

miRNA Databases: An Investigation of Regulatory RNAs Informatics

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Abstract— microRNAs (miRNAs) are one of the largest classes of non-coding RNAs that play major regulatory role in our normal body functions. They are also involved in pathogenesis of many diseases as they do translational repression or target mRNA degradation. There is bulk of data present on different processes related to miRNAs i.e. miRNA-mRNA interaction, miRNA target prediction and miRNA-disease related information, etc. To handle this data in an efficient manner, many databases have been developed which categorize miRNA related information in specific database classes. This review aims to summarize the current status of miRNA databases which will provide a large organized pool of information for researchers working on different aspects of miRNA. This, in turn, will aid in understanding genetic regulation more efficiently at molecular level.

Index Terms— bioinformatics, computer science, databases, disease, microRNA, non-coding RNA, target prediction.

1 INTRODUCTION

Non-coding RNAs have no capability to encode any protein but are functional and informative RNA molecules.

These are small regulatory RNAs that control homeostasis of body by keeping balance. These include small interfering RNA, transfer RNA, microRNA (miRNA), small nucleolar RNA and ribosomal RNA. miRNAs, as one of the most important class of non-coding RNAs, playing major role in genetic regulation and disease pathogenesis [1], [2].

miRNA are 22 nucleotides long RNA stretch that suppresses translation by doing non-perfect base-pairing of almost six to eight nucleotides with target mRNA. A recent estimation is that more than one third of total protein-encoding genes are partially controlled by miRNAs in humans [3]. Most of miRNAs are derived from transposones, pseudogenes or from exons and/or introns of non-coding/protein-coding transcripts [4], [5], [6]. Wahid et al. has studied miRNA biogenesis extensively [7], [8], [9].

miRNAs dysregulation is the causative phenomenon in pathogenesis of various diseases. In few recent studies it is shown that miRNAs are one of the key regulators in lipid metabolism [10], insulin secretion [11], beta cell differentiation [12], diabetes-associated heart problems [13], pancreatic islet development [14] and diabetes-associated kidney problems

[15]. miRNAs are crucially involved in cardiovascular system because of Dicer depletion which causes vessel formation, heart development and angiogenesis related defects [16], [17]. miRNA are also involved in many cancers such as human ovarian cancer [18], myeloproliferative disorder [19], Kaposi's sarcoma-associated herpesvirus [20], rhabdomyosarcoma [21] and breast cancer [22]. miRNA is also involved in nonsyndromic progressive hearing loss as well [23].

Regulatory RNAs Informatics is a novel branch of bioinformatics that focus only on databases and tools developed for regulatory RNAs and its related research. miRNAs are regulatory RNAs that are important in many human pathologies and normal body processes such as vertebrate organogenesis. Related bulk of data is available that are very important for in-depth analysis miRNAs. Huge amount of such data on miRNA is difficult to handle efficiently without developing specialized miRNA databases. With the advancements of bioinformatics and computational methodologies, many miRNA databases been developed that pool large amount of miRNA information in an organized form. Databases with their web links are listed in Table 1 below.

TABLE 1
DATABASES WITH THEIR WEB SITE LINKS.

Database	Web Link(s)
miRBase	http://microrna.sanger.ac.uk/ http://www.mirbase.org/
miRNAmap	http://mirnamap.mbc.nctu.edu.tw/
miRWalk	http://mirwalk.uni-hd.de/
miRSEL	http://services.bio.fli.lmu.de/mirsel
miR0'	http://ferrolab.dmi.unict.it/miro
miRandola	http://atlas.dmi.unict.it/mirandola/index.html
Plant miRNA database (PMRD)	http://bioinformatics.cau.edu.cn/PMRD
deepBase	http://deepbase.sysu.edu.cn/
RepTar	http://bioinformatics.ekmd.huji.ac.il/reptar/
miRecords	http://miRecords.umn.edu/miRecords
miRdSNP	http://mirdsnpc.ccr.buffalo.edu
miROrtho	http://cegg.unige.ch/mirortho
PhenomIR	http://mips.helmholtz-muenchen.de/phenomir
miRNEST	http://mirnest.amu.edu.pl http://lemur.amu.edu.pl/share.php?mirmest/home.php
miRDB	http://mirdb.org
miRTarBase	http://mirtarbase.mbc.nctu.edu.tw/
starBase	http://starbase.sysu.edu.cn/
Human microRNA disease database (HMDD)	http://202.38.126.151/hmdd/mirna/md/ http://cmbi.bjmu.edu.cn/hmdd

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2 GENERAL PURPOSE DATABASES

2.1 miRBase

miRBase is one of the most comprehensive databases of miRNAs. This database provides the miRNA gene nomenclature system for novel miRNA sequences. This database also contains miRNA sequence as well as annotation data while miRNA target genes are stored in miRNA Targets within miRBase [24]. In miRBase, short RNA deep-sequencing experiments of miRNA are used to map reads which can be visualized in web interface of miRBase. It also contains alternative isoforms of mature miRNAs, detailed evidence for miRNA annotations and relative expression levels of miRNA sequences [25].

2.2 miRNAmmap

miRNAmmap is a well-known database that collect the information of known miRNA genes and their known miRNA targets within human, dog, rat and mouse genomes in its initial version (miRNAmmap 1.0) [26]. Later version (miRNAmmap 2.0) [27] includes data of total two insects, one worm and nine vertebrates as compared to data of only four vertebrates. Also information on putative miRNA genes as well as their putative miRNA targets can also be found in this database. miRBase is used to obtain known miRNA genes and miRNA targets which are collected from experimentally validated literature as well as from TarBase [28].

RNAz identified putative miRNA precursors while putative mature miRNA are accurately determined by mmiRNA, a machine learning approach. Putative miRNA targets are then predicted by miRanda, RNAhybrid and TargetScan, present in the conserved regions of 3'-UTR. Filtration of predicted miRNA targets is done on three criterions including multiple sites containing target genes, accessible target site and prediction from minimum two tools from miRanda, RNAhybrid and TargetScan. This filtration in turn will lessen false positive prediction rate of miRNA target genes. Known miRNAs expression profiles, gene annotations and comparisons among different species are also available. Human 18 normal tissues are also profiled by Q-PCR. In its version 1.0, the experimentally validated miRNA genes are large i.e. 131 in humans, 196 in mice, 117 in rats and 6 in dogs [29]. Presently miRNA and their target genes are much more than previous version.

3 SPECIALIZED DATABASES

3.1 miRWalk

Validated and predicted information for miRNA-target interaction is stored in miRWalk. This database permits validation of new miRNA targets in promoter region, 3'-UTR and few regulatory regions of total known genes. Module for 'Validated Target' is updated on monthly basis while 'Predicted Target module' is updated biannually [30].

3.2 miRSEL

Currently, miRSEL contain literature derived largest collection of miRNA-gene associations. These associations are important to analyze regulatory network as well as miRNA target prediction tools development. miRSEL is a very popular database as it is updated daily. Many miRNA names collected from literature are

contained in miRSEL as synonyms. This database includes naming conventions for miRNA which are species specific.

It covers numerous spelling alternates in literature (e.g. miR-125b, micro-RNA-125b, miR125b, few more) that are having species identifiers or not (e.g. hsa-miR-125 and miR-125). In any PubMed abstract, relatively small number of unique miRNA loci can be identified. In rat, human and mice miRNA-target pairs, merely 360 different miRNA loci are identified by regular expression while only 280 different miRNA loci are identified by database derived synonyms [31].

3.3 miRDB

miRDB database is an extensible system that contain predicted as well as validated miRNA targets with detailed miRNA functional annotations. This database has powerful data mining facilities and updated automatically. This database integrates data from miRNA databases, ontologies databases, diseases databases and many more databases into a unified resource. Uniqueness of miRDB is the addition of a new feature based on miRNAs annotations that is the associations between genes and phenotypes/diseases/processes. Also most significant association can be find out in this database [32].

3.4 miRanda

miRanda is a comprehensive classification system of extracellular circulatory miRNAs, manually curated and important tool for biomedical research. miRanda in connection to miRDB, help to understand possible biological functions and their phenotypic relation. This database stores 2132 entries which have 21 types of samples and 581 distinct mature miRNAs. Extracellular miRNAs are classified into four major classes: miRNA-circulating, miRNA-exosome, miRNA-Ago2 and miRNA-HDL. This database stores additional miRNA information such as processes, associated tissues, family, functions, diseases, and possible roles as biomarkers [33].

3.5 Plant miRNA database (PMRD)

Plant miRNA database (PMRD) is one of the most important plant miRNA databases that integrated all miRNA related information from many resources. PMRD stores not only sequence, secondary structure and target genes but also expression profiles of a large number of plant miRNAs. The huge number of plant miRNA is gathered from many plant species that covers range from model plants to major crop species. Predicted miRNA target genes information has been stored for poplar, arabidopsis, rice, cotton, soybean, maize and medicage plant. Also microarray published data for maize, tomato, poplar, rice and Arabidopsis is also stored in PMRD [34].

3.6 deepBase

deepBase is an innovative database which enables interpretation of transcriptomic data for discovery of small RNAs and their complete annotation. Seven organisms related deep sequencing data is found that includes chicken, human, mice, Arabidopsis, Ciona intestinalis, Drosophila and C. elegans. 14,600,000 exclusive reads were analyzed which correctly plotted to almost 284,000,000 gene loci. By this analysis, many large scale annotations as well as identifications were done including 6,000,000 distinctive repeat-associated small, 380000

exceptional ncRNA-associated small RNAs, 4,000,000 unique exon-associated-small RNAs and 1,500,000 exclusive promoter-associated small RNAs. By using miRDeep and snoSeeker, a large number of snoRNA and miRNA candidates also predicted. 1,200,000 RNA clusters were grouped by mapping all reads [35]. deepView genome browser is also available in deepBase for comparative analysis of small RNA related data at multiple levels [36].

3.7 RepTar

RepTar is a relatively new database that enables numerous binding type miRNA target predictions which is based on RepTar that is its modular algorithm. RepTar database is built on repetitive elements identification in 3'-UTRs rather being based on conventional binding patterns or evolutionary conservation. This permits cellular target prediction of those viral miRNAs that are less conserved in evolution. RepTar prediction gives 71% sensitivity of results in viral miRNAs as in human and mouse. This user-friendly database offers genome-wide predictions of miRNAs of human as well as mouse. Validation of results is done by compiling 21 cellular genes direct targets that are experimentally validated [37].

3.8 miRecords

miRecords is a database of miRNA-target interactions in animal. This manually curated high quality database provides miRNA-target interactions that are experimentally validated. Supporting papers are also provided with every experiment and interaction. Presently miRecords contains 1135 records and results of more than 10 miRNA target prediction programs. miRecords contain records almost double to TarBase which is a very famous database of miRNA targets which are only experimentally validated [38].

3.9 miRdSNP

A unique database, miRdSNP, provides manually curated published disease-associated SNPs (dSNPs) on 3'-UTRs of human genes. Specifically, miRNA usually bind to 3'-UTR of human genes. Any SNP in this region of gene can change the efficiency of miRNA binding which can cause diverse diseases. miRdSNP incorporated dSNPs, diseases and miRNA target sites in it. Results with annotations even at sequence level can be visualized in this database for dSNPs as well as miRNA target sites on the whole 3'-UTR sequences. UCSC Genome browser is also supported with the integration of dSNPs in miRdSNPs [39].

3.10 miROrtho

miROrtho contains putative miRNA sequence data, conservation of RNA secondary structure data, ortholog multiple alignments and annotations. Though miRBase takes annotations of closely related homologs of miRNAs that are experimentally supported, the relative viewpoint is greatly biased towards experimentally preferred model species. miROrtho don't have heavily biasness towards desired experimental model species which is the best feature of data in this database [40].

3.11 PhenomiR

Manually curated PhenomiR database contains microRNA deregulation expression data of many biological processes as well as of biological complications such as diseases. PhenomiR contain annotation data of miRNA expression down or up variation, fold change variation, miRNA detection method, sample size and origin of analyzed sample. Comprehensive statistical analysis is also provided by PhenomiR. Statistical analysis is applied on important features such as genomic location of deregulated miRNAs or effect of origin of sample. PhenomiR based on disease type, contrast cell culture literature with patient literature using its dataset [41].

3.12 miRNEST

This broad database of animal, plant and virus microRNAs mainly deals with Expressed Sequence Tags (ESTs) as well. miRNEST is pooling information of 13 other databases and literature resources which include information of miRNA sequence, expression, polymorphism, target and sequencing data. This database does predictions that are carried out on ESTs of 202 plants and more than 221 animals. In 221 animals and 199 plants, miRNA examination is done based on sequence similarity on 10,004 miRNA candidates. Only 300 of these miRNA are reported in miRBase [42].

3.13 miRDB

miRDB is an online database of miRNAs that especially focus on collection of mature miRNA playing the most important role in regulation of genes among all other small RNA. In miRDB, miRNA functional annotation results as well as miRNA target prediction results are stored. Its most unique feature is the establishment of user-interactive interface which allow community-annotation miRNA functional catalog [43].

3.14 miRTarBase

miRTarBase is one of the most important curated and up-to-date experimentally supported repertoires of miRNA-target interactions. This database is the largest collection of MTIs till date as compared to previously developed databases. Mostly, miRNA-target interactions are experimentally authenticated by western blotting, various assays or microarray. miRTarBase is incorporating more miRNA-target interactions by constantly surveying research articles [44].

3.15 starBase

starBase is a database of sequencing (cross-linking immunoprecipitation-high-throughput sequencing- CLIP seq and Degradome-Sequencing) information related to miRNA experiments. It contains data on miRNA annotation, target interaction maps and discovery. A large amount of information is present on cleavage and Ago-binding sites as it contain two innovative web servers to spot these sites from both types of sequencing data. Interactive web server is also available that support user-friendly interface and diverse types of computational programs [45].

3.16 Human microRNA disease database (HMDD)

miRNA-disease associations from many experiments are

stored in this database. Human miRNA-associated disease database (HMDD) comprises many miRNA attributes such as miRNA names, dysfunction experimental evidence, disease names. HMDD is updated in year 2012. Two novel databases LncRNADisease

(<http://202.38.126.151/hmdd/html/tools/lncrnadisease.html>) and miREnvironment (<http://202.38.126.151/hmdd/tools/miren.html>) have been developed later for long non-coding RNAs (lncRNA) and miRNA, environmental factors, and phenotypes, respectively [46].

Number of entries, number of species with type of information present in above mentioned miRNA databases have been summarized in Table 2 below.

TABLE 2
SUMMARY OF ENTRIES IN MIRNA DATABASES.

Database	Species	Type of information	No. of entries
miRBase	140	miRNA gene loci	15000
		Distinct mature microRNA sequences	17000
miRNAmap	12	Distinct mature microRNA sequences	2176
		Experimentally validated miRNA genes	450
		Targets per miRNA on promoter	22132
miRWalk	3	Targets per miRNA on 5'UTR	499
		Targets per miRNA on CDS	4783
		Targets per miRNA on 3'UTR	3074
miRandola	1	miRNA-circulating	1083
		miRNA-exosome	856
		miRNA-Ago2	173
		miRNA-HDL	20
PMRD	121	Plant miRNA	8433
deepBase	7	Small RNA deep sequencing data	185
miRecords	7	miRNAs	301
		Target genes	902
		dSNP-disease associations	786
miRdSNP	1	Diseases	204
		dSNPs	630
mirOrtho	34	Putative miRNA genes	7887
		miRNA predictions	1437
PhenomiR	1	miRNA expression studies	542
miRNES T	544	miRNA	39122
		Curated experimentally verified MITEs	3576
miRTarBase	17	miRNAs	657
		miRNA target genes	2297
		Ago-binding clusters	~1 million
		Cleaved target clusters	~2 million
starBase	6	CLIP-Sequencing miRNA-target relationships	400 000
		Degradome-Sequencing miRNA-target relationships	66 000
HMDD	1	miRNA genes	591
		Diseases	396
		miRNA-disease associations	5076

4 CONCLUSION

Regulatory RNAs Informatics is a modern branch of bioinformatics that emphasis on databases and tools designed especially for regulatory RNAs. miRNAs are one of the most important class of regulatory RNAs that plays significant role in many human pathologies as well as maintenance of body homeostasis. miRNAs related databases contain variety of miRNA related information ranging from miRNA sequences up to miRNA complex network analysis. These databases ease the

biologists in large-scale research by providing an easy and open access to collection of regulatory RNAs data in an organized fashion. Summarizing all miRNA databases will help to do in-depth analysis of regulation in body by miRNA. Many attempts are being done to use miRNAs as diagnostic marker. Additionally, miRNA will facilitate the biologists to design advanced therapies against any disease. There is still a long way to go till the completeness of information on miRNA and there is huge scope of research in regulatory RNA informatics field.

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