative expression table on the output page, the NDUFB11 gene shows all down-regulated expression in all four different diseases (marked with red box in Supplementary Figure S7B). One can compare the quantitative transcript expression patterns across various diseases by selecting a gene, such as FXN, from the "Disease category-pairwise comparison of MPE gene expression heatmap" available in the database browse section of mitoPADdb (Supplementary Table S1). It was observed that the FXN expression is downregulated in Chronic irritable bowel syndrome (2 studies), Sensorineural hearing loss (3 studies), and Friedreich's ataxia (2 studies). On the other hand, it is upregulated in Early-onset colorectal cancer (3 studies). When we compared the expression patterns category-wise (Supplementary Table S2), we found that the FXN expression is down-regulated in Otorhinolaryngologic (3 studies) and Respiratory tract (2 studies) diseases categories, while it is up-regulated in Digestive system (3 studies), Urogenital (2 studies), and most of the studies in Neoplasms (7 studies, except one) disease categories. Here, the expression variation $\log_2$ fold change cut-off value ≥ 0.75 (a minimum 1.68 fold upregulation) or ≤ -0.75 (a minimum 1.68 fold downregulation) as compared to the control was taken to arrive at these conclusions.

6. Conclusion

The mitoPADdb provides comprehensive information on mutations and expression variations of MPE genes associated with diseases. As mitochondrial research in health and disease biology gradually increases, the mitoPAD database can be a useful tool for researchers and clinicians investigating mitochondrial dysfunction-related diseases. This database will also help to find out potential molecules for developing novel mitochondria-targeted therapy to mitigate diseases.

CRediT authorship contribution statement

Jagannath Das: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **Sudipto Bhattacharjee:** Methodology, Software, Visualization. **Sudipto Saha:** Conceptualization, Investigation, Project administration, Supervision, Writing – review & editing.

Data availability.

Prior registration or password is not required, and mitoPADdb is easily accessible at http://bicresources.jcbose.ac.in/ssaha4/mitopaddb/index.html.

GitHub link: https://github.com/PulmonomicsLab/mitoPADdb.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mito.2024.101927.

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