

ALLELE FREQUENCIES NET DATABASE

HLA and Adverse Drug Reactions

data upload instructions

Abbreviations used in this document:

ADR	adverse drug reaction
AFND	allele frequencies net database
HLA	Human leukocyte antigen
PMID	PubMed accession numbers (identification numbers assigned to each article within PubMed)

Along with this document, you received an excel spreadsheet file named **HLA_ADRs_authors.xlsx**. The file contains an empty template allowing you to insert your HLA-ADR data and upload the file to the AFND's ADR database. In order to do so, please carefully read and follow the instructions below.

It may be beneficial to have the AFND ADR website query page already open before starting to fill out the form. This webpage can be found at:

http://www.allelefrequencies.net/hla-adr/adr_query.asp

Study details

- 1) Open the **HLA_ADRs_authors.xlsx** file. Select the “**Study Details**” worksheet (if not already selected). The “**study_id**” column has already been filled to 10 rows; continue the numbering if more rows are required.
- 2) If the study has been published, enter the PMID number of the article in the “**pmid**” column. To find the PMID number, open a web browser page to the PubMed entry for the corresponding article and the PMID number will be located just below the article's abstract (see image below). If the study is not available on PubMed, leave a brief explanation in the **pmid** column (e.g. “unpublished data”).

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Abstract

Nucleic Acids Res. 2015 Jan;43(Database issue):D784-8. doi: 10.1093/nar/gku1166. Epub 2014 Nov 20.

Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations.

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Author information

Abstract

It has been 12 years since the Allele Frequency Net Database (AFND; <http://www.allelefrequencies.net>) was first launched, providing the scientific community with an online repository for the storage of immune gene frequencies in different populations across the world. There have been a significant number of improvements from the first version, making AFND a primary resource for many clinical and scientific areas including histocompatibility, immunogenetics, pharmacogenetics and anthropology studies, among many others. The most widely used part of AFND stores population frequency data (alleles, genes or haplotypes) related to human leukocyte antigens (HLA), killer-cell immunoglobulin-like receptors (KIR), major histocompatibility complex class I chain-related genes (MIC) and a number of cytokine gene polymorphisms. AFND now contains >1400 populations from more than 10 million healthy individuals. Here, we report how the main features of AFND have been updated to include a new section on 'HLA epitope' frequencies in populations, a new section capturing the results of studies identifying HLA associations with adverse drug reactions (ADRs) and one for the examination of infectious and autoimmune diseases associated with KIR polymorphisms-thus extending AFND to serve a new user base in these growing areas of research. **New criteria on data quality have also been included.**

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- 3) In the **disease** column, enter the medical condition for which the patients are being treated. For example if the patients are being treated for epileptic seizures, enter “epilepsy” into the column. Please note that many conditions have multiple names, we ask that you first refer to the AFND ADR website query page and click on the dropdown relating to **Patient disease** to see a list of conditions already present in the database. If a condition is already present in the database, use this term.
- 4) In the **drug/treatment** column, enter the name of the administered drug which is suspected of causing the adverse reaction in the patients. If more than one drug needs to be entered (e.g. if multiple drugs were administered and the study cannot identify the causative agent) then enter the name of all the drugs and leave a note in the **issues** column.

If the study investigated multiple drugs which can be separated, please enter these on separate rows.

- 5) The **city** and **province** columns are optional; however, the **country** field is mandatory. These refer to the location where the study was conducted – use the location where most or all of the patients were recruited from. For example, a study that recruited patients from the Royal Liverpool University Hospital in the United Kingdom would enter the following:

City: Liverpool

Province: Merseyside

Country: United Kingdom

If the study is international/multicentre please leave a brief explanation in the **country** column (e.g. “European”).

- 6) In the **ethnicity** column, enter the ethnicity of the patient and control groups. If the cohort is represented by multiple ethnic groups, use “diverse” and provide details in the **Control notes** column. If the statistical results of the study have been separated by ethnicity, then enter these as a separate study (i.e. use a new row).
- 7) The **patients(n)**, **tol_ctrls(n)** and **pop_ctrls(n)** refer to the patients who experienced an adverse event when exposed to the drug, the number of drug exposed controls who did not experience any adverse event and the number of healthy controls (not exposed to the drug) that were recruited as part of the study. In these columns, enter the total number of individuals.
- 8) The contact details for the corresponding author (**corr_auth**) and his/her email address (**email**) should be provided. This is to allow us to contact you if we have any questions regarding the data submitted to us. For reasons of privacy and security, the details of these 2 fields are not stored within the AFND-ADR database.
- 9) If there is any additional information that you feel will be relevant to include, please enter this in the **issues** column.

Association Data

- 1) Now select the **Association Data** worksheet to enter the details about each association.
- 2) The **id** column refers to the **study_id** assigned in the **Study Details** worksheet. Please enter the number corresponding to the **study_id** that matches with the association being entered.
- 3) Enter the **gene/allele** that was analysed as part of the study. Where possible, please use the up-to-date HLA nomenclature as set by hla.alleles.org (current standard was released in 2010). Use the format, for example: “HLA-B*15:02”.
- 4) Enter the adverse reactions observed in Induced Phenotype where multiple reactions are separated by a comma. Refer to the AFND ADR website query page, found at http://www.allelefrequencies.net/hla-adr/adr_query.asp and click on the dropdown relating to **ADR** to see a list of reactions already present in the database.
- 5) In the **patients_with_allele**, **tol_ctrls_with_allele** and **pop_ctrls_with_allele** columns (referring to the patients with adverse drug reactions (hypersensitivity, hepatotoxicity, agranulocytosis etc.), drug exposed controls and healthy controls respectively) enter the number of carriers that were counted in the study groups for this given allele.
- 6) Optionally, provide the calculated odds ratios and 95% confidence intervals for the patients compared to drug exposed controls and also for the patients compared to the healthy controls. Enter these into the **odds_ratio (adr_patients & tol_ctrls)**, **CI_Lower**, **CI_Upper** as well as the **odds_ratio (adr_patients & pop_ctrls)**, **CI_Lower**, and **CI_Upper** columns.
- 7) Provide the p-values results for the statistical analysis in the **p-value (adr_patients & tol_ctrls)** and the **p-value (adr_patients & pop_ctrls)** columns. If statistical correction was applied, please provide the adjusted p-values. Provide the threshold that determines level of significance in the **significance threshold** column.

- 8) In the **statistical method** column, provide the name of the test used to perform the statistical analysis (e.g. Fisher's exact test) and any methods applied to correct for multiple comparisons (including false discovery rate (FDR), Bonferroni correction, etc.) in the **statistical correction** column.
- 9) If there is any additional information that you feel will be relevant to include for this particular association, please enter this in the **issues** column.