

Review Article

Drug targets for lymphatic filariasis: A bioinformatics approach

Om Prakash Sharma, Yellamandaya Vadlamudi, Arun Gupta Kota, Vikrant Kumar Sinha & Muthuvel Suresh Kumar

¹*Centre for Bioinformatics, School of Life Science, Pondicherry University, Puducherry, India*

ABSTRACT

This review article discusses the current scenario of the national and international burden due to lymphatic filariasis (LF) and describes the active elimination programmes for LF and their achievements to eradicate this most debilitating disease from the earth. Since, bioinformatics is a rapidly growing field of biological study, and it has an increasingly significant role in various fields of biology. We have reviewed its leading involvement in the filarial research using different approaches of bioinformatics and have summarized available existing drugs and their targets to re-examine and to keep away from the resisting conditions. Moreover, some of the novel drug targets have been assembled for further study to design fresh and better pharmacological therapeutics. Various bioinformatics-based web resources, and databases have been discussed, which may enrich the filarial research.

Key words Bioinformatics; filariasis drug targets; filariasis elimination programmes; lymphatic filariasis; proteomics and genomics

INTRODUCTION

Parasitic diseases are widespread throughout the developing world and are associated with a heavy burden of morbidity and mortality. Human filarial nematodes, transmitted by arthropod vectors, are endemic in tropical and sub-tropical regions around the world¹. Lymphatic filariasis (LF) is one of the oldest and most debilitating diseases throughout the world and millions of people suffer from this disease. In 1995, the World Health Organization (WHO) ranked LF as the second-leading cause of long-term chronic disability worldwide².

LF is estimated to infect over 120 million people in at least 80 countries of the world. More than one billion people are at risk of getting affected with this life-threatening disease³. In India, it is a major public health problem accounting for 40% of the world disease burden^{4–5}. India has been one-third of the infected people from this disease and rests are in the South Asia, Western Pacific and in the part of Central America. LF has been found one of the potentially eradicable diseases. Therefore, in the 50th meeting of the World Health Assembly in May 1997 it was announced to eliminate LF by the year 2020⁶.

Various elimination programmes have been launched in India and globally to eradicate this disease. In 1998, WHO initiated a global programme for elimination of lymphatic filariasis (GPELF) employing mass drug administration (MDA) of annual single dose of a combina-

tion of diethyl carbamazine citrate (DEC) (6 mg/kg) or Ivermectin and Albendazole (400 mg)⁷ and Albendazole/Ivermectin in the endemic areas where the disease is co-endemic with onchocerciasis for at least five years⁸. Several recent studies suggest that the co-administration of these two drugs for LF is very effective. These combinations produced prolonged suppression of microfilaraemia (mf) than either drug alone^{9–11}. These drugs are able to kill the parasitic worms available in the blood, but are not completely effective against the adult worms. Moreover, recent studies suggest that albendazole is getting resistance for treatment of this disease^{12–13}.

To eradicate LF globally, research strategy is needed to develop or design other effective drugs and drug targets, new methods for vector control and diagnostic tools and techniques. At the same time, the treatment of LF requires supportive or disease-specific clinical care, and patient education with counseling to avoid this disease. Moreover, major filarial research should have to address the obstacles to eliminate LF and the outcome of post-MDA surveillance of various active LF elimination programmes. This outcome data may help to further modify (if needed) the current strategies for effective outcome of several LF programmes. These data can be stored and made publicly available as an open access database for researchers. Statistical analysis of these data and bioinformatics tools may speed-up and provide new view to the filarial research. Bioinformatics-based

proteomics and genomics approaches offer remarkable promising tools to address the molecular level of information and their role in infection, which provide an excellent opportunity to get an insight into the proteins or genome which may contribute to its inhibition process.

Overview of filariasis

The LF is one of the oldest vector-borne parasitic disease around the world that is transmitted by more than four genera of mosquitoes (*Aedes*, *Anopheles*—also a principal vector for malaria, *Culex quinquefasciatus*, and *Mansonia* sp)¹⁴, each one have different features and transmission procedure. LF is one of the leading causes of permanent and long-term disability around the world. It is a disease caused by a group of nematode worms belonging to the order “Filariidae” and transmitted to man by the infective bites of blood-sucking arthropods in man, and caused by three parasites namely: *Wuchereria bancrofti* (*Wb*), *Brugia malayi* (*Bm*) and *Brugia timori* (*Bt*). In all, 90% of these infections are caused by *Wb* and remaining by *Bm* and *Bt*^{13, 15}. In India, *Wb* is mainly transmitted by the ubiquitous vector, *Cx. quinquefasciatus* which grows on dirty and polluted water, whereas *Bm* prevalence is restricted to the rural areas of Kerala¹⁶. These worms occupy the lymphatic system, including the lymph nodes, and in chronic cases, these worms lead to the elephantiasis.

Global burden of lymphatic filariasis

The LF is the world’s second leading cause of long-term disability, suffering, morbidity and several social and economic burdens to individuals, their families and nation^{17–18}. It is estimated that 700 million people are living in the endemic areas of the Southeast Asian region (SEAR), which contribute >64% of the global burden¹⁹. Several research studies suggest that it causes the annual economic loss of several billions US\$.

Several private pharmaceutical companies have played very remarkable role in donating billions of doses of their drugs to the endemic countries during the several LF elimination programmes running under WHO. Albendazole, DEC and Ivermectin (Mectizan®) was donated by GlaxoSmithKline, Eisai and Merck & Company Inc., respectively, for the treatment of LF and onchocerciasis (river blindness) in most of the endemic African countries for MDA programmes. Recently, Sanofi, Eisai and Bill & Melinda Gates Foundation committed to donate DEC tablets from 2012 to 2020²⁰ and the estimated cost for MDA per person is US\$ 0.05–0.10²¹.

Global programme to eliminate lymphatic filariasis (GPELF) and global alliance to eliminate lymphatic filari-

asis (GAELF) estimated that currently, 81 countries are considered endemic for LF, and about 1.34 billion, persons are at the risk of infection. According to VI GAELF meeting of June 2010, 37 countries have completed ≥ 5 rounds of MDA at some of the endemic areas. Therefore, 22 million people have been protected with estimated economic saving of US\$ 24.2 billion. Still approximately >100 million persons are suffering from LF, and it is having a total global burden of 65% in the SEAR region, and 35% in Africa region (AFR)²². According to a WHO report, India, Indonesia and Bangladesh alone contribute >70% of the infection worldwide. Apart from these countries, six other countries, such as Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste are the other endemic countries, having more number of LF cases.

Role of bioinformatics in filarial research

Bioinformatics

Bioinformatics is a branch of science, which deals with the computer-based analysis for the biological datasets. Currently, biology and computer science are evolving like close friends which are mutually helping and influencing each other in the field. Bioinformatics has accelerated the investigation of the cellular process to understand the molecular mechanism. It has also accelerated several fields of biological sciences and drug discovery. In the past few years, bioinformatics approaches have been used in various fields of biological sciences to understand and solve the biological problems.

Genomic approach in filarial research

Genomic technology is a powerful technology of the bioinformatics which is rapidly being used to understand the structure and function of all the genes within an organism. Genomics help to mark the genes and other biological features in the entire DNA sequence of the organism. The field also includes evolutionary studies, intra-genomic phenomena such as heterosis, epistasis, pleiotropy and other interactions between loci and alleles within the genome²². Moreover, drug targets can be screened or identified using the genomics approach.

Using bioinformatics approach of phylogenetic analysis Casiraghi *et al*²³ have identified the gene sequence of mitochondrial cytochrome oxidase-I (COI) from 11 species of filarial nematodes and spiruid nematodes. Further, Hoerauf *et al*²⁴ found the mutualistic interaction between the intracellular bacteria (endobacteria) and filarial nematodes, which throws light on the filarial chemotherapeutic. Genetic diversity between the DNA sequences of two

strains could be predicted as Nuchprayoon *et al*²⁵ had identified the genetic diversity existing between the Myanmar and Thai strains of *Wb* using phylogenetic analysis using parsimony tool (PAUP).

Recently, nuclear genome draft of the first human filarial parasites of *Bm* (95-Mb) has been reported, which contains 88, 363, 057 bp of assembled sequence with 17.84% of protein coding sequence²⁶. The full genome data are available at the recent release of NEMBASE4 database. Analysis of these data using genomics approach can provide significant enrichment in our knowledge to understand the genetic principles that govern various essential functions for their survival²⁷ which can provide several fruitful drug targets.

Moreover, miRNAs are involved in various regulations and developmental process of nematodes. Genomics study can find a variety of genes which regulate or may take part in central role for miRNA processing. Several investigators have identified novel functions of miRNAs in filarial parasites, during the filarial comparison studies^{28–29}. These miRNAs processing genes may explore the knowledge about the involvement of various parasitic genes of nematodes through the silencing or knock-down approach^{30–31}, as in the case of *Ce* could also be targeted for drug discovery and design.

Proteomic approach in filarial research

The terms ‘Proteomics’ and ‘Proteome’, were first time used in 1995 for the large-scale study of proteins. Proteins are nothing but are macromolecules made up of strings of amino acids linked like a chain which are made up of 20 amino acids, these combined and formed more than thousand proteins, with specific shape and function. In addition, each protein undergoes post-translation modification that further influences its molecular structure and functions³². Traditionally, proteomics technology is based on highly efficient methods of separation using two-dimensional-poly acrylamide gel electrophoresis (2D-PAGE) and modern tools of bioinformatics.

Proteomic analysis of the several stages of *Bm* has identified 557 of the 805 *Wolbachia* endosymbionts from *Bm* (*wBm*) proteins and 11,508 protein coding genes in the initial draft of *Bm*. This information may be used to proteome map using reverse-phase liquid chromatography-tandem mass spectroscopy to define various proteins. Recently, Bennuru *et al*³³ have done the same to define excretory/secretory (ES) and somatic proteins produced by the adult, mf and infective stages of larvae.

Since molecular knowledge of protein plays a significant role for drug designing and vaccine development³⁴ several investigators have modeled the three-dimensional

structure of novel drug targets for LF and provided the molecular information of the respective proteins^{35–37}. For example, in the absence of the crystallographic structure of Glutathione-S-transferase (GST), Bhargavi *et al*³⁵ have modeled the 3-D structure of the GST which was further studied by Azeez *et al*³⁸ for the hunt of a better drug. In this study, potential drugs were identified using virtual screening, further tested for *in vitro* study which could be used for various phases of clinical trials. Other novel drug targets are also available for which molecular structures are not yet defined (Table 1). Using bioinformatics approach these novel drug targets can be modeled, and their molecular function could be interrupted for nematocidal effect using rational drug design approach of either ligand-based drug designing (LBDD) or structure-based drug designing (SBDD) (Fig. 1).

LBDD is a popular method for drug discovery and leads optimization. It provides crucial insights into the interaction between drug target and ligand molecule and allows us to understand the features of lead molecules for their biological activity³⁹. This method can also predict the novel molecular structure with desirable features for the interaction with the target molecule. For LBDD of LF, various drugs are available with their target protein (Table 2). These existing drugs could be re-studied for 3D-quantitative structural activity relationship (QSAR) and pharmacophore modeling that defines the minimum necessary structural characteristics of a small molecule possess to inhibit the target.

SBDD is a rapidly growing method with which many successes have achieved in recent years^{40–44}. Due to the explosion of proteomics and genomics various drug targets have been identified to design a drug. SBDD relies upon the knowledge of the 3D structure of the target protein obtained from the experimental method such as X-ray crystallography, NMR, electron microscopy, etc. If an experimental method is not available, homology modeling is the approach to build the 3D structure using target protein sequence⁴⁵. These macromolecules could be analyzed for the possible inhibitor binding site identification. Based on the binding site, potential inhibitor can be designed or identified from the small molecule databases such as ZINC database⁴⁶, DrugBank⁴⁷, ChemBank⁴⁸, PubChem⁴⁹, Cambridge structural database⁵⁰ and various other databases available at Lignad.Info: Molecule database⁵¹ to check the biological activity of the relevant protein.

Web-based available resources for LF

A database is a web-based resource or collection of data, which is organized so that various users or research-

Table 1. Novel drug targets for lymphatic filariasis

| S.No. | Novel protein targets | Protein functions |
|-------|--|---|
| 1. | Phosphoglycerate mutase | It catalyzes the interconversion of 2- and 3-phosphoglycerate in the glycolytic and gluconeogenic pathways. |
| 2. | Aminoacyl-tRNA synthetase (AARS) | It catalyzes the esterification of a specific amino acid or its precursor to one of all its compatible cognate tRNAs to form an aminoacyl-tRNA. |
| 3. | Trehalose-6-phosphate-synthase | It plays several physiological functions such as energy reserve, glucose uptake and egg hatching. |
| 4. | Prolyl-4-hydroxylase | It catalyzes the hydroxylation of prolines in the X-Pro-Gly repeats of collagen chains, it is an essential enzyme for the maturation of collagen in nematodes. |
| 5. | S-adenosyl-methionine decarboxylase | It is a key enzyme in polyamine metabolism and antioxidation. |
| 6. | Glutathione-s-transferases (GSTs) | GSTs are major phase-II detoxification enzymes and binding proteins. |
| 7. | Myristoyl-transferase | It plays crucial role in the fatty acid metabolism. |
| 8. | Farnesyl-transferase | It catalyzes the transfer of a farnesyl residue from farnesyl-pyrophosphate (FPP) to the thiol of a cysteine side chain of proteins, which carry at the C-terminal the so-called CAAX-sequence. |
| 9. | FAR protein or retinol binding protein | It is a structurally novel small helix-rich fatty acid and retinol binding protein. It's having a potential role in the generation of pathology, and parasite development. |
| 10. | Cystathionine- β -synthase | This enzyme acts in a chemical pathway and is responsible for using vitamin B6 to convert building block of proteins (amino acid) called homocysteine and serine to a molecule called cystathionine. |
| 11. | Prolyl-4-hydroxylase | It can alter protein conformation and protein-protein interactions. |
| 12. | Transglutaminase | Role in the growth, development and maturation of nematodes. |
| 13. | Translationally controlled tumor protein | It has been implicated in important cellular processes, such as cell growth, cell cycle progression, and malignant transformation and in the protection of cells against various stress conditions and apoptosis. |
| 14. | Secondary amines and tertiary amines | The secondary amines having longer alkyl chain ($n > 5$) would be responsible for eliciting macro [®] laricidal activity; and the tertiary amines having dialkyl chain ($n = 3$) show a vital role in predominantly micro [®] laricidal action. |
| 15. | Fructose-1,6-bisphosphate aldolase | It is a heat-stable and bi-functional protein that represents the pace-making ancestral gluconeogenic enzyme. It may be a potential vaccine target. |
| 16. | Filarial chitin | Chitin metabolism has also been proposed to be a parasite unique target, as the vertebrate host does not contain chitin. |
| 17. | DNA topoisomerase-II | It has an important role in DNA replication, repair and transcription. |
| 18. | Octopamine (OA) | OA plays an important role in the regulation of a number of key processes in nematodes, including pharyngeal pumping, locomotion and egg-laying. |
| 19. | Glutathione reductase | It is an important part of the antioxidant system of many living cells. It maintains the correct intracellular redox balance. |
| 20. | Glutathione-s-transferases (GSTs) | GSTs are one of the major detoxification systems ubiquitous among eukaryotes and have been found in a wide range of parasitic helminthes. |
| 21. | Glutathione peroxidases (GPXs) | GPXs protect the filarial worms from oxidative damage, and are thus important targets for novel chemotherapy. |
| 22. | Eicosanoid | It may act locally in the host and modify host-parasite interactions. The production of these lipid mediators may be one of the strategies for evading host immune responses. |

Table 2. Available drugs and their drug targets for lymphatic filariasis

| S.No. | Drug | Drug target |
|-------|---------------|---|
| 1. | Albendazole | Tubulin polymerization |
| 2. | DEC | Cyclo-oxygenase pathway and COX-1 |
| 3. | Ivermectin | Glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of the microfilaria |
| 4. | Benzimidazole | Tubulin polymerization |
| 5. | Levamisole | L-subtype nicotinic acetylcholine receptors in nematode muscles |
| 6. | Piperazine | GABA receptors, presumably causing hyperpolarization of nerve endings, resulting in flaccid paralysis of the worm |
| 7. | Mebendazole | Colchicine-sensitive site of tubulin |
| 8. | Imidazole | Tubulin polymerization |

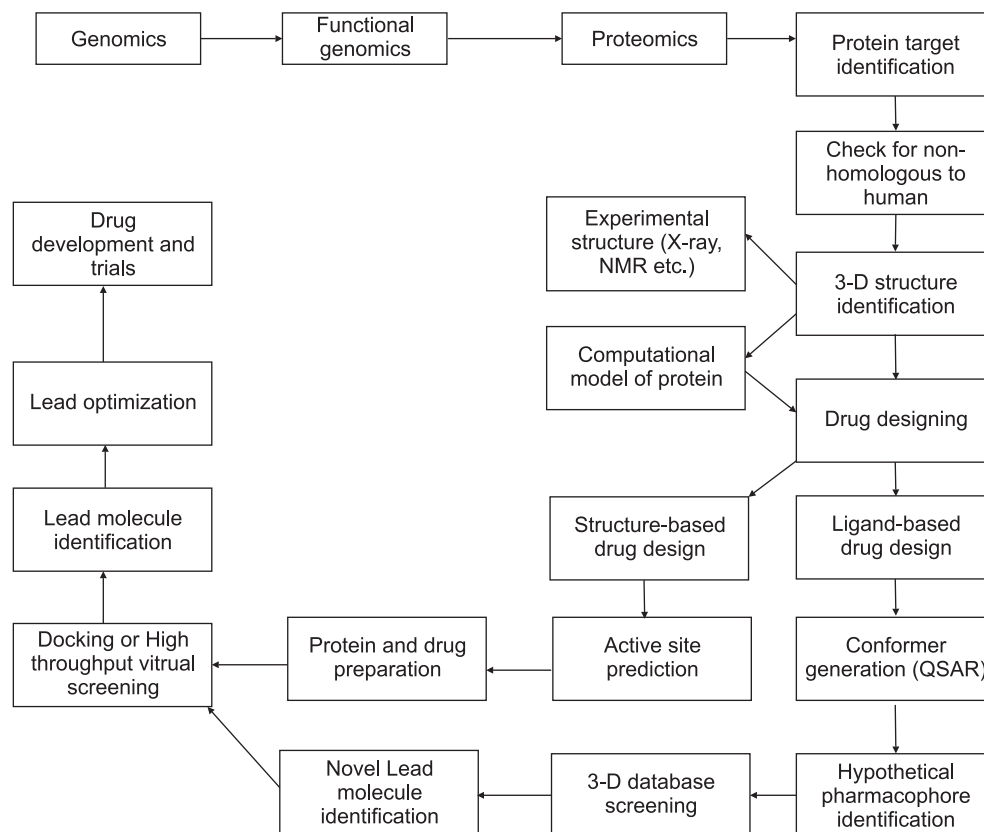


Fig. 1: Computational approach towards antifilarial drug discovery.

ers can access the available data or information at the same time through the internet worldwide. Biological database plays an important role in bioinformatics. It offers to the group of scientists or researchers to analyze the large amount of biological data available for nucleotide sequences, amino acid sequences and their 2D or 3D structures for the broad range of organisms and their drug targets. Currently, there are only few active databases available for LF (Table 3) but comprehensive and specified database for LF is not available. A specific-drug target database such as clostridium drug target database⁵², dengue drug target database (<http://www.bioinformatics.org/dengueDTDB/Pages/main.htm>) and the TDR targets database⁵³, there is an urgent need for LF drug target database to enhance the drug discovery and to avoid the drug resistance. Some of the important databases which are available for LF research have been discussed below.

NEMBASE: NEMBASE⁵⁴ contains EST datasets for nematodes, including filarial nematodes. They have the filarial genome project—a multinational project for the general information such as filarial biology and pathology and genome information such as filarial gene nomen-

clature, filarial genome mapping, and *Bm* genome survey sequencing (GSS). Currently, they have added genome sequencing of *wBm* and *Onchocerca volvulus* (*Ov*) with the Sanger Institute, NEB and TIGR.

WormBase: WormBase⁵⁵ is an open access database and repository for nematode biology which contains the genome browser for *Bm*, *C. elegans*, *H. contortus* and other related nematodes. It also contains the gene predictions and orthology assignments from a range of related nematodes.

FilaDB: It is a database for filarial patients where, clinico-immuno monitoring and management were developed for Kasturba Hospital and private practitioners to screen for filarial infections with the objective to provide information on an incidence of mf, types of acute, chronic and occult manifestations, age, sex and distribution area of filariasis cases. Relapse of filarial infections if any and compliance in clinico-immuno monitoring and treatment. These types of open access database may help researchers to fight with this type of chronic suffering diseases.

Filarial worm database at Broad Institute: Filarial worm database at Broad Institute is a newly built database at Broad Institute to study the crucial phenotypic

Table 3. Representative online web resources and databases for lymphatic filariasis

| S.No. | Name | Description | URL |
|-------|---------------------------|--|---|
| 1. | DBEMFDD diseases database | It is an annotated bibliography for filariasis, malaria, dengue and diarrheal. It also contains the findings of the literature survey. | http://ideas.repec.org/p/ess/wpaper/id2032.html |
| 2. | FilaDB | Database on filaria detection, clinico-immuno monitoring & management has been developed for Kasturba Hospital and private practitioners to screen the filarial infection. | http://www.jbtdrc.org/FilaDb.htm |
| 3. | NEMBASE2 | Contains the EST sequence for <i>Brugia malayi</i> and other nematodes. | http://www.nematodes.org/nematodeESTs/nembase.html |
| 4. | Filaria Journal | Full and freely access journal of filariasis. | http://www.filariajournal.com/ |
| 5. | Wormbase | It is an online database for the biology and genome of the <i>Ce</i> and related nematodes. | http://www.wormbase.org |
| 6. | WHO | It contains the related publication of filariasis, reports of elimination programme, control of neglected tropical diseases and some important links. | http://www.who.int/topics/filariasis/en/ |
| 7. | PHIS | It contains the news and updated from filariasis elimination programme. | http://umis.doh.gov.ph/fila |
| 8. | Disease database | It contains the general information regarding diseases. | http://www.diseasesdatabase.com/ddb4824.htm |
| 9. | TDR-lymphatic filariasis | It contains knowledge about the parasite genomes for African lymphatic filariasis and other diseases. TDR is now focusing on providing capacity to use the parasite genome data and on supporting developments in applied genomics and bioinformatics. | http://www.who.int/tdroid/diseases/lymphfil/default.htm |
| 10. | Filarial worms database | This database provides the genome sequence of organisms rapidly and broadly available to the scientific community. | http://www.broadinstitute.org/annotation/genome/filarial_worms/MultiHome.html |

difference between the closely related filarial species (<http://www.filariasiscenter.org/brugia-malayi-genomics-and-bioinformatics-resources>). It contains the genome information about the *Loa loa*, *Wb* and *Ov*. Furthermore, it also summarizes the sequence data on *Wolbachia* endosymbionts of *Wb*, *Ov* and *Bm*.

Since, filarial diseases are still remaining as a major public health concern in India. There is a need of comprehensive database, which should contain: (a) curated links between genes relevant to filariasis and their sequences in GenBank and SwissProt; (b) sequence homology between different filariasis causing genes; (c) primary and secondary information of pathogens; (d) availability of various drugs and their targets; (e) expressed sequence tagged (EST) sequences from different filarial species; (f) supporting references from published literatures; and (g) bioinformatics tools to analyze those data. Database should also contain the epidemiological data on age and gender-wise incidences of disease, remission and transition rates of disease sequelae.

CONCLUSION

In this review article, we have discussed the current research and the global burden due to the LF. In India, LF is one of the major health problems, and contributes >40% of the global burden and approximately 50% of the people at risk of getting infection. Here, proper treatment of patients with MDA and disease-specific care, patient education and their counseling is also necessary to create the awareness among the people and to avoid morbidity of the disease. Since, bioinformatics has emerged as a promising branch of science, and has a central role in various fields of life science, we have reviewed the major contribution of bioinformatics in filarial research, and found that still we can use various approaches of bioinformatics to understand this disease. Various novel drug targets have been listed in the manuscript, which could be re-examined or re-studied to understand the disease and to design antifilarial drugs.

ACKNOWLEDGEMENTS

OPS is grateful to the Council of Scientific & Industrial Research (CSIR), India for the Senior Research Fellowship (09/559/(0085)/2012/EMR-I). Research carried out at the laboratory of the Centre for Excellence in Bioinformatics, Pondicherry University, India is funded by the Department of Information Technology (DIT) and the Department of Biotechnology (DBT), Government of India, New Delhi.

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Correspondence to: Dr Muthuvel Suresh Kumar, Assistant Professor, Department of Bioinformatics, Centre for Bioinformatics, School of Life Science, Pondicherry University, Puducherry–605 014, India.
E-mail: suresh.bic@pondiuni.edu.in; muthuvels@hotmail.com

Received: 10 November 2012

Accepted in revised form: 13 June 2013