The EWAS Catalog: a database of epigenome-wide association studies

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Summary

Epigenome-wide association studies (EWAS) seek to quantify associations between traits/exposures and DNA methylation measured at thousands or millions of CpG sites across the genome. In recent years, the increase in availability of DNA methylation measures in population-based cohorts and case-control studies has resulted in a dramatic expansion of the number of EWAS being performed and published. To make this rich source of results more accessible, we have manually curated a database of CpG-trait associations (with $p < 1 \times 10^{-4}$) from published EWAS, each assaying over 100,000 CpGs in at least 100 individuals. From 2021-01-29, The EWAS Catalog contained 1,045,303 associations from over 1000 EWAS. This includes 652,530 associations from 264 peer-reviewed publications. In addition, it also contains summary statistics for 392,773 associations from 428 EWAS, performed in data from the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Gene Expression Omnibus (GEO). The database is accompanied by a web-based tool and R package, giving researchers the opportunity to quickly and easily query EWAS associations and gain insight into the molecular underpinnings of disease as well as the impact of traits and exposures on the DNA methylome.

The Ewas Catalog is available at: <http://www.ewascatalog.org>.

1 Introduction

EWAS assess associations between traits of interest and DNA methylation across the genome [1]–[3]. These associations may be used to gain mechanistic insights into disease and developmental processes or serve as molecular biomarkers in prediction applications [1]–[3]. Giving researchers easy access to the data will likely improve understanding of complex traits and may yield other translational benefits.

The EWAS Atlas has previously collated well-curated EWAS on traits in an online database and makes annotated CpG site-level results accessible via a website [4]. Other databases are available but are limited to certain diseases (e.g. MethHC [5]).

Ideally, a database of EWAS results will provide summary statistics, including effect estimates, standard errors, and p-values in an easily accessible manner, so that researchers can explore associations without having to retrieve the original article. For example, allowing comparison of effect estimates between studies or a look-up of specific associations to evaluate replication. Unfortunately, although EWAS Atlas does provide association p-values, it does not provide effect estimates and standard errors for download. For completeness, such a database should also where possible provide summary statistics for all potentially true associations beyond those passing conservative significance thresholds, but publications rarely report sub-threshold lists of associations. The contents of EWAS Atlas have to-date been restricted to published associations.

We therefore aimed to improve upon current databases to 1) provide all relevant summary statistics from a range of EWAS and 2) allow easy and programmatic access to results. To this end we have produced The EWAS Catalog, a manually curated database of currently published EWAS with additional data from 387 EWAS performed in ALSPAC [6], [7], and 41 EWAS performed with publicly available data from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/>). The process and data inclusion are summarised in **Supplementary Figure 1**. The EWAS Catalog also enables users to upload results, allowing collection of results not necessarily reported in publications.

2 Methods

2.1 Implementation

The EWAS Catalog web app was built using the Django Python package (<https://djangoproject.com>). The data is stored in a combination of a MySQL database and fast random access files [8], and can be queried via the web (<http://www.ewascatalog.org>) or the R package (<https://github.com/MRCIEU/ewascatalog-r>).

2.2 Overview of publication data extraction

To identify publications, we perform periodic literature searches in PubMed using the terms: "epigenome-wide" OR "epigenome wide" OR "EWAS" OR "genome-wide AND methylation" OR "genome wide AND methylation".

Our criteria for inclusion of EWAS are as follows:

1. The analysis contains over 100 humans
2. The analysis contains over 100,000 CpG sites
3. DNA methylation data is genome-wide (not a candidate gene study)
4. Results are not duplicated from a previous study
5. CpG-trait associations at $p < 1 \times 10^{-4}$ are reported

These criteria and the variables extracted are documented on the website (www.ewascatalog.org/documentation). Briefly, extracted variables include: the exposure variable, the outcome variable, the covariates, tissue, sample size, age, sex, reported ancestry or ethnicity, CpG IDs, effect estimates, standard errors, p-values. To unify representation of traits, they were mapped to Experimental Factor Ontology (EFO) terms, which were manually extracted from the European Bioinformatics Institute database (www.ebi.ac.uk/efo).

2.3 EWAS study data

2.3.1 Avon Longitudinal Study of Parents and Children (ALSPAC)

EWAS were conducted for 387 continuous and binary traits (**Supplementary Table 1**) using DNA methylation measured in peripheral blood of ALSPAC mothers in middle age (N = 940). The trait data were extracted from information collected at the same sampling point blood was drawn for DNA methylation assays. Quality control steps for the traits and information on the cohort are in the **Supplementary Material**.

2.3.2 GEO datasets

Full EWAS results were also estimated for studies that did not report complete summary statistics in their initial publication but where complete DNA methylation and trait of interest information were publicly available through the GEO database. We used the *geograbi* package (<https://github.com/yousefi138/geograbi>) to query GEO for experiments matching inclusion criteria (described above) and extract data for EWAS re-analysis. Details on the query and quality control can be found in the **Supplementary Material**. Both original published results and the full re-analysed GEO results have been included in The EWAS Catalog database. A list of all 41 traits with corresponding citations is provided in **Supplementary Table 2**.

Details on the statistical analyses for EWAS performed specifically for the EWAS Catalog can be found in the **Supplementary Material**.

From 2021-01-29, The EWAS Catalog contained 1,045,303 associations from over 1000 EWAS.

3 Results

The database can be queried at www.ewascatalog.org or by using the R package “ewascatalog.” The website provides a simple user interface with a search bar to explore the database as well as documentation on the catalog contents and how to cite its use (**Figure 1**). Basic queries may include a CpG identifier, gene symbol, genome region, trait, author name or PubMed ID. Query submission will then lead to an intermediate ‘splash page’ providing options for more specific queries. For example, a query for a specific trait would lead to a ‘splash page’ listing that trait, related traits, and all studies of that trait. Selecting one of these leads to a list of relevant EWAS associations, including CpG ID, trait, sample size, publication and association (effect size and p-value) (**Supplementary Figure 2**). This information, along with further details such as reported ancestry, outcome, exposure units and tissue analysed, are available for download as a tab-delimited text file. Alternatively, advanced queries are also supported wherein both a CpG identifier, gene symbol or genomic region are specified along with a trait, author name or PubMed ID. These queries are more specific and lead directly to a list of relevant EWAS associations.

Unlike other EWAS databases, we provide the option of downloading summary results for both the user’s search and for the entire database. For details of how to query the database using the R package, see **Supplementary Materials**.

Figure 1 The EWAS Catalog home page. From here users can search the database, view documentation and navigate to pages that allow for download of the full database and upload of user results. An example of results can be found in Supplementary Figure 2.

4 Discussion and future developments

The EWAS Catalog provides a database of summary statistics from currently published EWAS and an additional 428 currently unpublished EWAS. This database has similar aims to the EWAS Atlas but has additional data sources, provides extra useful information and a user upload option. The EWAS Catalog team will continue to collate and upload newly published EWAS and perform additional EWAS on available datasets, whilst encouraging EWAS authors to upload their own summary data. We are currently working to incorporate additional functionality to allow users to systematically compare their own EWAS findings to EWAS already in the database.

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Conflict of Interest: none declared.

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