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EpimiRBase: a comprehensive database of microRNA-epilepsy associations

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ABSTRACT

Summary: MicroRNAs are short non-coding RNA which function to fine-tune protein levels in all cells. This is achieved mainly by sequence-specific binding to 3' untranslated regions of target mRNA. The result is post-transcriptional interference in gene expression which reduces protein levels either by promoting destabilisation of mRNA or translational repression. Research published since 2010 shows that microRNAs are important regulators of gene expression in epilepsy. A series of microRNA profiling studies in rodent and human tissue has revealed epilepsy is associated with wide ranging changes to microRNA levels in the brain. These are thought to influence processes including cell death, inflammation and re-wiring of neuronal networks. MicroRNAs have also been identified in the blood after injury to the brain and therefore may serve as biomarkers of epilepsy. EpimiRBase is a manually curated database for researchers interested in the role of microRNAs in epilepsy. The fully-searchable database includes information on up- and down-regulated microRNAs in the brain and blood, as well as functional studies, and covers both rodent models and human epilepsy.

Availability: EpimiRBase is available at http://www.epimirbase.eu

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1 INTRODUCTION

Epilepsy is one of the most common neurological disorders, affecting approximately 65 million people worldwide. It is characterised by recurring seizures; abnormal, synchronous firing of groups of neurons within the brain that disrupt sensory, motor and other brain functions (Chang and Lowenstein, 2003; Fisher *et al.*, 2014). Although anti-epileptic drugs help control seizures for many patients, there is no cure for epilepsy and about one in three patients are drug-resistant. Analysis of brain tissue from patients and rodent models suggests there are large-scale changes in gene expression within affected brain regions (Pitkänen and Lukasiuk, 2011). Understanding what controls gene expression may open new avenues for treatment or prevention of epilepsy.

MicroRNAs are short non-coding RNAs which function to fine-tune protein levels in all cells. They achieve this mainly by sequence-specific binding to 3' untranslated regions of target mRNA (Bartel, 2004). The result is post-transcriptional interference in gene expression which reduces protein levels either by promoting destabilisation of mRNA or translational repression (Bartel, 2009). Targeting typically requires a 2-8 nt Watson-Crick base pairing (so-called "seed" region) between the 5' end of the microRNA and its mRNA target (Bartel, 2009). This interaction is mediated by proteins of the Argonaute (Ago) family, in particular Ago2 (Czech and Hannon, 2011).

Since 2010, research has emerged that shows microRNAs are important regulators of gene expression in epilepsy. Changes to many different microRNAs have been reported to date, through a combination of animal studies and analysis of human tissue samples. The regulated microRNAs are implicated in controlling levels of proteins involved in processes such as cell death, inflammation, re-wiring of neuronal networks and other cell functions (Jimenez-Mateos and Henshall, 2013; Dogini *et al.*, 2013). MicroRNAs have also been identified in the blood after injury to the brain and therefore may serve as biomarkers of epilepsy (Liu *et al.*, 2010; Gorter *et al.*, 2014; Wang *et al.*, 2015). A number of functional studies have determined that the manipulation of individual microRNAs can exert a powerful effect on seizures and seizure-induced neuronal death (Jimenez-Mateos *et al.*, 2012; Tan *et al.*, 2013).

As active investigators in this growing area of epilepsy research we recognised the need for a database to keep track of the rapidly expanding published literature on microRNAs and epilepsy. We have developed EpimiRBase in order to provide complete and up-to-date information on all publications relating to microRNAs and epilepsy. The database contains over 2,000 manually curated microRNA entries including: up/down-regulated microRNAs from high-throughput profiling studies of human brain tissue and rodent experimental models, after evoked seizures and in chronic epilepsy; low-throughput expression analysis and functional studies in which microRNAs have been manipulated in seizure models; and microRNA biomarker studies in which microRNAs have been surveyed in biofluids such as blood in epilepsy patients and animal models of epilepsy.

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2 IMPLEMENTATION

Initial studies for inclusion in EpimiRBase were selected using a PubMed search (Date: August 18th 2015) and the search terms "Epilepsy and microRNA" (returned 104 results) and "Seizure and microRNA" (returned 63 results). These two lists were cross-referenced and duplications removed. From the remaining list of published studies we selected only those reports that had intentionally investigated a role for microRNA in human epilepsy or an *in vivo* experimental seizure model. We have continued to update EpimiRBase as new publications become available. We apologise in advance to authors of any studies that we may have missed in this version of the database and urge them to contact us to ensure their inclusion in the next release.

MicroRNA names from each publication were mapped to miRBase 21 using the R package *miRNAmeConverter*. MicroRNAs that could not be unambiguously mapped to miRBase 21, or that were not included in miRBase 21 were removed. We also removed any microRNAs that were not human, mouse or rat (e.g. ebv, kshv, mghv) and novel microRNAs. We incorporated this database into a user-friendly web-based portal to facilitate discovery, browsing and searching for microRNAs which are or may be related to epilepsy. The database is searchable by any of the following parameters: microRNA name, regulation (up/down), type of study (i.e. low-throughput expression analysis and functional experiments or high-throughput profiling methods), species, publication authors and expression details. Users can input the exact microRNA name (such as mmu-miR-22-3p) or part of a name, for example the numeric portion (such as 22); searches are dynamic and can be partial or complete and become more refined as detail is added. After submitting a query all entries that are related to users' query are listed and users can sort the entries by any column (Figure 1). An advanced search is also available where the user can filter the data based on any or all of the above parameters.

Details are provided on the regulation (up or down), the study type (profiling, expression analysis or functional), the species and the microRNA expression patterns (timing of up or down regulation). We also provide links to: the miRBase entry for each microRNA (Kozomara and Griffiths-Jones, 2014); a PubMed link to the publication associated with each database entry; links to two databases of validated microRNA targets, TarBase (Vlachos *et al.*, 2015) and miRTarBase (Hsu *et al.*, 2014); and a link to a page which provides summary information on the experimental design (by clicking on 'Experimental Details'). Some authors have argued that many of the sequences in miRBase are not derived from bona fide microRNA genes, therefore, we have included a link for each microRNA entry to MirGeneDB, a recently published database of manually curated and highly supported bona fide microRNAs (Fromm *et al.*, 2015). For example, of the 1,881 human microRNAs listed in miRBase, only 523 meet the standards for microRNA annotation in MirGeneDB. The entire EpimiRBase database is available for download in CSV, XML and JSON formats.

Finally, authors are encouraged to submit data from recently published expression analysis, functional and profiling studies to us using the EpimiRBase submissions page. Once approved the submitted records will be included in the next version of the database and made available to the public.

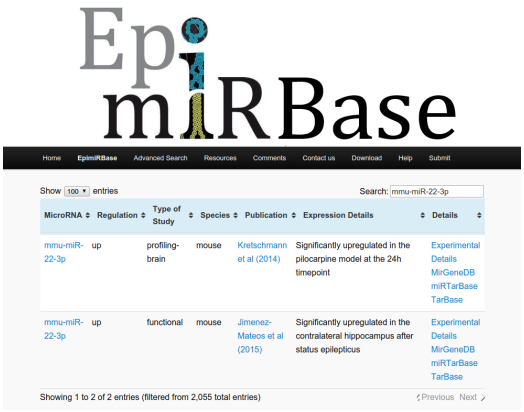

Fig. 1. The EpimiRBase user interface showing results of a search for "mmu-miR-22-3p".

3 DISCUSSION AND CONCLUSION

EpimiRBase is a comprehensive manually curated database of over 2,000 microRNA-epilepsy associations from 34 publications to date including 973 unique microRNA (1,191 up and 864 down regulated) from three species: human (161), mouse (849) and rat (1,045). We have categorised the microRNA into four study types: expression analysis (41), functional (12), profiling-biofluid (32) and profiling-brain (1,970). Information about the current version of the database and the most recent updates and statistics are available from the EpimiRBase website. The development and expansion of EpimiRBase will be ongoing and more publications describing microRNA involvement in epilepsy will be integrated into the database as they become available. We encourage authors of these studies to contact us and submit their data and members of the community to alert us to relevant publications we have not yet included. We hope that biologists and medical researchers working in the field of epilepsy research will find EpimiRBase a useful addition to their toolbox and that annotations found in EpimiRBase will help them design and prioritise further experimental epilepsy research.

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