Original Article

EyeMirDB: a Web-Based Platform of Experimentally Supported Eye Disease-miRNA Information

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Abstract

Background: Studies of microRNA biology have increased in numerous scientific research domains, including eye science. MicroRNAs (miRNAs) are small non-coding RNAs that operate as post-transcriptional regulators of gene expression by destroying or blocking the translation of target messenger RNA. Recent research has revealed the functions of several miRNAs in the regulation of pathological ocular disease, implying that miRNAs could be used as biomarkers and therapeutic targets in eye diseases. Many of the ocular miRNAs' target genes are still unknown. It seems that more research is needed to better understand their role. Despite significant efforts to investigate the miRNA of eye disease, a complete platform of frequent ocular disease with genes, pathways, and miRNA is still unavailable.

Material and Methods: Since the most important part of designing a platform is collecting reliable data, three well-known databases were used as the main data source: DisGeNET, OMIM, and KEGG. The curated genes involved in each disease were manually collected. Then, the annotation information like gene's sequence, description, chromosome's number, start and end loci were extracted from the Ensembl data source. Gene's pathway information was earned from KEGG and Reactome. Finally, experimentally validated gene's related miRNA has been collected from miRecords, miRTarBase, and TarBase. In order to consider miRNAs expression in ocular tissues, we reported their expression in terms of RPM (based on miTED).

Results: we present EyeMirDB (http://eyemirdb.databanks.behrc.ir/), a web-based platform of consisting of all predicted and validated miRNAs. Information on the annotation of miRNA-related genes was also collected in order to better understand the effects of miRNA. Pathways by which these genes are active were also identified. Right now, EyeMirDB contains 429 curated genes, 1258 pathways, and 2596 validated miRNAs of 25 prevalent ocular diseases.

Conclusion: We introduce EyeMirDB, a web-based platform of Eye diseases-related interactions including disease-gene, gene-miRNA, gene-pathway curated information, and annotations, with the optionality of studying all these entities from different viewpoints. This data portal is a good entry point for ocular disease researchers.

Keywords: Web-Based Platform; Eye Disease; Gene; miRNA; Pathway.

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Introduction

The Human Genome Project, which ran from 1990 to 2003, provided complete and exhaustive data on human genome configurations in all their complexities, ushering in the post-genomic era [1]. This time is set apart to a limited extent by broad examinations on non-coding RNAs (ncRNAs), which do not encode for proteins yet still record for over 98.5 % of human genome records [1-3]. Although many studies on the roles of transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) have been conducted, non-coding RNAs (ncRNAs) such as long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) have only recently been discovered to play a role in pathological and physiological processes. Among these regulatory ncRNAs, miRNAs are the most widely studied ncRNAs in biomedical research.

The discovery of microRNAs has been the most exciting new development in RNA biology in the last two decades (miRNAs). MiRNAs are members of the non-coding RNA family, which consists of genomically encoded untranslated RNA molecules ranging in size from 18 to 24 nucleotides. They regulate protein-coding genes by interfering with the mRNAs' original instructions. MiRNA expression is spatially and temporally regulated. This is why they were initially referred to as small temporal RNAs. MiRNAs have been discovered in some viruses as well as all multicellular eukaryotes such as algae, plants, and animals. MiRNAs regulate many important biological processes, including cell growth, cell death, development, and differentiation. According to the findings, miRNAs play an important role in the genome-wide regulation of gene expression and add a layer of complexity to gene expression regulation [2]. MiRNA dysregulation has been linked to a variety of diseases such as cancer, cardiovascular infections, and neurological disorders. MiRNA inherited variants have also been linked to a few acquired disorders, including hearing loss and embryo development. Given their biological significance, miRNAs are currently regarded as astute infection biomarkers and likely restorative focuses for expanding new intercessions [4-6].

The human eye is a complicated organ with multiple separate tissues (e.g., lens, cornea, retina, and iris) that all perform different activities in order to detect a visual image. The lens, for example, is a very simple structure made of columnar and elongated lens epithelial cells that focuses incoming light onto the retina. The retina, on the other hand, is a multilayered tissue that contains a variety of cell types, including photoreceptors, amacrine cells, ganglion cells, and bipolar cells, and analyzes and transmits visual signals to the brain. The role of miRNA in the development and function of the eye is unknown, but it is being investigated. Several studies published in the last five years have improved our understanding of ocular miRNA expression [7] . Growing evidence suggests that miRNAs and their biogenesis machinery are altered and dysregulated in neovascular eye diseases such as diabetic retinopathy (DR), age-related macular degeneration (AMD), and retinopathy of prematurity (ROP), suggesting the potential for miRNAs to be used as biomarkers and therapeutic targets [8] . Because of their critical roles in normal development and illness, recent research has shown that miRNAs are effective indicators or molecular targets for potential treatments. Following their recent discovery via miRNA expression analysis, researchers are now looking into the role of miRNAs in the eye. Many of the target genes of these ocular miRNAs are still unknown.

Although many efforts have been made to study miRNAs in ophthalmic diseases, there is still no comprehensive database of common ophthalmic diseases involving genes, pathways and miRNAs. Therefore, there is an urgent need for a reliable data source from miRNA data for eye diseases. The aim of this study is presenting EyeMirDB a novel source that, for the first time comprises 429 curated genes, 1258 pathways, and 2596 validated miRNAs associated with 25 common ocular disorders [9].

Materials and methods

Data sources

EyeMirDB currently holds 429 curated genes, and 2596 validated miRNA of humans, representing a comprehensive coverage of annotation profile for 25 common eye diseases. EyeMirDB data collection pipeline is shown in figure 1.

Since the most important part of designing a platform is collecting reliable data, three well-known databases were used as the main data source: 1. DisGeNET, a discovery platform that houses one of the most comprehensive publicly available libraries of genes and variations linked to human disorders [10], 2. OMIM, a free authoritative database of human genes and genetic traits that is updated daily [11] . 3. KEGG, a database resource for understanding high-level functions and utilities of biological systems, such as the cell, organism, and ecosystem, using molecular-level data, particularly large-scale molecular datasets generated by genome sequencing and other high-throughput experimental technologies [12-14].

As can be seen in the pipeline (Figure 1), to collect data, disease information was first searched in the KEGG and OMIM, and DisGeNet databases. The collected information was placed in the disease table. Then, the curated genes involved in each disease were manually collected from the three mentioned databases and placed in the gene-disease table. Duplicate genes were removed. In this table, in addition to gene symbol and disease name, three binary values were considered that indicate whether the reported gene was extracted from that source. The annotation information like gene's sequence, description, chromosome's number, start and end loci were extracted from the Ensembl data source (a genome browser for vertebrate genomes that aids comparative genomics, evolutionary biology, sequence variation, and transcriptional regulatory studies [15]), and Ensemble id, Entrez id, gene name, gene symbol, UniProt Id, OMIM Id obtained from NCBI [16]. This step was carried out using the R packages biomaRt [17] and org.Hs.eg.db [18]. All this data is available in the gene source.

Gene's pathway information was earned from KEGG and Reactome [19]. reactome.db [20] And KEGG.db [21] R packages were used to manage the pathways. The results are in Gene-Pathway and pathway table. Gene-Pathway entries are pathway names and related genes. For the pathways, their name, id in KEGG or Reactome, were extracted

And finally, experimentally validated gene's related miRNA has been collected from miRecords [22], miRTarBase [23], TarBase [24], and predicted gene's related miRNA was collected from diana_microt [25], elmmo [26], microcosm [27], Miranda [28], mirdb [29], pictar [30], pita [31], and targetscan [32]. The miRNA annotation information such as Accession, gene family, chromosome, hairpin, sequence, mature miRNA id from miRBase [33] . For these steps, multiMiR [34] and mirbase.db [35] R packages were used, respectively. In order to

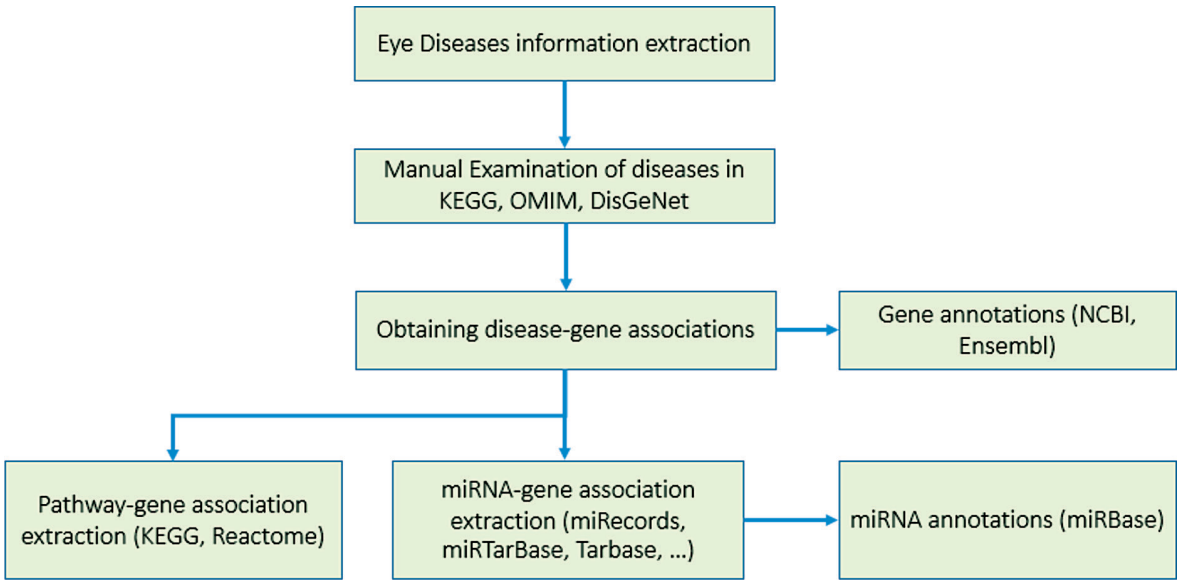


Figure 1: EyeMirDB data collection pipeline. First, the information of each disease was extracted manually from KEGG, OMIM and DisGeNet database. Then genes associated with each disease were obtained and their annotations were obtained from the Ensembl and NCBI databases using R packages biomaRt and org.Hs.eg.db. In addition, the pathway's data related to each gene were collected from two databases, KEGG and Reactome. In this process, reactome.db and KEGG.db R packages were used. Finally, miRNA data related to each gene were extracted from eleven different sources (diana_microt, elmmo, microcosm, Miranda, mirdb, pictar, pita, targetscan, miRecords, miRTarBase, TarBase). R Package multiMiR was used for this purpose. miRNA annotation data from miRBase was also collected with the help of the mirbase.db R package

consider miRNAs expression in ocular tissues, we inserted their expression level in terms of RPM based on miTED [36] database.

Results

As we mention before, we focused on 25 prevalent ocular diseases. Diseases are divided into three main categories: Neuropathy (Cataract, retinal neovascularization, corneal neovascularization, neuromyelitis optica, posterior capsule opacification), metabolic disease (diabetic retinopathy, diabetic cataract), Nervous system disease (myopia, primary open-angle glaucoma, glaucoma, Vogt-Koyanagi-Harada disease, keratoconus, retinitis pigmentosa), Cancer (uveal melanoma, retinoblastoma), Vascular disease (proliferative vitreoretinopathy, Behcet's disease), age-related disease (Exfoliation syndrome, age-related cataract, age-related macular degeneration), systemic autoimmune disorder (primary Sjögren's syndrome), Congenital disorder (pterygium, strabismus, Volkmann cataract) and Infectious disease (herpes simplex virus).

We collect data on 429 curated genes based on these diseases. We also retrieved annotation data for each gene. Approximately 11.6 % of the genes belonged to chromosome 1, 7.4 % to chromosome 6, and 81 % to the rest of the chromosomes. To complete the information, we looked at the pathways for each gene. The total number of detected pathways was

1258. Finally, we got 2596 miRNA, 16687 validated gene-miRNA associations. 164 and 145 of miRNAs are located in chromosome 1 and x respectively and for other chromosome we have less than this number. Result of this miRNA distribution on chromosomes, can show the effect of gender on the disease, this could be a matter for further investigation by researchers. Among validated gene-miRNA associations 11,839 of them are reported in the miRTarBase, 10138 in TarBase and only 183 of them repoted in miRecords. In the expriment column related to the validated gene-microRNA association table, we see 68 techniques, among which Degradome sequencing, PAR-CLIP and HITS-CLIP were the most common. Support type of these interactions belongs to Functional MTI, Functional MTI (Weak), Non-Functional MTI, Non-Functional MTI (Weak), negative and positive, The highest frequency is related to positive and Functional MTI (Weak).

Web portal

The EyeMirDB is developed by the .NET MVC technology. In the server-side, it is programmed by C#, powered by Razor, and in the client-side, JQuery, HTML5, and bootstrap. Its data technology is MSSQL with the LINQ object relational mappings and EntityFramework. The homepage of EyeMirDB is demonstrated in figure 2.

Using the three boxes of Eye Diseases, Genes, and Search miRNA, it is possible to study ocular diseases from different viewpoints. In the Eye Disease tab (Figure 3); all eye diseases are listed with the capability of detailed investigations.

As mentioned previously, these details contains of disease title, description, links to other sources and its involved genes, which could be viewed in details (shown in figure 4).

Moreover, the search tab includes the options of gene and miRNA research. As demonstrated in figure 5, inside the EyeMirDB, we provided

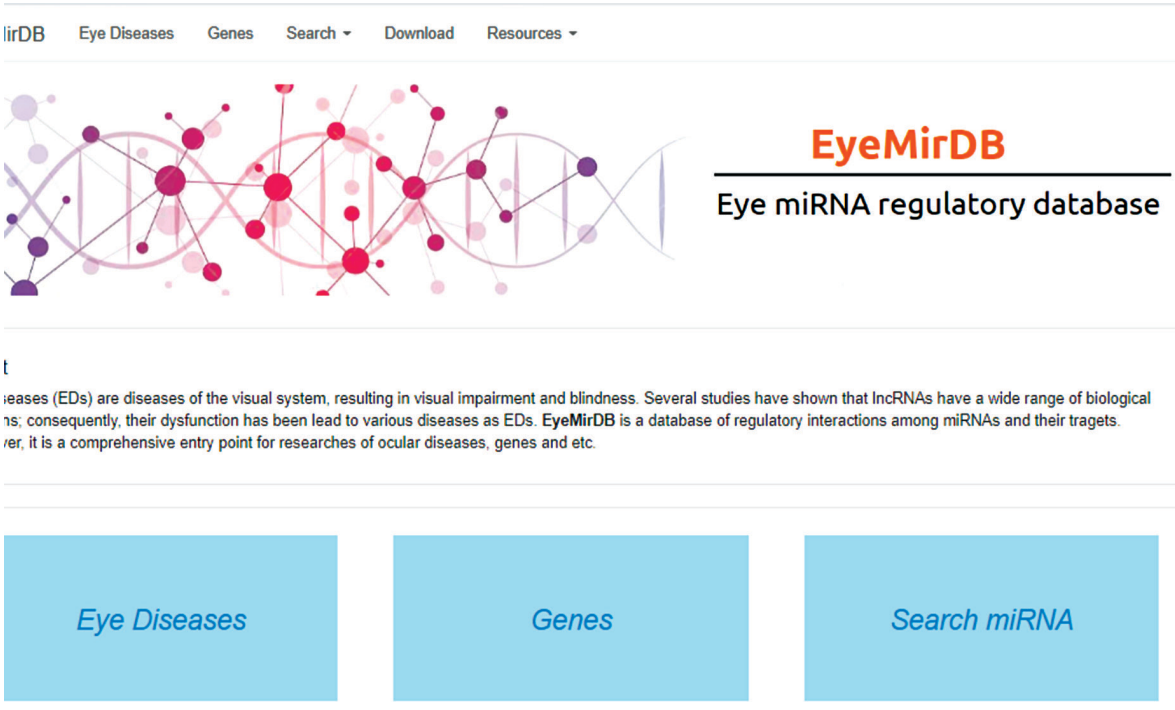
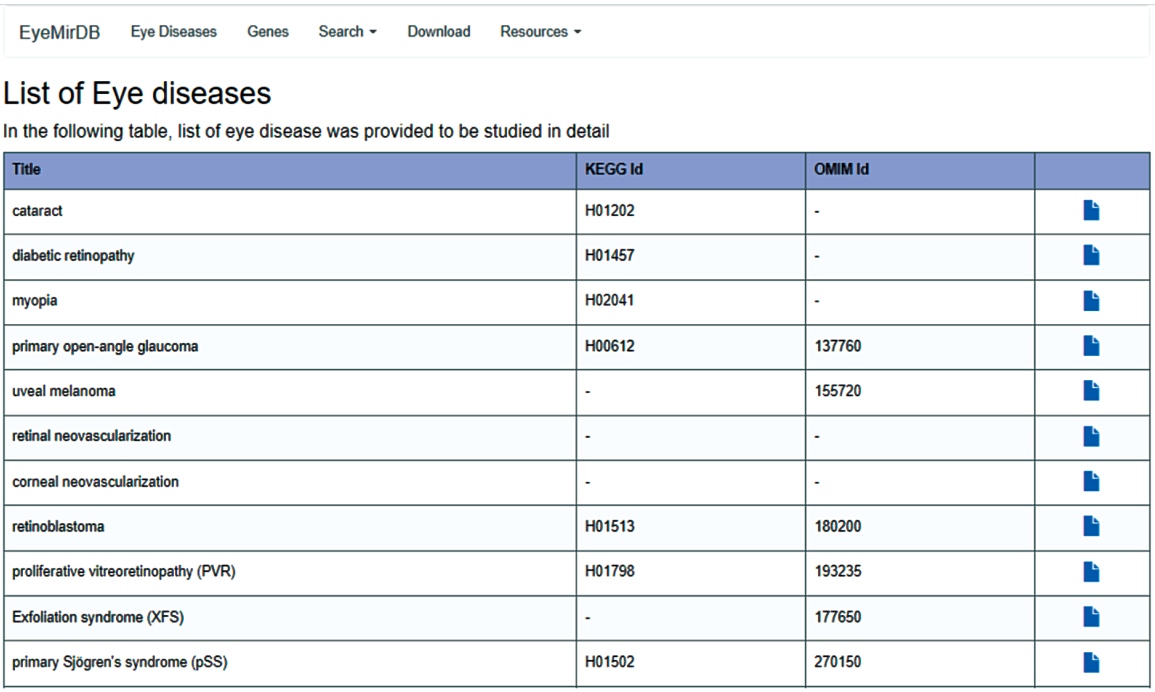


Figure 2: Home page of EyeMirDB



Title	KEGG Id	OMIM Id	
cataract	H01202	-	
diabetic retinopathy	H01457	-	
myopia	H02041	-	
primary open-angle glaucoma	H00612	137760	
uveal melanoma	-	155720	
retinal neovascularization	-	-	
corneal neovascularization	-	-	
retinoblastoma	H01513	180200	
proliferative vitreoretinopathy (PVR)	H01798	193235	
Exfoliation syndrome (XFS)	-	177650	
primary Sjögren's syndrome (pSS)	H01502	270150	

Figure 3: Eye Diseases list. For every record, the details information is provided

the capability of searching a microRNA using its Mature ID, Pre-Mature ID or its sequence. A typical search result is depicted in figure 6.

Discussion

Finding disease-related microRNA can help researchers better understand the mechanism of disease. It can also be effective in prescribing medication. In this platform, in order to help researchers, we tried to introduce disease-related microRNA in two groups: validated and predicted. We introduce EyeMirDB, a web-based platform of Eye diseases-related interactions including disease-gene, gene-

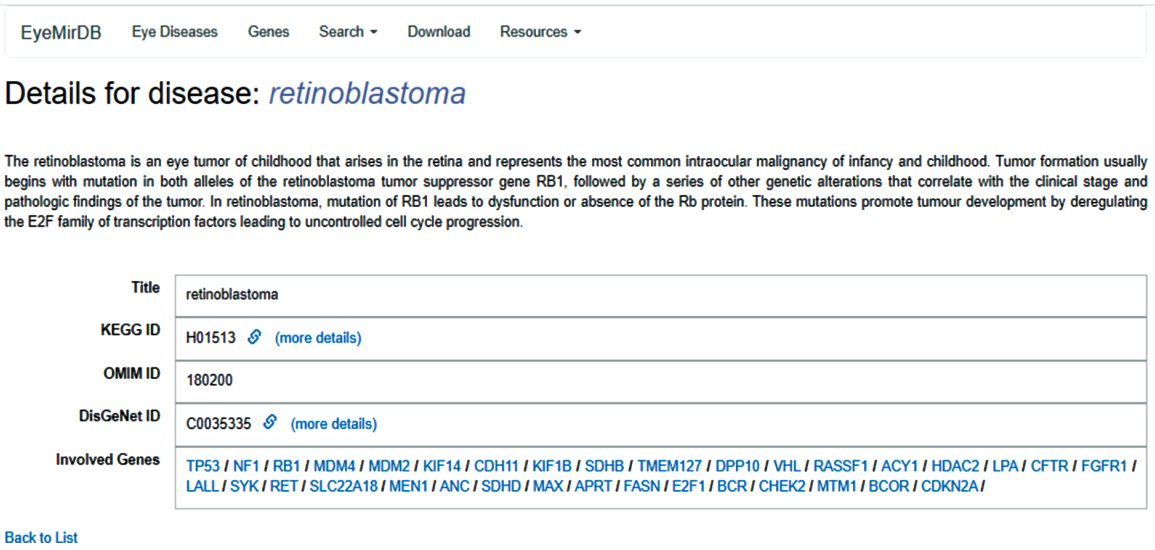


Figure 4: Disease Search Result page

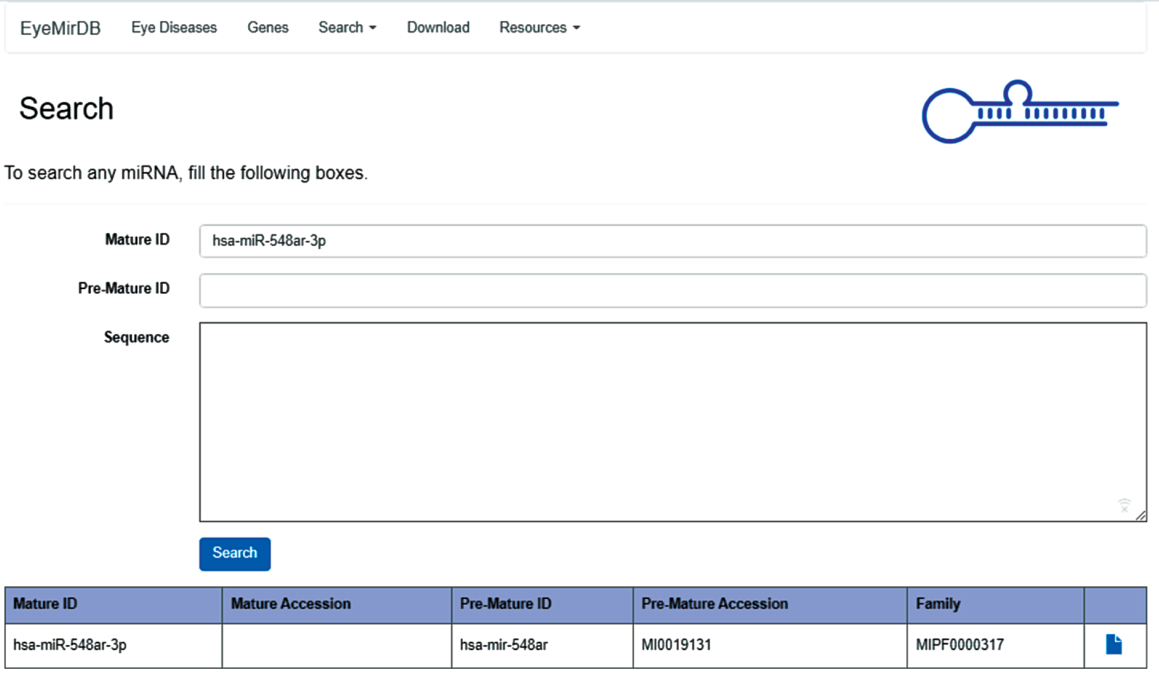


Figure 5: miRNA search form. In this page, looking for miRNAs are provided through their Mature ID, Pre-Mature ID, and their sequence

miRNA, gene-pathway curated information, and annotations, with the optionality of studying all these entities from different viewpoints. This data portal is a good entry point for ocular disease researchers [37].

Conclusion

miRNAs operate as post-transcriptional

Figure 6: miRNA search result

regulators of gene expression by destroying or blocking the translation of their target mRNAs. Recent studies have revealed the functions of several miRNAs in the regulation of pathological ocular disease, implying that miRNAs could be used as biomarkers and therapeutic targets in eye diseases. Herein, we introduce EyeMirDB, a platform of Eye diseases-related interactions including disease-gene, gene-miRNA, gene-pathway curated information, and annotations, with the optionality of studying all these entities from different viewpoints. This data portal is a good entry point for ocular disease researchers.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.