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NAR Breakthrough Article

dbMAE: the database of autosomal monoallelic expression

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ABSTRACT

Recently, data on ‘random’ autosomal monoallelic expression has become available for the entire genome in multiple human and mouse tissues and cell types, creating a need for better access and dissemination. The database of autosomal monoallelic expression (dbMAE; \url{https://mae.hms.harvard.edu}) incorporates data from multiple recent reports of genome-wide analyses. These include transcriptome-wide analyses of allelic imbalance in clonal cell populations based on sequence polymorphisms, as well as indirect identification, based on a specific chromatin signature present in MAE gene bodies. Currently, dbMAE contains transcriptome-wide chromatin identification calls for 8 human and 21 mouse tissues, and describes over 16,000 murine and \(\sim 700 \) human cases of directly measured biased expression, compiled from allele-specific RNA-seq and genotyping array data. All data are manually curated. To ensure cross-publication uniformity, we performed re-analysis of transcriptome-wide RNA-seq data using the same pipeline. Data are accessed through an interface that allows for basic and advanced searches; all source references, including raw data, are clearly described and hyperlinked. This ensures the utility of the resource as an initial screening tool for those interested in investigating the role of monoallelic expression in their specific genes and tissues of interest.

INTRODUCTION

Autosomal monoallelic expression (MAE) refers to mitotically stable, epigenetically controlled allele-specific expression of autosomal genes, with the initial non-predetermined (‘random’) choice of the transcriptional activity of the two alleles maintained in a given clonal cell lineage [recent reviews include (1–3)]. It is thought to result in massive diversity between cells within the same tissue.

MAE is a relatively recent addition to the number of known epigenetic mechanisms that involve separate regulation of the two alleles’ activity in mammalian cells, including X-chromosome inactivation (4), allelic exclusion in immunoglobulin loci (5) and genomic imprinting (6). After discovery of random allelic inactivation of olfactory receptor genes (7), there were scattered reports of MAE in a variety of mouse genes, including \textit{Il4} (8) and innate immunity receptor \textit{Tlr4} (9).

The advent of transcriptome-wide approaches – based first on hybridization to arrays (10,11) or beads (12) and then RNA sequencing (13–16) – revealed that MAE is widespread in human and mouse cells. Analysis of allelic expression in a limited number of clonal cell lines indicated that a small percentage of genes in a given cell type were subject to MAE. Importantly, for most genes subject to MAE, in some clonal lines the gene was expressed equally from both alleles. This makes the detection of MAE strongly dependent on the number of clonal cell lines available: the more lines analyzed, the higher the likelihood that MAE status for a gene will be detected in at least one line.

In addition to isogenic clonal cell lines, the approaches used in these studies depend on the existence of polymorphisms between maternal and paternal copies of a gene. Accordingly, much higher polymorphism density in F1 hybrid mouse crosses [e.g. (11)] compared to heterozygosity in hu-
man samples [e.g. (10)] resulted in a much greater fraction of genes being informative. Recently, it was shown that MAE can be identified regardless of sequence variation, on the basis of a characteristic signature of chromatin modifications in human (13) and mouse (14) cells. Based on this approach, the ability to classify genes as MAE or biallelically expressed has become available for the entire genome in multiple tissues and cell types in two organisms, human and mouse, creating a need for better data access and dissemination.

THE MAE DATABASE

The database of autosomal MAE genes described here is targeted to researchers interested in investigating MAE in individual genes or groups of genes. We compiled information from multiple reports of allele-specific expression and chromatin signature of MAE genes. Note that the relationship between chromatin modifications we assessed and allele-specific silencing has not been established for imprinted genes (17) or genes on the X chromosome. The same is the case of olfactory receptor genes, the largest gene family in mammalian genomes, for which expression of one allele per neuron is thought to be obligatory (18). Finally, we did not incorporate data from single-cell sequencing studies of allele-specific expression [e.g. (19)] since it is not yet clear how to distinguish mitotically stable autosomal MAE from stochastic transcription in single cells.

Data organization, accuracy and uniformity

dbMAE contains two broad classes of data: direct measurement of allele-specific expression (im)balance (termed ‘experimental’) and indirect chromatin-based inference (‘inferred’). Only data from peer-reviewed publications is included. The database maintains a clear distinction between these types of evidence, listing the entry’s MAE status according to all available sources. The user can also access the full set of data for each gene.

The database is publicly available and searchable via http://mae.hms.harvard.edu. Searchable fields include gene name, cell or tissue type and organism as well as gene allelic expression status. The gene name field accepts common gene names, Ensembl, RefSeq and Entrez IDs.

Search functionality is divided into basic and advanced modes (see online supplementary). In basic mode, the user can check if a gene is inferred or measured to have monoallelic expression in mouse or human tissues (e.g. *Msx2*), or how classes of genes behave (by checking the ‘Search for genus class prefix’ option and entering a partial name, e.g. ‘*Msx*’).

More complex searches can be carried out after clicking the ‘Advanced’ button. For example, it is possible to check the status of a gene in a specific organism and tissue (e.g. ‘*Msx2*’ with Organism: ‘Mouse’ and Tissue: ‘NeuronalProgenitor,GSE54016’). Advanced mode also allows searching by status to check if a class of genes is inferred/know to be monoallelically expressed anywhere (e.g. ‘*Msx2*’ with Status: ‘Monoallelic’ and Organism/Tissue: ‘Any organism’), or if a gene is inferred/know to show monoallelic expression in mouse fibroblasts specifically (‘*Msx2*’ with Status: ‘Monoallelic’ and Organism/Tissue: ‘Mouse Fibroblast’).
Figure 1. Results of queries to the databases can be examined to greater specificity by clicking on fields of interest. Shown are data panels from pages resulting from simple query by gene symbol ‘Msx2’. **Gene page:** Indicates overall gene status in the organisms currently in the database. ‘Monoallelic’ indicates that there is some evidence for monoallelic expression in at least one tissue. **Tissue page:** Accessed upon clicking one of the entries in the ‘gene page’; indicates inferred and experimental status of the gene in the selected organism in each tissue. Headers can be clicked to sort alphabetically. Clicking the ‘Download as csv’ button results in a csv file with the data as presented on the page. **Data page:** Accessed upon clicking one of the entries in the ‘tissue page’. The chromatin mark section shows quantile rank values for the chromatin marks H3K27me3 and H3K36me3 in the selected tissue for the query gene. The experimental data section shows clonal cell lines derived from the tissue in question, and whether the query gene was positively called (“1”) or undetermined (“0”) to be either biased or unbiased in each line.
To maintain a balance between providing the user with all available evidence and presenting it in a usable form, as a first step, we indicate whether a gene shows any evidence for MAE for a given context specified during the search (e.g. in any tissue type in either organism, or in a specific tissue/organism). Thus, a user is first presented with all matching searches in a summary page, where each matching entry is described as ‘monoallelic’ if it is either inferred or empirically determined to be monoallelic in at least one tissue (Figure 1). Clicking on the entry of interest opens the tissue page, where inferred and experimental data are described for each tissue or cell type. Clicking on the name of a specific tissue shows data used for prediction and/or allelic expression data from individual clones.

In addition, we have implemented a basic batch mode, where multiple comma-separated gene IDs can be entered. This yields all individual database entries for these IDs, in a comma-separated format.

Note that the inferred and experimental data do not necessarily come from the same biological sample, but are nevertheless matched for comparison purposes. For example, the experimental data on neuronal progenitor cells derived from datasets GSE54016 and E-MTAB-1822 are presented as separate datasets, since they involve different experiments from different labs. At the same time, both are compared with the same chromatin-based inference on neuronal progenitor samples.

Furthermore, measured and inferred allelic expression statuses are not always identical for the same cell or tissue type. Biological differences between samples, for instance due to genetic background or clonal derivation, may explain some of these inconsistencies. Limitations intrinsic to both approaches may also play a role. For instance, when assessing MAE using RNA-Seq in heterozygous clonal lines, the number of clonal lines assessed may not be sufficient to capture MAE that normally happens in a small proportion of cells. Conversely, chromatin signature may capture unstable MAE, or be confounded by bimodal distribution of expression across cells (e.g. if a gene is completely shut down in some cells, but is biallelic in other cells, we will observe a co-occurrence of chromatin marks for silencing and active transcription similar to those observed with MAE) [see (13,14)]. These approaches are complementary and presenting allelic expression and chromatin signature data side by side should be beneficial to users.

The database is maintained by the corresponding authors. Submissions of new or updated information based on peer-reviewed publications are encouraged.

SUPPLEMENTARY DATA
Supplementary Data are available at NAR Online.

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