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NeuroMuscleDB: a Database of Genes Associated with Muscle Development, Neuromuscular Diseases, Ageing, and Neurodegeneration

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Abstract

Skeletal muscle is a highly complex, heterogeneous tissue that serves a multitude of biological functions in living organisms. With the advent of methods, such as microarrays, transcriptome analysis, and proteomics, studies have been performed at the genome level to gain insight of changes in the expression profiles of genes during different stages of muscle development and of associated diseases. In the present study, a database was conceived for the straightforward retrieval of information on genes involved in skeletal muscle formation, neuromuscular diseases (NMDs), ageing, and neurodegenerative disorders (NDs). The resulting database named NeuroMuscleDB (http://yu-mbl-muscledb.com/NeuroMuscleDB) is the result of a wide literature survey, database searches, and data curation. NeuroMuscleDB contains information of genes in *Homo sapiens*, *Mus musculus*, and *Bos Taurus*, and their promoter sequences and specified roles at different stages of muscle development and in associated myopathies. The database contains information on ~ 1102 genes, 6030 mRNAs, and 5687 proteins, and embedded analytical tools that can be used to perform tasks related to gene sequence usage. The authors believe NeuroMuscleDB provides a platform for obtaining desired information on genes related to myogenesis and their associations with various diseases (NMDs, ageing, and NDs). NeuroMuscleDB is freely available on the web at http://yu-mbl-muscledb.com/NeuroMuscleDB and supports all major browsers.

Keywords Database · Genes · Myogenesis · Skeletal muscle · Ageing · Neuromuscular dystrophies · Neurodegenerative disorders

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Introduction

Muscles are the most highly organized structures required for survival [1], and arise as multinucleate syncytium resulting from the fusion of mononuclear myoblasts [2]. Myogenesis is a multistage developmental process characterized by distinct cellular events (Fig. 1). It begins with the commitment of myoblasts to the myogenic lineage, and their subsequent proliferation and differentiation into post-mitotic myocytes, and finally, the fusion of these myocytes to form multinucleated myotubes [3–5]. As myotubes mature, syncytial cell functions become specialized and cytoplasm is largely occupied by contractile apparatus and growth of myotubes/myofibers occurs in response to appropriate stimuli.

Muscle loss is a serious issue, and man is consistently reported to be a major contributor to high mortality in old age [6–10]. Decreasing muscle mass trends are also observed in neuromuscular diseases (NMDs) and in association with neurodegeneration [11]. Neuromuscular dystrophies (NMDs) encompass

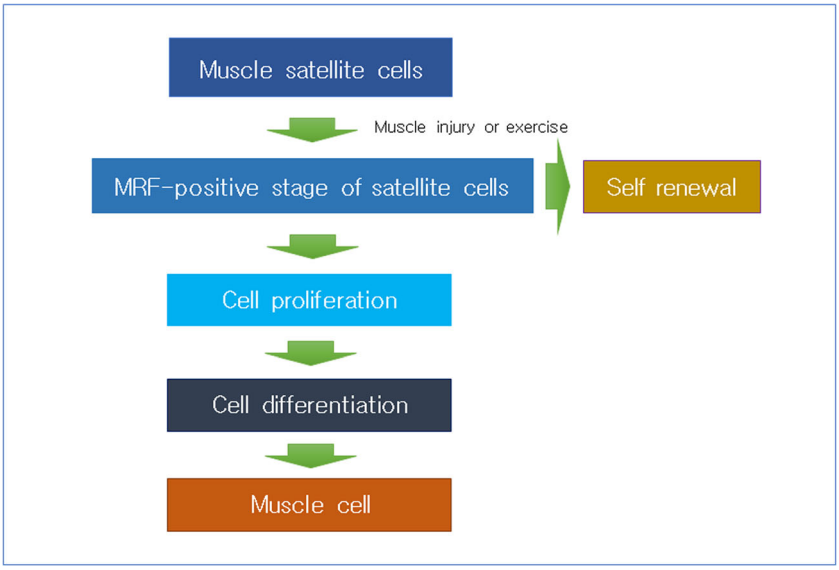

Fig. 1 Stages of muscle development

several medical conditions that impair muscle functioning and eventually lead to deformity and disability [12]. The adverse health outcomes attributed to muscle loss have led to increases in the number of investigations dedicated toward developing strategies to combat muscle loss in elderly humans and other animals.

Disease-associated complications related to reductions in muscle mass have raised serious concerns worldwide. Given advancements in technology and the interest shown by scientists, a large number of studies have been performed to elucidate the mechanisms responsible for the regulation of muscle development with a view toward combating disease-related muscle loss [13–15]. Techniques, such as microarray, transcriptome, and proteomic analysis, have generated much information [16–20], but limitations regarding the extracting relevant information demand an appropriate retrieval system. As the amount of sequencing data continues to accumulate, we considered a tailor-made retrieval system was required to better manage data and enable easy data retrieval. Biological databases offer an excellent solution to this type of problem by providing a systematic way of arranging and accessing biological data [21].

Many web resources and databases provide detailed description of genes in man and other organisms. NCBI (https://www.ncbi.nlm.nih.gov/gene) compiles information, such as gene ID, description, location, and alternative names in different categories, such as alternatively spliced, annotated, non-coding, and protein-coding genes and pseudogenes. GeneCards [22] is another popular human gene database that provides gene annotations and detailed and predicted information on human genes. DisGeNET [23] is one of the largest databases of genes and gene variants associated with human diseases. DisGeNET integrates data from curated databases/repositories, animal models, GWAS catalogues, and the published literature. The GeneTable of Neuromuscular Disorders [24] is an online resource of gene information on different types of neuromuscular diseases, which are classified into 16 categories of myopathies. Other web resources/databases like the Leiden Muscular Dystrophy pages (http://www.dmd.nl/) contain information on muscle-specific genes and their mutations, and the Online Mendelian Inheritance in Man (OMIM) database [25] provides information on human genes and genetic disorders.

Our rationale was to integrate available results and to enlist the reported roles of all muscle-associated genes found to have direct or indirect involvement in ageing and age-associated neurodegenerative diseases as a part of NeuroMuscleDB. A schematic representation of NeuroMuscleDB is shown in Fig. 2. NeuroMuscleDB will be updated manually by incorporating new data and resources, whenever available. The database will also be updated systematically to link myogenesis with other age-related diseases. In addition, we believe NeuroMuscleDB provides opportunities to translate the findings of different studies into clinical interventions.

Material and Methods

Data Collection and Curation

To develop an interactive database, an extensive search of muscle-related genes in *Homo sapiens*, *Mus musculus*, and *Bos taurus* was performed. Accurate and precise information on genes related to muscle development, their involvement at various functional stages, and their roles in different neuromuscular and neurodegenerative diseases were extracted from available literature and databases. The Perl scripts "NCBIGeneDB_Mapper.pl" and "GeneSeqParse.pl" used for compilation, integration, sequences extraction, and management of relevant information in the HRGFish database were adopted in this database as well [26]. The Gene database

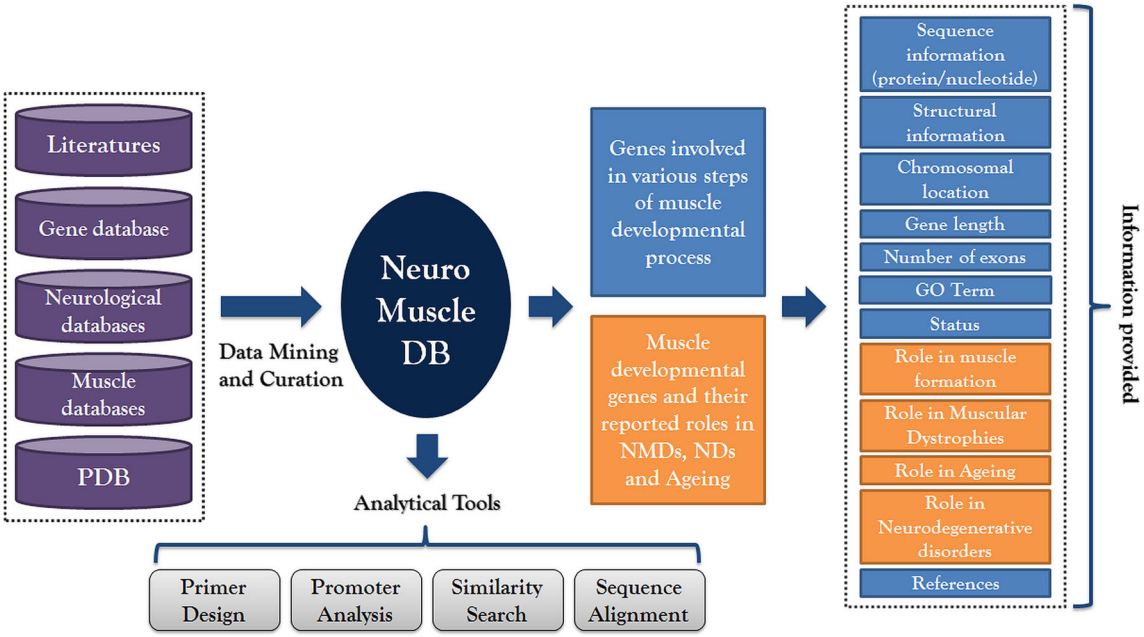

Fig. 2 A schematic representation of NeuroMuscleDB

[27] was used for parsing information of genes and their ontology terms, PubMed ID, mRNA and protein information and accession IDs of genes, mRNAs, proteins, and genomic sequences from the Gene database with the help of "NCBIGeneDB_Mapper.pl." Further, this program prepared numbers of data sheets according to designed schema of the database to populate the information in the respective tables. The program "NCBIGeneDB_Mapper.pl" also produced lists of the accession numbers for mRNA, protein, and gene-containing genomic sequences. In order to obtain sequences, the individual list of generated accession numbers was supplied in the Batch Entrez NCBI [28] and downloaded mRNA, protein, and genomic sequences in FASTA format. Later, Perl script "GeneSeqParse.pl" was employed for parsing the gene and upstream sequences from the downloaded genomic sequences by using their localized and orientation information. The promoter-related information for different genes was obtained from the EPD database [29]. Blast-compatible target datasets of genes, upstream regions, mRNAs, and proteins were constructed with help of the "formatdb" program of the Blast suite to perform alignments between queried and target sequences of NeuroMuscleDB. Extensive literature and database surveys and subsequent compilation and categorization of the information obtained were performed to enable the roles of different genes in various NMDs, neurodegenerative disorders (NDs), and the ageing process [24, 30, 31].

Database Design and Web Interface

MySQL was used to build the NeuroMuscleDB and manage data at the backend using the Linux operating platform. NeuroMuscleDB consists of seven tables that hold the following record types: "gene summary," which includes general information on genes and their functional stages; tables "gene2refseq," "gene2go," and "gene2pubmed" contain data collected from gene databases; tables "rna" and "cds" contain gene annotation information on genes; and 'promoters' contains promoter information. A responsive web interface was designed and integrated with the database using HTML5, PHP, JavaScript (version 1.7), CGI, CSS3, DBI (Database Interface), and Perl, to enable information retrieval and access.

Implementation of Analytical Tools

Analytical tools, including PCR primer design and sequence analysis (similarity searching, promoter analysis, and multiple sequence alignment) were implemented to enable searches and analyses of desired genes and sequences in the NeuroMuscleDB. A standalone version of Primer3 was used to generate multiple sets of forward and reverse primers using various parameters like melting temperature (Tm), GC content, start and end positions, and predicted size of the PCR product. The BLAST tool was implemented for similarity search analyses; this enables the analysis of homologous sequences of nucleotide and protein sequences using the BLAST program (blastp, blastn, blastx) using different parameters. Promoter-related information was extracted from the EPD database [29]. By adopting the approach used for compilation, integration, and management of relevant information in the HRGFish database [26], the reverse complement method was used to retrieve the sequences (3000 nt long; − 2900 to 100 positions corresponding to gene start site) of upstream

regions for genes. Multiple sequence alignment tools having algorithm using CLUSTAL W were incorporated into the web interface to enable alignments with desired sets of sequences.

Results

At present, NeuroMuscleDB contains organized and curated information of about 1102 genes, 6030 mRNAs, and 5687 proteins that participate in muscle development in three mammalian species (*Homo sapiens, Mus musculus*, and *Bos taurus)*. Gene categorization is done based on involvements in different functional stages (differentiation, proliferation, migration, etc.), roles in muscle development, and differential expressions under different disease conditions. The home page of the database contains a brief overview of the database and menu buttons for "Gene Information," "Primer design," "Sequence analysis," "About the database," "Disease," and "Contact" (Fig. 3).

Gene Information

Detailed gene information retrieved from NCBI and related sources, included Gene IDs, locations, short descriptions of genes (e.g., number of exons and start and end positions of genomic accession), PDB IDs, protein accession numbers, and UniProt IDs. A species-wise search algorithm was adopted and embedded in NeuroMuscleDB to provide information on the genes of particular species. After selecting a species, the user can choose functional stage from the dropdown menu and then simply click on the search button to display related genes and respective information in tabular form. Details on a particular gene can be retrieved by clicking the "more" option e.g., if *Homo sapiens* is selected and then "differentiation" is chosen from the functional stage dropdown and submitted for search. NeuroMuscleDB shows the results as several gene records browsed for species *Homo sapiens* and simultaneously display gene information in tabular form. Results include gene description, location, length, exons, and other details.

Analytical Tools

Primer design and sequence analysis (similarity searching, promoter analysis, and multiple sequence alignment) tools are incorporated in the web interface to enable straightforward and convenient analysis of a given gene. These tools were manually installed in the server, and are linked to the database using PERL scripts.

"Primer design" includes an interface to select a "Species" and desired gene from the "Gene list" dropdown menu, and this is followed by the selection of either "gene" or "upstream" in the "Sequence type." Clicking on "Design Primers" results in a set of forward and reverse PCR primers with suitable flanking region lengths. The Primer3 program [32] was implemented in NeuroMuscleDB to generate

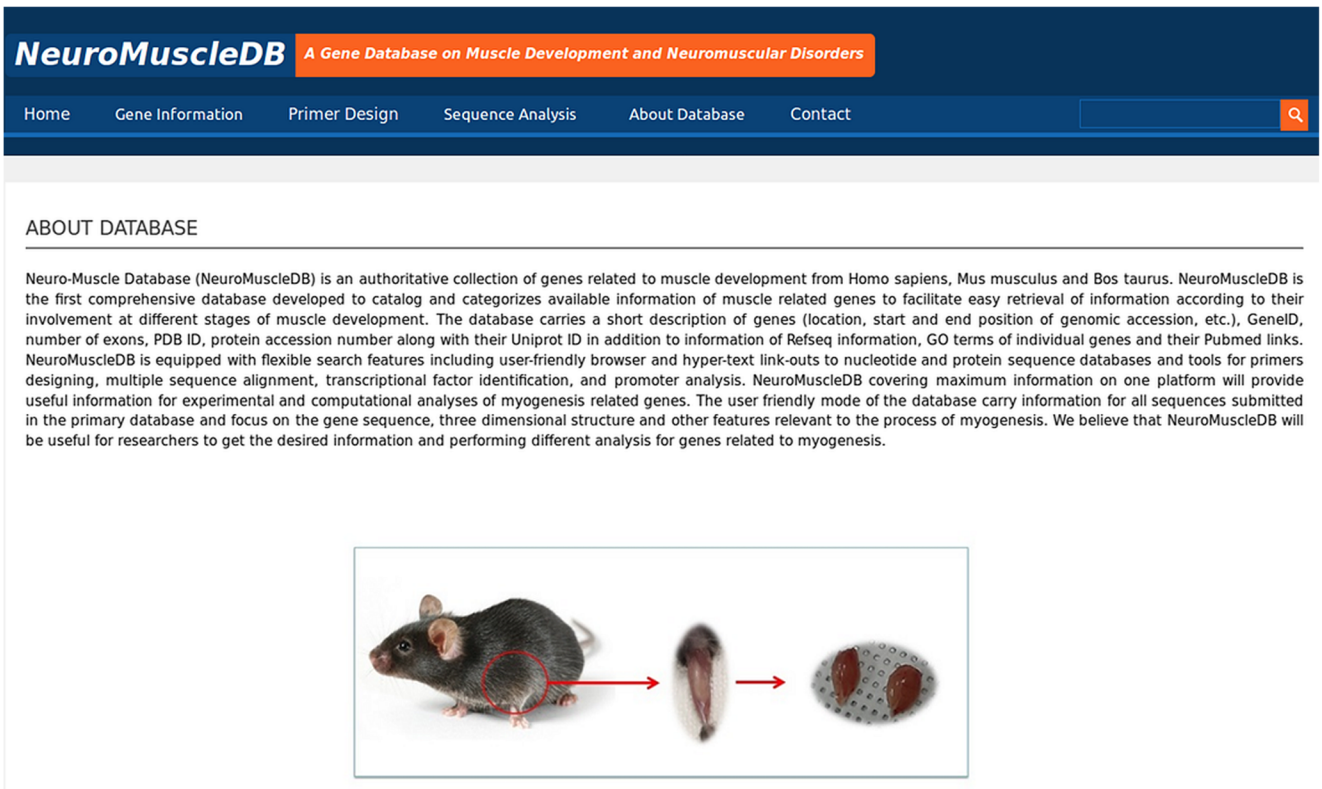

Fig. 3 The NeuroMuscleDB homepage

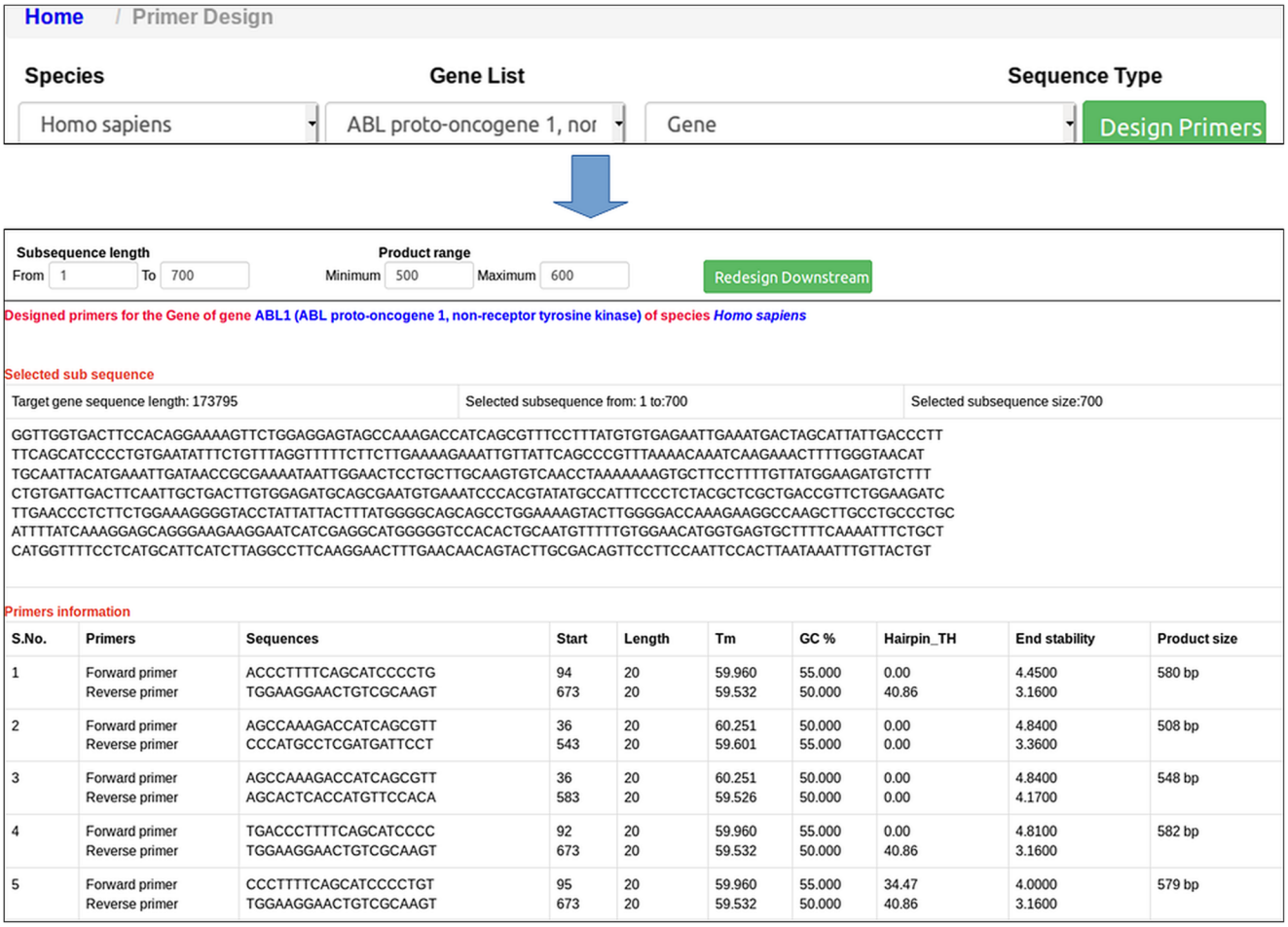

Fig. 4 Designing the primers the ABL1 gene using the "Primer Design" tool of NeuroMuscleDB

primers using methods described in FishMicrosat [33] and FMiR [34]. Figure 4 illustrates an example of designed primers for the ABL1 gene (ABL proto-oncogene 1, non-receptor tyrosine kinase) of *Homo sapiens*. Here, five sets of forward primer and reverse primer are displayed for the gene.

Similarity, search tools provide the opportunity to perform heuristic searches for nucleotides (gene, mRNA, and upstream regions) and protein sequences using different parameters and BLAST (BlastP, BlastN, and BlastX) [35, 36]. Multiple sequence alignment tools based on the "CLUSTALW" program were implemented at the web interface to enable multiple sequence alignments [37]. Figure 5 illustrates an example of the sequence analysis tools available in NeuroMuscleDB.

Diseases

An interactive disease-linked gene information facility regarding NMDs, ageing, and NDs is incorporated in NeuroMuscleDB. By selecting any of these three disease types from a dropdown list, the user can retrieve a list of muscle related genes involved in that particular disease type and their detailed information, which was retrieved from different resources, including the literature and available databases. For example, if a user wanted to search for myogenic genes involved in Alzheimer's disease, he/she would select the "Disease Associated Genes" section, and under "Disease Associated Genes" select "Neurodegenerative disorders" in the dropdown menus of "Category" and further select "Alzheimer's disease" in the "Disease involvement" section. This search results in a list of myogenic genes involved in Alzheimer's disease. The user can then access information related to any selected gene and literature citing the role of this gene in Alzheimer's disease. Each section is provided with option to "Download information" and "Download sequences" for a selected gene. The reported roles of genes in various NMDs, NDs, and during ageing are also provided in the database.

Keyword Search

The homepage of the NeuroMuscleDB web interface includes a search button that enables the retrieval of information matching query keywords. Users can search for information using the gene or species name, gene type, functional stage,

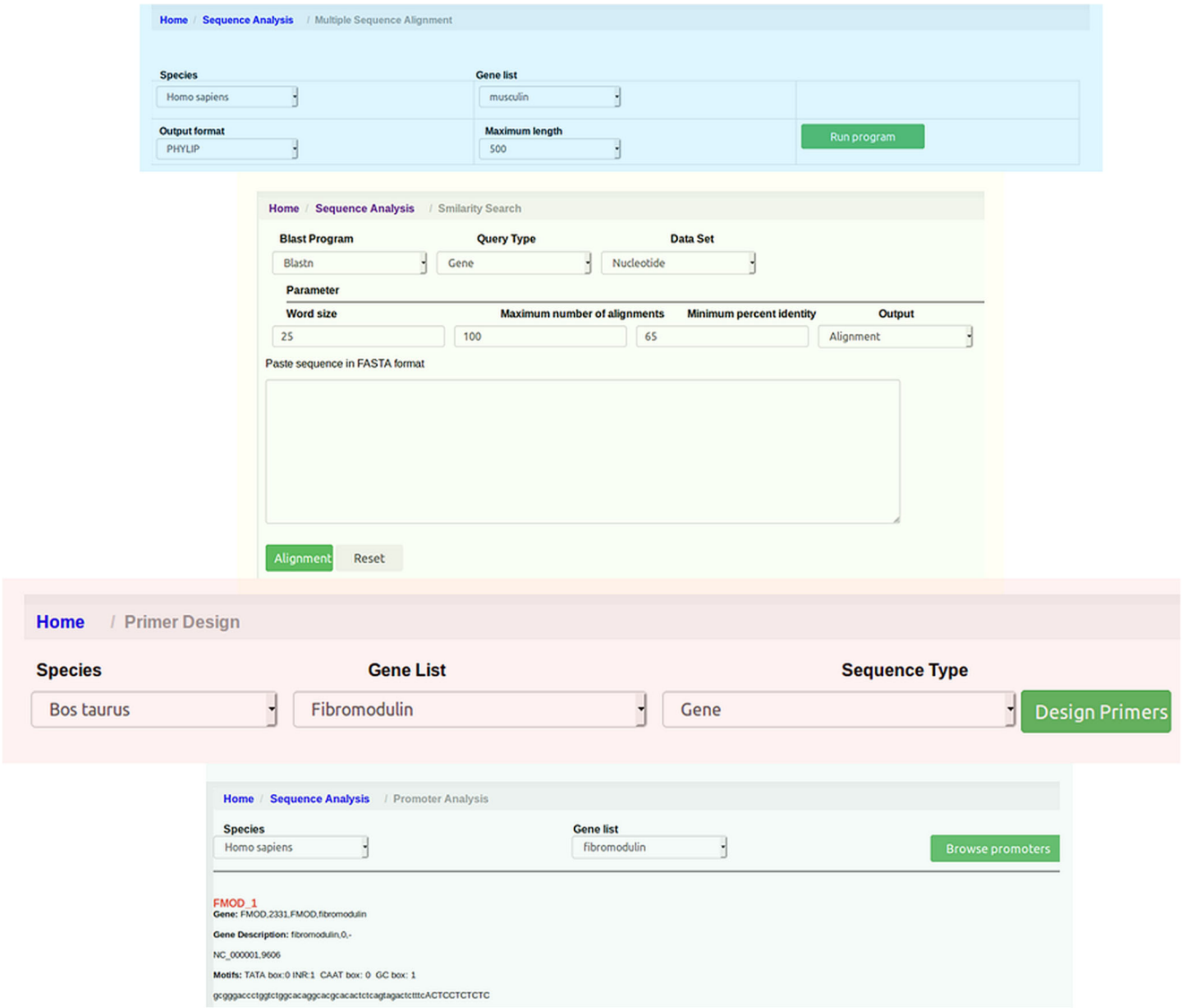

Fig. 5 Different sequence analysis tools available in NeuroMuscleDB

etc. Search relevant information available in the database is displayed in accord with the keywords used.

Discussion

Muscles are principal, critical tissues, and are responsible for receptive movement, physical endurance, strength, and mobility of an organism. As the myogenic process is regulated by many genes and associated genetic factors [38], studies of their involvements in muscle formation are considered to provide valuable insights of the regulatory mechanism underlying muscle development. Though available databases, such as MuscleDB (http://muscledb.org/), the GenAgeHuman Ageing Genomic Resource [39], and the GeneTable of Neuromuscular Disorders [24]; harbours information on muscle-related genes, ageing, and other NDs; the scattered nature of information available of these topics, emphasis on human data, and restricted use hampers data retrieval at the user interface. Furthermore, available muscle databases lack features for retrieving genes basis on their respective functions during different stages of muscle development, and these databases are restricted to provide the roles of different genes in various NMDs, NDs, and during ageing, but provide no information or link regarding the involvements of these genes in muscle formation. Accordingly, the present study was undertaken to develop a comprehensive database (NeuroMuscleDB) to categorize information on genes involved in myogenesis, NMDs, ageing, and neurodegeneration systematically on a single platform. In addition, to curate information on genes associated with different diseases, NeuroMuscleDB contains information on myogenic genes with focus on gene sequences, three dimensional structures, and features relevant to muscle development. In

NeuroMuscleDB, the roles of genes are classified in terms of stage of muscle development. The database can also provide the roles of muscle development–associated genes linked with NMDs, NDs, and the ageing process. Furthermore, all information is provided with proper citations and linkages between genes in these three disease types.

Currently, NeuroMuscleDB contains several gene records in the "Ageing" category and provides Gene name/ID, involvement in different myogenic functional stages, and other details for each entry with specific references. It is hoped that the information provided will be found helpful by those studying muscle-associated ageing. Diseases associated with muscles have been meticulously studied with focus on different types of muscular dystrophies. In NeuroMuscleDB, 20 different types of muscular dystrophies and their associated genes are enlisted with literature citations. This specific gene information holds greater credibility in therapeutic aspect of NMDs to find specific target gene. In addition, NeuroMuscleDB contains lists of muscle genes associated with NDs, especially Alzheimer's and Parkinson's diseases. It has been well established that neurodegeneration is an age-related type of disease, generally characterized by dementia and neuronal loss. Furthermore, our studies and those of several others show that a number of muscle-related genes are associated with ageing and neurological disorders [11, 40]. The layout of NeuroMuscleDB is designed for the easy retrieval of information and data. Currently, NeuroMuscleDB contains records of several myogenic genes that actively participate in Alzheimer's or Parkinson's disease. The provision of disease associated information on "Ageing," "Neuromuscular dystrophy," and "Neurodegenerative disorders" by NeuroMuscleDB make it a unique resource for researchers with interests in these topics.

The development of an interactive, user-friendly web interface containing information of genes related to myogenesis in *Homo sapiens*, *Mus musculus*, and *Bos Taurus* seems timely initiative. Information on *Bos Taurus* has not been compiled to date, and thus, the information on *Bos Taurus* in NeuroMuscleDB offers a unique means of performing comparative genomic studies. The "Sequence Analysis" menu of the web interface enables search, retrieval, and analysis of data and provides analytical tools for primer design, similarity searching, multiple sequence alignment, and promoter analysis. The homepage of the NeuroMuscleDB web interface contains a "Gene Information" menu that displays in tabular view (by species or functional stage) gene IDs, descriptions, locations, numbers of exons, and a "details" link with nucleotide and protein accession numbers and UniProt IDs. In addition, RefSeq information, PubMed links, and gene GO terms are also available under the "gene details" option. NeuroMuscleDB is equipped with flexible search options and includes a user-friendly browser and hypertext links to nucleotide and protein sequence databases. The similarity search tool uses BLAST to perform alignments for given query sequences using selected datasets, that is, gene, mRNA, upstream, and protein. A query may be a nucleotide or protein sequence and the BLAST program (blastP/blastN/blastX) can be selected using different alignment parameters, and an appropriate dataset and tool. The PCR primer design tool embedded in the web interface uses Primer3 (http://bioinfo.ut.ee/primer3-0.4.0/primer3/) to design primers for selected nucleotide sequence of a selected gene and/or its upstream region, and the multiple sequence alignment tool, which is based on CLUSTALW, performs multiple sequence alignments among all orthologous transcripts (variants) of species selected for a given gene.

NeuroMuscleDB contains detailed information on genes involved in ageing and age-associated NDs. Genes are classified according to their involvements in different neuromuscular diseases, such as myofibrillar myopathy, Miyoshi myopathy, Bethlem myopathy. When new gene information becomes available, NeuroMuscleDB will be updated with a focus on providing information about mutations observed for each gene and their effects on muscle development. Continuous addition of new information will be performed in an ongoing manner as will the systematic incorporation of new tools.

Conclusion and Future Prospects

NeuroMuscleDB provides an interface comprising of flexible tools that provides comprehensive information on genes and performs different types of analysis on muscle-related genes that are involved in different stages of the myogenic program. We believe that NeuroMuscleDB will prove to be an important source of information for human research aimed at devising measures to combat different muscle diseases, and will be useful to those in the scientific fraternity involved in muscle-related studies in normal and aged tissues by providing deeper insight of the natures of muscle-associated diseases.

Author Contributions IC conceived the idea; IR and MHB programmed for data manipulation, developed database, and application modules for browsing and analyzing the information; MHB, EJL, GR, and DC collected the data; and IC, ATJ, EJL, PS, GEB, and GMA helped compile the biological aspects of the database. IC, ATJ, GEB, GMA, MHB, IR, PS, and KA drafted the manuscript.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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